Arthritis & Rheumatism

ABSTRACT SUPPLEMENT

2012 ANNUAL MEETING

November 9–14, 2012
Washington, DC

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AMERICAN COLLEGE OF RHEUMATOLOGY
ABSTRACT SUPPLEMENT

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

AMERICAN COLLEGE OF RHEUMATOLOGY
76th Annual Meeting

ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS
47th Annual Meeting

November 9-14, 2012
Washington, D.C.

ACR/ARHP 2012 Annual Meeting Overall Needs Assessment/Practice Gaps

The American College of Rheumatology and the Association of Rheumatology Health Professionals are committed to providing comprehensive education to improve the knowledge and performance of physicians, health professionals and scientists. Through evidence-based educational programs, the organization strives to enhance practice performance and improve the quality of care in those with or at risk for arthritis, rheumatic and musculoskeletal diseases. The 2012 annual meeting program has been developed independent of commercial influence. The following groups were involved in the planning process: the ACR Committee on Education; the ACR Annual Meeting Planning Committee; the ARHP Education Committee and the ARHP Annual Meeting Program Planning Committee.

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

Program Highlights
- Educational tracks to help attendees identify content targeted to them. Tracks include: basic science, business/administration, clinical practice, clinical science, pain management and patient safety.
- Latest science and best-practices presented through peer-reviewed and selected clinical and scientific abstracts, and invited speakers providing clinical, evidence-based and quality focused content;
- Diverse formats of education delivery, including: didactic lectures, debates, and interactive sessions, such as poster tours, Meet the Professors and Workshop sessions;
- A larger forum for discussion of practical management issues such as the Curbside Consults – Ask the Professors session and Medical Aspects lectures;

- Extensive learning opportunities in the basic science of rheumatology, an area of the program developed by a subcommittee of US and internationally prominent basic scientists. Offerings include: Basic Science Symposia, State-of-the-Art Lectures, a series of Immunology Updates for the Clinicians, and a Basic Science pre-meeting course;
- Clinical management sessions, including the Thieves' Market, Curbside Consults – Ask the Professors, The Great Debate and the ACR Knowledge Bowl;
- Specific pediatric rheumatology content integrated throughout the program designed to provide a high-level educational program to pediatric rheumatologists; and relevant updates to adult rheumatologists;
- Formal presentations of new practice guidelines provided to alert the membership and explain, in an open forum, the data supporting the guidelines and propose approaches for implementation;
- Over 35 workshops designed to provide hands-on skills training.

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

Participation Statement

This annual meeting is sponsored by the American College of Rheumatology for educational purposes only. The material presented is not intended to represent the only or the best methods appropriate for the medical conditions being discussed, but rather is intended to present the opinions of the authors or presenters, which may be helpful to other healthcare professionals at arriving at their own conclusions and consequent application. Attendees participating in this medical education program do so with full knowledge that they waive any claim they may have against the College for reliance on any information presented during these educational activities. The College does not guarantee, warrant or endorse any commercial products or services.

The ACR's CME purpose is to provide comprehensive education to improve the knowledge and performance of physicians, scientists and other health professionals. The ACR will offer evidence-based educational activities designed to enhance practice performance and improve the quality of care in those with or at risk for arthritis and rheumatic and musculoskeletal diseases.

Global Learning Objectives
At the conclusion of the 2012 ACR/ARHP annual meeting, participants should be able to:
- identify recent developments in the diagnosis and management of patients with rheumatic diseases
- outline new technologies for the treatment of rheumatologic problems
- describe potential challenges in the delivery of care to patients with rheumatic diseases and to specify possible solutions
- utilize new research data to improve the quality of care of patients with rheumatic diseases
- summarize recent rheumatology research findings

Certificates of CME Credit or Participation

Accreditation Statement: The American College of Rheumatology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation Statement: The ACR designates this live educational activity for a maximum of 49.75 *AMA PRA Category 1 credits™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

International Physicians: International physicians who register as part of a group and require *AMA PRA Category 1 Credit(s)™*, must provide the following information to your tour leader: full name, mailing address, telephone and fax numbers, and e-mail address. The information will be used to verify your meeting attendance.

The American Medical Association has an agreement of mutual recognition of continuing medical education credit with the European Union of Medical Specialties. International physicians interested in converting *AMA PRA Category 1 Credit ™* to *EACCME* credit should contact the *UEMS*.

Health Professionals: Participants may claim hours to receive a Certificate of Participation for an activity designated for *AMA PRA Category 1 Credit(s)™*. For non-CME sessions, attendees may also request a certificate of participation.

Meeting Evaluations, CME Credit Certificates of Participation
Computers are available for you to complete your CME/Certificate of Participation and session evaluations online during the meeting at the CME/Internet Center located in the Concourse, near the entrance to the exhibit hall (Hall A).

International physicians, requiring a Certificate of Attendance, can find one enclosed in your meeting bag. If your country recognizes *AMA PRA Category 1 Credit(s)™* in accordance with *AMA PRA* requirements, please complete the session evaluations and CME application online using ***My Annual Meeting***.

Your evaluation of the meeting is very important. The ACR/ARHP annual meeting planning committees use feedback from attendees to assist in the development of future educational activities; therefore, we encourage you to complete your session evaluations and CME/Certificate application.

Conflict of Interest/Disclosure Statements
As an educational provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), the American College of Rheumatology must ensure balance, independence, objectivity and scientific rigor in all its educational activities. Therefore, all speakers and moderators participating in an ACR-sponsored activity are required to disclose to the planning committee and audience any financial or other relationships including, but not limited to:

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2. Research grants
3. Employment (full or part-time)
4. Ownership or partnership
5. Consulting fees or other remuneration (payment)
6. Non-remunerative positions of influence such as officer, board member, trustee or public spokesperson
7. Receipt of royalties
8. Speakers' bureau
9. Other

Speakers, moderators and abstract authors submitted their disclosure online prior to publication. Disclosures for invited speakers are listed in the indices by presenters' last name.

Abstract author disclosures are published online and in a supplement to the October issue of *Arthritis & Rheumatism*. Disclosures for the late-breaking abstracts are published online and in the December issue of *Arthritis & Rheumatism*. Any individual who refuses to disclose relevant financial relationships will be disqualified from being a planning committee member, a presenter, an author of a CME activity, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.

Disclosure Policy
It is the policy of the American College of Rheumatology to ensure that its CME activities are independent and free of commercial bias.

To ensure content objectivity and balance, and guarantee that the content presented is in the best interest of its learners and the public, the ACR requires that everyone in a position to control content disclose all relevant financial relationships with any commercial interest if the relationship is financial and occurred within the past 12 months. If there are relationships that create a conflict of interest, these must be resolved in accordance with the ACR's CME Resolution of Conflict policy prior to the participation of the individual in the development or presentation of CME content.

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The names, insignias, logos and acronyms of the ACR, the ARHP and the RRF are proprietary marks. Use of the names in any fashion, by any entity, for any purpose, is prohibited without the express written permission of the ACR.

Embargo Policy

Accepted abstracts are made available to the public online in advance of the meeting and are published in a special supplement of *Arthritis & Rheumatism*. Information contained in those abstracts may not be released until the abstracts appear online. Academic institutions, private organizations and companies with products whose value may be influenced by information contained in an abstract may issue a press release to coincide with the availability of an ACR abstract on the ACR website.

However, the ACR continues to require that information that goes beyond that contained in the abstract (e.g., discussion of the abstract done as part a scientific presentation or presentation of additional new information that will be available at the time of the meeting) is under embargo until 4:30 PM Eastern Time on Saturday, November 10, 2012. Violation of this policy may result in the abstract being withdrawn from the meeting and other measures deemed appropriate. Authors are responsible for notifying financial and other sponsors about this policy.

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MONDAY, NOVEMBER 12, 2012

TUESDAY, NOVEMBER 13, 2012

2:30 - 4:00 PM

WEDNESDAY, NOVEMBER 14, 2012

11:00 AM – 12:30 PM
ARHP Concurrent Abstract Sessions

ACR Poster Session A
Biology and Pathology of Bone and Joint
Sunday, November 11, 2012, 9:00 AM–6:00 PM

1

Evaluation of Synovial Inflammation Assessed by Macroscopic and Histological Criteria in Patients with Knee Osteoarthritis. Montserrat Romera-Baures Sr.[1], Ramon Valls-Garcia Sr.[2], Antonio Rozadilla Sr.[3], Marta Terricabras Sr.[4] and Joan Miquel Nolla Sr.[5]. [1]Hospital Universitari Bellvitge, Barcelona, Spain, [2]Hospital de Palamos, Girona, Palamos (Girona), Spain, [3]Hospital Universitari de Bellvitge, Barcelona, Spain, [4]Hospital Universitari de Bellvitge., Barcelona, Spain, [5]Hospital Universitario de Bellvitge, Barcelona, Spain

Background/Purpose: Although osteoarthritis (OA) is commonly described as a non-inflammatory joint disease, synovial inflammation is increasingly recognized as contributing to the symptoms and progression of OA. The aim of this study is the evaluation of synovial inflammation degree by macroscopic and histological findings in patients with knee OA.

Methods: Samples of synovial tissue were obtained from 22 patients with knee OA. The arthroscopy was performed under local anesthesia with sedation. During arthroscopy the joint is distended by infusion of sterile saline with a motorized suction shaver. Each patient underwent a systematic examination of the synovium from the suprapatellar poach, patellofemoral joint, lateral recesses and medial and lateral compartments of femoro-tibial joint. The arthroscopic findings were reflected in a data collection sheet. Biopsies of synovium were obtained from directly visualized areas with biopsy forceps. For macroscopic assessment of the synovial membrane we used a macroscopic semiquantitative scoring system based on the existence of vascularization and proliferation. Vascularization was assessed by the absence or presence of hyperemia and increased vascularity (score of 0 or 1). Synovial proliferation scored 0, 1 or 2 depending on the presence or absence of granularity and villous hypertrophy. The total score of the two components ranged from 0–4. The histological samples were processed with hematoxylin-eosin for histological semiquantitative scoring of synovitis. This scale was based on enlargement of the lining cell layer (0–3 points), density of the residents cells (0–3) and inflamatory infiltrate (0–3). According to the score the findings were classified in the absence of synovitis (0–1), low-grade synovitis (2–4) or high-grade synovitis (5–9 points).

Results: Samples were obtained from 20 of the 22 arthroscopies performed. Macroscopically, we observed pluricompartimental synovitis in 7 patients and localized in 6. In one patient, synovitis adjacent to chondral injury of the femoral condyle was found. Microcrystals were found in the synovium of 4 patients not previously diagnosed of microcrystalline arthropathy. Regarding the total score of macroscopic semiquantitative analysis, 10 patients (50%) scored between 2 and 4. No patient had scores of 0. Histological assessment was performed in 17 of the 20 patients, excluding those cases with presence of microcrystals or insufficient material. The microscopic semiquantitative score showed low-grade synovitis in 7 patients (41%) and high grade in 9 (53%). Only in one of the samples histological synovitis was not evidenced.

Conclusion: The frequency of synovitis in patients with osteoarthritis and synovial effusion assessed by macroscopic or histological criteria is high. Arthroscopic assessment of synovitis shows a good correlation between macroscopic dimension and microscopic histological analysis.

2

Microrna-558 Regulates the Expression of Cyclooxygenase-2 and IL-1beta Responses in Human Articular Chondrocytes. Su Jin Park, Eun-Jeong Cheon and Hyun Ah Kim. Hallym University Sacred Heart Hospital, Kyunggi, South Korea

Background/Purpose: Osteoarthritis (OA) is a chronic degenerative joint disease in which multiple factors contribute to cartilage degradation. It is widely accepted that excess production of proinflammatory cytokine, interlukin-1β (IL-1β), is associated with in the initiation and progression of cartilage destruction. In OA cartilage, IL-1β-stimulated COX-2 expresssion strongly contributes to the inflammation and cartilage destruction via upregulating PGE2 production. The objective of this study was to address whether miR-558, one of IL-1β-responsive microRNAs, can control IL-1β-mediated induction of COX-2 and catabolic effects in human articular chondrocytes.

Methods: Total RNA was extracted from the cartilage tissues of normal and OA donors or cultured human articular chondrocytes. The expression of miR-558 was quantified by TaqMan assay. To investigate the repressive effect of miR-558 on COX-2 expression, human chondrocytes and chondrogenic SW1353 cells were transfected with mature miR-558 or their antisense inhibitor (anti-miR-558). The expression of COX-2 protein was determined by western blot anaysis and the involvement of miR-558 on IL-1β-induced catabolic effects was examined by western blot anaysis and ELISA. Direct interaction between miR-558 and the putative site in the 3'-UTR of COX-2 mRNA was validated by luciferase reporter assay.

Results: Normal human articular cartilages expressed miR-558, and this expression was significantly suppressed in OA cartilages. Stimulation with IL-1β caused a significant reduction of miR-558 expression in normal and OA chondrocytes. IL-1β-induced activation of MAPK and NF-κB decreased miR-558 expression and induced COX-2 expression in chondrocytes. The overexpression of miR-558 directly suppressed the luciferase activity of a reporter construct containing the 3'-UTR of human COX-2 mRNA and significantly inhibited IL-1β-induced upregulation of COX-2, while treatment with anti-miR-558 enhanced IL-1β-induced COX-2 expression and reporter activity in chondrocytes. Interestingly, IL-1β-induced activation of NF-κB and expression of MMP-1 and MMP-13 were significantly inhibited by miR-558 overexpression.

Conclusion: These findings demonstrated that cartilage homeostasis is modulated by an elaborate network of functional microRNAs such as miR-558 that directly targets COX-2 and regulates IL-1β-stimulated catabolic effects in human chondrocytes.

3

Mesenchymal Stem Cells Differentiate Into Osteoblasts in Response to Inflammation. Koshiro Sonomoto, Kunihiro Yamaoka, Koichi Oshita, Shunsuke Fukuyo, Xiangmei Zhang, Kazuhisa Nakano, Yosuke Okada and Yoshiya Tanaka. University of Occupational and Environmental Health, Kitakyushu, Japan

Background/Purpose: Bone destruction due to enhanced osteoclast differentiation is a common observation in rheumatoid arthritis. It is well known that inflammatory cytokines cause osteoclatogenesis, however, the same cytokines also cause chronic enthesitis and excess abnormal bone formation as seen in ankylosing spondylitis. To elucidate the mechanism of this discrepancy, we herein investigated the effect of inflammation on osteoblastic differentiation property of mesenchymal stem cells (MSCs).

Methods: hMSCs were cultured in commercial osteogenic medium in the presence of inflammatory cytokines (TNF-α, IL-1β, IL-4, IL-6, IL-10 or IL-17) *in vitro*. Osteoblast differentiation was assessed by alkaline phosphates (ALP) staining and expression of osteoblastic markers and mineralization was evaluated by alizarin-red S staining.

Results: Inflammatory cytokines (TNF-α, IL-1β and IL-6) enhanced runt-related gene 2 (RUNX2) expression, ALP staining and mineralization. On the contrary, IL-4, IL-10 and IL-17 had no effect or slightly inhibited these markers. Among these cytokines, IL-1β most efficiently enhanced and promoted osteoblast differentiation, which is proved by expression of bone sialoprotein and osteocalcin. TNF-α, IL-1β and IL-6 did not alter the canonical wingless-type MMTV integration site (Wnt) signaling pathway but increase the expression of Wnt5a and its receptor, receptor tyrosine kinase-like orphan receptor 2 (Ror2), which are involved in non-canonical Wnt pathway, also known to possess important roles in osteoclastogenesis. siRNA of the Wnt5a or Ror2 completely inhibit enhanced osteoblast differentiation.

Conclusion: Inflammatory cytokines, which are well known to cause bone resorption by up-regulating osteoclast differentiation, also induced osteoblastogenesis of the hMSCs. This phenomenon indicates the involvement of MSCs in bone homeostasis under the circumstance of inflammation. Our data also indicates the quantitative or qualitative abnormality of MSCs can cause inadequate balance of bone resorption and bone formation.

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Pro-Inflammatory Effect of Extracellular RNA On Synovial Fibroblasts From Patients with Rheumatoid Arthritis. Birgit Zimmermann[1], Silvia Fischer[2], Markus Rickert[3], Stefan Rehart[4], Angela Lehr[4], Ulf Müller-Ladner[1], Klaus T. Preissner[2] and Elena Neumann[1]. [1]Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Justus-Liebig-University of Giessen, Medical School, Giessen, Germany, [3]University Hospital Giessen and Marburg, Giessen, Germany, [4]Markus-Hospital, Frankfurt, Germany

Background/Purpose: Extracellular RNA (exRNA) is present in the serum of patients suffering of different kinds of cancer. exRNA influences physiological processes like blood coagulation and endothelial cell permeability. In this study, we analyzed the presence of exRNA as well as RNase in joints and the effects of nucleic acids and nucleases on synovial fibroblasts (SF) of patients with rheumatoid arthritis (RA). RA is a chronic inflammatory disease, characterized by the destruction of cartilage as well as bone. RASF are activated cells acting as key players in cartilage destruction.

Methods: exRNA in synovium of RA (n=26), osteoarthritis (OA: n=26) and psoriatic arthritis (PsA: n=3) patients was stained in tissue sections with DAPI to locate DNA and SYTO® RNA Select™ Green Fluorescent Stain to locate RNA. RNase 1 was analysed in synovium (RA n=17; OA n=7) immunohistocally. RNase activity was measured in synovial fluid (RA n=14; OA n=5; PsA n=10) and supernatants of SF (RASF n=3; OASF n=3; PsA-SF n=4) and healthy donors (NSF) n=3) using the Quant-iT™ RNA Assay Kit. Release of exRNA by cultured SF (RASF n=3; OASF n=3; PsA-SF n=4; NSF n=3) was measured photometrically. The secretion of IL-6 was analyzed by ELISA after treating RASF (n=3) with 10 μg or 25 μg isolated autologous RNA or DNA for 15 h. Alternatively RASF (n=3) were pre-incubated for 24 h, then 5 U/ml RNase or DNase was added. In the SCID mouse model, the effect of RNase or DNase i.v. was analyzed towards migration and cartilage invasion (RNase n=10; DNase n=9; saline control n=9).

Results: Synovium of all patient showed RNA and DNA signals co-localized within the nuclei. In RA, exRNA was detectable in the lining layer. exRNA in OA lining was present only in single defined regions. PSA showed no exRNA in lining. RNase 1 was increased in lining. RNase activity (units/mg protein) in synovial fluid was significantly increased in RA (31.6±4.5 p=0.023) and OA (27.0±4.5 p=0.033) compared to PsA (18.2±2.3). RNase release (units/mg protein) by cultured cells was comparable (RASF 1.13±0.24; OASF 1.16±0.07; PsA-SF 1.05±0.18; NSF 1.01±0.15). exRNA release (ng/μg protein) was stronger in RASF (RASF 0.22±0.06; OASF 0.17±0.09; PsA-SF 0.17±0.06; NSF 0.11±0.07). RASF secretion of IL-6 was increased by RNA (10 μg 135±40%; 25 μg 118±15%) or DNA (10 μg 156±35%; 25 μg 220±59%). Only RNase reduced IL-6 release (77±14% of control, p=0.136). *In vivo*, RASF invasion was reduced at the coimplantation site by both nucleases (control 1.92±0.24; RNase 1.22±0.21 p=0.037; DNase 0.80±0.19 p=0.002). Fibroblast migration was only reduced with DNase (control 1.51±0.28; RNase 1.28±0.39 p=0.625; DNase 0.84±0.18 p=0.042).

Conclusion: Increased exRNA in the lining and the RNase activity in the synovial tissue and fluid of OA and especially in RA patients could represent a new unbalanced regulatory system in chronic inflammation including RA. The increased exRNA but unchanged RNase release by RASF *in vitro* indicates that RASF contribute to secretion of pro-inflammatory exRNA. exRNA mediates an increased cytokine release by RASF and cartilage invasion which could be inhibited by RNase application. The results illustrate the pro-inflammatory and destructive effect of exRNA in RA.

Disclosure: **B. Zimmermann**, None; **S. Fischer**, None; **M. Rickert**, None; **S. Rehart**, None; **A. Lehr**, None; **U. Müller-Ladner**, None; **K. T. Preissner**, None; **E. Neumann**, None.

5

Adalimumab Inhibits TNF-Enhanced Human Osteoclast Development More Effectively Than Other Biologic Agents Under in Vitro Conditions of Chronic TNF Exposure. Bohdan P. Harvey[1] and Zehra Kaymakcalan[2]. [1]Abbott Laboratories, Worcester, MA, [2]Abbott, Worcester, MA

Background/Purpose: TNF-alpha (TNFa) has been shown to contribute to osteoclastogenesis independently and in conjunction with M-CSF or RANKL, two key cytokines involved in osteoclast development. Both TNFa and RANKL have been concomitantly detected in the synovial fluid of RA patients. However, the role of TNFa in promoting human osteoclast differ-entiation and activity in the presence of RANKL is poorly understood. In this study, we sought to determine the impact of TNFa on RANKL-induced human osteoclast development and function under chronic conditions and to assess the effectiveness of various biologic agents in blocking the effect of TNF in this system.

Methods: Primary human osteoclast precursors (OCP) were exposed to various combinations of M-CSF, RANKL and TNFa (100 ng/mL) +/− increasing concentrations of adalimumab, etanercept or abatacept for up to 7 days. Prior to adding to the cells, the biologics were pre-incubated with the cytokine cocktail for 30 min. Osteoclast differentiation was determined by the presence of large multinucleated cells positive for tartrate-resistant acid phosphatase (TRAP) and by TRAP5b activity. Resorptive activity was assessed by measuring the release of either the degradation products of plate-bound Europium-labeled collagen (Eu-col) or the cross-linked C-telopeptide of type I collagen (CTX-I) from human bone chips.

Results: In the absence of biologics, the addition of TNFa to OCP cultures with exogenous RANKL promoted earlier differentiation (increased TRAcP5b activity by day 4) and enhanced osteoclast activity (increased CTX-I levels by day 7) compared to RANKL alone. Based on early time course assessments using Eu-col, TNFa enhanced the kinetics of osteoclast maturation by 13 hrs and maintained 3-fold higher levels of osteoclast activity for up to 122 hrs. Among the biologics, adalimumab restored the rate of osteoclast differentiation and activity to levels comparable to RANKL alone at concentrations 10-fold lower than etanercept (0.74 μg/mL and 20 μg/mL, respectively). Moreover, etanercept was unable to maintain its inhibitory effect even at the highest dose tested, while abatacept was ineffective in preventing TNF-mediated augmentation of osteoclast development at all concentrations tested. Interestingly, the levels of many TNFa-responsive pro-osteoclastogenic chemokines were similarly reduced in the presence of either adalimumab or etanercept, suggesting that both agents were able to neutralize TNF during early osteoclast development.

Conclusion: These findings demonstrate that TNFa can significantly enhance the kinetics of RANKL-induced osteoclast differentiation and activity. Moreover, under chronic in vitro exposure of OCP to TNF, adalimumab is more effective than etanercept (or abatacept) in mitigating the pro-osteoclastogenic effects of TNF. Overall, our results demonstrate the central role of TNF in RA joint destruction and the sustained potency of adalimumab as compared to other biologics in preventing bone erosion due to chronic TNF exposure.

Disclosure: **B. P. Harvey**, Abbott Laboratories, 3; **Z. Kaymakcalan**, Abbott Laboratories, 3.

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The Effect of Hydrogen Sulfide Donors On Inflammatory Mediators in Human Articular Osteoarthritic Chondrocytes. Elena F. Burguera[1], Angela Vela Anero[2], Rosa Meijide Failde[2] and Francisco J. Blanco. [1]Rheumatology Service, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [2]Department of Medicine, University of A Coruña, A Coruña, Spain

Background/Purpose: Hydrogen sulfide (H_2S) has recently been proposed as an endogenous mediator of inflammation in several pathology models. The aim of this work was to study the possible role of H_2S as an anti-inflammatory and anti-oxidant agent in human articular chondrocytes (CHs) from osteoarthritic (OA) tissue.

Methods: We analyzed the effects of different concentrations of a fast (NaHS) or a slow (GYY4137) release H_2S donor on three key aspects of the inflammatory process in OA, namely: 1) Nitric oxide (NO) production and inducible NO synthase (iNOS) levels; 2) Production of reactive oxygen species (ROS) and antioxidant enzymes superoxide dismutase 2 (SOD2) and catalase (CAT); and 3) The production of prostaglandin E-2 (PGE-2) and cyclooxygenase (COX)-1, -2 and PGE synthase 1 (mPGES-1). NO production was quantified through the Griess reaction. Protein levels were visualized through immunocytochemistry and quantified with appropriate software; mRNA expression levels were detected with qRT-PCR. ROS levels were quantified with a fluorescence microscope after dihydrorhodamine treatment. PGE-2 levels were quantified with a specific EIA. For all studies cells were cultured in medium with 0.5% FBS and stimulated with 5 ng/ml of IL-1b and the different concentrations of NaHS and GYY4137 (ranging from 50 mM to 1000 mM) for 48h. ANOVA tests were performed and differences were considered significant when p<0.05.

Results: The concentrations of H_2S-donors used did not significantly affect cell viability (p>0.05). Concentrations higher than 100 μM of the sulfur donors were effective in reducing NO production in IL-1β stimulated OA CHs in a dose-dependent manner, probably by ameliorating the induction

of iNOS synthesis, since both iNOS mRNA and protein levels were also reduced. ROS levels were reduced when 50 and 200 μM GYY4137 were used, but not by 1000 μM, and this was accompanied, at 200 μM GYY4137, by a reduction in the expression of SOD2 and CAT. NaHS was not effective in reducing ROS directly, and no correlation was found with SOD2 and CAT expression. PGE-2 values were reduced by all concentrations of GYY4137 and NaSH (except 1000 μM) and, in the case of GYY4137, both COX-2 and mPGES-1 were also downregulated at the higher concentrations ($>$100 μM) whereas COX-1 expression was not affected. Collectively, GYY4137 was found to be more effective than NaHS to ameliorate the IL-1β-induced OA-like markers of inflammation and oxidative damage, particularly at a 200 μM.

Conclusion: Results obtained so far suggest an anti-inflammatory and antioxidant role of certain H_2S donors which might be of interest in the alleviation of OA-related inflammation processes and that should be further explored as a therapeutic approach.

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

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Lamin A Deregulation in Human Mesenchymal Stem Cells Promotes an Impairment in Their Chondrogenic Potential and Imbalance in Their Response to Oxidative Stress. Jesus Mateos[1], Alexandre De La Fuente[2] Ivan A. Lesende-Rodriguez[2], Maria Carmen Arufe[2] and Francisco J. Blanco[1]. [1]Rheumatology Division, Proteomics Unit-ProteoRed/ISCIII, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [2]Department of Medicine, Area of Anatomy and Human Embryology, University of A Coruña-INIBIC, A Coruña, Spain

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

Methods: Mesenchymal stem cells (MSCs) from human umbilical cord (UC) stroma have previously been isolated, expanded and differentiated towards mesoderm cell lineages. For efficient gene delivery of wt LMNA, PG and GFP (Green Fluorescence Protein), we used a lentiviral expression system. GFP-transduced MSCs were used as control for the differentiation study since they present a differentiation capacity similar to that of untransduced MSCs. Osteogenic potential was studied by with alizarin red staining to assess calcium deposits as well as Real-Time PCR of ALP, OC and Runx2 to assess early and late osteogenic differentiation. Adipogenic potential was studied with Oil Red staining for lipid droplets and Real-Time PCR of LPL, FABP and ADIPOQ, for early and late adipogenic differentiation. Chondrogenesis and hypertrophy were studied using immunohistochemestry and Real-Time PCR of Aggrecan, MMP-13, Type II Collagen, Type I Collagen and Type I Collagen.

Results: We found that over-expression of LMNA or PG by lentiviral gene delivery leads to defects in differentiation potential. PG-transduced MSCs present defects in adipogenic and osteogenic potential, The chondrogenic potential is defective in PG-MSCs, which present a decrease in COL2 and Aggrecan as revealed by both immunohistochemystry and Real-Time PCR. LMNA and PG-transduced MSCs have an increase in hypertrophy markers (MMP-13 and Type X Collagen) during chondrogenic differentiation, as well as a decrease in manganese superoxide dismutase (MnSODM) and an increase of mitochondrial MnSODM-dependent reactive oxygen species (ROS). ROS synthesis was partially (51%) and totally reverted by N-Acetyl Cystein, ROS scavenger, (NAC) at 20 and 40 μg/mL respectively for 1 hour in culture. In addition, defects in chondrogenesis detected by immunohistochemestry and Real Time-PCR are partially reversed by incubations with NAC at 40 μg/mL for 1 hour.

Conclusion: Our results suggest that OA process could be enhanced by defects in stem cell differentiation, partially due to imbalance in oxidative stress.

Disclosure: **J. Mateos**, None; **A. De La Fuente**, None; **I. A. Lesende-Rodriguez**, None; **M. C. Arufe**, None; **F. J. Blanco**, None.

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Supercharged Sox9 Protein Induces Chondrogenic Differentiation of Bone Marrow-Derived Mesenchymal Stem Cells. Yuan K. Chou[1], Shili Wu[1], Camilo Avendano[2], Tom Caldwell[2], Brian Maniaci[2], Kentaro Yomogida[1], Yong Zhu[2] and Cong-Qiu Chu[3]. [1]Oregon Health & Science University, Portland, OR, [2]VivoScript, Inc, Costa Mesa, CA, [3]Oregon Health & Science Univ and Portland VA Medical Center, Portland, OR

Background/Purpose: Osteoarthritis (OA) is characterized by progressive breakdown of articular cartilage. Regeneration of cartilage has been an attractive approach to OA therapy. Sox9 is a transcription factor belonging to the Sox (Sry-type HMG box) gene family and has been identified as a "master regulator" of the chondrocyte phenotype. We investigated whether a super positively charged cell penetrating Sox9 fusion protein can induce bone marrow-derived mesenchymal stem cells (MSC) to differentiate into chondrocytes for potential use to promote cartilage regeneration *in situ*.

Methods: A bioactive supercharged Sox9 (scSox9) was generated by fusing Sox9 with a super positively charged green fluorescence protein (GFP) using molecular engineering technology. Human bone marrow-derived MSC at passage 5 were cultured with scSox9 in monolayer or in cell aggregate for differentiation into chondrocytes. Chondrogenesis was verified by toluidine blue staining for aggrecan and by RT-PCR and immunohistochemistry for collagen type I, II and X production.

Results: scSox9 could readily enter HHF cells, a human skin fibroblasts-derived cell line and human bone marrow- derived MSC. After one hour incubation with scSox9, both HHF cells and MSC showed intracellular expression of green fluorescence indicating entry of scSox9 into these cells. scSox9 was able to induce MSC proliferation and differentiation with no requirement of additional growth factors. The number of scSox9 treated MSC was increased two folds after 72 hours in culture compared with scGFP treated MSC. As early as 48 hours, scSox9 treated MSC started changing morphology to chondrocyte-like cells and the changed morphology maintained for 21 days in culture when observation was ended. These morphologically changed cells stained positive for toluidine blue, which suggests aggrecan production. Furthermore, scSox9 induced collagen type II expression and down- regulated collagen type I and type X production. Most importantly, one time addition of scSox9 at the initiation of chondrogenesis was sufficient to induce MSC chondrogenic differentiation and maintain the chondrocyte phenotype.

Conclusion: These *in vitro* data demonstrated that scSox9 is able to enter bone marrow-derived MSC and induce chondrogenesis and maintain chondrocyte phenotype. Further investigation is warranted for the potential therapeutic use in cartilage repair by promoting regeneration of hyaline cartilage.

Disclosure: **Y. K. Chou**, None; **S. Wu**, VivoScript, Inc, 3; **C. Avendano**, VivoScript, Inc, 3; **T. Caldwell**, VivoScript, Inc, 3; **B. Maniaci**, VivoScript, Inc, 3; **K. Yomogida**, None; **Y. Zhu**, VivoScript, Inc, 3; **C. Q. Chu**, None.

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Function of the Chondrocyte PI-3 Kinase-Akt Signaling Pathway Is Stimulus Dependent. Richard F. Loeser and Meredith Greene. Wake Forest School of Medicine, Winston-Salem, NC

Background/Purpose: Previous studies have shown that activation of the chondrocyte PI-3K-Akt signaling pathway by IGF-1 promotes chondrocyte survival and matrix synthesis. However, other studies have shown activation of this pathway by cytokines such IL-1 plus oncostatin M (OSM) can promote chondrocyte MMP production. Based on the latter studies, some investigators have proposed targeting this pathway for treatment of OA. The purpose of the present study was to clarify the function of this important signaling pathway in chondrocytes by directly comparing the effects of anabolic and catabolic stimuli.

Methods: Human articular chondrocytes were isolated from normal adult ankle (tali) and knee articular cartilage and from knee cartilage removed at the time of joint replacement for OA (n=3 donors each for normal and OA). Primary confluent cultures were made serum-free and stimulated with IGF-1 (100ng/ml), IL-1β (0.02ng/ml), OSM (10ng/ml) or IL-1β+OSM (0.02ng/ml+10ng/ml). The doses of IL-1 and OSM were based on previous studies demonstrating increased MMP production stimulated by the combination of the two. Stimulus independent activation of Akt was achieved by lentiviral infection of constitutively active (CA) Akt. Activation of signaling proteins was measured at 30 minutes by immunoblotting of cell lysates and MMP-13 production was measured in conditioned media after overnight stimulation.

Immunoblots were quantified by densitometry and normalized to total Akt and MMP-2 respectively. Proteoglycan (PG) synthesis was measured by sulfate incorporation and collagen production by ELISA and results normalized to cell numbers.

Results: In normal chondrocytes (ankle or knee), IGF-1 stimulated strong Akt phosphorylation while IL-1β did not stimulate pAkt and the others were weak (OSM 23% and IL-1β+OSM 24% of IGF-1 stimulation). The pattern was similar in OA cells except IGF stimulated pAkt was less than in normal. Production of MMP-13 was stimulated in normal cells by OSM and IL-1β+OSM and in OA cells by IL-1β+OSM but not by either cytokine alone. Despite strong pAkt, IGF-1 did not stimulate MMP-13 production. Inhibition of PI-3 kinase by LY294002 (5μM) inhibited by 88% the OA cell production of MMP-13 by IL-1β+OSM and completely inhibited normal chondrocyte production of MMP-13. Overexpression of CA-Akt markedly stimulated PG and collagen synthesis but did not increase MMP-13 production. Inhibition of Akt1 and Akt2 using Akt inhibitor XIII (1μM) did not affect ILβ+OSM stimulated MMP-13 production.

Conclusion: The function of the PI-3 kinase-Akt pathway in articular chondrocytes is stimulus dependent. IGF-1 stimulation of this pathway is pro-anabolic and activity of Akt alone is sufficient for this effect. IL-1β+OSM weakly activate Akt phosphorylation and Akt activation alone is not sufficient to induce MMP production. The inhibition of IL-1β+OSM induced MMP-13 by the PI-3K inhibitor suggests that PI3K acts in concert with additional pathways, such as the MAP kinases, to stimulate MMP-13 production. Inhibition of these pathways, rather than PI-3K-Akt would be a better therapeutic target given the pro-anabolic and survival functions of Akt.

Disclosure: R. F. Loeser, None; **M. Greene**, None.

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Fibronectin Fragment Induces Procatabolic Effects Through TLR-2 Signaling Pathway in Human Articular Chondrocytes. Su Jin Park[1], Eun-Jeong Cheon[1] and Hyun Ah Kim[2]. [1]Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [2]Hallym University Sacred Heart Hospital, Kyunggi, South Korea

Background/Purpose: Fibronectin fragments (FN-fs) are increased in the synovial fluid of osteoarthritis patients and have a potent chondrolytic effect. However, little is known about the cellular receptors and signaling mechanisms that are mediated by FN-fs. Here we investigated whether the 29-kDa amino-terminal fibronectin fragment (29-kDa FN-f) regulates cartilage metabolism through Toll-like receptor-2 (TLR-2) signaling pathway in human articular chondrocytes.

Methods: Human articular chondrocytes were enzymatically isolated from articular cartilage and cultured in monolayer. In order to investigate whether 29-kDa FN-f induces MMPs production through TLR-2, human chondrocytes were transfected with TLR-2 expression plasmid or small interfering RNAs (siRNAs) targeting TLR-2 and Myeloid differentiation factor 88 (MyD88). In 29-kDa FN-f-stimulated chondrocytes, the relative levels of mRNA for matrix metalloproteinase 1 (MMP-1), MMP-3, and MMP-13 were analyzed by real-time quantitative reverse transcription-polymerase chain reaction. Protein expression levels of MMP-1 and MMP-3 and the regulatory effect of TLR-2 on 29-kDa FN-f-mediated signaling pathways were assessed by immunoblotting. MMP-13 production was measured by ELISA assay. Association of 29-kDa FN-f with human chondrocytes through TLR-2 was evaluated by fluorescence microscopic analysis.

Results: The expression levels of TLR-2, 3, 4, and 5 in TLR family were remarkably elevated in OA cartilage compared to normal cartilage. But, TLR-1 expression of normal and OA cartilages was not significantly different. When human chondrocytes were stimulated with various fibronectin fragments, TLR-2 expression was highly increased by 29-kDa FN-f stimulation. Knockdown of TLR-2 expression using siTLR-2 significantly suppressed 29-kDa FN-f-induced MMPs production in human normal and OA chondrocytes. Conversely, overexpression of TLR-2 enhanced 29-kDa FN-f-stimulated MMPs production. Moreover, we found that knockdown of MyD88, a downstream adaptor in TLR-2 signaling pathways, led to marked reduction of MMPs production induced by 29-kDa FN-f. In addition, 29-kDa FN-f-mediated phosphorylation of IkBa and p38 was apparently inhibited by transfection of siTLR-2. However siTLR-2 treatment did not affect 29-kDa FN-f-induced activation of JNK and ERK. Notably, fluorescence microscopic analysis showed direct interaction between TLR-2 and 29-kDa FN-f in human chondrocytes.

Conclusion: MyD88-dependent TLR-2 signaling pathway plays an important role in 29-kDa FN-f-stimulated procatabolic responses of human chondrocytes. Modulation of TLR-2-mediated signaling may be as a potential therapeutic strategy for the prevention of cartilage degradation in OA.

Disclosure: S. J. Park, None; **E. J. Cheon**, None; **H. A. Kim**, None.

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Cartilage Tissue Engineering Using Collagen Scaffolds and Human Mesenchymal Stem Cells. Clara Sanjurjo-Rodriguez[1], Adela Helvia Martinez-Sanchez[1], Silvia Diaz-Prado[2], Emma Muiños-Lopez[1], Isaac M. Fuentes-Boquete[2], Francisco J. De Toro[2] and Francisco J. Blanco[1]. [1]Osteo-articular and Aging Res. Lab. CIBER-BBN. Rheumatology Div. INIBIC-Complejo Hosp. Univ. A Coruña, A Coruña, Spain, [2]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC- University of A Coruña, A Coruña, Spain

Background/Purpose: The aim of this study was to obtain cartilage-like constructs by chondrogenic differentiation of human bone marrow mesenchymal stem cells (hBM-MSCs) grown on different collagen scaffolds.

Methods: hBM-MSCs were characterized by flow cytometry using MSC markers and analysed for their multipotential differentiation capacity. These cells were cultured at a density of 200,000 cells/cm^2 on different collagen scaffolds: Col I + Col II (C1C2); Col I + Col II + Heparan Sulfate (C1C2HS); Col I + Col II + Chondroitinsulfate (C1C2CHS); Col I + Heparin (C1OLH3). hBM-MSCs were cultured during 30 days in a chondrogenic differentiation medium supplemented with TGFβ-3. We have analysed cell growth and cell morphology by histochemical analysis and Transmission (TEM) and Scanning (SEM) Electron Microscope. Chondrogenic differentiation was confirmed by histochemical and immunohistochemical analysis. Moreover, we have tested relative gene expression of characteristic chondrocyte genes such us SOX9 and COLII. Finally, collagen concentration in the cultures supernatant was measured using a collagen Assay.

Results: hBM-MSCs were able to grow in the surface and inside of all the scaffolds and they were able to synthesize extracellular matrix (ECM) around the cells. Cellular proliferation was observed in all the scaffolds by PCNA (*Proliferating Cell Nuclear Antigen*) immunostaining, obtaining the highest values in C1C2 and in C1C2HS scaffolds. The percentage of cells, regarding the area of the analysed scaffold, was higher than 50% in C1C2 and C1OLH3 and higher than 75% in C1C2HS and C1C2CHS scaffolds. By means of immunostainings we detected Col II in the ECM of C1C2HS constructs and in the cytoplasm of the cells in C1C2 constructs. Collagen was detected in cultures supernatants of all the scaffolds obtaining the highest collagen release between 11–21 days of differentiation. These results indicated the beginning of the chondrogenic differentiation. TEM showed that cells had large number of lipid vesicles, mitochondrias and high secretory activity. SEM allowed us to study the adherence of cells, morphology and the ECM. We have detected the expression of two markers of early chondrogenesis, SOX9 and COLII, in all the constructs at 30 days.
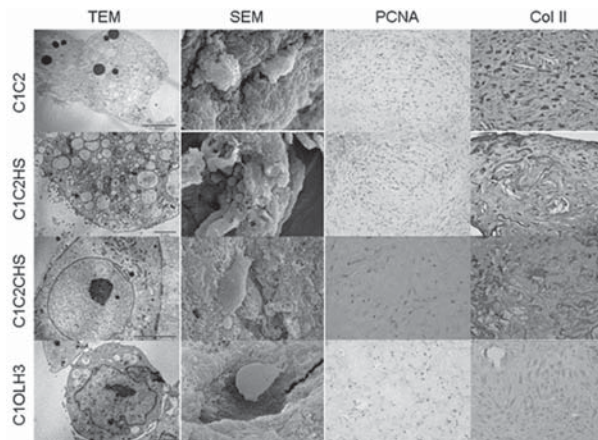
Figure. Image obtained from the different constructs by electron microscopy analysis and immunohistochemistry. Vertically in columns going from top to bottom are shown the different types of scaffolds and ordered in rows from left to right are shown the different analysis.

Conclusion: Our data showed that the best results were obtained with C1C2HS constructs. hBM-MSCs cultured in chondrogenic medium over these scaffolds were able to differentiate better into chondrocyte-like cells and

to synthesize more ECM than over the other scaffolds. Resulting cartilage-like constructs may be suitable candidates for Tissue Engineering. *Acknowledgements*: Opocrin S.P.A.; CIBER-BBN CB0–01-0040; SAI-UDC.

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Articular Cartilage Expresses the IL-15 Receptor Alpha-Chain and Responds to IL-15 with Increased Matrix Metalloproteinase Release.
Anjali Nair[1], Michael Huvard[2], Madeline Rollins[3], Arnavaz Hakimiyan[1], Lev Rappaport[1], Arkady Margulis[1], Susanna Chubinskaya[1] and Carla R. Scanzello[1]. [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois at Chicago, Chicago, IL, [3]Northwestern University, Chicago, IL

Background/Purpose: IL-15, known for its effects on survival of lymphocyte subsets, plays a role in synovitis of Rheumatoid Arthritis. We reported that IL-15 is also detectable in synovial fluid (SF) of patients with knee osteoarthritis (OA), and correlates with levels of matrix metalloproteinase (MMP)-1 and MMP-3. Serum levels have been associated with development and progression of radiographic OA changes, suggesting a possible role in cartilage loss. We investigated IL-15 and IL-15 receptor staining in synovium and cartilage, and tested whether cartilage can respond directly to IL-15.

Methods: Synovial membrane (SM) and cartilage samples from five organ donors collected within 24 hours of death were formalin-fixed and paraffin embedded. Additional SM biopsies from four patients with early-stage knee OA were also collected. Six-micron sections were stained for IL-15 and IL-15Rα using immunoperoxidase technique and polyclonal antibodies directed against IL-15 (rabbit anti-human IL-15, Abcam) or the IL-15Rα chain (goat anti-human IL-15 Rα, Santa Cruz Biotechnology). Non-immune rabbit IgG and goat IgG were used as negative controls. For explants culture, 4mm cartilage punch biopsies were prepared from the tibial surfaces of an additional organ donor; 2 explants per well were placed in a 24 well plate with DMEM (+100U/ml Penicillin-Streptomycin). After 24 hours, media was replaced with 1 ml of fresh media or media+ rhuIL-15 (100ng/ml, Peprotech, NJ) or TNFα and Oncostatin M (100ng/ml each, R & D Systems, MN). Every two days for 12 days and again at 15 days, culture supernatants were collected and replaced with fresh media +/− cytokines. Consecutive supernatants were analyzed for MMP-1, -3 and -9 content using a human MMP 3-Plex Immunoassay (Meso Scale Discovery).

Results: IL-15 and IL-15Rα staining was observed in SM mononuclear infiltrates in the OA patients. Il-15 Rα staining was also identified in the synovial lining and sublining vessels in both patients and donors. Positive staining for IL-15 and IL-15Rα was observed in chondrocytes from all layers (superficial to deep). *In vitro*, IL-15 increased MMP-1 and MMP-3 release from cartilage explants compared to media controls at each time point up to 15 days. Maximum MMP-1 release reached 89.5+/− 5.1 ng/ml at day 15 (vs. media control 0.002 +/− 0.003 ng/ml, p<0.05) while MMP-3 release reached 665.7 +/−13 ng/ml by day 12 (vs. media 12.2+/− 0.2 ng/ml, p < 0.001). Lesser magnitude MMP-9 release from cartilage was observed in response to IL-15, with peak concentration of 962.7 +/− 1.8 pg/ml (p<0.05 vs.control) at day 15. TNFa and OSM induced substantial MMP-1, -3 and -9 release from explants, often >10 times higher than IL-15 induced levels.

Conclusion: Both IL-15 and IL-15Rα are expressed in SM and cartilage indicating that both tissues may respond to this cytokine *in vivo*. IL-15 induced MMP-1, -3, and -9 release from cartilage explants compared to control but of lesser magnitude than levels induced by TNFa + OSM. This is the first demonstration that cartilage is responsive to IL-15, and suggests a role for IL-15 in cartilage catabolism in various forms of arthritis including OA.

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Visfatin/Nampt in Osteoarthritis: Sites of Production in Human Joints and Role of Its Enzymatic Activity.
Marie-Charlotte Laiguillon[1], Carole Bougault[1], Xavier Houard[1], Marjolaine Gosset[2], Geoffroy Nourissat[1], Sabrina Priam[1], Zvezdana Mladenovic[1], Claire Jacques[1], Francis Berenbaum[3] and Jeremie Sellam[4]. [1]Pierre et Marie Curie University Paris VI, Paris, France, [2]Paris Descartes University, Montrouge, France, [3]AP-HP, St Antoine Hospital, Paris, France, [4]Hopital Saint-Antoine, Pierre et Marie Curie University Paris 6, AP-HP, 75012, France

Background/Purpose: The role of cytokines produced by obese-derived adipose tissue, namely adipokines, in the pathophysiology of osteoarthritis (OA) is now well established. We recently suggested that one of them, visfatin, may play a role in OA by activating chondrocytes (1,2). Along with its cytokine effect, visfatin has an enzymatic activity called nicotinamide phosphoribosyltransferase (Nampt), which is the rate-limiting enzyme in the salvage pathway of nicotinamide adenine dinucleotide (NAD) biosynthesis from nicotinamide, an intracellular pathway involved in many biological processes including TNFα and IL-6 synthesis. Thus, we aimed to i) characterize the local site(s) of production of visfatin/Nampt by the human OA joint tissues ii) further investigate the role of its enzymatic activity in the expression of pro-inflammatory cytokines by chondrocytes and iii) determine whether visfatin/Nampt may also play a role in subchondral bone.

Methods: Human OA joint tissues (synovial membrane, cartilage, subchondral bone) from patients undergoing surgical knee replacement were incubated for 24h in serum-free media. Visfatin/Nampt release in media by the different tissues was evaluated using Western Blot and ELISA. Primary cultures of mouse chondrocytes and osteoblasts were stimulated with recombinant visfatin/Nampt (5μg/mL) for 24h. To determine the role of the enzyme activity, cells were pretreated or not 4h before visfatin/Nampt stimulation with APO866 (10nM), a pharmacologic inhibitor of Nampt activity (3). Effects of stimulation on IL-6, IL-8/Kc, IL-1β, MCP-1, VEGF and TGFβ expression, and on IL-6 and IL-8/Kc release were examined by quantitative RT-PCR and ELISA, respectively.

Results: All human OA joint tissues released visfatin/Nampt (synovium: 529 ± 356, cartilage: 237 ± 380, subchondral bone: 200 ± 104 ng/g tissue) with higher level for the synovium compared to cartilage (p<0.01). Visfatin/Nampt significantly induced IL-6, IL-8/Kc, IL-1β and MCP-1 expression by chondrocytes (n=6) and osteoblasts (n=5) (Table). Visfatin/Nampt increased the production of IL-6 and IL-8/Kc proteins by both cell types. Nampt activity inhibition by APO866 decreased pro-inflammatory cytokines expression at mRNA level (up to 97 % of inhibition) as well as at protein level (up to 63 % of inhibition) and was especially efficient in chondrocytes (Table). Effect of visfatin/Nampt was selective since VEGF and TGFβ were not modulated upon stimulation.

		Gene expression				Protein production	
		IL-6	Kc/IL-8	IL-1β	MCP-1	IL-6	Kc/IL-8
Chondrocytes (n=6)	Fold induction after visfatin/ Nampt stimulation (Mean ± SEM), p-value	10.6 ± 3 (p=0.015)	4.9 ± 1.3 (p=0.015)	878 ± 320 (p=0.015)	2.5 ± 0.4 (p=0.03)	5.8 ± 5 (p=0.016)	29.7 ± 33 (p=0.015)
	Mean % of inhibition by APO866	94%	83%	97%	62%	63%	57%
Osteoblasts (n=5)	Fold induction after visfatin/ Nampt stimulation (Mean ± SEM), p-value	296 ± 59 (p=0.03)	142 ± 64 (p=0.03)	396 ± 112 (p=0.03)	133 ± 83 (p=0.03)	51 ± 19 (p=0.05)	54 ± 23 (p=0.05)
	Mean % of inhibition by APO866	63%	79%	73%	84%	39%	49%

Conclusion: Visfatin/Nampt is produced by the cartilage, the subchondral bone and mostly by the synovial membrane. We demonstrate that Nampt activity of visfatin plays a major role in chondrocytes and osteoblasts activation, suggesting that targeting the Nampt enzymatic activity with a compound like APO866 (being tested in hematological malignancies) may be a new therapeutic approach of OA.

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EPAC1 Activation Is Required for NFkB Nuclear Translocation and Osteoclast Differentiation.
Aranzazu Mediero[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Previous work demonstrated that one mechanism by which bisphosphonates inhibit osteoclast differentiation and function is via inhibition of Rap1A isoprenylation and, as a result, function. As Rap1 is the

effector of the cAMP-binding EPAC protein (exchange *protein* directly activated by cAMP), we determined the role of EPAC1 in osteoclast differentiation.

Methods: Osteoclast differentiation was studied as the M-CSF/RANKL stimulated formation of multinucleated TRAP-positive cells from primary murine (C57Bl/6) bone marrow-derived precursors or EPAC1 knockdown (lentiviral shRNA for EPAC1) RAW264.7 cells in the presence/absence of the EPAC-selective cAMP analog 8-CPT-cAMP 100nM and EPAC inhibitor BFA ($10\mu M$). Rap1 activity assay was carried out according to the manufacturers' protocol. Signaling events (EPAC, NFkB and MAPK) were studied by Western Blot in EPAC1 KO RAW264,7 cells (scrambled shRNA transfection is control for these experiments). Osteoclast marker expression was studied by RT-PCR.

Results: The EPAC-selective cAMP analogue 8-CPT-cAMP did not significantly affect osteoclast maturation ($106\pm4\%$ of control, p=NS, n=5) but the EPAC inhibitor BFA inhibited differentiation ($59\pm9\%$ inhibition, p<0.001 vs control, n=5). Activation of Rap1 was maximal 10 minutes after RANKL stimulation ($161\pm4\%$ of control, p<0.001, n=4). NFkB nuclear translocation induced by RANKL was diminished 15 minutes after stimulation in EPAC1 KO cells ($63\pm3\%$ of scrambled shRNA infected cells, p<0.001, n=4) and TRAP staining revealed no osteoclast differentiation when EPAC1 was knocked down. Moreover, pERK1/2 and pJNK are marginally activated in control cells after RANKL stimulation ($117\pm3\%$ and $107\pm2\%$ of control, respectively, p=0.5, n=4) and deletion of EPAC1 slightly decreased this activation ($93\pm2\%$ and $95\pm1\%$ of control, respectively, p=NS, n=4). Interestingly, the MEK inhibitor U0126 restores RANKL-stimulated osteoclast formation in the EPAC1 KO cells ($109\pm2\%$ of control, p=NS, n=6). Finally, in EPAC1 knockdown cells inhibition of osteoclast differentiation is correlated with decreased expression of osteoclast differentiation markers Cathepsin K, NFATc1 and Osteopontin when compared to control (4 ± 0.7, 2.3 ± 0.5 and 3 ± 0.4 fold decreased respectively, p<0.001, n=3).

Conclusion: EPAC1 is a critical intermediate in osteoclast differentiation which permits increased ERK1/2 activation and NFkB nuclear translocation. Targeting this signaling intermediate may diminish bone destruction in inflammatory arthritis.

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Adenosine A_{2A} Receptor Stimulation Inhibits OC Formation by Suppressing NFkB Translocation to the Nucleus by A PKA-ERK1/2 Mediated Mechanism. Aranzazu Mediero[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Adenosine, a nucleoside released at sites of injury and hypoxia, mediates its effects via activation of G-protein-coupled receptors (A_1, A_{2A}, A_{2B}, A_3). Previously we reported that the $A_{2A}R$ agonist CGS21680 inhibits osteoclast (OC) differentiation in a dose-dependent manner. Here we dissected the intracellular pathways involved in $A_{2A}R$-mediated regulation of OC differentiation.

Methods: OC differentiation was studied as M-CSF/RANKL-stimulated differentiation of murine bone marrow precursors to TRAP+/multinucleated cells in the presence/absence of CGS21680 ($A_{2A}R$ agonist) and ZM241385 ($A_{2A}R$ antagonist) $1\mu M$ each, and PKA activators 8-Cl-cAMP and 6-Bnz-cAMP 100nM each and the PKA inhibitor PKI $10\mu/ml$. cAMP EIA assay and PKA activity assay were carried out according to manufacturers' directions. Signaling events (PKA, NFkB and MAPK) were studied by Western Blot in PKA knockdown (KO) (lentiviral shRNA for PKA) RAW264.7 cells (scrambled shRNA transfection is control for these experiments). OC marker expression was studied by RT-PCR.

Results: CGS21680 stimulated a maximal increase in cAMP 5–10 minutes after RANKL-CGS21680 activation (35.2 ± 3.5 fmol for CGS21680 vs. 14.4 ± 1.9 fmol for control, p<0.001, n=6) correlating with maximal PKA activity at 15 minutes (4.96 ± 0.2 units/ml vs. 3.07 ± 0.2 units/ml, CGS21680 v control, p<0.001, n=4). PKA-selective cAMP analogues 8-Cl-cAMP and 6-Bnz-cAMP inhibit OC maturation to $58\pm9\%$ and $47\pm3\%$ of control respectively (p<0.001, n=5) whereas a selective PKA inhibitor (PKI) increases OC differentiation ($126\pm6\%$ of control, p<0.001, n=5). Western Blot demonstrates that PKA activation increased over time in the presence of CGS21680, and CGS21680 inhibits NFkB nuclear translocation in control ($25\pm1\%$ inhibition, p<0.001, n=4) cells but not in PKA KO cells ($110\pm2\%$ of control, p<0.5, n=4). CGS21680 activates MAPKs (pERK1/2, p-p38 and pJNK), an effect which is blocked by ZM241385. ERK1/2 is activated by a PKA-dependent mechanism ($130\pm6\%$ of control, p<0.001, n=4), but p38 and pJNK activation is unaffected ($112\pm1\%$ and $110\pm2\%$ of control, respectively, p<0.5, n=4). $A_{2A}R$ activation inhibits the expression of OC differentiation markers (2 ± 0.05 and 1.6 ± 0.06 fold decrease for Cathepsin K and Osteopontin respectively, p<0.001, n=4) by a PKA-mediated mechanism (PKA KO cells).

Conclusion: Adenosine, acting at $A_{2A}R$, inhibits OC differentiation and regulates bone turnover via activation of PKA and inhibition of NFkB nuclear translocation. Because adenosine mediates the anti-inflammatory effects of methotrexate we speculate that the capacity of methotrexate to inhibit bone erosion in Rheumatoid Arthritis may be mediated by increases in adenosine which inhibit OC formation and function.

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Adenosine A_{2A} Receptor Diminishes Bone Destruction At Inflamed Sites, in Part, Via Downregulating Semaphorin4D-PlexinB1 Communication Between Osteoclasts and Osteoblasts. Aranzazu Mediero[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Communication between osteoclasts and osteoblasts is essential for bone homeostasis. Semaphorin4D (Sema4D), expressed on the surface of and secreted by osteoclasts, macrophages and T cells, is a potent inhibitor of bone formation; Sema4D binds to its receptor (PlexinB1) on osteoblasts which induces RhoA activation which suppresses osteoblast differentiation by attenuating insulin-like growth factor-1 (IGF-1) signaling. Adenosine, a nucleoside released at sites of injury and hypoxia, modulates cell function by interacting with specific cell-surface receptors (A_1R, $A_{2A}R$, $A_{2B}R$, A_3R). We have recently demonstrated that $A_{2A}R$ stimulation inhibits wear particle-mediated bone destruction and sought to determine whether $A_{2A}R$-mediated regulation of Sema4D expression might play a role in preventing bone destruction.

Methods: C57Bl/6 mice mice age 6–8 weeks were anesthetized and a 1cm midline sagittal incision was made over the calvaria. 4 mice received no particles (Control), and the rest received 3mg of polyethylene particles (UHMWPE) together with $20\mu l$ of saline 0.9% or CGS21680 $1\mu M$ (n=4 each) at the surgical site every day. Animals were sacrificed after 14 days and calvaria were prepared for histology. Sema4D expression was studied by RT-PCR and Western Blot in RAW267.4 cell-derived osteoclasts in the presence/absence of CGS21680 and ZM241385 ($A_{2A}R$ antagonist) $1\mu M$ each.

Results: As previously described, exposure to UHMWPE particles induce inflammatory infiltration that is significantly decreased in the presence of CGS21680. Exposure to UHMWPE particles significantly increased expression of both Sema4D (224 ± 5cells/Ipf compare to 40 ± 2cells/Ipf in control, p<0.001, n=4) and its receptor PlexinB1 (206 ± 5cells/Ipf compare to 86 ± 4cells/Ipf in control, p<0.001, n=4) on bone surfaces close to inflammatory infiltrates and CGS21680 treatment markedly diminished overexpression of both Sema4D and PlexinB1 (34 ± 3cells/Ipf and 85 ± 3cells/Ipf respectively, p<0.001, n=4). In *in vitro* studies, RANKL induced a 2.5 ± 0.1 fold increase in Sema4D mRNA expression (p<0.001. n=4) that is completely blocked by CGS21680 in a protein kinase A-dependent fashion.

Conclusion: Inflammation promotes Sema4D secretion and PlexinB1 activation. Targeting osteoclasts via $A_{2A}R$ activation prevents wear particle-stimulated bone resorption and the inhibition of Sema4D and PlexinB1 expression likely bone resorption by permitting greater osteoblast differentiation and bone formation. Moreover, these results suggest a novel approach to prevent bone resorption in inflammatory arthritis or infectious arthritis.

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Synovial Overexpression of Wnt and Wnt-1-Induced Secreted Protein 1 Induces Cartilage Damage by Skewing of TGF-Beta Signaling and Reduction of the Anti-Hypertrophy Factor Sox9. Martijn H. van den Bosch[1], Arjen B. Blom[1], Peter L. van Lent[1], Henk M. van Beuningen[1], Fons A. van de Loo[2], Esmeralda N. Blaney Davidson[1], Peter M. van der Kraan[1] and Wim B. van den Berg[2]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Although many osteoarthritis (OA) patients show significant synovial involvement, consequences are largely unknown. We found highly increased expression of canonical Wnts 2b and 16 and Wnt-1-induced secreted protein 1 (WISP1), a downstream protein, in knee joints in two experimental murine OA models. Wnt signaling has been implicated in OA incidence and modulation of the β-catenin pathway leads to OA-like changes in cartilage. In addition, TGF-β signaling is critical in cartilage maintenance. TGF-β signals via both ALK5 and ALK1, resulting in Smad 2/3 and Smad 1/5/8 phosphorylation respectively. In the present study we investigated the potency of canonical Wnts, produced by synovial cells, to induce early OA-like cartilage damage and whether canonical Wnts skew TGF-β signaling from the protective Smad 2/3 pathway to the chondrocyte hypertrophy-inducing Smad 1/5/8 pathway.

Methods: Experimental OA was induced by intra-articular injection of collagenase. Pathway analysis of microarray data was done using DAVID software. Detection of Smad 2/3 and Smad 1/5/8 phosphorylation was done by Western blot analysis. *In vivo* synovial overexpression of genes from the canonical Wnt signaling pathway was achieved by intra-articular injection of adenoviral vectors. Joint pathology was assessed by histology. Gene expression was analyzed by qPCR.

Results: Pathway analysis showed that both the Wnt and TGF-β signaling pathway were enriched in the synovium of mice with collagenase-induced OA. To determine if synovial overexpression of canonical Wnts leads to cartilage damage, adenoviral vectors for Wnts 8a and 16 were injected into murine knee joints. A significant increase in the incidence of early OA-like lesions at the medial margin of the medial tibial plateau was found 7 days after overexpression. The incidence was 92% (n=12) for Wnt8a overexpression compared to 17% (n=12) for the control virus and 80% (n=5) for Wnt16 overexpression, but only 20% (n=5) for the control virus. Because of their relatively small size, Wnts and WISP1 can enter the cartilage and possibly alter the chondrocyte phenotype. Synovial overexpression of Wnt8a and Wnt16 resulted in β-catenin accumulation in chondrocytes, a tell-tale sign of canonical Wnt signaling, indicating migration of Wnts to the cartilage. Moreover, pre-incubation with Wnt3a or WISP alone or Wnt3a + WISP1 together resulted in decreased TGF-β-induced phosphorylation of Smad 2/3, whereas phosphorylation of Smad 1/5/8 was increased *in vitro*. This implies a shift towards dominant TGF-β signaling via the hypertrophy-inducing ALK1 pathway. In addition, the expression of the anti-hypertrophic factor Sox9 was decreased after pre-incubation with Wnt3a and WISP1.

Conclusion: Canonical Wnts produced in the synovium may play an important role in OA pathology by inducing β-catenin signaling in the cartilage followed by cartilage damage. Increased expression of canonical Wnts in the synovium, as found in experimental OA, may lead to a phenotype change in articular chondrocytes, probably via modulation of the TGF-β signaling pathway, which is crucial for cartilage homeostasis. This underlines that synovial Wnt/WISP1 expression may be a potential target for OA therapy.

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Identification of 14-3-3å As a New Subchondral Bone Mediator Involved in Cartilage Degradation During Osteoarthritis. Sabrina Priam Jr.[1], Carole Bougault[1], Xavier Houard[1], Marjolaine Gosset[2], Colette Salvat[3], Francis Berenbaum[4] and Claire Jacques[1]. [1]Pierre et Marie Curie University Paris VI, Paris, France, [2]Paris Descartes University, Montrouge, France, [3]University Pierre et Marie Curie, Paris, France, [4]AP-HP, St Antoine Hospital, Paris, France

Background/Purpose: OA is a complex disease not limited to cartilage degeneration. Indeed, several experiments suggest that subchondral bone remodeling could initiate and/or contribute to cartilage loss in OA through a bone/cartilage interplay. We aimed to identify soluble mediators released by loaded osteoblasts/osteocytes that could induce the release of pro-catabolic factors by chondrocytes by using a novel and unique bone/cartilage communication model.

Methods: Thanks to a three dimensional (3D) culture model, murine osteoblasts were submitted to compression in Biopress Flexercell plates (1.7 MPa, 1Htz during 24h). Then, conditioned media from compressed (CM) or uncompressed (UCM) osteoblasts/osteocytes were used to stimulate mouse articular chondrocytes. Chondrocyte expression of matrix metalloproteinase 3 (MMP-3) and MMP-13, tissue inhibitors of metalloproteinases (TIMPs), and cartilage extracellular matrix components type II collagen and aggrecan were assessed by RT-PCR, western blot analysis and ELISA. Then, soluble mediators released by compressed osteoblasts/osteocytes were identified by iTRAQ®, a differential secretomic analysis approach.

Results: Media from compressed osteoblast (CM) strongly induced MMP-3 and -13 chondrocyte mRNA expression (Table). Consistently, CM also significantly stimulated the releases of MMP-3 and -13 by chondrocytes (respectively 10.6±0.75 fold, p<0.001, and 6.5±2.1 fold, p<0.01 compared to control). In addition, CM enhances TIMP-1 expression whereas it strongly inhibited TIMP-2 and -3 expressions (Table). CM also affected cartilage matrix proteins expressions by downregulating aggrecan and type II collagen mRNA levels (Table). Effects of CM on cytosolic type II collagen protein amounts were confirmed by western blot (a decrease of 31±9%, p<0.01). In order to identify osteoblast soluble mediators responsible for this chondrocyte phenotype, osteoblast conditioned media were analyzed by iTRAQ®. This sophisticated proteomic technique allowed identification of 105 proteins secreted by osteoblasts among which only 10% were upregulated in response to compression. Among them, 14-3-3ε dose-dependently induced the release of pro-catabolic factors by chondrocytes, mimicking the effects of CM osteoblasts/osteocytes media. Furthermore, 14-3-3ε was strongly released by human OA subchondral bone and stimulated MMP-3 expression in human OA chondrocytes.

Table. Effects of media from uncompressed or compressed osteoblasts on MMPs, TIMPs and matrix proteins chondrocytes mRNA expression.

	MMP-3	MMP-13	TIMP-1	TIMP-2	TIMP-3	Collagen II	Aggrecan
UCM	5,9±3	3,4±0,4	1,5±0,4	0,7±0,2	0,6±0,1	0,7±0,3	0,7±0,3
	ns	ns	ns	p<0,01	p<0,001	ns	ns
CM	50,9±14,5	18,3±10,9	5,2±1,6	0,5±0,1	0,1±0,05	0,4±0,1	0,2±0,1
	p<0,001	p<0,001	p<0,001	p<0,001	p<0,001	p<0,01	p<0,001

Results are expressed in fold compared to control (non-stimulated chondrocytes).
Conclusion: Therefore, we identify 14-3-3ε as a novel soluble mediator critical in the communication between subchondral bone and cartilage in OA leading to MMP expression by chondrocytes. We speculate that 14-3-3ε is a potential target for a future disease-modifying OA drug.

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Stress-Induced Cartilage Degradation Does Not Depend On NLRP3-Inflammasome in Osteoarthritis. Carole Bougault[1], Marjolaine Gosset[2], Xavier Houard[1], Colette Salvat[3], Lars Godmann[4], Thomas Pap[4], Claire Jacques[1] and Francis Berenbaum[5]. [1]Pierre et Marie Curie University Paris VI, Paris, France, [2]Paris Descartes University, Montrouge, France, [3]University Pierre and Marie Curie, Paris, France, [4]University Hospital Münster, Münster, Germany, [5]AP-HP, St Antoine Hospital, Paris, France

Background/Purpose: The cartilage matrix breakdown in osteoarthritis (OA) is due to both abnormal mechanical stress and activation of catabolic processes involving metalloproteinases (MMPs). Currently, IL-1beta is thought to have a major role in shifting the metabolic balance toward degradation. IL-1beta is first synthesized as an inactive precursor, which is cleaved into the secreted active form. This maturation process mainly occurs in the "inflammasome", where initiators (including NLRP3) and adaptor molecules (ASC) oligomerize to recruit and activate caspase-1, which in turn processes IL-1beta precursor. We aimed to clarify the role of both inflammasome and IL-1beta in cartilage breakdown.

Methods: First, amounts of IL-1β released from cartilage explants of 18 OA patients were assessed (ELISA). Second, in primary mouse articular chondrocytes cultures, LPS, IL-1alpha and TNF-alpha treatments were used to induce a pro-degradative phenotype, characterized by an increase in gene expression (real-time PCR) and in protein release of MMP-3, MMP-9 and MMP-13 (ELISA, zymography and Western-blot). Effects of a deficiency in NLRP3 (using NLRP3−/− mice), of an inhibition of caspase-1 (using Z-YVAD-FMK) and of a blockade of IL-1 (using IL-1RA) were investigated.

At last, excessive dynamic compression was applied on mouse cartilage explants to trigger degradation (0.5 Hz and 1 MPa for 6 h). Load-induced GAG release and increase in MMP enzymatic activity were assessed in WT, NLRP3−/− or IL-1R1−/− mice, the latter being deficient in IL-1 receptor type 1.

Results: Despite the expression of NLRP3, ASC and caspase-1 in OA chondrocytes, OA cartilage was not able to produce active IL-1beta. In mouse articular chondrocytes, LPS, IL-1alpha and TNF-alpha dose-dependently increased MMP-3, MMP-9 and MMP-13 both at gene and protein levels. This response was similar in NLRP3−/− chondrocytes and was unchanged by caspase-1 inhibition. These results demonstrate that the inflammatory stress-induced degradative phenotype was inflammasome-independent. Furthermore, the catabolic response to LPS and TNF-alpha was unchanged when IL-1 was inhibited by IL-1RA. In cartilage explants, excessive load induced an increase in GAG release (3-fold) and MMP activity (3.7-fold). This response was similar in NLRP3−/− and IL-1R1−/− -derived cartilage. Likewise, the load-induced degradative response was independent of NLRP3-inflammasome and of IL-1.

Conclusion: This study suggests that OA cartilage can be degraded independently of NLRP3- inflammasome activity. This result may explain, at least in part, why previous trials with IL-1beta inhibitors were all negative.

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Osteoclastogenesis Is Inhibited by Immune Complexes Through Activating Fcγ Receptors. Lilyanne C. Grevers[1], Peter L.E.M. van Lent[1], Teun J. de Vries[2], Vincent Everts[2], J. Sjef Verbeek[3] and Wim B. van den Berg[4]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]ACTA, UVA, VU University Amsterdam, Amsterdam, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Rheumatoid arthritis is characterized by chronic inflammation and osteoclast-mediated bone loss. Co-stimulatory signalling via ITAM- and ITIM-coupled receptors is essential for osteoclast formation and function. The ITAM- and ITIM-coupled Fcγ receptors (FcγR) play a crucial role in mediating inflammation and cartilage destruction in experimental arthritis, but their role in osteoclast-mediated bone loss is unknown. The aim of the present study was to investigate the role of FcγRs in osteoclastogenesis and osteoclast function.

Methods: Bone destruction was analyzed in arthritic knee joints of FcγRIIB-deficient, FcRγ-chain−/− (lacking expression of activating FcγRs), and wild type mice. Bone marrow-derived osteoclast precursors were differentiated *in vitro* towards osteoclasts in the absence or presence of immune complexes (ICs) and stimulated thereafter for 24 hrs with or without TNFα or LPS. Experiments were analyzed for the expression of FcγRs and osteoclast markers, osteoclast formation, and resorption pit formation on bone.

Results: Bone erosions and cathepsin K-positive osteoclast numbers were significantly increased (>2.6 fold) during antigen-induced arthritis in the knee joints of FcγRIIB-deficient mice. All FcγR classes were highly expressed on osteoclast precursors. Differentiation of osteoclast precursors in the presence of ICs significantly reduced osteoclast formation (37%), bone resorption (68%), and expression of the osteoclast markers cathepsin K, TRAP, CTR, DC-STAMP, and NFATc1. In the presence of ICs, osteoclastogenesis of FcγRIIB−/− precursors and bone resorption remained inhibited. In contrast, ICs could not inhibit osteoclast formation or bone resorption of FcRγ-chain−/− precursors. When IC-inhibited osteoclastogenesis was followed by stimulation with TNFα or LPS, the inhibitory effects of ICs were overruled, resulting in significantly increased osteoclast numbers and resorption levels as compared to unstimulated controls.

Conclusion: Activating FcγRs mediate IC-induced inhibition of osteoclastogenesis, which can be overruled in the presence of pro-inflammatory mediators like TNFα and LPS. This suggests that the balance of FcγR-mediated induction of inflammation, through pro-inflammatory cytokine production, as well as the direct inhibitory effect of ICs on osteoclastogenesis determines the net effect on bone loss.

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IL-32 and IL-17 Interact and Aggravate Osteoclastogenesis in Rheumatoid Arthritis. Bo Young Yoon[1], Young-Mee Moon[2], Yang-Mi Her[2], Hye Jwa Oh[2], Jae-Seon Lee[2], Kyoung-Woon Kim[3], Seon-Yeong Lee[2], Yun-Ju Woo[2], Kyung-Su Park[2], Sung-Hwan Park[2], Ho-Youn Kim[2] and Mi-La Cho[2]. [1]Inje University Ilsan Paik Hospital, Goyang, South Korea,[2]Catholic University of Korea, Seoul, South Korea,[3]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea

Background/Purpose: Interleukin (IL)-32 and IL-17 play critical roles in pro-inflammatory responses and are highly expressed in the synovium of patients with rheumatoid arthritis (RA). We investigated not only the related induction of IL-17 and IL-32 in fibroblast-like synoviocytes (FLSs) from RA patients and T cells from healthy donors, but also the summative ability of the two cytokines to stimulate osteoclastogenesis.

Methods: FLSs were isolated through surgical synovectomy obtained from patients with RA or osteoarthritis (OA) and peripheral blood mononuclear cells (PBMCs) were obtained from healthy donors. Splenic CD4+ and CD4− T cells and joint specimens were obtained from autoimmune arthritis mice.Real-time polymerase chain reactions were performed to evaluate the expression of IL-32, IL-17, orphan nuclear receptor Rorγt, tartrate-resistant acid phosphatase (TRAP), cathepsin K, calcitonin receptor (CTR), matrix metalloproteinase-9 (MMP9) mRNA. IL-17 protein was measured by enzyme-linked immunosorbent assay and the T helper (Th)17-expressing T cell count was detected by fluorescence-activated cell sorting. Immunohistochemical staining and TRAP staining were performed to determine the distribution of inflammatory cytokines and the presence of osteoclastogenesis.

Results: IL-17 induced the expression of IL-32 (4.3 fold) in the FLSs from RA patients, as assessed by microarray. The IL-32 and IL-17 levels in the FLSs from the RA patients were higher than those from the OA patients, and the expressions were colocalized. IL-32 production was increased by IL-17 through the nuclear factor (NF-ⱯêB)- kB and PI3 kinase signal pathways. When FLSs from RA patients and CD4+ T cells were cocultured, the CD4+ T cells differentiated into IL-17-producing Th17 cells, which stimulated the production of IL-32 in the FLSs. Moreover, IL-32 induced the production of IL-17 in human CD4+ T cells and also induced high expression levels of IL-17 in splenic CD4+ T cells of CIA mice. IL-32 and IL-17 were colocalized near TRAP-positive areas in joint specimens of autoimmune arthritis mouse models. IL-17 and IL-32 synergistically induced the differentiation of osteoclasts, as demonstrated by the expression of osteoclast-related genes such as TRAP, cathepsin K, CTR, and MMP9.

Conclusion: IL-17 affected the expression of IL-32 in FLSs of RA patients and IL-32 induced the production of IL-17 in CD4+ T cells. Both IL-17 and IL-32 cytokines can reciprocally influence each other's production in RA and autoimmune arthritis models. Separately, IL-17 and IL-32 each stimulated osteoclastogenesis without RANKL. Together, the two cytokines synergistically amplified the differentiation of osteoclasts, independent of RANKL stimulation.

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Protective Properties of Conditioned Media From Adipose Stem Cells On Osteoarthritic Chondrocytes. Maria Isabel Guillén[1], Julia Platas[1], Vicente Mirabet[2], Miguel Angel Castejón[3], Francisco Gomar[4] and Maria Jose Alcaraz[1]. [1]University of Valencia, Burjasot, Valencia, Spain, [2]Generalitat Valenciana, Valencia, Spain, [3]De la Ribera University Hospital, Alzira, Spain, [4]University of Valencia and University Hospital, Valencia, Spain

Background/Purpose: Adipose-derived mesenchymal stem cells (ASC) exhibit a high potential for cell therapy and they might also act as a cellular source for supplying soluble factors exerting anti-inflammatory or trophic effects on cells. Osteoarthritis (OA) involves the destruction of articular cartilage leading to disability. The purpose of this study was to investigate whether conditioned medium from adipose-derived mesenchymal stem cells (ASC-CM) improves the inflammatory and degradative response induced by interleukin-1β in OA chondrocytes and cartilage.

Methods: Adipose tissue from patients subjected to abdominal lipectomy surgery, was used for ASC isolation by collagenase treatment. Cells were incubated in DMEM/F12 containing 15% human serum. Cell phenotype was analyzed by flow cytometry with specific antibodies anti-CD105-PE, anti-

CD90PerCP-eFluo 710, anti-CD34APC, and anti-CD45-PE (International Society of Cellular Therapy), and cellular viability with propidium iodide. The conditioned medium (ASC-CM) was collected after 48h of culture, centrifuged and stored at -80°C in sterile conditions. Cartilage specimens were obtained from patients with diagnosis of advanced OA. Protocols were approved by the Institutional Ethical Committee. Chondrocytes were used in primary culture. Cartilage explants or isolated chondrocytes were stimulated with 10 ng/ml interleukin (IL)-1β for different times. Gene expression was analyzed by real-time PCR. Protein expression was investigated by ELISA. Nitric oxide (NO) production and matrix metalloproteinase (MMP) activity were measured as microplate fluorescence assays. Prostaglandin E$_2$ (PGE$_2$) was evaluated by RIA.

Results: IL-1β significantly increased the production of NO, PGE$_2$ and MMP activity, and the expression of IL-1β, tumor necrosis factor-α (TNFα), vascular endothelial growth factor (VEGF) and a wide range of chemokines, after 24h, with respect to basal conditions. ASC-CM treatment of OA explants or chondrocytes reduced the production of NO which was dependent on inducible NO synthase down-regulation. In addition, PGE$_2$ levels as well as MMP activity were significantly decreased. A lower expression of IL-1β, TNFα, VEGF and chemokines CCL-4, CCL-5, CCL-8, CCL-19, CCL-20, CXCL-1, CXCL-2, CXCL-3 and CXCL-8 was observed in chondrocytes treated with ASC-CM with respect to IL-1β controls. We have also evaluated the senescence marker β-galactosidase. In cells treated with IL-1β and ASC-CM for 7 days, we observed a significant reduction in senescence-associated β-galactosidase activity in comparison with chondrocytes treated with IL-1β.

Conclusion: The results of our study demonstrate the down-regulation of inflammatory and catabolic mediators by ASC-CM in OA explants and chondrocytes. Our data have revealed a protective role for ASC-CM in chondrocytes suggesting possible applications against cartilage degradation.

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Differential Effects of Bone Morphogenetic Protein 2 and 9 On Chondroprotective Transforming Growth Factor β Signaling.
Arjan P. van Caam[1], Esmeralda N. Blaney Davidson[1], Elly L. Vitters[1], Laurie de Kroon[1], Ellen W. van Geffen[1], Peter ten Dijke[2], Wim B. van den Berg[1] and Peter M. van der Kraan[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Osteoarthritis (OA) is a multifactorial disease characterized by loss of articular cartilage. TGFβ is considered as a protective factor against cartilage loss in young cartilage by inducing Smad2/3 phosphorylation via the TGFβ receptor ALK5. Smad2/3 phosphorylation (Smad2/3P) lowers MMP13 expression, and prevents deleterious terminal differentiation of chondrocytes. In contrast to Smad2/3P, Smad1/5 phosphorylation (Smad1/5P), induced by BMPs but also by TGFβ, is linked to terminal differentiation and MMP13 production. Type I receptors that phosphorylate Smad1/5/8 include ALK1 and ALK3. BMP-9 signals via ALK1 and BMP-2 via ALK3, and both ligands induce enhanced glycosaminoglycan synthesis in young cartilage. BMP2 is induced in damaged cartilage while BMP9 is constitutively present in high concentrations in body fluids. If and how these factors modulate chondroprotective TGFβ signaling is still unclear. Therefore, we analyzed BMP-2 and BMP-9 induced Smad signaling and gene expression in chondrocytes, and studied their interaction with TGFβ.

Methods: Primary bovine chondrocytes, isolated from the metacarpophalangeal joint of 2 year old animals, or the human G6 chondrocyte cell line were cultured to near confluency and incubated with TGFβ1, BMP-2, BMP-9 or a combination thereof. Smad phosphorylation kinetics were analyzed by specific Smad2P and Smad1/5P staining of Western blots. Expression patterns of Smad specific response genes: PAI-1 (Smad3 signaling), and ID-1, (Smad1/5 signaling) were analyzed from 0–48h by quantitative real time PCR (qPCR). Biological activity was tested with a CAGA$_{12}$-luc transcriptional reporter construct that produces luciferase in response to Smad3 signaling. Adenovirally transduced cells (MOI = 5) were serum starved for 8h, stimulated with growth factors for 20h, and luciferase activity was measured.

Results: In primary chondrocytes, both BMP-2 and BMP-9 potently induced Smad1/5 phosphorylation, which peeked after 1 h and lasted up to 3 h. BMP-9 was more potent than BMP2. Remarkably BMP-9 (5 ng/ml or more) was also capable of inducing Smad2 phosphorylation, whereas BMP-2 (50 ng/ml) was not. BMP-9-induced Smad2 phosphorylation lasted from 1 up to 3 hours. Moreover, in contrast to BMP-2, BMP-9 was also able to rapidly (from 2 up to 24h) induce PAI-1 transcription. Both growth factors potently induced ID1 expression. Gene transcription was reflected in biological activity, as BMP-9 induced luciferase production in the CAGA$_{12}$-luc assay. Interestingly, co-stimulation of TGFβ with these BMPs revealed an even more remarkable difference between both factors. BMP-2 was able to dose dependently inhibit Smad2 phosphorylation. On the contrary, BMP-9 synergized with TGFβ on Smad2/3 phosphorylation, resulting in a 50% increase in luciferase production after co-stimulation compared to TGFβ alone (p<0.01).

Conclusion: Both BMPs show a distinct difference in Smad phosphorylation and interaction with TGFβ. Although both BMPs promote matrix synthesis (Glycosaminoglycans production), long term effects of both factors on cartilage will most likely differ due to their different effects on chondroprotective Smad2/3 signaling.

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The Negative Effects of Glucocorticoids On Bone Are Primarily Mediated by Genes Involved in Osteoblast Differentiation and Bone Remodelling.
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Background/Purpose: Glucocorticoids are widely used as anti-inflammatory and immunosuppressive drug for the treatment of many inflammatory and auto-immune diseases. However, long-term and high-dose glucocorticoid treatment causes bone loss and can lead to secondary osteoporosis in both human and mice. The molecular mechanisms underlying the adverse effects of glucocorticoids on bone are not well understood. We have recently demonstrated that osteoblast-targeted disruption of glucocorticoid signalling attenuates glucocorticoid-induced bone loss in mice, indicating that the detrimental skeletal effects of glucocorticoids are predominantly mediated by osteoblasts. To elucidate the role of the osteoblast in glucocorticoid-induced bone loss, in the present study we determined the effects of glucocorticoids on the gene expression profile in bone cells.

Methods: Seven-week old male CD1 outbred mice were subcutaneously implanted with slow-release pellets containing either 1.5 mg corticosterone (CS) or placebo (PLC) over 28 days. Blood was obtained weekly and osteocalcin serum levels were measured by IRMA. RNA was isolated from tibia at endpoint (day 28) and Affymetrix Gene Array analysis (GeneSpring GX) was performed to assess changes in expression of genes associated with osteoblast differentiation and the regulation of bone remodelling. Genes considered to be regulated were at least 1.5-fold differentially expressed. Quantitative RT-PCR was employed to validate the gene array results on a selection of genes.

Results: By comparing gene expression profiles in tibial RNA from mice treated with CS or PLC, we found that CS specifically regulated 391 genes. To further investigate the genes targeted by corticosterone treatment we performed gene ontology analysis with the aid of heat maps. The expression of genes implicated in osteoblast differentiation and the regulation of bone remodelling was downregulated in mice treated with CS compared to the PLC-treated control group. More precisely, we observed a downregulation of the osteoblast markers Runx2, Colα1, osteocalcin and sclerostin in CS-treated mice compared to PLC. In addition, BMP4 and BMP7 followed the same pattern. Genes that were most profoundly downregulated in the array analysis were further validated by qRT-PCR. Consistent with mRNA levels, osteocalcin serum levels were suppressed to almost undetectable levels.

Conclusion: These results confirm that glucocorticoids primarily target genes involved in osteoblast differentiation and the regulation of bone remodelling. Gene expression profile analyses may point to the pathways involved in the negative effects of glucocorticoids on bone.

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Activation of the Canonical Wnt Signaling Pathway Is Tissue-Dependent in Osteoarthritic Joints: Distinct Mechanisms of Regulation by Wnt Antagonists. Thomas Funck-Brentano, Wafa Bouaziz, Hilene Lin, Valerie Geoffroy, Eric Hay and Martine Cohen-Solal. INSERM U606 Paris 7 university, Paris, France

Background/Purpose: Wnt signaling pathway is a major regulator of bone and cartilage remodeling. Modulation of this pathway has lead to controversial results on joint cartilage in murine osteoarthritis (OA) models. Therefore, this study aims to describe the in vivo activity of Wnt/βcatenin and the expression of Wnt antagonists in joint tissues during the development of OA.

Methods: Joint instability was induced by partial meniscectomy (MNX) at the right knee in TOPGAL mice, which express the lacZ gene under the control of Wnt-RE. Left knee was sham-operated. The mice were sacrificed at baseline, 2, 4, 6 and 9 weeks after surgery ($\geq$ 5 animals per time point). Analysis of the bone microarchitecture of the tibial epiphyses were assessed (Skyscan® 1172) and then the samples were prepared for quantification of OA score, X-gal staining and immunohistochemistry for the expression of Dkk-1, Sclerostin and sFRP-3.

Results: Compared to sham, the number of X-gal positive osteocytes per bone volume decreased at 4 weeks then progressively increased in the subchondral bone (ratios: 0.99 ± 0.01; 0.50 ± 0.08, p<0.05; 1.63 ± 0.43; 2.33 ± 0.81 for each time point, respectively). These changes paralleled those of bone volume/tissue volume. Xgal staining was strongly observed in growing osteophytes. The number of X-gal(+)-chondrocytes was low in articular cartilage at baseline, indicating an inhibition of Wnt pathway, but their number increased in the superficial layers with MNX until 6 weeks. The synovium showed marked staining in MNX knees compared to sham operated knees. Dkk-1 was highly expressed in normal non calcified cartilage and dramatically decreased with OA. Sclerostin and sFRP-3 were only expressed in the calcified layers and moderately increased with OA. The synovium also expressed Dkk-1 and sFRP-3 in OA knees.

Conclusion: During the course of OA, the canonical Wnt signaling pathway is mainly activated in growing osteophytes, subchondral bone and synovium while this activation was moderate in chondrocytes of articular cartilage. Distinct patterns of expression of Wnt antagonists are observed in the joint tissues that indicated multiple mechanisms of regulation of the canonical Wnt signaling pathway.

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Quantitative Analysis of Bone Damage/Morphological Changes in the Citrullinated Collagen Induced Arthritis Mouse Model Using Micro-CT. Anand Dusad[1], Michael J. Duryee[1], Dong Wang[2], James R. O'Dell[3], Ted R. Mikuls[4], Geoffrey M. Thiele[3] and Lynell W. Klassen[3]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Univ of Nebraska Medical Ctr, Omaha, NE, [3]Univ of Nebraska Med Ctr, Omaha, NE, [4]Omaha VA and University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Patients with rheumatic diseases given immunosuppressive therapy are susceptible to various types of infections, especially pulmonary infections that affect their vital prognosis. The aim of this large-scale, multi-center, prospective cohort study was to identify risk factors for development of pulmonary infection in patients receiving immunosuppressive treatment for rheumatic diseases (PREVENT study).

Methods: We enrolled those patients who were admitted to participating hospitals for treatment of rheumatic diseases and started immunosuppressive therapy with corticosteroids, conventional immunosuppressants, or biologics. Observation was stopped either 12 months after enrollment, or the day a patient developed predefined pulmonary infection or was lost-to- follow up, whichever came first. The validity of the diagnosis for pulmonary infection was assessed by an event-monitoring committee. We collected demographic data and clinical data for rheumatic diseases at baseline, data for candidate risk factors for pulmonary infection at baseline and month 6, and usage of drugs throughout the observation period. Risk factors for pulmonary infection were investigated by univariate and multivariate analyses.

Results: Of 766 patients enrolled, 668 patients (87.2%) were observed for 12 months, 32 patients (4.2%) died, and 66 (8.6%) patients were lost-to-follow up by month 12. Sixty-one patients (8.0%) developed pulmonary infection: bacterial pneumonia, 25; *Pneumocystis jirovecii* pneumonia, 20;

fungal pneumonia, 5; cytomegalovirus pneumonia, 3; tuberculosis, 3; others, 5. Kaplan-Meier curves showed a significantly lower cumulative survival rate in patients with pulmonary infection compared to those without pulmonary infection (p<0.01, log-rank test). Because treatment for RA patients without active extra-articular manifestation (articular RA patients, n=145) was significantly different from that for the rest of the patients, we performed multivariate analyses using COX hazard regression models in all patients (n=766) and in these patients excluding articular RA patients (n=621) (Table 1). Older age ($\geq$65 years-old), higher Brinkman index ($\geq$400), higher serum creatinine (sCr) level, and higher maximum prednisolone dose (mg/kg/day) during the first two weeks of treatment were significantly associated with development of pulmonary infection in all patients. Older age, higher Brinkman index, higher sCr level, and disturbed performance status were significantly associated with development of pulmonary infection in patients excluding articular RA patients.

Conclusion: This is the first large-scale, prospective study identifying risk factors for pulmonary infection in patients with rheumatic diseases in the literature. Prophylactic measures should be taken accordingly for better benefit-risk balance of treatment.

Table 1. Micro-CT parameters

	C-II	FCA-C-II	CIT-C-II
Bone mineral density [BMD (g/cm³)]	0.488 ± 0.036	$0.351 \pm 0.085*$	$0.435 \pm 0.041*$
Bone volume density [BV/TV (%)]	39.534 ± 1.903	$28.220 \pm 5.257**$	$36.090 \pm 2.153*$
Bone surface density [BS/TV (mm⁻¹)]	24.100 ± 0.541	$19.291 \pm 2.144**$	$21.818 \pm 1.484*$
Trabecular number [Tb. N (mm⁻¹)]	6.400 ± 0.200	$4.921 \pm 0.613**$	$5.640 \pm 0.483*$
Trabecular seperation [Tb. Sp. (mm)]	0.097 ± 0.004	$0.119 \pm 0.012**$	$0.110 \pm 0.008*$
Trabecular pattern index [Tb. Pf (mm⁻¹)]	-0.346 ± 1.970	$8.203 \pm 3.413**$	$2.888 \pm 3.001*$
Structural mean index [SMI]	0.642 ± 0.162	$1.166 \pm 0.223**$	$0.911 \pm 0.220*$
Degree of Anisotropy (DA)	0.759 ± 0.007	0.774 ± 0.026 (NS)	$0.778 \pm 0.016*$
Polar moment of inertia [MMI (mm⁴)]	0.0030 ± 0.00013	$0.0021 \pm 0.00045**$	$0.0028 \pm 0.0003*$
Fractal dimension [FD]	2.443 ± 0.024	$2.322 \pm 0.056**$	$2.404 \pm 0.015*$
Number of Objects [Obj. N]	10.25 ± 5.850	12.429 ± 4.429 (NS)	$18 \pm 7.349*$
Connectivity Density [Conn. Dn (mm⁻³)]	637.133 ± 61.640	$468.461 \pm 70.743**$	$543.144 \pm 70.529*$

*Significantly different from C-II, p < 0.05. **Significantly different from C-II, p < 0.001. NS: not significant

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Anti-Citrullinated Protein Antibodies As an Indicator of Bone Damage in the Citrullinated Collagen Induced Arthritis Model. Anand Dusad[1], Michael J. Duryee[1], Dong Wang[2], Carlos D. Hunter[1], Bartlett C. Hamilton III[3], James R. O'Dell[4], Ted R. Mikuls[5], Lynell W. Klassen[4] and Geoffrey M. Thiele[4]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Univ of Nebraska Medical Ctr, Omaha, NE, [3]University of Nebraska Medical Centre and Omaha VA Medical Center, Omaha, [4]Univ of Nebraska Med Ctr, Omaha, NE, [5]Omaha VA and University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Although the pathogenesis and cause of rheumatoid arthritis (RA) remains uncertain, various disease-driving auto-antigens and auto-antibodies with different specificities have been used as diagnostic tools. Anti-citrullinated protein antibody (ACPA) has been implicated in disease process and due to its high specificity also been used as a diagnostic tool. There have been many studies in the literature using ACPA as an indicator of radiological (X-Ray) joint damage in both RA patients and animal studies, although few have quantified bone damage using Micro-CT. This is important since this approach is increasingly considered the gold standard for analyzing and quantifying micro-structural changes in bone morphology. Therefore the purpose of this study was to correlate joint damage as quantitated by micro-CT with ACPA using our novel citrullinated collagen induced arthritis (CCIA) model.

Methods: Thirty DBA/1 mice were randomly divided into three groups. Mouse collagen (C-II) was modified [citrullinated (Cit)] using peptidyl arginine deiminase (PAD) and injected weekly for 5 weeks. As controls, mice were injected with unmodified C-II (negative control) and with Freund's complete adjuvant (FCA) as positive control. Mice were sacrificed at week 5 and micro-CT was done to quantitatively analyze bone damage. A commercially available anti-CCP antibody kit was used to measure ACPA levels in serum. Data was expressed as mean $\pm$ SD's. Pearson's 2-tailed correlation was used to correlate ACPA with measures of bone damage.

Results: Using ELISA, anti-CCP (ng/ml) was measured in serum and showed a significant increase in both Cit-C-II (29.03 ± 7.53, p = 0.03) and FCA-C-II (42.73 ± 4.56, p < 0.001) as compared to C-II (21.84 ± 5.20). Bone mineral density (BMD) showed significant loss in Cit-C-II (0.43 ± 0.04

g/cm^3, p = 0.018) and FCA-C-II (0.35 ± 0.08 g/cm^3, p = 0.001) as compared to C-II (0.49 ± 0.04 g/cm^3) group. Data was found to be consistent for several other parameters of bone quality (not shown). Significant negative correlations were observed for BMD, BV/TV, BS/TV, trabecular number, fractal dimension, connectivity density and polar moment of inertia all indicating that as ACPA increases these decrease suggesting that higher ACPA concentration is inversely associated with bone quality [Table 1].

Table 1.

	ACPA (ng/ml)
Bone mineral density [BMD (g/cm^3)]	−0.530*
Bone volume density [BV/TV (%)]	−0.654**
Bone surface density [BS/TV (mm^{-1})]	−0.662**
Trabecular number [Tb. N (mm^{-1})]	−0.628
Trabecular seperation [Tb. Sp. (mm)]	0.573**
Trabecular pattern index [Tb. Pf (mm^{-1})]	0.570**
Structural mean index [SMI]	0.510*
Fractal dimension [FD]	−0.666**
Connectivity Density [Conn. Dn (mm^{-3})]	−0.591**
Polar moment of inertia [MMI (mm^4)]	−0.647**

Pearson Correlation (2-tailed, n = 21). **Correlation is significant at 0.01 level, *Correlation is significant at 0.05 level.

Conclusion: Due to the fact that no exogenous immunogenic factor such as non-self protein or any adjuvant is used in this novel model, CCIA closely mimics the auto-immunogenic origin of RA. Using this model, we observed significant inverse associations of circulating ACPA with measures of bone quality including density, volume, surface and mechanical properties of bone. In conclusion ACPA levels in serum can successfully predict bone morphological changes in RA. Further studies focused on identifying the mechanisms underpinning these relationships are ongoing.

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Role of Microrna-455 Networks in Mesenchymal Cell Differentiation and Osteoarthritis. Fumiaki Ayabe[1], Shigeru Miyaki[2], Diana Brinson[1], Satoshi Yamashita[3], Hiroyuki Nakahara[1], Koji Otabe[1], Stuart Duffy[1], Shawn Grogan[1], Shuji Takada[3], Martin K. Lotz[1] and Hiroshi Asahara[1]. [1]The Scripps Research Institute, La Jolla, CA, [2]Hiroshima University, Hiroshima, Japan, [3]National Research Institute for Child Health and Development, Tokyo, Japan

Background/Purpose: The objectives of this study were to identify cartilage specific microRNAs (miRNAs, miR-) that are regulated by SOX9 and are increased in chondrogenesis, to determine changes in osteoarthritic (OA) cartilage, and to investigate the role of miR-455-5p and miR-455-3p (miR-455s) in human chondrocytes.

Methods: To identify miRNAs specifically expressed in chondrocytes, we performed microarray and quantitative polymerase chain reaction (qPCR) on cultured mouse chondrocytes using adenovirally induced SOX9 transcription. The expression of miR-455s was analyzed by qPCR on human articular chondrocytes, human mesenchymal stem cells (MSCs). The expression of miR-455s was monitored during chondrogenic differentiation of human MSCs in pellet cultures as well as in human articular cartilage from both normal and OA knee joints. We tested the effects of interleukin-1b (IL-1b) on miR-455s expression. Double-stranded miR-455s (ds-miR-455s) was transfected into chondrocytes to identify changes in gene expression associated with OA.

Results: The expression of miR-455s mirrors SOX9 expression, with large differences between human chondrocytes and human MSCs. During chondrogenesis, miR-455s expression in MSC cultures increased in parallel with the expression of SOX9, MAF and COL10A1. Normal human articular cartilage expressed miR-455s, with significant reduction in OA tissue. In vitro treatment of chondrocytes with IL-1b suppressed miR-455s expression. Transfection of chondrocytes with ds-miR-455s down-regulated expression of inflammatory genes.

Conclusion: This study shows that miR-455s expression is altered in concert with other chondrocyte differentiation-related expression patterns. The reduction in miR-455s expression in OA cartilage and in response to IL-1b may contribute to the abnormal gene expression pattern characteristic of OA.

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Level of IL-1â-Induced Epigenetic Modifications Differ in Chondrocytes From Different Histological Zones of Human Cartilage. Nahid Akhtar[1] and Tariq M. Haqqi[2]. [1]Case Western Reserve University/Metrohealth Medical Center, Cleveland, OH, [2]Metro Health Medical Center, Cleveland, OH

Background/Purpose: Osteoarthritis (OA) reduces mobility and function of the affected joint and is a leading cause of disability among the elderly. Recent evidence points to epigenetic regulation of genes in OA. Interleukin-1β (IL-1β) is the major cytokine involved in cartilage catabolism and induces the expression of pro-inflammatory genes. The aim of this study was to investigate whether IL-1β induces epigenetic changes in human chondrocytes obtained from upper, middle and deep zone cartilage.

Methods: Chondrocytes were derived by enzymatic digestion of upper, middle and deep-zone cartilage obtained from OA patients (n=10). Chondrocytes were stimulated with IL-1β (10ng/ml) *in vitro* for 24h. Global DNA methylation level was determined using MethylFlash™ Methylated DNA quantification kit (Epigentek). Total RNA was prepared and expression level of DNMT-1, DNMT-3A, DNMT-3B and HDAC-1 was quantified by TaqMan Assays. IL-1β-induced changes in the activity of total DNMT, DNMT-1, DNMT-3A, DNMT-3B, DNA demethylases and Thymine DNA glycosylase (TDG) was determined using ELISA-based assays (Epigentek). Un-stimulated and IL-1β-stimulated chondrocytes obtained from upper and deep zones were used to study the expression of 84 human epigenetic modification enzymes using mRNA array (SA Biosciences). **Results** were derived using Origin 6.1 software package and p<0.05 was considered significant.

Results: Global DNA methylation estimation showed the differential response of chondrocytes from different zones of the human cartilage to IL-1β. Total DNA methylation was significantly increased in the deep-zone chondrocytes (138%) and in upper-zone chondrocytes (18%) stimulated with IL-1β compared to controls. Expression levels of 84 key genes encoding enzymes known or predicted to modify genomic DNA and histones to regulate chromatin accessibility showed that 30 genes displayed significant differences upon IL-1β-stimulation. Among these, 29 genes were upregulated and 1 gene was downregulated. Interestingly, the mRNA array results showed a significant upregulation of DNMT-1, DNMT-3A and DNMT-3B expression in both upper and deep-zone chondrocytes stimulated with IL-1b and correlated with the increased total DNMT and DNMT-1 activity in the same chondrocytes. Activity of both DNA demethylases and TDG, enzymes essential for active DNA demethylation, was also increased in both deep and upper-zone chondrocytes by IL-1β suggesting a dynamic regulation of DNA methylation and demethylation in these chondrocytes. No significant difference in global DNA methylation, expression and activity of DNMT-1, DNMT-3A, DNMT-3B and demethylases was observed in chondrocytes from middle-zone in response to IL-1β.

Conclusion: We demonstrate a role of IL-1β-mediated epigenetic modifications in chondrocytes of the three histological zones of the human cartilage. Hypermethylation of genomic DNA in OA chondrocytes positively correlated with the expression and activity of DNA methylatranferases. This study also identify for the first time several new candidate genes that may be involved in DNA methylation, demethylation and histone modifications in response to IL-1β in human chondrocytes and thus may play a role in OA pathogenesis.

Disclosure: **N. Akhtar**, None; **T. M. Haqqi**, None.

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A Mouse Myeloid Precursor with Osteoclastogenic Function in Vivo. Julia F. Charles[1], Erene Niemi[2], Mary C. Nakamura[3] and Antonios O. Aliprantis[4]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]University of California, San Francisco; VA Medical Center, San Francisco, [3]SFVAMC/UCSF, San Francisco, CA, [4]Brigham and Women's Hsopital, Boston, MA

Background/Purpose: Osteoporosis and peri-articular erosions in patients with inflammatory arthritis are characterized by increased osteoclast resorptive activity. Although a great deal is known about how osteoclasts differentiate from precursors and resorb bone, the identity of the osteoclast precursor (OCP) in vivo remains elusive. Using ex vivo assays of osteoclast

differentiation, we previously demonstrated that the majority of bone marrow OCP activity resides in the CD11b$^{-/lo}$ Ly6C^{hi} cKit^{+} population.

Methods: Fluorescence activated cell sorting was used to examine multiple markers on OCP and to isolate OCP from mT/mG cathepsin K cre+ mice. mT/mg cathepsin K cre donor OCP are RFP+ at baseline and GFP+ in the presence of cre recombinase in mature osteoclasts. Donor OCP were transfered by intramedulary injection into NFATc1 fl/fl Mx1-Cre osteoclast deficient mice and donor derived osteoclasts were detected by IHC. Alternatively, donor OCP were injected intravenously into C57BL/6 mice 24 hrs after calvarial injection of 20mg/kg LPS. Ex vivo osteoclast, dendritic cell, and macrophage cutures and assays were performed according to standard techniques.

Results: Here we show that the CD11b$^{-/lo}$ Ly6C^{hi} cKit^{+} OCP population can be distinguished from the recently described quiescent osteoclast precursor by their proliferative capacity and absence of RANK (receptor activator of nuclear factor kappa B) expression. Similar to other myeloid precursors, OCP retain plasticity in vitro, differentiating into dendritic cells or phagocytic macrophages when stimulated with GM-CSF or MCSF, respectively. Adoptive transfer of this OCP population into osteoclast deficient hosts resulted in the formation of donor-derived mature, multinucleated TRAP^{+} osteoclasts in vivo. By combining adoptive transfer with an inflammatory stimulus (lipopolysaccharide injection into the calvaria) we further show that these OCP can be recruited to and differentiate at sites of inflammatory osteolysis. Thus, we demonstrate that bone marrow OCP can migrate to stimuli known to promote osteoclastic bone resorption.

Conclusion: We demonstrate that the CD11b$^{-/lo}$ Ly6C^{hi} cKit^{+} bone marrow population is a bona fide OCP. Furthermore, this work provides a model system to identify the chemokine and cytokine requirements for recruiting osteoclasts to sites of inflammatory bone loss in diseases such as rheumatoid and psoriatic arthritis.

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Anti Citrullinated Protein Antibodies From Synovial Fluid of Rheumatoid Arthritis Patients Enhance Osteoclastogenesis. Akilan Krishnamurthy[1], Nancy Vivar Pomiano[1], Catia Cerqueira[1], Elena Ossipova[1], Karin Lundberg[1], Ulrike Harre[2], Vivianne Malmström[1], Per Johan Jakobsson[1], Lars Klareskog[3], Georg Schett[2] and Anca Irinel Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Karolinska Institute, Stockholm, Sweden

Background/Purpose: Presence of anti CCP2 antibodies identifies a subgroup of RA patients that are more prone to develop bone erosions. We hypothesized that anti CCP2 IgG might have a direct effect on bone, and thus investigated the effect of anti CCP2 IgG isolated from synovial fluid (SF) of RA patients on osteoclastogenesis and bone destruction in an in vitro system.

Methods: SF (n=26) samples were collected from RA patients with anti-CCP2 IgG levels above 300AU/ml. Total IgG was isolated on Protein G columns, before applied to CCP2 affinity columns, kindly donated by EuroDiagnostica. A pool of the purified anti-CCP IgG fractions, as well as a pool of the corresponding column flow through IgG fractions were tested for the ability to influence osteoclastogenesis and bone destruction. CD14 positive cells isolated by positive selection from peripheral blood of healthy individuals were cultured in the presence of GM-CSF and IL-4 to generate immature dendritic cells. After 6 days of culture, cells were incubated in the presence of RANKL and M-CSF, with or without CCP2 IgG or flow through IgG (at a final concentration of 100ng/ml) for an additional 12 days. Osteoclasts formation was evaluated as total number of multinucleated TRAP positive cells. In parallel cultures were grown on osteologic discs and % of resorbed out of total disc areas were evaluated by computer assisted image analyses

Results: The CCP2 IgG pool significantly increased the formation of osteoclasts. In contrast the pool of the flow through IgG did not stimulate RANKL-driven osteoclastogenesis from immature dendritic cells. When assessing bone destruction CCP2 IgG but not flow through IgG was able to increase the percentage of synthetic bone resorption areas.

Conclusion: Here, we demonstrate that ACPA IgG, isolated from synovial fluid of RA patients, have the ability to enhance the RANKL-driven osteocalstogenesis from immature dendritic cells. Our findings suggest that ACPA might have a direct pathogenic effect in RA associated bone destruction.

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Development of a Quantitative Model of Endotoxin-Induced Calvarial Bone Erosion Utilizing Micro-Computed Tomography and Pax-It Imaging Analysis Software. Diane Thome, Donald Souza, Aruna Behera, Jie Zheng, Jennifer Swantek and Gerald H. Nabozny. Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT

Background/Purpose: To facilitate an understanding of the biological factors involved in inflammation- mediated bone loss, in vitro systems and murine models of bone loss, such as endotoxin-induced calvarial erosion have been utilized. However, challenges exist with in vivo model robustness, throughput and quantitation of bone erosions. Assessment of erosion is typically determined via micro-computed tomography (MicroCT) but quantitation has been hampered by mouse to mouse variability in bone morphology and lack of consistent robust erosion obtained by endotoxin alone. We set out to develop a robust, quantitative in vivo endotoxin-induced calvarial erosion model that would be amenable for in vivo testing of potential therapeutic agents and would allow for gaining insight into processes involved in inflammatory bone loss.

Methods: Lipopolysaccharide (LPS) was injected with or without receptor activator of NF-kB ligand (RANKL), over the calvaria of mice. On day 5 or 8, mice were euthanized and processed for MicroCT analysis. Skulls were scanned at medium resolution, 70 kVp, 114 μA. Scans were rendered into 3-D. Optimal viewing angles were chosen for creation of TIFF images, which were then examined using Pax-IT imaging analysis software (MIS, Inc), using a 4-pass analysis to generate 4 areas of erosion representing each of the 4 calvarial plates. The values obtained in the 4 areas of erosion were summed to provide a measure of total area of calvarial erosion. For further validation aimed at demonstration of the quantitative nature of the model, in vivo testing of therapeutic agents known to play a role in osteoclastogenesis was implemented.

Results: Five-day dose-response studies using RANKL + LPS in B10.RIII mice resulted in severe erosive events, but dose-dependent relationships were not consistent. We compared 5-day and 8-day models. At Day 8, mice exhibited consistent and strong dose-dependent calvarial erosion with co-administration of 25 μg LPS and 10ug RANKL per mouse. We determined inclusion of RANKL was necessary for optimal erosion. Summating four 8-day studies using B10.RIII mice, co-administration of 25 μg LPS and 10 μg RANKL led to an average area of erosion of 4080 + 259 mm^2, compared to the naïve (untreated) average area of erosion of 506 + 40 mm^2. The microCT/Pax-IT analysis method facilitated reproducible, quantitative results. Importantly, therapeutic agents known to play a role in osteoclastogenesis demonstrated statistically significant reductions in bone erosion further emphasizing the quantitative nature of this model.

Conclusion: We developed a robust, quantitative endotoxin plus RANKL-induced calvarial bone erosion model through use of MicroCT and Pax-IT analysis. This model and quantitation methodology allows for testing therapeutic agents to facilitate understanding of the biological factors and processes involved in bone erosion. The ultimate goal is to impact identification of better therapeutic options for patients.

Disclosure: **D. Thome**, Boehringer Ingelheim, 3; **D. Souza**, Boehringer Ingelheim, 3; **A. Behera**, Boehringer Ingelheim, 3; **J. Zheng**, Boehringer Ingelheim, 3; **J. Swantek**, Boehringer Ingelheim, 3; **G. H. Nabozny**, Boehringer Ingelheim, 3.

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Novel Targets for Blocking Osteoclast-Mediated Resorption in Inflammatory Disorders. Kevin P. McHugh[1], Tania N. Crotti[1], Jun Li[2], Jon Hill[3], Gerald H. Nabozny[2], Steven R. Goldring[4] and P. Edward Purdue[5]. [1]Center for Advanced Orthopedic Studies, Beth Israel Deaconess Medical Center, Boston, MA, [2]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [3]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, [4]Hospital for Special Surgery, New York, NY, [5]Hospital for Special Surgery, Weill Cornell Medical Center, New York, NY

Background/Purpose: Osteoclasts are specialized myeloid lineage cells that mediate both pathologic and physiologic bone remodeling Fully differentiated and functional osteoclasts are found exclusively associated with the bone surface, indicating that interaction with the bone substrate plays a pivotal

role in the regulation of osteoclast biology. Most *in vitro* studies on the formation and activation of osteoclasts have been performed using cells adhered to tissue culture plastic, and there is little information regarding the specific molecular mechanisms by which adherence to the bone surface regulates the terminal stages of osteoclast differentiation. To address this discrepancy, we have compared the transcriptional profiles of osteoclasts generated on a variety of substrates, including authentic bone and have identified the unique molecular signatures that are dependent and independent of integrin beta 3, a prototypical osteoclast regulator of osteoclast function.

Methods: Bone marrow derived macrophages from wild-type and integrin beta 3 deficient mice were cultured in the presence or absence of RANKL on plastic, hydroxyapatite, or calvarial bone discs. RNA was isolated at different stages of osteoclast generation and microarray analysis and pathway mapping were utilized to identify osteoclast signaling pathways regulated by the cytokine RANKL, bone substrate, and integrin beta 3. Pathway analysis was performed using GSEA and Ingenuity pathway analysis.

Results: Microarray analysis revealed RANKL-induced molecular profiles that were uniquely and specifically regulated in osteoclasts differentiated on the authentic bone substrate compared to the other substrates. Pathway analysis revealed coordinated downregulation by bone of a cluster of genes associated with cell cycle progression. The expression level of integrin beta 3, which is induced by RANKL during osteoclast differentiation, is further modulated by culture on the bone substrate. Interestingly, bone regulated genes could be divided into those that were dependent and independent of integrin beta 3.

Conclusion: In addition to cytokines and growth factors, interaction of osteoclasts and their precursor with the bone substrate regulates pathways that are involved in osteoclast formation and activation. Although integrin beta 3 has been regarded as the essential mediator of osteoclast attachment and activation, molecular pathways independent of this integrin also modulate the genetic program during osteoclastogenesis. Analysis of these genes and their pathways provides novel targets and approaches for therapeutic targeting of osteoclast-mediated bone loss in inflammatory and related bone disorders.

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Rebamipide Attenuates Pain Severity and Cartilage Degeneration in a Rat Model of Osteoarthritis by Downregulating Oxidative Damage and Catabolic Activity in Chondrocytes. Su-Jin Moon[1], Mi-La Cho[2], Yeon-Sik Hong[3], Sung-Hwan Park[2] and Jun-Ki Min[1]. [1]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]Catholic University of Korea, Seoul, South Korea, [3]Our Lady of Mercy Hospital, Inchon, South Africa

Background/Purpose: The development and progression of osteoarthritis (OA) are now believed to involve inflammation, even in the early stage of disease. Proinflammatory cytokines and chemokines are critical mediators of the disturbed homeostasis in the OA cartilage matrix. Also, OA is associated with oxidative stress. Excessive production of oxidants has been linked with apoptosis of cartilage chondrocytes both in vitro and in vivo. Rebamipide, a gastroprotective agent, exhibits an anti-inflammatory and radical-scavenging property. We investigated the effects of rebamipide on pain generation, cartilage destruction, and various indicators of local oxidative damage and inflammatory status in a monosodium iodoacetate (MIA)-induced OA rat model,

Methods: OA was induced in rats by intra-articular injection of MIA. Oral administration of rebamipide was initiated on the day of MIA injection or 3 days after. Limb nociception was assessed by measuring the paw withdrawal latency and threshold. We analyzed the samples macroscopically and histomorphologically, and used immunohistochemistry to investigate the expression of matrix metalloproteinase 13 (MMP-13), interleukin-1β (IL-1β), hypoxia-inducible factor-2α (HIF-2α), inducible nitric oxide synthase (iNOS), and nitrotyrosine in knee joints. Real-time quantitative reverse transcription-polymerase chain reaction was used to quantify the mRNA for catabolic and anticatabolic factors in human OA chondrocytes.

Results: Rebamipide showed an antinociceptive property and attenuated cartilage degeneration. Rebamipide reduced the expression of MMP-13, IL-1β, HIF-2a, iNOS, and nitrotyrosine in OA cartilage in a dose-dependent manner. Nitrotyrosine expression in the subchondral bone region was decreased in the rebamipide-treated joints. mRNA expression of MMP-1, -3, and -13, and ADAMTS5 was attenuated in IL-1β-stimulated human OA chondrocytes. By contrast, rebamipide induced the mRNA expression of tissue inhibitor of metalloproteinase -1 and -3.

Conclusion: The results show the inhibitory effects of rebamipide on pain production and cartilage degeneration in experimentally induced OA. The suppression of oxidative damage and the restoration of extracellular matrix homeostasis of articular chondrocyte suggest that rebamipide is a potential therapeutic strategy for OA.

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Changes in Tibial Bone and Cartilage Structure in a Mouse Surgical Model of Osteoarthritis. Brett A. Tonkin[1], Evange Romas[2], Natalie A. Sims[1] and Nicole C. Walsh[1]. [1]St Vincent's Institute of Medical Research, Melbourne, Australia, [2]St Vincent's Hospital, Melbourne, Australia

Background/Purpose: The destabilisation of the medial meniscus (DMM) mouse osteoarthritis (OA) model is commonly used to study OA joint degeneration. In DMM-OA, the knee is destabilised by transecting the medial-meniscotibial ligament, resulting in increased loading on the medial tibial compartment. Similar to human OA, this leads to articular cartilage damage, subchondral bone accrual and osteophyte formation. We conducted a longitudinal study to define temporal changes in tibial bone structure and cartilage integrity in this model.

Methods: 12-week old male C57BL/6 mice underwent DMM or sham surgery on the right knee; left knees served as contra-lateral controls. In vivo micro-CT was performed prior to surgery, and 4, 8, 12 weeks post-surgery. NRecon and CT-Analyser (Skyscan) were used for micro-CT data reconstruction and analysis; the latter was performed using a novel approach specifically developed for assessing bone of varying mineralisation states. Histologic assessment of cartilage damage was performed using the OARSI scoring matrix for mouse models of osteoarthritis. Statistics: 2-way ANOVA, Bonferroni post-hoc tests. Baseline bone volume/tissue volumes (BV/TV) and bone mineral density were similar in all limbs.

Results: Consistent with an increase in loading, micro-CT analyses demonstrated focal increases in medial subchondral bone in DMM-OA tibiae; BV/TV and bone mineral density were significantly increased at this site compared to sham from 4 weeks post-surgery (p<0.001). In contrast, the lateral subchondral bone BV/TV did not differ between DMM-OA and sham tibiae and the tibial trabecular BV/TV was similar in all limbs, indicating no systemic effects of DMM-OA on bone remodelling. Histologic assessment demonstrated proteoglycan loss in medial articular cartilage in DMM-OA tibiae from 4 weeks post-surgery, with cartilage erosion evident by 8 weeks post-surgery. Interestingly, medial subchondral bone BV/TV was similar between DMM-OA tibiae and their contra-lateral tibiae, suggesting alterations in gait may affect the subchondral bone structure in the contra-lateral knee; an observation also made in human OA. Articular cartilage was intact in these contra-lateral tibiae.

Conclusion: In summary, focal changes in subchondral bone structure occur early in DMM-OA in response to joint destabilisation, and precede proteoglycan loss and erosion of the articular cartilage. Altered bone structure in contra-lateral tibiae of DMM-OA mice, suggests that increased subchondral bone alone, does not necessarily impact overlying articular cartilage integrity, and also serves to highlight the need to include sham-operated mice when using this model.

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Role of FK506 Binding Protein 5 in Osteoclast Differentiation. Miho Kimura[1], Tatsuo Nagai[1], Reiko Matsushita[1], Atsushi Hashimoto[2], Toshiyuki Miyashita[3] and Shunsei Hirohata[1]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Sagamihara National Hospital, National Hospital Organization, Sagamihara, Kanagawa, Japan, [3]Kitasato University School of Medicine, Sagamihara

Background/Purpose: RA is a chronic, systemicinflammatory disease characterized by the destruction of bone in the joints. Moreover, it is well appreciatedthat systemic osteoporosis is common in RA.Previous studies have disclosed the enhanced expression of FK506binding protein 5 (FKBP5) mRNA in bone marrow CD34^{+} cells in RA. Sincebone marrow CD34+ cells are precursors of osteoclast, it is possible thatoverexpression of FKBP5 might

affect osteoclastgenesis. The current studies thereforeexplore the influences of FKBP5 in osteoclast differentiation from murineRAW264.7 cells.

Methods: We generated stable transfectant clones of FKBP5 gene of murine macrophage RAW264.7 cell line, using a plasmid containing pCAGGS-FKBP5(murine)-IRES-eGFP-pA-Neo. FKBP5 expression was confirmed by Westernblotting and RT-PCR. Osteoclast differentiation was induced by stimulation withreceptor activator of nuclear factor kappa B ligand (RANKL) and was evaluatedby TRAP staining and pit formation assay.

Results: FKBP5 transfectant clones of RAW264.7cell line generated a higher number of TRAP positive multinucleated cells withhigher activity of pit formation than mock transfentants (Figure 1). Theenhancement of osteoclast differentiation of FKBP5 transfectants was only partiallyreversed by transfection of a vector bearing a mutant form of IkB (NFkB super-repressor)(Figure 2). Consistently, the results of luciferase assay and NFkB p65 ELISA revealed only very modestincrease in NFkB activity in the presence of RANKL in FKBP5 transfectants comparedwith mock transfectants. Finally, glucocorticoidenhanced not only the osteoclast differentiation from nontransfectant RAW264.7 cells, but their expression of FKBP5 mRNA in a dose-dependent manner.
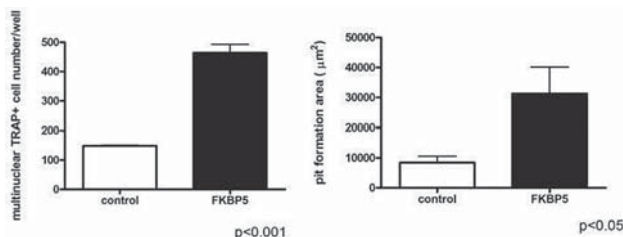
Fig 1. Effect of FKBP5 on the differentiation of osteoclasts.
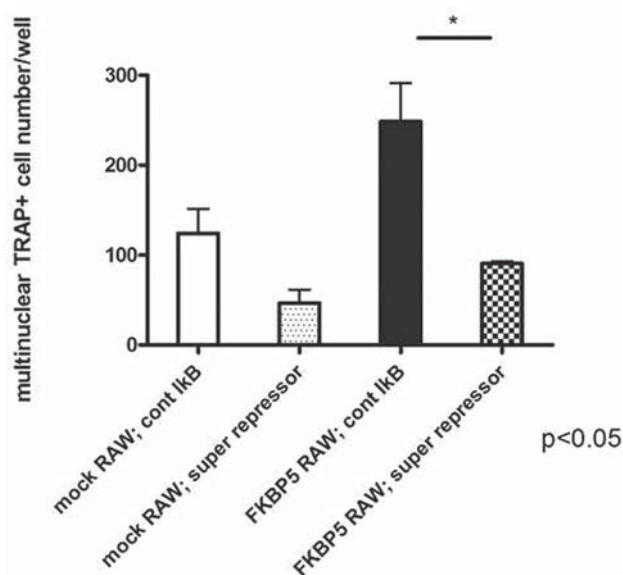
Fig 2. Effect of NF-kB superrepressor on osteoclast differentiation.

Conclusion: These results indicate that FKBP5promotes osteoclast differentiation by a mechanism distinct from NFkBactivation. Moreover, the data also suggest that FKBP5 might play a role in thedevelopment of osteoporosis in RA as well as in glucocorticoid-inducedosteoporosis.

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Development of a Mouse Model of Natural Osteoarthritis of Knee by Induction of obesity and Bipedal Walking. Hyun Ah Kim[1], Su Jin Park[2], Eun-Jeong Cheon[2], Hyun A. Jung[1] and Kyeong Min Son[3]. [1]Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [2]Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [3]Hallym University Chunchun Sacred Heart Hospital, Chunchun, South Korea

Background/Purpose: Animal models of osteoarthritis(OA) are used extensively in research of its pathogenesis and in search of disease modifying anti-OA drugs. However, whether current animal models of OA properly represent human OA is a critical question. In devising an animal model which can be extrapolated into human disease, 2 factors, obesity and bipedal walking inherent in human locomotion have been under-reporesented. In this study, we sought to investigate the influence of obligatory bipedal walking on OA development in C57BL6 mice. In addition, by inducing obesity, we observed whether excess body weight acts synergistically with bipedal walking in the development of OA.

Methods: Seventy-two 31 week-old C57BL6 mice were divided into 2 groups and one group was fed with 30% fat diet and another group with control diet for 2 months. After induction of obesity, mice from each group were again divided into 2 groups and obligatory bipedal exercise was induced with specially designed treadmill for 1–4 hours daily in each group, resulting in 4 experimental groups of mice (control, control bipedal, obese, obese bipedal). After 8,10 and 12 weeks of bipedal walking, animals were sacrificed. Knee joints were obtained and graded microscopically according to scoring system recommended by OARSI histopathology initiative and modified Mankin score. Serum levels of cartilage oligomeric matrix protein-(COMP) and type II collagen degradation product were measured with ELISA. Pain behavior was assessed with von Frey fiber test and regularity index measured by catwalk test.

Results: High fat diet for 2 months induced significant weight gain in C57BL6 mice without signs of physical illness. Typical findings of human OA cartilage, including surface fibrillation, proteoglycan matrix depletion and chondrocyte loss began to appear after 8 weeks of exercise in bipedal groups and progressed as the duration of exercise increased. At 12 weeks, vertical erosion to calcifed cartilage typical of mouse OA was observed in none of control and obese groups, and in 66.6 and 100% of control bipedal and obese bipedal groups. OA grading was significantly higher in bipedal groups compared to obese and control groups, and significantly higher in obese bipedal group compared to control bipedal group. OA change in bipedal groups was accompanied by synovitis and subchondroal bone thickening while osteophyte formation was not significantly increased. OA grading was not significantly different between obese and control group. Serum levels of COMP were significantly increased in bipedal groups compared to control or obese group at 8 and 10 weeks of exercise. Threshold for von Frey fiber test decreased significantly in bipedal groups compared to control group while it significantly increased in obese group. Abnormal gait pattern measured by regularity index in catwalk test tended to increase in obese bipedal group compared to other groups.

Conclusion: By induction of obesity and bipedal exercise, natural OA mimicking human OA was induced in C57BL7 mouse. The regulation of relevant signaling mechanism during progression of OA in this model would contribute to the understanding of pathogenetic mechanism of human OA and efficient evaluation of novel therapeutic agents.

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Bone Marrow Lesions On Magnetic Resonance Imaging Are Not Associated with Regions of Hypermetabolism in an Animal Model of Osteoarthritis. Arash Panahifar, Jacob Jaremko, Robert GW Lambert, Walter P. Maksymowych and Michael R. Doschak. University of Alberta, Edmonton, AB

Background/Purpose: The underlying histopathological basis for bone marrow lesions (BML) on magnetic resonance imaging (MRI) in osteoarthritis (OA) is unclear, but may be associated with pain and disease progression. BMLs are visible on fat-suppressed T2 and proton density weighted images by MRI, but not by radiography. It has been proposed that BML reflect hypermetabolic areas characterized by bone remodelling. We aimed to test this hypothesis by combining sequential *in vivo* micro-MRI with assessment of bone remodelling using a novel dynamic bone labelling methodology employing elemental strontium detection by electron probe microanalysis (EPMA).

Methods: Post-traumatic osteoarthritis (PTOA) was surgically induced in 9 rats, with an additional 3 rats included as sham-operated controls. *In vivo* micro-MRI images were obtained sequentially at baseline, 4, 8 and 12 weeks after surgery, utilizing 9.4 Tesla T2 and proton density weighted MRI to detect BML. Elemental strontium (sub-therapeutic tracer dosage) was administered daily commencing one day post-surgically until euthanasia at 12

weeks, when strontium incorporation in mineralizing tissues was assessed using EPMA.

Results: EPMA maps at all time-points demonstrated scant strontium deposition on trabecular surfaces and epiphyseal growth plates, but was most prominently incorporated at sites of developing osteophytes - indicating intensive bone turnover and new bone formation (Fig 1). Joint effusion, synovitis and occasional subchondral cysts were readily visible at 4 weeks under MRI (Fig 2), however, only tiny areas of potential BML-like signal (ill-defined increased T2 signal) were detected in this animal model starting at 4 weeks. Those foci were not located at the sites of strontium incorporation, but were seen at the margins of sub-articular cysts that developed between 4–8 weeks.
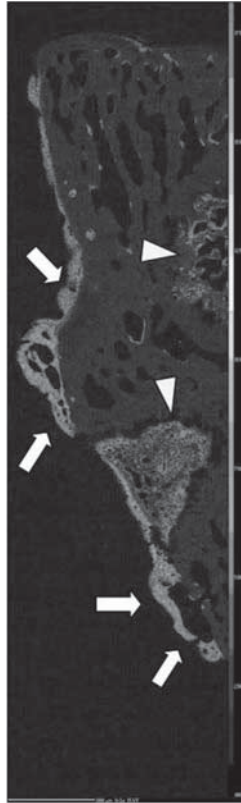
Fig 1. EPMA map of untreated rat shows hypermetabolic bone remodelling at joint margins leading to the formation of osteophytes (arrows). Growth plates are depicted with arrow heads.
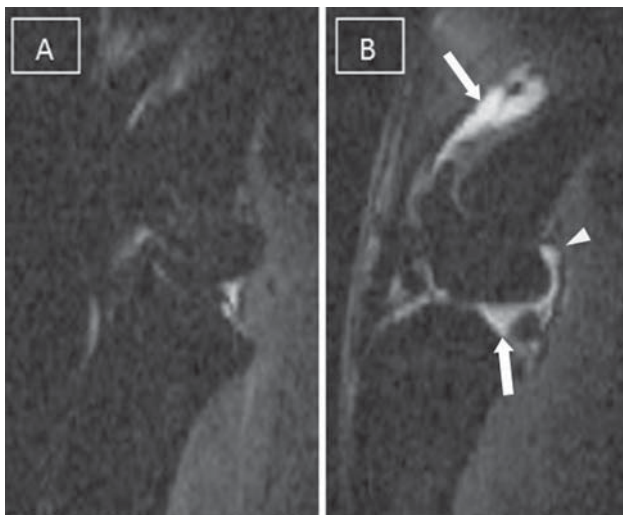
Fig 2. T2-weighted/fat suppressed MRI at: A) baseline B) 8 weeks exhibiting joint effusion (arrows) and synovitis (arrow head).

Conclusion: In this animal model of PTOA, joint degeneration was associated with florid synovitis, joint effusion, minimal subchondral cyst formation, OA-associated loose body appearance and massive osteophyte formation. In humans, such dramatic arthropathy would generally be accompanied by extensive BML. Although all of the other features of severe OA were present in these animals and hypermetabolism was demonstrated at the joint margins, we detected virtually no BML at 9.4T MRI.

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SDF-1 Induces Osteoclastogenesis in Rheumatoid Arthritis by Upregulating of RANKL Expression in Synovial Fibroblasts and CD4+ T Cells.

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Background/Purpose: Stromal cell-derived factor (SDF)-1 is involved in bone destructive process in rheumatoid arthritis (RA) and bony metastasis in malignancy, through inducing angiogenesis, producing matrix-degrading enzymes and increasing survival and migration of osteoclasts. This study aimed to determine the mechanism of SDF-1 on osteoclastogenesis in RA.

Methods: Synovial fibroblasts and CD4+ T cells were isolated from synovial tissues and peripheral blood of RA patients. The expression of SDF-1 and RANKL in the synovial tissues was evaluated using confocal microscopy. After synovial fibroblasts and CD4+ T cells were treated with rhSDF-1, the expression of RANKL mRNA was determined using real-time PCR. Osteoclastogenesis was analyzed in culture of human peripheral blood monocytes with SDF-1. Osteoclastogenesis was also determined after monocytes were co-cultured with rhSDF-1-stimulated RA synovial fibroblasts and CD4+ T cells.

Results: The expression of RANKL mRNA in RA synovial fibroblasts and CD4+ T cells was increased after SDF-1 stimulation. When RA synovial fibroblasts and CD4+ T cells were cultured with neutralizing antibody of TNF-a, the SDF-1-induced RANKL expression decreased, however, inhibition of IL-1b and IL-6 did not affect SDF-1-induced RANKL expression in both cell types. When CD14+ monocytes were cultured with SDF-1 in the absence of exogenous RANKL, the monocytes were differentiated into TRAP+ osteoclasts. Also, the monocytes were differentiated into TRAP+ osteoclasts when they were co-cultured with SDF-1-prestimulated RA synovial fibroblasts or CD4+T cells in the absence of exogenous RANKL.

Conclusion: SDF-1 induced osteoclastogenesis by up-regulating RANKL expression in RA synovial fibroblasts and CD4+T cells and this is mediated by TNF-a. The axis of SDF-1 and RANKL is a potential therapeutic target for bony destructive process in RA.

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Syndecan-4 Regulates Activation of WNT Signaling in Chondrocytes.

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Background/Purpose: Blockade of syndecan-4 (Sdc4) signaling protects mice from cartilage degradation in experimentally induced osteoarthritis (OA). Cartilage damage results in changes of chondrocyte phenotype induced by various signaling pathways including the activation of WNT signaling. Here, we hypothesized that Sdc4 modulates chondrocyte phenotype by the specific modulation of WNT signaling.

Methods: In vitro analyses were performed using neonatal wild type (wt) and Sdc4−/− chondrocytes, or a blocking Sdc4 antibody on wt chondrocytes. The influence of 100 ng/ ml WNT3a on glycosaminoglycan (GAG) production was analyzed using alcian blue staining of micromass cultures. The expression of chondrocyte marker genes (aggrecan, collagen 2, MMP13) was measured by quantitative RT-PCR. The effects of WNT3a on canonical

and noncanonical WNT signaling were analyzed using Western Blot detection of β-catenin, pLRP-6, pCamKII and pJNK and a TCF/LEF reporter assay. To investigate the in vivo relevance of the investigated pathways induction of OA in wt and Sdc4−/− mice was performed using the DMM model and stainings for β-catenin and pCamKII were performed.

Results: Micromass cultures revealed a higher basal GAG production by Sdc4−/− than wt chondrocytes. Furthermore, WNT3a stimulation led to a decrease in GAG in wt, which was not observed in Sdc4−/− chondrocytes. These findings were confirmed by a 10× higher basal production of aggrecan and collagen 2 in Sdc4−/− compared to wt chondrocytes. The expression of both genes was 10 fold increased by stimulation with WNT3a, whereas WNT3a led to a decrease in the expression of both genes in wt chondrocytes. Inverse results were found for MMP13, which was significantly less expressed in Sdc4−/− chondrocytes and was not upregulated upon WNT3a stimulation. Western blot analyses of canonical WNT signaling showed that β catenin is strongly reduced and not upregulated upon stimulation with WNT3a in Sdc4−/− chondrocytes. Confirming these findings we also found less phosphorylation of LRP6 and less activation of the TCF/Lef reporter upon WNT3a stimulation in Sdc4−/− chondrocytes. Noncanonical WNT signaling was increased in Sdc4−/− under basal conditions, but decreased upon WNT3a stimulation in Sdc4−/− and increased in wt chondrocytes. The same blockade of canonical and downregulation of noncanonical WNT signaling upon WNT stimulation were obtained by using a blocking Sdc-4 antibody. In vivo analyses of canonical WNT signaling confirmed the decreased basal activation and the missing increase after induction of OA in Sdc4−/− mice.

Conclusion: We conclude from our data that Sdc4 is a major regulator of cellular response to WNT through the prevention of the induction of canonical WNT signaling. Therefore, we suggest that the blockade of Sdc-4 protects from OA induced changes in chondrocyte phenotype by inhibiting WNT induced differentiation of chondrocytes.

Disclosure: **J. Bertrand**, None; **R. Stange**, None; **G. Nalesso**, None; **J. Sherwood**, None; **L. Godmann**, None; **F. Echtermeyer**, None; **F. Dell'Accio**, None; **T. Pap**, None.

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Long-Distance Physical Connections Between Chondrocytes; Cell-to-Cell Communication within Articular Cartilage.
Maria Dolores Mayan[1], Raquel Gago-Fuentes[1], Paula Carpintero-Fernandez[1], Patricia Fernandez-Puente[1], Purificacion Filgueira-Fernandez[1], Virgin Valiunas[2], Peter Brink[2], Gary Goldberg[3] and Francisco J. Blanco Garcia[1]. [1]Osteoarticular and Aging Research Group. Rheumatology Division, Biomedical Research Center (INIBIC). Hospital Universitario A Coruña, As Xubias de Arriba 84, 15006, A Coruña, Spain, [2]Department of Physiology and Biophysics. State University of New York, Stony Brook, New York, SC, [3]Department of Molecular Biology. Medical Center Drive, University of Medicine and Dentistry of New Jersey, Stratford, NJ

Background/Purpose: It is believed that chondrocytes in cartilage do not connect each other, as they are isolated inside their lacunae separated from each other by a distance between 5 to 60μm. In the same lacuna can co-exit several chondocytes interacting between them. However, how the chondrocytes from different lacuna interact between each other and timely respond to physical or chemicals stimuli, are largely unknown.

Methods: Scanning Electron Microscope. Immunofluorescence and Immunohistochemistry assays. For total RNA isolation: TRIZOL® method. Electrophysiology techniques: Dual Voltage-clamp methods, whole-cell/perforated patch experiments and study of glucose and oligonucleotides transference. Transwell co-culture system and mass spectrometry (LTQ Orbitrap). SILAC® Dulbecco's Modiffied Eagle's Medium containing L-lisina [$^{13}C_6$] and/or L-arginina [$^{13}C_6$, $^{15}N_4$]. Co-immunoprecipitation experiments. In-gel digestion of immunoprecipitated proteins separated by SDS-PAGE were analysed using the nano-liquid chromatography coupled to mass spectrometry (MALDI-TOF/TOF). The identification of proteins was performed using ProteinPilot™ 3.0 Software.

Results: We have found that articular chondrocytes have long cytoplasmic arms, between 5 to 200 μm in length, that travel across the ECM and physically connect the cytoplasm of cells located in distant lacuna. Our results suggest that chondrocytes communicate through gap junctions (GJ) channels form by different types of connexins. Patch-clamp methods demonstrate that cells interchange small molecules of nucleic acids through GJ channels form by Cx43. Transwell co-culture system combine with mass spectrometry

analysis have revealed that the cytoplasmic projections and GJ play a nutritional role by exchange of glucose and amino acids. On the other hand, alteration on connexin protein levels and longer cytoplasmic arms were found in cartilage from patients with osteoarthrosis (OA).

Conclusion: The results here presented demonstrated that cells in cartilage are physically connected and cell-to-cell communication occurs through GJ channels. These results will radically change the point of view of structural organization of cartilage, mechanotransduction, chondrocytes metabolism and cell signalling. Our results suggest that altered connexin channel functions are probably involved in the physiopathology of OA. These results will likely lead to the development of new therapeutic targets for OA.

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Role of Stromal Cell-Derived Factor-1 Alpha Through Smad and MAPK Pathway On Endochondral Ossification.
Gunwoo Kim[1], Seungwoo Han[1], Younkwan Jung[2], Eunju Lee[2], Hyeri Park[2], Shirine E. Usmani[3], Veronica Ulici[3] and Frank Beier[3]. [1]Daegu Fatima Hospital, Daegu, South Korea, [2]Fatima Research Institute, Daegu Fatima Hospital, Daegu, South Korea, [3]Schulich School of Medicine and Dentistry, London, ON

Background/Purpose: The main cellular events of articular chondrocytes during osteoarthritis are a loss of the traits as permanent cartilage, and a transition to hypertrophic chondrocytes responding to excessive stress. Persistant stress in an articular cartilage make the hypertrophied chondrocytes to be dead through apoptosis or form osteophytes through endochondral ossification. The research about molecular mechanisms controlling the endochondral ossification in the growth plate of bone can give us an important clue to understand the molecular mechanisms of osteoarthritis. Stromal cell-derived factor-1 alpha (SDF-1α) is elevated in joint fluid of osteoarthritis and is implicated in osteoarthritis, but it's exact function in chondrocyte biology or molecular mechanisms by which SDF-1α acts still remains unclear. In this study, we investigated the roles of SDF-1α on the endochondral ossification.

Methods: Primary chondrocytes and tibial explants from embryonic 15.5 day-old mice were cultured with PBS vehicle or recombinant mouse SDF-1α. Real-time PCR analysis was performed using Applied Biosystems 7900 HT Real-Time PCR System and TaqMan® Gene Expression Assays for *Sox9*, *Col2a1*, *Acan*, *MMP13, Col10a1*, *Runx2*. Western blot was performed with MMP13, Runx2, type 10 collagen, proliferating chondrocyte nuclear antigen (PCNA), SOX9, p-Smad1/5/8, p-ERK and p-p38. Organ culture tissues were stained with safranin O/fast green and alcian blue/alizarin red. Immunohistochemical analysis was also performed on tissue sections with Caspase3, MMP13, Runx2, type 10 collagen, PCNA and SOX9. For quantification of chondrocyte apoptosis and necrosis, cells were stained with FITC-conjugated annexin V and propidium iodide, and analyzed on a FACS Aria II.

Results: Primary chondrocyte cultures revealed that SDF-1α significantly increased the expression of *Acan*, and *Col10a1* (p$<$0.05). The master regulator gene of chondrocyte hypertrophy, *Runx2*, was also up-regulated in messenger RNA level by SDF-1α (p$<$0.05). SDF-1α increased the protein expression of Sox9, PCNA, Runx2, type 10 collagen. In addition, SDF-1α increased the phosphorylation of Smad1/5/8, Erk and p38 MAP kinase. The proportion of apoptotic cells which has Annexin V-FITC positive staining was 9.35 and 14.77% in untreated and SDF-1α treated cells, respectively. To gain further insights into the role of SDF-1α in endochondral ossification, we examined the effects of SDF-1α in tibia organ cultures. The length of tibias, compared with the controls, was significantly increased in SDF-1α treatment group (p$<$0.05). Immunohistochemical staining of organ cultures showed the expression of PCNA, the marker for chondrocyte proliferation and Sox9 markedly increased in chondrocytes of proliferating zone. In addition to proliferation marker, type 10 collagen, Runx2 and caspase3, were up-regulated in hypertrophic zone by SDF-1α.

Conclusion: Our findings reveal that SDF-1α has an effect on chondrocyte proliferation, hypertrophy and apoptosis by up-regulation of Sox9 and Runx2 through Smad and MAPK pathway during endochondral ossification.

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Serum Amyloid A Level in Knee Osteoarthritis: Systemic and/or Local Production and Pro-Inflammatory Properties On Human Chondrocytes and Fibroblast-Like Synoviocytes. Dominique de Seny[1], Gaël Cobraiville[1], Sophie Neuville[1], Edith Charlier[1], Biserka Relic[1], Florence Quesada Calvo[1], Olivier Malaise[1], Denis Malaise[2], Laurence Lutteri[3], Jean-Paul Chapelle[3] and Michel G. Malaise[1]. [1]GIGA Research - University of Liège - CHU Liège, Liège, Belgium, [2]University of Liège, Liège, Belgium, [3]Medical Chemistry - CHU Liège, Liège, Belgium

Background/Purpose: Knee osteoarthritis (OA) is a disease frequently seen in obese patients, but the relationship might be more linked to fat than to weight. A-SAA is an adipokine known to be produced by adipose tissue. Fat surrounding joints, fat within the synovium, as well as mesenchymal progenitor joint cell types might contribute to the presence of A-SAA in the joint cavity. The purposes of this work are: a) to analyse spontaneous production of A-SAA by synovial adipocyte (SA), chondrocytes and fibroblast-like synoviocytes (FLS); b) to detect A-SAA in the synovial fluid (SF) and serum of osteoarthritic patients; c) to analyse the consequences of A-SAA exposure on chondrocytes and FLS on cytokines and metalloproteinase (MMPs) production.

Methods: Synovial adipocytes, primary chondrocytes and FLS were isolated respectively from cartilage and synovial membrane obtained from knee OA patients during joint replacement. A-SAA expression level was studied by ELISA test. A-SAA levels in serum and synovial fluid were measured in knee OA (n=29) compared to matched healthy volunteers (n=35). Cytokines and MMPs were studied by ELISA test.

Results: Endogenous A-SAA secretion was observed by dedifferenciated chondrocytes and fat synovial explants. In primary chondrocytes and FLS, A-SAA was highly and selectively expressed in the presence of glucocorticoïds and in a less extent in the presence of IL-1β. A-SAA SF levels of knee OA patients were each time higher than corresponding serum levels. Both serum and SF A-SAA levels were correlated with the Kellgren-Lauwrence grades. Lastly, *in vitro*, exogenous A-SAA was capable to enhance cytokines (IL-6, IL-8, GRO-a, MCP-1) and MMPs (MMP-1, MMP-3, MMP-13) expression by human chondrocytes and FLS.

Conclusion: 1. A-SAA can be secreted by mesenchymal progenitor joint cell types: synovial adypocyte, chondrocyte and FLS. 2. However, although easily detected in the synovial fuid of osteoarthritis patients, A-SAA corresponding serum levels were each time higher suggesting a predominant systemic origin. 3. Both serum and SF levels of A-SAA were related to the severity of knee OA. 4. Systemic or local A-SAA production may act locally to enhance, at least *in vitro* cytokine and MMPs production. 4. A-SAA is therefore a relevant target for a tight metabolic control.

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Inhibition of WNT Signaling Pathway by Sclerostin Maintains Cartilage Homeostasis. Wafa Bouaziz, Thomas Funck-Brentano, Hilene Lin, Eric Hay and Martine Cohen-Solal. INSERM U606 Paris 7 University, Paris, France

Background/Purpose: Cartilage homeostasis is regulated by several mechanisms that influence the anabolic and catabolic tissue balance. Among them, the local activation of Wnt signaling pathway plays a major role in chondrocyte metabolism. Sclerostin, a Wnt inhibitor mainly produced by osteocytes, might regulate chondrocyte differentiation. Therefore, we aim to assess the role of Sclerostin in chondrocyte maintenance.

Methods: Primary murine chondrocytes, isolated from long bone epiphysis of 6 day-old mice, were cultured with or without Wnt3a and in the presence or absence of mouse recombinant Sclerostin (20ng/ml). Proteoglycan release induced by Wnt was quantified in the supernatant of chondrocytes by a colorimetric assay. Activation of the Wnt pathway was analyzed by the translocation of β-catenin (IF, TOP-GAL activity). Chondrocyte proliferation and apoptosis were investigated by BrdU and Tunel assays. The mRNA gene expression of anabolic and catabolic genes was quantified by RT-qPCR. We assessed the expression of Sclerostin in normal and osteoarthritic cartilage in mice with joint instability induced by partial meniscectomy (immunohistochemistry).

Results: The proteoglycan amount released in the chondrocyte culture supernatants was reduced by Wnt while it was rescued in the presence of Sclerostin. Wnt inhibited the gene expression of collagen type II (X18-fold), Sox9 (X140 fold) and Aggrecan (X90-fold) and increased the gene expression of metalloproteinases such as Adamts-4 (X5-fold), Adamts-5 (X5.5-fold), MMP3 (X7-fold) and MMP13 (X6.6-fold). In contrast, Sclerostin significantly prevented the increase of the catabolic genes induced by Wnt (X1.7-fold Adamts-4, $\times$ 1.6-fold Adamts-5, $\times$ 3.4-fold MMP3 and X4-fold MMP13) and rescued partially the expression of the anabolic genes ($\times$ 5- fold collagen type II, $\times$ 6-fold Sox-9 and X11-fold Aggrecan). Furthermore, Wnt enhanced the gene expression of collagen type X (X3-fold) which was abolished by Sclerostin (X1.6-fold). However, Sclerostin failed to exert any effect on the proliferation or the apoptosis of chondrocytes regardless of the presence of Wnt. Finally, we found that Sclerostin is expressed only in the calcified zone of the normal articular cartilage and this is increased after meniscectomy, suggesting that Sclerostin might participate to cartilage damage.

Conclusion: Herein, we showed that the inhibition of Wnt/β-catenin pathway by Sclerostin preserves chondrocyte maintenance by inhibiting chondrocyte catabolism and hypertrophy. These results further indicate the importance of Wnt antagonists in targeting cartilage degradation in OA.

Disclosure: **W. Bouaziz**, None; **T. Funck-Brentano**, None; **H. Lin**, None; **E. Hay**, None; **M. Cohen-Solal**, None.

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The Effects of Apremilast On Osteoclasts, Osteoblasts, and Osteocytes. Mary Adams and Peter Schafer. Celgene Corporation, Summit, NJ

Background/Purpose: Apremilast (APR), a small molecule specific inhibitor of phosphodiesterase 4, works intracellularly to modulate pro- and anti-inflammatory mediator production in both immune and non-immune cells. Here, the effects of APR on osteoclasts (OCL), osteoblasts (OBL), and osteocytes (OCY) were examined in vitro.

Methods: Human bone marrow mononuclear cells were differentiated into OCL using 10nM dexamethasone and 10nM vitamin D for 7 days. APR (0.1–10 μM) was added along with fresh medium on day 0 and day 3. OCL were stained for tartrate-resistant acid phosphatase 5 (TRAP5), and OBL were stained for alkaline phosphatase. OBL were differentiated into OCY using hydroxyapatite/tricalcium phosphate biphasic calcium phosphate ceramic particles (Graftys BCP), which was placed into polycarbonate filter well inserts and cell culture media changed every 3 days for a total of 28 days. Gene expression was measured by qRT-PCR for the following: receptor activator of nuclear factor kappa-B (RANK), RANK ligand (RANKL), sclerostin (SOST) and osteoprotegerin (OPG). Protein production was measured by enzyme-linked immunosorbent assay.

Results: In OCL cultures, the number of TRAP-5+ cells was reduced by APR by 21%, 49%, and 73% at 0.1 μM, 1 μM, and 10 μM, respectively. In the OCL cultures, APR significantly reduced the levels of sRANKL protein by 25%, 21%, and 38% at 0.1 μM, 1 μM, and 10 μM, respectively. APR 1 μM and 10 μM significantly inhibited RANK gene expression by 30% and 25%, respectively. Alendronate inhibited RANK gene expression by 77%. In OBL, APR reduced sRANKL protein levels by 25% at both 1 μM and 10 μM. Rolipram, alendronate, and sulfasalazine all had no significant effect on sRANKL protein levels in the OBL supernatants. In addition, APR significantly increased OPG protein levels by 42% at 0.1 μM. Overall, APR decreased the sRANKL/OPG protein ratio by 39%, 32%, and 40% at 0.1 μM, 1 μM, and 10 μM, respectively. By comparison, rolipram, alendronate, and sulfasalazine had no effect on the sRANKL/OPG ratio. In OCY, APR significantly reduced sRANKL production by 18%, 14%, and 17% at 0.1 μM, 1 μM, and 10 μM. APR also significantly reduced SOST protein levels by 16%, 20%, and 14% at 0.1 μM, 1 μM, and 10 μM.

Conclusion: These results demonstrate that APR inhibits osteoclastogenesis in vitro at clinically relevant concentrations (0.1–1 μM). This effect was associated with a decrease in sRANKL protein expression by OBL, but also may involve decreased RANK expression on the OCL. Since the osteoclastogenesis studied in this system was driven in part by dexamethasone, these findings indicate that APR may be useful for counteracting the bone catabolic effects of corticosteroids.

Disclosure: **M. Adams**, Celgene, 3; **P. Schafer**, Celgene, 3.

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Synovitis in Secondary Osteoarthritis Due to Rheumatoid Arthritis: A Proof-of-Concept Study.
Stefan Vordenbäumen[1], Tim Lögters[1], Philipp Sewerin[1], Thomas Pauly[2], Ellen Bleck[1], Paulina Philippski[1], Matthias Schneider[1], Michael Schädel-Höpfner[1] and Benedikt Ostendorf[1]. [1]Heinrich-Heine-University, Düsseldorf, Germany, [2]Rheinisches Rheumazentrum St. Elisabeth-Hospital, Meerbusch, Germany

Background/Purpose: Rheumatoid arthritis (RA) is characterized by considerable synovial inflammation which may result in secondary osteoarthritis (sOA). Primary OA (pOA) occurs in patients without predisposing disorders such as RA and displays varying degrees of synovial inflammation. Although it is conceivable that a major structural difference between sOA due to RA and pOA consists in synovial histology, direct research on such histological differences is limited. Moreover, the search for suitable biomarkers to distinguish OA subtypes is considered an important step in the search for medical treatments. We therefore investigated if synovitis in patients with sOA due to RA is different from pOA, and if it more closely resembles active RA.

Methods: Synovial tissue was collected and snap frozen at time of joint replacement in patients with (1) pOA (n = 8, hip), (2) sOA (defined as RA according to ACR/EULAR criteria plus OA in accordance with 2009 EULAR recommendations for diagnosis of knee OA (n = 4) or 1991 ACR criteria for hip OA (n = 3)), and (3) active RA without any signs of OA (n = 8 metacarpophalangeal joints; mean DAS28 5.2 ± 1.4) by arthroscopically guided biopsy or open synovectomy. Hematoxylin and eosin stained sections were used for determination of the Synovitis Score according to Krenn. Immunohistochemically stained sections were used for semiquantitative scoring or digital image analysis (% stained area) of CD68+ macrophages in a blinded fashion. Comparison of groups was by Kruskal-Wallis Test and Dunn's posthoc test. Correlations between methods of CD68 scoring were according to Spearman.

Results: High-grade synovitis was revealed by conventional histology in patients with sOA and RA (median scores: 6), but not in pOA where mild synovitis was predominant (median score 3; p = 0.012). This was largely due to the subscore on the inflammatory infiltrate with median scores of 3, 2, and 1 in sOA, RA, and pOA, respectively (p = 0.006), rather than subscores for lining layer hypertrophy (2, 2, 2.5; p = 0.013) or density of resident cells (1, 1.5, 2; p = 0.52). There was good agreement between semiquantitative scoring and digital image analysis for CD68 in all compartments (Spearman's R 0.85, 0.8, and 0.7 with p < 0.001 for lining, sublining, and total CD68 scoring, respectively). Significant differences between groups were observed in all compartments with the strongest effect in sublining CD68 staining (median stained area 35.6% vs. 15.3% and 2.9% in sOA, RA, and pOA; p = 0.0031). The difference to sOA in sublining CD68 staining was significant after posthoc analysis for pOA, but not RA. Receiver Operating Characteristic analysis confirmed sublining CD68 staining as an excellent marker to distinguish sOA due to RA from pOA (p = 0.026, AUC 0.96, LR 8).

Conclusion: Synovial tissue analysis reveals considerable inflammation in sOA due to RA. Both conventional histology and CD68 staining confirm that sOA is histologically distinct from pOA and more closely resembles active RA. Sublining CD68 is a suitable biomarker to distinguish both OA entities.

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Accumulation of CD34+ Hematopoietic Stem Cells in the Initial Inflammatory Human Fracture Hematoma Is Mediated Via Chemokine Receptor Type 3 Ligands.
Paula Hoff[1], Timo Gaber[1], Martin Hahne[1], Cindy Strehl[1], Katharina Schmidt-Bleek[1], Gerd R. Burmester[2], Gerhard Schmidmaier[3], Georg Duda[1], Carsten Perka[1] and Frank Buttgereit[4]. [1]Charité University Medicine, Berlin, Germany, [2]Charité - Universitätsmedizin Berlin, Berlin, Germany, [3]Heidelberg University Hospital, Heidelberg, Germany, [4]Charite University Medicine, Berlin, Germany

Background/Purpose: We have previously shown the early phase of human fracture healing to be characterized by hypoxia which promotes inflammation and chemoattraction. Hypoxia is also known to promote proliferation, survival and migration of different stem/progenitor cells like mesenchymal stem cells, endothelial progenitor cells or hematopoietic stem cells (HSC). However, the clinical relevance of hypoxia and inflammation in the early phase of fracture healing for HSC remains unclear.

To investigate immunological events in fracture healing, we quantified (i) CD34+ hematopoietic stem cells and (ii) inflammatory chemokines present in the early (<72h) human fracture hematoma (FH) at the fracture gap. To investigate the chronologic development, we also analyzed hematomas which resulted from the transection of the femur in patients receiving a total hip arthroplasty (THA). The THA-hematomas (THA-H) were defined as a model for fracture hematomas at time point 0h.

Methods: The proportion of HSC in the fracture hematoma from healthy patients (n=42) and patients receiving a THA (n=20) was analyzed by flow cytometry. Secreted factors were quantified by multiplex suspension array.

Results: A fracture destroys bone architecture and vascular network leading to bioenergetically restricted conditions such as hypoxia within the fracture hematoma. Although the cells present have to face those conditions, we were able to find a higher proportion of CD34+ hematopoietic stem cells in the FH as compared to THA-H (7.6±1.5 vs. 3.8±0.5 % of mononuclear cells) indicating proliferation and/or immigration of HSC in the FH. As CD34+ hematopoietic stem cells express CCR3, we investigated the concentrations of its ligands RANTES and Eotaxin. Indeed, both chemokines were present at significantly higher concentrations in the FH as compared to THA-H (RANTES: 16867±1632 vs. 9830±1397 pg/ml, p<0.01; Eotaxin: 327±76 vs. 125±15 pg/ml, p<0.001). We also identified the macrophage migration inhibitory factor (MIF) to be significantly increased in the FH (179431±28538 vs. 21751±2973 pg/ml, p<0.001).

Conclusion: Hypoxia and other bioenergetically adverse conditions in a FH contribute to the induction of inflammation, including the secretion of RANTES, Eotaxin and MIF. We suppose the high concentrations of RANTES and Eotaxin to facilitate the immigration of CD34+ HSC. The initial hypoxic conditions also mediate the secretion of the proinflammatory MIF which has been already shown to be important for successful fracture healing. Thus, the inflammatory microenvironment in the FH is among the crucial factors determining fracture healing.

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Tissue Engineering for Articular Cartilage Repair, Culturing Bone Marrow Mesenchymal STEM CELLS On Collagen and Heparan Sulphate Scaffolds.
Adela Helvia Martinez-Sanchez[1], Clara Sanjurjo-Rodriguez[1], Silvia Diaz-Prado[2], Emma Muiños[1], Isaac M. Fuentes[2], Francisco J. De Toro[2], Julia Buján[3] and Francisco J. Blanco[1]. [1]Osteoarticular and Aging Res. Lab. CIBER-BBN. Rheumatology Div. INIBIC-Complejo Hosp. Univ. A Coruña, A Coruña, Spain, [2]Osteoarticular and Aging Res. Lab. CIBER-BBN. INIBIC-University of A Coruña, A Coruña, Spain, [3]Department of Medical Specialties. University of Alcala de Henares, Madrid, Spain

Background/Purpose: The aim of this study was to evaluate the chondrogenic potential of bone marrow mesenchymal stem cells (BM-MSCs) grown on type I collagen and different concentrations of heparan sulfate (HS) scaffolds and the quality of the neosynthesized cartilaginous tissue.

Methods: BM-MSCs were cultured on scaffolds for 16 and 30 days. BM-MSCs were cultured in chondrogenic differentiation medium or DMEM with 20% FBS (Fetal Bovine Serum), in both cases plus 100 nM PTHrP (Parathyroid hormone-related protein). Chondrogenic differentiation and neosythesized cartilage quality were evaluated by histochemical and immunohistochemical analysis, transmission and scanning electron microscopy and molecular biology techniques. Culture supernatants were collected every 3–4 days to determine collagen presence by Elisa assays.

Results: Isolated cells were able to proliferate on type I collagen and various concentrations of HS scaffolds, showing high percentages of positivity for PCNA proliferation marker. Hematoxylin-eosin and Massonxs trichrome stainings showed that BM-MSCs proliferated better when cultured in chondrogenic medium than in growth medium (DMEM 20%). Stimulated cells spread throughout the biomaterials in high percentage, showing a good morphology at both times as well as a wide distribution of ECM. They showed high percentages of positivity for safranin O, Toluidine Blue, aggrecan and type II collagen. Degradation of biomaterials was gradual, as fibers were replaced with ECM. Molecular analysis indicated the *expression*

of cartilage-*characteristic* genes, such as Col II and Sox9. Scanning and transmission electron microscopy confirmed cell presence and ECM synthesis after 16 and 30 days of culture. Cells showed a high number of distended rough endoplasmic reticulum cisternae, electrodense vesicles and mitochondria. Finally, culture supernatants analysis showed the release of collagen in most of the time periods studied, confirming their differentiation and cartilage ECM characteristic compounds.
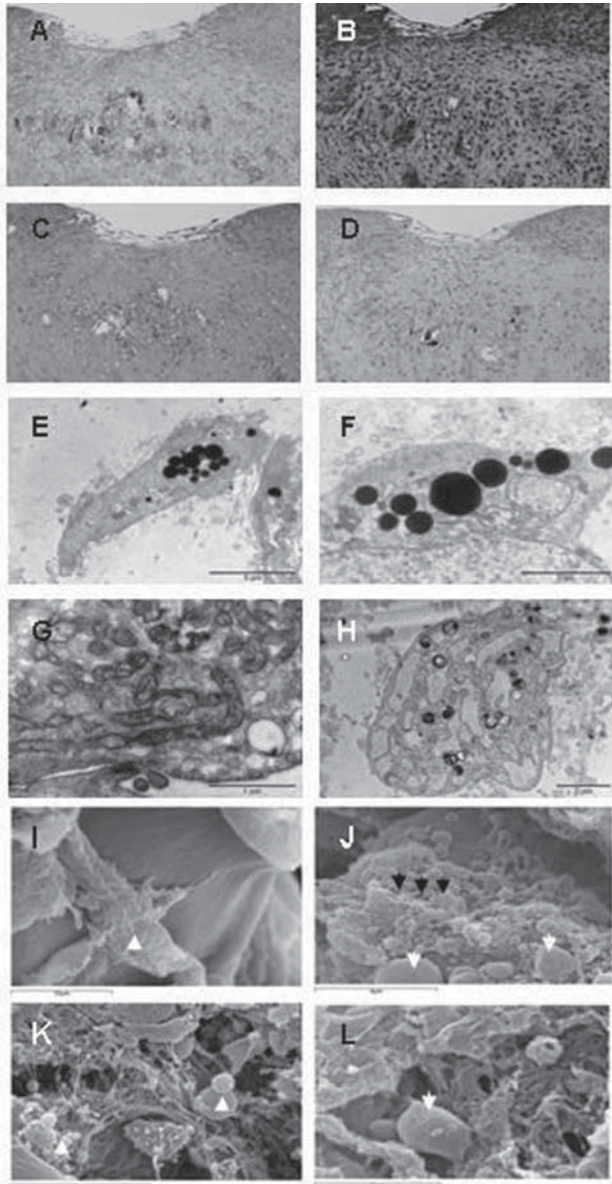
Figure 1. Analysis of BM-MSCs cultured over type I collagen and HS scaffolds on chondrogenic medium: Histochemical and immunohistochemical staining after 16 days in culture (A-D); transmission electron microscopy analysis after 16 days (E, F) and 30 days (G, H) in culture; scanning electron microscopy after 30 days in culture (I-L). White arrows: cells. Black arrows: ECM.

Conclusion: Our data demonstrated that type I collagen and HS scaffolds were optimal for BM-MSCs growth and differentiation towards chondrocytes-like cells after both 16 and 30 days in chondrogenic medium. Our scaffolds favour phenotypic maintenance of the differentiated cells and synthesis of cartilage-like tissue. *Acknowledgements:* Opocrin, S.P.A; CIBER BBN CB06-01-0040; SAI-UDC; P. Esbrit (Fundación Jiménez Díaz).

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The Spatial Energy Expenditure Configuration and Possible Applications in an Experimental Model of Arthritis. Susanne Klatt[1] and Rainer H. Straub[2]. [1]Laboratory of Exp. Rheumatology and Neuroendocrine Immunology, University Hospital, Regensburg, Germany, [2]University Hospital Regensburg, Regensburg, Germany

Background/Purpose: An autoimmune response with differentiation and proliferation of immune cells and the subsequent tissue-directed inflammatory process in the symptomatic phase of the disease are very energy-demanding. As recent calculations demonstrate, the activated immune system needs approximately 20% of the basal metabolic rate. Thus, energy regulation and cellular bioenergetics are of outstanding importance to serve a stimulated immune system. During inflammation, particularly during the chronic process of inflammation in long standing inflammatory diseases like rheumatoid arthritis, a reallocation of energy-rich fuels to the activated immune system is necessary in order to nourish the inflammatory process. Energy consumption and, thus, ATP generation can be measured by studying the consumption of oxygen. The energy expenditure in different organs at different time points has never been investigated during immunization (the symptomatic phase of the disease). We want to find out if, and how the energy expenditure in different organs changes during the course of experimental arthritis.

Methods: A new technique termed "spatial energy expenditure configuration (SEEC)" was developed to demonstrate bodily areas of high energy demand. SEEC is based on removal of tissue during the course of arthritis, and subsequent determination of oxygen consumption. For that purpose, small weighed pieces of the respective organ with a size of 4 mm are placed in 24-well multidishes with integrated oxygen sensors, which allows for non-invasive detection of oxygen consumption *in vitro*. SEEC was established in healthy control animals, arthritic animals and animals that underwent prior sympathectomy. The model of type II collagen arthritis in DBA/1 mice is used in order to develop an arthritic-specific SEEC. We determined the oxygen consumption in spleen, thymus, draining lymph nodes, liver, kidney, brain and knee joints during the course of experimental arthritis for 70 days. The values are given in μmol O_2/l/h and refer to 4 mm sized pieces as percentage of mouse weight.

Results: Concerning the draining lymphoid nodes, we were able to observe a marked increase in oxygen consumption (200 %) during the course of arthritis. Other investigated organs like liver or kidney decrease their oxygen consumption (control vs. arthritic animals).

Conclusion: The SEEC technique enables us to identify locations of high energy demand that are involved in the initiation and continuation of the autoimmune process in an animal model of arthritis. We identified the draining lymph nodes as target organ of the sympathetic nervous system, which will be further investigated. The technique will be applied to other chronic inflammatory disease models in order to detect further participating organs.

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Human Chondrocyte Dedifferentiation Is Accompagnied by CD105 Endoglin Expression, ALK-1/Smad1/5 Phosphorylation and Leptin Production - Stimulation by Prednisolone and Aldosterone Through the Glucocorticoid Receptor. Olivier Malaise, Biserka Relic, Mustapha Zeddou, Edith Charlier, Florence Quesada Calvo, Sophie Neuville, Dominique de Seny and Michel G. Malaise. GIGA Research - University of Liège - CHU Liège, Liège, Belgium

Background/Purpose: Leptin, mainly produced by the adipose tissue including fat neighboring the joint, is considered as pro-inflammatory in osteoarthritis (OA). Normal cartilage does not express leptin, while OA cartilage is a potential producer. We recently showed that joint derived-cells such as synovial fibroblasts (SF), but also bone marrow mesenchymal stem cells, were able to spontaneously produce leptin in vitro, strongly enhanced by glucocorticoids (prednisolone and dexamethasone) involving the ALK-1/Smad1/5 pathway as inducer and the ALK-5/Smad2 pathway as inhibitor. In this work, we have tested isolated human chondrocytes (CH) for leptin, leptin receptor (Ob-R) and balance ALK-5/Smad2 - ALK-1/Smad1/5, during dedifferentiation process. Secondly, we have studied if the glucocorticoid prednisolone and the mineralocorticoid aldosterone were able to induce leptin and Ob-R expression as well as the involvement of the glucocorticoid receptor (GR) or/and mineralocorticoid receptor (MR).

Methods: Humain CH were obtained during joint replacement. To detect

surface antigens, cells were immunolabelled with the following anti-human antibodies: CD90-APC, CD105–PE, CD73-PE and analysed on a FACS-CANTO with the CellQuest software. Cells were stimulated with pred-nisolone, aldosterone, mifepristone (GR inhibitor), spironolactone and epler-onone (MR inhibitors) or TGF-β1. Leptin was determined by ELISA, while Ob-R expression, Smad1/5 phosphorylation, Smad2 phosphorylation, ALK-1 and ALK-5 were determined by Western blot.

Results: 1. Primary (PCH) and dedifferentiated (DCH) chondrocytes were similarly positive for CD90 (98.5% $\pm$ 1.5 and 99.4% $\pm$ 0.3, respectively) and CD73 (84.9% $\pm$ 24 and 98.9 $\pm$ 0.2, respectively), whereas DCH significantly increased their CD105 (endoglin) expression (33.7% $\pm$ 21 and 68.6% $\pm$ 17.8, P$=$0,004). **2.** PCH did not produce leptin nor expressed Ob-R. Opposite, DCH significantly expressed leptin and Ob-R. Both leptin and Ob-R expressions were markedly induced by prednisolone. TGF-β1 signifi-cantly downregulated prednisolone-induced leptin and Ob-R. With chondro-cyte dedifferenciation, ALK-5/Smad2 phosphorylation was progressively decreasing, while ALK-1/Smad1/5 phosphorylation was increasing. **3.** Aldo-sterone, as prednisolone, significantly induced leptin and Ob-R expression in DCH, both stimulations significantly downregulated with the GR inhibitor mifepristone, but not with MR inhibitors spironolactone and eplerenone.

Conclusion: 1. PCH expressed low levels of CD105 endoglin, exhibited an ALK-5/Smad2 phosphorylation and did not produce leptin nor Ob-R **2.** On the contrary, DCH significantly increased their capacity to express CD105 endoglin, exhibited an ALK-1/Smad1/5 phosphorylation, and spontaneously produced leptin and Ob-R. **2.** Leptin and Ob-R expressions were inhibited by TGF-β1, but markedly increased by the glucocorticoid prednisolone and the mineralocorticoid aldosterone. **4.** Prednisolone and aldosterone increased leptin and Ob-R expressions through GR but not MR stimulation.

Disclosure: O. Malaise, None; **B. Relic**, None; **M. Zeddou**, None; **E. Charlier**, None; **F. Quesada Calvo**, None; **S. Neuville**, None; **D. de Seny**, None; **M. G. Malaise**, None.

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Phosphodiesterase 4 Expression in Rheumatoid Arthritis Synovium and Anti-Inflammatory Effects of Apremilast On Synovial Fibroblasts. Lei Wu, Mary Adams, Stacey Parton and Peter Schafer. Celgene Corporation, Summit, NJ

Background/Purpose: Apremilast (APR), a small molecule specific inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate pro- and anti-inflammatory mediator production in both immune and non-immune cells. The expression pattern of the major PDE4 enzymes was studied in rheumatoid arthritis (RA) synovium, in normal and RA synovial fibroblasts (RASF), and the effects of APR on the production of major destructive proteases by RASF were examined.

Methods: PDE4 protein expression was measured by semiquantitative immunohistochemistry (IHC) in synovium from individuals with RA (n=3) or normal controls (n=2). Quantitative analysis of PDE4 protein expression in normal (n=3) and RASF (n=3) was conducted using an iCyte Laser Scanning Cytometer. Gene expression in normal synovial fibroblasts (n=3), RASF (n=3), peripheral blood mononuclear cells from RA (n=10) and normal controls (n=10) was measured by qRT-PCR. RASF cell cultures (n=3) were treated with 0.1–10 μM APR and then stimulated with 10 ng/mL IL-1β, TNF-α, IL-17, or IL-6 for a total of 24 hours, then supernatants were collected for analysis of matrix metalloproteinase (MMP)1, MMP13, MMP14, and cathepsin K by ELISA.

Results: IHC staining of synovial samples showed that, compared with normal samples, the superficial synoviocytes and subsynovial histiocytes in RA samples had more prevalent and more intense staining of PDE4A, PDE4B, and PDE4D. PDE4B staining was slightly higher in fibroblasts from RA patients than controls, while PDE4D staining was slightly lower. Laser scanning cytometry of normal synovial fibroblasts and RASF showed similar strong cytoplasmic staining of PDE4A in normal and RA samples. PDE4B showed abundant cytoplasmic staining, with 45% higher staining in RASF compared with controls (p<0.01). PDE4D showed moderate to strong cytoplasmic staining in normal samples, but 45% weaker expression in RASF samples (p<0.05). qRT-PCR analysis of PDE4A and PDE4B gene expres-sion was similar in RASF and controls, but PDE4D gene expression was 60% lower in RASF compared with controls (p<0.01). In RASF cell cultures stimulated with IL-1β or TNF-α, APR significantly inhibited MMP1 and MMP14 production, while in the IL-17- or IL-6-stimulated cultures, no significant inhibition of these proteases was observed.

Conclusion: Overall, PDE4 protein expression was stronger in RA vs. normal synovium, largely due to increases in superficial synoviocytes, subsynovial histiocytes, and lymphoplasmacytic cells. In RASF, there is a

shift in expression away from PDE4D toward PDE4B, and APR is capable of inhibiting MMP production in response to the JAK-independent stimuli, IL-1β and TNF-α. This study provides the preclinical rationale for using APR in RA.

Disclosure: L. Wu, Celgene, 3; **M. Adams**, Celgene, 3; **S. Parton**, Celgene, 3; **P. Schafer**, Celgene, 3.

ACR Poster Session A
Epidemiology and Health Services Research:
Epidemiology and Outcomes of Rheumatic Disease I
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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The Validity of the Diagnosis Inflammatory Arthritis in Primary Care.
Markus M.J. Nielen[1], Jennie Ursum[1], François G. Schellevis[2] and Joke C. Korevaar[1]. [1]NIVEL (Netherlands Institute for Health Services Research), Utrecht, Netherlands, [2]VU University Medical Centre, Amsterdam, Nether-lands

Background/Purpose: Large population-based databases, such as elec-tronic medical records (EMRs) from patients in primary care, are useful data sources to investigate morbidity and health care utilization in patients with chronic diseases. These databases make it possible to study large groups of patients with the whole range of disease severity in a representative popula-tion, including control groups. In many countries, general practitioners (GPs) have a gatekeeper role for access to specialized care and therefore their EMRs include a complete record of all morbidity of their patients using a uniform methodology. Despite these advantages, EMRs include diagnoses which are usually not validated. In this study we investigated the validity of the diagnosis inflammatory arthritis (IA) in primary care based records.

Methods: Five general practices participating in the Netherlands Infor-mation Network of General Practice (LINH) were visited to collect diagnostic information. EMRs of 219 patients with a diagnostic code of IA (ICPC L88) in the LINH database were systematically reviewed on additional character-istics which are not routinely extracted for the LINH database: free text regarding contacts, prescriptions, medical history, referrals and correspon-dence with medical specialists. Based on coded and free text fields, all patient were categorized in one of the following groups: 1) IA, 2) osteoarthritis (OA), 3) gout, or 4) other diagnosis. These results were used to develop selection criteria to distinguish IA from non-IA in patients with all routinely available information in the LINH database.

Results: From the 219 patients diagnosed as IA in the database, the diagnosis IA was confirmed in 155 patients (70.8%), 18 patients were classified with OA (8.2%), 12 patients with gout (5.5%) and 34 patients with another diagnosis (15.5%). With these findings we developed selection criteria to include IA patients solely based on coded fields, starting with a first selection based on ICPC-code L88, followed by three sequential steps: 1) a repeat prescription for a disease-modifying antirheumatic drug (DMARD) or biological agent, 2) at least four contacts or one episode with a diagnostic code for IA, combined with at least two prescriptions (excluding DMARDs/ biological agents) with the IA diagnostic code, and 3) age at diagnosis $\leq$ 61 years. With these criteria it was not possible to distinguish between IA and OA patients with probable IA. Applying the selection criteria, resulted in a group of 139 IA patients including 77,7% IA patients and 7,9% OA patients with probable IA.

Conclusion: Based on additional diagnostic information, the diagnosis IA from EMRs of patients in primary care is sufficiently valid when using the proposed selection criteria. Since the group of IA patients still contain some patients without an IA related diagnosis, effects from studies with IA patients in primary care could be underestimated.

Disclosure: M. M. J. Nielen, None; **J. Ursum**, None; **F. G. Schellevis**, None; **J. C. Korevaar**, None.

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Comparison of Decision Rules for Identifying Patients with Rheumatoid Arthritis (RA) in Administrative Healthcare Databases. John G. Hanly, Kara Thompson and Chris Skedgel. Dalhousie University and Capital Health, Halifax, NS

Background/Purpose: Identification of RA cases in administrative healthcare databases is used to estimate disease frequency, healthcare utili-

zation and cost for RA. However, the optimal methodology for achieving this is unclear. Our aim was to examine and validate a variety of decision rules which can be applied to administrative databases to identify patients with RA.

Methods: The study was conducted at a single academic medical center and utilized administrative health care data from a geographic area of approximately 1 million people who had access to a universal healthcare system. A retrospective cohort study was performed through the Population Health Research Unit at our institution and utilized data from existing administrative databases. These included information on hospital discharges and physician billings over a 10 year period. Each RA study subject was matched by age and gender to randomly selected control subjects in the same datasets but without a diagnosis of RA or other inflammatory arthropathies. A total of 7 decision rules, some derived from previous studies, were applied to the administrative data to identify RA cases. The sensitivity, specificity, overall accuracy, positive (PPV) and negative (NPV) predictive values of these rules was compared to the diagnosis of a rheumatologist in the academic medical center as determined by chart review.

Results:

Decision Rule	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
#1 MacLean	87.6 (83.9, 90.7)	34.0 (27.7, 42.8)	71.9 (44.3, 64.0)
#2 MacLean/Lacaille	77.7 (73.2, 81.8)	58.3 (50.3, 66.0)	72.0 (44.9, 59.9)
#3 Shipton	89.1 (85.6, 92.0)	38.0 (30.6, 46.0)	74.0 (49.5, 69.1)
#4 Hospitalization	26.4 (22.1, 31.1)	94.5 (89.8, 97.4)	46.6 (30.7, 39.8)
#5 Rheumatologist	92.7 (89.7, 95.1)	31.9 (24.8, 39.6)	74.7 (53.5, 75.3)
#6 Combination	94.8 (92.1, 96.8)	22.7 (16.5, 29.9)	73.4 (51.1, 77.1)
#7 Single admin	96.6 (94.3, 98.2)	17.8 (12.2, 24.5)	73.2 (52.9, 82.4)

Decision Rule	PPV (95% CI)	NPV (95% CI)
#1 MacLean	76.1 (71.9, 80.0)	54.3 (44.3, 64.0)
#2 MacLean/Lacaille	81.5 (77.2, 85.4)	52.5 (44.9, 59.9)
#3 Shipton	77.3 (73.1, 81.1)	59.6 (49.5, 69.1)
#4 Hospitalization	91.9 (85.2, 96.2)	35.2 (30.7, 39.8)
#5 Rheumatologist	76.3 (72.2, 80.1)	65.0 (53.5, 75.3)
#6 Combination	74.4 (70.3, 78.2)	64.9 (51.1, 77.1)
#7 Single admin	73.6 (69.5, 77.4)	69.0 (52.9, 82.4)

Conclusion: The performance of decision rules for the identification of RA cases in administrative healthcare databases in variable and should be considered when comparing data across studies. This variability may also be used to advantage in study design when, for example, either sensitivity or specificity is the most critical issue for different population health research questions.

Disclosure: J. G. Hanly, None; **K. Thompson**, None; **C. Skedgel**, None.

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Use of Health Plan Data to Assess Feasibility of Large Pragmatic Clinical Trials in Rheumatoid Arthritis. Jeffrey Curtis[1], Lang Chen[1], Fenglong Xie[1], Jie Zhang[1], Kenneth G. Saag[2], Stacey Cofield[3], Kevin L. Winthrop[4], Nicole C. Wright[1] and Elizabeth S. Delzell[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Univ of Alabama at Birmingham, Birmingham, AL, [4]Oregon Health & Science University, Portland, OR

Background/Purpose: Large pragmatic clinical trials (PCTs) are increasingly used to conduct comparative effectiveness research (CER). PCTs typically have simple inclusion/exclusion criteria and hard outcomes (e.g. hospitalized infection, death) but can be challenging to conduct due to the large number of patients required. In the context of planning a safety PCT of the live zoster vaccine in older rheumatoid arthritis (RA) patients receiving anti-TNF therapy, we evaluated the use of various databases to assess the feasibility of recruiting the 4,000 patients needed for the trial (based upon sample size calculations required for 80% power) and to facilitate rheumatology site selection.

Methods: Using multiple health plan and registry databases (e.g. 100% sample of Medicare patients in 2009; younger RA patients enrolled in a commercial insurance health plan), we identified RA patients age >= 50 on the basis of physician diagnoses and receipt of received anti-TNF therapy in the last 90 days of 2009. Extrapolations were made to estimate the prevalence of anti-TNF use for patients whose pharmacy coverage data was not present in the available databases.

These eligible individuals were linked to individual rheumatologists (e.g. using National Provider Identification numbers) and cross referenced against multiple sources of information (e.g. FDA 1572 registry, known participation

in any U.S. RA registry or consortium) that) that allowed identification of rheumatologists with research experience. Rheumatologists were grouped together into practices (offices) using billing information, and offices were sorted by size based upon having the greatest to the least number of eligible patients. The number of rheumatologist offices needed to fully recruit to the needed sample size of 4,000 older RA patients on anti-TNF therapy was plotted as a function of the hypothesized patient recruitment rate (e.g. 25%, 33%, 50%).

Results: More than 150,000 RA patients receiving anti-TNF therapy at the end of 2009 were identified and grouped into the rheumatologists' offices at which they received care. The number of eligible RA patients was plotted for the largest 100 rheumatologists' offices (Figure, solid line). A majority of the largest offices had evidence that they participated in research, as evidence by the dotted line being almost superimposed with the solid line for the first 6000+ patients). Even with a participation rate that was < 30%, fewer than 40 rheumatologist offices with a prior history of clinical research would be required in order to successfully recruit the proposed PCT.
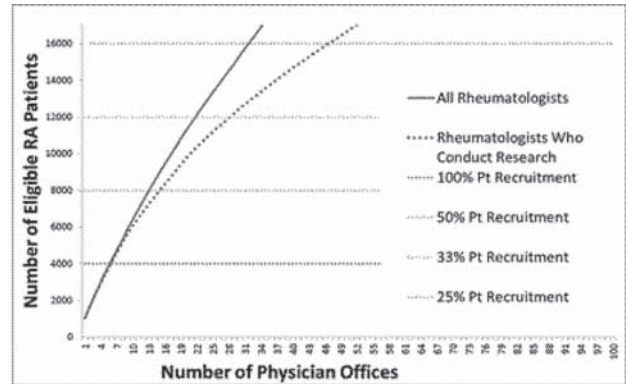
Conclusion: Large health plan and registry databases appear useful to assess feasibility of large pragmatic trials and to assist in selection of rheumatology sites with the greatest number of eligible patients. This novel approach is applicable to trials with simple inclusion/exclusion criteria that can be readily assessed in these data sources.

Disclosure: J. Curtis, Roche/Genetech, UCB< Centocor, Corrona,Amgen, Pfizer, BMS, Crescendo, Abbott, 2, Roche/Genetech,UCB, Centocor, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abbott, 5; **L. Chen**, None; **F. Xie**, None; **J. Zhang**, None; **K. G. Saag**, AHRQ, NIH/NIAMS, 2, Amgen;Abbott;Ardea:Lilly:Merck:Novartis: Regeneron:Savient:URL, 5, NOF;ACR, 6; **S. Cofield**, Teva Neruoscience, Centocor Ortho-Biotech Svcs LLC, Medimmune, american Shoulder and Elbow Society, Consortium of Multiple Sclerosis Centers, and Pythagorus, Inc, 5; **K. L. Winthrop**, Pfizer Inc, 5, Pfizer Inc, UCB, Abbott, Amgen, 2; **N. C. Wright**, Amgen, 2; **E. S. Delzell**, Amgen, 2.

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Accuracy of Canadian Health Administrative Databases in Identifying Patients with Rheumatoid Arthritis Seen by Rheumatologists. Jessica Widdifield[1], Sasha Bernatsky[2], J. Michael Paterson[3], Karen Tu[5], Ryan Ng[3], J. Carter Thorne[4], Janet E. Pope[5] and Claire Bombardier[1]. [1]University of Toronto, Toronto, ON, [2]Research Institute of the McGill University Health Ctre, Montreal, QC, [3]Institute for Clinical Evaluative Sciences, Toronto, ON, [4]Southlake Regional Health Centre, Newmarket, ON, [5]Western University of Canada, St. Joseph's Health Care, London, ON

Background/Purpose: In a predominantly universal single-payer health system, Canadian health administrative data are a valuable tool and increasingly used for research. Few studies have rigorously evaluated the accuracy of administrative data for identifying patients with rheumatoid arthritis (RA). The aim of this study was to validate administrative data algorithms to identify RA in the Canadian province of Ontario.

Methods: We performed a retrospective chart abstraction study among a random sample of 450 patients (unselected by diagnoses), from 18 rheumatologists. Using rheumatologist-reported diagnosis as the reference standard, the RA and non-RA patients were then linked to administrative data to validate different combinations of physician billing diagnoses (P), hospitalization diagnoses (H) and pharmacy (drugs dispensed) data (Rx) to estimate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in differentiating RA from non-RA patients.

Results: 149 rheumatology patients were classified as RA and 301 as

non-RA based on our reference standard definition. Most patients were female (77% RA cases; 65% non-RA cases) and the mean (SD) age for RA cases and non-cases was 62 (14) and 58 (17) years, respectively. Among non-RA cases, the most prevalent diagnoses were osteoarthritis (45%), seronegative spondyloarthropathies (19%) and connective tissue diseases (19%). Test characteristics of selected algorithms tested are reported in Table 1. Overall, using any physician-billing algorithms, sensitivity was very high (94–100%). Specificity and PPV were modest to excellent and increased when algorithms required multiple RA claims or claims by a specialist. There was a slight increase in sensitivity and decrease in specificity and PPV as the observation window for multiple billing diagnoses increased from 1 to 2 years. The addition of RA drugs (disease-modifying agents, biologics, or systemic steroids) in our algorithm had little impact on sensitivity but decreased both specificity and PPV.

Table 1. Test characteristics of selected algorithms

Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1 H ever	22	96	75	72
1 P ever	100	60	55	100
2 P in 1 year, any physician	98	77	68	99
2 P in 2 years, any physician	99	76	67	99
2 P in 3 years, any physician	99	75	66	99
3 P in 1 year, any physician	95	86	77	97
3 P in 2 years, any physician	97	82	73	98
3 P in 3 years, any physician	97	81	72	98
1 P ever by a specialist	99	77	68	100
2 P in 1 year at least 1 P by a specialist	98	83	74	99
2 P in 2 years at least 1 P by a specialist	99	82	73	99
2 P in 3 years at least 1 P by a specialist	99	81	72	99
3 P in 1 year at least 1 P by a specialist	95	88	80	97
3 P in 2 years at least 1 P by a specialist	97	86	77	98
3 P in 3 years at least 1 P by a specialist	97	85	77	98
1 H or 3 P in 1 year at least 1 P by a specialist	95	87	78	97
1 H or 3 P in 2 years at least 1 P by a specialist	97	85	76	98
1 H or 3 P in 3 years at least 1 P by a specialist	97	84	75	98
1 P AND 1 Rx	97	68	63	97
2 P AND 1 Rx	97	77	70	98

H: Hospitalization code; P=physician diagnostic code; Specialist = rheumatologist, internal medicine, orthopedic surgeon; Rx: oral corticosteroid, disease-modifying anti-rheumatic drug (DMARD) or biologic.

Conclusion: This study has demonstrated the accuracy of administrative data algorithms for identifying RA. We found that for RA patients that have seen a rheumatologist, physician-billing algorithms are highly sensitive in identifying these patients. Our findings suggest that pharmacy data do not improve the accuracy in identifying RA. One potential limitation is that our sample was drawn from rheumatology clinics, and thus our estimates may not be generalizeable on the population level. However, ongoing work to validate these algorithms in a random sample of 7500 patients from the general population is being done to further support our findings.

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A Validated Mathematical Model Using Electronic Health Records to Identify Rheumatoid Arthritis Patients for Observational Studies. Aarat M. Patel[1], Ilinca D. Metes[2], Larry W. Moreland[3], Melissa Saul[3], Stephen R. Wisniewski[4] and Marc C. Levesque[3]. [1]Univ of Pittsburgh Med Ctr/Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA

Background/Purpose: To develop and validate a search algorithm with a high specificity and sensitivity to identify rheumatoid arthritis (RA) patients in a large health care system linked by an electronic health record (EHR) system.

Methods: Records from the Medical Archival Retrieval System (MARS) at the University of Pittsburgh Medical Center (UPMC) were used to identify potential RA patients. We searched the UPMC MARS system for subjects with a 714.0 International Classification of Diseases, 9th revision (ICD-9) code and used a recursive partitioning method to develop a search algorithm for the identification of RA patients; the recursive partitioning method used the 714.0 ICD-9 code and tested 35 additional variables (serology, inflammatory markers, medications and specific words in physician notes). At each step during the development and validation of the algorithm, patients were classified by the algorithm into those likely or unlikely to have RA and representative sets of these patient records were reviewed to determine whether subjects met ACR/EULAR RA classification criteria.

Results: We initially analyzed the effect of the clinical setting (inpatient vs. outpatient rheumatology clinic) on the identification of RA patients. For inpatient subjects, there was a low PPV of a 714.0 ICD-9 code for the identification of RA patients (39.0%) whereas for outpatient-rheumatology subjects there was a high PPV of a 714.0 ICD-9 code for the identification of RA patients (87.3%), (n=95, p<0.0001; Fisher's exact test). When the records of outpatient-rheumatology patients with and without a 714.0 ICD-9 code were analyzed (N=400), the sensitivity, specificity, PPV and NPV of a 714.0 ICD-9 code was 98%, 88%, 87% and 98%, respectively. Using recursive partitioning a 3 variable algorithm was identified 1.) 714.0 ICD-9 code, 2.) ratio of the words "rheumatoid arthritis" per rheumatology visit and 3.) ratio of "RA" per rheumatology visit improved the specificity for identifying RA patients. The sensitivity, specificity, PPV and NPV of the algorithm was 93%, 95%, 94% and 95%, respectively (n=400). Validation of this algorithm with analysis of an additional 400 subjects produced similar results (95%, 96%, 96%, 95%, respectively). Using this algorithm to analyze all unique outpatient-rheumatology patients in the 2009 calendar year (n=5,859) resulted in the identification of 1,495 RA patients. The final validation step with a sample of these subjects (n=400) resulted in a sensitivity, specificity, PPV and NPV of 93%, 96%, 93% and 96%, respectively.

Conclusion: The ICD-9 code for RA (714.0) alone was not reliable for identifying RA patients in the inpatient setting and had suboptimal specificity in the outpatient rheumatology setting. We developed and validated a simple algorithm using recursive partitioning that used 3 variables to identify RA patients. This simple algorithm, which is now validated for an entire calendar year, represents a substantial improvement in terms of sensitivity and specificity over existing published algorithms. Using an EHR and this electronic search algorithm will enable large-scale comparative effectiveness studies on the treatment and management of RA in "real-world" clinical settings.

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A British Survey of Time to Presentation and Treatment of Rheumatoid Arthritis in Subjects of Black and Minority Ethnic Origin. Sonia Panchal[1], Ash Samanta[1], Arumugam Moorthy[1], Sawson Hayat[2], Ira Pande[2], Adewale O. Adebajo[3] and Kuntal Chakravarty[4]. [1]University Hospitals of Leicester, Leicester, United Kingdom, [2]Nottingham University Hospitals, Nottingham, United Kingdom, [3]Academic Rheumatology Group, D, Sheffield, United Kingdom, [4]University of Bedfordshire Post Graduate Medical School, Romford, United Kingdom

Background/Purpose: National guidelines mandate urgent referral of rheumatoid arthritis (RA) for specialist treatment if more than three months from symptom onset; initial combination therapy with disease modifying anti-rheumatic drugs (DMARDs) and only if not appropriate, monotherapy with rapid escalation[1]. A national audit of patients with RA conducted by The British Society for Rheumatology (BSR) showed that there were considerable delays from symptom onset to referral, from referral to specialist review, and initiation of DMARD therapy[2]. There were also wide variations regionally and a perception that there may be a differential between black and minority ethnic (BME) groups in terms of time of onset of symptoms to referral to a specialist centre and starting DMARDs. This study aimed to investigate the above features in centres that are geographically located within areas containing a high BME population and to compare this with the white Caucasian population.

Methods: Four centres were identified based on a high local BME population. Data were collected prospectively for potential time delays in the following areas: symptom onset to GP (general practice) consultation; GP to specialist referral; referral to specialist review; diagnosis to DMARD treatment, combination therapy, and biologic therapy. All consecutive BME and Caucasian RA patients on DMARDS attending outpatient clinics were included over an 8 week period.

Results: In total 189 patients were analysed. 111 (59%) were Caucasian vs. 78 (41%) BME (60 (77%) Asian, 2 (3%) Afro-Caribbean). 146 (77%) were female with an average age between 50–59 years, and average disease duration of 6–10 years. 30 (38%) of the BME group compared with 40 (36%) of the Caucasian group had more than six-months time delay from symptom onset to specialist referral. Time from referral to specialist review greater than three months was 10 (13%) BME group vs. 21 (19%) Caucasian group. 16 (21%) BME group vs. 18 (16%) Caucasian group had a delay of more than three months from diagnosis to initiation of DMARD therapy. Interestingly, 58 (74%) of the BME group had monotherapy in comparison to 79 (71%) of the Caucasian group. 17 (22%) of the BME group had biologic therapy with an average of 2–5 years post diagnosis, whilst 20 (18%) of Caucasians had biologic therapy.

Conclusion: Our results importantly highlight a significant delay in time from presentation and initiation of treatment for RA patients of BME origin. There may be a range of ethnically specific culturally centred reasons for such delay[3]. Culturally different migrant and non-migrant internal or national minorities may inadvertently be subjected to indirect discrimination and exclusion. It is paramount to gain a deeper understanding of potential underlying cultural differences in order to educate and facilitate appropriate healthcare and support within minority populations. The empowerment of patients of minority communities through culturally appropriate health education initiatives can encourage such persons to seek early medical advice and treatment thereby promoting equity amongst diverse populations.

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5 Million Patients and Not 0.34% Is Worrisome: Burden of Rheumatoid Arthritis in India Based On a Bone and Joint Decade India Community Oriented Program for Control of Rheumatic Disease. Arvind Chopra[1], R. Ghorpade[1], S. Sarmukkadam[2], VL Joshi[1], AJ. Mathews[3], L. Gauri[4], A. Rahim[5], K. Datta[6], S. Chaturvedi[7], B. Thakuria[8], A. Mahajan[9], R. Singh[10], A. Ghosh[11], R. Handa[12], M. Saluja[1], A. Venugopalan[1], V. Kunjeer[1], B. Paul[5], S. Pal[6], K. Wangjam[10], T. Kumar[11] and K. Mahendranath[13]. [1]Center for Rheumatic Diseases, Pune, India, [2]BJMC, Pune, India, [3]Government Medical College Hospital, Trivandrum, India, [4]SP Medical College, Bikaner, India, [5]Calicut Medical College, Calicut, India, [6]Advance Rheumatology Clinic, Hyderabad, India, [7]FRCH, Pune, India, [8]Guwahati Medical College & Hospital, Guwahati, India, [9]Government Medical College, Jammu, India, [10]Regional Institute of Medical Sciences, Imphal, Manipur, India, [11]Institute of Post Graduate Medical Education and Research, Kolkata, India, [12]AIIMS, New Delhi, India, [13]Rheumatology Clinic, Bangalore, India

Background/Purpose: The 1 % prevalence of RA Worldwide is a deep rooted ancient dogma. None of the recent WHO ILAR COPCORD (Community Oriented Program for Control of Rheumatic Diseases) surveys Worldwide support this contention (Best Pract Res Clin Rheumatol 2008; 22:583–604); Cuba & Mexico being exception (J Clin Rheumatol 2012;18: 167-69). COPCORD Bhigwan (India) reported (J Rheumatol 2002; 29: 614-21) an unusually high rural prevalence of RA 0.55% (ACR 1987) and encouraged a country wide exploration. We now present the results of RA prevalence in India.

Methods: We adopted the COPCORD Bhigwan model to complete non random population surveys (Stage I) at 12 sites (Fig)as per standard COPCORD methods (http://www.copcord.org); a cross sectional house to house population screen to identify cases with current/past pain (phase I) and evaluate (phase II) respondents for pain, impact, quality of life and rheumatology evaluation (phase III). All patients were examined by rheumatologists. 51,741 populations qualified for the current analysis. The classification/diagnosis was essentially clinical with minimal supporting investigations. Indigenously designed Windows based program was used for a central data entry and analysis using standard stat software.Data was further adjusted for age-sex standardization to India census population 2001; 95% confidence intervals shown in parenthesis. Site sample sizes, pain rates and prevalence of several rheumatic disorders are submitted in another abstract.

Results: 198 patients (83% women) were classified as clinical RA. The crude point prevalence was 0.38 (0.30, 0.44) and the adjusted rate was 0.34 (0.08, 0.79). The overall female to male ratio was 5:1. Patients were distributed in various age groups (years); 2% in 15–24, 42% in 25–44, 40% in 45–64, and 16% in 65+ age group. The adjusted prevalence rate of RA for each of the survey sites is shown in the figure. Except for the prevalence of 0.8% in a site in the state of Rajasthan (West India), a large number of sites in the rest of the country seem to be in the range 0.2 to 0.3%. However, even

a low prevalence of 0.34% would mean that India (1.2 billion populations) has probably 5 million patients.

COPCORD surveys are limited by lack of investigations and follow up. In India, RA may be overestimated clinically because of a large pool of seronegative inflammatory arthritis (RA mimics). COPCORD Pune (India) reported a crude point prevalence of 0.45% RA which when reclassified as per ACR 1987 criteria and further standardized was reduced to 0.19% (J Rheumatol 2009; 36: 614-22).

We believe that the true prevalence of RA in India is likely to be even less than 0.34% and that may bring some solace.
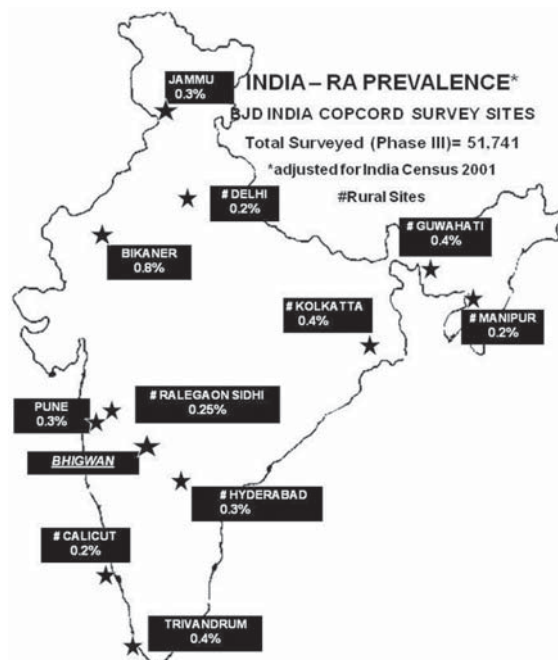
Conclusion: Though the prevalence of RA 0.34% in India is several folds less than the elusive 1% that has been taught for years, the burden of RA nonetheless is extremely high and needs to be seriously addressed at a national level.

Disclosure: A. Chopra, None; R. Ghorpade, None; S. Sarmukkadam, None; V. Joshi, None; A. Mathews, None; L. Gauri, None; A. Rahim, None; K. Datta, None; S. Chaturvedi, None; B. Thakuria, None; A. Mahajan, None; R. Singh, None; A. Ghosh, None; R. Handa, None; M. Saluja, None; A. Venugopalan, None; V. Kunjeer, None; B. Paul, None; S. Pal, None; K. Wangjam, None; T. Kumar, None; K. Mahendranath, None.

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A Staggering Burden of Pain and Rheumatic Disorders in India: A National Bone & Joint Decade India Community Oriented Program for Control of Rheumatic Disease Survey 2006–2011. Arvind Chopra[1], R. Ghorpade[1], S. Sarmukkadam[2], VL Joshi[1], AJ. Mathews[3], L. Gauri[4], A. Rahim[5], K. Datta[6], S. Chaturvedi[7], B. Thakuria[8], A. Mahajan[9], R. Singh[10], A. Ghosh[11], R. Handa[12], M. Saluja[1], A. Venugopalan[1], V. Kunjeer[1], B. Paul[5], S. Pal[6], K. Wangjam[10], T. Kumar[11], CP Rajendran[13], V. Gajalakshmi[14] and K. Mahendranath[15]. [1]Center for Rheumatic Diseases, Pune, India, [2]B J Medical College, Pune, India, [3]Government Medical College Hospital, Trivandrum, India, [4]SP Medical College, Bikaner, India, [5]Calicut Medical College, Calicut, India, [6]Advance Rheumatology Clinic, Hyderabad, India, [7]FRCH, Pune, India, [8]Guwahati Medical College & Hospital, Guwahati, India, [9]Government Medical College, Jammu, India, [10]Regional Institute of Medical Sciences, Imphal, Manipur, India, [11]Institute of Post Graduate Medical Education and Research, Kolkata, India, [12]AIIMS, New Delhi, India, [13]Madras Medical College, Chennai, India, [14]ERC Unit, Chennai, India, [15]Rheumatology clinic, Bangalore, India

Background/Purpose: The maiden COPCORD (Community Oriented Program for Control of Rheumatic Diseases) population survey in village Bhigwan (Pune) findings proposed a high burden of pain and arthritis in India (J Rheumatol 2002; 29: 614-21). We carried out a national survey using COPCORD Bhigwan fast track model.

Methods: COPCORD population survey (Stage I) was completed in 3 parallel phases: 1(cross sectional house to house survey for demographics and screening), 2 [record pain (human mannequin) and disability (validated Indian HAQ), 3 (standard of care rheumatology evaluation). 12 volunteer rheumatologists chose non-random sites (Fig) and survey sample as per COPCORD diktat (http://www.copcord.org). Population was essentially screened for current (last 7 days) and/or past pain in joints or musculoskeletal (MSK) soft tissues. Trained volunteers from the community completed phases 1 & 2. The classification/ diagnosis were essentially clinical with minimal supporting investigations. Indigenously designed Windows based program was used for a central data entry and analysis using std stat software (SPSS & Epi Info v6). Prevalence rates were age-sex standardized to India census population 2001; 95% confidence intervals shown in parenthesis. Response rate at all sites > 80%.

Results: 56,541 populations surveyed.16% (14.2, 18.3) self reported MSK pain(current &/or past, any site); frequent sites-knee 8.5%, back 6.2%, ankle/feet 3.8%,shoulder 3.2%, elbow 2.9%, hand/wrist 2.9%, neck 1.5%. The frequency of pain at several sites and overall in rural was nearly twice urban. Self reported MSK pain was the predominant ailment in the community.

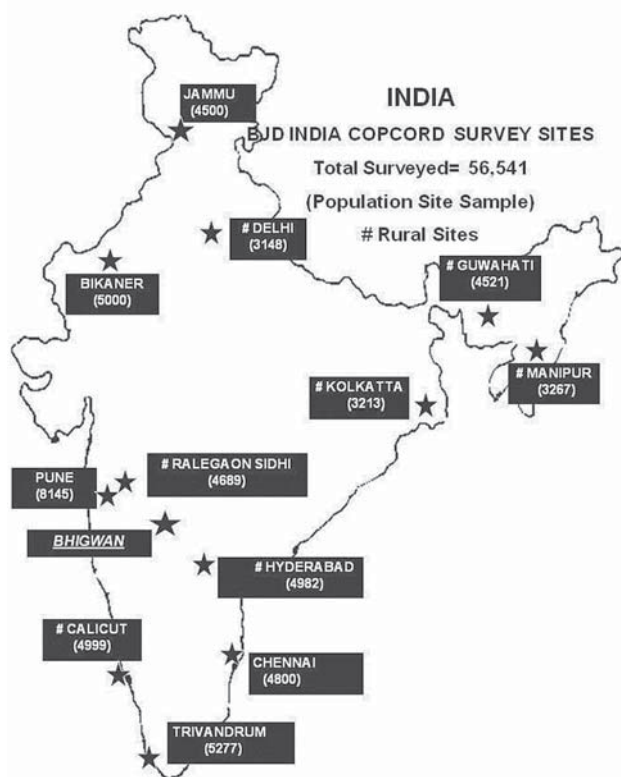**Table shows the point prevalence of selected clinical disorders.**

Disorder	Prevalence
Rheumatoid arthritis	0.34 (0.08, 0.79)
Undifferentiated inflammatory arthritis	0.22 (0.05,0.68)
Seronegative Spondyloarthritis	0.23 (0.05,0.68)
Ankylosing Spondylitis	0.03 (0.02, 0.05)
Osteoarthritis, any form	4.39 (3.30,5.61)
Osteoarthritis knee	3.34 (2.43, 4.47)
Gout	0.04 (0.03, 0.05)
Soft tissue rheumatism, any form	1.31 (0.77, 2.11)
Ill defined symptoms, non specific arthralgias	4.25 (3.23, 5.53)
Lupus & other connective tissue disorders	0.02 (0.01, 0.03)

INDIA
BJD INDIA COPCORD SURVEY SITES
Total Surveyed= 56,541
(Population Site Sample)
Rural Sites

JAMMU (4500)
DELHI (3148)
GUWAHATI (4521)
BIKANER (5000)
MANIPUR (3267)
KOLKATTA (3213)
RALEGAON SIDHI (4689)
PUNE (8145)
BHIGWAN
HYDERABAD (4982)
CALICUT (4999)
CHENNAI (4800)
TRIVANDRUM (5277)

Conclusion: In this 1.2 billion population country, the prevalence of MSK pain and several rheumatic disorders reported by this first ever national COPCORD survey confers a huge burden in millions of patients and paves way for a national prevention and control program.

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The Burden of Early Arthritis in Latin America: Utility Analysis Using Patient-Level Data From the Argentinian Consortium for Early Arthritis. Christian A. Waimann[1], Gustavo Citera[2], Hernan Maldonado Ficco[3], Oscar L. Rillo[4], Mariana Benegas[5], Rafael Chaparro del Moral[6], Antonio Catalan Pellet[7], Anastasia Secco[8], Lucila Marino[9], Alberto Berman[10], Horacio Berman[10], Ana Lucía Barbaglia[11], Juan Carlos Marcos[12], Josefina Marcos[12], Francisco Caeiro[13], Maria Haye Salinas[14], Ana C. Alvarez[15], Enrique Soriano[16], Zaida Bedran[17], Sergio Paira[18], Federico Ceccato[18], Gabriela Salvatierra[19], Ana Quinteros[20], Emilio Buschiazzo[21] and Edson Javier Velozo[22]. [1]Instituto de Rehabilitación Psicofisica, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofisica., Buenos Aires, Argentina, [3]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [4]Hospital Tornú, Buenos Aires, Argentina, [5]Hospital Tornu, Buenos Aires, Argentina, [6]CONAART, Argentina., Buenos Aires, Argentina, [7]Hospital Rivadavia, Buenos Aires, Argentina, [8]Rivadavia Hospital, Buenos Aires, Argentina, [9]Rivadavia Hospital, Buenos Aires, Argentina, [10]Centro Medico Privado de Reumatologia, Tucuman, Argentina, [11]Hospital Padilla, Tucuman, Argentina, [12]Hospital San Martin, La Plata, Argentina, [13]Hospital privado de Cordoba, Cordoba, Argentina, [14]Hospital Privado de Cordoba, Córdoba, Argentina, [15]Hospital Privado, Córdoba, Argentina, [16]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [17]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [18]Hospital Jose Maria Cullen, Santa Fe, Argentina, [19]Centro de enfermedades Reumaticas, Santiago Del Estero, Argentina, [20]Centro Integral de Reumatología San Miguel de Tucumán, San Miguel de Tucumán, Argentina, [21]Hospital Señor del Milagro, Salta, Argentina, [22]Sanatorio Adventista del Plata, Entre Rios, Argentina

Background/Purpose: Rheumatoid arthritis (RA) is estimated to be one of the leading causes of non-fatal burden in the world. However, data from developing countries including Latin America are limited, and the real burden of inflammatory arthritis in this population is unknown. The aim of our study was to evaluate the impact of disease activity on health-related quality of life (HRQOL) using a large cohort of Argentinian patients with early inflammatory arthritis.

Methods: We included patients with diagnosis of early RA (American College of Rheumatology 1987' criteria) or undifferentiated arthritis (UA) belonging to CONAART (Consorcio Argentino de Artritis Temprana - Argentine Consortium for Early Arthritis). CONAART is a prospective cohort of Argentinian patients with diagnosis of early arthritis (<2 years of disease duration). Data are collected every 3 months, including Health Assessment Questionnaire (HAQ), Clinical Disease Activity Index (CDAI) and pharmaco-economic data. The generic EuroQoL (EQ-5D) was derived from HAQ and patient's visual analogue scale of pain using previously validated regression models. Patients were stratified and compared according to diagnosis and disease activity levels (CDAI). All comparisons were adjusted for sex, age and comorbidities.

Results: We included 777 patients (RA=628; UA=149). Mean follow-up 14.5 ± 10.1 months (990 patients-year). Mean age was 48 ± 14 years, 82% were female and disease duration was 8.6 ± 6.3 months. On baseline visit CDAI and HAQ were 24.6 ± 14.4 and 1.2 ± 0.9, respectively. Mean EQ-5D score during follow-up was 0.74 ± 0.13. No difference regarding HRQL was observed between RA and UA (0.73 ± 0.12 and 0.75 ± 0.13, respectively). EQ-5D showed a negative correlation with disease activity (rho spearman=-0.74, p<0.0001). Mean EQ-5D in patients in remission was 0.91 ± 0.04, low disease activity=0.82 ± 0.81, moderate disease activity=0.72 ± 0.09 and high disease activity=0.61 ± 0.11 (Graph 1). Considering remission as the ideal situation, patients with early RA or UA in low disease activity entail a disease burden of 0.07 (95%CI= 0.06 – 0.08) quality-adjusted life-years (QALYs) after one year of follow-up. In similar conditions, patients with moderate disease activity lose 0.17 (95%CI= 0.16–0.18) QALYs, and those with high disease activity lose 0.28 (95%CI = 0.27–0.30) QALYs.

Graph 1. Health-related quality of life stratified by disease activity and diagnosis

Health-related quality of life stratified by disease activity and diagnosis
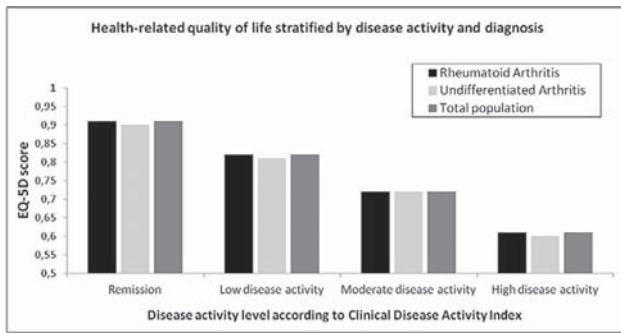
Conclusion: Regardless of the diagnosis of UA or RA, patients with early inflammatory arthritis and active disease inflict a substantial disease burden. The impact of arthritis in HRQL showed a linear relationship with disease activity level. This remarks the importance of an early and aggressive treatment in patient with this condition.

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Role of Health Literacy in Population Estimates of Musculoskeletal Disorders. Catherine L. Hill[1], Sarah L. Appleton[2], Tiffany K. Gill[3], Julie Black[4], Rima E. Rudd[5] and Robert J. Adams[2]. [1]The Queen Elizabeth Hospital, Woodville, Australia, [2]University of Adelaide, Woodville South, South Australia, Australia, [3]University of Adelaide, Adelaide, South Australia, Australia, [4]Arthritis SA, Marleston, Australia, [5]Harvard School of Public Health, Boston, MA

Background/Purpose: Disease diagnosis carries with it implications for self care and for healthful action. Public health campaigns, for example, are regularly launched to raise awareness of disease symptoms and new developments in medication and self management. In addition, self-report of musculoskeletal conditions is often used to provide population prevalence estimates and to determine disease burden and influence policy. However, self-report of certain conditions such as rheumatoid arthritis (RA) and osteoporosis are frequently inaccurate, suggesting that there is inadequate communication to the patient of their diagnosis. Such errors have consequences for treatment of those with musculoskeletal conditions, public health planning, and public policy.

Purpose: To examine the association between functional health literacy (FHL) and three commonly self-reported musculoskeletal conditions in a South Australian representative population survey

Methods: A cross-sectional random population survey was conducted in 2008 of 2824 participants aged 15 years and over, using an interviewer-administered questionnaire. Functional health literacy was measured using the Newest Vital Sign (scored as inadequate FHL (score 0–1), at risk of inadequate FHL (2–3) and adequate FHL (4–6)). Participants were also asked about self-reported medically diagnosed arthritis (including subtype; rheumatoid arthritis, osteoarthritis, 'other', 'don't know'), gout, and osteoporosis. Multiple logistic regression was performed using adjustment for age and sex.

Results: Of the 2824 participants, the prevalence of self-reported medically-diagnosed arthritis, gout and osteoporosis were 25.2%, 4.9% and 5.6%, respectively. The prevalence of those at-risk for inadequate FHL was 24.0% and of a high likelihood of inadequate FHL was 21.0%. However, over 50% of respondents with arthritis or gout had at risk or inadequate FHL, increasing to 70% of those self-reporting osteoporosis. After adjustment for age and sex, respondents in the arthritis subgroup of 'don't know', and

self-reported osteoporosis were significantly more likely to have inadequate FHL than the general population (Table 1).

Table 1. Associations of musculoskeletal conditions with limitations in functional health literacy.

	At risk or inadequate FHL		Inadequate FHL	
	% (n)	Adjusted*	% (n)	Adjusted*
All arthritis				
No	41.0%	1.00	18.1%	1.00
Yes	56.9%	1.14 (0.93-1.38)	29.4%	1.01 (0.81-1.27)
Arthritis type				
No arthritis	41.0%	1.00	18.1%	1.00
OA	51.0%	0.77 (0.58-1.02)	26.9%	0.81 (0.59-1.13)
RA	58.2%	1.46 (1.01-2.14)	22.4%	0.82 (0.52-1.29)
"don't know" type	65.0%	1.58 (1.18-2.13)	37.5%	1.47 (1.08-2.00)
other	40.6%	0.71 (0.34-1.50)	18.2%	0.63 (0.24-1.65)
Gout				
No	44.3%	1.00	20.3%	1.00
Yes	59.1%	0.96 (0.66-1.41)	35.5%	1.09 (0.74-1.62)
Osteoporosis				
No	43.5%	1.00	19.5%	1.00
Yes	70.3%	1.67 (1.15-2.44)	42.1%	1.62 (1.13-2.33)

*Adjusted for age and sex

Conclusion: This cross sectional population survey indicates a substantial burden of low health literacy amongst people with musculoskeletal disease in the general population. Those participants who 'don't know' the type of arthritis or who self-report osteoporosis are more likely to have poor FHL, suggesting that inadequate health literacy may influence communication and understanding of musculoskeletal diagnoses. This has implications for provider patient communication, individual health care, population estimates of musculoskeletal disease, and for the potential impact of public health messages.

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Clinical Implication of Rheumatoid Factor Formation According to Various Hepatitis B Virus Infection Status and Vaccination. Sang Tae Choi[1], Hyun Woong Lee[1], Jung-Soo Song[2], Soo Kon Lee[3] and Yong-Beom Park[3]. [1]Chung-Ang University School of Medicine, Seoul, South Korea, [2]Chung-Ang University College of Medicine, Seoul, South Korea, [3]Yonse University College of Medicine, Seoul, South Korea

Background/Purpose: Rheumatoid factor (RF) is produced as a result of polyclonal B cell activation, but the reasons for its production are still unknown. RF positivity can be seen in several diseases other than rheumatoid arthritis (RA), such as other rheumatic diseases and viral infection as well as in normal individuals. It was reported that RF was present in hepatitis B virus (HBV) infection. However, the types of antigens or antibodies of HBV and the hepatitis B viral load that play an important role in the development of RF remain obscure. In this study, we investigated the RF positive rates and titers of RF according to various HBV infection status and vaccination, and the relationship between the titers of RF and serum HBV DNA levels in HBV endemic areas.

Methods: The subjects were 13,670 individuals who visited the Severance Hospital Health Promotion Center in Seoul, Korea, for routine health check-up from January 2004 to December 2004. The samples were tested for RF (IgM type) and HBV infection by screening for the presence of HBsAg, anti-HBs (IgG type), and anti-HBc (IgG type). The HBeAg, anti-HBe (IgG type), and HBV DNA were analyzed in subjects positive for HBsAg. The RF positive rates and the titers of RF were evaluated based on the presence of each HBV viral marker, and correlation between the titers of RF and the serum HBV DNA levels was assessed.

Results: RF was positive in 3.5% of all subjects, and HBsAg was positive in 4.3%. HBsAg was positive in 21.7% of RF positive subjects. The HBsAg positive group had higher RF positive rate than negative group (17.5% vs 2.9%, $p < 0.001$). The RF positive rate was lower in those who had anti-HBs

after HBV vaccination than in HBsAg positive subjects (2.7% vs 17.5%, $p <$ 0.001). Among HBsAg positive subjects, the RF positive rate in the anti-HBs positive group was higher than that in the anti-HBs negative group (30.3% vs 16.8%, $p = 0.047$). However, there was no significant difference in the RF positive rate between the anti-HBc positive and negative groups, and HBeAg positive and negative groups. In multiple logistic regression analysis, the RF positive rate was increased in positive HBsAg (PR = 7.82, 95% CI 5.74 to 10.67, $p < 0.001$), female sex (PR = 1.21, 95% CI 1.01 to 1.46, $p = 0.042$) and older age (PR = 1.01, 95% CI 1.001 to 1.019, $p = 0.027$). Among the RF positive patients, the titer of RF in HBsAg positive patients were higher than those in HBsAg negative patients (159.7 ± 217.1 IU/mL vs 83.0 ± 179.2 IU/mL, $p = 0.001$). However, there were no significant differences in the titer of RF between anti-HBc positive and negative groups, and between HBeAg positive and negative groups. The load of HBV DNA may be closely correlated with the titer of RF in patients with chronic hepatitis B ($r = 0.508$, $p = 0.005$).

Conclusion: HBV infection is an important cause of the false positive RF in HBV endemic area. Especially hepatitis B viral load may be associated with the titer of RF. Therefore, HBV vaccination may decrease the risk of RF formation.

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The Association Between Silica and the Risk of Anti-Citrullinated Protein Antibody Positive RA in the Malaysian and Swedish Epidemiological Investigation of Rheumatoid Arthritis Studies. Abqariyah Yahya[1], Camilla Bengtsson[1], Lars Klareskog[2], Chun Lai Too[3], Shahnaz Murad[4] and Lars Alfredsson[1]. [1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden, [4]Institute for Medical Research, Kuala Lumpur, Kuala Lumpur, Malaysia

Background/Purpose: Silica exposure has been associated with an increased risk of developing ACPA+ (anti-citrullinated protein antibody) RA, especially among smokers (1). These findings were based on a Caucasian population. In this study we aimed at examining the association between silica exposure (and its interaction with smoking) and the risk of ACPA+ RA in an Asian population. In addition, we examined possible interaction between silica exposure and the major genetic risk factor for ACPA+ RA, i.e. the HLA-DRB1 shared epitope (SE) alleles, in both a Caucasian and an Asian population.

Methods: Data from the Malaysian EIRA (MyEIRA) and its sister study, the Swedish EIRA study were used. In total, 149 incident cases and 213 controls from MyEIRA and 823 incident cases and 1161 controls from EIRA, all men, were included. Self-reported silica exposure, defined as exposure to stone dust, rock drilling or stone crushing were taken into consideration. Smoking was defined as ever/never cigarette smokers. We examined the association between exposure to silica with the risk of ACPA+ RA, by calculating odds ratios (OR) with 95% confidence intervals (CI), using logistic regression. All analyses were adjusted for age and residential place. Interaction was evaluated by calculating the attributable proportion (AP) due to interaction and its 95% confidence interval (CI).

Results: In MyEIRA, an increased risk of ACPA+ RA (OR=2.88, 95%CI 1.02–8.14) was observed among those exposed to silica. Ever smokers exposed to silica had a particularly high risk of ACPA+ RA (OR= 8.27, 95%CI 1.64–41.44), compared with never smokers not exposed to silica. No association was found regarding ACPA- RA. When data from both studies were combined, we found that silica-exposed individuals with SE alleles had almost eleven times higher risk of ACPA+RA however the interaction was insignificant (AP=0.27, 95%CI -0.09–0.64).

Conclusion: Silica exposure in combination with smoking among men increased the risk of ACPA+ RA in an Asian population. These data extend previous results based on a Caucasian population reported from the Swedish EIRA study (1). In the combined analyses of these studies, there was an indication of interaction between silica and SE, though it was insignificant. We believe that this finding strengthen the hypothesis of modifiable lung exposure and risk for ACPA+ RA.

Reference
1. Patrik et al., *Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis*. Ann Rheum Dis, 2010. 69: p.1072–1076.

Disclosure: **A. Yahya**, None; **C. Bengtsson**, None; **L. Klareskog**, None; **C. L. Too**, None; **S. Murad**, None; **L. Alfredsson**, None.

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Use of Moist Snuff and the Risk of Developing Rheumatoid Arthritis; Results From the Swedish Epidemiological Investigation of Rheumatoid Arthritis Study. Lars Alfredsson[1], Lars Klareskog[2] and Camilla Bengtsson[1]. [1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden

Background/Purpose: Smoking is the major known environmental risk factor for RA, and notably this risk factor is exclusively seen in ACPA-positive RA. Whether this increased risk is due to nicotine or other substances of inhaled tobacco smoke is unclear. Smokeless tobacco contains nicotine and is often used as an alternative to smoking. The role of smokeless tobacco in the etiology of RA has to date only been reported from a Swedish study based on male construction workers, where no association was observed between the use of moist snuff and the risk of RA[1]. However, whether smokeless tobacco is related to the ACPA-positive or ACPA-negative RA remains to be elucidated. In this report we aimed at investigating the association between the use of moist snuff and the risk of RA, and if this exposure has different impact on ACPA-positive and ACPA-negative disease.

Methods: Data from EIRA (Epidemiological Investigation of Rheumatoid Arthritis), a population-based case-control study from Sweden, was used. In total, information from1962 incident cases and 2247 randomly selected controls (matched on age, sex and residency), aged 18–70 years, was analysed. Ever, current and past moist snuff users were compared with never users. We calculated odds ratios (OR) with 95% confidence intervals (CI) for RA overall and the ACPA-positive and ACPA-negative subsets, by means of unconditional logistic regression models. All analyses were adjusted for age, sex, residency, pack-years of cigarette smoking and alcohol consumption.

Results: In total, 254 (13%) cases were ever moist snuff users compared with 290 (13%) controls, resulting in an odds ratio of 1.0 (95% CI 0.8–1.2). When exposure to moist snuff was analysed in relation to the incidence of ACPA-positive and ACPA-negative disease, no associations were observed. Furthermore, neither current nor past moist snuff use was related to the risk of RA, or the two sub-groups of the disease.

Conclusion: The use of moist snuff was not associated with RA risk, neither with regard to ACPA-positive nor ACPA-negative RA. The increased risk of RA associated with smoking may thus not be due to nicotine.

1. Carlens C, et al: Smoking, Use of Moist Snuff, and risk of chronic inflammatory diseases. *Am J Respir Crit Care Med.* 2010;181:1217–22

Disclosure: **L. Alfredsson**, None; **L. Klareskog**, None; **C. Bengtsson**, None.

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Serum Inflammatory Biomarkers Correlated Stronger with a Panel of Serum Steroid and Pituitary Hormones in a Cohort of Pre-Rheumatoid Arthritis (pre-RA) Than in Non-RA Control (CN) Subjects. Alfonse T. Masi[1], Kevin B. Elmore[1], Azeem A. Rehman[1], Jean C. Aldag[1] and Robert T. Chatterton[2]. [1]University of Illinois College of Medicine at Peoria, Peoria, IL, [2]Northwestern University, Chicago, IL

Background/Purpose: Inflammatory cytokines influence steroid hormone production in tissue culture and affect serum levels and synovial fluid of active RA patients. Inflammatory biomarker and hormonal network correlations were compared in this nested prospective study of pre-RA and CN subjects, to identify differences in their associations prior to clinical RA onset.

Methods: Residents of Washington County, MD (21,061: 12,381 F, 8,680 M) enrolled in the Project CLUE cohort in 1974 and donated serum samples. After 3 to 20 (median 11) years, 54 cohorts were diagnosed ACR-definite RA (36 F, 18 M). Each pre-RA was matched on entry features with 4 non-RA (216 total: 144 F, 72 M) cohort members. Stored (−70 °C) sera were available on most subjects for assays of a comprehensive panel of 8 inflammatory markers, 15 steroids in women, and 8 in men. CRP and ASAA were assayed (mg/L) by high sensitivity ELISA at Boston University using reagents provided by Hemagen. A subset of female CRP assays was done by a modified-membrane ELISA method (mg/L) at Northwestern University (NWU). Quantikine cytokine assays (pg/mL) were done at

Specialty Laboratories, Inc., Santa Monica, CA, using reagents from R & D Systems, Inc. Cytokine assays included: IL-1β; IL-6 (F only); TNF-α; IL-1rα; sTNF-R1 and IL-2sRα. A panel of 15 steroids in women and 8 in men were tested by immunoassay methods in a hormone research laboratory at NWU. First, histograms of pre-RA vs CN immunomarkers and hormonal values, stratified by entry pre- vs post-menopausal and sex status, were compared to identify range differences (p<0.050). Next, matrix correlation tables of 8 inflammatory biomarkers and 18 hormones, and their P-P ratios (18 F, 8 M) were constructed using log-transformation and analyzed by age- and sex-adjusted partial Pearson (r_p) and unadjusted rank order Spearman (rho) methods to identify subject group differences (p<0.050). Principal component analysis (PCA) was performed on 148 subjects having values on 8 hormones, 6 immunologic markers, sex, entry age, and the study group variable (CN vs pre-RA).

Results: Among 225 total subjects with at least one paired immunologic and hormonal (I-H) test (46 pre-RA, 179 CN), 6 significant differences in correlations (deltas) were found, all stronger in the pre-RA vs CN (Table). PCA on 148 total subjects yielded 6 components, explaining 71.7% variance, which may be labeled as: (1) male sex-related hormones and sTNF-R1 (22.9%); (2) precursor hormones and estradiol (18.0%); (3) IL-1β and IL-1rα (10.2%); (4) cortisol, TNF-α, and entry age (7.7%); (5) CN vs pre-RA (6.9%), and (6) IL-2sRα (6.1%).

Differences Found in Correlations	Pre-RA Correlations			CN Correlations			Delta p values
	r_p	p	n	r_p	p	n	
CRP x Prolactin	0.413	0.005	46	0.047	0.539	179	0.021
ASAA x 17-OH Preg	0.303	0.091	34	−0.097	0.295	120	0.042
ASAA x Estradiol	0.631	<0.001	31	0.086	0.370	114	0.001
IL-1β x Testosterone	0.410	0.010	41	−0.041	0.630	143	0.009
IL-1βx Cortisol	0.295	0.068	41	−0.065	0.438	146	0.043
IL-2sRα x LH	−0.339	0.043	38	0.103	0.234	137	0.016

Conclusion: Stronger correlations of inflammatory biomarker and hormonal panels were found in pre-RA than in CN, and PCA indicated CN vs pre-RA as an independent component. These new data may lend support to a concept of neuroendocrine-immune dysregulation preceding clinical onset of RA, which deserves further investigation.

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Pre-Rheumatoid Arthritis (pre-RA) Subjects Had a Minority Excess with Clearly Low Serum Cortisol Levels and Females Had Lower Mean Androstenedione Levels Than Control (CN) Cohorts in Analysis of a Large Panel of Serum Steroids and Pituitary Hormones. Alfonse T. Masi[1], Kevin B. Elmore[1], Azeem A. Rehman[1], Jean C. Aldag[1] and Robert T. Chatterton[2]. [1]University of Illinois College of Medicine at Peoria, Peoria, IL, [2]Northwestern University, Chicago, IL

Background/Purpose: Low serum DHEAS may predispose a minority of premenopausal women to RA. A comprehensive panel of serum steroids, their related product-to-precursor (P-P) ratios and pituitary hormones has not been reported in pre-RA vs non-RA control (CN) subjects. This nested case-control prospective study permitted such comparison to assess adrenal and gonadal hormone alterations prior to clinical onset of RA.

Methods: Residents of Washington County, MD (21,061: 12,381 F, 8,680 M) enrolled in the Project CLUE cohort in 1974 and donated serum samples. After 3 to 20 (median 11) years, 54 cohorts were diagnosed ACR-definite RA (36 F, 18 M). Each pre-RA was matched on entry features with 4 non-RA (216 total: 144 F, 72 M) cohort members. Stored (−70 °C) sera were available on most subjects for assays of a comprehensive panel of hormones (15 F, 8 M) by immunoassay methods in a Northwestern University research laboratory. Histograms were compared of pre-RA vs CN hormonal levels and P-P ratios, stratified by entry pre- vs post-menopausal and sex status, to identify range differences (p<0.050). Hormonal correlations were also compared on age-adjusted, log-transformed values by partial Pearson and by Spearman methods. Principal component analysis (PCA) included 8 hormonal values, entry age, sex, and the study group variable (CN vs pre-RA).

Results: In 54 total pre-RA, 6 (11%) had abnormally low cortisol (< 120 nmol/L) levels vs 2 (0.93%) of 215 CN (p = 0.001). The respective P-P ratio of cortisol product to deoxycortisol precursor did not differ between study groups, or the preceding hydroxylated steroid P-P ratios. In females, mean (SEM) androstenedione ($\Delta 4A$) level (nmol/L) was 2.01 (0.44) in 28 pre-RA vs 3.52 (0.30) in 108 CN (p = 0.017). The lower $\Delta 4A$ level in pre-RA was consistent with a lower ratio of < 0.700 for the $\Delta 4A$ product to 17-OH progesterone precursor, found in 61% of pre-RA vs 34% of CN (p = 0.031). PCA of 11 variables yielded 4 components, explaining 75.2% of total variance: (1) sex and male-related hormones (30.2%); (2) precursor hormones, entry age, and estradiol (25.0%); (3) cortisol (10.5%), and (4) CN vs pre-RA (9.5%).

Principal Component Analysis: Factors and Loadings of 182 Subjects

Component # 1		Component # 2		Component # 3		Component # 4	
Factors	Loading	Factors	Loading	Factor	Loading	Factor	Loading
Sex	0.950	$\Delta 4A$	0.816	Cortisol	0.876	CN_RA	0.911
Testosterone	0.919	DHEA	0.715				
DHEAS	0.846	17-OH Prog.	0.711				
		17-OH Preg.	0.632				
		Entry Age	-0.586				
		Estradiol	0.537				

Conclusion: An excess minority of pre-RA had deficient cortisol levels, females had lower mean androstenedione than CN, and PCA identified cortisol and the CN vs pre-RA variable as independent components, findings which deserve further investigation.

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Increased Prevalence of Hypothyroidism Preceding Rheumatoid Arthritis - an Epidemiological Study. Anne M. Kerola[1], Tuomo Nieminen[2], Markku J. Kauppi[3], Hannu Kautiainen[4], Kari Puolakka[5], Lauri J. Virta[6] and Tuomas Kerola[3]. [1]Medical School, University of Helsinki, Helsinki, Finland, [2]Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland, [3]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland, [4]Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, [5]Department of Medicine, South Karelia Central Hospital, Lappeenranta, Finland, [6]Research Department, the Social Insurance Institution, Turku, Finland

Background/Purpose: Rheumatoid arthritis (RA) is associated with a wide set of comorbidities, including several autoimmune diseases such as autoimmune thyroiditis, which is a common cause of hypothyroidism. Whether the prevalence of hypothyroidism is elevated during the preclinical phase of RA when several autoimmune processes are already activated is not yet known. The aim of the study was to compare the prevalence of hypothyroidism among RA patients and non-RA-subjects at the time of RA diagnosis, and to determine whether the risk of hypothyroidism varies by age at the onset of RA, or by sex or rheumatoid factor (RF) status.

Methods: We identified 7,209 incident RA patients diagnosed between January 2004 and December 2007 from a Finnish nationwide register of special reimbursements for medication costs. The presence of hypothyroidism was identified from the same register based on special reimbursement decisions for thyroxine substitution. The prevalence of hypothyroidism at the onset of RA was compared to that of an age- and sex-matched Finnish population, and a standardized rate ratio (SRR) for hypothyroidism was calculated.

Results: The SRR for hypothyroidism preceding RA was 1.51; 95% confidence interval (CI): 1.35-1.67. The SRR was highest among younger RA patients, the excess prevalence of hypothyroidism decreasing steadily and wearing off among patients who were older at the time of diagnosis (Figure). The SRR for hypothyroidism was almost 2.5 among women between 20 and 49 years of age at RA diagnosis. The absolute prevalence of hypothyroidism, however, increased with age as it does in the general population. The SRR was similar between RF-positive and RF-negative patients: 1.46 (95% CI: 1.27-1.66) and 1.61 (95% CI: 1.34-1.91), respectively. Sex also did not modify the SRR point estimates, although the results did not reach statistical significance among men.
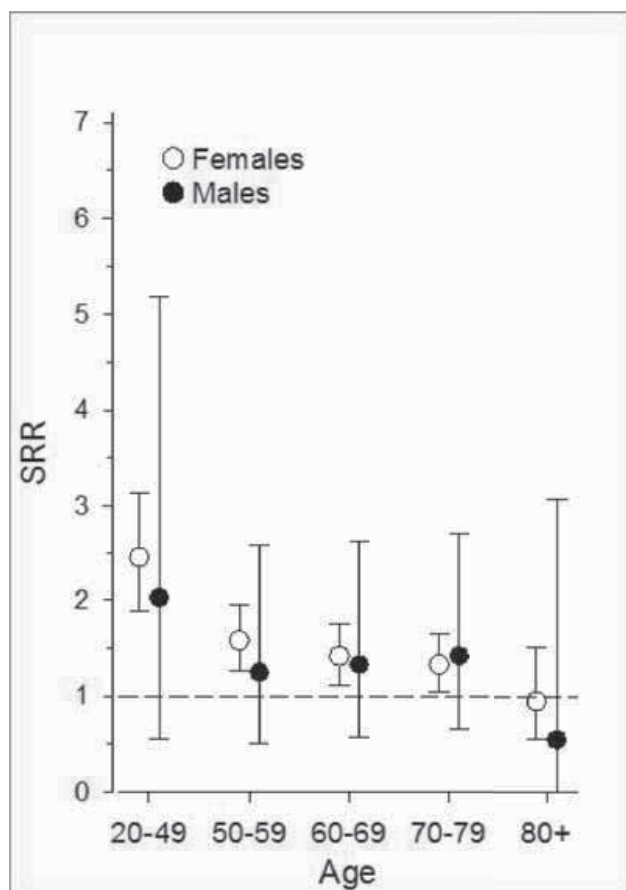
Figure. The standardized rate ratios (SRR) of hypothyroidism according to sex and age among 7,209 RA patients at disease onset compared with their age- and sex-matched non-RA equivalents. 95% confidence intervals are shown with whiskers.

Conclusion: The prevalence of hypothyroidism is already increased among RA patients at the disease onset, especially among young women. This calls for attention to screening for hypothyroidism in younger RA patients. Furthermore, the clinician should be mindful of the possibility of RA as the underlying cause of joint symptoms in young female patients with hypothyroidism.

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Cardiovascular Comorbidities Antedating the Diagnosis of Rheumatoid Arthritis. Anne M. Kerola[1], Tuomas Kerola[2], Markku J. Kauppi[2], Hannu Kautiainen[3], Lauri J. Virta[4], Kari Puolakka[5] and Tuomo Nieminen[6]. [1]Medical School, University of Helsinki, Helsinki, Finland, [2]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland, [3]Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, [4]Research Department, the Social Insurance Institution, Turku, Finland, [5]Department of Medicine, South Karelia Central Hospital, Lappeenranta, Finland, [6]Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased cardiovascular morbidity. Evidence suggests that RA patients are at an increased risk of coronary heart disease (CHD) early in the disease process. Whether the risk of CHD is elevated before the onset of RA symptoms remains to be ascertained. The aim of the study was to assess the prevalence of CHD, chronic hypertension and chronic congestive heart failure among incident RA patients at the time of diagnosis in comparison to age- and sex-matched non-RA-subjects. Furthermore, the impact of age at the onset of RA as well as sex and the presence of rheumatoid factor (RF) on the risk of cardiovascular diseases was evaluated.

Methods: A cohort of 7,209 incident RA patients diagnosed between January 2004 and December 2007 was identified from a Finnish nationwide register of special reimbursements for medication costs. The presence of cardiovascular diseases antedating the reimbursement decision for RA was identified from the same register. The prevalence of cardiovascular comorbidities at RA diagnosis was compared to the general Finnish population, and a standardized rate ratio (SRR) for each cardiovascular disease was calculated.

Results: The risk of having CHD at RA diagnosis was slightly elevated, the SRR being 1.10 (95% confidence interval [CI]: 1.01-1.20). Patients who were younger at the onset of RA had a trend towards a higher CHD rate ratio than older patients, although the risk was not significantly elevated in most age subgroups (Figure). The CHD rate ratio was essentially similar irrespective of RF status - 1.15 (95% CI: 1.00-1.32) among RF-negative and 1.08 (95% CI: 0.97-1.19) among RF-positive patients. The SRR of chronic hypertension was significantly increased only among the RF-negative RA cases (1.19, 95% [95% CI: 1.10-1.30]). The prevalence of chronic congestive heart failure did not differ between the incident RA patients and the general population.
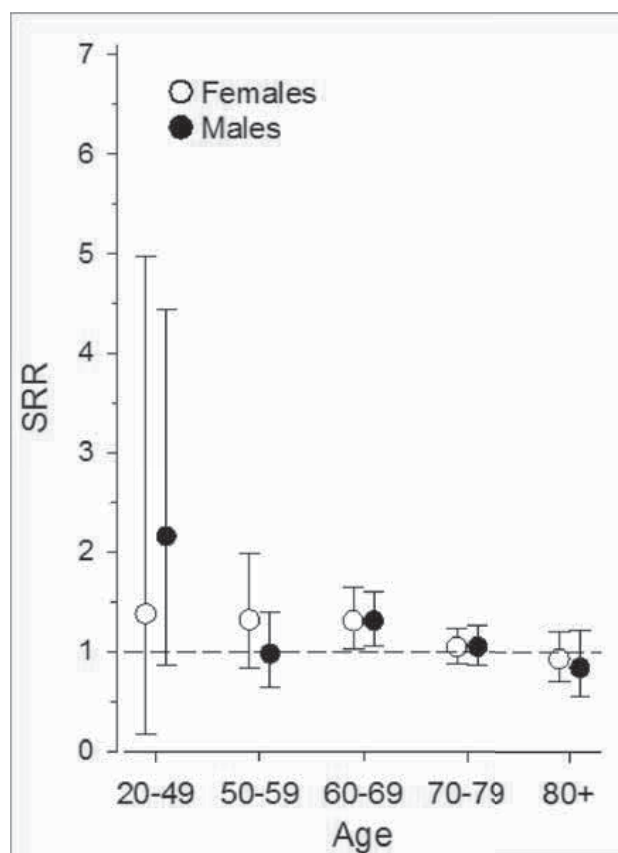
Figure. The standardized rate ratios (SRR) of CHD among 7,209 patients at the onset of RA according to sex and age (with 95% confidence intervals).

Conclusion: The CHD rate ratio is already augmented in RA patients at disease onset; the increase is more pronounced among younger patients and similar between RF-positive and RF-negative patients. The findings highlight the importance of early prevention of atherosclerosis regardless of RF status.

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The Presence of Asymptomatic Carotid Plaques in Patients with Inflammatory Joint Disease Results in Inadequate Treatment to Lipid Targets in Cardiovascular Disease Prevention. Anne G. Semb[1], Silvia Rollefstad[2], Inge C. Olsen[2], Desiree van der Heijde[3] and Tore K. Kvien[2]. [1]Diakonhjemmet Hospital, Olso, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The prevalence of asymptomatic carotid plaque (a-CP) is high in patients with inflammatory joint disease (IJD). Patients with a-CP should receive intensive lipid lowering (LL) treatment in cardiovascular prevention. Our aim was to evaluate presence of a-CP, if CV risk calculators predict presence of a-CP in patients with IJD and if optimizing cut off points in various risk calculators will improve this prediction.

Methods: We performed CV risk stratification in patients with IJD (n= 345), [rheumatoid arthritis (RA) (n=210), ankylosing spondylitis (AS) (n=87) and psoriatic arthritis (PsA) (n=49)] by using SCORE, Framingham and Reynolds CV risk algorithms with recommended cut off points at 5%, 10% and 10% respectively. Ultrasound of the carotid arteries was performed. Cross-tabulations, Chi^2 and ROC curves were used to calculate sensitivity/specificity, odds- and likelihood ratio (LR) for identifying a-CP. The ROC closest point (0.1) and 80% sensitivity was used for optimizing the identification of a-CP.

Results: A-CP was present with similar frequency in RA, AS and PsA (48.3%, 41.4% and 41.7% (p=0.46). Two hundred and eleven patients had SCORE<5% indicating no need for LL prevention (Table 1). However, 72 (34.1%) of these patients had a-CP and should receive intensive LL treatment. In patients with SCORE ≥5% (n=124), indicating a need for moderate LL prevention, 81 (65.3%) had a-CP and should therefore be categorized to intensive LL treatment. The sensitivity for identifying a-CP was 0.53, the specificity: 0.76 and LR+: 2.24. Optimizing the cut off value by using closest point (0, 1) (SCORE: 4%: specificity: 0.65, specificity: 0.72, LR+:2.33) or 80% specificity (SCORE: 2.65: sensitivity: 0.80 specificity: 0.56 LR+:1.83) did not improve the ability of SCORE to identify a-CP. According to the new guidelines for prevention of CV disease (2011)[1], the sensitivity, specificity and LR+ for identifying a-CP was 0.47, 0.77 and 2.05 respectively. The associations between a-CP and cut off values for other risk calculators are shown in Table 2.

Table 1. European heart SCORE according to presence of symptomatic carotid plaque

| | Carotid plaque n (%) | | | | | | | |
	SCORE ≥ 5%	SCORE < 5%	OR (95% CI)	p-value	Sensitivity	Specificity	LR+	LR−
IJD	81 (65.3)	72 (34.1)	3.64 (2.28, 5.80)	<0.0001	0.53	0.76	2.24	0.62
Closest point to (0,1)	**SCORE ≥ 4%**	**SCORE < 4%**						
IJD	100 (66.2)	53 (28.8)	4.85 (3.05, 7.71)	<0.0001	0.65	0.72	2.33	0.48
80% sensitivity	**SCORE ≥ 2.66%**	**SCORE < 2.65%**						
IJD	123 (60.6)	30 (22.7)	5.23 (3.19, 8.58)	<0.0001	0.80	0.56	1.83	0.35
	New SCORE classification: >5%, <10% & LDL >2.5 or ≥10%&LDL≥1.8	**New SCORE classification: otherwise**						
IJD	72 (63.2)	80 (36.4)	3.000 (1.88, 4.80)	<0.0001	0.47	0.77	2.05	0.68

Table 2. Framingham and Reynolds cardiovascular risk scores

| | Carotid plaque n (%) | | | | | | | |
	Framingham ≥ 10%	Framingham < 10%	OR (95% CI)	p-value	Sensitivity	Specificity	LR+	LR−
IJD	128 (61.2)	25 (19.8)	6.38 (3.80, 10.73)	<0.0001	0.84	0.56	1.88	0.29
Closest point to (0,1)	**Framingham ≥ 12.2%**	**Framingham < 12.2%**						
IJD	113 (64.6)	40 (25.0)	5.47 (3.41, 8.78)	<0.0001	0.74	0.66	2.17	0.40
80% sensitivity	**Framingham ≥ 11%**	**Framingham < 11%**						
IJD	122 (63.5)	31 (21.7)	6.30 (3.84, 10.33)	<0.0001	0.80	0.62	2.07	0.33
	Reynolds ≥ 10%	**Reynolds < 10.0%**						
IJD	63 (67.0)	84 (36.7)	3.51 (2.11, 5.83)	<0.0001	0.43	0.82	2.43	0.69
Closest point to (0,1)	**Reynolds ≥ 5.7%**	**Reynolds < 5.7%**						
IJD	102 (64.6)	43 (27.3)	4.86 (3.03, 7.79)	<0.0001	0.69	0.68	2.11	0.45
80% sensitivity	**Reynolds ≥ 4.5%**	**Reynolds < 4.5%**						
IJD	118 (61.8)	29 (22.0)	5.74 (3.47, 9.51)	<0.0001	0.80	0.59	1.94	0.34

Conclusion: Carotid ultrasound will assist in the correct classification of patients with IJD into intensive LL in about 1/3 of patients with SCORE<5% and 2/3 of patients with SCORE≥5%. The CV risk calculators are poor predictors of a-CP in patients with IJD.

Reference

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The Impact of Systemic Autoimmune Rheumatic Disease On One-Year Mortality in Congestive Heart Failure Patients: A Population-Level Analysis. Stephanie O. Keeling, Asvina Bissonauth, Becky Leung and Padmaja Kaul. University of Alberta, Edmonton, AB

Background/Purpose: Little is known about the prevalence of systemic autoimmune rheumatic diseases (SARDs) in patients with congestive heart failure (CHF) and its contribution to long-term adverse events. Therefore, we documented the prevalence of SARDs in an incident cohort of patients hospitalized with CHF in the province of Alberta, Canada and examined the association between SARDs and 1-year mortality after adjusting for traditional cardiovascular risk factors.

Methods: This retrospective cohort study examined all Alberta residents, aged 20 years and older, hospitalized with incident CHF between April 1, 1999 and December 31, 2008. Definitions of CHF, SARDs and other comorbidities were based on established ICD-9 &-10 codes. SARDs included rheumatoid arthritis, systemic lupus erythematosus, inflammatory myositis, systemic sclerosis, Sjogren's syndrome, overlap syndrome and other connective tissue diseases. Hospitalization records in the five years prior to the incident CHF hospitalization were examined to identify the presence of SARDs and other comorbidities. Baseline characteristics and comorbidity rates of SARDs/non-SARDs patients were described. The independent association of SARDs and mortality after adjusting for demographic and traditional cardiovascular risk factors was calculated with logistic regression. Kaplan-Meier analysis and the log-rank statistic examined the unadjusted one-year mortality between SARDs/non-SARDS patients.

Results: SARDs prevalence was 3.1% (1208 patients) out of 38,668 patients hospitalized with CHF. Patients with SARDs were younger, more likely female, and had lower rates of diabetes, hypertension, COPD, anemia and renal disease (Table 1). After multivariate adjustment, SARDs was associated with higher odds of 1-year mortality (adjusted Odds Ratio 1.3 (95% Confidence Interval 1.2–1.5) (Table 2). Kaplan-Meier analysis showed greater 1-year mortality in SARDs versus non-SARDs hospitalized CHF patients (not shown in abstract).

Table 1. Baseline characteristics of SARDs versus non-SARDs CHF patients

CHARACTERISTIC	SARDS	Non-SARDs	p-value
Age (mean (STD))	74.8 (13.2)	72.9 (12.7)	<0.01**
Male sex	18,842 (50.3%)	347 (28.7%)	<0.01
Diabetes	12624 (33.7%)	331 (27.4%)	<0.01
Hypertension	28432 (75.9%)	885 (73.3%)	0.04
Dementia	4832 (12.9%)	108 (8.9%0	<0.01
COPD	17756 (47.4%)	628 (52.0%)	<0.01
Anemia	14560 (38.9%)	724 (59.9%)	<0.01
Cerebrovascular disease	8016 (21.4%)	259 (21.4%)	0.95
Renal disease	6181 (16.5%)	248 (20.5%)	<0.01
Cancer	7042 (18.8%)	216 (17.9%)	0.40
PVD	6780 (18.1%)	236 (19.5%)	0.22
Atrial fibrillation	12549 (33.5%)	393 (32.5%)	0.46
1-year mortality	11238 (30.0%)	422 (34.9%)	<0.01

**p-value was based on Kruskal-Wallis one-way analysis of variance.
P-values of categorical variables are based on Chi-square test.

Table 2. Logistic regression of 1-year mortality in incident CHF

Effect	OR (95% Confidence Interval)
Male	1.2 (1.1–1.2)
Age	1.0
SARDs	1.3 (1.2–1.5)
Hypertension	0.7 (0.6–0.7)
Dementia	1.8 (1.7–2.0)
COPD	1.1 (1.0–1.1)
Anemia	1.3 (1.2–1.3)
Cerebrovascular disease	1.3 (1.2–1.4)
Renal disease	1.7 (1.6–1.8)
Cancer	2.5 (2.4–2.6)
PVD	1.2 (1.1–1.2)

Conclusion: Significant mortality risk exists among SARDs patients hospitalized with CHF despite lower rates of factors such as diabetes and hypertension. Agressive recognition and management of CHF in SARDs patients may improve survival rates. Further work is needed to examine the outpatient prevalence of SARDs in this population.

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The Association Between Preclinical Markers for Cardiovascular Disease and Rheumatoid Arthritis-Related Autoantibodies in First-Degree Relatives without Rheumatoid Arthritis. Ryan W. Gan[1], Jan M. Hughes-Austin[2], Kevin D. Deane[3], Elaine M. Urbina[4], Peter K. Gregersen[5], Michael H. Weisman[6], V. Michael Holers[3] and Jill M. Norris[1]. [1]Colorado School of Public Health, Aurora, CO, [2]Colorado School of Public Health/University of Colorado Anschutz Medical Campus, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [6]Cedars-Sinai Medical Center, Los Angeles, CA

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

Methods: RA-related autoantibody (Ab) positivity is defined as positivity for one of the following autoantibodies: rheumatoid factor by nephelometry (RF), RF isotype-IgM, IgA, IgG, or anti-cyclic citrullinated peptide (anti-CCP2). Ab positive and negative FDRs from the SERA parent cohort were evaluated after a 10-hour fast for the following outcome measures related to CVD: carotid intima media thickness (cIMT), carotid stiffness, flow-mediated dilation (FMD) of the brachial artery, abdominal adipose tissue using computed tomography (CT), blood pressure, lipids, lipoproteins and adipokines. Levels of these pre-clinical CVD phenotypes were log-transformed and compared by current autoantibody positivity status using linear regression.

Results: The Table presents data from the first 30 FDRs undergoing the CVD evaluation (planned enrollment n=100). Overall, Ab positive FDRs had *lower* (ie, better) intima media thickness of the internal carotid artery (both max and average measures) than Ab negative FDRs; there were no other significant differences between CVD-related measures and Ab status.

Table. CVD-related measures by RA-related autoantibody positivity. CVD variables are back-transformed after adjusting for age and gender using linear regression.

	Ab Positive n=16 Mean	Ab Negative n=14 Mean	p-value
Age (years)*	48.0	54.3	0.27
Gender (% Female)*†	81.3	57.1	0.24
Current Smoker (% Yes)*†	0%	14.3%	0.21
Blood Pressure			
Systolic (mm/Hg)	118.79	118.16	0.92
Diastolic (mm/Hg)	72.99	72.91	0.98
Lipids, lipoproteins and adipokines			
LDL (mg/dL)	98.39	114.92	0.27
HDL (mg/dL)	52.24	51.14	0.87
Cholesterol (mg/dL)	178.86	194.16	0.41
Triglycerides (mg/dL)	117.96	115.85	0.98
ApoB (mg/dL)	83.03	94.26	0.11
ApoA (mg/dL)	155.12	151.15	0.70
ApoB/ApoA	0.54	0.62	0.13
Adiponectin (ug/mL)	9.08	9.82	0.74
Leptin (ug/mL)	13.49	12.82	0.91
C-reactive protein (mg/L)	1.56	2.83	0.18
Adiposity			
BMI (kg/m^2)	28.70	27.47	0.63
Subcutaneous Fat Area (cm^2) at L4/5	271.54	317.52	0.48
Visceral Fat (cm^2) at L4/5	82.73	102.78	0.54
Carotid Intima Media Thickness (averaged over left and right cIMT)			
cIMT, carotid bulb (max mm)	0.86	0.98	0.19
cIMT, carotid bulb (avg mm)	0.70	0.78	0.26
cIMT, common carotid artery (max mm)	0.72	0.75	0.50
cIMT, common carotid artery (avg mm)	0.59	0.63	0.34
cIMT, internal carotid artery (max mm)	**0.65**	0.81	0.02
cIMT, internal carotid artery (avg mm)	**0.52**	0.64	0.03
Measures of Carotid Stiffness			
Peterson's Elastic Model (mmHg)	525.39	524.63	0.99
Circumferential Arterial Strain (no units)	0.093	0.094	0.91
Beta Stiffness Index (no units)	5.59	5.60	0.99
Elastic Modulus, Incremental (mmHg)	2493.73	2381.08	0.88
Young's Elastic Pressure Modulus (mmHg/mm)	466.90	455.57	0.94
Arterial Compliance (mm2/mmHg)	0.103	0.103	0.99
Flow Mediated Dilatation (Δ%)	5.01	3.92	0.21

*Variables are unadjusted.
†Variables are dichotomous and not log transformed.

Conclusion: This preliminary analysis suggests that the autoantibody-positive FDRs did not have worse indicators of vascular health compared to autoantibody-negative FDRs, which is contrary to our *a priori* hypothesis. These results tentatively indicate that the increased risk for CVD that is seen in RA is not detectable in the preclinical autoantibody phase of the disease, using the structural or functional vascular changes measured herein. Analysis of the larger cohort is warranted to confirm these results.

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Relationships Between Air Pollution and Presence of Rheumatoid Arthritis-Related Autoantibodies in Individuals without Rheumatoid Arthritis: Studies of the Etiology of Rheumatoid Arthritis. Ryan W. Gan[1], Kevin D. Deane[2], Gary O. Zerbe[3], Michael H. Weisman[4], Jane H. Buckner[5], P. K. Gregersen[6], Ted R. Mikuls[7], James R. O'Dell[8], Richard M. Keating[9], V. Michael Holers[2] and Jill M. Norris[1]. [1]Colorado School of Public Health, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]Colorado School of Public Health / University of Colorado Anschutz Medical Campus, Aurora, CO, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]Benaroya Research Institute at Virginia Mason, Seattle, WA, [6]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [7]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [8]Univ of Nebraska Med Ctr, Omaha, NE, [9]University of Chicago, Chicago, IL

Background/Purpose: Rheumatoid arthritis (RA) is characterized by the presence of circulating autoantibodies, which can be predictive of

future RA development in currently unaffected individuals. The specific etiology of RA is unknown; however, studies have suggested that respiratory exposures such as smoking and proximity to road traffic may be associated with development of RA. To elucidate the relationship between respiratory exposures and explore the potential that inhaled exposures may act early in the pathogenesis of RA, leading to early generation of RA-related autoimmunity, we evaluated the association between exposure to air pollution, measured by yearly average particulate matter (PM) 2.5 and 10, and presence of RA-related autoantibodies.

Methods: The Studies of the Etiology of Rheumatoid Arthritis (SERA) is a multicenter study evaluating first-degree relatives (FDRs) of a proband with RA. FDRs lack classifiable RA at enrollment and are serially assessed for the presence of RA-related autoimmunity and potential risk factors for RA development. Outcomes assessed were presence of rheumatoid factor (RF), and the High Risk profile (positive for anti-CCP autoantibody and/or ≥2 RF isotypes), demonstrated to be >96% specific for future RA. Exposure to PM was assigned using the Environmental Protection Agency Air Quality System and interpolated with inverse distance weighted spatial analyses using Geographic Information Systems. PM exposures were linked to resident zip codes of FDRs living within 50 km of an air monitoring station in five states. PM exposures were categorized by tertiles (low, moderate, high levels) due to evidence of nonlinear associations with autoantibodies. RA-related autoantibody status and PM tertiles were analyzed using nonlinear mixed models to account for repeated measures.

Results: Our study population had a mean age of 45 years, was 70% female, 72% non-Hispanic White, and mostly non-smokers (88%). A majority of our study population lived in Colorado (39.1%) followed by California (29.4%), Nebraska (12.6%), Washington (10.6%), and New York (8.3%). No significant associations were observed between RA-related autoantibody outcomes and PM 2.5 or PM10 tertiles (Table).

Table. Odds ratios (OR) for rheumatoid factor and high risk profile in relation to tertiles of PM 2.5 microns in diameter and PM 10 microns in diameter.

	Outcome			
	Rheumatoid Factor n=110 cases		High Risk Profile n=105 cases	
PM 2.5 (n=860 FDRs, 1743 visits)	OR	95% CI	OR	95% CI
Low (< 8.2 µg/m³)	1.00	ref	1.00	ref
Moderate (8.2 to 9.9 µg/m³)	0.74	0.34-1.63	0.41	0.16-1.07
High (> 9.9 µg/m³)	1.26	0.40-3.94	0.50	0.15-1.68
PM 10 (n= 728 FDRs, 1473 visits)	n= 93 cases		n= 96 cases	
Low (< 23.8 µg/m³)	1.00	Ref	1.00	Ref
Moderate (23.8 to 26.7 µg/m³)	0.95	0.44-2.05	0.59	0.25-1.40
High (> 26.7 µg/m³)	0.98	0.44-2.19	0.48	0.20-1.15

Adjusted for age, ethnicity, gender, current smoking status, education, and recruitment site. The reduced sample size for the PM10 analysis is due to a smaller number of air monitoring stations measuring PM10.

Conclusion: These results suggest that exposure to PM is not significantly associated with autoantibody positivity in individuals without RA, although there is a trend towards an inverse association between PM and the High Risk Profile, which is contrary to our *a priori* hypothesis that PM is associated with increased risk of RA-related autoimmunity. The observed results could be due to the aggregate nature of our exposure variable. Alternatively, exposure to PM may not be an initial trigger of autoimmunity but may act later to facilitate the development of clinically-apparent RA. Continued observation of this cohort is important to investigate the exact role of air pollution in the etiology of RA.

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Trends in 21st century Health Care Utilization in a Rheumatoid Arthritis Cohort Compared to the General Population.

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Background/Purpose: To study twenty-first century trends in health care utilization by rheumatoid arthritis (RA) patients compared to the general population.

Methods: Observational cohort study; using Swedish health care register data, we identified 3977 Region Skåne residents (mean age year 2001, 62.7 years and 73% women) consulting for RA (ICD-10 codes M05 or M06) in 1998–2001.We randomly sampled two referents from the general population per RA patient matched for age, sex, and area of residence. We calculated the year 2001–2010 trends for the annual ratio (RA cohort/referents) of the mean number of hospitalizations and outpatient clinic visits.

Results: By the end of the 10-year period 62% of RA patients and 74% of referents were still alive and resident in the region. From 2001 to 2010 the ratio (RA cohort/referents) of the mean number of hospitalizations for men and women decreased by 27% (p=0.01) and 28% (p=0.004), respectively. The corresponding decrease was 29% (p=0.005), and 16% (p=0.004) for outpatient physician care, 34% (p=0.009) and18% (p=0.01) for nurse visits, and 34% (p=0.01) and 28% (p=0.004) for physiotherapy (Figure 1 and 2).
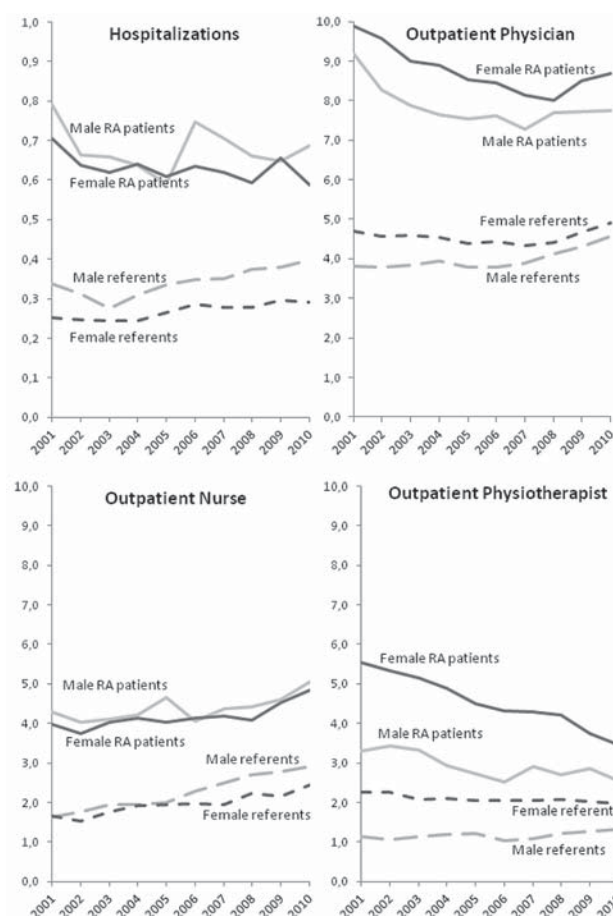
Figure 1. Health care utilization during the first decade of the twenty-first century by patients in a closed rheumatoid arthritis cohort and their matched referents from the general population. The y-axes show the mean number of visits per subject per calendar year.
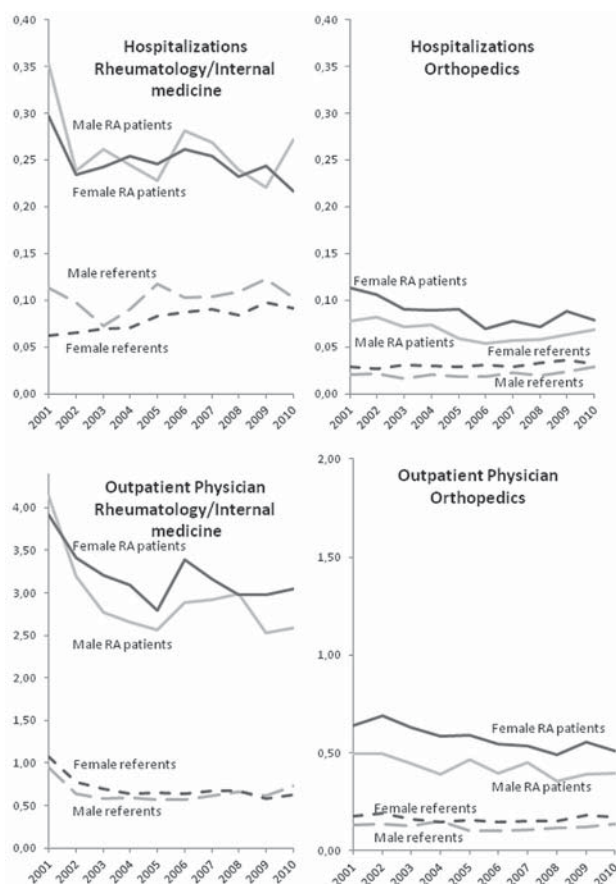
Figure 2. Health care utilization during the first decade of the twenty-first century by patients in a closed rheumatoid arthritis cohort and their matched referents from the general population. The y-axes show the mean number of visits per subject per calendar year.

Conclusion: During the twenty-first century, coinciding with increasing use of earlier and more active RA treatment including biological treatment, the overall inpatient and outpatient health care utilization by a cohort of RA patients decreased relative to the general population.

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Length of Stay for Rheumatoid Arthritis Related Orthopedic Surgery Has Improved Over the Past 3 Decades and Is Related to Disease Markers. Results From Two UK Multicentre Inception Cohorts (1986–2011) Compared with National Data. Elena Nikiphorou[1], Stephen Morris[2], David James[3], Patrick D. Kiely[4], David Walsh[5] and Adam Young[6]. [1]ERAS, St Albans City Hospital and University College London (UCL), St Albans, United Kingdom, [2]Research Department of Epidemiology and Public Health, 1–19 Torrington Place, United Kingdom, [3]Diana Princess of Wales Hospital, Grimsby, United Kingdom, [4]St. Georges Hospital, London, United Kingdom, [5]City Hospital, Nottingham, United Kingdom, [6]St Albans City Hospital, St Albans, United Kingdom

Background/Purpose: Length of Stay (LoS) is one of the main drivers of costs for orthopedic surgery in RA. Better medical and surgical treatments in recent years should result in shorter LoS. Studies have reported LoS trends in RA-related orthopedic interventions, but less is known about clinical factors affecting it. In the current economic climate, with over-pressurized health services, identifying and targeting such factors could result in reduced LoS, and improved health care utilization planning.

Methods: LoS has been examined in two very similar multi centre inception cohorts, the Early RA Study (ERAS) (n=1465, 1986–1999) and the Early RA Network (ERAN) (n=1236, 2002–2010). Details of orthopedic interventions included date, type of procedure and LoS. The results were validated against the National Joint Registry and Hospital Episode Statistics, and follow up based on the National Death Register. Standard clinical, laboratory and x-ray measures recorded at baseline and annually were used to investigate factors affecting LoS with univariate and multivariate regression analysis.

Results: There were 770 (29%) out of 2701 patients in ERAS & ERAN who had a total of 1602 procedures: 40% major, of which 88% were total joint replacements (mainly knee followed by hip); 24% were intermediate (mainly hand/foot surgery) & 16% were minor (soft tissue surgery surgery/tendon transfers). A gradual reduction in the median LoS was noted over 25 years for major, intermediate and minor procedures: 10, 4 & 2 days respectively (IQRs 7–15, 3–7, 1–4) in ERAS & 7, 3 & 1 days (IQRs 5–8, 1–7, 1–2) in ERAN. Figure 1 shows the changing median LOS for the commonest types of surgery: Total Knee & Hip Replacements (TKRs & THRs) over 25 years. Figure 2 shows TKR median LoS compared with national data. Extrapolation of national data suggests that in the 1990s TKRs resulted in longer LoS than in the 2000s. The cost of a TKR based on 5 days LoS currently in the UK is ≤5576. The decline in LoS across various procedures has resulted in reduced costs. In multivariate analyses LoS varied significantly by type of procedure, DAS, hemoglobin (HB) levels and HAQ scores. Normal baseline HB significantly reduced LoS by 1.8 days (p=0.001), baseline HAQ<1 by 1.8 days (p=0.002) & low 1year DAS (<3.2) by 1.1 days (p=0.051).

Figure 1.
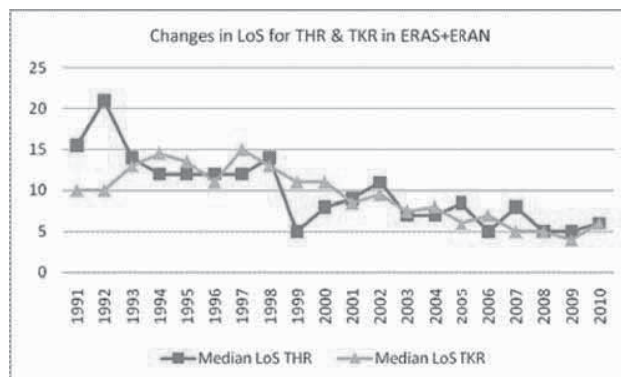
Figure 2.
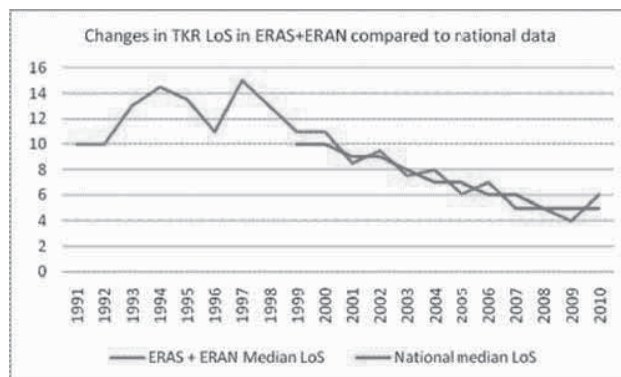
Conclusion: LoS in RA-related orthopedic surgery has declined over the last 25 years, which could be a reflection of improved management of RA, and medical and surgical in patient treatments. Normal baseline HB, low baseline HAQ and low DAS at 1 year were found to be significant predictors for LoS.

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Patient-Reported Outcomes Associated with Achieving and Maintaining Low Disease Activity in Rheumatoid Arthritis. Martin J. Bergman[1], James W. Shaw[2], Mary Cifaldi[2], Gourab De[3], Tony He[4], Rajeev Ayyagari[4] and James Signorovitch[4]. [1]Taylor Hospital, Ridley Park, PA, [2]Abbott Laboratories, Abbott Park, IL, [3]Analysis Group, Inc., New York, NY, [4]Analysis Group, Inc., Boston, MA

Background/Purpose: Treat-to-target (T2T) guidelines for rheumatoid arthritis (RA) recognize low disease activity (LDA) as an acceptable therapeutic goal, particularly in patients with longstanding disease. The guidelines advocate that treatment targets be maintained throughout the course of the disease. A study was conducted to assess associations of patient-reported outcomes (PROs) with achievement and maintenance of LDA.

Methods: Data were taken from four phase II/III randomized trials of adalimumab (ADA), alone or in combination with methotrexate (MTX), vs. MTX monotherapy for the treatment of RA in patients with early or late stage disease. Changes in scores for the Health Assessment Questionnaire Disability Index (HAQ-DI), the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) subscale, the four domains of the Work Productivity and Activity Impairment (WPAI) questionnaire, a visual analog scale measuring pain (VAS-P), and other PRO measures were compared between patient groups defined according to achievement of LDA after 12 weeks of treatment. Among those patients who achieved LDA, changes in PROs were compared between subgroups defined according to maintenance of LDA following an additional 12 or 14 weeks of treatment (based on the timing of study follow up). LDA was defined as having a composite disease activity score based on 28 joints and C-reactive protein (DAS28-CRP-4) <3.2 at a given assessment. The principle analyses were conducted using pooled data from the four trials with additional analyses being stratified by disease duration (i.e., early or late) or treatment received (i.e., ADA or MTX).

Results: A total of 2,533 patients with DAS28-CRP-4 assessments at baseline and after 12 weeks of treatment were included in the study. Compared with patients who did not achieve LDA after 12 weeks of treatment (N=1,820), those achieving LDA (N=713) had significantly greater improvements in scores for the HAQ-DI, FACIT-F, and VAS-P as well as the presenteeism, overall work impairment, and activity impairment domains of the WPAI. Among the 684 patients achieving LDA at week 12 with follow-up at week 24/26, those who maintained LDA (N=557) had significantly greater improvements in scores for the HAQ-DI, FACIT-F, VAS-P, and activity impairment domain of the WPAI than those who failed to sustain LDA (N=127). Similar results were obtained when performing analyses in disease duration and treatment subgroups.

Mean ± SD Changes in (A) Week 12 Outcomes for Patients with and Without LDA at Week 12 and (B) Week 24/26 Outcomes for Patients Who Maintained or Lost LDA after an Additional 12/14 Weeks of Treatment

Outcome	Change from Week 12 - Baseline (A)			Change from Week 24/26 - Baseline (B)		
	Did Not Achieve LDA	Achieved LDA	P-value	Did Not Maintain LDA	Maintained LDA	P-value
HAQ-DI [range: 0–3]	−0.51 ± 0.57	−0.90 ± 0.64	<0.0001	−0.67 ± 0.75	−1.01 ± 0.65	<0.0001
FACIT-F [range 0–52]	7.19 ± 10.73	11.33 ± 10.63	<0.0001	9.00 ± 11.45	12.16 ± 10.63	<0.0001
WPAI [range: 0–100]						
Absenteeism	−6.54 ± 30.62	−13.40 ± 33.25	0.0511	−13.57 ± 39.41	−9.54 ± 27.66	0.5907
Presenteeism	−13.71 ± 26.55	−24.66 ± 27.29	0.0004	−14.00 ± 27.98	29.25 ± 25.40	0.0917
Overall work impairment	−12.64 ± 29.42	−29.81 ± 33.25	<0.0001	−22.49 ± 41.05	31.55 ± 29.22	0.3495
Activity impairment	−19.65 ± 25.66	−33.78 ± 26.38	<0.0001	−12.94 ± 28.66	38.74 ± 26.22	<0.0001
VAS-P [range: 0–100]	−24.03 ± 27.89	−41.98 ± 24.78	<0.0001	−27.87 ± 30.38	44.44 ± 23.80	<0.0001

Notes: With the exception of the WPAI, which was administered in only one of the four trials, results are presented for analyses of the pooled trial data. Wilcoxon tests were performed to facilitate group comparisons. The FACIT-F was scored so that higher values indicated less fatigue. All other outcomes were scored so that higher values indicated worse functioning, work productivity, or pain.

Conclusion: RA patients achieving LDA after 12 weeks of treatment have significantly reduced disability, pain, work impairment, and fatigue compared to those who do not achieve LDA. A similar pattern of differences is observed between patients who maintain LDA and those who fail to do so after 24/26 weeks of treatment. The results of this investigation support the value of achieving and maintaining LDA, as recommended by the T2T guidelines.

Disclosure: M. J. Bergman, None; **J. W. Shaw**, Abbott Laboratories, 3, Abbott Laboratories, 1; **M. Cifaldi**, Abbott Laboratories, 1, Abbott Laboratories, 3; **G. De**, Abbott Laboratories, 5; **T. He**, Abbott Laboratories, 5; **R. Ayyagari**, Abbott Laboratories, 5; **J. Signorovitch**, Abbott Laboratories, 5.

The Difference in Performance of DAS28 and RADAI During Pregnancy Might Explain Discrepancies Between Older and More Recent Studies On the Impact of Pregnancy On Rheumatoid Arthritis. Jan Naterop[1], Johanna M.W. Hazes[2] and Radboud J.E.M. Dolhain[2]. [1]Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, The Netherlands, Rotterdam, Netherlands, [2]Erasmus Medical Center, Rotterdam, Netherlands

Background/Purpose: Pregnancy is the only condition in which Rheumatoid Arthritis (RA) shows spontaneous remission. Both older and more recent studies showed improvement of disease activity, which was more pronounced and occurred earlier in pregnancy in the older studies. An explanation for the difference in improvement could be that the older studies measured RA disease activity retrospectively using self-assessed questionnaires, whereas the more recent studies measured disease activity prospectively using a joint score. The Disease Activity Score in 28 joints (DAS28) and the self-assessed Rheumatoid Arthritis Disease Activity Index (RADAI) are both valid tools to determine the disease activity in RA. However the influence of pregnancy on the RADAI score has not been determined. Insight into this may contribute to a better understanding of the difference in outcome between older and more recent studies. Should the RADAI prove to be a valid instrument during pregnancy, it could be used for studies on RA and pregnancy. The aim of this study is to determine the validity of the RADAI during pregnancy in patients with RA by determining the correlation and agreement of the RADAI to the DAS28.

Methods: Pregnant RA patients were visited at their home-address (once before conception, during every trimester and three times post partum). During these visits the disease activity was measured by the RADAI and the DAS28. Correlation coefficients were determined for each time point. Furthermore, patients were stratified according to three disease states (high, intermediate, low and remission combined) based upon DAS28 and RADAI, with cut off points for the RADAI that are thought to be equivalent to those used for the DAS28.

Results: Disease activity determined by RADAI as well as by DAS28 showed a decrease during pregnancy and a flare after delivery (p< 0.01) (fig. 1). The correlations between DAS28 and RADAI were good (pre conception rho = 0.49, all other time points 0.61 < rho < 0.71 (p<0.01). When patients were stratified according to disease states, it was shown that according to the RADAI more patients showed remission or low disease activity during first trimester. (1st trim. RADAI 42,1%;DAS28 26.3%), whereas during the 3rd trimester these percentages were comparable (RADAI 43.3%; DAS 41.3%). After delivery, for both the RADAI and the DAS28, highest disease activity was observed at 12 weeks after delivery. Despite this the agreement on the disease activity states between RADAI and DAS28 was low (0.28 < kappa < 0.51).
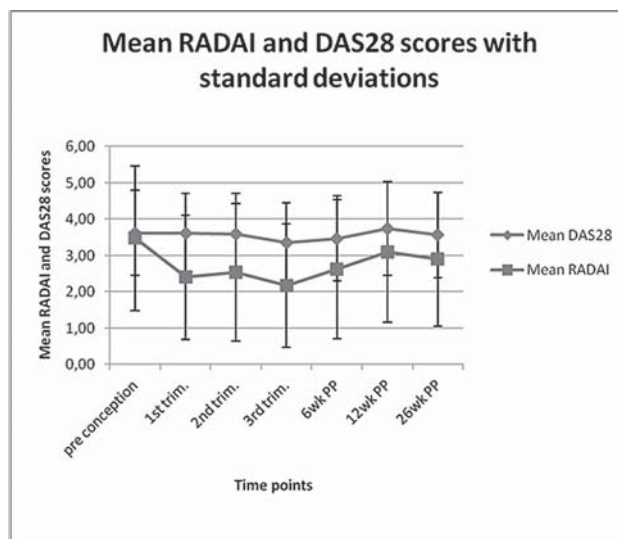

Fig 1.

Conclusion: The RADAI and DAS28 show moderate to good correlations. The RADAI might be a useful questionnaire to determine the disease activity for pregnant patients with RA. The study also shows that the RADAI

score drops earlier than the DAS28. This might explain why earlier studies that used self-assessed questionnaires show earlier improvements as compared to recent studies.

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Comorbid Conditions Do Not Explain Divergent Patient Assessments of Disease Activity and Global Health in Patients with Rheumatoid Arthritis. Dörte Huscher[1], Katja Thiele[2], Sascha Bischoff[2], Ulrich von Hinüber[3], Guido Hoese[4], Kirsten Karberg[5], Wolfgang Ochs[6] and Angela Zink[1]. [1]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Rheumatologist in Private Practice, Hildesheim, Germany, [4]Rheumatologist in Private Practice, Stadthagen, Germany, [5]Rheumatologist in Private Practice, Berlin, Germany, [6]Rheumatologist in Private Practice, Bayreuth, Germany

Background/Purpose: In the discussion of the 2010 ACR/EULAR remission criteria the issue has been raised to what extent patients are able to distinguish rheumatoid arthritis (RA) related disease activity from global health assessment. It was proposed that co-morbidity is a major driver of poor self-assessed global health when exceeding disease activity.

Methods: We used cross-sectional data of 2,242 RA patients, enrolled in the National Database of the German Collaborative Arthritis Centres between 2005 and 2010, for whom both self-assessed disease activity [VAS 0–100] and global health [NRS 0–10] were documented. Patients who were seen in more than one year were included only once. For comparison, the disease activity scale was transformed to NRS 0–10.

Results: 75% of the patients were female, their mean age was 62.3 years, the median disease duration 7.9 years. For 1,673 patients (75%) the ratings of disease activity and of global health were equal, 213 (10%) rated global health better and 356 (16%) worse. While mean global health scores in these three groups were rather similar, disease activity ratings revealed remarkable differences. Patients who rated their global health worse than their current disease activity were more frequently male, had low mean self-assessed disease activity, and a low DAS28 score. Their pain scores were, however, above their self-assessed disease activity. The proportions of patients with co-morbid conditions were comparable between the groups that rated "better" and "worse", but higher for those patients who gave the same scores for global health and disease activity. For patients with comorbid conditions, the average number of comorbid conditions was higher in patients who rated their global health better than those who rated worse.

Table 1. Characteristics of patients with better, the same or worse global health rating when compared to self-assessed disease activity. Displayed are mean (and median) if not indicated otherwise.

	Patient's assessment: global health compared to disease activity		
	better	the same	worse
N [% of all 2,242 patients]	213 [9.5%]	1,673 [74.5%]	356 [15.9%]
Male	25%	24%	31%
Age, years	61.1	62.7	60.9
Disease duration, years	8.6 (5.6)	10.9 (8.8)	9.3 (6.0)
Patient ass. disease activity [NRS 0-10]	5.1 (5.0)	4.5 (5.0)	2.2 (2.0)
Patient ass. global health [NRS 0-10]	3.3 (3.0)	4.5 (5.0)	4.1 (3.5)
Pain [NRS 0-10]	4.1 (4.0)	4.5 (5.0)	3.6 (3.0)
Number of tender joints	2.0 (0.0)	1.7 (0.0)	1.0 (0.0)
Number of swollen joints	1.3 (0.0)	1.2 (0.0)	0.9 (0.0)
ESR	26.1 (18.0)	22.9 (17.0)	22.9 (16.0)
CRP	1.4 (0.6)	1.0 (0.4)	1.0 (0.4)
DAS28(ESR, global health)	3.2 (3.0)	3.2 (3.0)	3.0 (2.8)
Physician ass. disease activity [NRS 0-10]	2.0 (1.0)	1.5 (1.0)	1.4 (1.0)
With comorbidity	66%	81%	68%
Number of comorbidities if any	2.5 (2.0)	2.6 (2.0)	2.1 (2.0)

Conclusion: The majority of patients with RA gave concordant ratings for disease activity and global health. Differences in ratings were mainly driven by higher disease activity, while global health scores were similar between the groups with concordant and discordant ratings. Comorbidity played no recognizable role for differences between both scores.

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Factors Influencing On the Discordance Between 2011 ACR/EULAR Criteria and Physician's Clinical Judgment for Remission in Rheumatoid Arthritis Patients. Yoon-Kyoung Sung[1], Bo Young Yoon[2], Soo-Kyung Cho[1], Chan-Bum Choi[1], Dae-Hyun Yoo[1], Jae-Bum Jun[1], Tae-Hwan Kim[1], Shin-Seok Lee[3], Tae-Jong Kim[3], Jisoo Lee[4], Jung-Yoon Choe[5], Sung-Hoon Park[5], Seung-Jae Hong[6], Yeon-Ah Lee[6], Jinseok Kim[7], Eun-Mi Koh[8], Hoon-Suk Cha[8], Jaejoon Lee[8], Won-Tae Chung[9], Sung Won Lee[9], Choong-Ki Lee[10], Hye-Soon Lee[11], Wan-Hee Yoo[12], Young Mo Kang[13] and Sang-Cheol Bae[14]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Inje University Ilsan Paik Hospital, Goyang, South Korea, [3]Chonnam National University Medical School, Gwangju, South Korea, [4]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [5]Catholic University of Daegu School of Medicine, Daegu, South Korea, [6]Kyung Hee University, Seoul, South Korea, [7]Jeju National University, Jeju, Korea, South Korea, [8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [9]Dong-A University Hospital, Busan, South Korea, [10]Yeungnam University Hospital, Daegu, South Korea, [11]Hanyang University Guri Hospital, Guri, South Korea, [12]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [13]Kyungpook National University School of Medicine, Daegu, South Korea, [14]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea

Background/Purpose: Remission is a primary end point in the treatment of rheumatoid arthritis (RA). To ensure more uniform reporting of outcome measures, American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) recently developed new definitions of RA remission. The 2011 ACR/EULAR remission criteria provide the stringent definition of remission, but do not always concordant with the state of remission defined by physicians. The purpose of this study was to compare the concordance between new remission criteria and physician's clinical judgment of remission and to identify influencing factors on discordance between them.

Methods: Total of 1,140 patients with RA were recruited from KORean Observational study Network for Arthritis (KORONA), a database generated by rheumatologist investigators across the South Korea. The frequency of remission was evaluated based on various definitions including the Boolean based ACR/EULAR criteria and physician's clinical judgment. The agreement between them was estimated by Cohen's kappa (κ). For the patients in remission according to Boolean based ACR/EULAR criteria and/or physician's judgment (n=279), we divided them into three groups; Group 1(remission according to both criteria and physician's judgment), Group 2 (remission only by criteria), and Group 3 (remission only by physician's judgment). On multinomial logistic regression analysis, we identified influencing factors for both discordant groups compared to concordance group in remission

Results: Remission rates with the Boolean based ACR/EULAR remission criteriam CDAI, and SDAI were 10.5%, 16.4% and 17.2%, respectively. Remission rate according to physician's clinical judgment was 18.4%, while DAS28 remission rate was 27.4%. The agreement between new criteria and physician's clinical judgment for remission was low (κ =0.202) and the concordant remission rate was only 4.1% (n=51, group 1), while the prevalence of remissions by only criteria and physician's judgment were 6.1% (n=69, group 2) and 13.9% (n=159, group 3), respectively. Multinomial logistic regression analysis shows that the pain affected on both discordant groups and sleep disturbance and fatigue were associated with remission only by physician's clinical judgment. These indicated that patient's subjective symptoms such as pain, fatigue, and sleep disturbance may influence on the discordance between 2011 ACR/EULAR criteria and physicians' clinical judgment for remission (Table).

Table. Multinomial logistic results for discordant remissions as compared to concordant remission between Boolean based ACR/EULAR criteria and physician's clinical judgment (N=279)

Variable	Remission according to Boolean based ACR/EULAR criteria only				Remission according to physician's clinical judgment only			
	Coefficient	SE	Significance	Odds ratio (95% CI)	Coefficient	SE	Significance	Odds ratio (95% CI)
Disease duration	−2.823	1.697	.096	.059 (.002-1.652)	−.002	1.618	.999	.998 (.042-23.806)
Age	−.026	.017	.124	.974 (.942-1.007)	−.009	.017	.592	.991 (.959-1.024)
Male	.181	.452	.689	1.198 (.494-2.903)	.119	.449	.791	1.126 (.468-2.713)
Normal ESR	−.034	.429	.937	.967 (.417-2.240)	−.175	.424	.680	.840 (.366-1.927)
Normal CRP	−.716	.401	.075	.489 (.223-1.074)	.089	.392	.821	1.093 (.507-2.354)
HAQ-DI	2.018	1.113	.070	7.527 (.850-66.645)	1.557	1.088	.152	4.744 (.563-39.982)
Fatigue	−.008	.010	.428	.992 (.974-1.011)	.023	.008	**.003**	**1.024 (1.008-1.040)**
Sleep disturbance	−.007	.017	.675	.993 (.961-1.026)	.025	.013	**.050**	**1.026 (1.000-1.052)**
Pain	.060	.030	**.043**	**1.062 (1.002-1.125)**	.105	.029	**<.001**	**1.110 (1.050-1.174)**

Conclusion: Although the 2011 ACR/EULAR remission criteria are stringent than physician's clinical judgment, their agreement was low and patients' subjective symptoms such as pain, fatigue, and sleep disturbance were associated with discordance between them.

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Physician's Global Assessment Is Affected by Physician's Age and Gender, but Not by Patient Age and Gender in Rheumatoid Arthritis Patients Treated in Routine Care. Data From the Danish Nationwide Danbio Registry. Cecilie Lindstrom Egholm[1], Theodore Pincus[2], Lene Dreyer[3], Torkell Ellingsen[4], Bente Glintborg[3], Marcin Kowalski[5], Tove Lorenzen[4], Ole Rintek Madsen[3], Henrik Nordin[6], Claus Rasmussen[7] and Merete L. Hetland[8]. [1]Copenhagen University Hospital/DANBIO at Glostrup, Copenhagen, Denmark, [2]NYU Hospital for Joint Diseases, New York, NY, [3]Copenhagen University Hospital at Gentofte, Gentofte, Denmark, [4]Region Hospital Silkeborg, Silkeborg, Denmark, [5]Aalborg Hospital, Aalborg, Denmark, [6]Rigshospitalet, Copenhagen, Denmark, [7]Vendsyssel Hospital, Hjoerring, Denmark, [8]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark

Background/Purpose: Several studies have shown that significant discordance exists between patient (PATGL) and physician (DOCGL) global measures of rheumatoid arthritis (RA) disease activity. These studies have focused on patient-related factors associated with discrepancy. However, relatively little is known about possible physician-related factors that might explain the DOCGL. The aim of the present study was to determine potential physician-related factors associated with the DOCGL score.

Methods: Physician data (e.g. age, sex, title and experience) were requested by questionnaire from physicians who use the Danish nationwide rheumatological DANBIO-registry in their clinical work. DANBIO data based on first encounters between patients and physicians in the registry were analysed. Patient data included: sex, age, duration of disease, Health Assessment Questionnaire (HAQ) score, C-reactive protein (CRP), swollen (SJC28) and tender joint counts (TJC28), treatment (biologic/non bio), and 100 mm visual analogue scales (VAS) for PATGL, pain and fatigue. Multivariate linear regression analysis was performed to determine physician- and patient-related factors that affected DOCGL.

Results: 90 physicians returned the questionnaire (34%). The physicians were matched with 8,970 patient encounters, for which physicians were 55% females, age 52 (47– 56) years (median, Interquartile Range (IQR)), 78% were consultants in rheumatology, no. of patients seen per month per physician was 80 (50–120). Patients were 74% females, age 61 (51–70) years, disease duration 7 years (2–15), CRP 6 (3–12) mg/L, HAQ 0.75 (0.25–1.375), SJC 1 (0–3), TJC 2 (0–6), pain 32 (14–57) mm and fatigue 42 (19–67) mm. 34% were treated with biologics. The median DOCGL was 12 (5–27) mm and PATGL 39 (17–64) mm - a difference of 27 mm.

Table 1 shows patient and physician factors associated with the DOCGL. DOCGL was higher in male physicians, in the younger half of physicians

and in physicians who were not consultants. Patient gender did not affect DOCGL, whereas SJC and TJC did. Patient age was statistically but not clinically significant for DOCGL. Thus, on average, the DOCGL in a male non-consultant less than 52 years old was 9.8 mm higher than that of a female consultant above 52 years of age.

Table 1. Results of multivariate linear regression analysis of physician and patients factors as predictors of DOCGL, only statistically significant variables included.

Variable	Estimate	95 % CI	p
Intercept	−0.577		
Physician			
Sex female	1		
male	3.345	2.672–4.018	<0.001
Age > 52 years	1		
≤ 52 years	3.461	2.754–4.168	<0.001
Consultant in rheumatology, yes	1		
No	3.126	1.747–4.505	<0.001
Patient			
Age (10 years' increase)	−0.0018	−0.0024−−0.0014	<0.001
Patient VAS-global	0.147	0.135–0.159	<0.001
CRP	0.116	0.100–0.133	<0.001
SJC28 (range 0-28)	2.775	2.672–2.878	<0.001
TJC28 (range 0-28)	0.745	0.680–0.809	<0.001

Referent group for continuous variables is represented by each 1-unit increase in that variable when not otherwise stated. Results adjusted for patient gender, clinic site, country for medical exam, research experience, experience with joint scoring, number of patients seen monthly, and assessed level of importance of inflammation, fibromyalgia, comorbidity and patient social factors. VAS = Visual Analogue Scale, measured on a 0-100 mm scale; CRP= C-reactive protein, measured in mg/L; SJC28 = swollen joint count on 28-joint assessment; TJC28 = tender joint count on 28-joint assessment. Adjusted R^2 = 0.69.

Conclusion: This study of 90 physicians matched with >8,000 RA patients treated in routine care showed clinically significant inter-physician variations in the physicians′ global score. Male physicians scored on average 3.1 mm higher than female, physicians that were < 52 years old scored 3.7 mm higher than their older counterparts, and consultants scored 3.1 mm lower than non-consultants. SJC and TJC, but not patient age and gender, also affected the physicians′ global score. The significant contribution of physician-associated factors may have implications for research involving measures of physicians′ global score and for clinical care.

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Validation of Remission of Rheumatoid Arthritis by Traditional Disease Activity Score and Provisional Criteria by American College of Rheumatology and European League Against Rheumatism: Patient Reported Outcomes Analyzed From 3 Phase III Golimumab Trials. Chenglong Han[1], E. Keystone[2], Roy Fleischmann[3], Josef S. Smolen[4], Paul Emery[5], Mark C. Genovese[6], Mittie K. Doyle[7] and Elizabeth C. Hsia[7]. [1]Johnson & Johnson Pharmaceutical Services, LLC, Malvern, PA, [2]University of Toronto, Toronto, ON, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [5]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [6]Stanford University Medical Center, Palo Alto, CA, [7]Janssen Research and Development, LLC, Spring House, PA

Background/Purpose: Remission by Boolean-based definition (all scores on the tender joint and swollen joint count, CRP (mg/dL), and patient global assessment ≤1) and by Simplified Disease Activity Index-based definition (SDAI, <3.3) were proposed by ACR/EULAR. Using patient reported outcomes as anchors, this analysis validated these remission criteria against traditional Disease Activity Score (DAS28) using CRP remissions (<2.6) in 3 RA patient populations.

Methods: The efficacy of golimumab (GLM) was assessed in methotrexate (MTX)-naïve RA patients (GO-BEFORE, N=637), RA patients with inadequate response to MTX (GO-FORWARD, N=444) and RA patients previously treated with biologic anti-TNFα agent(s) with baseline MTX use (GO-AFTER, N=305). Pooled data from patients who received placebo

(PBO) + MTX, or GLM (50 or 100mg) + MTX, q4 weeks were used for this analysis.Patient reported outcomes were measured with the following: Health Assessment Questionnaire (HAQ), Physical and Mental Component Summary Scores of 36-item short-form health survey (SF36 PCS and MCS), Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), and a Visual Analogue Scale (VAS, 0–10) of impact of RA on daily work productivity. Descriptive statistics were provided forpatient reported outcomes among patients in remission as defined by the 3 remission definitions.

Results: Greater proportions of patients treated with GLM + MTX vs patients treated with PBO + MTX achieved remission in the 3 studies by each remission definition.In the pooled analysis, the remission rate at wk 24 was the highest (20.2%) by DAS28, compared to remission by SDAI (10.6%, $p<0.001$) and remission by Boolean-based definition (8.6%. $p<0.001$). Patients with remission by DAS28 achieved normal physical function (HAQ≤0.5), normal SF-36 PCS, and MCS (≥50) by 67.8%, 38.4%, 62.2%, respectively; these parameters were numerically lower when compared to patients with remission by SDAI (81.3%, 62.8%, 72.1%, respectively) or by Boolean-based definition (82.0%, 63.5%, 74.3%, respectively). Patients in remission by DAS28 had higher HAQ scores (0.43 ±0.49) compared to patients in remission by SDAI (0.26±0.41) or Boolean-based criteria (0.28±0.44).Similar results were observed in measures of FACIT-fatigue and productivity VAS scores. Among MTX-naive patients in the GO-BEFORE study who achieved remission by DAS28, 71.3% achieved normal physical function compared to 86.9% of those in remission by SDAI and 86.5% of patients in remission by Boolean-based definition. Among anti-TNFα experienced patients in the GO-AFTER study, 62.1% of those in remission by DAS28 achieved normal physical function compared to 65.0% of those in remission by SDAI, and 66.7% of patients in remission by Boolean-based definition.

Conclusion: While disease remission has been adapted as a target in the management of RA, more stringent remission criteria proposed by ACR/EULAR can provide optimal patient-reported outcomes.
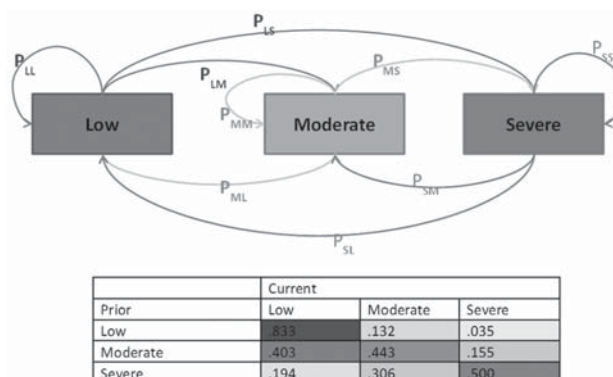
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Transitions Among Disease Activity States: Estimates and Models of Covariate Associations. George W. Reed[1], David H. Collier[2], Andrew S. Koenig[3],Katherine C. Saunders[4], Joel M. Kremer[5] and Sameer Kotak[6]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Amgen Inc., Thousand Oaks, CA, [3]Pfizer Inc., Collegeville, PA, [4]CORRONA, Inc., Southborough, MA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY, [6]Pfizer Inc., New York, NY

Background/Purpose: Many RA patients have variable disease activity over time due to disease variability, reduction in efficacy of current medications, environmental factors and other co-morbid disease changes. Prior methodologies have been developed but in the absence of application with real data the models have not been validated. The model applied to patient clinical data may potentially provide insights into clinically relevant associations to disease state transitions and enhance treatment methods.

Methods: Disease activity states of low, moderate and severe were defined using CDAI (Low:CDAI≤10; Moderate 10<CDAI≤22; and Severe 22<CDAI).A Markov Model for repeated measures allowing for covariate dependence was used to model transitions among three states (Figure 1a) - from a prior disease state to a current disease state.Population transition probabilities were estimated and a multinomial logistic regression model used to examine the impact of covariates on disease states and if the impact of covariates depended upon the prior disease state.Initiation of DMARDS, duration of RA, age and insurance were used as covariates of interest. Disease activity measures at repeated visits of RA patients were used from the CORRONA RA registry (Oct, 2001 to Feb, 2012).There were 160,262 visits from 24,136 RA patients with CDAI measured at the visit and at the prior visit.

Results: Estimated transition probabilities in the population are in Figure 1b, showing that if the disease state at the prior visit was low then the probability of remaining low (P_{LL}) is 0.833 and the probability of transitioning to moderate disease (P_{LM}) at the next visit is.132, and to severe (P_{LS}) is.035.Transition from any state to low disease was seen to improve from 2001-05 to 2009-12 with P_{LL} going from 0.79 to 0.84 ($p<0.001$). Logit models estimated the effect of covariates adjusted for time between visits. A patient in a prior state of moderate disease had a relative risk ratio of 7.6 (95%CI: 7.08–8.21) to be in moderate disease at the current visit (vs a patient in a prior state of low disease) if no DMARD was initiated on the prior visit.If a DMARD was initiated the risk was reduced to 4.08 (3.59–4.63). Longer duration of RA increased the risk of transition in a moderate or severe state. Age and insurance did not interact with prior disease states but showed an association with current disease state - with private insurance associated with lower levels of disease and age 50–64 with a larger risk for moderate and severe disease vs age <50.

	Current		
Prior	Low	Moderate	Severe
Low	.833	.132	.035
Moderate	.403	.443	.155
Severe	.194	.306	.500

Conclusion: Estimation of transition probabilities among disease states provides a snapshot of RA population risks dependent upon prior states and a methodology for examining factors associated with those risks. Current models estimate the impact of initiating DMARDS and the duration of RA and provide a proof of concept of the modeling framework that can be mined for examining further associations.

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Variability of the SF-6D Determinants Over Time in Early Arthritis: Results From the Espoir Cohort. Cécile Gaujoux-Viala[1], Bruno Fautrel[2], Kossar Hosseini[3], Francis Guillemin[3], René-Marc Flipo[4] and Anne-Christine Rat[5]. [1]Lorraine University, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy; Paris 6 - Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [2]Paris 6 - Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [3]Lorraine University, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy, France, [4]Rheumatology Department, Lille University Hospital, Lille, France, [5]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy, France

Background/Purpose: There is growing emphasis on the cost-effectiveness of treating rheumatoid arthritis. The SF-6D, derived from the SF36, is an indirect utility measure widely used to calculate quality-adjusted life-years in order to assess health benefits. Few trials directly record the health utility measures (or the SF36), needed for economic analyses. Consequently linear regression methods have been used to transform Health Assessment Questionnaire (HAQ) scores into utility measures.

Objective: 1) To assess which variables are associated with the SF-6D in early arthritis over 3 years

2) To check if these associations are stable over 3 years

Methods: – *Patients*: Between 2002 and 2005, the ESPOIR cohort enrolled 813 patients with recent arthritis in at least 2 joints with 6 weeks to 6 months disease duration.

– *Data available*: SF-6D utility measures were longitudinally assessed in 813 patients with EA (at baseline, 6 months, 1, 2 and 3 years). Clinical and biological variables and X-rays were also recorded.

– *Analysis*: The determinants of SF-6D-derived utility values at each time-point over 3 years were assessed by multivariate linear regressions to analyze which specific aspects of early arthritis were independently associated with the SF-6D.

Results: At baseline, higher HAQ, patient global evaluation, pain, fatigue, and lower mental status were significantly associated with lower SF-6D. HAQ and AIMS2-SF-mental scores explained 49 and 14% of the variance respectively. At 6 months, 1, 2 and 3 years, higher HAQ, patient global evaluation, fatigue, age and lower mental status were significantly associated with lower SF-6D. HAQ and AIMS2-SF-mental scores explained 7 to 13% and 55 to 57% of the variance respectively (figure).

% variance of the SF-6D explained

■HAQ ■Mental score ■Patient Global Assessment
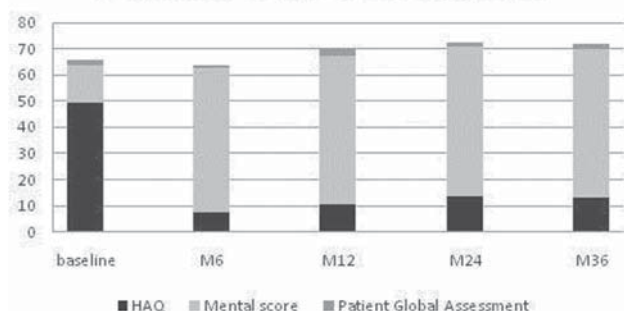
Conclusion: The determinants of the SF-6D varied over 3 years in EA patients. At baseline, the SF-6D was essentially determined by function whereas after 6 months, the SF-6D was essentially determined by mental status. Cost-effectiveness models should not use utility values derived from HAQ.

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Substantial Functional Disability Is the Key Determinant of Discrepancies Between EQ-5D and SF-6D Utility Measures in Early Arthritis: Results From the Espoir Cohort. Cécile Gaujoux-Viala[1], Bruno Fautrel[2], Kossar Hosseini[3], Francis Guillemin[4], René-Marc Flipo[5] and Anne-Christine Rat[4]. [1]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy; Paris 6 - Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [2]Paris VI University, Paris, France, [3]Lorraine University, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy, France, [4]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy, France, [5]Rheumatology Department, Lille University Hospital, Lille, France

Background/Purpose: The EQ-5D, a 5-dimensional multi-attribute questionnaire, and the SF-6D, derived from the SF36, are 2 indirect utility measures widely used to calculate quality-adjusted life-years in order to assess health benefits.

Objective: 1) To assess which variables at baseline are associated with EQ-5D and SF-6D in early arthritis 2) To assess which variables at baseline are associated with substantial utility differences between EQ-5D and SF-6D.

Methods: –*Patients*: EQ-5D and SF-6D utility measures were assessed in 813 patients included in the French nationwide ESPOIR cohort, which enrolled early arthritis (EA) patients with ≥2 swollen joints for less than 6 months and suspicion of RA.

– *Analysis*: Determinants of EQ-5D and SF-6D at baseline were assessed by multivariate linear regression. Multivariate linear regression was used to determine which aspects of EA were independently associated with the difference between the two utility measures in patients with substantial utility difference, i.e. l SF-6D – EQ5D l >0.074 (highest minimal important difference, MID).To assess the determinants of having substantial utility difference, patients were divided into 3 categories at baseline:l SF-6D-EQ-5D l >0.074 and SF-6D>EQ-5D, l SF-6D – EQ-5D l >0.074 and EQ-5D>SF-6D and the others corresponding to no substantial difference (reference category). Variables collected at baseline were analyzed by polytomous logistic regression, with the 3 categories as dependent variables.

Results: At baseline, mean values were 0.52±0.31 (range -0.59 to 1) for EQ-5D and 0.58±0.11 (range 0.30 to 0.92) for SF-6D. In the multivariate linear regression model, higher HAQ, pain and lower mental status (AIMS2-SF) were significant determinants of a lower EQ-5D. HAQ and AIMS2-SF-mental scores explained 41.4 and 7.9% of the variance respectively. Higher HAQ, patient global evaluation, pain, fatigue, and lower mental status were significantly associated with lower SF-6D. HAQ and AIMS2-SF-mental scores explained 49.3 and 14.5% of the variance respectively.

The majority of patients presented a substantial difference between the 2 utility values>0.074 (66.5%) (mean difference 0.064 [range -0.421;0.941]). In these patients, higher disability, lower mental status and higher CRP were associated with substantial difference between EQ-5D and SF-6D. HAQ and AIMS2-SF-mental scores explained 43.3 and 2% of the variance respectively.

In the polytomous logistic regression model, HAQ, lower mental status and higher pain were associated with substantial difference between EQ-5D and SF-6D. Lower disability was associated with the probability that EQ-5D was substantially superior than SF-6D in comparison with no substantial difference. Higher disability was associated with the probability that SF-6D was substantially superior to the EQ-5D.

Conclusion: Higher functional disability is the key element leading to substantial difference between the two utility measures in EA patients. EQ-5D and SF-6D are not interchangeable especially in patients with worse functional ability and the results of cost-utility studies using different utility instruments must not be compared.

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Benefits of Treat-to-Target Guideline Compliance in Patients with Rheumatoid Arthritis: A Retrospective Claims Analysis. Martin J. Bergman[1], James W. Shaw[2], Mary A. Cifaldi[2], Annie Guerin[3], Pooja Chopra[3] and James Signorovitch[4]. [1]Taylor Hospital, Ridley Park, PA, [2]Abbott Laboratories, Abbott Park, IL, [3]Analysis Group, Inc., Montreal, QC, [4]Analysis Group, Inc., Boston, MA

Background/Purpose: To achieve clinical remission/low disease activity in patients with rheumatoid arthritis (RA), the treat-to-target (T2T) guidelines recommend frequent disease monitoring through patient-rheumatologist interactions. The economic implications of treating to target have not been fully quantified.This study aimed to estimate the effects of compliance with T2T recommendations regarding patient follow-up on health care resource utilization (HRU) and medical service costs in RA patients newly initiated on a disease-modifying anti-rheumatic drug (DMARD).

Methods: Patients ≥18 years old with ≥2 RA diagnoses and ≥1 prescription fill for a DMARD that was preceded by a rheumatologist encounter (within 7 days) were identified from the MarketScan® Commercial Claims and Encounters database (1/2000 to 9/2011).A patient's index date was randomly selected among all new DMARD initiation dates with ≥3 months of continuous enrollment before and ≥15 months after that date. Patients with a follow-up rheumatologist visit within 90 days of the index date were defined as compliant, while all others were classified as noncompliant.HRU and costs (measured from a payer's perspective in 2010 US dollars) were measured over a 1-year period starting 90 days after the index date.Adjusted all-cause HRU and medical service costs were compared between compliant and noncompliant patients using multivariable regression.

Results: A total of 15,103 RA patients were selected with 10,739 (71.1%) being designated as compliant.The average age was 49.9 years, and 23.2% were male.After adjusting for potential confounding, compliant patients exhibited significantly fewer inpatient admissions and inpatient days, fewer emergency room (ER) visits, and less use of other medical services but significantly more outpatient visits than noncompliant patients.Consequently, compliant patients had significantly lower adjusted inpatient costs but significantly higher adjusted outpatient costs than noncompliant patients.The inpatient cost reduction offset the increase in outpatient costs such that there was no significant difference between the two cohorts with respect to aggregate adjusted medical service costs.

Comparison of all-cause HRU and medical costs between compliant and noncompliant RA patients

	Unadjusted Incidence Rate				Unadjusted Mean Medical Cost			
	Compliant [A]	Not Compliant [B]	Adjusted IRR (95% CI) [A]/[B]	P-value	Compliant [A]	Not Compliant [B]	Adjusted Cost Diff. (95% CI) [A]-[B]	P-value
All medical services					13,662	11,596	321 (−825, 1,487)	0.624
INPT visits					3,620	3,715	−933 (−1,721, −290)	0.020
No. INPT admissions	0.17	0.17	0.86 (0.77, 0.97)	0.010				
No. INPT days	0.97	1.04	0.78 (0.66, 0.94)	0.007				
Outpatient visits	20.35	17.75	1.05 (1.02, 1.07)	<0.001	8,793	6,515	1,665 (888, 2,843)	<0.001
ER visits	0.36	0.36	0.90 (0.83, 0.99)	0.023	305	303	−20 (−70, 20)	0.340
Other	3.38	3.25	0.93 (0.88, 0.98)	0.004	943	1,063	−135 (−294, 29)	0.124

Abbreviations: HRU, health resource utilization; RA, rheumatoid arthritis; IRR, Incidence Rate Ratio; CI, Confidence Interval; INPT, inpatient; ER, emergency room.
Notes: The other medical service category included laboratory, radiology, and other ancillary services. Given that the unadjusted incidence rates and means could have been biased due to confounding, comparative estimates were adjusted for age, region, insurance, comorbidities, index year, and HRU and costs at baseline (chosen based on P < 0.05).

Conclusion: RA patients benefit from being followed in a manner consistent with T2T guidelines.Notably, they exhibit fewer inpatient visits with lower length of stay and lower ER utilization without incurring an increase in medical service costs due to more frequent follow-up with a rheumatologist.However, more research is needed to assess the impact of rigorous follow-up on patient quality of life.

Disclosure: M. J. Bergman, None; **J. W. Shaw**, Abbott Laboratories, 3; **M. A. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1; **A. Guerin**, Abbott Laboratories, 5; **P. Chopra**, Abbott Laboratories, 5; **J. Signorovitch**, Abbott Laboratories, 5.

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An Innovative Strategy to Implement Clinical Practice Guidelines for Rheumatoid Arthritis and Osteoarthritis Patients Through Facebook.
Lucie Brosseau[1], George Wells[2], Sydney Brooks[3], Gino De Angelis[4], Mary J. Bell[5], Mary Egan[1], Stéphane Poitras[1], Judy King[1], Lynne Casimiro[6], Laurianne Loew[1] and Michael Novikov[1]. [1]University of Ottawa, Ottawa, ON, [2]University of Ottawa Heart Institute, Ottawa, ON, [3]The Arthritis Society, Ontario Division, Toronto, [4]Univeristy of Ottawa, Ottawa, ON, Ottawa, ON, [5]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, [6]Montfort Hospital, Ottawa, ON

Background/Purpose: A major issue in health research today is finding effective and efficient ways to exchange knowledge between researchers, clinicians and the general public. Evidence Based Clinical Practice Guidelines (EBCPGs) are systematically developed statements that help practitioners decide on appropriate health care in specific clinical circumstances. The purpose of the study is to determine if an updated online evidence-based educational program delivered through *Facebook* is effective in improving the knowledge, skills, and self-efficacy of patients with arthritis in relation to evidence-based self-management rehabilitation interventions (updated Ottawa Panel EBCPGs) for OA and RA.

Methods: Adult patients (>18 years old) with self-reported OA or RA were eligible for the study. A total of 110 participants were recruited from the general public and different arthritis patient organizations throughout Canada. Eleven participants were selected to participate in a focus group using the Delphi process to rank and select effective self-management strategies for OA and RA according to level of implementation burden. Ninety-nine participants were then selected to participate in the online *Facebook* intervention which included a "group" web-page providing case-based video clips on how to apply the selected self-management interventions. Over a 3-month period, participants were asked to complete 3 online questionnaires regarding their previous knowledge, intention to use/actual use of the self-management strategies, self-efficacy and confidence in managing their condition.

Results: Knowledge acquisition scores improved among OA and RA participants with a mean difference of 1.8 (p<0.01) when compared from baseline to immediate post-intervention. At 3 months post-intervention, almost all self-management strategies were successful with participants following through on their intention to use the self-management strategies, however, statistically significant results were only demonstrated for "aquatic jogging" (p < 0.05) and"yoga" (p < 0.05) among OA participants, and "aquatic therapy" (p<0.01) among RA participants. Statistically significant knowledge acquisition scores improved by 31% for ice massage (p<0.01),

22% for transcutaneous electrical nerve stimulation (p<0.05), 21% for bed rest (p<0.05), 19% for balneotherapy (p<0.01), 14% for yoga (p<0.05), 12% for low level laser therapy (p<0.05), and 11% for semi-rigid inserts in extra depth shoes (p<0.05). Self-efficacy was maintained from immediate post-intervention to 3 months follow-up, and confidence improved as the study progressed.

Conclusion: Patients were able to perform the interventions in the privacy and comfort of their own home, discuss and learn from experience of other individuals afflicted with the same disease using this popular social networking site. This online program can provide patient organization representatives with the opportunity to learn about evidence-based self-management strategies for OA and RA, to increase their awareness of useful community resources, and support their efforts to disseminate the information to others with arthritis.

Disclosure: L. Brosseau, None; **G. Wells**, None; **S. Brooks**, None; **G. De Angelis**, None; **M. J. Bell**, None; **M. Egan**, None; **S. Poitras**, None; **J. King**, None; **L. Casimiro**, None; **L. Loew**, None; **M. Novikov**, None.

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Longitudinal Hypertension Diagnosis and Control Among a Primary Care Medically Homed Population with Rheumatoid Arthritis.
Katya Voelker[1] and Christie M. Bartels[2]. [1]Univ of Wisconsin School of Medicine and Public Health, Madison, [2]Univ of Wisconsin School of Medicine and Public Health, Madison, WI

Background/Purpose: Hypertension is a key risk factor for cardiovascular disease (CVD) in patients both with and without rheumatoid arthritis (RA). In their review on hypertension in RA, Panoulas et al (2008) cited relative risks of hypertension for CVD events ranging from 1.5 to 4.3.Reports vary further regarding hypertension prevalence in RA largely due to varying case definitions and timing of observations. Herein we examined hypertension prevalence, diagnosis and control using standard Joint National Committee-7 (JNC-7) hypertension diagnostic criteria applied to a medically homed RA population.

Methods: Using a cohort design we studied all adult patients with rheumatoid arthritis who were medically homed receiving primary care and rheumatologic care within a large multispecialty practice. Patients were considered "medically homed" for each consecutive year (2005–2011) that they met definitions requiring ≥2 visits over a 24 month baseline (including at least 1 primary care visit and 1 rheumatology visit). RA was determined using algorithms requiring two ICD-9 claims of 714.0–714.4 in 24 months (modified Katz 1997, MacLean 2000). Hypertension diagnosis eligibility was defined by applying Joint National Committee-7 (JNC-7) hypertension diagnostic criteria: 3 or more blood pressures >140/90 or 2 or more pressures >160/100 on >2 separate visits. An algorithm was used to search for >1 ICD-9 hypertension code (Tu 2007) or any antihypertensive medication to indicate hypertension diagnosis. Total hypertension prevalence counted diagnosed and undiagnosed cases meeting JNC definitions. Control was also based on JNC-7 criteria requiring 3 normal blood pressures <140/90. Descriptive statistics were used to report hypertension prevalence, diagnosis and control during the baseline and subsequent medically homed period.

Results: In our population of 1,099 medically homed RA patients (mean age 56; 76% female) the prevalence of hypertension was 30% at baseline and 56% during follow up.Hypertension generally increased with age (Fig. 1). Compared to older patients, a higher proportion of younger patients remained undiagnosed. Although older patients were more often diagnosed, three quarters remained uncontrolled.

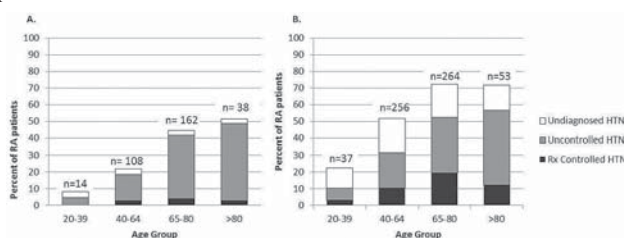Figure 1. Hypertension diagnosis and control in medically homed RA patients at (A) baseline and (B) longitudinal follow up.

Conclusion: Our examination of medically homed RA patients receiving both primary care and rheumatology care highlights the importance of examining longitudinal data for assessing diagnosis and control of hypertension among patients with RA. These data illustrate that point prevalence

estimates may under report hypertension rates relative to standard JNC definitions using multiple observations. Overall, young hypertensive RA patients were proportionally less likely to be diagnosed and control remained poor across all age groups.

Disclosure: K. Voelker, None; C. M. Bartels, None.

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Prediction of Mortality in Rheumatoid Arthritis Using a Serum Cytokine Profile. Agustin Escalante[1], Roy W. Haas[1], Daniel F. Battafarano[2] and Inmaculada Del Rincon[1]. [1]University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]Brooke Army Medical Ctr, San Antonio, TX

Background/Purpose: Cytokines are important in the pathogenesis of RA. Their concentration in the serum rises immediately prior to RA onset, and may be associated with disease outcome. We are not aware of any studies of serum cytokines in relation to mortality in RA. In the present study we examined the accuracy of a profile of 38 cytokines in the prediction of mortality in an RA cohort.

Methods: We studied RA patient participants in a longitudinal study of RA outcomes who were recruited at a routine visit to a rheumatologist.After a baseline assessment that included a collection of a serum specimen, which was stored for future study, patients were tracked yearly for follow-up.We identified deaths thorough next of kin, physician or public database reports, confirmed by death certificate.We used stepwise logistic regression to examine the association between serum cytokine levels and mortality, adjusting for the confounding influence of age and sex. We used receiver operator characteristic(ROC) curves to measure accuracy of mortality prediction.

Results: We studied 1,328 RA patients.A serum sample for cytokine measurement was available in 1,217 patients, who accrued 5,965 person-years of observation, or an average of 4.9 years per patient (range 1 day to 15 years).During this time, 204 deaths occurred for a mortality rate of 3.4 per 100 patient-years, 95% CI 3.0 to 3.9.Using age- and sex-adjusted stepwise logistic regression to identify cytokines associated with mortality, we found that the serum concentrations of the following 8 cytokines were independently associated with increased mortality: IP-10, 1.48 (1.03, 2.11); EGF, 1.27 (1.05, 1.54); TNF-a, 1.47 (1.12, 1.91); MCP-1, 1.60 (1.14, 2.24); IL-8, 1.75 (1.36, 2.23); IL-3, 1.67 (1.05, 2.67); IFN-g, 1.4 (1.08, 1.80); and GRO, 2.08 (1.40, 3.09). In the same model, the following 5 cytokines were independently associated with reduced mortality:MDC, 0.36 (0.26, 0.51); GCSF, 0.54 (0.39, 0.74); MIP-1a, 0.75 (0.62, 0.90); and IL-17, 0.71 (0.57, 0.89).Values shown are odds ratios (95% CI). The area under the mortality prediction ROC curve for a model including age and sex plus the above 13 cytokines was significantly higher than a model that included age and sex alone (0.876 vs. 0.776, P < 0.001) (see figure).
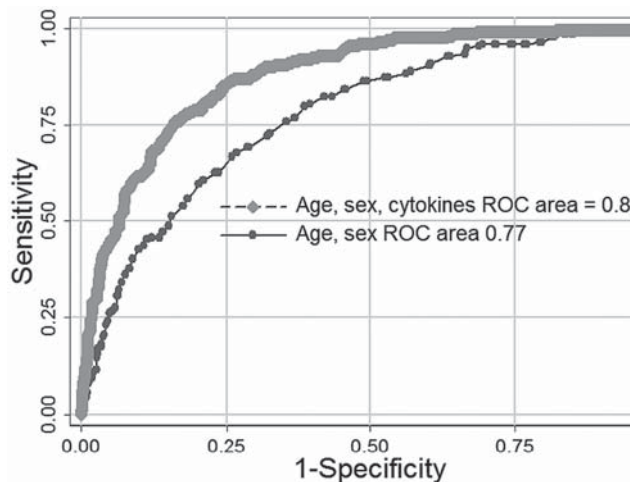
Conclusion: A serum cytokine profile is significantly associated with mortality in RA, and its accuracy in predicting mortality within 5 years is superior to that of age and sex alone. We are not aware of any previous reports of mortality prediction in RA using serum cytokine profiles.

Disclosure: A. Escalante, None; R. W. Haas, None; D. F. Battafarano, None; I. Del Rincon, None.

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The Effect of Weather On Patient Symptoms in Rheumatoid Arthritis: A Systematic Review of the Literature and Exploration of "weather sensitivity". Annika Cutinha[1], Frederick Wolfe[2] and Kaleb Michaud[3]. [1]University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Patients with rheumatoid arthritis (RA) often attribute an exacerbation of their symptoms to changes in the weather. There are several studies examining this relationship. We conducted a systematic review of the existing literature on the effect of weather on symptoms in RA, and a follow up study that characterized patients with RA that reported being "weather sensitive".

Methods: A systematic review of Medline and Embase from inception until November 2011 looked for articles that report the effect of any aspect of weather on any symptom or outcome of patients with arthritis and 765 articles qualified. Then only included were non-duplicative articles in English with RA patients. We identified a subset of patients as "weather sensitive"(WS) based on patients reporting worse symptoms with increased weather. We observed that the percentage of WS patients in the studies reviewed, along with the difference in study methods, played a role in determining the final results. In order to identify WS patients and determine if they differ from other patients, we queried a cohort of 6901 US rheumatic disease patients (including 4655 RA, 1206 osteoarthritis (OA), and 374 fibromyalgia (FMS)) participating in an observational study and compared their demographic and clinical characteristics.

Results: Only 19 articles (N=3357 RA patients) qualified for our review. These studies did not find a consistent association between weather and RA symptoms. For example, 4 studies found a positive correlation between temperature and symptoms like pain and stiffness, 4 others found a negative correlation, and 4 more found no correlation. We had similar results for 11 articles studying humidity and RA outcomes: 6 positive, 1 negative, and 4 had no correlation. For atmospheric pressure, 3 were positive, 1 was negative, and 6 had no correlation. Of the 4655 RA patients we surveyed, 63% reported being WS (compared to 71% of OA and 78% of FMS), 20% were not, and the remaining 17% did not know. Columns 2–3 of Table 1 list their characteristics. Patients in the WS group were younger, less male, less educated, and had shorter RA duration. They also had worse RA symptoms as measured by HAQ, pain VAS, and SF36. The logistic multivariable regression for WS odds ratios are provided in column 4. We accounted for possible over reporting of symptoms by including a patient symptom count and polysymptomatic distress scale.

Table. Characteristics of RA patients by weather sensitivity and multivariable logistic regression.

	Not weather sensitive (N=926) (SD)	Weather sensitive (N=2926)	Odds ratio (95%CI)
Age (years)	64.8 (12.0)	62.1 (12.3)	0.98 (0.97, 0.99)
Male (%)	25.6	15.0	0.71 (0.58, 0.88)
Education (0-17 years)	14.7 (2.2)	14.1 (2.3)	0.91 (0.88, 0.95)
RA duration (years)	19.7 (12.1)	18.6 (SD 12.3)	0.99 (0.99, 1.00)
HAQ (0-3)	0.61 (0.7)	1.10 (SD 0.7)	1.26 (1.02, 1.55)
Pain VAS (0-10)	2.16 (2.4)	3.97 (SD 2.7)	1.09 (1.04, 1.15)
SF36 Physical CS Score	44.3 (11.4)	36.0 (SD 10.8)	0.97 (0.96, 0.99)
Symptom count (0-37)	4.9 (4.6)	8.4 (6.0)	1.05 (1.03, 1.08)
Polysymptomatic distress scale (0-31)	6.2 (6.5)	11.5 (7.9)	1.02 (1.00, 1.04)

Conclusion: Although widely believed, no consistent association in the literature between weather and RA symptoms was seen.Patients with worse function and pain are more likely to report being WS even after controlling for sociodemographic status and general symptoms. Future studies aimed at objectively measuring WS are needed to further evaluate whether subjective symptoms are more correlated with weather possibly through increased pain sensitization.

Disclosure: A. Cutinha, None; F. Wolfe, None; K. Michaud, None.

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Poor to Moderate Performance of Patient Self-Report in Indentifying Periodontitis in Patients with Rheumatoid Arthritis. Ted R. Mikuls[1], Jeffrey Payne[2], Harlan Sayles[3], Shawneen Gonzalez[2], Jeffrey Markt[4], Mark Beatty[2], Grant W. Cannon[5], David McGowan[5], Gail S. Kerr[6], Robert Redman[7], Andreas M. Reimold[8] and Garth Griffiths[8]. [1]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Lincoln, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]Omaha, NE, [5]George E. Wahlen VA Medical Center, Salt Lake City, UT, [6]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [7]Washington DC VA, Georgetown and Howard University, Washington, DC, [8]Dallas VA and University of Texas Southwestern, Dallas, TX

Background/Purpose: Periodontitis (PD) is a putative risk factor for rheumatoid arthritis (RA) risk and progression.PD is defined as inflammation of the supporting tissues of the teeth, progressive attachment and bone loss and is characterized by pocket formation and/or gingival recession. No single definition of PD has been well established and consistently applied in research. Although results from standardized periodontal examinations are considered the 'gold-standard' for PD classification, studies examining the relationship of PD with RA have also relied on patient self-report for case ascertainment. The goal of this study was to examine the performance of patient self-reporting in identifying PD based on results from a standardized periodontal exam in patients with established RA.

Methods: In a multicenter study, RA patients satisfying ACR classification criteria underwent a standardized, calibrated, periodontal evaluation. PD was defined as the presence of clinical attachment loss 6 mm for 2 or more teeth and one or more sites with a probing depth $\geq$ 5 mm (consistent with severe PD). Characteristics of patients with and without PD were compared using the Student's t-test or Chi-square test. Patients responded to 6 questions previously used in research studies to assess for a history of PD, treatment, and/or related signs and symptoms (Table); the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the questions were calculated.

Results: Of the RA patients examined (n = 245), 82 (33.5%) had PD based on examination.Factors associated with an increased PD frequency included age (mean 62 vs. 57 yrs for PD vs. no PD, p = 0.014), male gender (82% vs. 53%, p < 0.001), ever smoking (78% vs. 55%, p < 0.001), and seropositivity for RF (92% vs. 81%, p = 0.025) or anti-CCP antibody (93% vs. 77%, p = 0.004). There were no associations of race, education, alcohol use, select comorbidity (diabetes, hypertension, heart disease), or medication use (prednisone, methotrexate, or biologic therapy) with the presence of PD. The metric properties of PD-related questions are shown:

	RA/+PD	RA/No PD	Sens.	Spec.	PPV	NPV
Do your gums bleed after you brush your teeth?	32%	14%	0.317	0.858	0.531	0.713
Have you ever been told that you have periodontal or gum disease involving bone loss or deep pockets?	37%	16%	0.366	0.839	0.536	0.722
Have you ever been told that you need periodontal or gum treatment (e.g. scaling and root planning or a "deep cleaning")?	39%	20%	0.390	0.804	0.500	0.724
Do you see a periodontist for treatment or cleanings?	28%	25%	0.284	0.748	0.365	0.672
Do you have "loose" teeth?	21%	4%	0.207	0.957	0.708	0.706
Have you ever had periodontal surgery?	16%	13%	0.159	0.875	0.394	0.670
Positive response to $\geq$ 1 PD screening question	70%	50%	0.707	0.497	0.414	0.771

Affirmative responses to the PD-questions were all more common (p $\leq$ 0.002) in RA patients with PD vs. No-PD, with differences in all but questions 4 and 6 being statistically significant.

Conclusion: In studies examining the relationship of PD with RA, patient self-report does not represent an adequate surrogate of clinically defined PD.In this study severe PD is very common in patients with established RA, affecting 1 in 3 patients. Although demonstrating moderate to good specificity in some cases, questions commonly used to assess for the presence of PD yield insufficient sensitivity (< 40%) in this population. Both PPV and NPV of these questions were consistently below 80% in this population, suggesting that misclassification and study bias are likely to occur in RA studies using patient self-report for PD case ascertainment.

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Physical Function, Pain and Fatigue Are Related to Sleep Disturbance in Females with Rheumatoid Arthritis. Cathrine Austad[1], Tore K. Kvien[2] and Till Uhlig[2]. [1]Diakonhjemmet Hospital, Norway, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: Sleep quality is an important aspect of health and well-being and the Outcome Measures in Rheumatology Clinical Trials group has identified sleep quality as a key concern for rheumatoid arthritis (RA) patients[1]. Patient reported sleep-disturbance is included in the RAID (RA Impact of Disease) score, but not in many other core patient reported outcomes (PROs) and is rarely reported in clinical trials.The aim of this study was to assess self-reported sleep disturbance in a large sample of patients from a population based RA registry and identify factors associated with self-reported sleep disturbance.

Methods: In a population based RA registry in Oslo, Norway, 868 patients aged 20–79 years (mean (SD) age 59.9 (12.3) years, disease duration 13.0 (10.8) years, 77.1% females) responded to a mailed questionnaire in 2009 (response rate 60.6%). 844 patients answered the numeric rating scale (NRS) on sleep disturbance due to RA (part of the RAID questionnaire) within the last week, and reported use of benzodiazepine like sleeping drugs (zopiclone/zolpidem = z-hypnotics) and other medications used in the treatment of RA. Other PROs included 100mm visual analogue scales (VAS) for pain, fatigue and patient global disease activity, HAQ (0–3, 3 worst), SF-36 with physical (PCS) and mental (MCS) component scores (0–100, 0=worst), RA Disease Activity Index (RADAI, 0–10, 10 worst) and RAID score (0–10, 10=extreme/very poor). Multivariate linear regression analyses were used to identify factors independently associated with sleep disturbance (0–10 NRS, 10=extreme sleep disturbance) and adjusted for age and disease duration.

Results:

Table 1. Clinical findings in females and males

	Female Mean (SD)	Male Mean (SD)	p-value
Significant gender differences			
· Disease duration (years)	13.5 (11.1)	11.5 (9.7)	0.02
· VAS fatigue (0-100)	45.9 (28.8)	40.5 (28.7)	0.02
· HAQ (0-3)	0.97 (0.73)	0.64 (0.62)	<0.001
· PCS (0-100)	36.0 (11.6)	37.9 (11.6)	0.05
· RAID (0-10)	3.46 (2.14)	2.96 (2.14)	0.004
· Sleep disturbance (0-10)	3.19 (2.79)	2.41 (2.71)	0.001
· Use Z-hypnotics	20.8%	12.6%	0.004
No significant gender differences			
· Age (years)	59.9 (12.6)	59.7 (11.4)	0.83
· VAS pain (0-100)	34.9 (24.3)	31.6 (25.1)	0.11
· VAS patient global (0-100)	37.8 (24.9)	34.5 (24.6)	0.10
· MCS (0-100)	46.8 (11.6)	47.3 (11.8)	0.61
· RADAI (0-10)	3.25 (1.70)	3,00 (1,72)	0.07
· Use sDMARD	60.5%	60.6%	0.99
· Use biologics	20.3%	18.7%	0.61
· Use prednisolone	35.4%	35.9%	0.91

Multivariate linear regression analyses, adjusted for age and disease duration, with sleep disturbance assessed by NRS(0–10) as dependent variable, identified significant independent associations with female gender (B=0.40, 95% CI 0.06, 0.74), HAQ (B=0.40, 95% CI 0.13, 0.67), RADAI (B=0.42, 95% CI 0.27, 0.57), VAS pain* (B=0.15, 95% CI 0.041, 0.27), VAS fatigue* (B=0.18, 95% CI 0.11, 0.25) and MCS* (B= -0.52, 95% CI -0.65, -0.38). *per 10 unit change.
Use of z-hypnotics was significantly associated with MCS, PCS, HAQ, RADAI, RAID, NRS sleep disturbance, VAS pain/fatigue/patglob (all p<0.001), and disease duration (p=0.03).

Conclusion: Sleep disturbance in RA is to a higher degree reported by females, and is independently associated with pain, fatigue and worse mental and physical function. Sleep is independently associated with RA disease impact and therefore merits attention in clinical care.

(1) Kirwan JR, Newman S, Tugwell PS, Wells GA. Patient Perspective on Outcomes in Rheumatology A Position Paper for OMERACT 9. J Rheumatol 2009; 36(9):2067-70.

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Correlations of Single Item Health Literacy Screening Questions with Established Measures of Health Literacy in Subjects with Rheumatoid Arthritis. Itziar Quinzanos[1], Joel M. Hirsh[1] and Liron Caplan[2]. [1]Denver Health Med Ctr, Denver, CO, [2]Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO

Background/Purpose: Preliminary research suggests that Health Literacy (HL) is associated with the functional status of rheumatoid arthritis (RA) patients.Single Item Health Literacy Screening (SILS) questionnaires are a convenient method of establishing the health literacy of patients. However, the wording of SILS, version 2 (SILS2, "How comfortable are you filling out medical forms by yourself?" Wallace LS, et al. J Gen Intern Med. 2006;21:874-7.)) may be misinterpreted by RA patients as an query regarding their physical limitations.We assessed the construct validity of the SILS2 by correlating scores with standardized HL measures.

Methods: English-speaking adult RA patients at Denver Health enrolled in a cross-sectional study. Subjects were asked to complete the SILS2, an older version of the SILS (SILS1, "How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?" Chew, et al. Fam Med 2004;36:588–594), as well as two longer HL measurement tools (Short Test of Functional Health Literacy in Adults [STOFHLA] and the Rapid Estimate of Adult Literacy in Medicine [REALM-]).Pearson correlation was used to assess the construct validity of the various tools.

Results: 110 subjects participated in the study. There was a strong correlation between the two SILS versions (Table 1). The correlation of SILS2 and REALM or STOFHLA was less robust (Table 1), but still moderately well correlated, though the distribution of scores within each SILS2 category demonstrated substantial scatter (Figures 1 and 2).

Table 1. Correlations of various measures of health literacy in subjects with RA

	SILS1	SILS2	REALM
SILS2	0.693	–	–
REALM	0.385	0.411	–
STOFHLA	0.416	0.439	0.554

STOFHLA = Short Test of Functional Health Literacy in Adults;
REALM = Rapid Estimate of Adult Literacy in Medicine;
SILS = Single-Item Literacy Screener
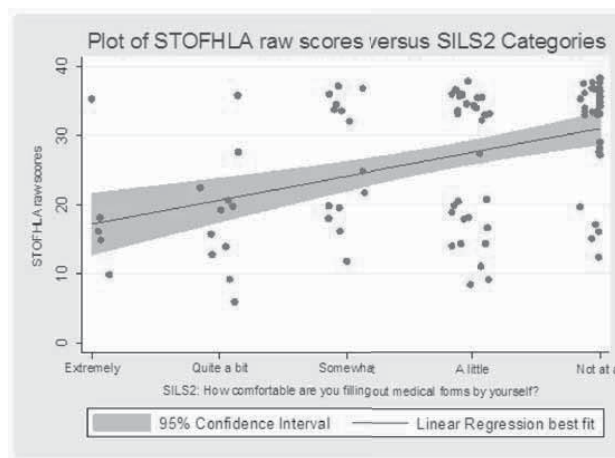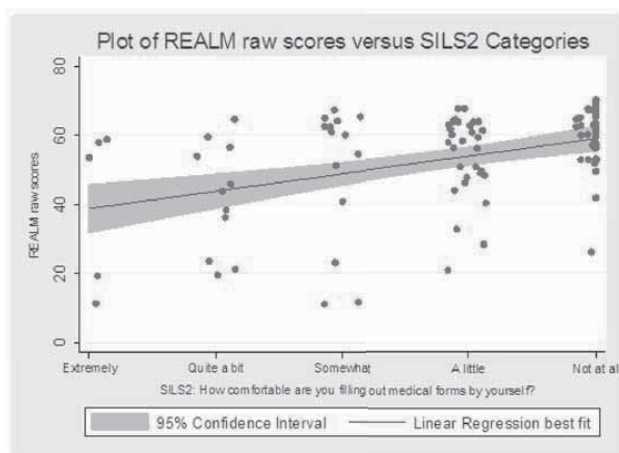
Conclusion: The SILS2 has construct validity in the assessment of HL in patients with RA. The SILS instruments are moderately good reflections of HL for groups of RA patients, however the substantial scatter of scores within each SILS category likely limits the clinical utility of the SILS in determining the HL on any one subject.

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Combined Response Index in Diffuse Systemic Sclerosis (CRISS)–Which External Anchors to Use When Developing the Index? Baseline Analysis. Dinesh Khanna[1], Veronica Berrocal[1], James R. Seibold[2], Peter A. Merkel[3], Maureen D. Mayes[4], Kristine Phillips[1], Robert W. Simms[5], Shervin Assassi[4], Philip J. Clements[6] and Daniel E. Furst[6]. [1]University of Michigan, Ann Arbor, MI, [2]Scleroderma Research Consultants LLC, Avon, CT, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Texas Health Science Center at Houston, Houston, TX, [5]Boston University School of Medicine, Boston, MA, [6]UCLA School of Medicine, Los Angeles, CA

Background/Purpose: As part of an NIH sponsored effort to develop a data-driven CRISS, we evaluated the face, content, and construct validity (convergent and discriminant) of patient (Pt) and physician (MD) assessments for use as the "external gold standards" or "anchors" to compare against individual core set items developed as part of a consensus meeting conducted by the Scleroderma Clinical Trial Consortium (Khanna D, Ann Rheum Dis 2008). This methodology has been used for developing other response criteria.

Methods: We recruited patients with early diffuse SSc (< 5 years) at four scleroderma centers in the United States. Pre-defined outcome measures were collected. These included demographics (e.g., age, disease duration), patient-reported outcomes (e.g., HAQ-DI, SF-36), physical examination (e.g., skin score, joint count), and physiological/ radiological tests (e.g. echocardiogram, pulmonary function tests).We assessed the test characteristics of 8 potential Likert anchors (3 MD-derived: global assessment; activity of skin involvement; severity of skin involvement and 5 Pt. derived: patient global assessment; activity of skin involvement; limitations due to skin involvement; overall pain; transition question regarding overall health)against the above measures. The associations between anchors and outcome measures were assessed using Spearman correlation. The discrimination between the anchors (trichotomized) and outcome measures was assessed using parametric or non-parametric tests. Each anchor was ranked (1[weakest]-8 [best]) based on the strength of the correlation (convergent validity) and significance of p value for trichotomized variables (discriminant validity) vs. each outcome measure. Due to skewness in the distributions, the median of the rankings for each anchor was used to identify anchors with the best convergent and discriminant validity.

Results: 200 patients completed the baseline visit. The mean (SD) age was 50 (11.9) yrs, disease duration was 2.4 (1.6) yrs, modified Rodnan skin score was 20.6 (10.1), and HAQ-DI was 0.96 (0.79). All 8 anchors have face validity. MD global, Pt. global, and Pt-activity skin have content validity as they assess overall SSc/ skin involvement [major feature of the SSc]. There were high correlations between the 3 MD anchors (r= 0.57–0.69) but wide variation forpt. anchors (r=0.17–0.58). The pt. anchors complemented MD anchors (r=0.18–0.47).Among the MD-administered anchors, global assess-

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ment had the best convergent and discriminant validity (Table). Of the patient-administered anchors, patient global assessment and pain had the best convergent and discriminant validity (Table).

Anchors	Median Ranking* (Convergent)	Median Ranking* (Discriminant)
MD global assessment	5	6
MD activity-skin	3	4
MD severity-skin	6	5
Pt global assessment	5	5
Pt activity-skin	5	4
Pt limitations due to skin	5	5.5
Pt overall pain	6	5.5
Pt Transition question	1	2

* Higher number denotes higher median ranking

Conclusion: All anchors (except transition anchor) have high convergent and discriminant validity. These measures will serve as key anchors in the analysis of the CRISS longitudinal database and the development of a composite index.

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Health State Utilities in Systemic Sclerosis: Results From the UCLA Scleroderma Quality of Life Study.

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Background/Purpose: Health state utility values (HSUVs) are used as weightings for quality-adjusted life years (QALYs) in economic analyses. It is not clear whether available instruments yield similar results or what domains of health are contributing to the overall score in a sample of patients with systemic sclerosis (SSc).

Methods: Our study included 223 individuals with rheumatologist-confirmed SSc from one academic center. An interviewer administered direct heath state utilities including the Time Trade Off (TTO), Visual Analogue Scale (VAS), and Standard Gamble (SG). We calculated the Short Form 6D from SF-36. Other clinical and health services variables were also collected.

Results: The mean age of the SSc sample was 51 years (SD 15) with the majority being female (84%).Mean (SD) health state utility values were 0.65 (0.13) for the SF-6D, 0.76 (0.28) for the TTO, 0.84 (0.22) for the SG, and 0.67 (0.19) for the VAS (P = 0.02).These measures are moderately correlated and appear to discriminate across measures of disease severity and function such as the physician's global assessment, digital tip ulcer count, swollen joint count, and tender joint count. Most HSUV measures show a monotonic descending relationship with measures of increased severity.

Table 1. Discriminant ability of health state utility value measures.

Disease Severity Measure	Category	SG	TTO	VAS	SF6D
			Mean	(SD)	
Physician's Global Assessment (0-10)	<2	.90(.16)	.85(.22)	.75(.15)	.72(.13)
	2-6	.82(.25)	.74(.30)	.63(.20)	.63(.12)
	>6	.80(.24)	.67(.31)	.63(.20)	.59(.10)
Digital Tip Ulcers	<0	.84(.22)	.76(.29)	.67(.19)	.65(.13)
	0-1	.85(.26)	.82(.30)	.63(.21)	.64(.14)
	>1	.88(.21)	.85(.22)	.84(.12)	.75(.19)
Rodnan score	<2	.83(.25)	.77(.28)	.69(.20)	.66(.13)
	2-13	.89(.16)	.81(.25)	.68(.19)	.66(.13)
	>13	.78(.27)	.66(.33)	.63(.19)	.63(.11)
Tender joint count	<0	.86(.21)	.79(.26)	.68(.19)	.67(.13)
	0-1	.68(.37)	.55(.38)	.61(.27)	.62(.07)
	>1	.83(.24)	.72(.32)	.63(.19)	.62(.13)
Swollen joint count	<0	.85(.22)	.77(.28)	.67(.19)	.65(.13)
	0-1	.62(.44)	.54(.45)	.59(.26)	.55(.17)
	>1	.88(.17)	.80(.26)	.72(.17)	.72(.14)

Conclusion: Different methods to generate HSUVs appear to provide different estimates, which have important implications for economic analysis. However, all of the methods appear to display construct validity with respect to clinical and health services variables.

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Medical Costs and Health Care Resource Use in Patients with Systemic Sclerosis in an Insured Population.

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Background/Purpose: Systemic sclerosis (SSc) is a chronic connective tissue disease affecting the skin and/or internal organs. Data on US economic burden of SSc is scant or old. The objective of this study was to estimate the medical costs and health care resource utilization of subjects with newly diagnosed and existing SSc in a large national US insurer.

Methods: Subjects at least 18 years of age and with claims-based evidence of SSc (ICD-9-CM 710.1x) were identified from a health plan database during 2003–2008. Subjects were divided into two cohorts; newly diagnosed and existing based on claims history of SSc. Subjects were matched using a ratio of 1:3 to unaffected controls, based on demographic and clinical characteristics. Healthcare costs and resource use were captured during a 12 month post-index period. A generalized linear model (GLM) was used to predict costs, controlling for demographic and clinical characteristics.

Results: 1,103 subjects with newly diagnosed SSc were matched to 3,309 controls, and 1,648 existing SSc subjects were matched to 4,944 controls. Mean overall annual healthcare costs were substantively higher among newly diagnosed subjects than matched controls ($18,934 vs. $5,302, p<0.001) and among existing disease subjects than matched controls ($17,365 vs. $5,508, p<0.001). Ambulatory costs were the largest driver of overall costs among both newly diagnosed and existing SSc subjects (mean annual ambulatory costs = $7,455 newly diagnosed; $6,713 existing). When adjusting for clinical and demographic characteristics (including comorbid conditions) with a GLM, the cost ratio of newly diagnosed SSc subjects to controls was 2.132 (95%CI: 1.84–2.47), and the cost ratio of subjects with existing SSc to controls was 1.988 (95%CI: 1.77–2.23). Predictors for higher costs after controlling for other variables were: evidence of lung disease, GI bleeding, renal disease, useof systemic corticosteroids, or drugs used to treat pulmonary hypertension (PAH)(all p<0.001). Significantly higher proportions of newly diagnosed and existing SSc subjects had post-index ambulatory visits, primary care physician visits, specialist visits, emergency department visits, and inpatient hospital stays (all p<0.001) than matched controls. Of the selected medications studied, a greater proportion of SSc subjects (both newly diagnosed and existing) than controls had claims for systemic corticosteroids, methotrexate, mycophenolate mofetil, cyclophosphamide, bosentan, and sildenafil (all p<0.001).

Conclusion: Medical costs and resource use associated with treating either new or existing SSc are high (compared to unaffected controls), and subjects with serious disease complications experience the highest costs. These findings emphasize the need to develop more effective therapeutic management strategies for multi-system diseases like SSc.

Smoking Is Associated with Worse and More Widespread Pain, Worse Disease Activity, Function, Fatigue and Health Related Quality of Life in Patients with Axial Spondyloarthritis–Results From a Population Based Cohort. Ann B. I. Bremander[1], Ingemar F. Petersson[2], Emma Haglund[3], Stefan Bergman[4] and Lennart TH Jacobsson[5]. [1]Halmstad University School of Business and Engineering, Halmstad, Sweden, [2]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [3]Spenshult Hospital for Rheumatic Diseases, Halmstad, Sweden, [4]R&D Center Spenshult, Oskarström, Sweden, [5]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Background/Purpose: In subjects with early axial Spondyloarthritis (SpA) smoking has recently been associated with earlier onset of disease, worse lesions of the sacroiliac joints and in later stages syndesmophyte progression. The aim was to study associations of smoking habits with self-reported information in a large population based cohort of patients with axial SpA.

Methods: A cross-sectional questionnaire survey performed in 2009 included all health care seeking subjects aged >18 years with a diagnosis of SpA according to ICD 10 codes identified by a regional health care register (n=3711). Smoking habits were studied in patients with ankylosing spondylitis (AS, ICD M45) and in patients who fulfilled criteria for "non AS axial SpA" (*without* having one of AS). Criteria for non AS axial SpA were based on data from the questionnaire: pain for 3 months or more during the last 12 months together with 2 or more features out of 5 (inflammatory back pain, history of psoriasis, uveitis/tendinitis, inflammatory bowel disease or heredity). The questionnaire included data on smoking (never smokers vs. ever smokers), disease activity (BASDAI) physical function (BASFI), general health (BAS-G) all measured with numerical rating scales 0–10 (best to worst), health related quality of life (EQ-5D, 0–1 worst to best), pain, fatigue (numerical rating scales 0–10 best to worst) and number of painful regions noted on a pain mannequin (0–16 best to worst). Linear regression analysis was performed and all data were controlled for sex and age.

Results: Response rate was 76% whereof 2167 (58%) returned the questionnaire and 18% declined participation in the study. 598 subjects had an AS diagnose and 572 fulfilled the criteria for non AS axial SpA.

The AS group had a mean age of 54 (SD14) years and 35% were women. Never smokers constituted 48% of the AS group. Ever smokers had worse scores in all studied variables compared with never smokers.

The linear regression analysis showed that ever smokers in the AS group had worse self-reported scores in BASDAI with age-sex adjusted parameter estimate (B) = 0.60 (95% CI 0.21; 1.00), BASFI B = 0.51 (95% CI 0.11; 0.91) and fatigue B = 0.51 (95% CI0.06; 1.00). There was a tendency to worse scores for ever smokers also in EQ-5D B = -0.04 (95% CI -0.09; 0.001).

Mean age in the non AS axial SpA group was 55 (SD 14) years and 68% were women. Never smokers constituted 38% of this group. Also in the non AS axial SpA group the linear regression analysis showed that ever smokers had worse self-reported scores in BASDAI with age-sex adjusted parameter estimate (B) = 0.59 (95% CI 0.23; 0.94), BASFI B = 0.59 (95% CI 0.17; 1.00), pain B = 0.45 (95% CI 0.08; 0.82) and fatigue B = 0.43 (95% CI0.03; 0.83), no of painful areas B = 0.73 (95% CI0.06; 1.46) and also in EQ-5D B = -0.06 (95% CI -0.11; -0.002).

Conclusion: In a large population based axial SpA cohort, both patients with AS and non AS axial SpA who were ever smokers reported worse clinical features compared with never smokers. Further longitudinal studies are needed to better understand cause and effect. However, smoking cessation should be recommended not only due to general health perspectives but also due to disease specific issues.

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Quality of Care: Reference and Counter Reference From Family Physicians and Rheumatologists' perspectives- A Pilot Study. Thiago D. Baumgratz[1], Raphael Battisti[1], Mirella Cuziol[1], Ana Carolina Reiff Janini[1], R.A. Levy[2] and Mirhelen M. Abreu[3]. [1]Medical Student at Universidade Federal de São Carlos, São Carlos, Brazil, [2]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [3]Universidade Federal de São Carlos, São Carlos, Brazil

Background/Purpose: We delineated family physicians' and rheumatologists' point of view when primary care is facing cases of rheumatic diseases. We also tried to identify barriers in the reference and counter reference.

Methods: This is a pilot study, transversally designed, with family physicians and rheumatologists in a single city. The methodological steps were: (1) Development and preparation of three clinical scenarios that simulate and address different levels of clinical severity; (2) application of these scenarios in the population of family physicians and rheumatologists; (3) validation of the study scenarios. The final scenarios constructed were: (a) *Scenario one:* a patient with an autoimmune disease diagnosis presenting fever and fatigue; (b) *Scenario two*: a patient with fibromyalgia and with poor adherence to the healthcare plan, requiring a medication to relief the symptoms; (c) *Scenario three:* patient with septic arthritis, prostration, and in poor clinical conditions. The scenarios were presented to two groups of physicians, which should choose regarding three decisions: (Decision 1) To apply a healthcare plan (investigation and/or treatment) and refer to a rheumatologist; (Decision 2) to prescribe medication and do not reference to rheumatologist; and (Decision 3) to refer to a rheumatologist with no primary care intervention. Finally, a multiple-choice questionnaire addressing potential factors that lead to barriers in the reference process of and counter reference was applied. Descriptive analysis was performed to map the results. As this was a pilot study, we used bootstrap method for constructing hypothesis tests.

Results: Twenty-two family physicians and rheumatologists were involved. Family physician's initiative to refer to specialized care was similar to the rheumatologist' expectation (median: 1.5 [minimum 1.5 to maximum 1.7], for family physicians and 1.6 [1.3 to 2] for rheumatologists). For *Scenario one*, the majority of interviewee chose Decision 1 [1.27 (1 –3), SD 0.59)]. For the *Scenario two*, respondents chose the decision 2 [2 (1 – 3), SD 0.76)]. For the *Scenario three, Decision three* was the preferred [1.47 (1–3), SD 0.83)]. For the reference and counter-reference system evaluation, family physicians tend to refer any clinical case that could be a rheumatic disease. They consider that there is a poor communication between family physician and rheumatologist [4.2 (2–5), SD 1.01)].

Conclusion: There is a tendency for referral to rheumatologists and a poor perception of risk. This posture can contribute to the quality of care impairment. Proper communication seems to be a hurdle for the reference and counter reference system.

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Systematic Review of Explanatory and Predictive Models in Rheumatology: Lack of Adhearance to Methodologic Standards. Daniel A. Albert. Dartmouth-Hitchcock Med Ctr, Lebanon, NH

Background/Purpose: Prognostic and explanatory models are frequently utilized in clinical medicine to assist in judgments about diagnosis, prognosis, and treatment options. I surveyed predictive and explanatory models in rheumatology by conducting a systematic review using a PubMed (Medicine) search of a two year period, starting January 1, 2010, and ending December 31, 2011. This identified 564 articles using the key words: "Rheumatology," and "prediction," "models," "stepwise," "regression," "multivariate," "survival," "prognosis," "propensity scores," "cost-effectiveness," "decision analysis," and "diagnosis."

Methods: Out of the 564, I identified 76 articles, which I reviewed by abstract, and of these 42 articles were selected for review of their full text for adherence to methodologic standards.

Results: Studies addressed a variety of issues including diagnosis, prognosis, identification of risk factors, biomarker studies, and disease activity. Data sets included institutional, multi-institutional, and national registries. Prospectively acquired, retrospectively acquired, and cross-sectional data was used. Regression techniques included logistic, linear, generalized estimating equation (GEE) and generalized linear model (GLM). Two studies used classification and regression trees (CART) analysis, 2 used a Bayesian approach, and one used neural network. Only one study explicitly described a power calculation. Internal validation by bootstrapping, split sample, or similar techniques was used in 13 of 42 studies, but only 4 used an external validation step. Discrimination (ROC Curves) or clinical utility (sensitivity and specificity) was described in 12 studies, but only 3 were subjected to calibration.

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Conclusion: A minority of published prognostic and explanatory models adhered to established methodologic standards. Very few studies contained a validation study and those that did were small and thus subject to over fitting. Several studies provided information on discrimination; however, few of these were calibrated using data from the validation study. A consensus scoring system of prognostic and explanatory models similar to that which has been utilized for systemic reviews needs to be constructed and adopted by the rheumatologic clinical epidemiology and clinical trial community.

Disclosure: D. A. Albert, None;

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How to Assess Risks for Pulmonary Infection in Patients Receiving Immunosuppressive Treatment for Rheumatic Diseases? A Report From a Large-Scale Prospective Cohort Study. Hayato Yamazaki[1], Ryoko Sakai[1], Ryuji Koike[1], Yasunari Miyazaki[1], Michi Tanaka[1], Toshi-hiro Nanki[1], Kaori Watanabe[1], Shinsuke Yasuda[2], Takashi Kurita[2], Yuko Kaneko[3], Yoshiya Tanaka[4], Yasuhiko Nishioka[5], Yoshinari Takasaki[6], Kenji Nagasaka[7], Koichi Amano[8], Shigeto Tohma[9], Makoto Dohi[10], Takahiko Sugihara[11], Haruhito Sugiyama[12], Yasushi Kawaguchi[13], Nao-hiko Inase[1], Sae Ochi[14], Hiroyuki Hagiyama[15], Nobuyuki Miyasaka[1] and Masayoshi Harigai[1]. [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Hokkaido University, Sapporo, Japan, [3]Keio Univ School of Medicine, Tokyo, Japan, [4]University of Occupational and Environmental Health, Kitakyushu, Japan, [5]The Univeristy of Tokushima Graduate School, Tokushima, Japan, [6]Juntendo University School of Medicine, Tokyo, Japan, [7]Ome Municipal General Hospital, Ome, Japan, [8]Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, [9]Sagamihara National Hospital, Sagamihara, Japan, [10]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [11]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan, [12]National Center for Global Health and Medicine, Tokyo, Japan, [13]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [14]Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan, [15]Yokohama-city Bay Red Cross Hospital, Yokohama, Japan

Background/Purpose: Patients with rheumatic diseases given immunosuppressive therapy are susceptible to various types of infections, especially pulmonary infections that affect their vital prognosis. The aim of this large-scale, multi-center, prospective cohort study was to identify risk factors for development of pulmonary infection in patients receiving immunosuppressive treatment for rheumatic diseases (PREVENT study).

Methods: We enrolled those patients who were admitted to participating hospitals for treatment of rheumatic diseases and started immunosuppressive therapy with corticosteroids, conventional immunosuppressants, or biologics. Observation was stopped either 12 months after enrollment, or the day a patient developed predefined pulmonary infection or was lost-to- follow up, whichever came first. The validity of the diagnosis for pulmonary infection was assessed by an event-monitoring committee. We collected demographic data and clinical data for rheumatic diseases at baseline, data for candidate risk factors for pulmonary infection at baseline and month 6, and usage of drugs throughout the observation period. Risk factors for pulmonary infection were investigated by univariate and multivariate analyses.

Results: Of 766 patients enrolled, 668 patients (87.2%) were observed for 12 months, 32 patients (4.2%) died, and 66 (8.6%) patients were lost-to-follow up by month 12. Sixty-one patients (8.0%) developed pulmonary infection: bacterial pneumonia, 25; *Pneumocystis jirovecii* pneumonia, 20; fungal pneumonia, 5; cytomegalovirus pneumonia, 3; tuberculosis, 3; others, 5. Kaplan-Meier curves showed a significantly lower cumulative survival rate in patients with pulmonary infection compared to those without pulmonary infection (p<0.01, log-rank test). Because treatment for RA patients without active extra-articular manifestation (articular RA patients, n=145) was significantly different from that for the rest of the patients, we performed multivariate analyses using COX hazard regression models in all patients (n=766) and in these patients excluding articular RA patients (n=621) (Table 1). Older age (≥65 years-old), higher Brinkman index (≥400), higher serum creatinine (sCr) level, and higher maximum prednisolone dose (mg/kg/day) during the first two weeks of treatment were significantly associated with development of pulmonary infection in all patients. Older age, higher Brinkman index, higher sCr level, and disturbed performance status were significantly associated with development of pulmonary infection in patients excluding articular RA patients.

Table 1. Multivariate analysis using COX hazard regression models in all patients with rheumatic diseases and in these patients excluding articular RA patients

Characteristics	All patients (n = 766)		Patients excluding articular RA patients (n = 621)	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (≥65 years)	4.00 (2.27–6.98)	<0.01	4.20 (2.35–7.50)	<0.01
Female	1.07 (0.55–2.09)	0.84	1.12 (0.56–2.23)	0.75
Brinkman index ≥400	2.56 (1.33–4.94)	0.01	2.65 (1.34–5.22)	0.01
Serum Cr (mg/dl)	1.21 (1.04–1.41)	0.01	1.23 (1.06–1.43)	0.01
Performance status (III or IV)	1.71 (0.93–3.17)	0.09	1.89 (1.01–3.52)	0.04
Maximum dose of PSL, 0–2W (mg/kg/day)	3.57 (1.44–8.81)	0.01	2.12 (0.82–5.48)	0.12
Number of mPSL pulse therapy, 0–2W	0.97 (0.62–1.54)	0.91	0.99 (0.62–1.57)	0.96
Use of immunosuppressants, 0–2W	0.82 (0.46–1.45)	0.49	0.81 (0.44–1.48)	0.49
Use of biologics, 0–2W	1.40 (0.52–3.77)	0.51		

RA, rheumatoid arthritis; HR, hazard ratio; 95% CI, 95% confidence interval
Cr, creatinine; PSL, prednisolone; mPSL, methylprednisolone
Performance status was graded by the Eastern Cooperative Oncology Group scale.
0–2W, duration during first two weeks from the enrollment of the study.
Immunosuppressants include azathioprine, methotrexate, cyclophosphamide, tacrolimus, cyclosporin, mizoribine, mycophenolate mofetile and leflunomide.
Biologics include infliximab, etanercept, adalimumab, tocilizumab, rituximab and abatacept.

Conclusion: This is the first large-scale, prospective study identifying risk factors for pulmonary infection in patients with rheumatic diseases in the literature. Prophylactic measures should be taken accordingly for better benefit-risk balance of treatment.

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Cancer Iincidence and Type of Malignancy in Rrheumatologic Ddiseases in Korea: Head-to-Head Comparison. Sung Hae Chang, Jin Kyun Park and Eun Bong Lee. Seoul National University Hospital, Seoul, South Korea

Background/Purpose: Rheumatic diseases (RD) are associated with increased risk of developing cancer. However, it remains to define, if particular cancers are more frequent in certain rheumatic diseases. To address this, the incidence and site of cancer were analyzed in a large cohort of patients with rheumatoid arthritis (RA), dermatomyositis/polymyositis (DM/PM), systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS).

Methods: All patients with a confirmed diagnosis of a RA, AS, SLE, DM/PM, and SSc who underwent clinical care in our institution between January 2000 and April 2012 were enrolled in this retrospective study. Data on site, staging, treatment, and outcome of cancer were ascertained per chart review. The cancer incidence rates in RDs were compared with those of the National Cancer Registry and standardized incidence ratios (SIR) were calculated.

Results: A total of 4,726 patients with RD (female, 71.0 %) were analyzed. During the follow-up duration of 34,447 person-years (PY), 244 (female, 71.7 %) patients developed cancer with an overall incidence rate of 5.2%. The SIR of cancer was significantly higher at 1.7 in patients with RD (95 % confidence interval (CI), 1.51–1.90) than the general population. In a subgroup analysis, RA (SIR 1.81, 95 % CI, 1.52–2.14), DM/PM (SIR 3.11, 95 % CI, 2.21–4.16), and SLE (SIR 1.65, 95 % CI, 1.29–2.04) were associated with a higher cancer incidence, whereas SSc (SIR 1.43, 95 % CI, 0.94–2.01) and AS (SIR 1.11, 95 % CI, 0.512–1.39) were not (**Table 1**). In RA, breast cancer was most common with 29 (22.0 %) cases, followed by 26 (19.7%) gastric, 24 (18.2%) lung, and 14 (10.6%) colon cancer. In DM/PM, lung cancer was most common with 7 (17.9 %) cases, followed by 5 (12.8 %) colon, 4 (10.3 %) gastric and 3(7.7 %) breast cancer. In SSc, lung cancer was most common with 10 (35.7%) cases, followed by 3 (10.7%) gastric, 2 7.1%)

cervix, and 2 (7.1%) colon cancer. In SLE, thyroid cancer was most common with 12 (16.2%) cases, followed by 7 (9.5%) breast, 7 (9.5%) cervix, and 7 (9.5%) liver and intrahepatic bile ducts cancer. In AS, liver cancer was common with 3 (17.9%) cases, followed by 2 (12.5%) lymphoid leukemia, and 2 (12.5%) thyroid cancer.

Table 1. Standardized incidence ratios (SIRs) and 95 % confidence interval (CIs) of cancer in rheumatic diseases.

Rheumatologic disease	Person-year (PY)	Observed cases	Expected cases	SIR	95% CI
All rheumatic diseases	34,447	244	169.7	1.7	1.51-1.90
Rheumatoid arthritis	8,230	132	72.8	1.81	1.52-2.14
Dermatomyositis/Polymyositis	1,988	39	12.5	3.11	2.21-4.16
Systemic Sclerosis	3,094	28	19.6	1.43	0.94-2.01
Systemic Erythematosus Lupus	12,118	74	44.9	1.65	1.29-2.04
Ankylosing Spondylitis	7,709	16	17.8	1.11	0.512-1.39

Conclusion: To the best of our knowledge, this is the first study to show different malignancy risks among rheumatologic diseases in a head-to-head comparison. As particular cancer types are more frequent in certain rheumatic diseases, patients might benefit from cancer surveillance tailored to their RD.

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Further Evidence On Biased Cancer Risk Estimation in Studies Comparing A Subpopulation to the General Population. Koray Tascilar[1] and Hasan Yazici[2]. [1]Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, [2]Istanbul University, Cerrahpasa Medical School, Rheumatology, Istanbul, Turkey

Background/Purpose: We had previously proposed a selection bias in studies estimating cancer risk in patients with rheumatoid arthritis (RA) stemming from the comparison of a selected subpopulation to the general population (Arthritis Rheum. 2011;63;2543-4). Biased estimates would be the result of a) death of a part of the subpopulation due to cancer before being selected, b) prevention of an autoimmune/inflammatory condition by cancer treatment and c) a lower probability of being selected/detected merely because of having cancer. These would cause the rate of accumulation of cancer cases in the selected subpopulation to be lower than that in the general population and hence a decrease in the comparative incidence if tracked over time. We had also demonstrated such a decrease in the comparative incidence over time in studies reporting cancer risk in RA patients (Ann Rheum Dis 2012;71(Suppl3):456). We conducted a systematic literature search to see whether such a bias exists in studies reporting the cancer risk in other autoimmune/inflammatory disorders.

Methods: We conducted multiple PubMed searches using the search terms "polymyositis", "dermatomyositis", "sarcoidosis", "psoriasis", "Crohn's", "ulcerative", "lupus", "SLE", "Sjogren", "ANCA", "polyarteritis", "Wegener", "polyangiitis", "vasculitis", and "scleroderma" between June 2001 and February 2012. We combined these terms with "cancer" and "standardized" to capture studies that reported standardized incidence ratios or standardized morbidity ratios. We retrieved full-text manuscripts of studies that reported comparative incidence. Studies that reported multiple incidence ratios with respect to follow-up time were included.

Results: Our search identified 192 articles and we retrieved 36 articles of relevance in full-text. Among the 36 articles retrieved, 10 reported incidence comparison of overall cancer at multiple timepoints. There were 3 studies on inflammatory myopathies, 1 study each with scleroderma, Wegener's granulomatosis, ulcerative colitis, Crohn's disease, polymyalgia rheumatica, SLE and sarcoidosis. Number of timepoints ranged from 2 to 10, sampling period ranged from 10 to 48 years. The comparative incidence at the latest timepoint was lower in 9 of the 10 articles by 56 to 98% as compared to the earliest.

Conclusion: We provide further evidence that current methods of comparision of cancer incidence in a selected subpopulation to the general population results in biased estimates.

Disclosure: K. Tascilar, None; **H. Yazici**, None.

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

Background/Purpose: The 1-year cumulative incidence of gout in patients with new onset end stage renal disease is 5% and rises to 15% by 5 years, far exceeding the risk in the general population. This higher prevalence of gout could be explained by hyperuricemia as a consequence of reduced renal function and subsequent development of gout or due to common risk factors. Although the risk of developing gout is high among those with end stage renal disease, the risk of gout for those with moderate kidney dysfunction is unclear. We estimated the risk of developing gout over a range of estimated glomerular filtration rate (eGFR) values in participants enrolled in the Atherosclerosis Risk in Communities (ARIC) cohort study.

Methods: ARIC is a prospective population-based cohort recruited in 1987–1989 from 4 US communities, consisting of 4 visits over 9 years. Participants were included in this analysis if they answered the gout query and were free of gout at baseline. Incident gout was defined as self-reported onset after baseline. Serum creatinine was estimated using a modified kinetic Jaffé reaction. Glomerular filtration rate (eGFR) was estimated using the CKD-Epi equation and categorized as $\geq$90, 60–90, or <60 ml/min/1.73 m^2. Using a Cox Proportional Hazards model (age as time scale), we estimated the hazard ratio (HR) and 95% confidence intervals (CI) of incident gout by baseline eGFR, adjusted for confounders (sex, race, and center) and clinical factors (diuretic use, diabetes, hypertension, obesity, and alcohol intake). Additionally, we adjusted for visit 2 serum urate level (measured with the uricase method) to test for mediation.

Results: A total of 10,871 ARIC participants met the study criteria. The study population was 43% male, 21% African American and the mean age at cohort entry was 54 years (SD=5.7). The mean eGFR was 92 (SD=14.9) ml/min/1.73 m^2. At baseline, 217 (2%) participants were classified as having eGFR<60 ml/min/1.73 m^2; 4,502 (41%) with an eGFR between 60 and 90 ml/min/1.73 m^2; and 6,152 with an eGFR >90 ml/min/1.73 m^2 (57%). There were 274 incident gout cases. The results are presented in the table. After accounting for confounders and clinical factors, a 10 ml/min/1.73 m^2 decrease in eGFR was associated with increased risk of gout (HR=1.15, 95% CI: 1.10–1.25). Compared to those with an eGFR $\geq$90, the adjusted HR of incident gout was 1.13 (95% CI: 0.88–1.46) for those with an eGFR between 60 and 90 ml/min/1.73 m^2 and 2.57 (95% CI: 1.58–4.17) for those with an eGFR< 60 ml/min/1.73 m^2. eGFR was not associated with incident gout after accounting for V2 serum urate level, suggesting full mediation. There was no evidence of effect measure modification by race (p=0.46) or sex (p=0.39).

Table. Risk of Gout by eGFR

	HR of Gout (95% CI)	P-value
Model 1: Unadjusted		
eGFR for each 10 unit decrease	1.12 (1.03, 1.22)	0.004
eGFR≥90	Ref	0.01
60≤eGFR<90	1.08 (0.84, 1.38)	
eGFR <60	2.80 (1.74, 4.50)	
Model 2: Adjusted sex, race, and center		
eGFR for each 10 unit decrease	1.18 (1.09, 1.27)	<0.0001
eGFR≥90	Ref	0.002
60≤eGFR<90	1.17 (0.91, 1.51)	
eGFR <60	2.93 (1.82, 4.73)	
Model 3: Adjusted sex, race, center, diuretic use, hypertension, diabetes, obesity, continuous alcohol intake		
eGFR for each 10 unit decrease	1.15 (1.10, 1.25)	0.0003
eGFR≥90	Ref	0.009
60≤eGFR<90	1.13 (0.88, 1.46)	
eGFR <60	2.57 (1.58, 4.17)	
Model 4: Adjusted sex, race, center, diuretic use, hypertension, diabetes, obesity, continuous alcohol intake, serum urate level at visit 2.		
eGFR for each 10 unit decrease	0.97 (0.90, 1.05)	0.47
eGFR≥90	Ref	0.20
60≤eGFR<90	0.82 (0.63, 1.06)	
eGFR <60	0.88 (0.52, 1.48)	

Conclusion: Moderately reduced kidney function was associated with a 2.6-fold increased risk of gout independent of comorbid conditions. These findings suggest that kidney function may be a risk factor for gout that is partially mediated by increased serum urate levels.

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ACR Poster Session A
Imaging of Rheumatic Diseases:
Ultrasound, Nuclear Medicine and Fluorescence Imaging
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Sonographic Assessment of Normal Peripheral Joints: Evaluation According to Demographics Parameters. Flavia S. Machado, Rita N.V. Furtado, Rogerio D. Takahashi, Ana Leticia P. de Buosi and Jamil Natour. Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: to describe quantitative and semiquantitative joint ultrasound measurements in healthy people and compare them among different demographic parameters.

Methods: Bilateral ultrasound measurement of small, medium and large joints were performed in 130 healthy volunteers, stratified into five age groups (A: 18–29, B: 30–39, C: 40–49, D: 50–59, E: 60–80 years). Forty six joint recesses per patient were studied: radiocarpal, distal radioulnar, ulnocarpal, 2nd metacarpophalangeal (MCP) (dorsal, palmar, radial), 3rd MCP (dorsal, palmar), 2nd and 3rd proximal interphalangeal joint of the hand (dorsal, palmar), coronoid fossa; olecranean fossa, glenohumeral (GU) axillary recess, posterior GU recess, hip, knee, talocrural, talonavicular, subtalar, dorsal 1st metatarsophalangeal joint (MTP), dorsal 2nd MTP and 5th MTP (dorsal, lateral). Quantitative measurements of synovial recess (QSR) and semiquantitative measures of synovial hypertrophy (SSH), Power Doppler (SPD), bone erosion (SBE) (score 0–3) and articular cartilage (AC) (score 0–4) were performed by a blinded radiologist using a linear probe (6–18 MHz; Esaote, Genoa, Italy). Sonographic measurements were correlated with age group and other demographic parameters.

Results: Five thousand nine hundred and eighty joint recesses were studied in 130 healthy adults; mean age 44.84, 76,9% women, 62,3% white. The highest values of QSR were found in the hip (6.35mm), axillary GU recess (2.46mm) and posterior GU recess (2.45mm). The joint recess with greater frequency of supposed pathological scores were: 2nd MTP (78.8%) and 1st MTP (69.3%) for SSH; radiocarpal (17.7%) and 1st MTP (15.8%) for SPD; posterior GU recess (23.1%) and ulnocarpal (4.2%) for SBE. The highest QSR and the worst SSH measurement (p<0.02) were observed in age groups D and E and the worst SPD and SBE (p<0.041) were observed in age group E. Minor AC changes (score 1) (p <0.001) were observed in age groups D and E. There were positive correlations among ultrasound measurements with height, age, weight and body mass index (BMI) in 26,1%, 34,8%, 43,5% and 43,5%, respectively, of all the articular recesses studied.

Conclusion: Articular sonographic measurements were performed in several types of joints in healthy adults at different age groups. Mainly synovial hypertrophy, but also Power Doppler, bone erosions and articular cartilage were associated with the worst measurements scores at oldest age groups.

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A Pragmatic Musculoskeletal Ultrasound Screening Protocol Does Not Add to a Predictive Algorithm for Persistent Inflammatory Arthritis in a UK Early Arthritis Clinic. Arthur G. Pratt[1], Alice R. Lorenzi[2], Gillian Wilson[2], Philip N. Platt[2] and John D. Isaacs[3]. [1]Newcastle University, Newcastle Upon Tyne, United Kingdom, [2]Freeman Hospital, Newcastle upon Tyne, United Kingdom, [3]Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University and Newcastle upon Tyne NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom

Background/Purpose: Analyses of large clinical datasets from early arthritis cohorts permit the development of algorithms that may be used for outcome prediction in individual patients. The value added by routine use of musculoskeletal ultrasound (MSUS) in an early arthritis setting, as a component of such predictive algorithms, remains to be determined.

Methods: A retrospective analysis of a large, true-to-life, observational inception cohort of early arthritis patients in Newcastle, UK, which included patients with inflammatory arthralgia but no clinically swollen joints, was undertaken. All patients underwent a pragmatic, 10 minute MSUS assessment protocol during their first visit. Logistic regression was used to develop two "risk metrics" that predicted the development of a persistent inflammatory arthritis (PIA), their derivation differing only according to whether or not MSUS parameters were allowed to be incorporated into the final prediction model.

Results: 379 included patients were assigned definitive outcome diagnoses after ≥12 months follow-up (median 28 months), of whom 162 (42%) developed a persistent inflammatory arthritis. A simple risk metric, derived purely from 12 readily obtainable baseline clinical and serological parameters, had an excellent discriminatory utility with respect to an outome of PIA (area under ROC curve 0.91; 95% CI 0.88–0.94). A similar metric, derived from the same 12 parameters in addition to 5 MSUS parameters, had an almost identical, and not significantly superior, discriminatory utility (area under ROC curve 0.91; 95% CI 0.89–0.94)
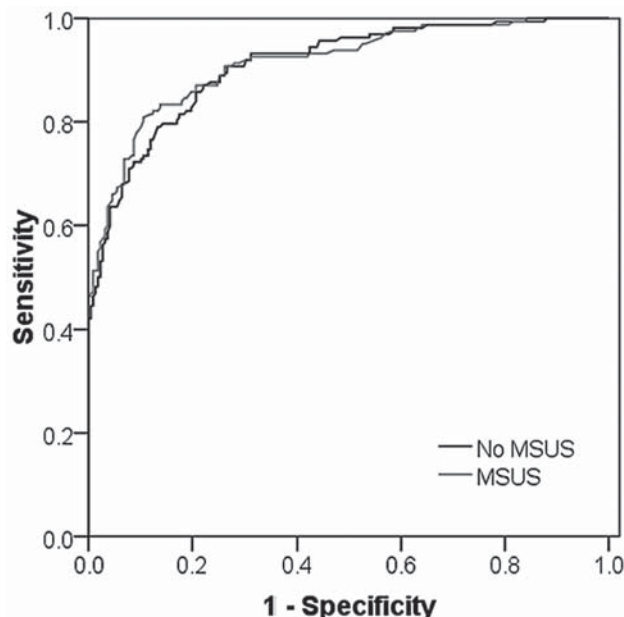
Conclusion: MSUS use as a routine component of assessment in an early arthritis clinic does not add substantial discriminatory value to a risk metric for predicting PIA. More work is needed to refine a precise role of this imaging modality as a diagnostic tool in this clinical setting.

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The Usefulness of A NEW Musculoskeletal ULTRASOUND Scoring System of the Hands and Wrist Joints (US10) for Evaluation of EARLY Rheumatoid Arthritis Patients. Karine R. Luz, Rita N.V. Furtado, Marcelo M. Pinheiro, Giovanna S. Petterle and Jamil Natour. Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Ultrasound (US) can be a useful tool for monitoring rheumatoid arthritis (RA). However, it can be time consuming when applied to too many joints as there is lack of uniformly standardised scoring system. Thus the aim of the present study was to propose a new US score of the hands and wrist joints (US10) and to evaluate its correlation with clinical, laboratory and functional status during a 48-weeks follow-up.

Methods: Forty-eight early RA patients with less-than-1 year symptom with no previous use of disease-modifying antirheumatic drugs (DMARD) were enrolled on the study. The patients underwent clinical, laboratory assessment and blinded US examination at baseline, 3, 6, 9 and 12 months. The US10 included the following joints: wrist, second and third metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. This score was

composed by the following 10 parameters, according to inflammation: qualitative (0–1; range of 0–16) and semi-quantitative (0–3; range of 0–48) scoring to synovial proliferation (SPQ10, SPSQ10) and to power Doppler (PD) (PDQ10, PDSQ10), and qualitative (0–1) gray scale and PD scores for tenosynovitis/paratendinosis (GSTN10, PDTN, range of 0–10). A second US finding was categorised according to joint damage: a qualitative (0–1) and semi-quantitative (0–3) scoring to bone erosions (ERQ10, range of 0–12; ERSQ10, range of 0–36) and to cartilage damage (CAQ10, range of 0–4; CASQ10, range of 0–12). The following were clinical and laboratory assessments: C-reactive protein level (CRP), 28-joint Disease Activity Score (DAS 28) and Health Assessment Questionnaire (HAQ). All patients were treated with the same protocol of treatment and by just one rheumatologist.

Results: The mean ± duration of the symptoms was 7,58 (± 3,59) months. All patients had high activity disease with mean ± DAS 28 of 6,50 (± 1,29). At baseline, there was significant correlation between all US parameters for inflammation (p<0,05) and the US parameters for joint damage (ERQ10, ERSQ10 and CASQ10) also had a good significant correlation (p<0,05) with synovial proliferation parameters. Besides, significant correlation (p<0,05) between all the US10 parameters for inflammation and CRP was observed. In addition, the PD and tenosynovitis scores showed a significant correlation (p<0,05) with DAS28. Longitudinal changes through out 12 months for the inflammation parameters (SPQ10, SPSQ10, GSTN and PDTN) and for bone erosions scores showed a highly significant correlation (p<0,05). There was a significant correlation between changes in the US parameters for synovial proliferation for tenosynovitis and the DAS28 changes (SPQ10/DAS28: r=0,33, p<0,05; SPSQ10/DAS28: r=0,30, p<0,05; TNQ10/DAS28: r=0,48, p<0,05; TNQPD10: r=0,48, p<0,48) in a 12-month period. After one year, there was also a significant correlation between changes in the inflammation scores, in the CRP and in HAQ.

Conclusion: A new US scoring system of hand and wrist joints (US10) seemed to be a useful tool to monitor inflammation and joint damage in early RA patients with a significant correlation to longitudinal changes of disease activity criteria.

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Combined Synovial and Structural Ultrasound Score for the Diagnosis of RA. Gary A. Kunkel, Grant W. Cannon and Daniel O. Clegg. George E. Wahlen VA Medical Center, Salt Lake City, UT

Background/Purpose: Current ultrasonographic scoring systems used to assess the degree of finger joint synovitis in rheumatoid arthritis (RA) are not designed for distinguishing healthy or osteoarthritis (OA) patients from those with RA in clinical settings. In this pilot study we explore a novel scoring approach using structural as well as quantitative synovial ultrasonographic features to distinguish between healthy and OA finger joints and those with RA.

Methods: 22 patients with RA, 16 healthy controls, and 14 OA controls received a comprehensive ultrasound of one hand's metacarpophalangeal and proximal interphalangeal joints, with scores assigned using a modification of a previously reported RA scoring system called the Semiquantitative Synovial Score (SSS), and using the novel approach called the Combined Structural/ Synovial Score (CSSS). The SSS relied on the presence or absence of hypoechoic synovial tissue/fluid bulging over the lines between the joint-forming bones or extending to the diaphysis. If either condition was met the joint was classified as supporting the diagnosis of RA ("RA-supported"). The CSSS utilized structural features of osteophyte and erosion, as well as measured thickness of the synovial cavity over the bony diaphysis and Doppler signal. If >1+ Doppler signal, >2mm of synovial thickness, or an erosion >1mm in two orthogonal planes was imaged the joint was classified as "RA-supported." The number of joints classified as "RA-supported" was tallied for each of the two scoring methods. Sensitivity and specificity for each method were calculated with respect to the clinical diagnosis of RA, and receiver operating characteristic (ROC) curves plotted across the range of possible scoring cutoffs.

Results: The SSS was highly sensitive (100%), but without specificity (0%) for the diagnosis of RA, when RA was defined as having more than 1 joint classified as "RA-supported." The CSSS had high sensitivity (95%) and moderate specificity (77%) when RA was defined as having any joint classified as "RA-supported". Moderate sensitivity (73%) and high specificity (97%) were found when having more than 1 joint classified as "RA-supported" was required to diagnose RA. Results of a sensitivity analysis of

several different variations of the CSSS show some differences in the sensitivity and specificity of this system when different parameters are used such as volar or dorsal-only scans.

"RA-supported" >0	Semiquantitative Synovial Score	Combined Structural/ Synovial Score
Sensitivity-RA	1	0.95
Specificity-O	0	0.57
Specificity-H	0	0.94
Specificity-All	0	0.77

"RA-supported" >1	Semiquantitative Synovial Score	Combined Structural/ Synovial Score
Sensitivity-RA	1	0.73
Specificity-O	0	0.93
Specificity-H	0	1
Specificity-All	0	0.97
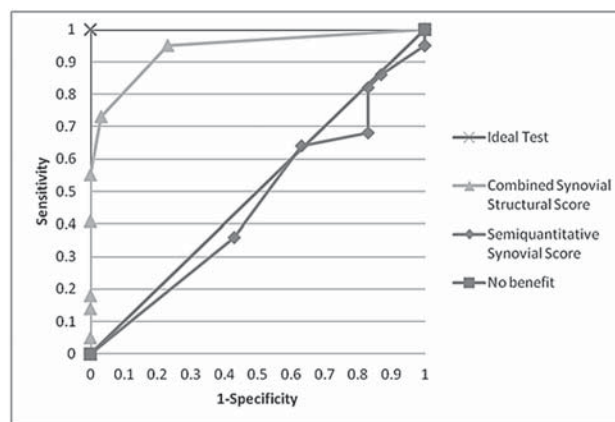
Conclusion: A novel combined structural and quantitative synovial hand joint scoring system was capable of distinguishing OA and healthy controls from RA subjects in this pilot evaluation.

Disclosure: G. A. Kunkel, None; **G. W. Cannon**, None; **D. O. Clegg**, None.

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Development of a 6 Joint Simplified Ultrasonographic Score to Assess Disease Activity in Patients with Rheumatoid Arthritis. Tomas Cazenave[1], Christian A. Waimann[2], Gustavo Citera[3] and Marcos G. Rosemffet[1]. [1]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofisica, Buenos Aires, Argentina, [3]Instituto de Rehabilitación Psicofísica., Buenos Aires, Argentina

Background/Purpose: Ultrasound has become a routinely available bedside method for the evaluation of patients with Rheumatoid Arthritis (RA). However, it is time consuming, making it difficult to use in daily clinical practice. The aim of our study was to develop a new standardized ultrasound score including only 6 joints that could be applied to daily monitoring disease activity in patients with RA.

Methods: We included RA patients (American College of Rheumatology 1987 criteria). Each patient underwent clinical, radiological and ultrasonographic (US) evaluation. Clinical data included 28-joints count and disease activity index 28 (DAS28). Ultrasound evaluation was performed by two rheumatologists who were blind to clinical examination. Six joints were evaluated: bilateral wrist (dorsal view of radio and intracarpal joint), second metacarpophalangeal (2MCP; dorsal and palmar view), and fifth metatarsophalangeal (5MTP; dorsal view). US synovitis was defined as a gray scale (GS) score ≥1. Synovial vascularity was assessed by power Doppler (PD) and graded from 0 to 3, according to OMERACT standards. The US score comes from the addition of the presence of synovitis (one point) and the degree PD, with a total score ranged from 0 to 40 (synovitis subscale = 0–10; PD subscale = 0–30). Final score was correlated with clinical variables (Spearman's rho) and stratified according to patients' disease activity (Kruskal Wallis and post-hoc tests).

Results: 124 patients were included. Mean age was 53 ± 13 years, 86% were female, and disease duration was 9.4 ± 8.5 years. Tender and swollen joints count were 3.3 ± 4 and 3.5 ± 4.5, respectively. DAS28 score was 3.8 ± 1.4. A total of 744 joints were evaluated. 548 (74%) exhibited

ultrasonographic changes (PD ≥ 1 = 35%; synovitis = 69%). 2MCP and 5MTP showed erosions in 70% and 83%, respectively. Mean ultrasonographic score was 11.4 $\pm$ 6.5 (Doppler subscale 4.8 $\pm$ 6.5; Synovitis subscale 6.6 $\pm$ 2.2). The score had a moderate correlation with swollen joint count and DAS28 (Spearman's rho 0.60 and 0.54, respectively; p<0.001). The score was able to discriminate patients with high disease activity from those with moderate, low activity and remission (Remission= 8 $\pm$ 4, low activity= 9 $\pm$ 5, Moderate activity= 11 $\pm$ 5, High activity= 19 $\pm$ 8; p<0.01). Excluding the 5MTP and synovitis subscale did not affect the results, showing an excellent correlation with primary score (Spearman's rho 0.98 and 0.96, respectively; p<0.001). US examination was fast, taking 8 minutes per patient, including documentation.

Conclusion: A reduced US score of 6 joints showed to be fast and a valid tool to detect and monitor disease activity in patients with RA. Ultrasonographic assessment of bilateral wrist, second MCP and fifth MTF could be enough for evaluating overall inflammatory activity, reducing the examination time, thereby making it possible to integrate the ultrasound to the daily rheumatologic practice.

Disclosure: **T. Cazenave**, None; **C. A. Waimann**, None; **G. Citera**, None; **M. G. Rosemffet**, None.

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Sensitivity to Change of the Ultrasound synovitis SONAR Score in RA Patients: Results of the Scqm Cohort. Pascal Zufferey[1], Almut Scherer[2], Hans Rudolf Ziswiler[3], Giorgio Tamborrini[4], Laure Brulhart[5] and Burkhard Moeller[6]. [1]Lausanne University Hospital, Lausanne, Switzerland, [2]SCQM Foundation, Zurich, Switzerland, [3]Inselspital, University of Bern, Bern, Switzerland, [4]University Hospital, Zurich, Switzerland, [5]Geneva, Switzerland, [6]Inselspital Bern, Bern, Switzerland

Background/Purpose: Since the end of 2009, an ultrasound scoring call SONAR has been implemented for RA patients as a routine tool in the SCQM registry (Swiss Clinical Quality Management registry for rheumatic diseases). A cross-sectional evaluation of patients with active disease and clinical remission according to the DAS28$_{ESR}$ and the novel ACR/EULAR remission criteria from 2010 clearly indicated a good correlational external validity of synovial pathologies with clinical disease activity in RA (2012 EULAR meeting

Objective: of this study was to evaluate the sensitivity to change of B-mode and Power-Doppler scores in a longitudinal perspective along with the changes in DAS28$_{ESR}$ in two consecutive visits among the patients included in the SCQM registry

Methods: All patients who had at least two SONAR scores and simultaneous DAS28$_{ESR}$ evaluations between December 2009 and June 2012 were included in this study. The data came from 20 different operators working mostly in hospitals but also in private practices, who had received a previous teaching over 3 days in a reference center. The SONAR score includes a semi-quantitative B mode and Power-Doppler evaluation of 22 joints from 0 to 3, maximum 66 points for each score. The selection of these 22 joints was done in analogy to a 28 joint count and further restricted to joint regions with published standard ultrasound images. Both elbows and wrist joints were dynamically scanned from the dorsal and the knee joints from a longitudinal suprapatellar view in flexion and in joint extension. The bilateral evaluation of the second to fifth metacarpophalangeal and proximal interphalangeal joints was done from a palmar view in full extension, and the Power-Doppler scoring from a dorsal view with hand and finger position in best relaxation

Results: From the 657 RA patients with at least one score performed, 128 RA patients with 2 or more consultations of DAS28$_{ESR}$, and a complete SONAR data set could be included. The mean (SD) time between the two evaluations was 9.6 months (54). The mean (SD) DAS28$_{ESR}$ was: 3.5 (1.3) at the first visit and was significantly lower (mean 3.0, SD.2.0, p:<0.0001) at the second visit. The mean (SD) of the total B mode was 12 (9.5) at baseline and 9.6 (7.6) at follow-up (p=0.0004). The Power-Doppler score at entry was 2.9 (5.7) and 1.9 (3.6), at the second visit, p <0.0001.

The Pearson r correlation between change in DAS28$_{ESR}$ and the B mode was 0.44 (95% CI: 0.29, 0.57, p < 0.0001),and 0.35 (95% CI: 0.16, 0.50, p = 0.0002) for the Power-Doppler score,. Clinical relevant change in DAS (>1.1) was associated with a change of total B mode score >3 in 23/32 patients and a change a Doppler score >0.5 in 19/26.

Conclusion: This study confirms that the SONAR score is sensitive to change and provides a complementary method of assessing RA disease activity to the DAS that could be very useful in daily practice.

Disclosure: **P. Zufferey**, None; **A. Scherer**, None; **H. R. Ziswiler**, None; **G. Tamborrini**, None; **L. Brulhart**, None; **B. Moeller**, None.

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Disparity Between Sonographic and Clinical Criteria of Remission in Psoriasis Arthritis. Christian Dejaco[1], Rusmir Husic[1], Judith Gretler[2], Winfried B. Graninger[1] and Josef Hermann[1]. [1]Medical University Graz, Graz, Austria, [2]Auenbruggerplatz 15, Graz, Austria

Background/Purpose: To compare ultrasound and clinical definitions of remission in psoriasis arthritis (PsA).

Methods: Prospective study of 70 consecutive PsA patients [mean age 51.1 ($\pm$SD 11.6) years, 30% female, median disease duration 7.0 (range 0–44.7) years]. Clinical and ultrasound examination was performed at 68 joints and 14 entheses (lateral epicondyle, triceps insertion, quadrizeps insertion, proximal and distal insertion of patellar ligament, Achilles tendon, plantar fascia), and Disease Activity index for PSoriatic Arthritis (DAPSA), composite psoriatic disease activity index (CPDAI), HAQ and PASI were calculated. The following clinical definitions of remission were applied: DAPSA ≤ 3.3, CPDAI (joint, entheses and dactilytis domains) =0 or a Boolean definition with a score ≤ 1 in all of the following categories: tender joints (TJ), swollen joints (SJ), CRP, patient's (PGA) and evaluator's global assessment (EGA), enthesitis and dactylitis. Sonography was performed by two rheumatologists blinded to clinical data using an ESAOTE Twice ultrasound device. Power Doppler (PD) signals were graded from 0 to 3. The presence of perisynovitis and tenosynovitis was also recorded. Ultrasound remission was defined by a PD-score of 0 at joints, entheses and tendons.

Results: Fifteen (21.4%), 12 (17.1%) and 11 (15.7%) PsA patients were in remission according to the CPDAI, DAPSA and the Boolean definitions. A lower prevalence of PD signals in at least one joint or tendon was found in patients in remission according to DAPSA (58.3% vs. 84.5%, p=0.039 and 8.3% vs. 38.6%,p=0.043, respectively) and the Boolean definition (54.5% vs. 84.7%, p=0.022 and 9.1% vs. 37.9%, p=0.06, respectively) whereas the prevalence of active synovitis was similar in inactive and active disease groups according to CPDAI (66.7% vs. 83.6%, n.s.). Tenosynovitis tended to be more prevalent in cases with active disease according to CPDAI compared to patients in remission (38.9% vs. 13.3%, p=0.06). Frequencies of active enthesitis and perisynovitis were similar in groups with active and inactive disease according to CPDAI, DAPSA and the Boolean definitions.

Three (4.3%) patients had no PD-signal in joints, entheses and tendons. Comparing patients with PD-score=0 [n=14 (20%)] and PD-score≥ 1 at joints we found a lower number of SJ [0 (0–4) vs. 1 (0–15), p=0.007] and lower ESR [6.5 (1.0–17.0) vs 10.0 (1.0–74.0), p=0.049] among patients with inactive disease. CPDAI, DAPSA, TJ, CRP, PGA; EGA and HAQ were similar in both groups.

Patients without PD-signals at tendons [n=46 (65.7%)] had lower DAPSA [9.9 (0.1 –70.2) vs. 17.4 (0.2 –60.8), p=0.012], lower PGA [30 (0–80) vs. 40 (0–80), p=0.024], lower CRP [2.0 (0–20.3) vs. 4.8 (0.6–49.5), p=0.013] and lower ESR [6.0 (1.0–47.0) vs. 18.0 (5.0–74.0), p<0.001] compared to patients with active tenosynovitis.

Patients without PD signals at entheses [n=27 (38.6%)] did not differ from patients with active disease regarding clinical scores and laboratory measures.

Conclusion: Our data demonstrate a disparity between ultrasound and clinical definitions of remission in PsA. DAPSA and Boolean based definitions of remission are closer to ultrasound defined remission than a CPDAI based definition.

Disclosure: **C. Dejaco**, None; **R. Husic**, None; **J. Gretler**, None; **W. B. Graninger**, None; **J. Hermann**, None.

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Does Joint Sonography Really Add Clinically Important Information Beyond Clinical Joint Examination? Miriam Gärtner[1], Helga Radner[1], Gabriela Supp[1], Peter Mandl[1], Daniel Aletaha[1], Klaus P. Machold[1] and Josef S. Smolen[2]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Sonographic assessment of joint activity in patients with rheumatoid arthritis (RA) is considered to be more sensitive than

the respective clinical assessment. However, this difference may be less dependent on the physical technique used (i.e. palpation vs. ultrasound), but rather related to differences in arbitrary definitions of the presence or absence of "joint activity". We aimed to evaluate the differences in numbers of clinically and sonographically active joints in RA, with special regard to the impact of sonographic definitions of activity.

Methods: We performed sonographic imaging of 22 joints of the hands of RA patients in clinical remission (n=60; defined as Clinical Disease Activity Index=CDAI $\leq$ 2.8). Each joint was assessed for grey scale synovial hypertrophy (GSSH) and power Doppler (PD) signal on a four point scale (0=no, 1=mild, 2=moderate and 3=marked). We investigated the sensitivity and specificity of clinically swollen joints for presence of sonographic activity, when using different cut points and combinations of sonographic definitions of activity. For the clinical assessment we used the strict conventional approach of not calling a joint swollen in case of any doubt. We then assessed changes of CDAI if the clinical swollen joint count (SJC) was replaced by sonographically active joints.

Results: Among the 1320 joints of patients in remission a total of 887 (67.2%) were GSSH positive and 269 (20.4%) were PD positive.

Clinical joint swelling was 100% specific for sonographic activity, even when stringent sonographic criteria (score=3) were applied. The maximum sensitivity was 25% using the most stringent sonographic criteria (GSSH=3 and PD=3).

Calculating CDAI by replacing the number of clinically swollen by the number of sonographically active joints (sCDAI) according to the various definitions above, resulted in high values using GSSH$\geq$1 or PD$\geq$1 (mean sCDAI=15.5) compared to the clinical CDAI of 1.4. However, sCDAI values approached the clinical CDAI with increasing stringency of the sonographic definition used, and were even numerically identical when accepting only grade 3 PD signals (Figure).

CDAI values calculated using diffent sonographic definitons
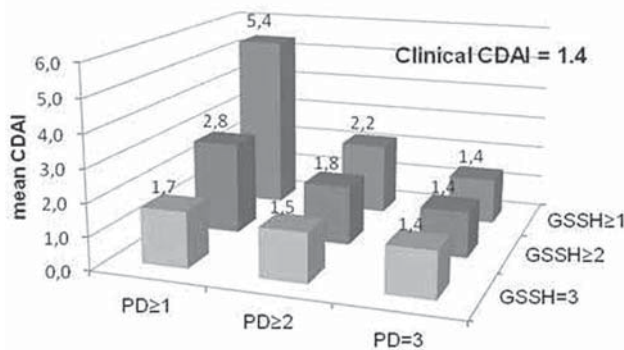
Conclusion: Sonography revealed residual signals of joint activity in patients in CDAI remission. Changing the stringency of the sonographic criteria toward higher signals for determination of joint activity led to similar results when considered in the context of overall disease activity, such as in the CDAI.

Disclosure: M. Gärtner, None; **H. Radner**, None; **G. Supp**, None; **P. Mandl**, None; **D. Aletaha**, None; **K. P. Machold**, None; **J. S. Smolen**, None.

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Comparing Palmar and Dorsal Ultrasound Assessment of Small Joint Synovitis in Rheumatoid Arthritis: Dorsal Greyscale Mode Yields Significantly Better Concordance with Power Doppler. Matthias Witt[1], Felix Mueller[1], Hendrik Schulze-Koops[2] and Mathias Grunke[1]. [1]Division of Rheumatology, Medizinische Klinik und Poliklinik IV, University of Munich, Munich, Germany, [2]Division of Rheumatology, Medizinische Klinik and Poliklinik IV, University of Munich, Munich, Germany

Background/Purpose: MCP and PIP joints are frequently involved in rheumatoid arthritis. Complete ultrasound assessment of these joints requires the palmar and the dorsal approach for both the grey scale (GSUS) and the power Doppler (PDUS) modality. However, depending on the approach used, the frequency of findings consistent with synovitis seems to differ considerably. As ultrasound assessment increasingly influences our understanding of disease

remission, this study was undertaken to investigate the role of palmar versus dorsal GSUS and PDUS in therapy-naive patients with rheumatoid arthritis.

Methods: Patients with newly diagnosed and therapy-naive RA were included. Patients were assessed by clinical examination and ultrasound. Ultrasound was performed with grey scale (GSUS) and power Doppler (PDUS) of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, using the dorsal and palmar approach. Synovitic findings in GSUS and PDUS were graded semiquantitatively from 0 to 3 as specified before. After the initial assessment, patients were treated with anti-rheumatic drugs according to national guidelines and were seen on a regular outpatient basis. Clinical and sonographic reevaluation together with assessment of EULAR responses was performed at month 6.

Results: Sofar, 40 patients with RA were included into this ongoing study. Palmar and dorsal GSUS identified 44.4% and 27.3% synovitic findings, respectively (p < 0.05). MCP joints with GSUS synovitis were tender and/or swollen in 53.4% and 62.6% in the palmar and volar approach, respectively (differences not significant). MCP joints with GSUS findings were PDUS positive in 17.8% using the volar approach compared to 71.7% using the dorsal approach (p < 0.001). Similar results were seen in the PIP joints with no significant differences concerning clinical concordance, while ultrasound concordance with PDUS was statistically significant between the palmar and dorsal approach.

Conclusion: In therapy naïve RA patients, marked discrepancies between palmar and dorsal GSUS can be observed. While palmar GSUS detects significantly more synovitic findings than dorsal GSUS, both the clinical and PDUS concordances are low. The dorsal approach, on the other hand, shows significantly better concordance between GSUS and PDUS. The reasons are manifold and include anatomical differences between the palmar and the dorsal aspect of the joints resulting in different sensitivities for GSUS and PDUS. In order to optimize ultrasonographic evaluation of small joints in RA, these findings require further clarification. Further analysis is underway to reassess GSUS and PDUS in these patients at month 6 of treatment.

**Disclosure: M. Witt**, None; **F. Mueller**, None; **H. Schulze-Koops**, None; **M. Grunke**, None.

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Ultrasound Measurement of Metacarpal Cartilage Thickness Correlates with Joint Space Narrowing in the Metacarphalangeal Joints of Patients with Rheumatoid Arthritis. Peter Mandl[1], Helga Radner[1], Gabriela Supp[1], Peter V. Balint[2], Daniel Aletaha[1] and Josef S. Smolen[3]. [1]Medical University of Vienna, Vienna, Austria, [2]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: To correlate cartilage thickness as measured by ultrasound (US) with joint space narrowing as measured by conventional radiography in the metacarpophalangeal (MCP) joints of patients with rheumatoid arthritis.

Methods: In this pilot study we examined 120 MCP joints of 15 patients with rheumatoid arthritis (RA). The cartilage layer of the metacarpal heads and proximal phalangeal bases of digits 2–5 were assessed bilaterally using a 15 Mhz linear transducer (GE Logic E9) from a dorsal longitudinal view in midline, with joints in 90° flexion. Cartilage thickness was measured in mm with an integrated caliper on static images. Joint space narrowing (JSN) was evaluated using the van der Heijde modified Sharp scoring method (vdHS) performed on conventional posterior-anterior radiographs of both hands. Cartilage thickness was correlated with x-ray findings using Spearman correlation, while differences of JSN within groups of different cartilage thickness (using tertiles) were evaluated by Kruskal-Wallis test.

Results: Mean disease duration was 9.3+6.2 years, mean CDAI 8.3+7.4; 63% of the patients were rheumatoid factor positive. US measurement of metacarpal cartilage thickness was 0,38+/−0,17 mm and correlated with total JSN of MCP 2–5 (r=0.54, p<0.001) as well as with the total vdHS (r=0.53, p<0.001). No correlation was found between phalangeal cartilage thickness and JSN. Metacarpal cartilage thickness correlated better with JSN than the sum score of metacarpal and phalangeal cartilage thickness (r=0.54 p<0.01 vs. 0.47 p<0.05). Moderate correlation was found between the left and right hand with regard to metacarpal cartilage thickness (r=0.56, p<0.05). Correlation was slightly higher between metacarpal cartilage thickness of the left hand and JSN (r=0.57 vs. 0.53; p<0.05). Significant differences of total vdHS, total JSN and JSN sum score for the MCP joints (JSN.mcp) were found between tertiles of metacarpal cartilage thickness using Kruskal-Wallis Test (Figure 1). No correlation between cartilage thickness and disease activity, functional disability, or disease duration was seen.
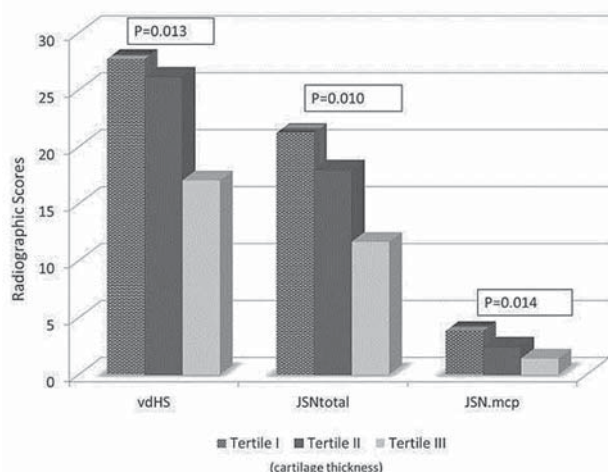
Figure 1. Differences of JSN between groups of different cartilage thickness using tertiles. Tertile I: mean cartilage size 0.0189 (±0.003) mm; Tertile II: mean cartilage size: 0.035 (±0.005) mm; Tertile III: mean cartilage size: 0.058 (±0.009) mm

Conclusion: JSN by radiography indeed represents cartilage thickness at least in MCP joints. When radiographic scoring is not available, US measurement of cartilage thickness of the metacarpal head might be a feasible alternative to depict cartilage damage in patients with rheumatoid arthritis. Phalangeal cartilage thickness has no added value beyond the measurement of metacarpal cartilage thickness.

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Time-Integrated Synovitis Activity Assessed by Power Doppler Ultrasound Significantly Correlates with Radiographic Progression in Rheumatoid Arthritis Patients Treated with Methotrexate Alone but Not in Those Treated with TNF Antagonists, Kei Ikeda, Daiki Nakagomi, Yoshie Sanayama, Mieko Yamagata, Ayako Okubo, Taro Iwamoto, Hirotoshi Kawashima, Kentaro Takahashi and Hiroshi Nakajima. Chiba University Hospital, Chiba, Japan

Background/Purpose: Although a number of studies have shown a higher sensitivity of ultrasound than clinical joint examination in detecting synovitis in patients with rheumatoid arthritis (RA), only a few studies have actually demonstrated the superiority of ultrasound to conventional measures in evaluating synovitis that causes structural damage. In this study, we aimed to demonstrate that structural damage progression is associated with time-integrated power Doppler (PD) signals more significantly than with time-integrated DAS28 in RA patients receiving methotrexate or biological agents.

Methods: Patients with an established diagnosis of RA who required new or additional treatment with either methotrexate (MTX), TNF antagonists, or tocilizumab (TCZ) were consecutively enrolled in this study. Patients underwent clinical, laboratory, and ultrasonographic assessment at baseline and at 12 and 24 weeks of follow-up. Patients also underwent radiographic assessment at baseline and at 24 weeks. A systematic multiplanar ultrasound examination of 28 joint regions was performed and gray-scale (GS) synovitis and PD signals were recorded with semi-quantitative scores (0–3).

Results: Forty-eight RA patients were enrolled. All 17 patients in MTX group were treated with MTX alone, whereas 20 out of 23 patients in TNF group and all eight patients in TCZ group received combination therapy with MTX. Changes in DAS28 and CDAI significantly correlated with those in total GS and PD scores between baseline and 12 weeks. The absolute values of standardized response means (SRM) for total PD scores between baseline and 12 weeks tended to be larger (TNF antagonists, 1.43; TCZ, 1.93) than those for DAS28 (TNF antagonists, 1.39; TCZ, 1.71), CDAI (TNF antagonists, 1.07; TCZ, 1.03), or total GS scores (TNF antagonists, 1.40; TCZ, 0.86) in patients treated with biological agents. When time-integrated disease activity was calculated by summing scores at three visits, the correlation between time-integrated total PD scores and changes in total Sharp scores during 24 weeks was statistically significant, whereas the correlations between time-integrated DAS28 or total GS scores and changes in total Sharp

scores were not statistically significant. In sub-group analyses for each treatment regimen, time-integrated total PD scores significantly correlated with changes in total Sharp scores in patients treated with MTX alone, but not in those treated with TNF antagonists (Figure).
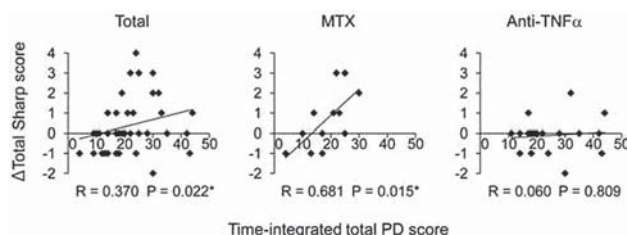
Conclusion: PD ultrasound represents synovitis activity that causes joint damage progression more directly than DAS28 or GS synovitis does. The lack of correlation between time-integrated total PD scores and changes in total Sharp scores in patients treated with TNF antagonists may reflect the protective effect of TNF antagonists against joint damage that is independent of synovitis activity.

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Power Doppler Signal Is Frequently Positive Among Patients with Rheumatoid Arthritis in Clinical Remission and Normal Serum Matrix Metalloproteinase-3 (MMP-3) Levels. Tadashi Okano, Tatsuya Koike, Masahiro Tada, Kenji Mamoto, Yuko Sugioka, Atsuko Kamiyama and Hiroaki Nakamura. Osaka City University Medical School, Osaka, Japan

Background/Purpose: Serum matrix metalloproteinase-3 (MMP-3) is useful bio markers of synovitis associated with rheumatoid arthritis (RA). Ultrasonography (US) has recently become more popular as a method of evaluating joint synovitis. The purpose of this study is to determine the significance of grey scale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) scores by comparison with serum biomarkers and clinical disease activity assessment.

Methods: We selected 151 consecutive patients with RA at our hospital outpatient clinic. The patients underwent musculoskeletal ultrasonography at 26 synovial sites in the following joints: bilateral first to fifth MCP (dorsal recess), first IP and second to fifth PIP (dorsal recess) joints and the wrists (dorsal radial, dorsal median and dorsal ulnar). The GS and power PD signals were scored in each joint using a scale from 0 to 3. The GSUS and PDUS scores are the sums of the scores obtained for the 26 synovial sites. Correlations among serum CRP, ESR and MMP-3 values and disease activity evaluated using the DAS28-ESR, DAS28-CRP, SDAI, CDAI were analyzed along with the PDUS positive ratio in patients in remission and in patients with normal MMP-3 values.

Results: The clinical characteristics of the 151 patients (128 females and 23 males; mean age, 60.5 ± 13.1 years) with RA were as follows. They received only DMARDs (n = 80), and biological DMARDs (n = 71). The GSUS and PDUS scores were significantly and positively correlated with ESR, CRP, MMP-3, DAS28-ESR, DAS28-CRP, SDAI and CDAI. The PDUS score >1 was positive in 28 of 34 patients (82.3%) in remission with DAS28-CRP (< 2.6) and in 52 of 61 (85.2%) with normal serum MMP-3 levels. The PDUS score >2 was positive in 10 of 34 (29.4%) patients in remission with DAS28-CRP and in 30 of 61 (49.2%) with normal serum MMP-3 levels. The levels of PDUS score in the remission patients using biological DMARDs was less than the remission patients using only DMARDs.

Conclusion: Both GSUS and PDUS scores were closely correlated with clinical disease activity and serum biomarkers. These results indicate that US findings accurately reflect the pathogenesis of RA. However, patients in remission and normal serum MMP-3 levels also had a high rate of positive PD scores. We considered that US is more accurate for clinically evaluating patients with RA.

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US Examination of Wrists and Hands: A Comparison Between Rheumatoid Arthritis and Psoriatic Arthritis. Andrea Delle Sedie[1], Elisa Cioffi[1], Linda Carli[1], Elena Sardano[2], Stefano Bombardieri[1] and Lucrezia Riente[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Immunology Unit, University of Pisa, Italy

Background/Purpose: very little is known about the differences in joint and periarticular structure involvement in rheumatoid or psoriatic arthritis (PsA). The main pathological features detected by US in rheumatoid arthritis (RA) are synovitis and bone erosion while, in spondyloarthropathies, entheseal inflammation is the common feature. Tendon involvement is particularly frequent and dactylitis is a typical PsA manifestation. Aim of the study was to find possible differences in ultrasound (US) involvement of wrist and hand in PsA and RA.

Methods: bilateral US examination of the wrist and hand was performed, by the same physician blinded to the diagnosis, in a consecutive, unselected, group of subjects affected by RA and PsA, using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with a linear probe (14 MHz). Radiocarpal, intercarpal, metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints and flexor and extensor tendons (in wrist and hand) were examined bilaterally. Bone erosion and tenosynovitis were diagnosed according to the OMERACT definitions [1], while synovitis was considered when a synovial hypertrophy (with or without power Doppler signal) was present. The patients were recruited on a time-criteria (the last who came for an outpatient visit). The RA and PsA diagnosis was given by other rheumatologists, according to the 1987 ACR and Caspar criteria, respectively.

Results: mean age and disease duration were comparable for both groups, while male/female ratio was different (as expected) (Table 1). US findings are reported in Table 1. The number of hand joints involved was higher in RA than in PsA (182 vs 150). Given the results, it is interesting that the total number of proliferative tenosynovitis was significantly greater in RA (49/68 vs 7/34 in PsA at the wrist level and 58/98 vs 13/63 in PsA at the hand level).

Table 1.

	RA (N=55)	PsA (N=55)
F/M	48/7	28/27
Mean age (yrs)	60.7±12.7	57.4 ± 12.5
Disease duration (months)	113.3 ± 97.7	100.6 ± 95.6
Wrist synovitis (N of pts; %)	38;69	24;44
Hand synovitis (N of pts; %)	28;51	37;67
Wrist tenosynovitis (N of pts; %)	23;43	16;29
Hand tenosynovitis (N of pts; %)	22;40	25;45
Hand erosions	30;54	26;47

Conclusion: Wrist synovitis occurred significantly more frequently in RA patients than in PsA subjects, while no significant differences were observed in hand synovitis between the groups. There was no difference in tendon involvement for frequency between RA and PsA groups considering the number of patients with tenosynovitis but it became significantly different when considering the total amount of tenosynovitis (as well as the number of proliferative tenosynovitis). The latter aspect could be determined by a more aggressive inflammation of the tendons in those patients that present tendon involvement and are affected by RA (only 10 RA patients had hand proliferative tenosynovitis, compared to 7 in the PsA group, indicating a lower frequency of synovial proliferation in the second group). There were no other significant differences in the results of the two groups.

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Composite Ultrasound Score in Spondyloarthropathies. Maria L. Acosta Felquer[1], Cristian Quiroz[1], Santiago Ruta[2], Javier Rosa[1], Marina Scolnik[2], Leandro Ferreyra Garrott[1], Ricardo Garcia-Monaco[3] and Enrique R. Soriano[4]. [1]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, [4]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina

Background/Purpose: A comprehensive ultrasound (US) scoring system which includes enthesitis tenosynovitis and synovitis for use in patients with spondyloarthropathies (SpA) is not yet available. The objective of the study was to develop an US composite scoring system, including both enthesitis tenosynovitis and synovitis, suitable for the evaluation of patients with SpA.

Methods: Consecutive patients with SpA according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial, and/or peripheral spondyloarthritis and Rheumatoid arthritis (RA) patients fulfilling ACR/EULAR criteria (control group) in whom an US was performed were included. US examination was done by an experienced rheumatologist using both grey scale US and power Doppler (PD). The following articular areas were assessed: 2–3 MCP joints, 2–3 proximal PIP joints, wrist, knee and second and fifth MTP joints. Knee and ankle entheses were examined. Both second and third flexor and fourth and sixth extensor tendons of the hands were examined for tenosynovitis. Synovitis, tenosynovitis and enthesitis were defined according to OMERACT preliminary definitions. Both GS and PD synovitis were graded on a semiquantitative scale from 0 to 3. For each one of the structures examined (enthesis, tendons and synovial) an initial US score was obtained by multiplying the semiquantitative scale by the number of sites involved. Using that score patients were classified into a new US structure specific (enthesis, tendons and synovial) activity score ranging from 0 (no activity) to 3 (severe activity) for that structure. Finally adding the US structure specific activity scores a composite US activity score was constructed ranging from 0 (no activity) to 3 (severe activity).

Results: 33 patients with SpA (70% males, mean (SD) age: 51 (14.6) and 35 with RA (97% females, mean (SD) age: 55.7 (16) were included.

Table. Comparison of different variables related to disease activity in the different US composite activity score classification groups in patients with SpA and RA.

					SpA	
US composite activity score classification	N patients (%)	Mean DAS28 (SD)	Mean ESR (SD)	Mean HAQ (SD)	Mean VAS Physician (SD)	Mean CPDAI (SD)
0 (none involvement)	1 (3)	2.3 (0)	18 (0)	0.25 (0)	20 (0)	0 (0)
1 (mild)	26 (79)	3.99 (0.9)	21 (15.8)	0.63 (0.54)	46.5 (20)	3.3 (1.9)
2 (moderate)	6 (18)	5.15 (1.3)	36 (31)	1.33 (0.8)	46.7 (27)	4.2 (3.9)
3 (severe)	0 (0)	-	-	-	-	-
P value (1-mild vs 2-moderate) Mann Whitney		0.1366	0.2107	0.0477	0.9197	0.9363

					RA	
US global severity classification	N patients (%)	Mean DAS28 (SD)	Mean ESR (SD)	Mean HAQ (SD)	Mean VAS Physician (SD)	Mean CDAI (SD)
0 (none involvement)	0 (0)	-	-	-	-	-
1 (mild)	24 (69)	4.6 (1)	21 (15.8)	0.94 (0.83)	40.6 (22)	17.9 (8.6)
2 (moderate)	11 (3)	5.7 (0.7)	36 (31)	1.22 (0.9)	63 (20)	29.2 (9.2)
3 (severe)	0 (0)	-	-	-	-	-
P value (1-mild vs 2-moderate) Mann Whitney		0.0067	0.2551	0.386	0.008	0.0051

Most patients were classified as with mild disease activity by the US composite activity classification score in both diseases SpA and RA. In both diseases patients with higher US cmposite score had higher indices of disease activity although the differences were not always significant.

Conclusion: An US composite activity classification score taking into account synovial, enthesis and tendons involvement proved to correctly discriminate patients with SpA and RA in different activity status according to classical activity indices.

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Correlation Between Clinical and Ultrasonographic Examination of the Calcaneal Enthesis in Patients with Ankylosing Spondylitis: A Controlled Study. Suellen Narimatsu[1], Rita N.V. Furtado[1], Andre Rosenfeld[2], Germana. B. Q. Estrela[1], Jorge E. P. Proglhof[3] and Jamil Natour[4]. [1]Universidade Federal de São Paulo - UNIFESP, São Paulo, Brazil, [2]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo - UNIFESP, Sao Paulo, Brazil, [4]Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: 1 – To compare US findings of calcaneal entheses between AS patients and healthy subjects; 2 – To assess the calcaneal entheses by US and correlate with clinical, functional and inflammatory aspects in patients with AS.

Methods: We conducted a cross sectional study of 50 patients with AS and 30 healthy volunteer subjects matched for age and sex. The clinical evaluation of patients included a global health scale, visual analogue scale (VAS) for pain and edema, calculation of BASDAI, BASFI, BASMI, HAQ-S, ASDAS-VHS and enthesitis index SPARCC (Spondyloarthritis Research Consortium of Canada Enthesitis Index). The US exam was performed at right and left entheses of samples by a radiologist expert in musculoskeletal "blind" to clinical findings. The analysis of the US was based on MASEI index (Madrid Sonographic Enthesis Index) and the total analysis of its subitems. For evaluation was used the Esaote MyLab60 machine equipped with a linear transducer with a frequency of 6–18 MHz.

Results: Were evaluated by the US 160 calcaneal entheses in the whole sample. The patients had ages between 18–65 years (43.44 + 9.91) and healthy subjects 18–65 years (38.7 +8.52). The mean disease duration was 11.11 (+ 6.77) years. The comparison of average Masei between patient and control groups (16.32 + 11.11 / 10.70 + 5.27) was not significantly different (p = 0.519). The comparison of each find in the US between groups showed statistical significance for the detection of erosion (17 patients / healthy 0) with p = 0.00 and power Doppler (PD) (6/0) with p = 0.053. There was no correlation between the presence of bursitis, calcification, erosion, thickening, structural change in the US evaluation of calcaneal tendon with clinical, functional, inflammatory activity in patients. However, the PD of the entheses was correlated with VAS pain (0.344, p= 0.00) and VAS edema (0.486, p = 0.00). The VAS pain and VAS for edema of the calcaneal entheses correlated statistically (0.653, p = 0.00).

Conclusion: The US of the calcaneal entheses of individuals with AS had more erosion and capture the PD when compared with control subjects. The PD on these entheses was the only parameter on US that correlates with clinical variables.

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Ultrasound for Diagnosis of Carpal Tunnel Syndrome – Comparison of Different Methods to Determine Median Nerve Volume and Value of Power Doppler Sonography. Christian Dejaco, Martin Stradner, Dorothea Zauner, Werner Seel, Nicole E. Simmet, Alexander Klammer, Kerstin Brickmann, Judith Gretler, Florentine Moazedi-Fürst, Rene Thonhofer, Rusmir Husic, Josef Hermann and Stefan Quasthoff. Medical University Graz, Graz, Austria

Background/Purpose: Routine use of sonography for the diagnosis of carpal tunnel syndrome (CTS) is hampered by the lack of consensus regarding anatomical landmarks for the measurement of median nerve volume and difficulty of determining thresholds for abnormal median nerve swelling. This study was conduced to compare ultrasound measurement of median nerve cross-sectional area (CSA) at different anatomical landmarks and to analyze the value of Power Doppler (PD) signals within the median nerve.

Methods: We prospectively studied 135 consecutive patients with suspected CTS undergoing clinical and electrophysiological evaluation at two subsequent visits within three months. Final diagnosis of CTS was established by the evaluating neurologist based on findings from these conventional methods at both visits. Median nerve sonography was performed by two rheumatologists using a GE Logiq E9. CSA was

measured at 5 different levels at forearm and wrist; and CSA wrist to forearm ratios or differences were calculated. Intra-neural PD-signals were semiquantitatively graded (scale 0–3). Diagnostic values of different ultrasound methods were compared by receiving operating characteristic (ROC) curves using SPSS (v19.0).

Results: CTS was diagnosed in 111 (45.5%) wrists; 84 (34.4%) had no CTS and 49 (20.1%) were possible CTS cases. Diagnostic values were comparable for all sonographic methods to determine median nerve swelling with AUCs ranging from 0.75 to 0.84. Thresholds of 9.8 and 13.8 mm2 for the largest CSA of the median nerve yielded a sensitivity of 91% and a specificity of 92%, respectively. In cases of mild median nerve swelling the relative increase in CSA between the entrapment area and forearm provided additional diagnostic certainty (AUCs from 0.60 to 0.67). Increased vascularity as indicated by a PD-score ≥2 had a specificity of 90% for the diagnosis of CTS. Reliability of sonographic median nerve volumetry was good as indicated by an intra-class correlation coefficient of 0.90 (95% CI: 0.79–0.95).

Conclusion: Sonographic assessment of median nerve swelling and tissue vascularity at different anatomical landmarks allows for a reliable confirmation of the diagnosis in patients with clinically suspected CTS

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Colour Doppler Sonography of the Knee Joint: A Useful Tool to Discriminate Arthritis From Osteoarthritis? Wolfgang Hartung[1], Nelly Beitinger[1], Boris P. Ehrenstein[1], Christian Lüring[2], Joachim Grifka[3], Benno Schreiner[3], Martina Müller[4] and Martin Fleck[1]. [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [2]Universitiy Clinic Aachen, Aachen, Germany, [3]University of Regensburg, Bad Abbach, Germany, [4]University Clinic Regensburg, Regensburg

Background/Purpose: To determine the diagnostic value of Colour Doppler ultrasound (CDUS) in patients with inflammatory arthritis (IA) versus osteoarthritis (OA) of the knee joint.

Methods: Standardized CDUS examinations have been performed in 111 knee joints of 106 patients (70 female, 36 male) presenting with severe OA (n=72) or confirmed IA (n=39) of one or both knee joints, to determine the degree of synovial inflammation in a semiquantitative fashion. To definitely distinguish inflammatory from non-inflammatory disease, synovial fluid has been obtained from every patient within 24 hours after sonography and analyzed synovial fluids containing up to 1000 white blood cells (wbc)/ul were considered non-inflammatory, whereas 5000 or more wbc/ul have been classified as inflammatory, respectively.

Results: The CDUS sum score of OA patients was determined at 3.3 (range 0–8). In contrast, IA patients exhibited significantly elevated synovitis scores at 5.3 (range 3–9) (p < 0.001). However, high synovial CDUS activity could be observed in OA patients sporadically. Therefore, there is no definitive CDUS threshold that clearly separates OA from IA patients.

Table 1. Mean CDUS scores of the patients with osteoarthritis vs. arthritis of the knee.

Scan	OA patients (n = 73)	IA patients (n = 39)
suprapatellar	0.14 (0–2)	0.64 (0–2)
infrapatellar	0.14 (0–2)	0.44 (0–2)
medial longitudinal	1.2 (0–3)	2.0 (1–3)
lateral longitudinal	2.0 (0–3)	2.3 (1–3)
Total score	3.3 (0–8)	5.3 (3–9)**

OA = Osteoarthritis, IA = inflammatory arthritis of the knee, ** (Chi square test: p value < 0.001).

Conclusion: CDUS is a valuable instrument to assist clinicians in distinguishing OA from IA of the knee, but nevertheless should always interpreted within the clinical context.

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Ultrasound (US) Findings in Patients with Knee Pain: Sensitivity and Specificity for the Diagnosis of Knee Osteoarthritis and Development of an US Prediction Score. Erika Catay[1], Santiago Ruta[2], Javier Rosa[1], David A. Navarta[1], Ricardo Garcia-Monaco[3] and Enrique R. Soriano[4]. [1]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, [4]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires and Fundacion PM Catoggio, Buenos Aires, Argentina

Background/Purpose: The diagnosis of knee osteoarthritis (OA) is based mainly on clinical examination and radiological features. The objectives were to evaluate the sensitivity and specificity of different ultrasound (US) findings and to develop an US score for the diagnosis of knee OA.

Methods: Consecutive patients complaining of knee pain with and without previous diagnosis of knee OA (ACR criteria) and no other known rheumatologic condition were included. US examinations were performed by an experienced rheumatologist, blinded to clinical data, using a My Lab 70 machine (Esaote) provided with a multi-frequency linear transducer (4–13 MHz).The following US abnormal findings were investigated (presence/absence): joint effusion (increased hypoechoic or anechoic intraarticular material, within synovial recesses greater than 4 mm), osteophytes (cortical protrusions at the joint margin), menisci protrusion (a distance between the peripheral border of the meniscus and the outline of the tibial plateau greater than 2 mm), degenerative femoral hyaline cartilage involvement (loss of sharpness of the cartilage margins and/or loss of homogeneity of the cartilage layer and/or focal or extended cartilage thinning) and Baker's cyst (abnormal hypo-anechoic, displaceable and compressible material within the gastrocnemius-semimembranosus, with a transverse diameter greater than 4 mm). We developed a US score using logistic regression analysis (OA as dependant variable) with US features included in the model. Weighting of each of these variables was obtained using the regression OR

Results: 75 knees were examined in 52 patients without knee OA (mean age 59.5 ± 16 years, 34 female/18 male) and 127 knees were examined in 87 patients with knee OA (mean age 72.6 ± 8.3 years, 70 female/17 male).

Table 1. Diagnostic characteristics of different US abnormal findings for the diagnosis of knee OA.

	Sensitivity %, (95% CI)	Specificity %, (95% CI)	PPV %	NPV %
Joint effusion	89.8 (83–94)	32 (22–44)	69	64.8
Osteophytes	85.8 (78–91)	77.3 (66–86)	86.5	76.3
Menisci protrusion	48 (39–57)	93.3 (85–98)	92.4	51.4
Degenerative femoral hyaline cartilage involvement	92.9 (87–97)	84 (74–91)	90.7	87.5
Baker's cyst	16.5 (10–24)	82.7 (72–90)	61.7	36.9

Table 2. US score.

Variables		OR	Points
Joint effusion	Ifpresent	1	1
Degenerative femoral hialine cartilage involvement	Ifpresent	44	4
Osteophytes	Ifpresent	5.8	3
Menisci protrusion	Ifpresent	1.5	2
Maximum Total score			10

Knees with OA had significantly higher scores than knees without OA (mean (SD): 8.1 (2.3) vs 2.1 (2.7); p<0.001, respectively. The area under the Receiver operative curve (ROC) was 0.93 (95% CI: 0.89–0.97). A value ≥ than 5 had a sensitivity of 92 % and specificity of 81 % for the diagnosis of knee OA (LR + 4.9).

Conclusion: The identification of both osteophytes and degenerative femoral hyaline cartilage involvement by US showed the best diagnostic performance among all the US features investigated for the diagnosis of knee OA. A combined US score showed very good discriminative value for the diagnosis of knee OA in our population. A prospective cohort study would be needed to confirm these results.

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Evaluation of Joint Involvement in Patients Suffering From Early Polymyalgia Rheumatica Using High Resolution Ultrasound. Sandra Balser[1], Emmanuelle LeBras[1], Boris P. Ehrenstein[1], Martina Müller[2], Martin Fleck[1] and Wolfgang Hartung[1]. [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [2]University Clinic Regensburg, Regensburg

Background/Purpose: The new EULAR/ACR 2012 classification criteria for polymyalgia rheumatica (PMR) are the first classification criteria that contain musculoskeletal ultrasound (MUS) in an additional algorithm resulting in an increased specificity. Therefore, the joint involvement has been investigated by MUS in a cohort of recent onset PMR patients analyzing the distribution of the novel ultrasound criteria.

Methods: All patients of our tertiary rheumatology center with newly diagnosed PMR between 01/2011 and 06/2012 were included in this retrospective study. MUS has been performed in all patients with suspected PMR. The final diagnosis of PMR was established by a rheumatologist according to physical examination, laboratory analysis, MUS, and after excluding other conditions mimicking PMR.

Results: In 35 patients the diagnosis of PMR was established. Pathological MUS findings of shoulder or hip joints were present in 80.0 % of these patients. Biceps tenosynovitis, subdeltoid bursitis or glenohumeral synovitis of at least one shoulder were observed in 74.3% patients. Of those patients with pathological MUS findings of the shoulder, 92.3 % had a biceps tenosynovitis of at least one shoulder, 80.8 % presented with bilateral biceps tenosynovitis, whereas only 46.2 % had a subdeltoid bursitis and 34.6 % a glenohumeral synovitis of at least one shoulder. Synovitis or trochanteric bursitis of at least 1 hip could be detected in 25.7 % of all PMR patients. 66.7 % of the patients with hip affection in MUS presented with pathological MUS findings of both hips and both shoulders (Tab. 1).

Table 1: MUS findings in PMR patients.

	PMR-Patients (n = 35)
At least 1 shoulder with biceps tenosynovitis, subdeltoid bursitis or glenohumeral synovitis	26 (74.3%)
Both shoulders with biceps tenosynovitis, subdeltoid bursitis or glenohumeral synovitis	24 (68.6%)
At least 1 shoulder with biceps tenosynovitis or subdeltoid bursitis	26 (74.3%)
Both shoulders with biceps tenosynovitis or subdeltoid bursitis	22 (62.9%)
At least 1 shoulder with biceps tenosynovitis	24 (68.6%)
Both shoulders with biceps tenosynovitis	21 (60.0%)
At least 1 hip with synovitis or trochanteric bursitis	9 (25.7%)
Both hips with synovitis or trochanteric bursitis	7 (20.0%)
Patients with no pathological finding as above	7 (20.0%)
At least 1 shoulder and 1 hip with findings as above	7 (20.0%)
Both shoulders and both hips with findings as above	6 (17.1%)

Conclusion: The most common pathological ultrasound finding in patients with PMR was a (bilateral) biceps tenosynovitis. Pathological ultrasound findings of the hips were less frequent, but in two thirds of these patients combined with pathological findings of both hips and both shoulders.

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The Diagnostic Value of Color Doppler Ultrasonography in Giant Cell Arteritis. Merete L. Hetland[1], Geirmund Myklebust[2], Glenn Haugeberg[2] and Andreas P. Diamantopoulos[2]. [1]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [2]Hospital of Southern Norway HF, Kristiansand, Norway

Background/Purpose: Color Doppler Ultrasonography (CDUS) has been shown to be a non-invasive promising tool to diagnose Giant Cell Arteritis (GCA). The aim of our study was to evaluate the diagnostic value of CDUS in patients suspected to have GCA in clinical care.

Methods: Patients referred to our outpatient clinic between January 2010 and April 2012 with a tentative diagnosis of GCA were consecutively examined. A clinical evaluation was performed and the temporal arteries and the large vessels (carotid and axillary arteries) were assessed using a Siemens

Acuson Antares ultrasound system (high frequency transducer 7–14 MHz). CDUS was considered positive when the typical sign of halo (arterial wall swelling in transverse and longitudinal view) was observed in the temporal arteries. The patients were diagnosed with large vessels vasculitis (LVV) when intima-media complex thickness was homogenous and more than 1.5 mm in the carotid artery and more than 1 mm in the axillary artery. After the CDUS examination, unilateral biopsies of the temporal artery were carried out in the majority of the patients. The diagnostic value of CDUS, temporal artery biopsy and the American College of Rheumatology classification criteria for the GCA (ACR-GCA) were tested against the gold standard, for this study defined as final clinical GCA diagnosis established by an experienced rheumatologist.

Results: Seventy-eight patients (48 females, 30 males) were successively referred to our outpatient clinic. Thirty-six were diagnosed with GCA (27 females, 9 males) and all of them had a positive CDUS of the temporal artery. In addition, we found 4 patients with positive CDUS of the temporal artery but with other diagnoses (1 polyarteritis nodosa, 1 granulomatosis with polyangiitis and 2 with infections). Among the 36 patients with GCA, 32 fulfilled the ACR-GCA classification criteria. Temporal artery biopsy was positive in 20 of the 28 GCA patients who had a biopsy performed. Large vessel involvement was observed in 13 patients (36%). The mean time between the first presentation of symptoms and the diagnosis was 2.3 months (3.0 months in GCA patients with LVV and 1.7 months in classic GCA). In our series, sensitivity and specificity was 100% and 91% for CDUS, 64% and 95% for the temporal artery biopsy and 94% and 90% for the ACR-GCA classification criteria, respectively.

Conclusion: We conclude that CDUS has an excellent sensitivity and a high specificity to diagnose GCA in daily clinical care. CDUS do also have the advantage to identify large vessel involvement in GCA patients. We recommend the use of CDUS as a first line assessment tool in diagnosing GCA.

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Grey-Scale Ultrasonography with Power Doppler Technique: An Available Tool for the Assessment of Subclinical Joint Inflammatory Activity in Juvenile Idiopathic Arthritis. Paz Collado[1], Rosa Merino[2], J. Graña Sr.[3], Sagrario Bustabad-Reyes[4], MariLuz Gamir[5], Mari Luz García[6] and Inmaculada Calvo[7]. [1]Severo Ochoa University Hospital, Madrid, Spain, [2]Hospital Universitario La Paz, Madrid, Spain, [3]Hospital Juan Canalejo, Spain, [4]Hospital Universitario de Canarias, La Laguna. Tenerife, Spain, [5]Ramon y Cajal University Hospital, Madrid, Spain, [6]Hospital de Basurto, Bilbao, Spain, [7]Hospital de La Fe, Valencia, Spain

Background/Purpose: To investigate the usefulness of ultrasonography with power Doppler (PDUS) in detecting synovitis compared with clinical examination on large number of joints in JIA.

Methods: This multicenter study included 42 children with active JIA. Clinical and PDUS assessments were performed blindly on 44 joints. Active disease was defined by high acute phase reactants with clinically active arthritis. Active arthritis on US was defined as synovial hypertrophy, effusion, or increased vascularity on power Doppler (PD) scan. McNemar test was used to compare the percentage of joints showing synovitis detected by clinical examination and by PDUS.

Results: In total, 1848 joints were examined both clinically and by PDUS. Physical examination showed 277 joints (15.0%) having clinically active synovitis, and of these, 184 (10%) had synovitis confirmed by US. Furthermore, up to 177 joints (9.6%) were shown to have synovitis on US examination alone. The percentage of joints with synovitis confirmed by PDUS (19.5%, n=361 joints) was statistically higher than the percentage of joints having clinically active synovitis, 15.0% ($p < 0.0005$). Of the 361 joints with GS synovitis detected by US examination, 116 (32.1%) joints were shown to have inflammatory activity by PD signal detected in SH. Subclinical active synovitis was confirmed by PDUS in 51/177 joints (28.8%) that only seemed to have synovitis on US examination.

Conclusion: The study shows that the PD-technique along with GS examination increases the sensitivity of US in detecting subclinical synovitis in JIA. However, longitudinal studies in children are required to know subsequent structural damage.

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Detection of Synovitis in Clinically Inactive Juvenile Idiopathic Arthritis Patients by Ultrasonography with POWER Doppler. Paz Collado[1], Mari-Luz Gamir[2], Rosa Merino[3], Consuelo Modesto[4], Indalecio Monteagudo[5] and Juan Carlos Lopez-Robledillo[6]. [1]Severo Ochoa University Hospital, Madrid, Spain, [2]Ramon y Cajal University Hospital, Madrid, Spain, [3]Hospital Universitario La Paz, Madrid, Spain, [4]Hospital Valle de Hebron, Barcelona, Spain, [5]Gregorio Marañón Hospital, Madrid, Spain, [6]Hospital Niño Jesus, Madrid, Spain

Background/Purpose: The advances in therapeutic effectiveness have created a need for looking for imaging tools that describe more precisely the clinical state of disease inactivity. The well-known advantages of ultrasonography with power Doppler (PDUS) makes that this technique is ideal for evaluation of the pediatric population in the clinical setting and lets clinicians choose an appropriate treatment to induce remission. The purpose of this study was to determine the prevalence of abnormalities detected by ultrasonography (US) in JIA patients presenting clinically inactive disease (ID) –on medication and off medication – and to compare between two groups.

Methods: Study design: Cross-sectional, multicenter study. Patients: Inclusion criteria: 1) JIA patients, age from 4 to 16 years old, 2) remission according to clinical assessment by their consultant doctor for a minimum of 6 months prior to the screening, 3) taking stable disease modified antirheumatic drugs (DMARDs) therapy or have discontinued medications for JIA for a minimum of 6 months, 4) biologics naïve patients. Exclusion criteria: Intra-articular steroid injection in the last 6 months. Data collected: Clinical and PDUS assessments were performed blindly on 44 joints. Other clinical and laboratory markers of activity disease were collected. For the analysis the Outcome Measure in Rheumatology in Clinical Trials (OMERACT) definitions for rheumatoid arthritis of synovitis and tenosynovitis were applied in our patients. The presence of Doppler signal inside the intraarticular synovium or in the synovial sheath was considered as inflammatory activity.

Results: 34 patients, of whom 23 patients have attained clinical remission on medication (CRM) with DMARD therapy and 11 patients have attained inactivity disease off medication (CR) (3). The mean (SD) disease duration was 48.10 (35) months. Half of the study patients have attained one or more previous inactivity disease state, but there was no significant difference between the 2 groups. Thirteen (38.2%) patients had evidence of ≥1 US findings, although the number of US abnormalities detected in CRM patients was higher than CR group, there were no significant differences between the 2 groups in detecting GS synovitis (p=0.86) and PD signal (p=0.38). US examination showed 37 joints presented GS synovial hypertrophy and 18 (48 %) of 37 joints with GS synovitis presented increased PD signal.

Conclusion: Our study shows that a proportion of patients presenting clinically inactive disease presented GS synovitis and some of them seem to present inflammatory activity detected by PDUS. The significance of these findings has importance in order to obtain an accurate definition of disease status in the growing skeleton of JIA patients.

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(1) Wallace CA, Ruperto N, Giannini EH. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31: 2290–4

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Reliability of an Ultrasound Scoring Measure for Juvenile Localized Scleroderma (jLS). Suzanne C. Li[1], Melissa S. Liebling[2], Andrea S. Doria[3], Molly Dempsey-Robertson[4], Carsten Hamer[5], Sven Opitz[5], Faridali Ramji[6], Stephanie Edgerton[6], Jose Jarrin[3], Tanicka Kornyat[2], Michael Malone[6], Arun Mohanta[3], Shuzhen Zhang[4] and Knut M. Wittkowski[7]. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Hackensack University Medical Center, Hackensack, NJ, [3]Hospital for Sick Children, Toronto, ON, [4]Texas Scottish Rite Hospital, Dallas, TX, [5]Schon Klinik Hamburg Eilbek, Hamburg, Germany, [6]University of OK Health Science Center, Okc, OK, [7]Rockefeller University, New York, NY

Background/Purpose: Although ultrasound (US) shows great potential for aiding assessment of LS disease activity, its use has been limited because both image acquisition and interpretation are operator dependent. Our multidisciplinary group (LOCUS, LOcalized scleroderma Clinical and Ultrasound

Study group) has worked to develop an US scoring measure (U-DA) to help standardize sonographic interpretation of jLS patients (Pediatr Rheumatol 2010;8:14). The U-DA evaluates echogenicity and vascularity (color Doppler signal) differences in each tissue layer of the lesion compared with the corresponding normal tissue layer. A score of 0 represents no difference n the lesion compared with the normal site.

Objective: To assess the reliability of an ultrasound scoring measure (U-DA) for jLS.

Methods: LOCUS conducted a 3-day workshop meeting in 2009 on acquiring and interpreting US scans from jLS patients, which was attended by 12 radiologists and sonographers from 5 pediatric rheumatology centers. The group had developed a preliminary ultrasound scoring measure in 2007, and this preliminary measure was reviewed in conjunction with jLS US images showing the range of sonographic differences that had been observed up to the time of the meeting. This review led to modification of U-DA; definitions for scoring levels were then finalized. A tutorial on U-DA scoring was conducted, followed by individual scoring of two jLS US scans and collective review of scoring of these scans. Eleven attendees then scored a randomly-ordered set of 16 jLS scans, with 10 attendees rescoring the same set in a different random order on a second day. Kendall coefficients of concordance were calculated to determine intra-and inter-rater reliability, and scoring of each U-DA was separately analyzed to evaluate for potential issues.

Results: Raters showed moderate to high intra-rater reliability for scoring total echogenicity (Kendall's coefficient 0.77 to 0.92) and vascularity (Kendall's coefficient 0.64–0.92), where total refers to sum of scores from each identifiable tissue layer (dermis, hypodermis, deep tissue). A moderate level of inter-rater reliability was found for scoring total echogenicity (Kendall's coefficient 0.64, 0.56) and vascularity (0.58, 0.57). A high level of agreement was observed for dermis scoring (for example, majority of raters agreed on dermis vascularity score for 15/16 scans), with a much lower level of agreement observed for deep tissue scoring (majority agreement for 10/16 scans on deep tissue vascularity score).

Table 1. Intra- and Inter-rater reliability of U-DA Total Echogenicity, Total Vascularity

U-DA Scoring Parameter	Kendall's Coefficient	P value
Total Echo: Inter-rater, 1st reading	0.64	<0.0001
Total Echo: Inter-rater, 2nd reading	0.56	<0.0001
Total Echo: Intra-rater reliability range	0.77–0.92	0.118 to <0.0001
Total Vasc: Inter-rater, 1st reading	0.58	<0.0001
Total Vasc: Inter-rater, 2nd reading	0.57	<0.0001
Total Vasc: Intra-rater reliability range	0.64–0.92	0.1374 to <0.0001

Conclusion: The U-DA was found to have a moderate level of intra- and inter-rater reliability for total echogenicity and vascularity. Among the different tissue layers, deep tissue layer showed the lowest concordance. More training in deep tissue layer evaluation may further improve the reliability of scoring the U-DA.

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Borderline Right Ventricular Involvement in Patients with Systemic Sclerosis without Pulmonary Hypertension. Luna Gargani[1], Piotr Gosciniak[2], Cosimo Bruni[3], Serena Guiducci[3], Silvia Bellando Randone[3], Lorenza Pratali[1], Gergely Agoston[4], Alberto Moggi Pignone[5], Albert Varga[4], Rosa Sicari[1], Eugenio Picano[1] and Marco Matucci Cerinic[3]. [1]Institute of Clinical Physiology, National Research Council, Pisa, Italy, [2]WSZ, Department of Cardiology, Szczecin, Poland, [3]Department of Biomedicine, Division of Rheumatology AOUC, Excellence Centre for Research, Florence, Italy, [4]University of Szeged, Faculty of Medicine, 2nd Dept of Internal Medicine & Cardiology Center, Szeged, Hungary, [5]University of Florence, Department of Medicine, Division of Rheumatology, Florence, Italy

Background/Purpose: Cardiac dysfunction in systemic sclerosis (SSc) is associated with poor prognosis. Right ventricular involvement is tipically associated to pulmonary hypertension (PH) in these patients. However, primary myocardial involvement, independently of pulmonary hypertension and without significant renal or pulmonary involvement, may also be present. The aim of the present study was to evaluate left and right ventricular function by transthoracic Doppler echocardiography in SSc patients without PH.

Methods: Sixty-five SSc patients without Doppler-derived signs of PH (49 women, mean age, $46+12$ years) and 29 healthy age-matched controls (18 women, mean age $49+15$ years, p=ns) prospectively underwent a comprehensive transthoracic 2D and Doppler echocardiography, including tissue Doppler imaging analysis (TDI) of both right and left ventricle.

Results: SSc patients showed similar left ventricular systolic and diastolic function parameters compared to controls, but significantly worse values in systolic and diastolic right ventricular function (see table below), although still within normal limits.

Echo variables	SSc 65 pts	Controls 29 pts	p
EF (%)	63.0 ± 5.1	65.6 ± 6.4	.07
MAPSE (mm)	15.9 ± 2.5	15.8 ± 3.1	.86
LV S′ TDI (cm/sec)	9.5 ± 1.9	9.0 ± 1.8	.31
LA area (cm^2)	16.6 ± 3.8	16.4 ± 4.6	.93
E/E′	7.8 ± 2.1	7.0 ± 2.1	.12
TAPSE (mm)	22.5 ± 4.3	26.7 ± 4.6	<.0001
RV S′ TDI (cm/sec)	13.5 ± 2.8	15.7 ± 2.0	<.0001
RV E′ TDI (cm/sec)	12.7 ± 3.9	14.7 ± 3.7	<.05
PASP (mmHg)	24.7 ± 5.5	24.8 ± 5.5	.95

Conclusion: In SSc patients without overt cardiac dysfunction and no PH, borderline right ventricular primary involvement can be detected by transthoracic Doppler echocardiography. The clinical implications of these very early alterations are still to be determined.

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Ultrasonography of Salivary Glands: Diagnostic and Prognostic Value in Primary Sjögren's Syndrome. Nicoletta Luciano[1], Chiara Baldini[1], Rachele Pascale[2], Francesco Ferro[1], Alessandro Paolicchi[2], Davide Caramella[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Diagnostic and Interventional Radiology, University of Pisa, Pisa, Italy

Background/Purpose: To assess the accuracy of ultrasonography of the salivary glands (US) in the diagnosis of primary Sjögren's syndrome (pSS) and to verify whether US abnormalities can be correlated to patients' clinical features, to the histopathological score of minor salivary gland biopsies and to the patients' unstimulated sialometry of whole saliva.

Methods: Consecutive patients with a diagnosis of pSS made according to the AECG criteria were enrolled in the cross sectional prospective study. The control group consisted of subjects with suspected SS who did not fulfill the AECG criteria for pSS. US examination of the parotid and submandibular salivary glands was performed by a real-time US (Esaote Technos MPX) equipped with a 7.5/10 MHz linear transducer. The size, parenchymal echogenicity and fibrosis of major salivary glands were evaluated by the same observer who was not aware of the patients' clinical diagnosis. Parenchymal inhomogeneity was assessed scoring as 0 = completely normal, 1 = slight abnormalities/few hypoechogenic areas, 2 = multiple hypoechogenic areas or 3 = many or confluent hypoechogenic lesions. US abnormalities were compared with patients' clinico-serological data, sialometric findings and minor salivary gland focus score. For statistical comparisons, the t-test, the chi square test and logistic regression analysis were employed. P-values <0.05 were considered significant.

Results: Out of the 122 consecutive patients included in the study, 74/122 (71 F:3M, age 54.7±11.8 yrs) met the AECG criteria for pSS while the other 48/122 (45 F:3M, age 54.8±14.9 yrs) represented the control group. US abnormalities were found in 53/74 pSS patients vs 10/48 control group (p<0.0001); the grading values 2 and 3 resulted more frequent in the pSS group (36/74 vs 2/48; p<0.0001). Overall, the sensitivity of US was 71%, specificity 79% (96%, if we considered only parotid inhomogeneity), positive predictive value 84% and negative predictive value 64%. Parenchymal inhomogeneity of both parotid and submandibular glands correlated with antinuclear antibodies (ANA), anti-Ro/SSA, hypergammaglobulinemia and Rheumatoid Factor positivities. Patients with score 3 had significantly higher ESSDAI score (grade 3 vs 1, p=0.004; grade 3 vs 2, p=0.037) and showed trends towards lower salivary flow in comparison to other subgroups (grade 3 vs 1, p = 0.01; grade 3 vs grade 2, p= ns). When pSS patients where

stratified according to parenchymal inhomogeneity, no difference was found in the presence of focal sialadenitis.

Conclusion: Major salivary glands US may be a specific tool in the diagnosis of pSS. US abnormalities should be investigated particularly in pSS patients with positive serological markers.

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Ultrasonographic Evaluation of the Hands of Patients with Primary and Secondary Sjögren's Syndrome. Cristina Hernández-Díaz[1], Luis M. Amezcua-Guerra[2], Angélica Vargas[2], Alberto Lopez-Reyes[3] and Carlos Pineda[1]. [1]Instituto Nacional de Rehabilitación, Mexico City, Mexico, [2]Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico, [3]Instituto Nacional de Rehabilitacion, Mexico City, Mexico

Background/Purpose: Primary Sjögren's syndrome (pSS) is an auto-immune disease characterized by lymphocyte infiltration of various exocrine glands, often associated with joint involvement traditionally described as non-erosive. On the other hand, patients with secondary Sjogren's syndrome (sSS) to rheumatoid arthritis (RA) can show a pattern of arthritis indistinguishable from that observed in patients with RA without SS associated. The description of these differential patterns of disease activity was described by plain X-ray films. The advent of new imaging techniques such as magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSUS) have changed paradigms of subclinical structural damage in various rheumatic diseases. Objective: To characterize by MSUS the morphologic and structural changes in the joints of the hands of patients with SS.

Methods: Patients with the diagnosis of pSS according to the European-American criteria for the classification of Sjögren's syndrome and sSS patients with associated AR as a control group. A Siemens Acuson Antares ® MSUS equipment was used, using a hockey stick type probe (7–12 MHz) images were obtained from the carpal recess, metacarpal and interphalangeal joints of both hands. The presence of synovitis (synovial hypertrophy or joint effusion), erosions and Doppler signal were intentionally sought. MSUS pathology definitions were used as described by the OMERACT group study.

Results: Seventeen patients with pSS and 18 sSS were evaluated, mean age of 60.2 ± 11.91 years. Time evolution of the disease in pSS group was 3 years and 9 years for sSS. Fourteen patients (82%) of the pSS group were positive for rheumatoid factor compared with one hundred percent of individuals with sSS *(p= ns)*. Anti-Ro/SSA antibody was positive in 59% (10) of patients with the primary presentation of the syndrome, unlike the secondary form which was only found in 2% (11) *(p = 0.004)*. Anti-La/SSB antibody was positive in 6 patients with pSS (35%) compare to 0% (0) from the sSS group *(p = 0,007)*. Anti-cyclic citrullinated protein antibodies were positive in most patients with the secondary form of SS (72%), while only 1 out of 17 patients with pSS were positive (6%) *(p = <0.001)*. None of the patients evaluated in this study were positive for anti-Sm antibody. Synovitis of the radiocarpal and midcarpal recesses were found in 62% (21) of the 34 wrists evaluated in pSS group and 81% (29/36) of sSS,; erosions were found in 3 (9%) wrists of patients with pSS and in 14 (39%) of sSS *(p = 0.004)*. Synovitis was present in several joints (wrists, MCP and PIP) in both groups of patients evaluated (Fig.1), predominantly the 2nd and 4th MCP joints of patients with sSS *(p < 0.05)*.

Conclusion: High resolution MSUS confirms that pSS arthropathy is as inflammatory as sSS associated with RA, however is clearly not as erosive.

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Quantitative Assessment of Synovitis in Patients with Rheumatoid Arthritis Using Fluorescence Optical Imaging. Valentin S. Schäfer[1], Wolfgang Hartung[1], Patrick Hoffstetter[1], Jörn Berger[2], Martina Müller[3], Martin Fleck[1] and Boris P. Ehrenstein[1]. [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [2]mivenion GmbH, Berlin, Germany, [3]University Clinic Regensburg, Regensburg

Background/Purpose: To prospectively evaluate quantitative assessment of indocyanine green (ICG)-enhanced fluorescence optical imaging (FOI) for differentiation of synovitic from non-synovitic joints in patients suffering from rheumatoid arthritis (RA).

Methods: FOI of the hands was performed in patients with active RA as

recommended by the manufacturer (Xiralite system, Mivenion GmbH, Berlin, Germany; ICG bolus of 0.1 mg/kg/ body weight, sequence of 360 images, one image per second, stratified fluorescence readout (FLRO) of 3 phases (I: 1 – 120 s; II: 121 – 240 s; III: 241 to 360 s)). To dissect the effect of the overall perfusion of the hand from the perfusion due to active synovitis, a fluorescence ratio (FLRA) was calculated for each individual joint dividing the readout of the joint by the readout of the eponychium of the index finger. For comparison, absence or presence of synovitis in 5 joints of the clinical predominant hand (carpal joint, metacarpophalangeal and proximal interphalangeal joints of digits II & III) were analyzed using grayscale (GSUS) and power Doppler (PDUS) ultrasonography, or magnetic resonance imaging (MRI). The mean FLRO and FLRA were compared between joints with absent vs. present synovitis determined by GSUS, PDUS and MRI using student's t-test.

Results: Ninety joints of 18 patients (8 female (44%), mean (± SD) age 63±10 years) with RA were included. The quantitative analysis for individual joints yielded values for the FLRO ranging from 4.4 to 49.0 × 10³, and the FLRA ranging from 0.37 to 2.27. A comparison of mean (±SD) of FLRO and FLRA is depicted in table 1. Overall, the analyses based on the FLRA revealed a higher discrimination than the analyses related to the FLRO. The most significant differences were observed for mean values of phases II & III. A sensitivity of 26/39 (67%) and a specificity of 31/40 (77%) were calculated for the FLRA of phase III using a cut-off value of more than 1.2 to detect MRI-diagnosed synovitis with FOI.

Table 1. Mean fluorescence readout and fluorescence ratios for joints with vs. without evidence of synovitis determined by established imaging techniques.

Synovitis	n	phase I 1–120 s mean ± SD FOI readout	p	phase II 121–240 s mean ± SD FOI readout	p	phase III 241–360 s mean ± SD FOI readout	p
GSUS yes	39	21.0 ± 11.4	ns	23.5 ± 10.4	<.01	15.8 ± 7.9	<.01
GSUS no	51	17.7 ± 7.5		16.6 ± 6.8		10.5 ± 4.8	
PDUS yes	23	24.1 ± 12.3	<.05	23.8 ± 9.3	<.05	15.0 ± 5.9	ns
PDUS no	67	17.5 ± 7.7		18.2 ± 8.7		12.0 ± 7.0	
MRI yes	39§	20.9 ± 10.1	ns	22.3 ± 9.5	<.05	14.8 ± 7.3	<.05
MRI no	40§	17.8 ± 9.6		17.2 ± 9.2		10.9 ± 6.5	
		FOI ratio		**FOI ratio**		**FOI ratio**	
GSUS yes	39	1.06 ± 0.47	ns	1.33 ± 0.48	<.05	1.37 ± 0.48	<.01
GSUS no	51	0.91 ± 0.32		1.10 ± 0.26		1.12 ± 0.26	
PDUS yes	23	1.22 ± 0.46	<.01	1.52 ± 0.52	<.01	1.53 ± 0.53	<.01
PDUS no	67	0.89 ± 0.33		1.09 ± 0.26		1.12 ± 0.26	
MRI yes	39§	1.11 ± 0.46	<.01	1.38 ± 0.47	<.001	1.41 ± 0.46	<.001
MRI no	40§	0.86 ± 0.33		1.06 ± 0.26		1.08 ± 0.26	

Fluorescence readout results are displayed for better readability divided by 10³, FOI= fluorescence optical imaging, GSUS=grey scale ultrasonography, PDUS=power Doppler ultrasonography, MRI=magnetic resonance imaging; §11 joints could not be evaluated with MRI; ns comparison was not significant (p≥.05) with student's t-test.

Conclusion: ICG enhanced FOI has a potential for visualizing synovitis in subjects with RA. For adequate FOI interpretation, phases II & III appear to be most relevant. Utilizing the presented quantitative approach, significant differences of the mean FLRO and particularly of the FLRA could be demonstrated comparing synovitic to non-synovitic joints in patients with active RA. However, a definitive cut-off value for either analytic method could not be established.

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Comparison of Automated, Computer-Based Assessment and Visually Assessed Disease Activity Scores in ICG-Enhanced Fluorescence Optical Imaging in Patients with Rheumatic Disorders: A Feasibility Study. Stephanie G. Werner[1], Michael Schirner[2], Hans-Eckhard Langer[3], Mathias Cziumplik[2], Jörn Berger[2], Marina Backhaus[4] and Malte Bahner[2]. [1]RHIO (Rheumatology, Immunology, Osteology) Duesseldorf, Duesseldorf, Germany, [2]mivenion GmbH, Berlin, Germany, [3]Duesseldorf, Germany, [4]Charite University Hospital, Berlin, Germany

Background/Purpose: Modern diagnostic imaging technologies including US and MRI become increasingly important in the management of rheumatic joint disorders. Semiquantitative scores, like the RAMRIS or the

US7 – score aim at measuring disease activity especially for clinical trials. Most recently, fluorescence optical imaging (FOI) became clinically available for diagnostic imaging. Most recently, it has been shown that automatic, computer-based image analysis of FOI using dedicated software is technically feasible and offers high reproducibility. Measurement of areas of high signal intensity expressed as DACT value may provide a reliable quantitative readout for inflammatory activity. In this feasibility study we compared the results of visual reading of FOI using the semiquantitative scoring system FOIAS (fluorescence optical imaging activity score) for visually assessment with this automatic, computer-based algorithm for quantitative analysis.

Methods: 45 patients (34 f, mean age 55y, mean DAS28 4.2) were selected. First 4 readers analyzed all 45 image data sets individually, and then 2 of the four readers performed a consensus reading. For articular location of increased signal intensities (ISI) the FOIAS was used. For extraarticular location the signals were graded semiquantitatively on a scale of 0 to 2. These values were added to a single number representing the overall fluorescence signal intensity of the hands (cFOIAS, complete FOIAS). For DACT the automatically generated composite images were generated. Using dedicated parameters of the histograms, automatic extraction of the hands from the image background was performed by the computer. The algorithm separated the hands from the forearm in a standardized manner by using a multiple of the length of the middle finger. A threshold in the fluorescence intensity curve was set to discriminate high and low intensity areas. The area of high intensity was calculated and the values of each patient were divided by the 90th percentile of normal individuals which was defined as reference value. DACT was expressed as high signal intensity area $_{patient}$ / healthy reference. DACT in healthy individual equaled 1. Then cFOIAS and DACT value were compared.

Results: Correlation of the cFOIAS and the DACT value was high, while all 4 readers and the consensus readings showed good interreader reliability. Two sample scatter plots are shown in the figure.
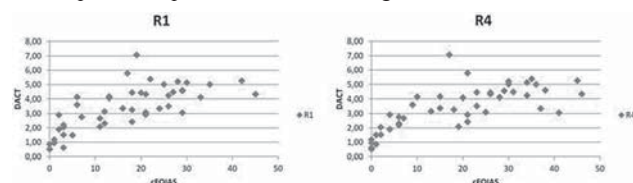
Conclusion: Assessment of disease activity in FOI using automated, computer-based algorithms correlated well with visual assessment with a scoring system. While the semiquantitative assessement is time consuming and can be biased by the reader, the automatic calculation may be an objective and fast tool for assessment of disease activity. Following work should concern to proof this and the potential value of DACT for monitoring of treatment response in longitudinal, interventional studies.

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Is Bone Scintigraphy Still Useful to Diagnose Rheumatoid Arthritis After the Appearance of 2010 ACR/EULAR Classification Criteria? Ji Young Kim[1], Soo-Kyung Cho[2], Min-Kyung Han[2], Yun Young Choi[1] and Yoon-Kyoung Sung[2]. [1]Hanyang University College of Medicine, Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: For many years, the importance of bone scintigraphy to measure inflammation in the joints of patients with RA has been emphasized. Moreover, increased blood pool activity of involved joints in bone scintigraphy corresponds to inflammatory synovitis which is characteristic feature in early RA. Therefore, bone scintigraphy especially with blood pool phase, might be useful in suggesting early joint involvement in RA. The aim of this study was to investigate the usefulness of bone scintigraphy in the diagnosis of rheumatoid arthritis (RA) with assisting the 2010 ACR/EULAR classification criteria.

Methods: A total of 156 patients who firstly visited the rheumatology department and had taken bone scintigraphy and blood pool image with screening laboratory and radiologic tests to confirm RA diagnosis were retrospectively enrolled. Gold standard RA patients were defined as the patients who started disease modifying anti-rheumatic drugs within 3 months

of their first visit. After dividing patients into two groups according to the presence or absence of arthritis on their first presentation, we evaluated the diagnostic validity of bone scintigraphy as an independent diagnostic tool (BS only) and as an assistant tool for physicians' application of 1987 and 2010 criteria (BS assisted diagnosis) to detect RA. In BS assisted diagnosis, the number, symmetricity, and distribution of involved joints were evaluated with BS results instead of physician's assessment.

Results: Seventy-five (48.1%) of the 156 patients had active arthritis on physical examination (Group I) and the others of 81 patients did not have arthritis at first visit (Group II). Among them, 56 (74.7%) in group I and 5 (6.2%) in group II were RA patients, respectively. For group I patients (n=75), who were eligible to 2010 criteria, the sensitivity of the bone scintigraphy alone was extremely low (42.9%) with elevated specificity (100%), though those of 2010 criteria assessed by only physician (82.1% and 94.7%, respectively). For this group, the sensitivity of BS assisted diagnosis (75.0%) was slightly lower than that of the diagnosis by physician. For group II patients (n=81) who are not eligible for 2010 criteria, only BS or BS assisted diagnosis identified 2 more RA patients among 5 gold standard RA patients who did not satisfy either 1987 or 2010 criteria (Table).

Table. Comparison of the diagnostic validities of the bone scintigraphy (BS) and BS assisted diagnosis

	Subjects	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95% CI)
Group I. Patients with Arthritis at presentation (who eligible for 2010 criteria, n=75)						
	BS only	42.9	100	100	37.3	-
1987 criteria	Physician only	66.0	99.2	97.4	86.1	0.864 (0.770–0.958)
	Physician with BS	58.9	100	100	45.2	0.911 (0.844–0.977)
2010 criteria	Physician only	82.1	94.7	97.9	64.3	0.923 (0.803–1.0)
	Physician with BS	75.0	94.7	97.7	56.2	0.943 (0.883–1.0)
Group II. Patients without Arthritis at presentation (who are not eligible for 2010 criteria, n=81)						
	BS only	40.0	98.7	66.7	96.2	-
1987 criteria	Physician only	0	100	-	93.8	0.636 (0.362–0.909)
	Physician with BS	20.0	100	100	95.0	0.696 (0.355–1.0)
2010 criteria	Physician only	0	100	-	93.8	0.861 (0–1.0)
	Physician with BS	40.0	100	100	96.2	0.862 (0–1.0)

Conclusion: In usual practice, BS assisted diagnosis is not superior to physician's assessment, especially after appearance of 2010 ACR/EULAR classification criteria. However, bone scintigraphy is still helpful to rule out non RA patients in patients with arthritis and to find out RA patients among patients without arthritis on physical examination.

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Subclinical Arthritis Visualised by Positron Emission Tomography and Macrophage Targeting Precedes Clinical Flare in Rheumatoid Arthritis Patients in DAS28 Remission. Y.Y.J. Gent, A.E. Voskuyl, N. Ahmadi, N. Hoetjes and C.J. van der Laken. VU University Medical Center, Amsterdam, Netherlands

Background/Purpose: Macrophages play an important role in the pathophysiology of Rheumatoid Arthritis (RA). Targeting of macrophages by (R)-[^{11}C]PK11195 positron emission tomography (PET) has previously been successfully used for imaging of (subclinical) synovitis in preclinical and established RA patients. It is known that a considerable number of RA patients with minimal disease activity or remission may have subclinical disease activity as well. Therefore, we have performed a prospective pilot study in which (R)-[^{11}C]PK11195 PET was used to visualise subclinical inflammation in hand and/or wrist joints of RA patients that are in DAS28 clinical remission, in relation to magnetic resonance imaging (MRI) at baseline and clinical outcome within 3 years.

Methods: High spatial resolution (R)-[^{11}C]PK11195 PET scans and contrast-enhanced MRI scans of both hands and wrists were performed in twenty-nine RA patients without any signs of arthritis according to a 28-joint count and fulfilling DAS28 clinical remission. PET tracer uptake was scored semiquantitatively according a 0–3 scale and MRI scans were scored for presence of synovitis and bone marrow edema (BME) according to the OMERACT RAMRIS score. Cumulative scores were calculated by adding

up joint scores of all metacarpophalangeal, proximal interphalangeal and wrist joints (range PET 0–66; range MRI 0–222).

Results: *(R)*-[^{11}C]PK11195 PET scans showed evidence of subclinical arthritis in at least one hand and/or wrist joint in 16/29 (55%) of patients. Flare of clinical arthritis was found in 17/29 (59%) of patients within 3 years of clinical follow-up. Patients with cumulative PET scores >6 (n=3) and scores of 4–5 (n=2) developed arthritis in hands/wrists within respectively 26 weeks and 52 weeks. Patients with high cumulative PET scores of >6 also depicted high cumulative MRI scores of >37. In patients without flare of clinical arthritis within 3 years (n=12), PET scores were always low or negative (≤1), but MRI scores varied between 0 and 27.

Conclusion: This prospective pilot study shows that macrophage targeting by *(R)*-[^{11}C]PK11195 PET visualises subclinical synovitis in hand/ wrist joints of RA patients in DAS28 remission. At patient level, high cumulative PET scores may predict a short-term flare of arthritis activity. *(R)*-[^{11}C]PK11195 PET may be of additive value to MRI for detection of subclinical synovitis in DAS28 remission patients, in particular with regard to specificity, but this needs to be confirmed in larger patient cohorts.

Disclosure: **Y. Y. J. Gent**, None; **A. E. Voskuyl**, None; **N. Ahmadi**, None; **N. Hoetjes**, None; **C. J. van der Laken**, None.

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FDG-PET Evaluation of Axillary Lymph Nodes and Large Joints of Patients with Rheumatoid Arthritis Treated with Anti-TNF Drugs.
Koichi Okamura[1], Yukio Yonemoto[1], Tetsuya Kaneko[1], Kimihiko Takeuchi[2], Tsutomu Kobayashi[1] and Kenji Takagishi[1]. [1]Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [2]Isesaki Fukushima Hospital, Isesaki, Gunma, Japan

Background/Purpose: F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used to image synovial inflammation in patients with rheumatoid arthritis (RA). The development of molecular imaging methods would be beneficial, especially in RA patients. In the present study, we evaluated whether the FDG uptake of the affected joints and the axillary lymph nodes (AxLN) represented by the standardized uptake value (SUV) correlated with the clinical assessment of patients with RA. In addition, we evaluated if there was a correlation between the differences in the SUV and the improvement of the clinical findings in RA patients receiving anti-TNF therapies.

Methods: Forty-two patients (10 male, 32 female; average age: 55.67 (18–74) years) who underwent anti-TNF therapies (infliximab (IFX) for 17 patients, etanercept (ETN) for 14 patients and adalimumab (ADA) for 11 patients), were enrolled in this study. The average disease duration of these patients was 11.7 (0.6–49) years. Clinical disease activity was assessed by using disease activity scoring (DAS) 28, DAS28-CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and numbers of 28 tender and swollen joints count (TJC, SJC) and measuring erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum matrix metalloproteinase-3 (MMP-3) and rheumatoid factor (RF) at baseline (0M) and after 6 month (6M) of the therapies. FDG-PET/CT was performed 0M and 6M. The PET images were interpreted by two experienced nuclear physicians and increased FDG uptake in bilateral shoulder, elbow, wrist, hip, knee, and ankle joints and bilateral AxLN were recorded. Therapeutic response was evaluated by the changes in the sum of the maximal SUV (total SUVmax) of all 12 measured joints and the clinical findings.

Results: Before treatment, the total SUVmax was correlated with the DAS28 (r=0.532,p=0.001), DAS28-CRP (r=0.529,p<0.001), SDAI (r=0.491, p=0.001), CDAI (r=0.457, p=0.002), ESR (r=0.506, p=0.001), CRP (r=0.385, p=0.012), TJC (r=0.416, p=0.007) and SJC (r=0.467, p=0.002), respectively. The SUVs of AxLN were correlated with the SUV of the ipsilateral wrist joints. The ΔSUV, the difference in the total SUVmax before and after treatment, significantly correlated with the ΔDAS28 (r=0.498, p=0.001), ΔDAS28-CRP (r=0.517, p<0.001), ΔSDAI (r=0.550, r<0.001), ΔCDAI (r=0.534, p<0.001), ΔESR (r=0.485, p=0.001), ΔCRP (r=0.437, p=0.003), ΔTJC (r=0.447, p=0.003) and ΔSJC (r=0.525, p<0.001), respectively. ΔSUV of AxLN did not correlate with ΔCRP, ΔESR and ΔMMP-3, however, correlated with the Δ SUV of the same or other side of the wrist joint.

Conclusion: FDG-PET can image the extent of inflammation in patients with RA. In addition, the FDG uptake of the axillary lymph nodes might reflect the disease activity especially in the wrist joints. FDG-PET can be used to evaluate the response of RA patients to biological treatment.

Disclosure: **K. Okamura**, None; **Y. Yonemoto**, None; **T. Kaneko**, None; **K. Takeuchi**, None; **T. Kobayashi**, None; **K. Takagishi**, None.

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Utility of PET-CT Imaging in IgG4-Related Disease.
Arezou Khosroshahi, Leslie Lee, Mollie Carruthers, Rusen Acu, Pietro Bonaffini, Vikram Deshpande, Dushyant Sahani and John H. Stone. Massachusetts General Hospital, Boston, MA

Background/Purpose: IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition characterized by unique pathological features that affect a wide variety of organs. The disease process may be active long before patients present with symptoms from the mass effect of the IgG4-related lesions or the organ damage. Morphologic and functional imaging studies are increasingly used in the diagnosis and monitoring of response to therapy in inflammatory diseases. Positron-emission tomography/computed tomography (PET/CT) enables the acquisition of whole-body images and provides functional information about disease activity. The purpose of our study was to describe the PET/CT findings in patients with histologically-proven IgG4-RD and to evaluate their correlation with disease activity.

Materials/Methods: We searched the IgG4-RD Registry at Massachusetts General Hospital. Between March 2007 and May 2012, 20 patients (7 female and 13 male; median age 57 years, range 27–81), underwent whole body ^{18}F-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (FDG PET-CT) imaging. All 20 patients had diagnoses of IgG4-RD based on the characteristic histology and immunostaining findings for this condition. We compared the sites of disease activity identified by PET/CT to the sites identified by their clinicians through symptoms, signs, laboratory findings, and other imaging studies.

Results: Patients presented with various symptoms including: flank/back pain (7 patients), face swelling (3), neck swelling (3), proptosis (2), cough (2), weight loss (2), sinus congestion (2), and dry mouth/eyes (1). Thirteen of 20 patients (65%) had multi-organ disease at presentation, affecting some combination of the pancreas, bile ducts, liver, gallbladder, lung, salivary glands, orbitals, aorta, thyroid, kidney, retroperitoneum, and lymph nodes. The mean number of organs involved among patients with multi-organ disease was 4.1 (ranging 2–7 organs). Seven patients (35%) had localized disease at presentation (5 RPF, 1 lymphadenitis, 1 orbital pseudotumor).

The serum IgG4 was elevated in 8 patients at the time of PET-CT imaging (mean 635.6 mg/dL). FDG PET was positive in all 20 patients (mild to intense uptake in 19 and low in 1 subject). In 17/20 patients (85%), FDG uptake was concordant with clinical manifestations of active inflammation. In addition 7/20 patients (35%) had FDG uptake in organs not suspected of involvement on a clinical basis alone (RPF, lymph nodes, thoracic aorta, lung, lacrimal glands and nasopharynx).

Conclusion: In IgG4-RD, FDG PET-CT is a sensitive imaging tool for the detection of subclinical disease. This modality can demonstrate additional sites of disease not obvious by clinical presentation or on conventional CT imaging, therefore providing a more complete assessment of the extent of organ disease. It's utility as a tool for monitoring treatment response and guiding therapy requires prospective studies.

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ACR Poster Session A
Metabolic and Crystal Arthropathies
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Co-Existence of Gout in Rheumatoid Arthritis: It Does Happen! A Population Based Study.
Adlene Jebakumar, Cynthia S. Crowson, P. Deepak Udayakumar and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Even though there are a few cases in the literature reporting co-existence of gout and rheumatoid arthritis (RA), it has been a long time popular belief that gout does not occur in patients with RA. We aimed to assess the occurrence, clinical presentation, and possible risk factors for gout in patients with RA.

Methods: We retrospectively reviewed a population-based incidence cohort of patients who fulfilled 1987 ACR criteria for RA in 1980–2007. All subjects were longitudinally followed through their complete community medical records until death, migration, or April 2012. Gout was defined using the physician diagnosis, along with typical monosodium urate crystal positivity in synovial fluid or the 1977 ARA clinical criteria for gout. We

excluded the patients with pseudogout, hyperuricemia without gout, septic arthritis, traumatic arthritis, and RA initially misdiagnosed as having gout. Cumulative incidence of gout in RA adjusted for the competing risk of death was estimated. Cox models were used to assess risk factors for gout in RA.

Results: The study population included 813 patients, 537 (66%) were rheumatoid factor positive; 33% had rheumatoid nodules, and 53% had erosive joint disease. During 9771 total person-years of follow-up (mean 12.0 years per RA patient), 22 patients developed gout by clinical criteria. The great toe was the most common site of gout (12 of 22 patients). The 25 year cumulative incidence of gout diagnosed by clinical criteria was 5.3%. Typical intracellular monosodium urate crystals were present in 9 of 22 patients with acute gout; all had developed gout after the RA incidence date. The 25 year cumulative incidence of gout diagnosed by clinical criteria including presence of urate crystals is 1.3%. The prevalence of gout in RA on Jan 1, 2008 was 1.9% (11 of 582 patients) as opposed to expected prevalence of 5.2% (or 30 patients) based on National Health and Nutrition Examination Survey (NHANES) data using age and sex specific prevalence rates.

Risk factors for gout in RA were: older age (hazard ratio [HR] 1.5 per 10 year increase; p = 0.04), male sex (HR 3.18; p = 0.03) and obesity (HR 3.5; p = 0.03). The presence of erosive RA joint disease reduced the risk of gout (HR 0.24; p = 0.03). Gout has become more common in patients diagnosed with RA in recent years (1995–2007) than in previous years (1980–1994; HR 5.6; p = 0.007).

Conclusion: Gout does occur in patients with RA though at a lower rate than in the general population, with a minimum/maximum cumulative incidence of 1.3/5.3%. Risk factors for gout in RA generally mirror those in the general population.

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A Pilot Study of the Efficacy of IL1 Blockade by Anakinra in Acute Calcific Periarthritis of the Rotator Cuff. Pascal Zufferey, Melanie Faucherre, Pierre A. Varisco, Berengere Aubry Sr., Isabelle Fabreguet and Alexander K. So Sr.. CHUV, Lausanne, Switzerland

Background/Purpose: Calcific periarthritis of rotator cuff can induce acute and severe shoulder pain and is accompnied by signs of acute inflammation. The calcific deposits are composed of calcium phosphate crystals such as hydroxyapatite or basic calcium phosphate. These crystals stimulate the production and release of IL1b from macrophages, in an analogous manner to MSU and CPPD crystals. As IL1 blockade is effective in reducing signs and symptoms of inflammation in acute gout, we performed a pilot study to study if it is also effective in calcific periarthritis

Methods: 5 consecutive patients were included (mean age: 62, 3 females, 2 males) between March 2011 and March 2012. Symptoms of acute shoulder pain at rest had to be present for <7 days before inclusion, associated with limitation of shoulder mobility and the presence on calcification in the rotator cuff by conventional radiography. None of the patients had responded to at least 48 hours of high doses of NSAIDs. Exclusion criteria included no corticosteroid therapy in the last 2 weeks and the exclusion of other rheumatologic or infectious diseases-.Clinical evaluation consisted of patient assessment of pain (total, rest and activity) by VAS (100mm scale) at days 0, 1, 3, 15, 42 and clinical examination of shoulder mobility at days 0, 3, 15. ESR and CRP were measured at days 0, 3. Plain radiographs were performed at days 0 and 15 and an ultrasound examination (including Doppler) was performed at days 0, 3, 15. Anakinra 100mg daily was administered for 3 consecutive days after the first evaluation (day 0). Rescue analgesics were allowed and recorded.

Results: At inclusion, all patients had severe shoulder pain: mean (SD) VAS day pain of 72mm (±25mm), mean VAS night pain of 96 (± 5) and impaired shoulder mobility. CRP was elevated in all of them (mean of 3X). Treatment with anakinra lead to rapid relief of pain in all patients, starting already on the first night following the first injection. The reduction of VAS pain was particularly striking for rest pain: mean (SD) VAS of 4mm (± 5) at day 1 and this response was maintained for the 5 patients at the end of the three injections without any need of rescue medication. Mean rest VAS was 6 (±8) at day 3. The effect on day pain was less spectacular: mean (SD) VAS at D1 of 30 (± 18), at D3 of 27 (± 11). Shoulder mobility also improved and the CRP normalized in 4 of 5 patients at day 3. At day 42, 4 of 5 the patients were still totally asymptomatic. On X rays and US, the calcifications were reduced in size: mean maximal diameter of 21 mm at day 0 to 12 mm at day 15, but did not disappear in any patient. The main change

on US was a significant and rapid (at day 3) reduction of Doppler activity around the calcification.

Conclusion: This pilot open study suggests that IL-1β inhibition may be an interesting therapeutic approach in acute calcific periarthritis, especially in patients who have not responded adequately to NSAIDs. The effect on pain seems to be more rapid (within a few hours) than steroid injection although a randomized controlled study needs to be performed to confirm this observation.

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A Delphi Exercise to Identify Characteristic Features of Gout—a Study of Opinions From Patients and Physicians to Inform New Classification Criteria. Rebecca Prowse[1], Nicola Dalbeth[2], H. R. Schumacher[3], Tuhina Neogi[4], Tim L. Jansen[5], Jaap Fransen[6] and William Taylor[1]. [1]University of Otago, Wellington, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA, [4]Boston Univ School of Medicine, Boston, MA, [5]St Radboud University Nijmegen Medical Centre, Netherlands, [6]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Updated classification criteria for gout are required. The aim of this study was to identify a comprehensive list of features that might discriminate between gout and similar conditions, for use in a subsequent case-control study for developing and testing new classification criteria.

Methods: Two Delphi exercises were conducted using web-based questionnaires; one with physicians who have an interest in gout and one with patients who have gout. Physicians rated a list of potentially discriminating features that were identified via literature review and expert opinion and patients rated a list of features that they generated themselves. Agreement was defined by the RAND/UCLA disagreement index. Multiple iterations were conducted until consensus was reached or no changes in participant ratings were observed.

Results: Forty-four highly experienced physicians (62% response rate) and nine patients (11% response rate) responded to all iterations. For physicians, 71 items were identified by literature review and 15 more were suggested by physicians. The physician survey showed agreement for 26 discriminatory features and 15 that were not discriminatory. The patients identified 46 features of gout for which there was agreement on 25 items as being discriminatory and seven items being not discriminatory. The results of highly rated features for both physician and patient surveys are summarised in the Table (showing areas of agreement and disagreement). Patients and physicians agreed upon several key features of gout: suddenness of onset, redness, marked tenderness and swelling of the affected joint, elevated serum urate levels, presence of tophi, presence of urate crystals in synovial fluid and involvement of the first metatarsophalangeal joint. Physicians emphasized imaging and patterns of symptoms, whereas patients emphasized functional impact, dietary triggers and idiographic perception of symptoms.

Table. The overlap and differences between features highly rated (median 7 to 9) by physicians and patients. US: ultrasonography, CT: computed tomography, DECT: dual energy CT, MRI: magnetic resonance imaging

Highly rated by physicians	Highly rated by physicians and patients	Highly rated by patients
Typical X-ray erosion	Hyperuricaemia	Difficulty walking
Snowstorm joint effusion appearance on US	MSU crystals in joint/tissue aspirate	Can't use affected joint
Tophi on US, DECT, CT or MRI	Tophi	Interrupts sleep
Double-contour sign on US	Podagra ever	Medication helps
Monoarthritic attacks in first few years, becoming oligo-, then polyarthritic over time	Abrupt and severe pain	Throbbing/severe, sharp annoying pain
Podagra at first attack	Redness around the affected joint	Gout attack often occurs after eating seafood/shellfish/alcohol
Complete resolution of attacks	Marked joint tenderness	The affected joint is hot or burning
Resolution of an attack within 7-14 days	Monoarticular joint involvement	The affected joint enlarged/swollen
Mid-foot joint involvement		If you injure an area that has been affected by gout, it takes longer to heal than one that has not been affected by gout
Uric acid nephrolithiasis		Only one foot is usually affected at a time
		The pain is less present even when the affected joint is not being moved/used

Conclusion: Physicians' and patients' perceptions of the key features of gout have some similarities but many differences. The list of features with a

median rating of 7 to 9, generated by both patients and physicians, will be examined in a case-control study to identify the most sensitive and specific combination for the classification of crystal-proven gout.

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Monosodium Urate Crystals Inhibit Tenocyte Viability and Function: Implications for Periarticular Involvement in Chronic Gout. Ashika Chhana[1], Karen E. Callon[1], Bregina Pool[1], Dorit Naot[1], Gregory Gamble[1], Brendan Coleman[2], Fiona M. McQueen[1], Jillian Cornish[1] and Nicola Dalbeth[1]. [1]University of Auckland, Auckland, New Zealand, [2]Middlemore Hospital, Auckland, New Zealand

Background/Purpose: Recent advanced imaging studies have demonstrated that urate deposition in periarticular structures is common in gout. Urate deposition has been observed both adjacent to and within tendons, suggesting that monosodium urate monohydrate (MSU) crystals are likely to be in direct contact with tenocytes, the stromal cells of tendons. The aim of this study was to determine the effects of MSU crystals on tenocyte viability and function.

Methods: Cultures of primary rat tenocytes were prepared from Wistar rat tails. Primary human tenocytes were prepared from patients undergoing orthopedic surgery. MTT assays were used to assess tenocyte viability following culture with MSU crystals. Cells cultured with MSU crystals for various times were stained with Annexin V and propidium iodide, and flow cytometry was used to determine changes in the levels of apoptosis. Real-time PCR was used to determine changes in gene expression and Sirius red staining to detect changes in collagen deposition in tenocytes cultured with MSU crystals.

Results: MSU crystals reduced viability in a dose-dependent manner in both primary rat and human tenocytes (Figure). Differing MSU crystal lengths and increased serum levels in cultures did not alter this effect. The reduction in tenocyte viability was specific to MSU crystals, as soluble uric acid did not reduce cell viability. Flow cytometry showed that MSU crystals rapidly induced cell death, but apoptosis levels remained unchanged. Culture with MSU crystals reduced mRNA expression of collagen types 1 and 3; and tenocytic markers, including tenomodulin, scleraxis and tenascin-C. Collagen deposition was inhibited in tenocytes cultured with MSU crystals in a dose dependent manner.
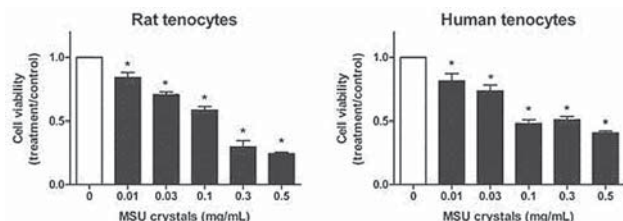
Figure. Effects of MSU crystals on primary rat and human tenocyte viability. Cell viability was assessed using the MTT assay following 24 hours of culture with MSU crystals. Data shown are mean (SEM); one-way ANOVA (P<0.0001) with *post hoc* Dunnett's test *p<0.0001 versus control (no MSU crystals).

Conclusion: These data indicate that MSU crystals directly interact with tenocytes to reduce cell viability and function. These interactions may contribute to tendon damage in patients with chronic gout.

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Evaluating Appropriate Use of Prophylactic Colchicine and Urate Lowering Therapy in Gout. Michael George[1], Sally W. Pullman-Mooar[2] and H. Ralph Schumacher[3]. [1]Hospital of the University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania and Philadelphia Veterans Hospital, Philadelphia, PA, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA

Background/Purpose: Colchicine is recommended to prevent gout flares in patients initiating and increasing uric acid lowering therapy until serum uric acid is ≤ 6 mg/dL. Many patients, however, are prescribed colchicine without adequate urate lowering therapy or remain on colchicine after uric acid targets have been met. The recent dramatic increase in colchicine cost in the United States has made it even more important to examine current prescribing practices, identify variables that influence these practices, and promote appropriate colchicine use.

Methods: Pharmacy identified 193 patients at a VA medical center with active outpatient colchicine prescriptions on 11/4/2011. Electronic medical record review revealed 126 patients prescribed colchicine for ≥ 30 days for prophylaxis of gout flares. Colchicine prescribing was defined as inappropriate if 1) no concurrent urate lowering therapy was prescribed, 2) uric acid was not at goal and urate lowering therapy had not been initiated or increased in the past 3 months, or 3) uric acid goals were met for > 1 year and flares had resolved in the absence of tophi. Demographic and clinical variables in appropriate and inappropriate groups were compared.

Results: Of 126 patients prescribed prophylactic colchicine, 34 (27.0%) were prescribed no urate lowering therapy, 50 (39.7%) were not at uric acid goal and had not had urate lowering therapy increased in the prior 3 months, and 9 (7.1%) were at uric acid goal for more than one year with no flares or tophi. Colchicine use was considered appropriate in 33 patients (26.2%) – 20 (15.9%) with urate lowering therapy initiated or increased in the past 3 months, 12 (9.5%) at uric acid target for < 1 year, and 1 (0.8%) at uric acid target for > 1 year but with continued flares. Patients appropriately prescribed colchicine were younger, had shorter time on colchicine, and were more likely to have been seen by Rheumatology as opposed to being managed solely by primary care. Allopurinol dose and allergy, uric acid level, and renal function were similar in the two groups (see table).

Comparison of Patients Appropriately and Inappropriately Prescribed Prophylactic Colchicine

	Appropriate (N=33)	Inappropriate (N=93)	P Value
Age, yrs	65 [33–89]	70 [37–89]	0.01
Male, no. (%)	33 (100.0)	92 (98.9)	1.0
Colchicine daily dose, mg	0.6 [0.3–1.2]	0.6 [0.3–1.2]	0.57
Time on colchicine, yrs	1.12 [0.07–17.4]	3.26 [0.05–14.1]	0.0002
Allopurinol dose, mg	200 [100–400]	200 [100–400]	0.34
Allopurinol allergy, no. (%)	1 (3.0)	7 (7.5)	0.36
Crystal confirmed, no. (%)	33 (42.4)	37 (39.8)	0.79
Uric acid level, mg/dL	6.7 [4.2–14.2]	7.4 [3.6–13.2]	0.36
Creatinine, mg/dL	1.29 [0.8–2.3]	1.24 [0.7–2.9]	0.93
GFR, mL/min/1.73m^2	64 [37–126]	67 [27–144]	0.87
Rheumatology visit ≤ 1 yr, no. (%)	19 (57.6)	20 (21.5)	<0.0001
Rheumatology visit ever, no. (%)	25 (75.8)	51 (54.8)	0.04

Skewed data expressed as median [range]. Percentages may not add up to 100 because of rounding.

Conclusion: Our results demonstrate a high incidence of what we considered inappropriate prophylactic colchicine use, driven largely by failure to prescribe concurrent urate lowering therapy or adequately increase these medications. Rheumatology consultation was associated with improved colchicine prescribing. Increased education of primary care physicians about current standards of care is needed to avoid unnecessary colchicine exposure and excessive health care system costs.

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Lack of Effect of Supplemental Vitamin C On Serum Urate in Patients with Gout. Lisa K. Stamp[1], Christopher Frampton[1], John L. O'Donnell[2], Jill Drake[3] and Peter T. Chapman[3]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]Canterbury Health Laboratories, Christchurch, New Zealand, [3]Christchurch Hospital, Christchurch, New Zealand

Background/Purpose: The key to effective long-term management of gout is sustained reduction of serum urate (SU) <0.36mmol/L. It has been suggested that supplemental vitamin C reduces SU in healthy controls via its uricosuric effect. However, it is unclear whether the reduction in SU is of a similar magnitude in patients with gout (who have reduced urate excretion) or whether co-administration of allopurinol lessens the magnitude of SU reduction from vitamin C. The aims of this study were to determine effects of modest dose supplemental vitamin C on SU in patients with gout both as monotherapy and in combination with allopurinol.

Methods: Patients with gout and a SU >0.36mmol/L were recruited. 20

patients already receiving allopurinol were randomised to either increase the dose of allopurinol or commence vitamin C 500mg/d. 20 patients not receiving urate lowering therapy were randomised to either start allopurinol or vitamin C 500mg/d. Plasma ascorbate, creatinine, SU, urine urate and creatinine were measured at days 0 and week 8.

Results: 18/20 patients who received Vitamin C were male with a mean age of 61.2 years (39–86). 18/20 patients who did not receive vitamin C were male with mean age of 55.0 years (27–78). There was no significant difference in baseline SU or eGFR between those who received vitamin C and those who did not (SU 0.50 ±0.11mmol/l vs. 0.50 ± 0.09mmol/l p=0.89; eGFR 65.5 ± 15.7 vs. 67.9 ± 20.7 p=0.67). 30% in the vitamin C group were receiving diuretics compared to 25% in the no vitamin C group (p=0.72).

In the 20 patients receiving supplemental vitamin C there was a significant increase between week 0 and week 8 in plasma ascorbate (34.2μmol/l; p<0.001). There was no significant change in plasma ascorbate in those who did not receive vitamin C. The reduction in SU was significantly less in those 20 patients receiving vitamin C compared to those who started or increased the dose of allopurinol (0.014mmol/l vs. 0.118mmol/l p<0.001) (Figure). Allowing for eGFR did not affect these results.

Since Vitamin C is uricosuric we assessed change in urinary urate excretion using the Simkin index. In those patients already receiving allopurinol, addition of Vitamin C or an increase in allopurinol dose had no effect. In contrast, in those patients starting allopurinol there was a significant reduction in the Simkin index compared to those starting vitamin C (−0.13 vs. 0.002 p<0.011).
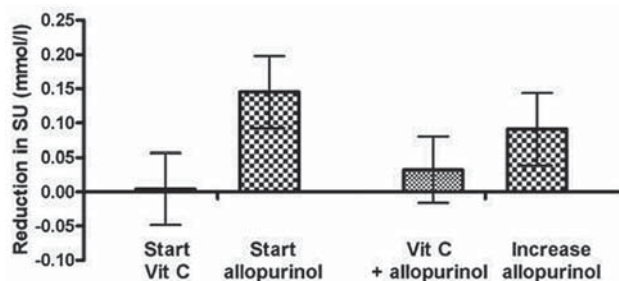
Figure. Effect of vitamin C and allopurinol on serum urate.

Conclusion: In this study supplemental vitamin C at modest dose (500mg/d) for 8 weeks had no significant urate lowering effect in patients with gout despite increasing plasma ascorbate concentrations. These results differ from findings in hyperuricaemic healthy controls. The uricosuric effect of modest dose vitamin C appears less in patients with gout both as monotherapy and in combination with allopurinol. Whether larger doses will be effective remains to be determined.

Disclosure: **L. K. Stamp**, None; **C. Frampton**, None; **J. L. O'Donnell**, None; **J. Drake**, None; **P. T. Chapman**, None.

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Patients That Continue to Flare Despite Apparent Optimal Urate Lowering Therapy. Dinesh Khanna[1], Puja Khanna[1], David Hagerty[2], Chris Storgard[2], Robert Mischler[2] and Robert Morlock[2]. [1]University of Michigan, Ann Arbor, MI, [2]Ardea Bioscience, San Diego, CA

Background/Purpose: Gout is a common inflammatory arthritis and its worldwide prevalence is increasing. The purpose of this study is to describe physician, patient and treatment characteristics in those patients who are considered "controlled" by their physician with xanthine oxidase (XO) inhibitor therapy, despite having 2 or more flares per year and assess sUA levels by XO inhibitor and XO inhibitor dose.

Methods: Data were assessed from a survey of US physicians about gout disease management. Patient results were confirmed through in-depth chart audits assessing diagnosis, comorbid conditions, and laboratory assessments. Disease severity was measured using a physician global assessment (mild, moderate or severe), flare counts, joint damage and presence of tophi. Type and dose of XO inhibitor, length of current treatment, physician type and patient socio-demographics factors were identified. XO inhibitor control was defined using a 10-point physician assigned score with higher scores indicating more control ("Do you consider this patient to be well controlled on their current urate lowering therapy (ULT) therapy, where control means there is no desire to increase the dose to achieve better control?"). Patients with a

score of >=7/10 were classified as "controlled". Multivariate and descriptive statistics were used to describe patients having more than 2 flares per year (excluding treatment initiation flares) where physicians reported "no desire to increase dose" of the current ULT.

Results: Physicians interviewed included 125 rheumatologists and 124 primary care physicians. Of the 1245 patients with gout, 81% were male and the average age was 57 (sd=13). 858 (69%) patients were treated with a XO inhibitor of which 278 (32%) patients classified as controlled but experienced 2 or more flares in the last year. 101 (36%) achieved sUA <= 6mg/dL. Patients defined as controlled and reporting 2 or more flares a year were more likely to have tophi (30% vs. 18%; p<0.01) compared to patients classified as controlled and having 1 or less flares a year. Likewise patients defined as controlled and reporting 2 or more flares a year had higher sUA (7.0 vs. 6.4 mg/dL; p<.01), whereas patients classified as uncontrolled had an average sUA > 8.0mg/dL across XO inhibitors and there was no difference by dose. A backward stepwise multivariate model predicting patients classified as controlled and continuing to flare (2+ flares in the last year) found chart documented co-existing kidney disease (OR 2.4; p<0.01), alcoholism (OR 2.4; p<0.01) and depression (OR 1.8; p<0.05) to be associated with higher flares. Additionally, treatment with anti-hyperglycemic agents (OR 1.6; p<0.05) and physician identified tophi (OR 1.6; p<0.05) also predicted perceived control in patients with 2 or more flares in the last year.

Conclusion: Only 26% of the 621 patients receiving allopurinol were flare free in the 12-month period. Less than 50% of patients obtain sUA < 6mg/dL regardless of treatment. Despite patients being considered controlled, 38% continued to have > 2 flares per year. These patients are more likely to have kidney disease and other comorbid conditions. Current treatment options for these patients may not be sufficient to adequately control gout flares.

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Effectiveness of Prophylaxis with Anti-Gout Medications On Risk of Gout Attacks. Tuhina Neogi[1], Clara Chen[2], Jingbo Niu[1], Christine E. Chaisson[2], David J. Hunter[3], Hyon K. Choi[1] and Yuqing Zhang[4]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University School of Public Health, Boston, MA, [3]University of Sydney, Sydney, Australia, [4]Boston University, Boston, MA

Background/Purpose: While a few studies have examined colchicine's ability to prevent gout attacks, NSAIDs have not been formally studied in this regard, despite use of naproxen and its apparent efficacy in the febuxostat trials. Little data are available on effectiveness of prophylaxis with anti-gout medications on risk of gout attacks as used in the community. Further, dosing and choice of NSAID type for prophylactic purposes may vary widely in the community. We evaluated the association of colchicine and NSAID use with risk of recurrent gout attacks in an internet-based cohort of persons with gout.

Methods: We conducted an internet-based case-crossover study (each person acts as his/her own control, eliminating the effect of time-invariant confounders) to assess risk factors for gout attacks among persons with pre-existing gout. Subjects with gout who had ≥1 attack in the prior year were recruited online from across the US, with their gout diagnosis verified through medical records review. Participants logged onto the study website when they had a gout attack and provided exposure information (including medication use) over the 14-day period prior to the gout attack (case-period) using an online questionnaire. The same questionnaire was collected for a 14-d period during an intercritical period (control-period). Medication use between 3–14 days was not collected in an earlier study period ('03-'07) and was imputed assuming the data was missing at random. We examined the relation of colchicine and NSAID use, respectively, over specific time spans (prior 1–2 days, 1–7 days, and 1–14 days) to the risk of gout attacks using conditional logistic regression.

Results: Of the 724 participants (from 49 US states and D.C.) who experienced ≥1 gout attack during the study period, 78.5% were male, 89% were White, and 58% had a college education. 38.4% were on some form of ULT on study entry (majority on allopurinol 300mg/d). Colchicine was taken primarily as 0.6mg/d and the most common NSAID used was ibuprofen. Colchicine protected against gout attacks when taken consistently over a 14 day period, but not over shorter periods (Table). The increased risk of gout attacks when colchicine was used only in the prior 2 days (i.e., without having taken it in the prior 3–14 days) likely indicates its use in anticipation of an

impending gout attack (confounding by indication). However, very few only took colchicine in the prior 1 or 2 days only, limiting its interpretability. NSAID use did not appear to protect against gout attacks, regardless of consistent use (Table).

Table. Effect of consistent use of anti-gout prophylactic medication over a 2-week period

Time-Period over which medication was taken**	Adjusted* ORs (95% CI)	
	Colchicine	NSAIDs
Taken daily in prior 14 days	0.46 (0.30–0.69)	1.05 (0.75–1.46)
Taken daily in prior 7 days only	0.62 (0.17–2.24)	1.17 (0.53–2.58)
Taken in prior 1 or 2 days only	2.16 (1.28–3.65)†	1.11 (0.84–1.46)
Not taken at all in prior 14 days	1.0 (ref)	1.0 (ref)

*adjusted for diuretic and aspirin use, purine, alcohol, water and caffeine intake, use of the other prophylactic medication (NSAIDs or colchicine, as appropriate) and urate-lowering medications; Results were similar when limited to those who met ACR criteria for gout.
** Note: the majority of persons who used these medications in the prior 1-2 days also used the medication daily in the prior 3-14 days
†These results may reflect confounding by indication – those who are taking these medications only recently (i.e., without longer-term use) may be doing so because of concern regarding risk of impending gout attack, or because they only recently started ULT; very few took the medication only in the prior 1 or 2 days only.

Conclusion: Colchicine was effective in protecting against gout attacks when taken consistently; intermittent or short-term use did not confer protection. We cannot exclude the possibility that particular formulations and/or doses of NSAIDs are effective; nonetheless, as used in the community, NSAIDs were not associated with lower risk of gout attacks.

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Efficacy of Canakinumab Versus Triamcinolone Acetonide According to Multiple Gouty Arthritis-Related Health Outcomes Measures. Ari Gnanasakthy[1], Andrew Sarkin[2], Rachel Lale[2], Kyle Choi[2] and Jan D. Hirsch[3]. [1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [2]Health Services Research Center, University of California, San Diego, CA, [3]Skaggs School of Pharmacy & Pharmaceutical Sciences, University of California, San Diego, CA

Background/Purpose: Canakinumab (CAN), a selective, fully human, anti-IL-1β monoclonal antibody, may be a potential therapeutic option for treating acute gout attacks and delaying new attacks in these patients (pts). Efficacy and safety of canakinumab was previously demonstrated in two 12-week, multicenter, double-blind, double dummy, active controlled trials (β-RELIEVED [N=228]; β-RELIEVED II [N=226]).[1] Health-related quality of life was also measured in these studies, but not all patients completed each questionnaire. Therefore, a composite health outcomes response endpoint was developed to better interpret each patient's overall response to treatment.

Methods: This analysis used pooled data from the β-RELIEVED program, which included pts meeting ACR 1977 preliminary criteria for acute GA and contraindicated, intolerant or unresponsive to NSAIDs and/or colchicine.[1] A composite response endpoint representing overall change in gout-related health outcomes, from baseline to 12 weeks, included clinical markers (serum urate and flare activity); patient-reported data from the Gout Impact Scale (GIS) of the Gout Assessment Questionnaire[2] 2.0 (comprising 6 items related to pain and quality of life); and the SF-36 (Table). Variables represented outcome domains comprising a composite response to GA treatment as recommended by expert rheumatologists.[3] Patients were categorized as responders for each variable if they had greater than a minimally important change (per published literature) from baseline. Variable values [1 (responder) or 0 (nonresponder)] were added to create a composite responder endpoint for each patient (Cronbach's α = 0.76).

Results: For 8 out of 12 variables measured, the percentage of CAN responders was significantly greater than that for TA (Table, $P<0.05$). Mean composite response scores were significantly higher for CAN pts vs TA pts (mean [SD]; 4.7 [2.7] vs 3.7 [2.4], $P<0.001$). Overall, pts receiving CAN also met a higher percentage of response criteria (65%) than pts given TA (49%), $P<0.001$. Treatment differences remained even after serially removing individual responder variables and domains from the composite endpoint, indicating that the differences between CAN and TA were robust.

Table 1. Responders (%) for Gouty Arthritis-Related Health Outcomes Measures at 12 weeks

Outcome Domain	Variable	Responder Definition	CAN		TA	
			n	%	n	%
Urate	Serum urate	>25% reduction[3]	199	6.5	204	8.8
Flare frequency	Flare past 4 weeks	No	115	90.2***	113	68.1
	New flare during trial	No	225	71.6***	229	51.1
	Use of rescue medications	No	225	58.7***	229	38.4
Pain	Gout pain severity past 4 weeks (GIS, 1-10 scale)	>2 point reduction[4]	113	85*	116	74.3
	Bodily pain (SF-36, 0-100 scale)	>10 point reduction[5]	192	66.1	181	58.6
Patient global response	How well doing past 4 weeks (GIS, 1-10 scale)	>2 point reduction[4]	113	69.0	113	58.8
	Global treatment response	Acceptable, good or excellent	211	94.3**	213	85.4
	GIS Global Scale (GIS, 0-100)	>8 points[4]	114	81.4*	115	70.2
Health related quality of life (Disease specific) (GIS, very poor – excellent)	Gout related quality of life	>1 point improvement[4]	65	41.5**	85	18.8
	Gout related physical health	>1 point improvement[4]	62	30.6**	77	10.4
	Gout related mental health	>1 point improvement[4]	61	31.1	82	19.5
OVERALL	Average percentage responder criteria met	-		65.0%***		49.0%

* $P<0.05$; ** $P<0.01$; *** $P<0.001$.

Conclusion: These results demonstrate superior efficacy, across multiple health-outcomes variables comprising clinical markers and patient reported outcomes, of CAN versus TA over 12 weeks in patients contraindicated, intolerant or unresponsive to NSAIDS and/or colchicine.

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Proposed Gout Treatment Guidelines and Meeting Serum Urate and Flare Goals. Jasvinder A. Singh[1], David Hagerty[2], Chris Storgard[2], Robert Mischler[2] and Robert Morlock[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Ardea Bioscience, San Diego, CA

Background/Purpose: Although gout is a relatively common condition, treatment is often not ideal with many patients continuing to experience multiple flares and some developing complications associated with the disease. To improve patient care the American College of Rheumatology (ACR) recently proposed a draft set of recommendations for treating patients with gout. The purpose of this study is to assess the percentage of patients that meet the recently proposed treatment guidelines and the impact of following guideline recommendations on reaching serum uric acid (sUA) and flare targets.

Methods: Data were assessed from a quantitative survey of US physicians about gout disease management. Laboratory and clinical data were confirmed through chart audits using a structured case report form. The sample was restricted to patients treated with allopurinol or febuxostat. Xanthine oxidase (XO) inhibitor and initial dose, use of prophylactic medication, sUA level, physician type (rheumatologist vs. primary care physician [PCP]), patient socio-demographics factors, and flare rates (treatment and non-treatment related) were recorded/abstracted. Descriptive statistics were used to describe quality indicators consisting of the number of patients initiating XO inhibitor therapy with anti-inflammatory prophylaxis medication, titration of allopurinol and having multiple sUA assessments. A multivariate model was used to assess the impact of patient, clinician, and quality indicators on achieving sUA < 6 and < 1 flare over a 12-month period.

Results: The sample included 125 rheumatologists and 124 PCPs. Of the 1,245 patients with gout, 858 (69%) were treated with a XO inhibitor: 621 (72.4%) were treated with allopurinol and 237 (27.6%) were treated with febuxostat. Rheumatologists managed the care for 500 (58.3%) patients and

PCPs managed the care for 358 (41.7%) patients. Anti-inflammatory prophylaxis treatment was used in 67% of cases treated by rheumatologists and only 37% of cases treated by PCPs. Multiple sUA assessments over a 12-month period were done in 68% and 53% of patients managed by rheumatologists and PCPs, respectively. Allopurinol dose was titrated above 300mg in 8% of patients treated by a PCP and 29% of patients treated by rheumatologists (p<0.01). Only 25% of patients obtained sUA < 6 and reported < 1 flare per year. Controlling for confounding factors, a multivariate model found quality indicators for the use of prophylaxis flare prevention at treatment initiation, multiple sUA assessments and physician type as predictive of achieving sUA and flare goals.

Conclusion: Only 25% of patients reach sUA < 6 and < 1 flare over a 12-month period. Adherence to draft ACR guidelines vary by physician type. Patients receiving guideline recommended care are more likely to achieve treatment goals, yet, significant opportunities exist to improve care for the majority patients regardless of physician specialty, including use of prophylactic treatment, dose titration of urate-lowering therapy and/or effective treatment strategies to bring patients to sUA goal and eliminating flares.

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Long-Term Safety of Canakinumab in Patients with Gouty Arthritis.
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Background/Purpose: Gouty arthritis (GA) is a chronic inflammatory disease. Targeting the inflammatory pathway through IL-1β inhibition with canakinumab (CAN) may provide significant long-term benefits. CAN safety versus triamcinolone acetonide (TA) over initial 24 weeks (blinded study) for patients (pts) with history of frequent attacks ($\geq$3 in year before baseline) was reported earlier from core (β-RELIEVED [β-REL] and β-REL-II) and first extension (E1) studies[1]. Herein we present full 18-month long-term CAN safety data, including open-label second extension (E2) studies.

Methods: GA pts completing β-REL E1 and β-REL-II E1 studies[1] were enrolled in these 1-year, open-label, E2 studies. All pts entering E2, whether randomized to CAN or TA, received CAN 150 mg sc on demand upon new attack. Data are presented only for pts randomized to CAN, and are reported cumulatively, i.e. including corresponding data from previously reported core and E1 studies. Long-term safety outcomes and safety upon re-treatment are presented as incidence rate per 100 patient-years (pyr) of study participation for AEs and SAEs. Deaths are reported for all pts (randomized to CAN or TA). Selected predefined notable laboratory abnormalities are shown (neutrophils, platelets, liver and renal function tests). Long-term attack rate per year is also provided.

Results: In total, 69/115 (60%) and 72/112 (64.3%) of the pts randomized to CAN in the two core studies entered the two E2 studies, of which 68 and 64 pts, respectively completed the E2 studies. The 2 study populations had differing baseline comorbidity and geographic origin. Lab data (not time adjusted) for neutropenia appears worse after retreatment in β-REL E2, and deterioration of creatinine clearance appears worse after retreatment (Table 1). The time-adjusted incidence rates for AEs were 302.4/100 pyr and 360/100 pyr, and for SAEs were 27.9/100 pyr and 13.9/100 pyr in β-REL E2 and β-REL-II E2 respectively (Table 1). The time-adjusted incidence rates of any AEs, infection AEs, any SAEs, and selected SAEs before and after re-treatment are presented in Table 1. Incidence rates for AEs and SAEs declined after re-treatment, with the exception of SAEs in β-REL-II E2, which increased from 2.9/100 pyr to 10.9/100 pyr (no infection SAEs after retreatment in β-REL-II E2, and other SAEs fit no special pattern). In the total safety population (N=454, core and all extensions), there were 4 deaths, 2 in the core studies previously reported[1] and 2 during the β-REL E2 study (one patient in the CAN group died from pneumonia; one patient in the TA group who never received CAN died of pneumococcal sepsis). None of the deaths was suspected by investigators to be study drug related. The mean rates of new attacks per year on CAN were 1.21 and 1.18 in β-REL E2 and in β-REL-II E2.

Table 1.

Time-adjusted AEs*/ SAEs*	β-RELIEVED E2 Randomized to CAN* 150 mg sc (N=113)**			β-RELIEVED-II E2 Randomized to CAN* 150 mg sc (N=112)		
	All CAN (N=113)	Retreated with CAN (N=69)		All CAN (N=112)	Retreated with CAN (N=62)	
		Before	After		Before	After
AEs and SAEs	All values: n (IR/100 pyr)					
Any AEs	336 (302.4)	136 (400.1)	112 (224.3)	388 (360.0)	127 (370.0)	163 (354.8)
Infections	55 (49.5)	23 (67.7)	21 (42.0)	51 (47.3)	17 (49.5)	21 (45.7)
Any SAEs	31 (27.9)	10 (29.4)	13 (26.0)	15 (13.9)	1 (2.9)	5 (10.9)
Individual system organ class with IR/100 pyr >2.0 in any column						
Cardiac disorders	5 (4.5)	1 (2.9)	2 (4.0)	2 (1.9)	0	1 (2.2)
Eye disorders	2 (1.8)	2 (5.9)	0	0	0	0
Infections & infestations	3 (2.7)	2 (5.9)	1 (2.0)	3 (2.8)	1 (2.9)	0
Metabolism & nutrition dis.	2 (1.8)	1 (2.9)	1 (2.0)	1 (0.9)	0	1 (2.2)
Musculoskeletal & connective tissue disorders	2 (1.8)	2 (5.9)	0	2 (1.9)	0	0
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1 (0.9)	0	1 (2.0)	1 (0.9)	0	1 (2.2)
Nervous system disorders	5 (4.5)	1 (2.9)	4 (8.0)	4 (3.7)	0	2 (4.4)
Renal & urinary disorders	5 (4.5)	1 (2.9)	3 (6.0)	0	0	0
Laboratory results, notable abnormalities (not time-adjusted)	All values: n (%)					
Neutrophils (<1.0 10^9/L)†	5 (4.4)	2 (2.8)	2 (2.9)	5 (4.5)	1 (1.6)	5 (8.1)
Platelets (<75.0 10^9/L)†	0	0	0	0	0	0
ALT (≥5xULN)†	0	0	0	1 (0.9)	0	1 (1.6)
AST (≥5xULN)†	0	0	0	1 (0.9)	0	1 (1.6)
Total bilirubin (≥2xULN if ALT and/or AST ≥3 × ULN)†	0	0	0	0	0	0
Serum creatinine (≥3xULN)†	1 (0.9)	0 (0)	0 (0)	1 (0.9)	1 (1.6)	1 (1.6)
Creatinine clearance (≥25% decrease from baseline)†	21 (19.3)	7 (10.4)	13 (19.4)	19 (17.0)	5 (8.1)	10 (16.1)

*Primary system organ class; CAN: canakinumab; IR/100 pyr: incidence rate per 100 patient-years.
**2/115 pts were misrandomized and thus excluded from analysis (only 113 analyzed).
†Newly occurring or worsening notably abnormal values (not time-adjusted).

Conclusion: The clinical safety profile of CAN upon re-treatment was maintained long-term with no new infection concerns.

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Prevalence of Non-Gout Arthritis in Patients with Gout: Not As Sparing As Previously Thought.
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Background/Purpose: the presence of other chronic inflammatory disease has been historically and academically thought to be "protective" conditions for the development of gout.

Objective: to evaluate the presence of concomitant chronic arthritis in patients with gout.

Methods: analysis of a dataset from a 20-year cohort of patients with gout prospectively included for follow-up. Diagnosis of associated rheumatic diseases at baseline or during follow-up were included if present. Classification criteria for such concomitant diseases varied depending on the classification criteria at the moment diagnosis was made.

Results: from 904 patients with 3,315 patient-year observation. Diagnosis of gout was based on crystal observation in 731 (80.8%). The number of patients and cumulated prevalence (n/%) of pyrophosphate arthritis (PPA), rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA) were 46/5.09, 5/0.55, 4/0.44, 3/0.33 respectively, very close to that

expected in the general population. All patients with a diagnosis of both disease had crystal-proven gout (MSU crystals) or crystal (CPP)+X-ray proven PPA. Previous PPA was present in 3/46 patients, and both CPP and MSU crystals were observed in the same synovial fluid sample in 13/46, in the 23 left PPA appearing after properly controlled gout, no MSU crystals being observed in synovial fluid. Previous RA was present in 4/5 patients, previous PsA in 3/3, and previous SpA in 3/3. Only a patient developed RA 2-year after being satisfactorily treated for crystal proven gout, and showing high titers of RF and anti-CCP antibodies.Patients with PPA and RA showed higher age and more frequent chronic kidney disease than patients with PsA or SpA. Diuretic use, a risk factor for gout, was frequent in all groups (Table 1).

	Age	Serum urate (mg/dl)	CKD (% 3–5)	BMI (kg/sqm)	DIURETICS (%)
PPA	73 ± 10	8.75 ± 1.31	52	27.8 ± 4.1	48
RA	67 ± 11	9.06 ± 1.17	40	27.9 ± 2.9	20
PsA	56 ± 9	9.80 ± 2.04	0	29.2 ± 4.5	25
SpA	58 ± 6	8.73 ± 1.72	33	27.7 ± 0.1	33

Conclusion: the cumulated prevalence of other arthritis is as much in patients with gout as expected in the general population. Systematic analysis of synovial fluid samples, despite a previous and well established previous diagnosis allows to identify MSU and CPP crystals in patients suffering from other joint diseases but also to identify CPP crystals in patients with gout.

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The Treatment of Acute Gouty Arthritis in Complex Hospitalized Patients with Anakinra. Mary Bach, Jane Park, Pradipta Ghosh, Peter A. Simkin and Gregory C. Gardner. University of Washington, Seattle, WA

Background/Purpose: The management of acute crystal-induced arthritis in the hospital setting may be a difficult clinical problem due to co-morbidities that limit the use of traditional treatment options. Anakinra, an anti-IL1 receptor antagonist, has been successful in the treatment of acute/ chronic gout in 3 published series and 4 case reports totaling 27 patients and 2 case reports of calcium pyrophosphate dihydrate (CPPD) disease. We have previously reported our experience with 17 medically complex patients (16 gout, 1 CPPD) who had received 24 courses of anakinra which successfully treated their acute arthritis. The purpose of this study is to add additional case experience in the use of anakinra in this same population.

Methods: We reviewed our consult records over the past 5 years to identify inpatients with acute crystal-induced arthropathy treated with anakinra. Data extracted from the charts included age, gender, BMI, co-morbidities, uric acid level, joint(s) and soft-tissue sites involved, anakinra dosing, time to initial improvement, time to complete resolution of signs and symptoms of inflammation, and any possible side effects (i.e. infection or leukopenia).

Results: Twenty-six patients who had received 40 courses of anakinra were identified. Eighteen patients had failed colchicine and/or steroids, and an additional 8 patients were felt not to be candidates for traditional therapy due to co-morbid disease. None of the patients were candidates for NSAID therapy. In 29 of the 40 episodes, the arthritis was polyarticular. Foot and ankle joints were most commonly affected (44.5%) followed by hand and wrist (25%), knees (18.5%), shoulders, elbows and tendons (12%). Following first dose of anakinra, 67.5% of patients demonstrated significant pain improvement within 24 hours and 85% had significant relief by 48 hours. Complete resolution of signs and symptoms of gout occurred by day 5 in 72.5%. Seven patients received up to 5 courses with no apparent decrement in response. Anakinra was well-tolerated and no adverse outcomes were attributed to the drug. Only one patient appeared to be refractory to this form of IL-1 inhibition.

Conclusion: Anakinra is an effective and safe alternative treatment for acute gouty arthritis in medically complex patients who fail or cannot undergo more conventional therapy

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Improvements in Long-Term Health-Related Quality of Life in Chronic Gout Patients Refractory to Conventional Therapies Treated with Pegloticase: Results From Responder Cohort. Dinesh Khanna[1], Puja Khanna[2] and Faith D. Ottery[3]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Savient Pharmaceuticals, Inc., East Brunswick, NJ

Background/Purpose: In replicate, 6-month, randomized, placebo-controlled Phase 3 clinical trials a subgroup of patients with treatment-refractory chronic gout (RCG) who received pegloticase infusions (8 mg) every 2 weeks (q2wk) demonstrated statistically significant improvements in multiple patient-reported outcome (PRO) measures derived from the HAQ and SF-36. Patients who showed sustained urate-lowering (defined as responders in the blinded trials) could continue treatment for up to an additional 2.5 years in an open-label extension (OLE) study, thus providing data on health-related quality of life (HRQoL) with long-term pegloticase administration in a responder cohort.

Methods: The OLE enrolled patients at 46 centers in the US, Mexico and Canada. Patients enrolled in the blinded trials were >18 years of age, with baseline uric acid (UA) ≥8 mg/dL and at least one of the following: 3 or more self-reported gout flares during the prior 18 months, 1 or more tophi, or gouty arthropathy (defined clinically or radiographically) and contraindication to allopurinol or failure to normalize UA during 3 or more months of treatment at the maximum medically appropriate dose. Pegloticase dosing regimen (8mg q2wks or q4wks) was determined at study entry and could be adjusted twice during the trial. All patients received prophylaxis for infusion reactions (IRs) and flares. A responder was defined as uric acid levels <6 mg/dL for at least 80% of the time during months 3 and 6. Data from the final visit of the blinded trials was used as the baseline value for the OLE study. Subjects completed the SF-36 and HAQ-DI at 3, 6, 12, 18, 24 and 30 months.

Results: 57 patients receiving q2wk pegloticase completed the blinded trials (36 responders, 29 non-responders). 35 of the 36 responders entered the OLE study; 21 continued with q2wk dosing and 14 elected once monthly dosing at study entry. The table presents mean change from baseline for multiple HRQoL measures.

Study	Visit	HAQ-DI change from baseline		Physician's GA change from baseline		HAQ Pain change from baseline		SF-36 PCS change from baseline	
		N	Mean	N	Mean	N	Mean	N	Mean
RCT (months)	3	36	−0.13*	36	−7.45*	36	−8.78*	36	3.48*
	6	35	−0.21	33	−19.94	36	−19.89	36	6.48*
OLE (months)	3	32	−0.29	30	−16.97	33	−20.91	33	6.04
	6	31	−0.33	28	−21.21	31	−20.03	32	6.98
	12	30	−0.31	28	−19.86	31	−21.81	31	6.97
	18	27	−0.30	25	−18.20	27	−18.56	29	5.99
	24	2	−0.44	1	−46.00	2	−27.00	2	10.42
	Final	32	−0.27	30	−19.63	33	−21.58	33	5.36

GA: global assessment, PCS: Physical Component Summary.

Conclusion: Pegloticase treatment during the OLE was associated with improvements in PROs for an additional 2.5 years among patients identified as urate responders during the first 6 months of blinded treatment.

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Towards a Preliminary Definition of Remission From Gout. William Taylor[1], Nicola Dalbeth[2], Jasvinder A. Singh[3], Kenneth G. Saag[4] and H. R. Schumacher[5]. [1]University of Otago, Wellington, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Univ of Alabama-Birmingham, Birmingham, AL, [5]University of Pennsylvania and VA Medical Center, Philadelphia, PA

Background/Purpose: There is currently no agreed criterion for remission in chronic gout. The aim of this study was to develop a preliminary definition for remission in chronic gout.

Methods: Eighty unique paper patient profiles were generated by creating plausible baseline and 12-month values of measures for each core domain recommended by OMERACT for chronic gout trials. Rheumatologists

interested in gout were invited by email to evaluate each profile within an online survey and to decide whether the 12-month values indicated that the paper patient had attained a state of remission or not and the confidence in that decision (scale of 0 to 10). The exercise also asked respondents to consider whether the change in measures from baseline to 12-months represented a response to treatment or not, but those results have been reported separately. The distribution of the confidence ratings (-10 meaning high confidence of not in remission to $+10$ meaning high confidence of being in remission) for each patient profile were examined by a panel of 5 very experienced rheumatologists, who made a judgement that the distribution of confidence ratings indicated remission, not remission or uncertainty. An agreement of at least 80% was required amongst the 5 experts, to classify the remission status of the profile otherwise it was classified as 'uncertain'.

Results: There were 35 respondents. The median number of respondents per rated profile was 22.5 (range 22 to 33). This represents a median of 64% profiles that were rated by every respondent (range 63% to 94%). Two respondents did not rate any profiles and 63% (n=22) rated all 80 profiles. Of the 80 paper profiles, there was agreement by the panel of 5 experts that only 3 were in remission, 18 were uncertain and 59 were not in remission.

The mean, minimal value and maximal value for each measure, by remission status are shown in the Table. The p-value refers to ANOVA, comparing values across the 3 groups.

Table. Mean (range) of core domain measures for different categories of remission status

	Judgement of remission status			
	Not remission (n=59)	Remission (n=3)	Uncertain (n=18)	p-value
SUA (mmol/L)	0.45 (0.20 to 0.80)	0.23 (0.20 to 0.30)	0.31 (0.20 to 0.40)	<0.001
Attack frequency (over previous 3 months)	3.53 (0 to 7.00)	0 (0 to 0)	1.06 (0 to 4.00)	<0.001
Tophus size (mm^2)	823.94 (0 to 1800)	0 (0 to 0)	380.56 (0 to 1350)	<0.001
Tophus number	2.75 (0 to 6)	0 (0 to 0)	1.50 (0 to 7)	0.004
Mental health component of SF-36	70.73 (50 to 86)	78.67 (72 to 85)	76.78 (66 to 93)	0.021
Physical health component of SF-36	74.46 (50 to 91)	84.67 (80 to 88)	80.44 (58 to 90)	0.025
Pain VAS (0 to 100)	27.17 (14 to 83)	20.00 (16 to 26)	21.89 (10 to 35)	0.267
HAQ-DI	0.87 (0 to 2.20)	0 (0 to 0)	0.53 (0 to 2.10)	0.001
Patient Global VAS (0 to 100)	53.02 (26 to 85)	33.00 (28 to 36)	41.22 (26 to 62)	0.001

Conclusion: The domains that showed the greatest discrimination between remission and non-remission were SUA, tophi and flares. Pain between flares did not appear to discriminate between remission and non-remission status. The following definition of remission is proposed, based approximately on the maximal values observed in those who attained remission:

SUA no more than 0.36 mmol/l AND no gout attacks in prior 3 months AND no tophi AND patient global assessment no more than 3 (0 to 10 scale).

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Natural Language Processing in the Evaluation of Gout Quality Indicators.
Gail S. Kerr[1], J. Steuart Richards[2], Carl A. Nunziato[3], Olga V. Patterson, Scott L. DuVall[5], David D. Maron[3] and Richard L. Amdur[6]. [1]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [2]Washington DC VA and Georgetown University, Washington, DC, [3]Washington, DC, [4]VA Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [5]Washington DC VA and Georgetown Unviversity, Washington, DC

Background/Purpose: Gout is a common inflammatory arthritis with significant impact on both patients and health care systems. Despite ACR/EULAR management guidelines and gout quality indicators (QI) developed to improve outcomes, standard of care is often suboptimal and infrequently measured. We evaluated the standard of care of in a cohort of Veterans Affairs (VA) gout patients, using QI that include medication, laboratory and counseling criteria.

Methods: During a 4 year period, VA administrative data was used to identify gout outpatients (ICD 9 codes: 274.xx and at least 2 related visits). QIs assessed were QI 1: patients with creatinine clearance < 60 ml/min, initial allopurinol dose to be < 300 mg/day; QI 2: uric acid (UA) within 6 months of allopurinol start; QI 3: if on colchicine CBC, CPK done within 6 months; QI 4: counseling on gout specific diet, weight loss and alcohol consumption. For QI 4, natural language processing (NLP), a technique that analyzes large amounts of text to identify key words and/or phrases, was used to extract dietary, alcohol and weight loss counseling data from electronic medical records. Data collected were socio- demographics, comorbidities [HTN, DM, CVD, hyperlipidemia, obesity and chronic kidney disease (CKD)] and number of rheumatology outpatient visits for gout. QI compliance versus non-compliance was compared using chi-square analyses.

Results: Of 2,280 gout patients, 2,260 (99.1%) were male, with mean age of 66.8 years. Comorbidities were common: HTN in 2,102 (92.2%); Obesity in 1,578 (69.2%); CVD in 1,384 (60.7%); hyperlipidemia in 1,170 (51.3%); DM in 1,075 (47.1%); and CKD in 748 (33.8%). Most 1,587 (69.6%) had at least one rheumatology outpatient visit, and more than half received specific gout therapy: colchicine was dispensed to 1424 (62.5%) and allopurinol to 1,336 (58.6%) patients. Compliance with each QI was as follows: QI 1: 92.1%; QI 2: 44.8%; QI 3: CBC monitoring 70%; but only 6.3% for both CBC and CPK (only 1 patient had CPK without CBC). For QI 4, there was counseling for weight loss in 1008 (44.2%), diet in 390 (17.1%), alcohol in 137 (6.0%) and 51 (2.2%) had counseling on all 3 elements. Of those on new allopurinol prescriptions, target serum uric acid (< 6 mg/dl) was achieved in 64 (30.1%) patients within one year. Compared with non-compliant patients, patients compliant with QI 2 had more rheumatology visits (3.5 vs. 2.6; p< 0.001), while those compliant with QI 3 (CBC) were older (67.3 vs 64.9 years p<0.001) and had more CKD (p<0.001), DM (p<0.001) and CVD (p<0.001). Patients with DM, obesity, and hyperlipidemia were more often counseled on diet compared to those without comorbidities. Alcohol counseling was less frequent in gout patients with hyperlipidemia (p= 0.024) and DM (p=0.012) compared to patients without comorbidities.

Conclusion: In our study cohort, compliance with QI for uric acid and CPK monitoring were subpar. In gout patients, specific dietary counseling appeared to be directed by other comorbidities. NLP proved a valuable tool for evaluating dietary QI in patients with gout.

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Ulodesine (BCX4208) Long-Term Safety When Added to Allopurinol in the Chronic Management of Gout: A Phase 2 24-Week Blinded Safety Extension and Vaccine Challenge Study.
Alan S. Hollister[1], Andreas Maetzel[1], Michael A. Becker[2], Robert Terkeltaub[3], David Fitz-Patrick[4], Valerie Smith[5] and William P. Sheridan[1]. [1]BioCryst Pharmaceuticals, Inc., Durham, NC, [2]University of Chicago, Chicago, IL, [3]VA Medical Ctr, San Diego, CA, [4]East-West Medical Research Institute, Honolulu, HI, [5]Pharpoint Research, Inc., Durham, NC

Background/Purpose: A majority of gout patients treated with 300 mg/d allopurinol do not reach the therapeutic goal range serum uric acid concentration (sUA) of <6.0 mg/dL. Added to allopurinol, ulodesine (BCX4208), a purine nucleoside phosphorylase inhibitor, synergistically reduces sUA and allows a greater proportion of gout patients to reach sUA <6.0 mg/dL. The objectives of this study were (1) to extend the safety assessment of a 12 week efficacy study through 24 weeks of drug administration, (2) to evaluate immune responses to vaccine challenge, and (3) to confirm continued efficacy of ulodesine.

Methods: 278 gout patients (M:F=266:12) with sUA >6.0 mg/dL despite allopurinol 300 mg/d received placebo or ulodesine at 5, 10, 20, or 40 mg/d for 12 wks. 160 subjects entered the combination treatment extension to 24 wks on their blinded treatment assignment; 27 on placebo, and 39, 32, 33, and 29 on BCX4208 5, 10, 20, and 40 mg/d. All subjects received gout flare prophylaxis with colchicine or naproxen. At 16 or 20 wks, subjects were vaccinated with tetanus toxoid (TT) and/or multivalent pneumococcal polysaccharide vaccine (PPSV), and antibody levels were measured before and 4 wks after vaccination in 84 subjects.

Results: Subject mean (range) age was 49 y (19–69), BMI was 35.9 (22.8–62.2), 45% had mild or moderate renal impairment, and 14% had diabetes in a mostly white population (79%). Total adverse event (AE) rates by 24 weeks were 45.3 per 100 patient-months (pt-mo) for placebo and 33.8, 41.0, 41.3, and 58.2 in the ulodesine 5, 10, 20, and 40 mg/d treatment arms. Infectious AE rates were 8.3 for placebo and 6.3, 6.5, 7.3, and 5.1 per 100 pt-mo, for the respective ulodesine arms. Infection severity, type, location,

and causative agent were similar among study arms. There were no opportunistic infections. The ulodesine dose-related reduction of total lymphocyte count and lymphocyte subsets remained at a plateau reached between week 8 and 12. There were 4 and 11 protocol-specified withdrawals for CD4+ cell count <350 cells/mL in the ulodesine 20 and 40 mg/d arms by 24 weeks. The proportion of antibody responses to vaccination with TT (≥4-fold increase in antibody titers) and PPSV (>2-fold increase in antibody titers to >4 of 6 antigens) was similar or greater in ulodesine- than in placebo-treated subjects. The proportion of subjects with sUA levels <6.0 mg/dL among those completing week 24 was 25% (6 of 24) in the placebo group, and 40% (14 of 35), 50% (13 of 26), 46% (12 of 26), and 55% (12 of 22) in the 5, 10, 20, and 40 mg/d ulodesine arms.

Conclusion: Ulodesine was safe and generally well tolerated when added to allopurinol for up to 24 wks. Patients generated a healthy immune response to vaccination. Adverse event frequency and severity was similar among all groups and no differences were seen in the rate or severity of infections. There were no protocol-driven study drug withdrawals due to low lymphocyte counts in the placebo, 5 mg/d, and 10 mg/d groups. The efficacy of ulodesine in reducing sUA at 12 wks was sustained at 24 weeks.

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Management of Gout Attacks in the Community. Tuhina Neogi[1], Clara Chen[2], Christine E. Chaisson[2], David J. Hunter[3], Hyon Choi[1] and Yuqing Zhang[4]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University School of Public Health, Boston, MA, [3]University of Sydney, Sydney, Australia, [4]Boston University, Boston, MA

Background/Purpose: We previously examined management of gout attacks in the community in 2003-4. Since then, new agents have become available and gout publications have increased, potentially raising awareness about appropriate gout attack management. We therefore re-evaluated these patterns in a large community sample.

Methods: We conducted an internet-based prospective cohort study of gout (2003–2012). Subjects with gout who had ≥1 attack in the prior year were recruited online from 49 states and D.C., with their gout diagnosis verified through medical records review. Subjects provided information about comorbidities, baseline medications, treatment of their gout attacks and whether they consulted a healthcare professional (HCP) for attacks that occurred during one year of follow-up. We estimated the risk of having '1 and ≥2 attacks in one year using life table methods. We determined the frequency and predictors of definitely inappropriate (use of urate-lowering therapy (ULT) acutely in absence of prophylactic use) and potentially inappropriate (use of analgesics alone, alternative remedies alone, or no medications) management of gout attacks.

Results: 1015 subjects with gout were followed for one year (78% male, mean age 53.6, mean BMI 31.9). Since 2005 (N=783), 63.5% had ≥1 self-reported comorbidity (hypertension 56%, kidney disease 19%, kidney stones 14%, diabetes 14%, CHF 7%, peptic ulcer disease 4%). ULT was used by 45%: allopurinol 42%, probenecid 2%, febuxostat 0.9%, sulfinpyrazone 0.1%. Colchicine was used for prophylaxis by 23%; 5% used it without ULT. Similarly, 23% used NSAIDs for prophylaxis; 8% used it without ULT.

The risk of having ≥1 attack and of ≥2 attacks in 1 year was 74.4% and 50.6%, respectively. Medications used to manage gout attacks, either alone or in combination were NSAIDs (52%), colchicine (34%), analgesics (27%), oral glucocorticoids (13%), alternative remedies (0.4%), and ULT acutely (without prior prophylactic use) (0.7%). No medications were used in 12%. Potentially and definitely inappropriate attack treatment occurred in 17.7% and 0.7%, respectively, an improvement from 2003-4 (Table 1). 53% never consulted a HCP for any attack, 25% only did so sometimes, and 22% did so for each attack, a substantial change from 2003-4. The most common HCP consulted for an attack were primary care (51%), ER (10%), rheumatologist (8%), podiatry (5%), and nurse practitioner (5%). In contrast to our previous study, consulting a HCP resulted in lower chance of inappropriate attack management. Age, gender, and disease durationwere also associated with inappropriate management (Table 2).

Table 1. Management of acute gout attacks in 2003–2004 and 2005–2012

NSAIDs	2003–2004 (N=232) 67%	2005–2012 (N=783) 52%
Colchicine	35%	34%
Analgesics +/− other meds	23%	27%
Analgesics alone	22%	6%
Oral glucocorticoids	9%	13%
Alternative remedies	2%	0.4%
No medications	9%	12%
Any ULT acutely in absence of prior use	5%	0.7%
Allopurinol acutely in absence of prior use	3.4%	0.4%
Inappropriate management of acute gout attack:	26%	18.4%
Definitely inappropriate	5%	0.7%
Potentially inappropriate	21%	17.7%
Consulted a HCP for acute gout attack:		
Always	54%	22%
Sometimes	24%	25%
Never	21%	53%

Table 2. Factors related to use of any inappropriate therapy for acute gout attack management

	Adjusted* OR (95% CI)
Consulted HCP for the attack	0.49(0.35–0.68)
Age (for every 10-year increase)	1.13(1.01–1.28)
Female sex	1.46(1.01–2.10)
Disease duration ≤1 year	1.36(1.00–1.88)

*Adjusted for age, sex, BMI, race, education, total # of attacks in one year, consulted HCP for the attack, comorbidities (HTN, renal disease, CHF, diabetes, peptic ulcer disease), disease duration.
HCP=healthcare professional.

Conclusion: In this large cohort of gout patients recruited from across the US, overall management of gout attacks appears to have improved over the past 8 years. Gout management education efforts still need to be focused on primary care, ER and particularly patients themselves as they are the most likely to manage gout attacks.

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Rilonacept for Gout Flare Reduction: Estimation of Number Needed to Treat to Benefit (NNTB). Robert R. Evans[1], Steven P. Weinstein[1], George D. Yancopoulos[2] and Yuhwen Soo[2]. [1]Regeneron Pharmaceuticals Inc, Tarrytown, NY, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background/Purpose: Two similarly designed phase 3 randomized clinical trials (PRESURGE-1 and PRESURGE-2) in gout patients initiating urate-lowering therapy (ULT) showed that subcutaneous treatment with the IL-1 antagonist rilonacept 80 or 160 mg weekly resulted in a significant reduction in the mean number of gout flares (GFs) per patient by 71%-80% relative to placebo over 16 weeks. Analyses were performed to estimate the number needed to treat to benefit (NNTB).

Methods: Using pooled data for the placebo and rilonacept treatment groups (n~160 per pooled group), NNTB was estimated using 1) classical calculations based on binary outcomes, 2) graphical analyses based on the distributions within each treatment group of the number of flares experienced by each patient, and 3) the estimated distributions of flares per patient in the placebo and rilonacept group using negative binomial and Poisson distributions, and the distribution of the difference between groups.

Results: Approximately half the placebo patients (48.4%) did not have a GF, but the other half averaged 2.2 GFs/patient. Approximately 30% more patients on rilonacept vs placebo had less than 1 GF, and approximately 25% more patients on rilonacept vs placebo had less than 2 GFs. NNTBs are ~4 based on either one of these individual binary outcomes. However, considering NNTB based on these binary outcomes individually does not account for the partial overlap of subgroups that benefit, nor for uncaptured flare reduction among patients with multiple GFs. Graphical analysis suggests that almost all of the patients destined to flare would likely have benefited from rilonacept treatment. A patient who would have had one GF would likely have none, and those destined to have multiple GFs would have fewer. With an estimated mean reduction in GFs of 74% with rilonacept, patients destined

to flare would average about 1.6 fewer GFs. Combining these benefits shows that of 2 patients initiating ULT, 1 would not be expected to flare, even without prophylaxis, but the other patient would be expected to flare and would benefit from rilonacept, resulting in an NNTB of ~2. The difference in the negative binomial distributions and the difference in the Poisson distributions (Skellam distribution) independently confirm an NNTB of ~2; conditional on benefit with rilonacept, the mean benefit is about 1.65 fewer GFs. The most common category of adverse event (AE), infections, was balanced among treatment groups; the most frequent treatment-related AE, injection site reaction, was greatest with rilonacept 160 mg. The incidence of SAEs was low and similar across treatment groups.

Conclusion: This analysis shows that approximately 50% of patients with gout who are initiating ULT would benefit from treatment with rilonacept, resulting in an NNTB of ~2. Conditional on benefit with rilonacept, patients would experience about 1.6 fewer GFs with treatment.

Disclosure: R. R. Evans, Regeneron, 3, Regeneron, 1; **S. P. Weinstein**, Regeneron, 1, Regeneron, 3; **G. D. Yancopoulos**, Regeneron, 1, Regeneron, 3, Regeneron, 6; **Y. Soo**, Regeneron, 1, Regeneron, 3.

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Prevention of Recurrent Calcium Stones in Subjects with Hyperuricosuria: A Randomized Controlled Trial of Febuxostat Vs Allopurinol. David S. Goldfarb[1], Patricia A. MacDonald[2], Lhanoo Gunawardhana[3], Solomon Chefo[3] and Lachy McLean[4]. [1]New York Universtiy Langone Medical Center, New York, NY, [2]Takeda Pharmaceuticals USA, Inc., Deerfield, IL, [3]Takeda Global Research & Development Center, Inc., Deerfield, IL, [4]Takeda Global Research & Development Center, Inc, Deerfield, IL

Background/Purpose: About one-third of patients with recurrent calcium oxalate (CaOx) stones have hyperuricosuria as a urinary risk factor. Febuxostat (FEB), a newer xanthine oxidase inhibitor (XOI), may be superior to allopurinol (ALLO) in stone prevention. ALLO treatment has been shown to reduce the incidence of recurrent CaOx stones in hyperuricosuric stone formers (SF). We studied whether FEB would reduce 24h urinary uric acid (uUA) excretion and prevent stone formation and pre-existing stone growth.

Methods: In this 6-month, double-blind, multicenter, randomized, controlled trial, hyperuricosuric (>700 mg/d) adult subjects with a history of CaOx stones and ≥1 3-mm stone in its longest in-plane diameter as seen by multidetector computed tomography (MDCT) were randomized to receive daily FEB 80 mg, ALLO 200 or 300 mg (based on baseline Ccr), or PBO. Patients were excluded if they had a history of gout or secondary hyperuricemia, if they had received ALLO within the past 2 years or ever received FEB. Primary end-point was percent change from baseline (CFB) to month 6 in 24h uUA; secondary end-points were percent CFB in size of index stone, CFB in number of stones and in 24h creatinine clearance (Ccr).

Results: Of 99 subjects enrolled, 86 completed the study. Key baseline characteristics were balanced. Most subjects were men (86%), had a mean lifetime history of 10.9 stone episodes, mean largest stone diameter of 9.9 mm and a mean number of stones 5.7 on MDCT. Normal renal function was present in 97% of patients (mean baseline Ccr was 147 mL/min/1.73m^2). Mean baseline serum urate (sUA) was 6.3 mg/dL, 24h urine calcium excretion was 272.2 mg/d, and 24h uUA was 952.7 mg/d. FEB led to significantly greater reduction from baseline in 24h uUA than either PBO or ALLO. Reductions in stone size and number with FEB were not statistically greater than with ALLO or PBO. In all groups, there were no statistically significant changes in 24h Ccr and serum creatinine did not change. Rates of adverse events (AE) were similar across the treatments groups. One patient in the placebo group experienced a serious AE of nephrolithiasis, but remained in the study.

	PBO (n=33)	FEB 80 mg (n=33)	ALLO 300 mg (n=33)
Baseline uUA (mg/d)	909.4 ± 166.4	1000.6 ± 224.0	948.1 ± 231.2
Treated 6-month uUA (mg/d)	783.5 ± 288.0	411.4 ± 288.4	580.0 ± 301.8
CFB in uUA (%)	−12.7 ± 28.8	−58.6 ± 28.6[a,b]	−36.4 ± 37.0
Baseline sUA (mg/dL)	6.3 ± 1.24	6.2 ± 1.63	6.3 ± 1.49
Treated 6-month sUA (mg/dL)	6.2 ± 1.28	3.3 ± 1.11	4.6 ± 1.26
CFB in sUA (%)	−1.04 ± 13.5	−47.3 ± 16.7[b,c]	−26.2 ± 12.6
CFB in stone size (%)	3.2 ± 23.70	−6.5 ± 28.36	0.6 ± 12.61
CFB in stone number	0.1 ± 1.82	−0.1 ± 1.61	0.3 ± 1.95

mean±SD; [a]P=0.003 vs ALLO; [b,c] P<0.001 vs PBO and ALLO, respectively.

Conclusion: FEB 80 mg lowered 24h uUA significantly more than ALLO 300 mg in SF with hyperuricosuria. Neither XOI was associated with

significantly reduced stone number or size compared with PBO after 6 months of treatment. Extended duration of FEB treatment leading to greater 24h uUA reductions may demonstrate improved prevention of CaOx stone recurrence.

Disclosure: D. S. Goldfarb, Takeda Pharmaceuticals USA, Inc, 5; **P. A. MacDonald**, Takeda Pharmaceuticals USA, Inc, 3; **L. Gunawardhana**, Takeda Global Research & Development Center, Inc, 3; **S. Chefo**, Takeda Global Research & Development Center, Inc, 3; **L. McLean**, Takeda Global Research & Development Center, Inc, 3.

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Dual-Energy Computed Tomography As a Diagnostic Tool for Gout During Intercritical Periods. Gabriel S. Breuer[1], Naama Bogot[2] and Gideon Nesher[1]. [1]Shaare Zedek Medical Center, Jerusalem, Israel, [2]Shaare Zedek Medical Center p o box 3235 Jerusalem, Israel, Israel

Background/Purpose: Dual-energy computed tomography (DECT) is a sensitive method for identifying uric acid deposits in joints and periarticular soft tissues in patients suspected of having gout. Diagnosis of gout cannot be confirmed by polarized microscopy during asymptomatic (intercritical) periods as joint aspiration is not feasible in most cases. We estimated the yield of dual-energy computed tomography (CT) in detection of uric acid tissue deposits during intercritical periods in patients suspected of having gout.

Methods: Patients aged at least 18 years with a history of recurrent, short-lived mono- or oligo-arthralgia or arthritis, referred to the rheumatology clinic for diagnosis of their condition, were included. All had uric acid levels >6 mg/dl and were completely asymptomatic at the time of clinical and radiological evaluations. Patients with a confirmed diagnosis of gout and patients on urate-lowering medicationswere excluded. DECT screened the specific joints and periarticular soft tissues that were previously involved in each case.

Results: 22 patients (18 men, 4 women) were included. Their mean age was 57+17 years. Articular or soft-tissue urate deposits were identified by DECT in 11 cases (50%). Uric acid level did not differ significantly between the groups with or without deposits (8.5+2 and 8.7+1.2 mg/dl, respectively). The table shows the yield of DECT in various anatomic locations:

Area screened	feet	knees	elbows	hand
Number of cases	18	8	1	4
Cases with urate deposits	7	2	0	3
% with urate deposits	39%	25%	0	75%

Conclusion: In asymptomatic hyperuricemic patients with a history of recurrent short-lived mono- or oligo-arthralgia or arthritis, DECT identified urate crystals in 50%, confirming a diagnosis of gout. DECT is a valuable tool in diagnosing gout during intercritical periods.

Disclosure: G. S. Breuer, None; **N. Bogot**, None; **G. Nesher**, None.

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Accuracy of International Classification of Disease Codes for Calcium Pyrophosphate Disease in the Veterans Adminstration Healthcare System. Karri A. Huber[1], Lawrence M. Ryan[2] and Ann K. Rosenthal[2]. [1]MCW Froedtert Hospital, Milwaukee, WI, [2]Medical College of Wisconsin, Milwaukee, WI

Background/Purpose: Calcium pyrophosphate disease (CPPD) commonly affects elderly patients, but few advances in our management of this disease have occurred in the 50 years since it was first described. Progress has been hampered by the absence of large population-based studies of CPPD. The National Veterans Administration (VA) system would be an ideal location to perform such studies. However, the accuracy of the diagnostic codes for CPPD in this database have not been confirmed. We set out to determine the accuracy of International Classification of Disease (ICD) codes for pseudogout/other disorders of calcium metabolism (275.49) and chondrocalcinosis (712.1–712.39) for the diagnosis of CPPD in a single VA hospital database and to describe the clinical picture of this disease in the VA population.

Methods: After approval by the IRB, 256 patients identified as having CPPD by ICD-9 codes for chondrocalcinosis (712.1–712.39) and pseudogout/other disorders of calcium metabolism (275.49) were identified at the Clement J. Zablocki VA Medical Center in Milwaukee, WI for the years 2009–2011. A chart review was performed by a second year rheumatology fellow for each patient and patients were categorized as having definite, probable, possible CPPD or no evidence of CPPD based on the diagnostic criteria proposed by

McCarty and Ryan. Other data collected included patient demographics, the number and type of joints involved, whether the patients had been seen by the VA rheumatology service, and co-morbidities including renal disease and diabetes.

Results: Based on the medical records review, 227/256 (88.6%) patients met criteria for CPPD. Of these, 46 patients met definite criteria, 163 met probable criteria, and 18 met possible criteria for CPPD. Of these 227 patients, 107 (47.1%) patients had ICD-9 code 275. Seventy three (32.1%) had ICD-9 code 712, and 47 (20.7%) had both codes documented. The average age was 73.28 years (range 32–94 years), and, consistent with VA demographics in this age cohort, 98.2 % were men. Sixty-one (26.8%) had stage III or greater chronic kidney disease and 79 (34.8%) had diabetes. Many patients had both acute and chronic arthritis, as 166 (73.1%) had at least one documented episode of acute arthritis, while 208 (91.6%) had chronic articular symptoms. Knee involvement occurred in 86 patients, followed in frequency by involvement of the hand (68), wrist (64), foot (35), ankle (34), elbow (20), and olecranon bursa (10). The average number of joints involved for patients with chronic arthritis was 2.35 (range 1–6) and for acute was 2.012 (range 1–6). Rheumatology had evaluated 51.5% of these patients, including 83% with definite CPPD, 43.6% with probable CPPD, and 44.4% with possible CPPD.

Conclusion: We found a high correlation between evidence of CPPD documented in medical records and the ICD codes 275.49 and 712 in the medical records database at a single VA medical center. The demographics of this population and pattern of joint involvement confirm prior studies of the epidemiology of this disease and further support the accuracy of these codes. These findings suggest that the national VA healthcare database may be useful for future clinical studies of CPPD.

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Menopause and the Prevalence of Gout and Hyperuricemia: An Age-Matched Case Control Study. Eswar Krishnan[1] and Mihoko Bennett[2]. [1]Stanford University, Stanford, CA, [2]Stanford University, Palo Alto, CA

Background/Purpose: Among women, the prevalence of gouty arthritis (gout) and hyperuricemia (serum urate>6.0 mg/dL) increases steeply after the age 60. This increase has been attributed to menopause, and its attendant declines in circulating concentrations of reproductive hormones. However it is not clear whether the 'effect' of menopause is merely a reflection of increasing age as these two factors are tightly correlated.

Methods: We performed multiple unmatched and age matched case-control analyses using data on women aged 20–60 years from the NHANES1999–2010 cycles. For the latter, each case of gout, defined as self-reported physician diagnosis, 3 age-matched controls were chosen at random. Menopause was defined as absence of menstrual bleeding in the preceding 12 months, excluding those caused by pregnancy, medications, hormones, medical conditions or surgical procedures. Unmatched and matched multivariable analyses were performed by Survey weighted logistic regressions that adjusted for age, body mass index, ethnicity, hypertension and serum creatinine. Models were repeated with hyperuricemia as the outcome variable.

Results: A) Gout: In unmatched analyses, the bivariate and multivariable odds ratio for menopause were 3.0(1.4,6.5) and 1.3(0.6,2.7) respectively. In the age-matched analyses, bivariate odds ratio was 0.9 (0.4,1.8) and multivariate odds ratio was not significant. B) Hyperuricemia: In unmatched analyses the odds ratio for menopause in bivariate and multivariable models were 2.3 (2.0–2.8) and 1.25(1.01–1.54) respectively. In age-matched logistic regression models, the bivariate and multivariable odds ratios were 1.3(1.1,1.4) and 0.98(0.86–1.11) respectively

Conclusion: After offsetting the effect of age by matching, menopausal status was not associated with increased prevalence of gout or hyperuricemia.

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Prevalence of Gout Among Adults with Chronic Kidney Disease in the United States, 2009–10. Eswar Krishnan. Stanford University, Stanford, CA

Background/Purpose: The kidney is a major route of clearance of uric acid, a product of purine metabolism. The links between kidney disease, hyperuricemia, and gout in the general population are not well understood.

Our objective was to estimate prevalence of gout and hyperuricemia among people with chronic kidney disease (CKD) in the US general population.

Methods: The study was designed as a cross-sectional analysis of the most recent National Health and Nutrition Examination Surveys (NHANES 2009–2010), a nationally representative sample of civilian men and women aged 20 years or older (n=5,589). Gout was defined per self-reported physician or health professional diagnosis. Hyperuricemia was defined as serum urate > 7.0 mg/dL for men and > 6 mg/dL for women. Estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease-EPI equation was used to classify CKD as mild, moderate or severe.

Results: In 2009–2010, there were 5.2 million men and 2.3 million women with gout in the US. Of these, 1.25 million men and 0.78 million women had moderate or severe CKD. The prevalence of gout and hyperuricemia was 5-fold higher among those with moderate or severe CKD compared to those with no CKD. In multivariable logistic regression analyses that adjusted for age, gender, body mass index, hypertension, diabetes, hypertension medications including diuretics, blood lead levels, and hyperlipidemia the odds ratios of gout and hyperuricemia were 5.8 (1.2, 26.5) and 19.5 (3.8, 99.2) among those with severe CKD compared to those with no CKD.
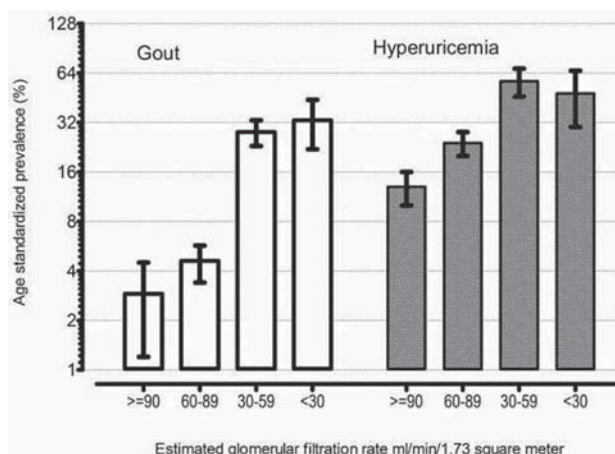
Conclusion: Gout is a major comorbidity of CKD with about 2 million Americans suffering from gout and moderate to severe CKD. The prevalence for gout and hyperuricemia increases as the severity of CKD worsens.

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Focus Groups Reveal Knowledge Gaps in Patients with Gout-A Qualitative Study. Puja Khanna[1], Veronica Berrocal[1], Tonya Hays[2], Daniel J. Clauw[1] and David A. Williams[3]. [1]University of Michigan, Ann Arbor, MI, [2]UCLA, Los Angeles, CA, [3]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: Gout is the most treatable arthritis in the Western World and there are effective medications available to treat both acute episodes and chronic gout. Prior studies have shown that treatment of chronic gout leads to improvement in patient-reported outcomes, and inadequate control has a substantial economic impact on the patient, employer, and society. Despite this, gout has the lowest adherence to medications (38%) across common chronic conditions such as hypertension, osteoporosis and diabetes mellitus. Currently, demographics, comorbidities, and poor adherence to chronic therapy are considered important attributes in developing poorly controlled gout. There is limited qualitative research assessing barriers to treatment and management among patients and health care providers. Therefore, we performed focus groups in patients with gout to identify conceptual gaps from patients' perspective.

Methods: A trained moderator conducted formal in-depth focus groups in gout patients, who were enrolled using an online screening survey where they provided details of their gout management including medications. The script for the focus group included questions to test their knowledge about the natural history of gout, understanding about different aspects of treatment of gout (acute treatment vs. prophylaxis vs. chronic urate-lowering therapy), beliefs about how long the treatment should be taken, discussion on adherence

to their medications, perceptions about the association between diet and alcohol and gout flares, and coping with an acute attack of gout. Adherence to medications was measured using a validated eight-question adherence instrument, Morisky Medication Adherence Scale, which is scored as low, medium, and high adherence.

Results: Twenty-four patients participated in 4 focus groups that lasted 90 minutes each. Baseline demographics showed predominantly white males (75%), 18% Hispanic, mean age 47.8 (15.4) years, 33% had tophaceous gout as diagnosed by their physician, and 62% were on ULT. Majority were receiving care from their primary care physicians (PCP, n=13), 4 from a rheumatologist, and remaining from PCP/ other subspecialties (n=5), or self-treated (n=2). The following themes emerged upon transcription of the scripts from these sessions: 1) Patients did not have a clear understanding of the natural history of gout; 2) patients did not realize that recurrent acute flares resulted in chronic joint damage; 3) there was lack of knowledge regarding treatment options and duration of therapy for acute and chronic gout; 4) patients felt that physicians did not spend enough time explaining the progression, i.e. natural history of the disease and its long-term effects; 5) patients did not grasp the need for chronic ULT to avoid complications and disability; and 6) patients were not aware of treatment goals for hyperuricemia, as evident by adherence to their gout medications. In these groups, 38% had low and 42% had medium adherence to their gout medications, respectively (per MMAS).

Conclusion: This qualitative study provides important insight into key modifiable variables that can be targeted to develop educational materials for patients.

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Clinical Efficacy Outcomes with up to 3 Years of Pegloticase Treatment for Refractory Chronic Gout. Michael A. Becker[1], Herbert S. B. Baraf[2], Robert A. Yood[3], Aileen M. Dillon[4], Janitzia Vazquez-Mellado[5], Faith D. Ottery[6], Dinesh Khanna[7] and John S. Sundy[8]. [1]University of Chicago, Chicago, IL, [2]Arthritis & Rheumatism Associates, Wheaton, MD, [3]Reliant Medical Group, Worcester, MA, [4]Kaiser Foundation Hospital, San Francisco, CA, [5]Hospital General de Mexico, Mexico city, Mexico, [6]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [7]University of Michigan, Ann Arbor, MI, [8]Duke University Medical Center, Durham, NC

Background/Purpose: Pegloticase, a recombinant modified mammalian uricase conjugated to mPEG, was approved for use in refractory chronic gout in the US in 2010. The Phase 3 clinical program comprised replicate, randomized, placebo-controlled trials (RCTs) followed by an open-label extension (OLE) study for a total treatment duration of up to 3 years. Here we focus on tophus resolution, flares, and tender/swollen joint counts with long-term pegloticase administration.

Methods: Patients entering the RCTs were >18 years of age, had baseline uric acid (UA) ≥8 mg/dL and at least one of the following: 3 or more self-reported gout flares during the prior 18 months, 1 or more tophi, or gouty arthropathy and contraindication to allopurinol or failure to normalize UA during 3 or more months of treatment at the maximum medically appropriate dose. The OLE enrolled patients at 46 centers in the US, Mexico and Canada who completed a RCT. Pegloticase dosing regimen (8 mg q2wks or q4wks) was determined at entry to the OLE and could be adjusted twice during the trial. All patients received prophylaxis for infusion reactions and flares. A tophus complete response was defined as 100% reduction in the measured area of at least 1 tophus of baseline diameter ≥5 mm without growth of any other baseline tophus or appearance of any new tophi. 547 evaluable tophi were present in 113 patients at baseline. Serial physician's global assessments (GA) were scored on a visual analogue scale from 0 (very good) to 100 (very bad) as a measure of patient well-being resulting from disease activity and assessments of 54 joints for swelling or tenderness were also performed.

Results: Most subjects completing blinded treatment (151/157) entered the OLE study. Among the 149 patients treated with pegloticase in the OLE study (2 elected observation only), 110 had received pegloticase during randomized testing and 39 had received placebo. Mean UA was 10 mg/dL at the OLE baseline (see baseline definition below). After 1 year of OLE treatment (week 52 visit), 59% of patients remaining in the study (62/105) had UA levels below 6 mg/dL. Secondary endpoints over time are presented in the Table below at study baseline, Week 13 (first measurement), one year, and final visit.

Efficacy variable	OLE Baseline*	Week 13	Week 52	Final Visit (LOCF)
Patients with SUA less than 6 mg/dL (%)	0.7%* (1/147)	48% (59/122)	59% (62/105)	45% (63/141)
Patients with tophus CR	RCTs baseline used	45% (36/80)	74% (50/68)	60% (56/94)
Mean tender joint counts (0-54 joints)	12*	5	3	4
Mean swollen joint counts (0-54 joints)	9*	4	2	3
Physician GA score (0-100)	48*	20	13	17

	Flare Data per 3 Month Period			
	Months 1-3	Months 4-6	Months 10-12	Months 22-24
Subjects with flares (%)	52%* (78/149)	38% (51/136)	26% (30/114)	17% (14/83)

*OLE baseline was defined as baseline data from the RCTs in patients treated with pegloticase and with a gap in therapy of <4 weeks between studies; for all other patients OLE baseline data was collected prior to the first OLE infusion. LOCF includes the data for all evaluable patients "carried forward" from the time of their final visit in the study.

Conclusion: Treatment with pegloticase for up to an additional 2.5 years beyond the 6 months of blinded trial participation was associated with ongoing benefits for patients. The OLE population data shown provides a conservative estimate of benefit as data are pooled for responders and non-responders. Patients undergoing sustained treatment with pegloticase can be expected to show meaningful clinical improvements with up to 3 years of therapy.

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Pegloticase Long-Term Safety: Data From the Open-Label Extension Trial. Michael A. Becker[1], Herbert S. B. Baraf[2], Robert A. Yood[3], Aileen M. Dillon[4], Janitzia Vazquez-Mellado[5], Faith D. Ottery[6], Dinesh Khanna[7] and John S. Sundy[8]. [1]University of Chicago, Chicago, IL, [2]Arthritis & Rheumatism Associates, Wheaton, MD, [3]Reliant Medical Group, Worcester, MA, [4]Kaiser Foundation Hospital, San Francisco, CA, [5]Hospital General de Mexico, Mexico city, Mexico, [6]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [7]University of Michigan, Ann Arbor, MI, [8]Duke University Medical Center, Durham, NC

Background/Purpose: Pegloticase is a recombinant modified mammalian uricase conjugated to mPEG and approved for treatment of refractory chronic gout. Pegloticase safety was evaluated during 2 replicate, 6-month randomized, placebo-controlled trials (RCTs).[1] An open-label extension (OLE) of these trials for up to 2.5 additional years of therapy evaluated long-term safety.

Methods: Patients completing one of the RCTs (n=157) could enroll in the OLE study conducted at 46 sites in the US, Canada, and Mexico. Patients (n=149) received pegloticase 8 mg infusions Q2 weeks or Q4 weeks. Patients received prophylaxis for infusion-related reactions (IRs) and gout flares (flare prophylaxis could be discontinued after 3 months in the OLE). Safety was evaluated with special interest in gout flares and IRs (defined as any adverse event occurring during or within 2 hours after infusion and not reasonably attributable to another cause).

Results: Of 157 RCT completers, 151 (96%) entered the OLE study and 149 received pegloticase (2 patients chose observation only). Patients received a mean of 28 ± 18 (SD) pegloticase infusions (range= 1–59) and were followed for a mean of 25 ± 11 months in the OLE study. The most common reasons for study withdrawal were AEs in 18% (27/149) of patients and loss of urate-lowering response in 11% (16/149). Nearly all patients (98%) had at least one AE during the OLE study. Gout flares and IRs were the most frequently reported adverse events (see table below); these were less common in patients sustaining urate-lowering response to treatment and those receiving the q2wk dosing regimen. Most AEs were investigator-rated (worst category per patient) as moderate (53%) in intensity. Overall, 54 patients (36%) had AEs rated as severe; these were deemed treatment-related in 25 (17%) patients. The most common treatment-related severe AEs were IRs and flares in 11 (7.4%) and 10 (6.7%) subjects, respectively. No patients with sustained urate-lowering response to treatment had a severe treatment-related IR or a severe gout flare.

Among the 13 serious AEs considered possibly related to pegloticase, there were 11 IRs, 1 skin necrosis, and 1 nephrolithiasis. Among the 11 serious IRs, all but one (91%) occurred when serum UA exceeded 6 mg/dL. A total of 4 deaths occurred during the OLE study; all were judged as unlikely related to study drug by the investigator. Laboratory assessments (CBC, CMP and U/A) identified no significant treatment-related change from baseline (except in UA).

Adverse Events in the OLE study	All treated patients (N=149) N (%)
Subjects with any AE	146 (98)
Subjects with serious AEs	51 (34)
Subjects with serious AEs related to study drug	13 (9)
Discontinuations due to AE	11 (7)
Most common AEs (incidence >10%)	
Gout flare	106 (71)
Infusion-related reaction	65 (44)
Arthralgia	29 (20)
Upper respiratory tract infection	27 (18)
Pain in extremity	26 (17)
Back pain	25 (17)
Diarrhea	22 (15)
Peripheral edema	21 (14)
Urinary tract infection	20 (13)
Nausea	17 (11)
Headache	16 (11)
Fatigue	15 (10)
Sinusitis	15 (10)
Nasopharyngitis	15 (10)

Conclusion: The safety profile of long-term pegloticase treatment was consistent with that observed during the 6-month RCTs with no new safety signals identified. As all but one of the 11 serious IRs reported during this study occurred when the UA level was >6 mg/dL, UA should be measured prior to infusions and pegloticase should be discontinued when UA levels rise >6 mg/dL after an initial response.

1. Sundy et al. *JAMA*. 2011;306:711–20

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Increased Serum Uric Acid: Consequence or Cause of Increased Cardiovascular Risk.
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Background/Purpose: Reports on cardiovascular (CV) disease in hyperuricemia and gout show conflicting results. Some studies show hyperuricemia to be an independent risk factor for CV events and death, others find no such associations or only with gouty arthritis. Gout and hyperuricemia have also been associated with individual CV risk factors such as increasing age, male sex, overweight, hypertension, dyslipidemia, diabetes and inflammation. Studies evaluating the complex associations between serum uric acid, inflammation, gouty arthritis and CV risk are lacking. This study was done to investigate the associations between serum uric acid and cardiometabolic risk factors and estimated CV risk in patients with gouty arthritis, non-gouty arthritis, and degenerative joint disease. To explore the effect of uric acid lowering therapy (ULT) on CV risk.

Methods: Analysis of the relation between serum uric acid and estimated 10-year risk of CV death (SCORE risk calculation, low risk version corrected for diabetes by increasing age with 15 years) and individual CV risk factors, i.e. systolic blood pressure (SBP), TC/HDL ratio (TC/HDL), diabetes and smoking in patients with osteoarthritis (OA, n=197), rheumatoid arthritis (RA, n=675) and gouty arthritis (GA, n=201) in a cohort of consecutive patients attending the Arthritis Center Twente in 2009. Subanalysis of the effect of uric acid lowering therapy (ULT; allopurinol or benzbromarone, target serum uric acid 0.36 mmol/L) on estimated 10-year CV risk in GA patients. Differences between groups and associations between CV risk variables and tertiles of serum uric acid were tested with ANOVA (for continuous cardiovascular risk factors) or Chi squared statistics (for nominal cardiovascular risk factors), adjusted for differences by age and sex.

Results: mean estimated 10-year CV risk was significantly higher in GA (GA 9.5% vs 5.7% in OA and RA, p<0.05). In RA and OA mean estimated 10-year cardiovascular risk as well as individual cardiometabolic parameters (OA: mean SBP, mean TC/HDL; RA: mean SBP, mean TC/HDL, prevalence diabetes. p<0.05) correlated with serum uric acid values. None of these correlations were present in GA. In GA plasma uric acid was lower in patients on ULT (0.32 mmol/l ULT vs 0.47 mmol/l non-ULT, p<0.05), age and frequency of CV events did not differ from non-ULT users. ULT did not affect mean estimated 10-year CV risk (9.7% ULT vs 8.9% non-ULT, p<0.05).

Conclusion: Gouty arthritis is a red flag for increased CV risk, as shown by higher prevalence of previous CV events and increased metabolic parameters of CV risk. Serum uric acid is associated with metabolic parameters of CV risk and 10-year risk of CV death. Effective ULT does not affect 10-year CV risk. Increased serum uric acid is therefore probably secondary to a high cardiometabolic risk profile.

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Metabolic Syndrome: The Genesis of Nephrolithiasis in Gout Patients?
Filipi M. Mello[1], Rafael B. Tomita[2], Ricardo Fuller[2], Marco Antonio G. P. Filho[2], Thiago B. M. Barros[2], Leandro L. do Prado[2], Kristopherson L. Augusto[2] and Claudia Goldenstein-Schainberg[2]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Rheumatology Division - University of São Paulo, São Paulo, Brazil

Background/Purpose: Gout patients have a high frequency of metabolic syndrome (MS), a disorder known to be associated with hyperinsulinemia. The latter condition augments proximal tubular sodium reabsorption and leads to reduced renal urate excretion and hyperuricemia. There are no data, however, evaluating whether MS can influence gout-associated clinical characteristics. Thus, we aimed to determine the prevalence of MS in our population and to investigate if the presence of MS would characterize a particular clinical and laboratorial gout profile.

Methods: This was a cross-sectional study of 158 gout patients (ACR criteria). MS was defined in accordance to the National Cholesterol Education Program ATP III (NCEP-ATP III) and the International Diabetes Federation (IDF) criteria. Demographic, anthropometric (body mass index - BMI) and clinical data were evaluated. Fasting serum levels of UA, glucose, triglycerides and cholesterol fractions were analyzed by routine laboratory tests.

Nephrolithiasis was demonstrated by usual ultrasonography and urate under-excretion defined as UA clearance lower than 7.5 ml/min. Statistical comparisons were performed using *Fisher's exact*, chi-square, student's T and Spearman's tests and P<0.05 was considered significant.

Results: The frequency of MS in gout patients was 73% and 71% according to NCEP ATPIII and IDF criteria respectively. Further comparison of 125 patients with MS and those 33 without this condition revealed similar mean ages (63.0 ± 11.5 vs 62.5 ± 12.9; p>0,05) and male predominance (94% and 75%). As expected, those with MS had higher BMI (30.2 + 5.5kg/m2 vs 27.0 ± 5.8kg/m2; p= 0.005) and higher prevalences of systemic arterial hypertension (93.3% vs 75% p= 0.012) and diabetes (25.8% vs 0, p= 0.001), though comparable frequency of coronary artery disease (22.5% vs 16.7%; p = 0.469). With regard to gout clinical/laboratorial characteristic, patients with MS had more nephrolitiasis (37.1% vs 16.7%, p= 0.026), but they did not differ from patients without MS concerning the presence of tophi (52.8% vs. 55.6%; p= 0.780) or uric acid underexcretion (83.1% vs 94.4%; p= 0.148). Current alcohol consumption, mean estimated creatinine clearance and mean serum levels of uric acid, were alike in both groups (p>0.05).

Conclusion: The novel demonstration that MS in gout is associated to nephrolithiasis suggests that this condition may underlie the genesis of uric acid stones. Whether insulin resistance may account for a renal alteration that may ultimately impair buffering and amplification of acidic urine remains to be determined. Moreover, the elevated prevalence of MS in gout patients from our country (almost ¾) is higher than overall rates of 63% MS in gout worldwide, indicating possible influence of dietary, geographical and/or genetic background.

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Evaluating Allopurinol Therapy and Serum Uric Acid Levels in Medicare Beneficiaries with Gout.
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Background/Purpose: Higher serum uric acid levels in gout patients have been associated with an increased frequency and risk of gout flares and greater subsequent healthcare costs. Despite the wide availability of allopurinol, achieving a therapeutic serum uric acid (sUA) level remains problematic for clinicians and patients. The objectives of this study included identifying predictors of an sUA response to allopurinol and investigating the associated healthcare costs.

Methods: A retrospective cohort study of a large health benefits company was conducted among Medicare Advantage Prescription Drug (MAPD) plan patients with gout newly initiated on allopurinol between 1/1/08 and 12/31/10. Patients were separated into two cohorts defined by their sUA response to allopurinol (sUA < 6 mg/dL or sUA > 6 mg/dL). Mean allopurinol adherence, as measured by proportion of days covered (PDC), was reported at 12 months follow-up. Multivariate logistic regression was used to determine factors associated with allopurinol response. A generalized linear model was developed to assess the association between allopurinol response and total healthcare costs.

Results: Of the 2,703 patients initiated on allopurinol, 57% had a baseline sUA and 33% had sUA ≤ 6 mg/dL in the follow-up period. Higher adherence was associated with achieving an sUA < 6 mg/dL compared to > 6 mg/dL (PDC=0.74 and 0.59, respectively, p<.0001). Predictors of sUA < 6 mg/dL included female sex, higher allopurinol PDC, and allopurinol dose >100 mg/day (OR:1.74, CI:1.41–2.13; OR:12.28, CI:8.25–18.28; OR:5.84, CI: 4.73–7.20, respectively). Hispanic ethnicity, higher baseline sUA, renal impairment (Stage 3 vs. Stage 1), colchicine use, and NSAID use were associated with lower odds of responding to allopurinol therapy (OR:0.32, CI:0.14–0.76; OR:0.60, CI:0.56–0.66; OR:0.41, CI:0.30–0.55; OR:0.79, CI:0.65–0.97; OR:0.68, CI:0.55–0.85, respectively). There were no significant differences in total healthcare costs between the two cohorts.

Conclusion: A large percentage of patients initiated on allopurinol did not have adequate sUA monitoring, and did not achieve an sUA < 6 mg/dL. Drivers of a therapeutic response included increased adherence and dose escalation. This study demonstrates that ample opportunity exists for clinicians and patients to improve sUA monitoring and treatment adherence when initiating urate lowering therapy.

Disclosure: M. Ward, Competitive Health Analytics, Inc., 3; **A. M. Louder**, Competitive Health Analytics, Inc., 3; **K. A. Szymanski**, Takeda Pharmaceuticals America, Inc., 3; **L. Tamariz**, Takeda Pharmaceuticals America, Inc., 2.

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The Prevalence of Gout in a Large Tertiary Hospital and the Impact of in-Hospital Attacks of Acute Gout On Patient Outcomes and Health Resource Utilisation – a Nested Case-Control Study.
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Background/Purpose: Acute gout can develop in hospitalised patients either as a new event or as a recurrence of established disease. To date there have been no studies examining the effect of in-hospital acute gout on hospital length of stay (LOS) or health resource utilisation. This study was performed to investigate the burden of gout in a hospitalised population and to assess the impact of acute gout on patient outcomes and health resource utilisation.

Methods: The study utilised hospital administrative data from The Royal Melbourne Hospital, Victoria over a ten year period (1 January 2001 to 31 December 2010). Gout was defined according to The International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) codes and subdivided into three categories: 'P-gout' (gout was the primary reason for admission or was a pre-existing condition requiring treatment initiation/adjustment during admission), 'C-gout' (gout occurred as a complication during hospitalisation and was not a pre-existing condition), or 'A-gout' (gout was an associated diagnosis and did not require specific treatment during admission). The overall burden of gout was measured by determining the prevalence of gout diagnoses affecting all hospital admissions (excluding day case admissions) over the study period. The effect of acute gout on patient outcomes and health resource utilisation was measured in a nested case control study with matching of 'C-gout' patients to controls (ratio of 1:5) by age, gender, and principal diagnosis. Outcome measures included LOS, 28-day hospital readmission rates, and total number of hospital days in the 12 months post hospital discharge. For comparisons between 'C-gout' and matched control cases, the student T-test or Wilcoxon ranksum test for continuous data and Chi[2]test for categorical data were used. A p-value of <0.05 was considered significant.

Results: There were 278,491 multi-day hospital admission episodes during the 10 year study period. Of these, 1,400 (0.5%) had an ICD-10-AM code for gout ('P-gout'=1,058, 'C-gout'=307 and 'A-gout'=35). A steady increase in the annual burden of gout of 0.22% over 10 years was noted. Patients who experienced an in-hospital attack of acute gout had a substantially longer LOS than the controls (median 13 days (IQR 7–25) vs. 5 days (IQR 2–11), p<0.001) and also had higher readmission rates in the first 28-days (p=0.002) and during the first 12 months (p<0.001) of hospital discharge.

Conclusion: Our study demonstrates a growing burden of in-hospital gout attacks and increased utilisation of health resources in patients who experience acute gout as a complication of their hospital stay. It was not possible from the design of our study to exclude other potential confounding factors which may have contributed to the observed increased hospital LOS.

Disclosure: J. H. Moi, None; **M. Tacey**, None; **C. Roberts**, None; **C. Brand**, None; **A. Gorelik**, None; **S. Van Doornum**, None.

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Colchicine Is Associated with a Decreased Rate of Myocardial Infarction in Gout Patients: Interim Results From a Retrospective Cohort Study.
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Background/Purpose: Atherosclerosis is an inflammatory process, but to date no anti-inflammatory agent has definitively been shown to alter cardiovascular (CV) risk. Colchicine is an anti-inflammatory agent that

inhibits macrophages, endothelial cells, and neutrophils, all implicated in atherosclerosis. In a cross-sectional study, we found that colchicine use was associated with reduced prevalence of myocardial infarction (MI) in gout patients [1]. To further evaluate the relationship between colchicine and CV risk, we initiated a retrospective cohort study. Here we present an interim analysis.

Methods: We identified all active New York Harbor VA patients with an assigned ICD-9 code for gout or hyperuricemia between 2000-09. Charts were manually screened to confirm a diagnosis of gout utilizing ACR criteria, and pharmacy records were used to identify subjects on daily colchicine for $\geq$ 30 days (colchicine group). Subjects receiving no colchicine prescriptions formed the control group. Baseline characteristics including CV risk factors and medication use were ascertained. We excluded patients who did not meet our diagnostic criteria for gout, who received as-needed colchicine only, or with $\leq$ 3 months of follow-up time available for evaluation. We defined colchicine lapse as any period of non-colchicine use beginning 2 weeks after medication cessation (to account for the elimination time of the drug). The primary outcome was MI during the study period.

Results: 7819 subjects had requisite ICD-9 codes. Among 1031 charts reviewed to date, 214 patients met gout criteria and 183 were enrolled. Of these, 121 subjects (66%) used colchicine (totaling 363.8 patient-years of exposure) and 62 subjects (34%) used no colchicine (totaling 249.8 patient-years of follow-up). Colchicine and control groups had similar rates of hypertension (0.85 vs 0.92, p=0.2), diabetes (0.37 vs 0.3, p=0.4), hyperlipidemia (0.66 vs 0.56, p=0.3), coronary artery disease (0.29 vs 0.37, p= 0.3), and allopurinol use (0.22 vs 0.21, p= 1.0), as well as similar BMI (30.6 vs 29.8, p=0.3), serum urate (8.4 vs 8.2 mg/dL, p=0.6), and creatinine (1.3 vs 1.4 mg/dL, p=0.7). Colchicine users experienced no MIs while on their medication. In contrast, control patients had 4 MIs (0 vs 6.4%; p=0.01), and 3 MIs occurred during colchicine lapses (3%; lapse vs colchicine p=0.09; lapse vs control p=0.43; mean time from last colchicine use to MI 5.9 months). We also compared rates of MI per patient-year between colchicine exposure (0.0), control follow-up (0.016), and colchicine lapse follow-up (0.018) periods, and observed significant differences between colchicine vs control (p=0.036) and colchicine vs lapse (p=0.035), but not between control vs lapse group MI rates (p=0.26).

Conclusion: In this interim analysis, gout patients taking colchicine had a significantly reduced rate of MI vs non-users, and vs themselves during periods when not taking colchicine. These data suggest that colchicine is protective against MI, though probably only during active use. Evaluation of the remaining 6,788 patients is ongoing.

[1] Crittenden DB et al. J Rheum 2012 E Pub.

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Low-Dose Allopurinol Promotes Greater Serum Urate Lowering in Gout Patients with Chronic Kidney Disease Vs Normal Renal Function.

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Background/Purpose: Patients with chronic kidney disease (CKD) may be at increased risk for allopurinol (ALLO) hypersensitivity, possibly because impaired renal excretion causes accumulation of the active ALLO metabolite oxypurinol (OXY). For this reason, lower doses of ALLO are recommended when initiating urate lowering in CKD patients. OXY accumulation suggests that ALLO should also be more efficacious in CKD patients, a hypothesis not previously tested. We therefore assessed whether ALLO is more effective at lowering serum urate (sUA) in patients with CKD vs those with normal renal function.

Methods: Using the electronic medical record of the NY Harbor VA Health Care System, we identified all gout patients taking 100 mg or 300 mg of ALLO daily between August 2007 and August 2008 for whom both pre- and post-treatment sUAs were available. ALLO use was identified using pharmacy records and confirmed by individual chart review. Baseline characteristics were obtained. Patients in each ALLO dose group were categorized by National Kidney Foundation stages, and mean change in sUA for each ALLO dose according to CKD stage was determined.
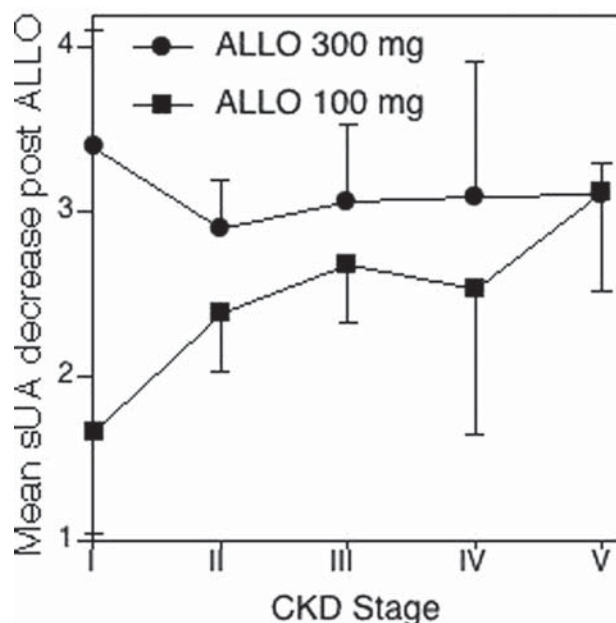
Results: Among 1288 charts reviewed, 199 patients met entry criteria and had sufficient data to permit evaluation. 95 patients were taking 100 mg and 104 were taking 300 mg ALLO daily. 100 mg vs 300 mg groups were similar in age (71.4±1.2 vs 68.7±1.1 years) and BMI (29.1±0.6 vs 30.9±0.6). Overall, patients taking 300 mg experienced a trend toward greater sUA decrease vs those taking 100 mg (2.9±0.2 vs 2.5±0.2 mg/dL, p=0.13), resulting in a lower post-treatment mean sUA in the 300 mg group (7.0±0.2 mg/dL for 100 mg dose, 6.1±0.2 mg/dL for 300 mg dose, p=0.001). Across increasing degrees of renal insufficiency, mean decreases of sUA in patients taking 300 mg did not change significantly. In contrast, in patients taking 100 mg, decreases in sUA (in mg/dL) increased progressively from stage I to V CKD: stage I (n=10) sUA decrease = 1.7±0.6, stage II (n=25) = 2.4±0.4, stage III (n=46) = 2.7±0.4, stage IV (n=8) = 2.5±0.9, stage V (n=6) = 3.1±0.6. Whereas patients with normal renal function (stage I) experienced greater sUA lowering with 300 mg vs 100 mg (3.4±0.7 vs 1.7±0.6 mg/dL, p=0.04), 100 mg ALLO was as efficacious as the 300 mg dose in patients with stage V CKD (sUA decrease 3.1±0.6 vs 3.1±0.2 mg/dL, p=0.5).

Conclusion: In patients with gout, low-dose ALLO is progressively more effective for sUA lowering in proportion to increasing degrees of renal insufficiency, presumably owing to OXY accumulation. No such effect was seen at the 300 mg dose, suggesting that sUA-lowering effects may reach a ceiling in CKD patients. These data support the strategy of starting gout patients with CKD on low-dose ALLO and titrating upwards only as needed, not only to minimize toxicity, but also because lower doses may be more effective in CKD patients, and higher doses may confer little or no additional benefit.

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Serum Uric Acid Control and Risk of Flare According to Different Cut-Offs in Patients with Gout: Longitudinal Analysis From the King Study of the Italian Society for Rheumatology. Maria Manara[1], Carlo Alberto Scirè[2], Marco A. Cimmino[3], Marcello Govoni[4], Fausto Salaffi[5], Greta Carrara[1], Carlomaurizio Montecucco[6], Marco Matucci-Cerinic[7], Giovanni Minisola[8] and Kick-off of the Italina Network for Gout (KING) Study Group[9]. [1]Epidemiology Unit -Italian Society for Rheumatology, Milano, Italy, [2]Epidemiology Unit -Italian Society for Rheumatology, Milan, Italy, [3]Rheumatology - Department of Internal Medicine - University of Genoa, Genova, Italy, [4]Section of Rheumatology - Department of Clinical and Experimental Medicine - University of Ferrara, Ferrara, Italy, [5]Rheumatology Unit - Polytechnic University of the Marche, Jesi, Italy, [6]Division of Rheumatology - University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy, [7]Department of Biomedicine & Division of Rheumatology AOUC - University of Florence, Florence, Italy, [8]Rheumatology Unit - San Camillo Forlanini Hospital, Rome, Italy, [9]SIR, Italy

Background/Purpose: The therapeutic goal of the management of gout is to promote crystal dissolution and prevent crystal formation. For this reason national and international guidelines recommend to maintain the serum uric acid (sUA) below the saturation point for monosodium urate (from 5 to 6.38 mg/dl). In this analysis we evaluated the influence of different sUA levels on the risk of acute attack in an observational setting.

Methods: This is a longitudinal analysis of an ongoing multicentre cohort study including 450 patients with prevalent clinically diagnosed gout from 30 rheumatology centers across Italy (Kick-off of the Italian Network for Gout, KING, promoted by the Italian Society for Rheumatology - SIR; NCT01549210) recruited from June 2011 and January 2012. Participants were centrally selected from clinical registers by random sampling. All patients underwent full clinical evaluation at baseline, including general and disease-specific characteristics. During the first 6 months of follow-up the number of flares, sUA and concurrent treatment were collected.

The relationship between sUA and risk of flare was analyzed using logistic models on complete data, and estimation of the risk of flare is presented as odds ratios (OR) and 95% confidence intervals (CI). The optimal cut-off of sUA was explored by identifying the minimum cut-off associated with a significant increase of risk of flare.

Results: A total of 178 patients were included in the analyses: 92.7% were male with a mean (SD) age of 64.5 (10.9) years, 22.9% had tophaceous and 18.7% polyarticular disease. Mean (SD) sUA was 6.1 (1.6) mg/dl, of which 26.9% $<$5mg/dl, 26.4% from 5–6mg/dl, 16.8% from 6–7mg/dl and 29.8 above 7mg/dl. During the follow-up of 6 months 60 patients (33.7%) presented at least one flare with a total of 140 flares.

SUA levels were linearly associated with an increased risk of flare: OR[95%CI] of 1.39 [1.13,1.71] per each mg/dl increase. The adjusted analyses confirmed a similar increase of risk of flare regardless of changes in urate-lowering therapy or prophylactic treatment: OR 1.38 [1.12,1.71]. The minimum cut-off associated with a significant increase of risk of flare was 5.9 mg/dl with an OR of 1.90 [1.01,3.59]. Consistently, using sUA$<$5mg/dl as reference category, 5–6mg/dl was not associated with a significant increase of risk of flare (OR 1.54 [0.60, 4.15]) while 6–7mg/dl and $>$7mg/dl were associated with significant ORs: 2.90 [1.03,8.16] and 3.52 [1.43,8.62], respectively.
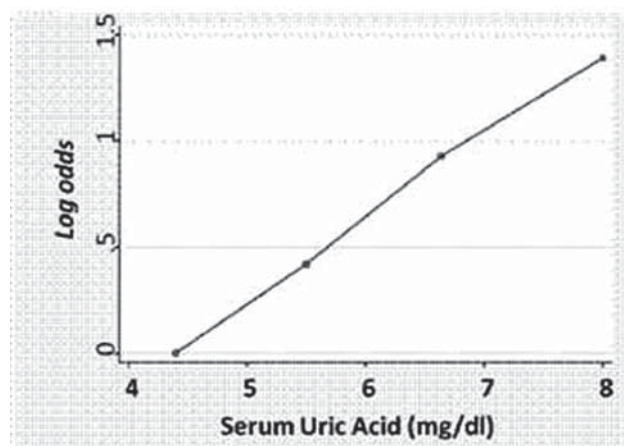
Conclusion: The optimal management of gouty patients requires strict control of serum uric acid levels. A virtual absence of risk of flare is associated with levels of uric acid levels below 4mg/dl, but the operative cut-off of 6mg/dl is a robust limit to discriminate patients with increased risk of relapse.

Disclosure: M. Manara, None; **C. A. Scirè**, None; **M. A. Cimmino**, None; **M. Govoni**, None; **F. Salaffi**, None; **G. Carrara**, None; **C. Montecucco**, None; **M. Matucci-Cerinic**, None; **G. Minisola**, None;

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Allopurinol Use Is Associated with a Decreased Risk of Myocardial Infarction. Lamiae Grimaldi-Bensouda[1], Annick Alpérovitch[2], Elodie Aubrun[1], Nicolas Danchin[3], Michel Rossignol[4], Lucien Abenhaim[5], Pascal Richette[6] and PGRx MI Group[7]. [1]LA-SER, Paris, France, [2]Inserm U708-Neuroepidemiology, La Pitié-Salpêtrière Hospital, Paris, France, [3]Coronary disease unit, Georges Pompidou European Hospital, Assistance Publique-Hôpitaux de Paris and Paris-Descartes University, Paris, France, [4]LA-SER, Centre for Risk Research, Montreal, [5]LA-SER Europe Ltd, London, United Kingdom, [6]Lariboisière Hospital, Paris, France, [7]Paris, France

Background/Purpose: Xanthine oxidase inhibitors (XOI) reduce both urate levels and the oxidative stress in the vasculature, which are known cardiovascular risk factors. However, the effects of XOI on major cardiac events such as myocardial infarction (MI) are unknown. The objective was to investigate whether XOI use is associated with a modified risk of myocardial infarction.

Methods: We used a matched case-control study comparing patients with first ever MI with controls. Cases were retrieved from a myocardial infarction registry consisting of 63 cardiology centers, whereas controls were selected from general practice settings. The association between XOI or colchicine use and MI was assessed by adjusted OR from conditional logistic regression.

Results: Data are from 2277 MI patients matched to 4849 controls. Allopurinol was by far the most frequent XOI taken by participants of this study. The adjusted OR (95% CI) for MI in allopurinol users was 0.75 (0.56–1.01), and it was 0.66 (0.49–0.89) using the whole pool of referents (n=8444). The effect of allopurinol persisted across subgroups by sex, presence of hypertension, and in ST-segment elevation MI patients. In contrast, colchicine use was not associated with a modified risk of MI: aOR= 1.17 (0.70–1.93).

Conclusion: Allopurinol, but not colchicine use, is associated with around a 30% reduction in the risk of myocardial infarction. Besides its urate lowering property, allopurinol might have a cardio protective effect.

Disclosure: L. Grimaldi-Bensouda, None; **A. Alpérovitch**, None; **E. Aubrun**, None; **N. Danchin**, None; **M. Rossignol**, None; **L. Abenhaim**, None; **P. Richette**, None;

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Post-Marketing Safety Surveillance Data Reveals Patterns of Use for Pegloticase in Refractory Chronic Gout. Kenneth M. Bahrt, Anthony E. Yeo, Tina L. Howson and Faith D. Ottery. Savient Pharmaceuticals, Inc., East Brunswick, NJ

Background/Purpose: Pegloticase is a recombinant modified mammalian uricase conjugated to mPEG which was approved in the US in 2010 for treating hyperuricemia in patients with refractory chronic gout. The pegloticase development program comprised 2 randomized, placebo-controlled trials (6 months; N=212) followed by an open-label extension study for a total treatment duration of up to 3 years. Trial entry was preceded by a 1 week washout period for urate-lowering therapies. Patients were considered "responders" if they met the primary efficacy endpoint of uric acid (UA) $<$6 mg/dL for 80% of time during months 3 and 6. 42% of patients met this definition (vs. 0% with placebo; p$<$0.001) in the randomized trials[1].

Post-hoc analyses revealed a significant relationship between a loss of urate-lowering response to therapy and the presence of high titer anti-pegloticase antibodies. Loss of response was also associated with increased risk of infusion reactions (IRs). Further analyses confirmed that the great majority of IRs occurred in patients who had already lost their urate-lowering response to therapy (20/22 or 91% for patients receiving pegloticase 8 mg q2wks and 24/34 or 71% for patients treated q4wks). These two findings led to clear guidance that patients treated with pegloticase should discontinue treatment if UA levels rose above 6 mg/dL (particularly with 2 consecutive levels $>$6 mg/dL). New information provided by post-marketing pharmaco-

vigilance suggests a relationship between serum UA levels <6 mg/dL, IRs and concomitant use of xanthine oxidase inhibitors (XOIs).

Methods: Post-marketing AE data were collected as standard, unsolicited reporting and summarized from September 14, 2010 to November 30, 2011 to evaluate concomitant XOI use.

Results: During approximately one year of commercial pegloticase use in the US, IRs were reported in 20 patients and anaphylaxis in 8 patients. Among the reports of IRs, 8 patients had UA >6, 7 had UA <6 and UA was unknown at the time of the IR in 5. Among the reports of anaphylaxis, 4 patients had UA levels >6, 2 had UA levels <6 and 2 had unknown UA. Importantly, AE reporting revealed that 40% of patients (8/20 IRs and 3/8 cases recorded as anaphylaxis) were receiving one or both XOIs in addition to pegloticase. Details of these 11 patients are provided in the table.

Patients with infusion reactions receiving concomitant XOIs

ID	SUA on XOI	Infusion #	Previous SUA	Demographic
Patient A	8.2 mg/dL on febuxostat	3rd	Previous infusion 5-6 mg/dL range	Caucasian male, unspecified age
Patient B	3.4 mg/dL on febuxostat	2nd	4.1 mg/dL at baseline on febuxostat	87 year old (yo) white male
Patient C	9.5 mg/dL on febuxostat	3rd	Previous 4.5 mg/dL prior to 2nd infusion	49 yo Caucasian male
Patient D	undetectable on febuxostat	3rd	Previous very low (unspecified)	57 yo Caucasian male
Patient E	8.6 mg/dL on allopurinol	4th	Previous 5.2 mg/dL prior to 3rd infusion	55 yo Caucasian male
Patient F	6.8 mg/dL on allopurinol	3rd	Previous 1.3 prior to 2nd infusion	31 yo male, of unknown origin
Patient G	5.5 mg/dL on both XOIs	3rd or 4th	Previous 5.3 mg/dL	38 yo Caucasian male
Patient H	7.4 mg/dL on both XOIs	3rd	Previous 4.6 mg/dL prior to 2nd infusion	42 yo African-American male

Patients with anaphylaxis receiving concomitant XOIs

ID	SUA on XOI	Infusion #	Previous SUA	Demographic
Patient I	6.7 mg/dL on allopurinol	3rd	Previous 7.6 mg/dL but had missed appt	58 yo white male
Patient J	4.3 mg/dL on allopurinol	2nd	Previous 4.3 mg/dL prior to 2nd	60 yo white male
Patient K	7.1 mg/dL on febuxostat	3rd	Previous <0.5 prior to ??2nd infusion	47 yo white male

Conclusion: Post-marketing adverse event reporting provided valuable information regarding pegloticase administration in the real world setting. Importantly, the use of concomitant urate-lowering therapies has the potential to mask the rise of UA levels in patients treated with pegloticase and confound the use of UA as a biomarker of response. XOIs should be discontinued prior to initiation of pegloticase and not restarted while on treatment. Further, UA monitoring and discontinuation of pegloticase upon loss of efficacy are critical to safe and effective care.

1. Sundy et al. *JAMA* 2011;306:711–20.

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Relative Risk of Infusion Reactions with KRYSTEXXA® (pegloticase) From Post-Approval Safety Data: Results From Sept 2010 to June 2012. Raymond L. Malamet, Tina L. Howson, Anthony E. Yeo, Kenneth M. Bahrt and Marsha Wolfson. Savient Pharmaceuticals, Inc., East Brunswick, NJ

Background/Purpose: During randomized clinical trials (RCTs) with pegloticase, the incidence of infusion-related reactions (IRs) was 26% including 5 cases of anaphylaxis (determined post-hoc using published criteria).[1,2] Post-hoc analyses revealed a relationship between loss of urate-lowering response and IRs. This relationship could not have been detected during the trials as investigators were blinded to pre-infusion uric acid (UA) values. These analyses led to guidance on measuring UA levels as a biomarker of therapeutic response and IR risk, and included the recommendation that patients discontinue pegloticase if serum uric acid (UA) was >6 mg/dL, particularly at 2 consecutive q2wk infusions.[3] In order to determine whether this guidance was effective in reducing the incidence of IRs, the company reviewed IRs from post-approval safety data.

Methods: We estimated the incidence of IRs by comparing usage information from the RCTs and the post-approval period (Sept 14, 2010 to June 1, 2012). An estimate of the total number of infusions given in the post-approval period was derived from the number of vials sold during that period compared to the number administered to a defined number of patients in the 6-month RCTs.

Results: 852 individual vials for infusion were administered to the 85 patients receiving the approved dose of pegloticase during the RCTs (8 mg every 2 weeks) and there were 22 reports of IRs (see Table). During the post-approval period, 5727 vials were sold and the company received 58 reports of IRs and anaphylaxis (43 reports of IRs, 15 reports of anaphylaxis). The above information was used to estimate the relative risk reduction for IRs during the post-approval period compared with the RCTs period. When determined this way, there was a 61% reduction (95% CI: 36.3 to 75.9) in the risk of IR during the post-approval period vs. the RCTs.

While providing evidence for relatively low rates of IRs, these estimates have substantial limitations. The actual number of patients receiving infusions is difficult to estimate from vials sold. In addition, the number of IRs depends on voluntary reporting and some adverse events are reported to the FDA and not to the company. Finally, these estimates are valid only for the time period of collection as practice patterns may change with accrued clinical experience.

	IR present	IR absent	Total
Post-approval safety surveillance	58	5669	5727
Pooled RCTs	22	830	852
Totals	80	6499	6579

Conclusion: The risk of IRs estimated for pegloticase during a defined post-approval period was reduced by 61% relative to rates of IRs seen in the RCTs. Post-approval surveillance will continue to assess whether IR risk is adequately mitigated by adherence to the recommended stopping rules based on elevated serum UA. Additional real world data with pegloticase, collected over a longer time period, should provide more robust estimates of IRs that can be compared to the clinical trials experience.

References
1. Sundy et al. *JAMA.* 2011;306:711–720.
2. Sampson et al. *Annals Emerge Med.* 2006;47:373–380.
3. KRYSTEXXA prescribing information.

ACR Poster Session A
Infection-related Rheumatic Disease
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Disease Modifying Agents Combined with Isoniazid for Latent Tuberculosis in Patients with Rheumatic Diseases. Josiane Bourré-Tessier[1], Mireia Ariño i Torregrosa[2] and Denis Choquette[3]. [1]Institut de Rhumatologie de Montréal, Université de Montréal, Montréal, QC, [2]Universitat de Valencia, Massanassa, Spain, [3]University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC

Background/Purpose: Reactivation of latent tuberculosis (LTB) has been described with the use of anti-TNF for the treatment of rheumatic diseases. Combined treatment of isoniazid (INH) and DMARDs such as methotrexate (MTX) and sulfasalazine (SSZ) can potentially increase the risk of liver toxicity. The goal of this study was to investigate the risk of liver toxicity in rheumatic patients taking isoniazid (INH) and disease modifying agents (DMARDs) or biologics.

Methods: We reviewed the Institut de Rhumatologie de Montréal database (RhumaData®) for rheumatic patients with positive tuberculin skin test who took INH and at least one concomitant DMARD or biologic between August 2001 and April 2011. Liver function tests (LFT) were tested at baseline and during therapy.

Results: Of 922 patients screened with tuberculin skin test, 87 patients tested positive and received INH. During INH treatment, 75.9% were taking concomitant DMARDs (71.3% MTX, 19.5% hydroxychloroquine (HCQ), 5.7% SSZ, 3.4% leflunomide), 82.0% were taking concomitant biologics, and 46.0% were using NSAIDs on a regular basis. Twenty-four percent had

abnormal liver enzymes during INH therapy. Most of them were mild or transient, but 8% (7 patients) had significant abnormalities leading to INH discontinuation. Among these patients, mean (min, max) was 241 (52, 617) for AST and 262 (92, 669) for ALT. Concomitant medications taken by patients who stopped INH were: biologics (4 patients), MTX (1), biologic and MTX (1), biologic, leflunomide and HCQ (1).

Conclusion: The use of INH for LTB was generally well tolerated in patients with rheumatic diseases on a background regimen of DMARDs or biologics. However, the rate of significant abnormalities is our study is higher than the reported rates for INH hepatitis in the literature. There is no evident association between liver anomalies and specific combination with DMARDs. Therefore, it is prudent to follow LFT closely on patients taking combination therapy.

Disclosure: J. Bourré-Tessier, None; M. Ariño i Torregrosa, None; D. Choquette, None.

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A Systematic Review and Meta-Analysis of Antibiotic Treatment for Reactive Arthritis. Claire E. Barber[1], Joseph Kim[2], R. D. Inman[3], John Esdaile[4] and Matthew T. James[5]. [1]University of Calgary, Calgary, AB, [2]University of Calgary, Calgary, [3]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [4]University of British Columbia, Vancouver, BC, [5]Univeristy of Calgary, Calgary

Background/Purpose: Although bacterial infections are a common precipitant, it is unclear whether antibiotic treatment is effective for reactive arthritis. The purpose of this study was to conduct a systematic review and meta-analysis of randomized controlled trials to examine the efficacy and safety of antibiotic treatments for reactive arthritis.

Methods: Medline, Embase, Pubmed, Cochrane CENTRAL Register of Controlled trials were searched up to November 2011 using MeSH terms and keywords pertaining to two major themes: *reactive arthritis* and *antibiotic therapy.*Randomized controlled trials of antibiotic use for reactive arthritis reporting on: remission, joint counts, pain or patient global scores were included. Two reviewers independently extracted information on the definition of reactive arthritis, features of study quality, type of treatment and outcomes. Pooled relative risks for binary outcomes (failure to achieve remission and adverse events) and pooled mean differences for continuous variables (joint counts, pain and patient global scores) were computed. Potential sources of heterogeneity were investigated using stratified analyses and meta-regression.

Results: Twelve trials were eligible for inclusion and 10 provided adequate data for meta-analysis. The pooled relative risk of failure to achieve remission from a random effects model showed no significant benefit of antibiotic treatment (seven trials, 375 participants RR 0.74, 95% CI 0.49–1.10); however, substantial heterogeneity was observed ($I^2=76.3\%$, $p<0.0001$). The treatment effect did not significantly differ by the type of organism triggering the reactive arthritis (*Chlamydia* versus other), use of combination versus mono-therapy, or risk of bias. However, when only blinded trials were pooled, the treatment effect was attenuated and heterogeneity decreased significantly (RR 0.87, 95% CI 0.70–1.10, $I^2=32.8\%$, $p=0.19$). No significant effects of antibiotic treatment were observed on swollen joint counts (six trials, 375 participants weighted mean difference 0.21, 95% CI 1.16, 0.75, $I^2=82.9\%$, $p<0.0001$) tender joint counts (five trials, 326 participants, standardized mean difference 0.10, 95% CI -0.58, 0.78, I^2 86.9%, $p<0.0001$), pain (three trials, 220 participants, standardized mean difference 0.16, 95% CI -0.15, 0.46, I^2 12.6%, $p= 0.381$), or patient global scores (four trials, 284 participants, standardized mean difference 0.15, 95% CI -0.08, 0.39, I^2 0.0%, $p= 0.499$); however, antibiotics were associated with a 97% increase in gastrointestinal adverse events.

Conclusion: Trials of antibiotic treatment for reactive arthritis have produced heterogeneous results which may be related to differences in study quality. The current evidence base does not support the use of antibiotics in routine clinical practice for the management of reactive arthritis.

Disclosure: C. E. Barber, None; J. Kim, None; R. D. Inman, None; J. Esdaile, None; M. T. James, None.

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Latent Tuberculosis Screening and Treatment in Rheumatoid Arthritis Patients Eligible for Anti-TNF Therapy in Endemic Areas: Does It Work? Ieda Laurindo, Ana C. M. Ribeiro, Julio C. B. Moraes, Carla G.S. Saad, Karina Rossi Bonfiglioli, Fernando H.C. Souza, Ana L. G. Calich, Mariana G. Waisberg, Lissiane K. N. Guedes and Eloisa Bonfa. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: Background: Current recommendations for latent tuberculosis infection (LTB) screening and treatment in patients eligible for anti-TNF agents are not well established in endemic regions. Thus, the aim of this study is to evaluate the long-term efficacy of LTB screening and treatment in RA patients under TNF blockers tight control therapeutic strategy.

Methods: Two hundred and two RA patients (1987 criteria) eligible for anti-TNF agents were initially screened for LTB by PPD test, chest X-ray and history of contact. Two hundred and nine patients receiving traditional DMARDs comprised the control group. Patients and controls were regularly followed at 1–3 months interval, from January 2007 to December 2011. During the study period, PPD was repeated in patients with TB clinical suspicion or due to extended (>12 months) interruption/re-start of biologic treatment.

Results: 202 patients were treated with anti-TNF blockers, 85(42%) with one agent and 117(58%) with two or more: 181 received infliximab, 93 adalimumab and 75 etanercept. LTB screening (PPD and/or history of contact and/or X-ray) was positive in 69(34%) patients. In 65%(45 patients) PPD was positive, 36%(n=25) had history of contact and 21%(n=15) with X-ray alterations. Of note, in the 24 LTB patients with negative PPD, contact history accounted for 75% and X-ray for 37% of the positive screened cases. LTB treatment with isoniazid during 6 months was administered to all positive screened patients and none developed TB during follow-up. Regarding the 133 remaining screening negative patients none had TB during the first twelve months of anti-TNF therapy. PPD test was repeated in only 53 patients (26%) due to interruption/re-start of biologic treatment (51cases) or clinical TB suspicion (2 cases). PPD turned out to be positive in five patients: three that received LTB treatment and the two patients with clinical TB suspicion, both diagnosed as active TB (after 14 and 36 months of anti-TNF treatment) and properly treated with standard TB treatment. In those RA patients under traditional DMARDs, three cases (1.5%) of active TB were observed. Thus, the frequency of TB in RA patients during five years of observation was similar in patients under biological and traditional DMARDs (1% vs. 1.5%, p=0.68), although higher than the expected for the area (60/100,000/ per year).

Conclusion: The present study provided evidence that the recommended screening and treatment protocol for LTB in patients under anti-TNF treatment was also efficient in endemic areas, with a special attention to contact history in those with negative PPD. Active TB diagnosis during anti-TNF treatment seems not to be related to screening failure, reinforcing the importance of constant clinical surveillance.

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Prevalence, Risk Factors, and Functional Impact of Arthralgias Among Patients with Chronic Hepatitis C Virus Infection. Samir Bhangle[1], Vincent Lo Re[1], W. Gina Pang[1], Kyong-Mi Chang[2], Valerianna Amorosa[2], Jay Kostman[1], H. Ralph Schumacher[3] and Alexis Ogdie[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]Philadelphia VA Medical Center, Philadelphia, PA, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA

Background/Purpose: The prevalence, risk factors and functional impact of joint pain are not well described in chronic hepatitis C virus (HCV)-infected patients, particularly in the setting of human immunodeficiency virus (HIV) coinfection. Our objectives were to determine if the prevalence of arthralgias was higher among chronic HCV-infected patients compared to HIV/HCV-coinfected persons and those with HIV alone, and to evaluate the risk factors and functional impact of joint pain in chronic HCV patients.

Methods: A cross-sectional study was performed among patients with chronic HCV infection aged 18–80 years followed at the infectious disease and hepatology clinics. Patients with HIV infection seen in the same clinics were enrolled as a comparison group. HIV was chosen as a comparison given that it is a chronic infection with similar risk factors. Joint pain was defined by patient self-report. Standardized interviews by trained personnel were conducted and the Multidimensional Health Assessment Questionnaire (MD-HAQ) was administered to assess the impact of joint pain on physical function and emotional well-being. The electronic medical records of all participants were reviewed up to the date of study visit to abstract relevant clinical data for hypothesized risk factors.

Results: Of the 210 patients enrolled, 178 had HCV infection (90 mono, 88 co-infected with HIV) and 32 had HIV only. Joint pain was reported by 63/90 (70%) of the HCV-mono-infected, 48/88 (54%) of the HCV-co-

infected, and 17/32 (53%) of the HIV-mono-infected patients. The MD-HAQ results in the 178 HCV-infected patients demonstrated a mean pain score of 5.9/10, mean physical function score 2.5/10, mean global assessment of function 4.2/10, and mean RAPID3 12.7. No differences were observed between subjects with and without joint pain with regards to age (p=0.62), sex (p=0.53), race (p=0.32), and clinical site (p=0.32). Differences in clinical characteristics among those with and without joint pain among patients with chronic HCV infection are displayed in the table below.

Analysis of Potential Risk Factors Among Patients with Chronic HCV

	HCV (mono and co-infected) N= 178 (%)	Joint pain N= 111 (%)	No Joint pain N= 67 (%)	P value
Current HCV treatment	23 (13)	15 (14)	8 (12)	NS*
HIV	88 (49)	48 (43)	40 (60)	0.03
Genotype 1	135 (76)	86 (77)	49 (73)	NS
2	6 (12)	2 (2)	4 (6)	
3	6 (12)	2 (2)	4 (6)	
Smoking	65 (37)	52 (47)	13 (19)	<0.001
Alcohol	5 (3)	5 (5)	0	0.07
Sleep Disturbance	85 (48)	74 (67)	11 (16)	<0.001
Dry eyes	25 (14)	24 (22)	1 (2)	<0.001
Dry mouth	55 (31)	50 (45)	5 (8)	<0.001
Peripheral neuropathy	37 (21)	37 (33)	0 (0)	<0.001
Myalgia	36 (20)	36 (32)	0 (0)	<0.001
Depression	70 (39)	60 (54)	10 (15)	<0.001
Anxiety	79 (44)	70 (63)	9 (13)	<0.001
AST†, Mean (SD)	63.8 (50.5)	67.9 (5.5)	57 (4.9)	NS
ALT†, Mean (SD)	58.8 (48.7)	59.8 (5.0)	57.2 (5.6)	NS
HCV viral load, Mean (SD)	3.1 million (6.8)	3.3 million (7.9)	2.8 million (4.2)	NS

*NS: p-value>0.05, †AST= alanine amino transferase and ALT= alanine amino transferase.

Conclusion: Joint pain was common (62%) among patients with chronic HCV and was associated with diminished functional status and emotional well-being. HCV/HIV co-infected and HIV mono-infected have significantly lower rates of joint pain compared with HCV mono-infected patients, possibly due to T-cell moderation by HIV resulting in decreased effects of the hepatitis C virus or the intensive outpatient follow-up many HIV patients receive.

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The Impact of Hepatitis Screening On Diagnosis and Treatment in Rheumatoid Arthritis. Richard Conway, Michele Doran, Finbar (Barry) D. O'Shea and Gaye Cunnane. St James's Hospital, Dublin, Ireland

Background/Purpose: Hepatitis testing is an important pre-requisite to the diagnosis and treatment of patients with rheumatic disease. Joint symptoms may be a manifestation of acute or chronic hepatitis B or C. Immunosuppressive treatment may increase viral load in patients with undiagnosed viral hepatitis. The prevalence of hepatitis varies amongst populations, but even in areas with low endemic levels, it is imperative to identify those in whom current or past infection may influence clinical outcome. The CDC recommends testing for 4 components: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody and hepatitis C antibody. Although ACR recommendations do not specifically recommend hepatitis screening, they do advocate vaccination against hepatitis B in all patients. This study was conducted in order to identify new cases of hepatitis in a cohort of patients with RA attending a large university teaching hospital and to evaluate the extent of the hepatitis screen undertaken.

Methods: One hundred consecutive patients, with a diagnosis of RA, were retrospectively assessed for completeness of hepatitis screening by reviewing their hospital records. A dedicated teaching session for all members of the rheumatology team was then conducted, highlighting the results of the survey and explaining the rationale for complete hepatitis screening in all patients with RA. Paper reminders were placed on all desks to alert staff to screen patients at clinic review. A prospective study of hepatitis screening of a separate cohort 100 consecutive out-patients with RA was then performed.

Results: In the initial 100 patients, 21% were male, mean age was 65 years. 85% were taking methotrexate and 22% were on biologic treatments (18% anti-TNF agent, 4% Rituximab). Liver profile was abnormal in 20%. A complete hepatitis screen was present in only 8%, while 12% had a hepatitis B core antibody checked and 53% had a test for hepatitis C.

In the 100 patients assessed after staff education, 26% were male, mean age was 63 years. 86% were taking methotrexate and 27% were on biologic treatments (23% anti-TNF agent, 4% Rituximab). Liver profile was abnormal in 30%. A full hepatitis screen was available in 63%, while 65% had a hepatitis B core antibody checked and 81% had a test for hepatitis C.

In the total 200 patients, we identified 3 cases of positive hep B core antibody, 11 cases of positive hep B surface antibody and 1 case of positive hep C antibody. On retrospective analysis, 2 had identifiable risk factors for blood-borne infections (both healthcare workers).

Table 1. Completeness of Hepatitis Screening

	Pre education, n=100	Post education, n=100
Any hepatitis screen	54%	81%
Full hepatitis screen	8%	63%
Hep B surface antigen	40%	77%
Hep B surface antibody	46%	77%
Hep B core antibody	12%	65%
Hep C antibody	53%	81%

Conclusion: Even in populations where hepatitis B or C is not endemic, laboratory screening will reveal new cases of hepatitis that should be identified prior to immunosuppressive treatment. Educational initiatives are helpful in teaching staff working in busy clinical environments to screen patients, but ongoing reminders are likely to be essential.

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Prevalence and Associations of Hepatitis C Arthritis in Chronic Hepatitis C Virus Infection. Elizabeth D. Ferucci[1], Holly S. Ryan[1], Tammy L. Choromanski[1], Lisa J. Townshend-Bulson[1], Stephen E. Livingston[1], Brian J. McMahon[1] and Mark H. Wener[2]. [1]Alaska Native Tribal Health Consortium, Anchorage, AK, [2]University of Washington, Seattle, WA

Background/Purpose: Chronic infection with hepatitis C virus (HCV) has been reported to cause inflammatory arthritis and/or fibromyalgia. Case series of patients with HCV-associated arthritis have been described, but population-based studies of individuals with chronic HCV including systematic interview and evaluation by a rheumatologist have been limited.

Methods: Study participants were recruited from a population-based cohort with chronic HCV. Any individual in the cohort who had not been treated with anti-viral therapy was invited to participate. The study visit included an interview for joint symptoms and fatigue, including the London Fibromyalgia Epidemiology Study Screening Questionnaire; assessment of functional status with the Health Assessment Questionnaire disability index (HAQ-DI); examination by a rheumatologist including joint count and tender point count; and a blood draw. Sera were tested for the following autoantibodies: cyclic citrullinated peptide (CCP), rheumatoid factor (RF) by nephelometry, RF isotypes (IgG, IgM, and IgA) by ELISA, and ANA by immunofluorescence. After the study visit and medical record review, participants were categorized as follows: 1) HCV-associated arthritis; 2) RA; and 3) no inflammatory arthritis.

Results: To date, 71 study participants have been recruited, of whom 6 (8.5%) were classified as HCV-associated arthritis, 4 (5.6%) as RA, and 61 (85.9%) as no inflammatory arthritis. CCP and RF were more common in those with RA, when compared to HCV arthritis and no inflammatory arthritis groups (CCP 67%, 0%, and 2%, respectively, p =0.006; RF 100%, 20%, and 40%, p=0.03). Of the RF isotypes, only RF IgG prevalence differed by group (75%, 0%, and 27%, p=0.04). ANA prevalence did not differ by group (50%, 80%, and 35%, p=0.09). The mean HAQ-DI was similar across groups (0.41, 0.52, and 0.29, p=0.29), and the prevalence of fatigue interfering with activities was also similar (50%, 83%, 48%, p=0.29). There was a difference between groups in screening positive for fibromyalgia on the questionnaire (25%, 67%, and 15%, p=0.01), but no difference in mean number of tender points on examination (10.5, 8.2, 4.6, p=0.06) or in the proportion with 11 or more tender points present (50%, 33%, and 16%, p=0.09).

Conclusion: In chronic HCV infection, CCP, RF, and RF IgG differ in the groups with HCV arthritis, RA, and no inflammatory arthritis. Positive fibromyalgia screen by questionnaire is more common among those with HCV arthritis, but disability, fatigue, and the number of tender points on exam are similar. Future studies are ongoing with a goal to expand our ability to characterize HCV associated arthritis.

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Antibodies to Citrullinated Peptides in Tuberculosis. Isabella Lima[1], Rodrigo Oliveira[2], Ajax Atta[2], Samyra Marchi[3], Lúcio Barbosa[3], Eliana Reis[3], Mitermayer G. Reis[3] and Mittermayer Santiago[1]. [1]Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil, [2]Universidade Federal da Bahia, Salvador, Brazil, [3]Fundação Oswaldo Cruz, Salvador, Brazil

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetric polyarthritis, rheumatoid factor positivity (RF) in the majority of patients, and bone erosions shown in radiographs. More recently, research has been conducted into anti-citrullinated peptides antibodies (ACPAs) to which greater sensitivity and specificity have been attributed than RF for diagnosis of RA. However, these antibodies have also been described in infectious diseases, particularly tuberculosis, placing the high specificity of the test in doubt. The aim of the present research was to study the presence of ACPAs in patients with tuberculosis (TB).

Methods: Patients with bacteriologically confirmed pulmonary tuberculosis, RA according to the American College of Rheumatology criteria, in addition to healthy controls (C) were included in the study. ACPAs were researched by two methods: anti-CCP (INOVA) and anti-MCV (Orgentec), in addition to RF by ELISA, in accordance with the protocol recommended by the manufacturers.

Results: The study was conducted in 50 patients with TB, 50 with RA and 20 healthy controls. Anti-CCP antibodies were found in 39 (78%) of the patients with RA, median titer: 128 U (interquartile interval: 24 to 233) whereas anti-MCV antibodies were found in (50%) of the patients with RA, median titer of 21U (interquartile interval: 10 – 218). Of the patients with TB two (4%) had positivity for anti-CCP and anti-MCV and no patient in the control group tested positive for these antibodies. Sensitivity of anti-CCP for diagnosis of RA was 78% (CI: 63 to 88%) and specificity of 97% (CI: 89 to 99%) while the sensitivity of anti-MCV was 50% (CI: 35 – 64%) and specificity of 97% (CI: 89 to 99 %). RF was positive in 40 (80%) of the patients with RA, in 30 (60%) of those with TB and in 1 (5%) of the controls. Thus, sensitivity of RF was 80% (CI: 65 to 89%) and specificity of 55% (CI: 43 to 67%) for diagnosis of RA.

Conclusion: Our findings showed high sensitivity of anti-CCP and high specificity of both anti-CCP and anti-MCV antibodies for diagnosis of RA, even in a population with high incidence of tuberculosis. The higher frequency of positivity of ACPA in TB observed in previous studies may be attributed to methodological factors.

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Intravenous Immunoglobulin in Parvovirus B19 Mediated Pure Red Cell Aplasia: A Retrospective Study in 10 Patients and a Review of 123 Cases. Yoann Crabol Hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

Background/Purpose: The efficacy of intravenous immunoglobulin (IVIg) therapy in patients with pure red cell aplasia (PRCA) related to human parvovirus B19 (HPV-B19) infection is mainly supported by cases reports and few small retrospective studies.

Methods: We conducted a retrospective study and reviewed all cases of HPV-B19 PRCA treated with IVIg in the Assistance Publique-Hôpitaux de Paris hospitals between January 2000 and December 2005. In addition all published HPV-B19 PRCA cases treated with IVIg were reviewed from 1980 to 2012.

Results: Among the 36 cases collected, PRCA was confirmed in 22, and among these 22, only 10 had proven HPV-B19 infection. 9 patients were immunocompromised including 4 who had undergone transplantation. All patients had severe anemia (hemoglobin 5.0 ± 1.9 g/dL (mean$\pm$standard deviation (SD)). Three presented severe clinical symptoms related to anemia, and six had symptoms consistent with HPV-B19 infection. HPV-B19 PCR was positive at diagnosis on bone marrow aspiration in 7/7 patients. Patients received 2.7 ± 2.1 IVIg courses at a dose of 1.3 ± 0.54 g/kg/course. Hemoglobin correction was achieved in 9/10 cases within 80 ± 54 days. The only non responsive patient had underlying myelodysplasia. Negativation of blood HPV-B19 PCR was achieved in 35 to 159 days. Side effects of IVIg were noted in 4 patients: acute reversible renal failure and pulmonary edema, 2 cases each.

Including our series, we reviewed in literature 133 patients with HPV-B19 PRCA treated with IVIg. All except 2 of them were immunocompromised, including 39 HIV infected patients and 63 solid organ transplanted. After first IVIg course, hemoglobin correction was observed in 124 cases but 42 patients relapsed, in a mean time of 4,3 months. Among the 96 patients in whom the 12 months response to IVIg treatment was available, hemoglobin correction was achieved in 45 patients while persistant anemia was noticed in 51. In univariate analysis, HIV infection and absence of anti HPV-B19 IgM at diagnosis were associated with 12 months anemia persistence. Mean first IVIg dose (2,2g/Kg) didn't differ significantly between responders and non responders. Overall survival was significantly better in responders patients. Side effects were noticed in 18 cases, including 9 cases of acute renal failure.

Conclusion: IVIg therapy is efficient and relatively safe in immunocompromised patients with HPV-B19 PRCA. Deepness of immunosuppression seems to be an important determinant of persistence response to treatment.

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ACR Poster Session A
Miscellaneous Rheumatic and Inflammatory Diseases:
Periodic Fever Syndromes
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Evaluation of Anakinra Therapy in Seven Adults After Suboptimal Response to Etanercept Therapy for Tumor Necrosis Factor Receptor-Associated Periodic Fever Syndrome. Amanda K. Ombrello[1], Patrycja M. Hoffmann[1], Anne Jones[1], Karyl S. Barron[2] and Daniel L. Kastner[1]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]NIAID-NIH, Bethesda, MD

Background/Purpose: Tumor Necrosis Factor Receptor-Associated Periodic Fever Syndrome (TRAPS) is an autoinflammatory disease inherited in an autosomal dominant fashion. TRAPS develops secondary to mutations in *TNFRSF1A*. Associated symptoms include periodic attacks of peritonitis, constipation, arthritis in large joints, arthralgia, migratory rash with underlying myalgia, periorbital edema, conjunctivitis, splenomegaly, and increased risk for AA amyloid deposition. Typically, attacks last from days to weeks. The common treatment modalities are corticosteroids, the p75:Fc fusion protein, etanercept, and IL-1 antagonists. Recent studies suggest that multiple cytokines are involved in the pathogenesis of TRAPS. To date, there are limited data comparing the efficacy of etanercept and IL-1 inhibitors in TRAPS. To explore this, we have analyzed the response of seven patients with TRAPS who were transitioned from etanercept to anakinra due to modest response while on etanercept.

Methods: CRP and ESR were measured serially in seven patients with TRAPS who had been initially treated with etanercept and were subsequently switched to anakinra. Patient records were evaluated for clinical and laboratory associations. Patients with the R92Q and P46L variants were excluded from our analysis.

Results: Seven adult patients with TRAPS were switched from etanercept to anakinra therapy due to poor symptom control and persistent elevation in inflammatory markers. Among all seven patients, the range of ESR before starting anakinra (no patients were actively flaring at the time labs were drawn) was 37–91 mm/hr and after was 5–18 mm/hr. The range of CRP before starting anakinra was 18.10–186 mg/L and after was <0.5–8.85 mg/L. The etanercept doses ranged from 50mg weekly to 75mg weekly. The anakinra doses ranged from 100mg daily to 300mg daily. One patient with AA amyloidosis had normalization of proteinuria and stabilization of creatinine within 16 months of starting anakinra. Patients reported fewer flares, shorter duration of flares, and decreased necessity for additional medications during flares (corticosteroids and narcotics).

Conclusion: Our findings indicate that in some patients, anakinra therapy is superior to etanercept therapy for TRAPS. Of the seven patients, all of them experienced clinically significant decreases in inflammatory markers including CRP and ESR as well as clinical improvement in symptoms related to TRAPS upon the initiation of anakinra.

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Safety of Canakinumab in a Large Cohort of Patients with Cryopyrin-Associated Periodic Syndrome: Results From the β-Confident Registry.
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Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS) is an extremely rare autoinflammatory disorder associated with over-production of interleukin-1β (IL-1β). Canakinumab, a fully human, selective, anti-IL-1β monoclonal antibody, is approved for the treatment of CAPS (including familial cold autoinflammatory syndrome [FCAS] and Muckle-Wells syndrome [MWS]). In order to enhance long term data, the β-Confident Registry, a global, prospective, observational study, is monitoring safety and disease progression in patients treated with canakinumab over a 5-year period.

Methods: CAPS patients receiving canakinumab as part of their routine medical care are included in the registry. Data are collected during routine clinical assessments (no mandatory visits), and the registry is updated every 6 months. Assessments include adverse events (AEs); physician's global assessment of autoinflammatory disease activity; and C-reactive protein (CRP) and serum amyloid A (SAA) levels. Data reported here are adverse events through 18 months of follow-up (cut-off date, March 2012). Additional safety data will be updated with the presentation, as available.

Results: Since December 2009, 229 patients with CAPS and other autoinflammatory diseases have enrolled. Selected baseline characteristics are shown in the Table. Overall, 59 AEs (25.8%) were reported in 29 patients (12.7%). Infections were the most common AE, with 12 AEs (5.2%) reported in 8 patients (3.5%), and upper respiratory type infections accounted for most. CNS disorders were the second most common AE, with 7 AEs (3.1%) reported in 5 patients (2.2%), and headache accounted for most. 11 Serious AEs (4.8%) were reported in 8 patients (3.5%), including 1 malignancy (rectal adenocarcinoma in a 76 yo MWS patient) and 2 infections (pneumonia in a 40 yo female CAPS patient with later hospital discharge; aseptic meningitis in a 25 yo female CINCA patient with recovery). There was only 1 permanent canakinumab discontinuation, due to patient preference.

Table. Baseline characteristics of enrolled patients

	Overall (N=229)	FCAS (n=35)	MWS (n=135)	NOMID (n=18)	Others (n=29)
Age groups:					
< 18y	74	7	33	11	18
≥ 18y	155	28	102	7	11
Sex:					
Male	107	12	68	10	15
Female	122	23	67	8	14
NLRP3 mutation, n(%)					
Yes	183 (79.9)	35 (100.0)	126 (93.3)	15 (83.3)	7 (24.1)
No	16 (7.0)	0	3 (2.2)	1 (5.6)	12 (41.4)
Unknown/missing	30 (13.1)	0	6 (4.4)	2 (11.1)	10 (34.5)
Mean disease duration, months	312	403	316	154	228
History of rash/ arthralgia/ headache/ conjunctivitis, %	79/81/55/58	100/94/54/63	81/80/59/67	89/94/89/67	76/93/38/28
Prior canakinumab treatment, n	191	28	117	17	29
Prior treatment duration, Median (range), wk.	87.3 (8.9–139.4)	85.1 (8.9–126.3)	87.3 (8.9–139.4)	82.9 (43.9–122.0)	65.4 (13.3–139.4)
Prior number of injections/ patients, mean±SD	6.4±4.4	4.3±2.7	6.8±3.9	8.6±5.2	6.1±6.2

FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease.

Conclusion: Consistent with the earlier 12-month assessment, the safety of canakinumab treatment at 18 months was maintained and no unexpected safety signals were reported.

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Thiopurine S-Methyltransferase Levels in Patients with Behçet's Disease.
Hakan Emmungil[1], Melike Kalfa[1], Raika Durusoy[2], Figen Yargucu Zihni[1], Gokhan Keser[1] and Kenan Aksu[1]. [1]Dept. of Internal Medicine, Division of Rheumatology, Ege University, Izmir, Turkey, [2]Department of Public Health, Ege University, Izmir, Turkey

Background/Purpose: Azathioprine (AZA) is an immunosuppressive agent which is widely used not only for the treatment of Behcet's disease (BD), but also for the treatment of many systemic inflammatory diseases including systemic lupus erythematosus (SLE) and various systemic vasculitis. Thiopurine S-methyltransferase (TPMT) is a genetically moderated key enzyme involved in the metabolism of AZA. Low TPMT levels may cause a tendency for AZA-related adverse effects. In the present study, TPMT levels in patients with BD were compared with healthy controls, as well as with patients with SLE or with systemic vasculitis, as disease control groups. We investigated the relationship between TPMT levels and AZA-related adverse effects, and also whether TPMT levels were affected by AZA treatment.

Methods: In the present cross-sectional study, 101 patients with BD (M/F: 61/40; mean age 42.15±10.33 years), 74 patients with SLE (M/F: 11/63; mean age: 39.86±11.69 years), 44 patients with systemic vasculitis (M/F: 21/23; mean age 47.09±13.36 years) and 101 healthy controls, age and sex matched with BD were included. Detailed past medical data were available for all patients. The TPMT activity in red blood cells was measured using ELISA. AZA was stopped three days before measurements in patients already receiving this drug. Data were presented as mean ± SD. Mean TPMT levels (mIU/ml) were compared with Student's t, Mann Whitney U and Kruskal Wallis tests, and Receiver Operating Characteristic (ROC) analysis was used to determine whether TPMT could be used to predict toxicity.

Results: Mean TPMT levels in BD (22.80±13.81) were comparable with healthy controls (22.71±13.49), but significantly lower than in patients with SLE (29.37±11.39) (p<0.001). There were 130 patients, 77 with BD, 35 with SLE, and 18 with systemic vasculitis who had used or have been currently using AZA treatment. TPMT levels were not significantly different between patients with and without AZA treatment. AZA-related adverse effects involving gastrointestinal tract, liver and bone marrow were identified in 8 out of 130 patients (5 with BD and 3 with SLE). Although the mean TPMT levels were significantly lower in patients suffering from AZA-related adverse effects (14.08±9.49) than in patients without adverse effects (25.62±12.68) (p=0.013), a cut-off value for predicting AZA-related adverse effects could not be determined with ROC analysis (Area under the curve: 0.249).

Conclusion: This was the first study evaluating TPMT activity in Turkish adult population. Despite more frequent AZA-related adverse effects in the presence of low TPMT levels, absence of a certain cut-off value for TPMT levels implicate that variation in the level of this enzyme may not be the only factor determining AZA-related adverse events. Clinical relevance of TPMT testing should further be determined with larger prospective studies.

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Comprehensive Analysis of Protein Expression in Peripheral Blood Mononuclear Cells From Patients with Behçet's Disease.
Takuya Yoshioka[1], Manae Kurokawa[1], Yukiko Takakuwa[1], Hiromasa Nakano[2], Seido Ooka[2], Nobuko Iizuka[1], Toshiyuki Sato[1], Mitsumi Arito[1], Kouhei Nagai[3], Kazuki Okamoto[1], Naoya Suematsu[1], Noboru Suzuki[1], Shoichi Ozaki[2] and Tomohiro Kato[1]. [1]St. Marianna Univ School Med, Kawasaki, Japan, [2]St. Marianna University School of Medicine, Kawasaki, Japan, [3]Kinki Univ., Kinokawa, Japan

Background/Purpose: To elucidate the pathophysiology of Behcet's disease (BD) and to establish biomarkers for the disease, we comprehensively analyzed protein expression of peripheral blood mononuclear cells (PBMCs).

Methods: PBMCs were obtained from 16 patients with BD, 16 patients with rheumatoid arthritis (RA), and 16 healthy control (HC) subjects. Proteins, extracted from the PBMCs, were separated by 2-dimensional differential gel electrophoresis. Proteins were identified by mass spectrometry.

Results: As a result, a total of 563 protein spots were detected. Compared to HC, 14 spots showed significantly higher intensity with more than 1.2 folds, and 9 spots showed significantly lower intensity with less than 1/1.2 folds in BD. The spots with higher intensity included proteins involved in T cell activation, metabolism of pre-mRNAs, and protein trafficking. The spots with lower intensity included cytoskeltal proteins. Similarly, compared to RA, 98 spots showed significantly higher intensity with more than 1.2 folds, and 17 spots showed significantly lower intensity with less than 1/1.2 folds in BD. The spots with higher intensity in BD than in RA included proteins associated with bacteriolysis, oxidation/reduction, activation of transcription, regulation of kinases, and modulation of glycosylation. We completely discriminated the BD patients from the HC subjects and from the RA patients by multivariate analyses of 23 and 35 protein spots, respectively. The analyses using only 1–3 protein spots provided areas under the receiver operating characteristic curves of 0.797–0.898 in the discrimination of the BD patients from the HC subjects, from the RA patients, and from the both HC subjects and RA patients.

Conclusion: Taken together, the protein spots which contributed to the discrimination could be biomarker candidates for BD. In addition PBMC-derived proteins, expression of which was significantly altered in BD, may be involved in the pathophysiology of BD.

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A Strong Association Between HLA-A*26 and Behçet's Syndrome in Japanese Patients: From Two-Center Cohort Study of Behçet's Syndrome. Tatsuo Kobayashi[1], Mitsumasa Kishimoto[2], Kazuki Yoshida[1], Yuri Ohara[2], Hiroto Nakano[1], Masahiro Minoda[1], Hideto Oshikawa[1] and Kazuo Matsui[1]. [1]Kameda Medical Center, Kamogawa City, Chiba, Japan, [2]St. Luke's International Hospital, Chuo-ku, Tokyo, Japan

Background/Purpose: An association between Behçet's Syndrome (BS) and HLA-B*51 is widely reported among many different ethnic groups. Recently, a few reports from Taiwan, Greece and Japan were published that indicated HLA-A*26 is also associated with BS independently from HLA-B*51, but these studies may have some limitations. These limitations include small numbers, were not written in English, only analyzed BS with ocular lesions, or were mainly led by ophthalmologists. Therefore, the association between HLA-A*26 and BS still remains unclear. For this report we studied phenotype frequencies (PF) of HLA-A and HLA-B in Japanese BS patients seen by not only ophthalmologists but also experts in different specialties, mainly rheumatologists.

Methods: All BS patients seen at tertiary care centers of Kameda Medical Center and St. Luke's International Hospital in Japan between 2003–2012 were included in the analysis. Patients were mainly seen by rheumatologists, followed by neurologists, dermatologists, ophthalmologists, and gastroenterologists. The diagnosis of BS was made on clinical manifestation and expert opinions. Charts were reviewed for DNA typing of HLA alleles and disease manifestations. To compare PF, we adopted data from the central bone marrow data center registry of Japanese Red Cross Society (n=263016) as a control for the general population in Japan. The significance of the distribution of phenotypes was analyzed by one-sample proportions test and the primary P-values were corrected by using the Bonferroni correction (Pc). We analyzed manifestations by Fisher's exact probability test or t-test.

Results: As for HLA-A and HLA-B, 80 and 81 patients were tested respectively (88 patients were eligible for HLA-B*51 analysis) and 6 HLA-A and 19 HLA-B alleles were detected. Of all, PF of HLA-A*26 was significantly higher than the general Japanese population (42.5% vs. 22.6%, Pc=8.0 × 10^{-4}). The same is true for HLA-B*51 (44.3% vs. 17.1%, Pc=7.1×10^{-10}). No significant differences were seen in other HLA alleles. Secondly, we analyzed the difference in manifestations of BS patients stratified by HLA-A*26 or HLA-B*51. No significant difference was seen except for age of onset, which was younger in patients with HLA-B*51 than without it (mean±SD (years): 34.1±13.6 vs. 41.3±17.9, P=0.041). There is also a tendency that gastrointestinal (GI) lesions are less likely for patients with HLA-B*51 (28.2% vs. 46.9%, P=0.082). We detected no significant

difference of manifestations between HLA-A*26 positive patients and negative patients.

Table 1. Phenotype frequency of HLA-A and HLA-B in BS patients compared with the general population in Japan (extracted data were shown)

	PF of BS patients (%)	PF of the general Japanese (%)	P-value	Pc-value
HLA-A*02	46.3	42.9	0.62	
-A*24	58.8	60.1	0.83	
-A*26	42.5	22.6	3.6 × 10^{-5}	8.0 × 10^{-4}
-A*33	58.8	60.1	0.06	
HLA-B*51	44.3	17.1	3.2 × 10^{-11}	7.1 × 10^{-10}
-B*52	16.1	21.0	0.34	
-B*54	16.1	14.6	0.83	

Conclusion: HLA-A*26 is found to be alleles for BS susceptibility among BS patients not only with ocular lesions but also various manifestations in Japan. Moreover, our study also showed that patients with HLA-B*51 have younger onset and a lower tendency of GI lesions.

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The Retrospective Review of 39 Intestinal Behçet's Disease Focusing On the Requirement for the Immunosuppresive Drugs Other Than Corticosteroid. Yoshitaka Kimura[1], Kurumi Asako[1], Hirotoshi Kikuchi[2], Akiteru Takeuchi[3] and Hajime Kono[4]. [1]Department of Internal Medicine, Teikyo University school of medecine, Tokyo, Japan, [2]Teikyo University, Tokyo, Japan, [3]6-7-8 Arakawa, Tokyo, Japan, [4]Teikyo University School of Medicine, Tokyo, Japan

Background/Purpose: To examine the demography, clinical characteristics, features of intestinal lesions, treatment, and prognosis in patients with the intestinal Behçet's disease currently followed at a university hospital in Tokyo especially focusing on the factors that correlated with additional immunosuppresive therapies to corticosteroid.

Methods: The records of 39 patients with intestinal Behçet's disease were retrospectively reviewed who were treated at the Teikyo University Hospital between August 1st, 2011 and March 31th, 2012. We compared the well-controlled patients treated only with steroid or 5-ASA/SASP, with the poorly-controlled patients who required additional immunosuppressive drugs or anti-TNFa antibodies.

Results: The patients were consisted of 26 male and 13 female with the average age of 56.8 ± 13.1 years old. The mean age at onset of Behçet's disease was 35.5 ± 11.2 years. They developed the intestinal lesions at mean age 41.3 ± 13.0 years. HLA-B51 or HLA-A26 were positive in 35.4% or 32.3%, respectively. Seventeen cases were complete Behchet's and 22 were incomplete type. Almost all patients had oral ulcerations and skin lesions. Twenty five cases had arthritis, 7 had epididymitis. Vascular and central nervous system involvements were seen in 8 and 2 patients, respectively. The most frequent initial symptom for intestinal Behcet's was abdominal pain (22 cases). Other initial symptoms were melena/bloody stool (16 cases) and diarrhea (9 cases), fever (5 cases), dysphagia (2 cases). The intestinal lesions existed in various lesions of the gastrointestinal tract including esophagus (3 cases) and small intestine (4 cases), ileo-cecal area (31 cases), ascending colon (7 cases), transverse colon (3 cases), descending colon (3 cases), sigmoid colon (2 cases), rectum (5 cases). They (28 cases) were treated with predonisolone of the average 32.5mg daily as the initial dosage. Thirty two patients were treated 5-ASA or SASP. Fourteen cases were added with methotrexate, and 3 cases with cyclosporine. Infliximab was administrated in 6 cases. In the patients who needed immunosuppressive drugs or anti-TNFa antibodies other than steroids, we found the significantly higher HLA-B51 positivity (42%) and higher CRP at the beginning of treatment (10.5±8.5 mg/dL). In addition, the poorly responded patients with corticosteroid and sulfasalazopyridine showed more frequent atypical intestinal lesions.

Conclusion: The restrospective review revealed that the requirement for the additional immunosuppresive therapies could have a linkage to the HLA-B51 in patietnts with intestinal Bachet's disease.

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Long-Term Efficacy and Safety of Tumour Necrosis Factor Antagonists for Patients with Behçet's Disease with Uveitis As Main Involvement. M. Victoria Hernández, Marina Mesquida, Gerard Espinosa, Victor Llorens, Laura Pelegrin, Juan D. Cañete, Ricard Cervera, Alfredo M. Adan and Raimon Sanmarti. Hospital Clínic of Barcelona, Barcelona, Spain

Background/Purpose: To assess the long-term efficacy and safety of tumour necrosis factor (TNF) antagonists (infliximab [IFX], adalimumab [ADA] and golimumab) for the treatment of patients with Behçet's disease (BD) with uveitis who failed to respond or did not tolerate conventional treatment.

Methods: Retrospective study of patients with BD and uveitis treated with anti-TNF therapy in a tertiary reference hospital. Data analyzed were: demographic characteristics; disease duration and type of uveitis; visual acuity; previous treatments; dosage, type and duration of biological agent used; outcome (remission, loss of efficacy, adverse events). The characteristics of uveitis, including the degree of inflammation and disease course, were analyzed according to the definitions of the Standardization of Uveitis Nomenclature (SUN) criteria.

Results: We included 15 patients (8 male, mean age 36.9 ± 8.3 years) with BD and severe intraocular inflammation. Mean disease duration was 9.6 ± 5.7 years; 66.6% had panuveitis and 26.6% posterior uveitis. All patients had previously received oral glucocorticoids (GC) and 60% had received > 2 immunosuppressive (IMS) drugs. Thirteen patients were treated with IFX and 2 with ADA as initial anti-TNF therapy. Six of 13 patients treated with IFX were switched to another anti-TNF agent due to adverse events or loss of efficacy: 5/13 were switched to ADA and 1/13 was switched to golimumab. Globally, 7/15 patients were treated with ADA. IFX was infused at a dose of 5 mg/kg for a mean of 10.4 months (range: 2–24). ADA 40 mg was administered subcutaneously every 2 weeks for a mean of 29 months (range: 9–44). The mean follow-up was 37 months (range: 10–72). Twelve (80%) patients achieved remission. Three patients were able to discontinue all systemic IMS and GC drugs. Best corrected visual acuity remained stable or improved in 27/29 eyes. Three serious adverse events requiring IFX withdrawal were reported: 1 severe infusion reaction, 1 disseminated tuberculosis, and 1 prostatitis.

Conclusion: Infliximab and adalimumab are effective biologic agents for the treatment of uveitis in patients with Behçet's disease, achieving remission in 80% of patients. The treatments were, generally, well tolerated and only three patients required withdrawal.

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Long-Term Infliximab Therapy in Patients with Behcet's Disease Is Well Tolerated without Increasing Risk of Serious Infections. Sho Ueda[1], Hiroshi Tsukamoto[1], Yasushi Inoue[1], Masahiro Ayano[1], Satomi Hisamoto[1], Naoko Ueki[1], Atsushi Tanaka[1], Shun-ichiro Ohta[1], Naoyasu Ueda[1], Yojiro Arinobu[1], Hiroaki Niiro[1], Takahiko Horiuchi[1] and Koichi Akashi[1]. [1]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Background/Purpose: Infliximab (IFX) is a monoclonal antibody against tumor necrosis factor-a (TNF-a) and is increasingly used in various immune-related diseases including rheumatoid arthritis (RA), ankylosing spondylitis, inflammatory bowel diseases and Behcet's disease (BD). Among patients with RA, serious hospitalized infection rates were previously reported as 8.16 (IFX) and 7.78 (nonbiological regimens) per 100 person-years and 2-year continuation rates of IFX were previously reported as around 40%. On the other hand, there are few reports regarding the long-term safety and persistent response of IFX therapy in BD patients. It is of importance to assess the safety and the efficacy of IFX for BD, since the backgrounds of these diseases are different.

Methods: We retrospectively studied consecutive 109 patients who met the established criteria by the Behcet's Disease Research Committee of Japan for the diagnosis of BD, and were continuously followed up between January 2007 and December 2011 in a single center (Department of Clinical Immunology and Rheumatology/Infectious Disease of Kyushu University Hospital). During this period, 39 patients with BD received IFX therapy and 70 did not. Among the 39 patients, 36 were treated with IFX for uveitis. Serious hospitalized infections and the discontinuations of IFX were investigated based on medical records. The frequency data were compared using Chi-square test. The continuous data were compared using Wilcoxon non-parametric tests. The time-course data were analyzed by Kaplan-Meier method.

Results: Between patients with and without IFX, there were no significant differences in median [IQR] age (37 [26–42] vs 43 [32–54] years), median duration of disease (4.1 [0.7–7.8] vs 4.2 [1.0–11.0] years), median follow-up period (2.4 [1.4–3.9] vs 2.4 [0.9–5.0] years), and percentage of concomitant prednisolone (>10mg/day) user (10.3% vs 14.3%). On the other hand, significant ($p<0.01$) differences were observed in the proportion of males (76.9% vs 41.4%), manifestation of uveitis (92.3% vs 37.1%) and genital ulcers (48.7% vs 78.6%), and concomitant use of immunosuppressive drugs (41.0% vs 17.1%). Serious infection rates were comparable between two group; 2.01 with IFX and 1.54 without IFX per 100 person-years. Among BD patients with IFX therapy, bacterial colitis and pelvic inflammatory disease occurred in 2 patients and both occurred within 1 year from initiation of IFX therapy. IFX infusion was interrupted in 5 of the 39 patients due to adverse events (n=3) and removals (n=2). Two-year continuation rate was estimated as 85.3%.

Conclusion: In the treatment of BD, IFX therapy was not associated with an increased risk of hospitalizations for serious infections. In addition, 2-year continuation rate of IFX was considerably higher than that previously reported in RA patients.

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Effect of Colchicine On Cholesterol Levels in Patients with Familial Mediterranean Fever and Behçet's Syndrome. Serda L Ugurlu[1], Emire Seyahi[2], Idil Hanci[1], Huri Ozdogan[3], Seval Masatlioglu-Pehlivan[4] and Hasan Yazici[5]. [1]MD, Istanbul, Turkey, [2]Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey, [3]MD, Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [4]MD, Rheumatology, Istanbul, Turkey, [5]Istanbul University, Cerrahpasa Medical School, Rheumatology, Istanbul, Turkey

Background/Purpose: We and others have previously shown that patients with Familial Mediterranean Fever (FMF) had low cholesterol levels when compared to healthy controls (1–2). The causes of this abnormality are not understood. It could be due to an inherent effect of FMF or due to a lipid lowering effect of colchicine. We conducted a 12 week study to determine whether colchicine would decrease serum lipid levels in patients with FMF and Behcet syndrome (BS).

Methods: Blood cholesterol and triglycerides levels were measured in 24 patients with FMF (11 M, 13 F) and 16 (8 M, 8 F) patients with BS who were registered at the outpatient clinic of Cerrahpasa Medical Faculty. All patients were naive to colchicine or immunosuppressive treatment or any other lipid lowering drugs at study entry. Blood cholesterol and triglycerides levels were measured again after 12 weeks of colchicine 1.5 mg daily.

Results: There were 19 (8 M, 11 F) patients with FMF and 15 (7 M, 8 F) patients with BS who completed 12 weeks period. Patients with FMF were (mean age: 33.8 ± 14.1 years) significantly younger than BS patients (mean age: 36.5 ± 9.5) (P = 0.001). Colchicine did not change significantly cholesterol and triglycerides levels in patients with FMF (Table). This was also true for patients with BS (Table). Mild diarrhea was observed in 2 patients with FMF and in 1 with BS.

Table. Lipid levels before and after colchicine treatment

	FMF (n = 19)			BS (n = 15)		
	Before colchicine	After colchicine	P	Before colchicine	After colchicine	P
T. cholesterol	168.95 ± 77.1	181.26 ± 48.3	0.58	181.43 ± 50.9	172.3 ± 44.4	0.53
Triglycerides	122.2 ± 82.26	128.21 ± 69.56	0.75	111.7 ± 62.9	106.5 ± 52.1	0.18
LDL cholesterol	120.37 ± 44.3	112.16 ± 39.9	0.35	115.14 ± 38.43	106.1 ± 39.7	0.85
HDL cholesterol	42.11 ± 13.4	47.11 ± 10.9	0.1	47.93 ± 9.205	48.3 ± 9.9	0.3

Conclusion: This study provided no evidence that colchicine changes lipid levels in patients with FMF and BS.

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Etiology of Uveitis: A Hospital-Based Study in a Referral Centre. Claudia Ferrari[1], Rosaria Talarico[1], Michele Figus[2], Chiara Stagnaro[1], Anna d'Ascanio[1] and Stefano Bombardieri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Ophthalmology Unit, University of Pisa, Pisa, Italy

Background/Purpose: Defined as an intraocular inflammation, uveitis may be associated to a systemic disease or represent an isolated entity. It affects people from all parts of the world, and it is a significant cause of severe visual impairment, accounting for 10% of blindness in the Western world. Screening for associated extra-ocular manifestations is mandatory in uveitis patients. The aim of the study was to analyse the etiology and the pattern of uveitis in a cohort of patients followed in the context of a *uveitis clinic* of a rheumatologic referral centre

Methods: The study included 120 patients (M/F: 86/34; mean age at disease onset 35 years) with uveitis examined from January 2009 to May 2012. All patients had a comprehensive rheumatologic and ophtalmological evaluation, including: clinical history, Snellen visual acuity, slit-lamp examination, applanation tonometry, dilated fundus examination and/or visual field and/or fluorescein-angiography and/or optical coherence tomography. Moreover, all patients underwent the standard protocol of serological examinations for uveitis, including routine examination, acute phase reactants, HLA typing, serum fluorescent treponemal antibody absorption detection, main viral and bacterial screening, serum angiotensin-converting enzyme, serum lysozyme, tuberculin reaction tests, non-organ specific auto antibodies profile and, when required, chest X-Ray.

Results: Seventy percent of patients referred by ophthalmologists, 27% patients directly attending our department and 3% referred by general practitioners. Posterior uveitis was the most common feature (46%), followed by anterior uveitis (28%), panuveitis (16%), and intermediate uveitis (10%). For 57 of 120 (47%) patients with uveitis, a specific aetiologic diagnosis was established, while 53% of patients were found to have idiopathic uveitis. In the posterior uveitis group (n=55), a specific diagnosis was made for 21 patients (38%); the most frequent forms were represented by toxoplasmosis (48%) and Behçet's disease (25%). In the anterior uveitis group (n=34), a specific diagnosis was made in 19 patients (56%). The most common diagnoses included herpetic infection (53%), Fuchs' heterochromic iridocyclitis (22%), HLA-B27-positive anterior uveitis ± associated to a spondylarthropathy (20%). Among patients with panuveitis (n=19), 15 (79%) had a specific aetiologic diagnosis, in the majority of cases linked to Behçet's disease (88%). In the intermediate uveitis group (n=12) only two etiologies were identified: sarcoidosis and multiple sclerosis.

Conclusion: In this hospital-based study, the most common cause of uveitis is idiopathic. However, a multi-disciplinary approach may surely improve the diagnosis of uveitis secondary to autoimmune diseases.

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Pedal Swelling As a Characteristic Phenotype of the New Category of Autoinflammatory Disease Associated with NOD2 Gene Mutations. Qingping Yao. Cleveland Clinic, Cleveland, OH

Background/Purpose: Autoinflammatory diseases are characterized by seemingly unprovoked episodes of inflammation, without high titer autoantibodies or antigen specific T cells, and derive from genetic variants of the innate immune system. We previously reported a case series of a new autoinflammatory disease associated with nucleotide oligomerization domain (NOD2) gene mutations. Herein, I report a characteristic phenotype as an addition to further define this disease entity.

Methods: Six patients with pedal swelling and other autoinflammatory phenotypes were enrolled between January 2009 and April 2012. These patients were tested for NOD2 gene mutations.

Results: All 6 patients were non-Jewish Caucasians, with 5 female, 1 male. The mean age at disease diagnosis was 49 years (range 29–63) and disease duration was 3.9 years (range 0.4–10) (Table 1). These patients usually presented with weight loss, self limiting fever, dermatitis, and inflammatory polyarthritis/polyarthralgia. Apart from previously reported characteristic spongiotic dermatitis, all patients also shared a prominent clinical feature: ankle/foot swelling/pain (Figure 1) which was primarily unilateral. There was no convincing evidence of inflammatory bowel disease, sarcoidosis, or Blau's syndrome. All patients carried the NOD2 gene mutations, with R702W/IVS8^{+158} in 4 and 2 having rare variants R703C and T189/wild type.

Conclusion: The current cohort has affirmed and extended that dermatitis, pedal swelling and positive NOD2 mutations may characterize this entity.

Disclosure: **Q. Yao**, None;

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NLRP3 Gene Analysis for Patients with Schnitzler's Syndrome. Cong-Qiu Chu[1], Carrie R. Austin[2], Trudy M. Doyle[2], Kelley A. Goodwin[2], Noha El Torgomen[2], Regina Treudler[3] and Tammy M. Martin[4]. [1]Oregon Health & Science Univ and Portland VA Medical Center, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]Universitätsklinikum Leipzig AöR, Leipzig, Germany, [4]Oregon Health & Science Univ, Portland, OR

Background/Purpose: Schnitzler's syndrome is characterized by chronic urticaria, intermittent fever, arthralgia, bone pain, gammopathy and marked systemic inflammation. The striking response to IL-1 blockade suggests that Schnitzler's syndrome is an IL-1 mediated condition of the expanding spectrum of systemic autoinflammatory disorders. However, the mechanism leading to the increased IL-1 activity has remained elusive. We aim to identify genetic predisposition in patients with Schnitzler's syndrome.

Methods: Genomic DNA was extracted from peripheral blood mononuclear cells from 4 patients with a clinical diagnosis of Schnitzler's syndrome. DNA sequencing was performed in both directions of NLRP3 gene regions, including exon 3 which contains the majority of mutations associated with the cryopyrinopathies. Genetic data of patients was compared with the reference sequence for mutations.

Results: Of the 4 patients with Schnitzler's syndrome, 2 had classical findings of monoclonal IgM, kappa; one with polyclonal IgA; and one with polyclonal IgG and IgA. All of the 4 patients were refractory to non-biologic immunosuppressive treatment but achieved sustained clinical remission with daily use of anakinra. DNA sequence analysis of NLRP3 revealed a disease-associated mutation encoding the V198M substitution in the patient with polyclonal IgG and IgA. However, this mutation was not found in the other 3 patients. No other disease-associated mutations were identified in NLRP3 for this patient or in the other 3 patients.

Conclusion: Genetic studies of Schnitzler's syndrome have been scanty primarily due to the rarity of the condition and the results have been mixed. Our 4 patients consist of classical (2 cases) and atypical (2 cases) Schnitzler's syndrome. The V198M mutation was found in one with atypical Schnitzler's syndrome (polyclonal IgG and IgA). Interestingly, this mutation was previously reported in one patient with classical Schnitzler's syndrome with monoclonal IgM, kappa (1). However, another genetic study on a patient with classical Schnitzler's syndrome found no mutations in NLRP3 (2). The distinct feature of Schnitzler's syndrome is its gammopathy which is poorly responsive to IL-1 blockade suggesting that IL-1 may not mediate the gammopathy. Complete analysis of NLRP3 exons and their flanking regions in this cohort is underway as disease-associated mutations outside of exon 3 have been reported and there may be as yet unknown mutations involved in this phenotype. The presence of an NLRP3 mutation in another patient with Schnitzler's syndrome confirms the finding that this disorder is inflammasome-mediated.

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Analysis of Genes Involved in Autoinflammatory Diseases in Adult Onset Still's Disease.

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Background/Purpose: Adult Onset Still's Disease (AOSD) is a systemic inflammatory disease characterized by fever, skin rash, articular involvement, lymphadenopathy, hepatosplenomegaly and serositis. Due to the absence of autoantibodies and autoantigen-specific T cells and the efficacy of treatment with IL-1β blocking agents, AOSD has been considered an autoinflammatory disease. Some entities of this group are inherited diseases caused by mutations in genes related with the processing of IL-1β. The cryopyrinopathies are caused by heterozygous gain-of-function mutations in NLRP3 gene (Nucleotide-binding domain Leucine Rich repeat family Pyrin domain containing 3) and share some clinical features with AOSD like fever, cutaneous and musculoskeletal involvement and serositis. Heterozygous gain-of-function NOD2 (Nucleotide Oligomerization Domain 2) mutations are associated with Blau syndrome, which is characterized by uveitis and, like AOSD, fever and chronic arthritis. The aim of this study is to analyze the potential involvement of mutations in the NALP3 and NOD2 genes in AOSD patients.

Methods: Eighteen patients with AOSD from two hospitals in Spain were enrolled. All the patients fulfilled the Yamaguchi criteria and informed consent was obtained from each participant. The study protocol was approved by the ethics committee from the Hospital Universitari Germans Trias i Pujol. Genomic DNA was extracted from whole blood using the Roche MagNAPure Compact (Roche Diagnostics, Indianapolis, IN). Exon 4 of NOD2 gene (GeneBank NM 022162.1) and exon 3 of NLRP3 gene (GeneBank NM 001243133.1) were amplified by polymerase chain reaction. Bidirectional fluorescence sequencing was performed using an ABI BigDye Terminator version 3.1 Cycle Sequencing kit and run on a 3730XL DNA Analyzer. As control population, the European Caucasic samples from 1000 Genome Project (n=379) were used. Differences in frequencies of alleles and genotypes between AOSD patients and controls were examined using the Chi-squared method, Fisher's exact test and logistic regression with Statistical Analysis Software (SAS).

Results: Most AOSD patients showed no pathogenic variants in NALP3 or NOD2 gene. Of interest, two patients were carriers of a NOD2 polymorphism associated with Crohn disease (p.R702W, rs206684) without having any symptom suggestive of inflammatory bowel disease, and another one was carrier of a rare NOD2 variant of uncertain significance that was previously reported in a patient with spondyloarthritis (p.R791Q, rs104895464). In the NALP3 analysis, one patient was carrier of the variant of uncertain significance p.V198M (rs121908147).

Conclusion: AOSD has some similarities with inherited autoinflammatory syndromes like the clinical presentation and the efficacy of treatment with IL-1β blocking agents. Although in our series none of the AOSD patients carried a true disease-associated mutation, the possibility of an inherited autoinflammatory disease should be considered in the differential diagnosis and ruled out by means of genetic analysis.

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Clinical and Laboratory Findings in A Cohort of Italian Patients with Adult Onset Still'S Disease: The Role of IL-18 As A Disease Biomarker.

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Background/Purpose: Adult Onset Still's Disease (AOSD) is a systemic inflammatory syndrome driven by interleukin (IL)-18. Since differential diagnosis between AOSD, sepsis and other inflammatory conditions can be difficult, we aimed to investigate IL-18 serum levels in AOSD and to assess whether this cytokine could be used as disease biomarker.

Methods: Patients with AOSD (Yamaguchy criteria) were evaluated. Disease activity was assessed with Pouchot's and Rau's criteria and patients were defined active if they had ≥4 criteria. Serum IL-18 levels were detected by ELISA (Immuno-Pharmacology Research, Italy) in patients with AOSD and sepsis (according to ACCP/SCCM Consensus Conference). Furthermore, patients with Rheumatoid Arthritis (RA), Sjögren Syndrome (SS), Systemic Lupus Erythematosus (SLE) and healthy subjects (NHS) served as controls. Area under the receiver operating curve (ROC-AUC) analysis was used to evaluate the diagnostic utility of the IL-18.

Results: Clinical and laboratory features of 50 AOSD patients are described in table.

AOSD patients		N=50
Male/Female		23/27
Age at onset [mean (range), years]		34 (17–64)
Symptoms	**N**	**%**
Fever	50	100.0
Arthralgia	39	78.0
Rash	38	76.0
Sore Throat	30	60.0
Lymphadenopathy	29	58.0
Arthritis	24	48.0
Hepatomegaly	19	38.0
Splenomegaly	19	38.0
Myalgia	15	30.0
Pleuritis	3	6.0
Pericarditis	2	4.0
Abdominal Pain	1	2.0
Laboratory features	**mean**	**range**
ESR (mm/h)	74.8	20–124
CRP (mg/dl)	84.8	3–354
WBC (cells/μl)	19004.7	8600–35900
Ferritin (ng/ml)	5582	69–32800
AST (UI/l)	67.4	8–404
ALT (UI/l)	91.6	4–535

Two patients experienced DIC, one with fatal outcome. Considering Pouchot's and Rau's criteria, active patients were 18/50 (36%) and 21/50 (42%), respectively. Mean ferritin was higher in active than non active patients (p=0.001). IL-18 was detected in 30 patients with AOSD, 7 with sepsis, 21 with RA, 21 with SS, 20 with SLE and 21 NHS. IL-18 significantly correlates with AOSD activity score (p<0.0001) and ferritin level (p=0.0127). Mean IL-18 was significantly higher in AOSD than in sepsis [1298.7 pg/ml (range 0–6015) vs 113.5 pg/ml (range 52–328), p=0.008]. The ROC-AUC analysis for IL-18 serum levels between AOSD and sepsis was 0.712 [cut-off=179 pg/ml, specificity (sp)=69.7%, sensitivity (se)=87.5%, likelihood (LR)=2.89]. IL-18 serum levels were significantly higher in active than non active patients and sepsis (p=0.0039 and p=0.007, respectively). The ROC-AUC analysis for IL-18 between active AOSD and sepsis was 0.845 (cut-off=223 pg/ml, sp=87.5%, se=80.9%, LR=6.48). The ROC-AUC analyses for IL-18 between AOSD patients and other groups (NHS, RA, SS, SLE) were respectively 0.853 / 0.720 / 0.750 / 0.791 (NHS: cut-off=293.7 pg/ml, sp=85.19%, se=85.71%, LR=5.79; RA: cut-off=335.5 pg/ml, sp=81.48%, se=52.38%, LR=2.83; SS: cut-off=424.3 pg/ml, sp=74.07%, se=66.67%, LR=2.57; SLE: cut-off =268.2 pg/ml, sp=85.19%, se=60%, LR=4.05).

Conclusion: The clinical and laboratory findings of our cohort overlap with the literature. Ferritin parallels disease activity, suggesting that the Rau's criteria could be more accurate. AOSD prognosis is usually favourable but severe complications may occur. Finally, a significant difference in IL-18 serum levels between patients with AOSD and sepsis was observed, and IL-18 can represent a useful biomarker in the differential diagnosis between AOSD and other inflammatory conditions. Moreover, IL-18 serum levels reflects disease activity.

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Tocilizumab in Adult Still's Disease: The Israeli Experience. Ori El-kayam[1], Nizar Jiries[2], Zvi Dranitzki[3], Shaye Kivity[4], Merav Lidar[5], Ofer Levy[6], Mahmoud Abu-Shakra[7], Hagit Sarvagil-Maman[1], Hagit Padova[1], Dan Caspi[8] and Itzhak Rosner[9]. [1]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Bnai Zion Medical Center, Israel, [3]Hadassah hebrew university, Jerusalem, Israel, [4]Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, Tel-Hashomer, Israel, [5]Sheba Medical Center, Ramat Gan, Israel, [6]Asaf Harofe Medical Center, [7]Soroka Medical Centre and Ben Gurion University, Beer-Sheva, Israel, [8]Tel Aviv, Israel, [9]Bnai Zion Medical Center / Technion Faculty of Medicine, Haifa, Israel

Background/Purpose: The objective of this study was to review the clinical and laboratory characteristics of patients with adult's Still disease treated with tocilizumab (TCZ) in Israel.

Methods: Israeli rheumatologists who have ever treated a patient suffering from adult Still's disease with TCZ were asked to review their files with special emphasis on the symptoms of the disease (arthralgias/arthritis, fever, sore throat, pleura-pericarditis, hepatitis), number of tender and swollen joints, ESR, CRP and dosage of prednisone at the initiation of TCZ, after 6 months and at the end of follow-up.

Results:: 11 cases were ascertained. All the patients fullfilled the Yamagushi classification criteria for adult Still's disease: 7 men, aged 33 ± 12, mean duration of disease of 7 years (range 1–25 years). Until treatment with TCZ, the mean number of disease modifying drugs, including $TNF\alpha$ blockers was 4; 7 out of 11 have previously failed $TNF\alpha$ blockers. TCZ was administered at a dosage of 8 mg/kg every 4 weeks in 8 patients and every 2 weeks in 3 patients. The mean follow- up was 15 months. All the patients, except 2, completed at least 6 months of treatment. At the start of TCZ treatment, despite a mean prednisone of $31mg \pm 28$ mg/d, all the patients reported joint pain; the mean tender and swollen joints count was 12 and 8, respectively. In addition, fever was reported in 7 patients, rash in 5, pleuritis in 3 and hepatitis in 2.The mean ESR and CRP were 65 and 13, respectively. After 6 months of treatment and at the end of follow-up, the number of swollen and tender joints, the ESR and CRP and the dosage of prednisone decreased significantly (Table 1). At the end of follow up, only 2 patients still complained of mild arthralgias and none reported systemic symptoms.

	Start of TCZ	After 6 months	End of follow-up
Swollen joints count	8 ± 6	1.25 ± 1.7*	0.7 ± 1.2*
Tender joints count	11.9 ± 7.7	2.25 ± 2*	1.2 ± 0,7*
ESR	65 ± 32	3.4 ± 1.5*	4.3 ± 2.26*
CRP (mg/dl)	13 ± 17	0.47 ± 0.17*	0.46 ± 0.6*
Prednisone dosage (mg/d)	31 ± 28	4.8 ± 3.5*	3.5 ± 5*

* Mean±SD; p<0.05
Mean; SD

Conclusion: TCZ is extremely efficacious in adult Still's disease. Although randomized controlled studies are needed to confirm this observation, TCZ should be strongly considered in the treatment of patient with adult Still's disease.

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Long-term Efficacy of Tocilizumab in A Patient with Amyloidosis and Interstitial Pneumonia Secondary to Multicentric Castleman's Disease (MCD). Michihito Katayama[1], Soichiro Tsuji[1], Satoshi Teshigawara[1], Eriko Kudo-Tanaka[1], Maiko Yoshimura[1], Akane Watanabe[1], Akiko Yura[2], Yoshinori Harada[2], Yoshinori Katada[2], Jun Hashimoto[1], Masato Matsushita[3], Yukihiko Saeki[1] and Shiro Ohshima[1]. [1]Osaka-Minami Medical Center, Kawachinagano City, Japan, [2]Kawachinagano City, Japan, [3]Osaka Minami Medical Center, Osaka, Japan

Background/Purpose: Castleman's disease is a benign lymphoproliferative disorder characterized histologically by follicular hyperplasia and capillary proliferation with endothelial hyperplasia. In addition, overproduction of Interleukin-6 (IL-6) was shown in the germinal centers of hyperplastic lymph node of patients with multicentric Castleman's disease (MCD), and is implicated in the pathogenesis of MCD. We evaluated long-term efficacy of IL-6 blockade therapy in a patient with both amyloidosis and interstitial pneumonia secondary to MCD.

Methods: A 61-year-old male had abnormal shadows on his chest radiography pointed out by medical checkup in June 1999. Based on the results of a lymph node biopsy in April 2004, he was diagnosed with plasma cell-type MCD. Abnormal shadow on chest radiography indicating interstitial pneumonia, marked anemia, hypoalbuminemia, hypergammaglobulinemia and proteinuria were observed, and got worse gradually. In November 2007, the patient was admitted to our hospital. He showed marked lymphadeno-pathy at multiple sites, general malaise, low grade fever, loose stool, edema, coughing and dispnea on exercise were observed. The administration of Tocilizumab (TCZ) (8 mg/kg, every 2 weeks) was initiated in December 2007. As his disease activity was extremely high, it is necessary to use concomitant administration of low dose prednisolone to maintain the inflammation low. We monitored clinical findings, laboratory findings, functional test, imaging, and quality of life (QOL) evaluated by SF36 in the patient for four years after initiation of the IL-6 blockade therapy. Moreover, we examined the efficacy of TCZ for the treatment of amyloidosis by intestinal biopsies both at the baseline and one year after first administration of TCZ.

Results: At the baseline, abnormal laboratory findings were as follows; severe anemia, hypoalbuminemia, hypergammaglobulinemia, an elevated CRP level, an elevated serum amyloid A protein (SAA) level, an elevated IL-6 level and proteinuria (2.39 g/day). The results of the respiratory function test indicated obstructive dysfunction of the lung, and blood gases on room air showed hypoxia. Chest CT scan revealed interstitial pneumonia with multiple cysts distributed throughout the lung fields and generalized lymph node enlargement. Endoscopic biopsy of the stomach and duodenum revealed heavy deposition of AA amyloid at the baseline indicating amyloidosis secondary to MCD. TCZ reduced the levels of both CRP and SAA, and improved anemia and hypoalbuminemia. Disappearance of urinary protein was achieved within a year. Lymph nodes throughout the body decreased in size. The results of the images and functional test demonstrated improvement in the patient's interstitial pneumonia. One year after initiation of treatment with TCZ, endoscopic biopsy of former sampling site of the stomach and duodenum revealed disappearance of AA amyloid. The result of SF36 indicated the improvement both in physical and mental QOL. No severe side effect were observed during the treatment period.

Conclusion: This case report indicates the long-term efficacy of TCZ for the treatment of MCD. Moreover, TCZ is effective for the treatment of amyloidosis, interstitial pneumonia secondary to MCD.

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Inflammatory Arthritis in Patients with Myelodysplastic Syndrome: French Multicenter Retrospective Study. Arsene Mekinian[1], Olivier De-caux[2], Geraldine Falgarone[3], Thorsten Braun Sr.[4], Eric Toussirot[5], Loic Raffray[6], Bruno Gombert[7], Bruno de Wazieres[8], Anne Laure Buchdaul[9], Jean-Marc Ziza[10], David Launay[11], Guillaume Denis[12], Serge Madaule[13], Pierre Fenaux[14] and Olivier Fain[15]. [1]Jean Verdier Hospital, Bondy, France, [2]Hôpital Sud, Rennes, France, [3]Hopital avicenne, Paris, France, [4]Avicenne hospital, Bobigny, France, [5]CIC Biotherapy 506 and Rheumatology and EA 4266 Pathogens and Inflammation, Besançon, France, [6]CHU de Bordeaux, Bordeaux, France, [7]La Rochelle hospital, La Rochelle, France, [8]CHU de Nimes, Nimes, France, [9]Douai hospital, Douai, France, [10]Hopital Croix Saint Simon, Paris, France, [11]Internal Medicine, CHRU Claude Huriez, Lille, France, [12]Rochefoucault hospital, Rochefoucault, France, [13]Albi hospital, Albi, France, [14]Avicenne Hospital, France, [15]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France, Bondy, France for the Société Nationale Française de Médecine Interne (SNFMI), the CRI (Club Rhumatismes Inflammation) and Groupe Français d'étude des syndromes myélodysplasiques.

Background/Purpose: To describe the characteristics and the outcome of inflammatory arthritis in patients with myelodysplastic syndrome (MDS).

Methods: French multicenter retrospective study which included patients with MDS and inflammatory arthritis. Patient's clinical, biological and radiological data at the diagnosis, during the follow-up were recorded, as well as treatment regimen. Patients with isolated arthritis were compared to MDS-associated vasculitis (n=22).

Results: Twenty-two patients with myelodysplastic syndrome (77.5 years [69–81]; 10 women) were included. IPSS score of the myelodysplastic syndrome was 0.75 [0–1.4]. Inflammatory arthritis was present in all patients, with polyarthritis in 14 (64%) and symmetric involvement in 15 cases (68%).

At the diagnosis of the arthritis, median DAS28-CRP was 4.5 [2–6.5], with the presence of anti-CCP antibodies in 2 cases (9%) and radiological erosions in 1 case. The median time between the diagnosis arthritis and MDS was of 9 [2–30] months, with median articular symptoms duration of 3 months [2–8]. The appearance of these 2 diseases was concomitant in 6 (27%) cases; arthritis preceded MDS in 12 (55%) and occurred after MDS in 4 (18%) cases. Characteristics of arthritis and of MDS, as well as treatments at the different points are in table 1. Whereas the number of swollen and tender joints significantly diminished during follow-up, as was the median DAS28-CRP (from 4.3 [3.8–4.6] at baseline to 2.9 [1.75–3.3]; p<0.05, C-reactive protein remained elevated (CRP>20 mg/l in 14 (64%) at baseline versus 8 (42%)). Nevertheless, no patients show any radiographic progression and new anti-CCP positivity during the follow-up of 29 [9–76] months. No correlation was found in concern the evolution of MDS and inflammatory arthritis. In concern the treatments, whereas almost all patients have corticosteroids, the associated treatment was present in only 4 cases (hydroxychloroquine in 2 cases, salazopyrine and etanercept, n=1; each). Eleven patients died during the follow-up from complications of MDS treatment or acutisation. In patients with MDS-associated vasculitis (n=22), death occurred in 17 cases (77%), but survival was not different from patients with only inflammatory arthritis.

Table 1.

Number of evaluable patients	Baseline assessment N=22	First visit N=19	Second visit N=11	Third visit N=9	Last visit N=19
Arthritis characteristics					
Delay from the diagnosis (months)	-	6 [3–14]	14 [8–32]	19 [13–27]	38 [17–61]
Arthralgias	22 (100%)	13 (68%)**	6 (55%)**	3 (33%)**	9 (47%)**
Arthritis	16 (73%)	5 (26%)**	2 (18%)**	1 (11%)**	3 (16%)**
Number of swollen joints	6 [4–8]	2 [0–4]**	4 [0–4]*	0 [0–3]**	0 [0–4.5]**
Number of tender joints	3 [0–4.5]	0 [0–2]**	0 [0–1]*	0 [0]*	0 [0]**
Morning stiffness (hours)	1 [0–1]	0 [0–0.5]**	0 [0–0.5]**	0 [0–0.5]*	0 [0]**
Erosion present	1 (5%)	1 (5%)	–	-	1 (5%)
C-reactive protein (mg/l)	30 [10–58]	10 [5–30]*	25 [3.5–56]	25 [8–140]	10 [3.5–55]
CRP>20 mg/l	14 (64%)	7 (37%)	5 (45%)	4 (44%)	8 (42%)
DAS28-CRP	4.3 [3.8–4.6]	3 [1.8–3.7]**	2.7 [2.2–4]*	2.8 [1.6–3.3]**	2.9 [1.75–3.3]**
Efficacy (by physician)		15 (79%)	7 (64%)	6 (67%)	15 (79%)
RA treatments					
Corticosteroids (prednisone)	16 (73%)	12 (63%)	10 (91%)	8 (89%)	14 (74%)
Corticosteroids (prednisone; mg/day)	27.5 [16–35]	15 [10–25]	10 [9.5–20]	9.5 [5–17]*	8 [5–15]**
Steroid dependence	-	5 (26%)	4 (36%)	1 (11%)	2 (11%)
Other treatments	4 (18%) hydroxychloroquine (n=2) etanercept salazopyrin	4 (21%) hydroxychloroquine (n=2) etanercept salazopyrin	3 (27%) hydroxychloroquine (n=2) salazopyrin	2 (22%) hydroxychloroquine	4 (21%) hydroxychloroquine (n=3) anakinra
MDS characteristics					
Hemoglobin (g/dl)	9 [8–11]	11 [8.5–11.5]	11 [8.7–13]	10 [8–11]	10 [8–12]
Platelets (n/mm3)	163 [62–657]	114 [50–242]	233 [75–250]	150 [40–244]	75 [12–146]*
Neutrophils (n/mm3)	260 [740–5070]	1500 [1000–3000]	1300 [1150–2500]	1200 [1000–3105]	2300 [1000–4550]
Blastes (%)	0 [0–8]	0 [2]	0 [0–0]	0 [0–2.5]	0 [0–1]
MDS aggravation	-	3 (16%)	2 (18%)	4 (44%)	4 (21%)
MDS treatment	4(18%)	6 (32%)	3 (27%)	3 (33%)	6 (32%)

* p<0.05 versus baseline
* p<0.005 versus baseline

Conclusion: This study describes the characteristics of associated inflammatory arthritis in MDS. At the difference of other inflammatory arthritis, the use of other than steroids immunosuppressors is very poor, probably in relation with the underlying hemopathy. The use of biologics in this condition could be preferred to methotrexate, but need prospective studies.

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Sarcoidosis in Northern New England. Clinical Characteristics and Predictive Factors for More Aggressive Therapy. Alireza Meysami[1], Kevin F. Spratt[2] and Christopher M. Burns[3]. [1]Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]Geisel School of Medicine at Dartmouth, Lebanon, NH, [3]Dartmouth Medical School, Lebanon, NH

Background/Purpose: Sarcoidosis is characterized by a variable clinical presentation. DMARDs and biologics have been used for resistant and/or organ-threatening disease. We analyzed the cases of sarcoidosis in a tertiary medical center in northern New England.

Methods: This was a retrospective review of the medical charts of patients who presented to Dartmouth-Hitchcock Medical Center from 2005–2010. Data were extracted from the electronic medical records using ICD-9 code. Patients with biopsy-proven non-caseating granuloma or Lofgren's syndrome were included. Patients were divided into those requiring either no treatment or steroids alone (non-immunosuppression (Non-IMS) group) and those requiring immunosuppressive medication beyond steroid (IMS group).

Results: 402 charts were reviewed and 120 patients met the inclusion criteria. Comparison was made with data from the ACCESS study (736 patients, Baughman et al., 2001). See table1. In addition, Comparison was made between IMS and Non-IMS group in the study. Of 29 patients in the IMS group, 82.7% had 2 or more organs involved (P<0.0005). 68.9% were followed by Rheumatology service in IMS group (P<0.0001). Eye (P<0.003), Musculoskeletal (P<0.0004) and nervous system (P<0.030) involvement often required IMS. The average ACE level (Unit/L) was 66.8 in IMS and 48.3 in Non IMS group (P<0.0339). See Table 2.

Table 1.

Parameter	Result	P value compared with ACCESS Study (*indicates clin. Sign.)	Details
Sex: Male/Female	46 (38.3%)/74 (61.6%)		
Race: White/Black	(118) 98.3%/(2) 1.6%		
Mean age	50.6 years		
Mode of diagnosis			Transbronchial biopsy: 67 (55.8%)
Biopsy	108 (90%)		Mediastinoscopy: 26 (31.2%)
Clinical (Lofgren's)	12 (10%)		Skin biopsy: 19 (15.8%)
			Bone marrowbiopsy 3 (2.5%)
			Other: 12 (11.1%)
Chest xray/Chest CT	110 (91.6%)		
Stage 0	5 (4.5%)	P < 0.130	
Stage I	76 (69%)	P < 0.0001*	
Stage II	17 (15.4%)	P < 0.0001*	
Stage III	11 (10%)	P < 0.721	
Stage IV	1 (0.9%)	P < 0.0631	
Organ involvement			Number of organ involvement
Lung	105 (87.5%)	P < 0.021*	One: 51 (42.5%)
Musculoskeletal	43 (35.8%)	P < 0.001*	Two: 40 (33.3%)
Skin	38 (31.6)	P < 0.001*	Three: 25 (20.8%)
Eye	8 (6.6%)	P < 0.108	Four: 4 (3.3%)
GI	7 (5.8%)	P < 0.0732	
Neurology	6 (5%)	P < 0.854	
Cardiac	4 (3.3%)	P < 0.502	
Kidney	4 (3.3%)	P < 0.021*	
Other	6 (5%)		
Treatment (TX):			Type of Immunosuppressive medication
No TX/Steroid alone (NonIMS group)	91 (75.7%)		Methotrexate: N = 14
			Hydroxychloroquine: N = 12
Steroid+ other immunosuppressive medications (IMS group)	29 (24.3%)		Infliximab N = 3
			Azathioprine N = 2
			Rituximab N = 1

Table 2.

Parameter	P=value *=Statistically Significant	NON-IMS group (N = 91)	IMS group (N = 29)
Disease activity	P < 0.0001*	18	26
Lofgren's syndrome	P < 0.68	10	4
Sex	P < 0.96		
Female		56	18
Male		35	11
Mode of diagnosis	P < 0.45		
Biopsy		83	25
Clinical		8	4
Number of organ Involvement			
One	P < 0.023*	46	5
Two or more	P < 0.005*	45	24
Organ involvement			
LUNG	P < 0.39	81	24
SKIN	P < 0.71	28	10
GI	P < 0.78	5	2
HEART	P < 0.13	4	0
NEURO	P < 0.023*	2	4
KIDNEY	P < 0.26	2	2
EYES	P < 0.001*	2	6
MSK	P < 0.001*	26	18
OTHER	P < 0.16	3	3
Presence of Cancer	P < 0.73	15	4
Presence of other	P < 0.16	3	3
Autoimmune disease			
ACE level at diagnosis (unit/L)	P < 0.033*	48.3	66.8

Conclusion: We have characterized a unique sarcoidosis population in rural northern New England, mainly Caucasian with more musculoskeletal, skin and kidney involvement and less lung involvement compared to existing data. 24% of our patients required treatment beyond steroid (IMS group). The use of IMS was associated with the number of organs involved ($>=2$), and the specific organ involvement (eye, musculoskeletal, nervous system) at the time of diagnosis. We also observed a trend toward higher ACE levels in patients requiring the use of IMS. Rheumatologists followed most patients on IMS treatment, perhaps due to familiarity with these agents and/or seeing more complicated cases in their clinic.

Disclosure: **A. Meysami**, None; **K. F. Spratt**, None; **C. M. Burns**, None.

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Collapsing Glomerulopathy in Collagen Vascular-Like Disease. Rawad Nasr[1], Christine Johns[2] and Elie Gertner[3]. [1]University of Minnesota, Minneapolis, MN, [2]Regions Hospital, St Paul, MN, [3]Regions Hospital and University of Minnesota Medical School, St. Paul, MN

Background/Purpose: Collapsing Glomerulopathy (CG) is an uncommon podocytopathy with distinct clinical and pathological characteristics. It is usually associated with HIV disease or parvovirus B19 infection. There are a few case reports of CG in association with well defined connective tissue diseases mainly SLE. The rheumatological literature does not describe patients with CG and marked serological abnormalities who do not have sufficient clinical findings to diagnose definite collagen vascular disease.

Objective: Our objective is to expand the spectrum of rheumatological disease that may accompany CG to include patients with marked serological abnormalities, but minimal clinical findings that do not meet criteria for definite collagen vascular disease. These patients all appear to have a very similar mode of presentation and course. Rheumatologists should be aware of this condition and its association with marked serological abnormalities.

Methods: A review of all kidney biopsies performed at Regions Hospital from 2004 till 2012 revealed four cases of CG not associated with other diseases. We conducted a chart review of these patients. These four cases were then compared with the sixteen cases of collagen vascular-like disease in the renal literature to construct a profile of patients with collagen vascular-like disease and CG.

Results: Four patients (all non-Caucasian) were identified. Ages ranged from 29 to 51 years. All patients presented with massive proteinuria (approximately 20 grams / 24 hours) and renal insufficiency. None of the renal biopsies showed evidence of lupus nephritis, immune complex deposition or vasculitis. All had evidence of CG. All testing for HIV, parvovirus B19, and other known causes of CG were negative.

Age	Sex	Ethnicity	Clinical	Cr (mg/dl)	Proteinuria (gr/24 hr)	ANA	Other	Rx	Outcome
38	M	AA*	Arthralgias Dry mouth	3.7	21	1:160	High titer Anti-RNP, IgG ACLA*	Prednisone, MMF*	Improved at 6 mo f/u
51	M	Cambodian	None	3.4	20	1:80	Low titer ds-DNA	Prednisone	On PD* after 3 mo
25	F	African	Alopecia	2.4	12	1:1280	High titer Anti-RNP, IgA/ IgM ACLA*, ds-DNA	Prednisone, Cyclosporine, and Hydroxychloroquine	On HD* after 3 years
29	F	Hispanic	Headaches	7.6	Notdone	1:640	High titer Anti MPO, low C3	Prednisone	On HD* at onset

* ACLA=Anti-cardiolipin Antibodies, PD= Peritoneal Dialysis, HD= Hemodialysis, AA= African American, MMF=Mycophenolate Mofetil

In comparison, the few cases of collagen vascular-like disease and CG in the renal literature also had marked proteinuria, renal insufficiency, and were treated with prednisone $+/-$ immunomodulatory therapy like MMF. Most patients became dialysis dependent within two years of diagnosis (some sooner) despite initial response to steroids.

Conclusion: Rheumatologists may be asked to see patients with collagen vascular-like disease (minimal symptoms and marked serological abnormalities) with severe proteinuria and renal insufficiency due to CG. The presence of high titer antibodies suggests that immune activation may play a role in the podocytopathy of some patients with CG. Treatment with steroids and the agents described to date does not seem to be effective in the long term. Further definition of these patients and treatment trials are necessary.

Disclosure: **R. Nasr**, None; **C. Johns**, None; **E. Gertner**, None.

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Diagnostic Predictors and Clinical Outcomes in Patients Presenting Solely with Lymphadenopathy. Huifang Lu, Xerxes Pundole and Khanh Vu. UT MD Anderson Cancer Center, Houston, TX

Background/Purpose: Patients presenting solely with radiologic evidence of lymphadenopathy (LAD) to tertiary cancer centers are often diagnosed with malignancy or autoimmune diseases such as sarcoidosis. However, the baseline characteristics predictive of a cancer or sarcoidosis diagnosis, clinical outcomes and follow-up time are unknown.

Methods: Retrospective chart review of adult patients (age $>$ 18) presenting with LAD and without an apparent mass at other sites, such as the breast or prostate; seen at Mary Ann Weiser Suspicion of Cancer Clinic and rheumatology clinics at The University of Texas MD Anderson Cancer Center, new consultation from January 1, 2003, to June 30, 2007, and followed to December 31, 2011. Data collected and analyzed included age, sex, follow-up time, comorbidities, B symptoms, laboratory test results, imaging studies, histopathology analyses, and final diagnosis. Multiple logistic regression was used to asses baseline characteristics predictive of a cancer diagnosis.

Results: Of the 66 patients studied, 36 (55%) were diagnosed with cancer; the most common type was lymphoma. Sarcoidosis (17%) and reactive hyperplasia (23%) were the most commonly seen benign causes of LAD. Malignancy was diagnosed in 94%, 79%, and 70% of patients with supraclavicular, retroperitoneal, and abdominal LAD, respectively, suggesting an association between these locations and a cancer diagnosis. A benign diagnosis was more common with localized LAD than with generalized LAD (63% vs 37%). The final multiple logistic regression models showed age (used as a continuous variable) (p=0.0342) and hypertension (p=0.0399) to be associated with a cancer diagnosis. Another model using age as a dichotomized variable ($<$50, $\geq$50) (p=0.0447) and hypertension (p=0.0245) showed both to be associated with a cancer diagnosis, suggesting hypertension and age as independent factors in predicting a cancer diagnosis. Other comorbidities like history of smoking, history of alcohol, history of prior cancer and rheumatologic disease did not have a significant association with a cancer diagnosis. Mean serum levels of angiotensin-converting enzyme (ACE) checked in 24 of the 66 patients, were higher in patients without cancer than in patients with cancer. No significant statistical correlation was observed between B symptoms and a cancer diagnosis. On histopathology varying proportions of cell types were found in the lymph node specimens and a conclusive relationship with a particular diagnosis was not evident overall. The average follow-up time was 7 months, although in 1 of the patients a conclusive diagnosis was arrived at after 1 year. None of the patient's with sarcoidosis progressed to a cancer diagnosis.

Conclusion: Older patients with hypertension presenting to a cancer center with abdominal, retroperitoneal, or in particular supraclavicular LAD are at risk for the diagnosis of hematologic malignancy. We recommend that they should be followed for at least 1 year for a definitive diagnosis. A larger prospective study should be conducted to analyze other factors such as localized vs. generalized LAD or ACE levels (or other laboratory values) and their correlation with a cancer diagnosis.

Disclosure: **H. Lu**, None; **X. Pundole**, None; **K. Vu**, None.

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Joint, Hand and Feet Swelling As a Presenting Symptom of Hereditary Angioedema. Maria J. Gutierrez[1] and Timothy J. Craig[2]. [1]Penn State College of Medicine Milton S. Hershey Medical Center, Hershey, PA, [2]Penn State College of Medicine Milton S. Hershey Medical Cente, Hershey, PA

Background/Purpose: Hereditary Angioedema (HAE) is a rare disorder caused by deficiency or impaired function of C1 esterase inhibitor. Early and accurate diagnosis of HAE is important to initiate appropriate therapy and avoid potentially fatal outcomes. However, HAE symptoms can mimic other conditions potentially leading to incorrect diagnosis and delay in treatment. Our purpose was to investigate the proportion of hand, feet and joint swelling as presenting signs of hereditary angioedema across different countries.

Methods: A web-based survey was conducted among physicians who treated HAE patients within their practice in over 30 countries in North and Latin America, Europe, Asia, Africa and Oceania. Physicians voluntarily accessed and completed the internet-based survey between November 2010 and February 2011.

Results: A total of 201 international physicians who treated HAE patients completed the survey. Most patients treated by surveyed physicians were under 35 years-old (67%) and symptoms had first presented during childhood or adolescence in 77% of all cases. Among respondents there was widespread consensus about delay between the first HAE attack and diagnosis. Overall, only 14% of treated patients had been diagnosed within the first year and in 48% of cases there was a reported delay of 4 or more years. The patient's most common complaint that prompted evaluation for HAE was facial swelling. Nonetheless, hand, feet or joint swelling were listed as one of the two most common symptoms at onset by 40% of physicians. Interestingly, hand, foot and joint swelling were also ranked among the three most problematic symptoms during attacks by 35% of physicians surveyed.

Conclusion: HAE is a rare condition that usually presents during the first two decades of life and may present with hand, feet and joint swelling as main symptom. In addition, an important proportion of surveyed physicians thought that this is one of the most problematic symptoms of patients with HAE. Accordingly, HAE should be included in the differential diagnosis of certain types of joint and extremity edema, and thus, increased awareness of the pediatric rheumatology community could lead to a decrease in the morbidity and mortality of this condition.

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Rheumatic Manifestations and Connective Tissue Diseases in Autoimmune Hepatitis of the Child and the Adult. Federico Zazzetti[1], Nora C. Fernandez[1], Javier Benavidez[1], Luis A. Colombato[1], Graciela R. Rodriguez[2], Graciela Nardi[2], Carolina Bru Morón[3], Oscar L. Rillo[4], Nelo A. Quadrini[3], Stella M. Garay[5], Mariana Fabi[5], Teresita Gonzalez[5] and Juan C. Barreira[1]. [1]Buenos Aires British Hospital, Buenos Aires, Argentina, [2]Hospital Dr. Ignacio Pirovano, Buenos Aires, Argentina, [3]Hospital Dr. Enrique Tornú, Buenos Aires, Argentina, [4]Hospital Tornú, Buenos Aires, Argentina, [5]Hospital IAEP Sor María Ludovica, La Plata, Argentina

Background/Purpose: Autoimmune hepatitis (AIH) is a progressive fibrosing inflammatory disease of the liver of unknown etiology, leading to cirrhosis. Its course is usually fluctuating and its clinical manifestations protean. Forty % of type I AIH and 80% of type II is diagnosed in childhood. Up to 30% of patients with AIH will develop rheumatic manifestations. Moreover, AIH can be associated with various connective tissue diseases (CTD), although there is a lack of studies comparing pediatric and adult populations in this regard. The aim was to analyze the frequency of rheumatic manifestations and CTD in patients with AIH in a pediatric population (≤ 16 years old) compared with adults.

Methods: Patients of any age who fulfilled the 1998 modified diagnostic criteria for AIH of the Autoimmune Hepatitis International Group assisted in Hepatology services of the intervening centers. They were clinically evaluated by a hepatologist and referred to a rheumatologist. Demographic, clinical and serological variables, as well as additional studies and biopsies were recorded. Rheumatic manifestations and CTD were registered and defined according to ACR criteria. Means were reported for numeric variables and percentages for categorical. To compare two groups Mann Whitney and X^2 tests were applied. A 0.05 α-error was chosen.

Results: Forty-eight patients with AIH were analyzed: 28 adults, 89% female, mean age at inclusion 50 ± 17 years (range=19–75) and age at diagnosis of AIH 41 ± 18 years (range=18.6–70), and 20 pediatric, 75% female, mean age at inclusion 13.8 ± 4 years (range=5–16) and age at diagnosis of AIH 9.7 ± 4 years (range=1.5–16). Sixty-four % (18/28) of adults and 55% (11/20) of pediatric had at least one rheumatic manifestation (p=n/s). There were no differences in the type and frequency of rheumatic manifestations analized in the two age groups, including malar rash, oral ulcers, parotitis, photosensitivity, xerophthalmia, xerostomia, telangiectasias, Raynaud's, vasculitis, xeroderma, subcutaneous nodules, arthralgia, arthritis, myositis, interstitial lung disease, serositis, citopenias, glomerulonephritis, proteinuria and nervous system involvement. Nine CTD were found, 5 in adults (17.8%, SLE=4, Sjögren=1) and 4 in pediatric patients (20%, SLE=3, JIA = 1). Comparing both groups, the pediatric group had more jaundice (p=0.03), hepatomegaly (p=0.0001), cirrhosis (p=0.03), splenomegaly (p=0.003), anemia (p=0.003), ESR (p=0.04), AST (p=0.0006), ALT (p=0.006), FAL (p=0.01), total bilirubin (p=0.003), ANA (p=0.04), ASMA (p=0.0001) and LKM (p=0.03). There were no differences regarding histological findings of liver biopsies. Autoimmune thyroiditis was more frequent in adults 4/28 vs 1/20 (p=0.001).

Conclusion: The frequency of rheumatic manifestations and CTD was similar in both groups, but pediatric patients had a more severe hepatic involvement and higher levels of autoantibodies. Regardless of age, 2 of 10 patients with AIH presented an associated CTD, and at least half of them developed rheumatic manifestations. Systemic lupus was the most frequent CTD associated to both groups. The systematic search for defined CTD and/or rheumatic manifestations should be an essential part of the clinical evaluation of AIH.

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High Rate of Autoimmune Manifestations During Idiopathic CD4 Lymphocytopenia. Alexis Régent[1], Brigitte Autran[2], Guislaine Carcelain[2], Benjamin Terrier[3], Alain Krivitzky[4], Eric Oksenhendler[5], Nathalie Costedoat-Chalumeau[6], Pascale Hubert[2], Olivier Lortholary[7], Nicolas Dupin[8], Patrice Debré[2], Loic Guillevin[9] and Luc Mouthon[1]. [1]Hopital Cochin, Paris, France, [2]Laboratoire d'Immunologie Cellulaire Et Tissulaire, Paris, France, [3]Cochin Hospital, Paris, France, [4]Département de médecine interne, Hôpital Avicenne, AP-HP, Bobigny, France, [5]Département d'Immunologie Clinique, Hôpital Saint-Louis, AP-HP, Paris, France, [6]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [7]Service de maladies infectieuses, Hôpital Necker-Enfants malades, AP-HP, Paris, France, [8]Service de Dermatologie, Hôpital Cochin, AP-HP, Paris, France, [9]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France

Background/Purpose: When first described by the Center for Disease Control, idiopathic CD4 lymphocytopenia (ICL) was characterized by opportunistic infections in patients with a CD4 count≤300/mm3 or ≤20% lymphocytes. It is now well established that auto-immune manifestations occur during primary or secondary immunodeficiencies.

Methods: We prospectively included 36 patients (21 females) with ICL between January 1991 and June 2011. T lymphocyte phenotyping and lymphocyte proliferation assay were realized at diagnosis. Infectious, auto-immune manifestations and malignancies during a mean follow-up of 7.6±6.7 years were recorded and correlated with data at inclusion.

Results: Twenty four patients showed infections (11 with human papillomavirus infection), 11 autoimmune symptoms, 5 malignancies and 7 mild or no symptoms. Autoimmune and/or inflammatory manifestations include immune thrombocytopenic purpura (n=5), autoimmune hemolytic anemia (n=3), central nervous system vasculitis (n=1), Goodpasture syndrome (n=1), grade II duodenal villous atrophy (n=1), Crohn disease (n=1), antiphospholipid syndrome (n=1) and Hashimoto's thyroiditis (n=1). At the time of diagnosis, mean $CD4^+$, $CD8^+$, $CD19^+$ and natural killer (NK) cell counts were 126/mm3 (range 4–294), 238/mm3 (1–1293), 107/mm3 (3–547) and 115/mm3 (5–416), respectively. Most patients exhibited deficiency in $CD8^+$, $CD19^+$, and/or NK cells. Patients with infections had a significantly lower NK cell count (p=0.03) and those with autoimmune manifestations higher $CD45RO^+CD8^+$ count (p=0.02). T-cell proliferation induced by mitogens and antigens revealed great discrepancies. Six patients died (16.6%) during follow-up. $CD4^+$ T-cell count < 150/mm3 and NK cell count <100/mm3 were predictors of death.

Conclusion: 30.5 % patients with ICL show auto-immune manifestations during clinical course. These patients had higher $CD45RO^+CD8^+$ count at diagnosis. In addition to CD4 lymphocytopenia, patients often have CD8, CD19 and NK cell defects. Mortality is related to an initial $CD4^+$ count≤ 150/mm3 and NK cells≤100/mm3.

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Diseases Associated with Markedly Elevated Ferritin Levels. Reshma Marri, Payal J. Patel, Amita Thakkar, Rochella A. Ostrowski, Eric McBride and Rodney Tehrani. Loyola Univ Medical Ctr, Maywood, IL

Background/Purpose: Adult onset Still's disease (AOSD) is a rare form of inflammatory arthritis with inflammatory systemic disease of unknown

etiology. It is a diagnosis of exclusion and can be a diagnostic challenge. A patient with suspected AOSD at our institution prompted a retrospective chart review of all patients with markedly elevated ferritin levels.

The patient, a 59 year old male with fever of at least one month who underwent an extensive negative evaluation for infection, malignancy, and other autoimmune etiologies was treated with high dose corticosteroids. A ferritin level at admission was 2200 ng/mL and rapidly rose to almost 50,000 ng/mL. Treatment for AOSD with IL-1 and IL-6 inhibition was unsuccessful and he died within one month from multi-organ failure. A bladder wall biopsy obtained just prior to death revealed an anaplastic large cell lymphoma.

Methods: In order to determine the association of autoimmune disease, including AOSD, with markedly elevated ferritin levels, in comparison to non-autoimmune diagnoses, we conducted a retrospective chart review of patients with elevated ferritins > 10,000 ng/mL seen at our institution from January 2000 to July 2011. Cases were divided into two subgroups, those with values between 10,000–15,000 and >15,000 ng/ml for analysis. The highest ferritin value was used when an individual subject had multiple values. There were 108 charts identified and reviewed for diagnoses at the time of the elevated ferritin level. Patients with either autoimmune disease, malignancies, liver disease, and/or infection were included in the analysis. Patients with hemoglobinopathies were excluded to avoid confounding of the ferritin levels by frequent blood transfusions. The remaining 88 cases were included for analysis.

Results: Twenty six patients with ferritin levels between 10,000–15,000 ng/ml were identified. The mean age of patients in this subgroup was 46.6 years. Of these patients, 10/26 (38%) had elevated ferritin levels secondary to liver disease, 7/26 (27%) malignancy/infection, 6/26 (23%) malignancy alone, 1/26 (4%) autoimmune disease, and 1/26 (4%) infection and liver disease/infection respectively. There were 62 patients with ferritins greater than 15,000 with a mean age of 44.3 years. Of these patients, 29/62 (47%) had liver disease, 9/62 (14%) malignancy, 7/62 (11%) autoimmune, 7/62 (11%) infection, 4/62 (6%) liver disease/infection, 4/62 (6%) malignancy/infection and 2/62 (3%) autoimmune/infection.

Conclusion: The observation that both ferritin groups include higher percentages of patients with liver disease and malignancy compared to autoimmune disease. Although not a part of the diagnostic criteria for AOSD, the presence of hyperferritinemia is commonly used to assist with diagnosis. These findings suggest that other diagnoses such as malignancies or liver disease should be considered in the differential diagnoses of markedly elevated ferritin levels. The diagnosis of AOSD is a diagnosis of exclusion and other underlying causes need to be ruled out.

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Clinical Course Factors Associated with Outcome of Monoarthritis: A Retrospective Study of 173 Cases. Hyemin Jeong[1], Eun-Jung Park[2], Jiwon Hwang[2], Ji Young Chai[3], Joong Kyong Ahn[4], Eun-Mi Koh[5] and Hoon-Suk Cha[6]. [1]Samsung Medical Center, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Jesang Hospital, Seongnam-si Gyeonggi-do, South Korea, [4]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Seoul, South Korea, [6]Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea

Background/Purpose: To evaluate the clinical features and outcomes in patients with monoarthritis and to investigate predictive factors associated with the clinical course in terms of a definite diagnosis and polyarticular involvement.

Methods: A retrospective analysis of 173 patients who had undiagnosed monoarthritis (UMA) at least six weeks' duration at a single tertiary hospital between January 2001 and January 2011. Baseline characteristics, laboratory data, radiographic findings and clinical course were reviewed.

Results: Of 173 patients (80 males and 93 females), the mean age was 43.1 ± 15.1 years. The median follow-up duration was 21 months (range, 1.5 to 120). Most commonly involved joints were the knee (23.7%) and wrist (23.7%), followed by the ankle (18.5%). A definite diagnosis was made in 71 patients (40.5%); 27 patients with rheumatoid arthritis (RA) based on the 2010 ACR/EULAR classification criteria, 18 patients with Behcet's disease (BD) according to the diagnostic criteria of the BD research committee of Japan, 23 patients with peripheral arthritis of spondyloarthropathy (SpA) based on the ASAS criteria, 2 patients

confirmed with infectious arthritis (one with *Nontuberculous mycobacterium* and one with methicilline-resistant *Staphylococcus aureus*), and one patient as SAPHO syndrome. The other 102 patients (59.5%) remained unclassified because of lacking in requirements and seemed to have shorter follow-up duration (23.0 versus (vs) 16.5 months, p = 0.08). Of total 173 patients, 24 patients (13.9%) were progressed to oligo- or polyarthritis and 92 patients (53.2%) remained UMA. The rate of patients treated with non-steroidal anti-inflammatory drugs without disease modifying antirheumatic drugs is higher in UMA group than diagnosed group (53.3% vs 22.2%, p < 0.001). The UMA patients were related to lower baseline C- reactive protein (CRP) (OR 0.67, 95% CI 0.53 to 0.85, p = 0.001), and the negativity of anti-cyclic citrullinated protein antibody (ACPA) (OR 0.34, 95% CI 0.13 to 0.89, p = 0.027). Rheumatoid factor did not show significant association (OR 0.75, 95% CI 0.37 to 1.51, p = 0.418). HLA-B27 was checked in 27 patients only who were suspicious of SpA and the positivity was 44.4%. The initial site of joint involvement was predictive for later diagnosis; the wrist joint for RA (odds ratio (OR) 9.09, 95% confidence interval (CI) 3.70 to 22.34, p < 0.001), the knee joint for BD (OR 3.43, 95% CI 1.29 to 9.15, p = 0.01) and the ankle joint for peripheral SpA (OR 6.19, 95% CI 2.38 to 16.08, p < 0.001). The presence of bony erosion at initial visit was associated with the progression to oligo-or polyarthritis (OR 2.88, 95% CI 1.09 to 7.59, p=0.03).

Conclusion: Our data showed clinical course of monoarthritis. A definite diagnosis was made in less than half of the patients and remaining UMA patients seemed to have favorable prognosis. Initial site of joint involvement, the bony erosion on initial radiograph, baseline CRP and the ACPA status can help to predict the course of monoarthritis.

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Characterization of Joint Disease in Mucopolysaccharidosis Type I Mice and the Effects of Enzyme Replacement Therapy. Patricia Oliveira[1], Guilherme Baldo[2], Fabiana Mayer[2], Barbara Martinelli[2], Luise Meurer[2], Roberto Giugliani[2], Ursula Matte[2] and Ricardo M. Xavier[3]. [1]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, [2]Hospital de Clinicas de Porto Alegre, [3]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Background/Purpose: Mucopolysaccharidosis type I (MPS I) is a lysosomal disorder caused by deficiency of alpha-L-iduronidase, which leads to storage of glycosaminoglycans. Patients with MPS I present destructive changes in their joints in a process not well understood. The MPS I animal model is a useful tool to study the disease pathogenesis; however the changes in the MPS I joints were never investigated. This work aimed to describe the joint disease progression in the murine model of MPS I, and the effect of treatment with enzyme replacement therapy (ERT).

Methods: Normal (wild type) and untreated MPS I mice were sacrificed at different time points (from 2 to 12 months). In addition, some MPS I mice were treated with ERT and sacrificed at 6 months. The knee joints were collected and hematoxylin and eosin staining was used to evaluate the articular architecture. Safranin-O and Sirius-Red staining was used to analyze proteoglycans (PGs) and collagen content. In addition we analyzed the expression of matrix-degrading metalloproteinases (MMPs), MMP-2 and -9, by immunohistochemistry.

Results: We observed progressive joint alterations from 6 months, including presence of synovial inflammatory infiltrate, destruction and thickening of the cartilage extracellular matrix and PGs and collagen depletion. Also, we observed an increase in the expression of MMP-2 and -9, which could explain the degenerative changes. We also investigated the effect of ERT when started at 2 months, which showed no benefits, suggesting that the poorly vascularized cartilage is difficult to reach, and an ancillary therapy might be needed for patients.

Conclusion: Our results suggest that the degenerative joint and bone disease in MPS I animals presents some similarities to osteoarthritis. More important, our results evidence the need for and an ancillary therapy for patients.

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Idiopathic Inflammatory Myositis Is Associated with an Increased Incidence of Systemic Sclerosis. Shreyas H. Chaudhary[1], Susanna Proudman[2] and Vidya S. Limaye[2]. [1]Medical Student University of Adelaide, Adelaide, Australia, [2]Royal Adelaide Hospital, Adelaide, Australia

Background/Purpose: Systemic sclerosis (SSc) and idiopathic inflammatory myositis (IIM) are two systemic autoimmune connective tissue diseases with predominant effects on skin and muscle respectively. Although they generally occur as distinct disease entities, some features of SSc and IIM may be seen together in "overlap syndromes" or in mixed connective tissue disease (MCTD). The aim of this study was to determine the occurrence of SSc in IIM, and vice versa, in patients without features of MCTD or overlap syndromes. We also sought to compare the incidence of SSc in IIM, with that of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and primary Sjogrens syndrome (pSS).

Methods: The South Australian (SA) Myositis Database has registered all patients with biopsy-proven IIM in SA subsequent to 1980. All adult muscle biopsies performed in SA are reported in a central diagnostic laboratory and are subjected to peer review. The criteria used to diagnose IIM are those based on current published literature. Myositis-associated antibodies (MAA) and myositis-specific antibodies (MSA) have been measured on 138 patients with myositis. The South Australian Scleroderma Register similarly registers all patients in SA diagnosed with limited or diffuse SSc. Fisher's exact T-test was used for statistical comparisons.

Results: The incidence of SSc in IIM was 18/426 (4.2%). A greater proportion of IIM patients had SSc (18/426) than RA (2/426, p=0.003) or MCTD (4/426, p=0.004).There was a trend towards a greater proportion of IIM patients having SSc than SLE or pSS (each 8/426, p=0.07). There was no difference in the proportion of females amongst patients with IIM alone (231/426) compared with IIM and SSc (13/18, Fishers exact T test p =0.15. Of the 18 patients with SSc and IIM, 14 had polymyositis, 3 dermatomyositis, 2 inclusion body myositis and one had necrotizing myopathy. Four patients had antibodies to PM-Scl (3 of these had polymyositis, one had dermatomyositis). Antibodies to other MSA or MAA were detected as follows: Ku (n=2), MI-2 (n=1), PL12 (n=1), Jo-1 (n=1) and Ro52 (n=2). Of the 177 patients on the SA Scleroderma Register, 22 had suspected IIM (incidence of IIM in SSc =12.4%). Of these 22 patients, 18 had elevations in creatinine kinase levels, and ten had biopsy confirmation of IIM.

Conclusion: Although the population incidence of RA, SLE and pSS is greater than SSc, in IIM, there is a greater incidence of SSc and SSc is the commonest autoimmune connective tissue disease in IIM. The co-occurrence of these two conditions raises the possibility of shared disease susceptibility.

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Clinical, Laboratory, and Cellular Responses in the Rituximab in Myositis Trial in Patients Enrolled At the National Institutes of Health. Lisa G. Rider[1], Adrienne L. Yip[1], Iren Horkayne-Szakaly[2], Rita Volochayev[1], Joseph A. Shrader[3], Maria L. Turner[4], Heidi H. Kong[4], Minal S. Jain[3], Anna V. Jansen[1], Chester V. Oddis[5], Thomas A. Fleisher[6] and Frederick W. Miller[1]. [1]National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, [2]Joint Pathology Center, Silver Spring, MD, [3]Rehab Medicine, NIH Clinical Center, Bethesda, MD, [4]NCI, NIH, Bethesda, MD, [5]University of Pittsburgh, Pittsburgh, PA, [6]Laboratory Medicine, NIH Clinical Center, Bethesda, MD

Background/Purpose: To assess changes in myositis core set measures, clinical and laboratory data, and paired muscle biopsies from NIH patients enrolled in the Rituximab in Myositis (RIM) trial.

Methods: Eighteen patients (5 dermatomyositis [DM], 8 polymyositis [PM], 5 juvenile DM) completed muscle and skin assessments, patient-reported outcome measures (PROs), and laboratory tests following administration of rituximab. Adult patients had muscle biopsies at weeks 0 and 16. Percent change and

standardized response means (SRM) were examined over 44 weeks, and the percent change in the definitions of improvement (DOI) was compared.

Results: Core set activity measures improved by 18–70% from weeks 0–44, although creatine kinase was the least sensitive to change (SRM 0.6 for CK vs. 1.2–2.0 for other core set measures). Response rates at week 44 ranged from 72–94% by various DOIs for myositis. For DM patients, strength and functional measures improved by 17–64%, and skin measures by 0–43% (Table). Muscle strength measures (SRM 1.3–2.2) were more sensitive to change than skin assessments (SRM 0.6–1.1). Constitutional, gastrointestinal, and pulmonary systems improved 44–70% (SRM 0.9–2.7). PROs, including SF-36 and PedsQL Fatigue scale, improved 25–28% (SRM 1.0–1.2), but the Fatigue Severity Scale and a dyspnea score did not change.

CD20 B cells were generally depleted in the peripheral blood and frequently depleted in muscle. No effects were observed on blood or muscle T cells or on other muscle biopsy parameters (inflammation, regeneration, vascular abnormalities, and fibrosis). Seven of 10 patients with CD20 in the muscle at baseline depleted CD20 in the muscle and peripheral blood at week 16. Of these, only one achieved the DOI at week 16, and 6 patients achieved the DOI at week 44. One patient who responded clinically at weeks 16 and 44 depleted CD20 in the periphery and had reduced, but did not deplete, CD20 in the muscle. Three patients had reduced or depleted CD20 in the periphery but increased CD20 in the muscle, and all 3 met the DOI at weeks 16 and 44. In terms of memory B cells in the peripheral blood, 1 adult DM patient did not deplete CD20+CD27+ cells but met the DOI, and 2 juvenile DM patients depleted CD20+CD27+ cells but did not meet the DOI. The other 11 patients with CD20+CD27+ cells depleted these cells and met improvement criteria.

Measure [potential range]	Median Baseline value	Median % change Week 0–44	Standardized Response Mean Week 0–44
Muscle			
MMT-8 Score [0–80]	54.5	28c	2.2
Total MMT Score [0–260]	188.0	24c	2.1
QMT-8 [0–250 lb.]	61.8	64b	1.3
MDAAT Muscular VAS [0–10 cm]	4.8	48c	1.5
DAS Muscle [0–11]	8.0	17a	1.4
CMAS [0–52]	34.0	26a	1.2
HAQ/CHAQ [0–3]	1.4	50a	1.2
Skin			
CDASI [0–168]	17.5	17	0.9
DLQI [0–30]	4.5	43a	0.6
MDAAT Cutaneous VAS [0–10 cm]	3.4	28	1.1
DAS Skin [0–9]	6.0	0	1.0

a $P < 0.05$,
b $P < 0.01$,
c $P < 0.005$.

Conclusion: Myositis patients enrolled at the NIH had similar high rates of clinical response to rituximab compared with patients in the overall RIM trial. Most measures were very responsive, but muscle measures had a greater degree of change than skin. Depletion of CD20+ cells in the periphery and target tissue did not always correlate with clinical response.

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Interferon-Driven Chemokines Are Associated with Changes in Disease Activity Among Rituximab-Treated Refractory Myositis Patients with Pulmonary Involvement—the RIM Study. Cynthia S. Crowson[1], Ann M. Reed[1], Molly Hein[1], Abigail B. Green[1], Consuelo Lopez de Padilla[1], Rohit Aggarwal[2], Dana P. Ascherman[3], Marc C. Levesque[4] and Chester V. Oddis[4]. [1]Mayo Clinic, Rochester, MN, [2]University of Pittsburgh Medical Center, Pittsburgh, PA, [3]University of Miami, Miami, FL, [4]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: The Rituximab in Myositis (RIM) Study provides a unique resource for biomarker investigation of homogeneously treated refractory adult and juvenile myositis patients. Building on prior cross-sectional findings, we examined the longitudinal utility of Type 1 interferon (IFN)-driven chemokines as clinical biomarkers of disease activity in myositis patients treated with B cell depletion.

Methods: All 200 enrolled refractory myositis patients (failed steroids and ≥1 other immunosuppressive agent) received 1 gram of rituximab on 2 consecutive weeks–weeks 0/1 (Early) or weeks 8/9 (Late). Using serum samples

collected at weeks 0 and 16, multiplexed sandwich immunoassays (Meso Scale Discovery) quantified IFN-regulated chemokines and other pro-inflammatory cytokines. An IFN chemokine score combining IFN-inducible T-cell chemoattractant (I-TAC), IFN-inducible 10-kd protein (IP-10), and monocyte chemotactic protein 1 (MCP-1) was computed. Data collected at each visit included: muscle enzymes, physician global, muscle and extramuscular visual analog scale (VAS) scores (0–10 cm) and Myositis Disease Activity Assessment Tool variables (i.e., VAS score for organ involvement). Pulmonary involvement was defined as VAS>1 cm and included active interstitial lung disease (ILD) and respiratory muscle weakness (i.e., dysphonia and dyspnea). Changes in IFN chemokine and VAS scores were calculated as week 16–week 0, and correlations were assessed using Spearman methods.

Results: In 181 patients (87 Early, 94 Late) with available serum samples, changes in IFN chemokine score correlated with changes in physician global (r=0.19 p=0.017), muscle (r=0.19 p=0.019) and extramuscular VAS (r=0.24 p=0.002). These associations persisted after adjusting for muscle enzymes (global r=0.15 p=0.056; muscle r=0.16 p=0.046 and extramuscular r=0.25 p=0.002), suggesting that the IFN chemokine score is complementary to muscle enzymes. The IFN chemokine score at week 0 correlated with change in extramuscular VAS (r=−0.18 p=0.027), but not with change in global or muscle VAS (r<0.1).

In patients with pulmonary involvement (n=70), IFN chemokine score at week 0 was more strongly correlated with changes in disease activity (global r=−0.37 p=0.004; muscle r=−0.36 p=0.005; extramuscular r=−0.41 p=0.001) than in patients without pulmonary involvement (n=111; r=0 to 0.14). The change in IFN chemokine score was also more strongly correlated with the change in disease activity by VAS among patients with pulmonary involvement (global r=0.27 p=0.04; muscle r=0.45 p<0.001; extramuscular r=0.41 p=0.001) compared to patients without pulmonary involvement (r=0.06 to 0.15). Results for patients with active ILD (n=32) were similar to those for non-parenchymal pulmonary involvement.

Conclusion: Changes in IFN chemokine score correlated with changes in disease activity, particularly among myositis patients with pulmonary involvement (with or without active ILD). The IFN chemokine score may be a useful clinical biomarker for patients with myositis, especially in patients with lung involvement. In addition, these chemokines may provide useful insights into the pathogenesis of myositis or specific manifestations.

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Outcome of Muscle Function and Disease Activity in Patients Recently Diagnosed with Polymyositis and Dermatomyositis–Preliminary Results of a 1-Year Follow-up Registry Study.

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Background/Purpose: Most patients with polymyositis (PM) and dermatomyositis (DM) develop sustained muscle impairment. The aim of this study was to evaluate the muscle endurance (Functional Index 2, FI-2), muscle strength (MMT-8) and disease activity (selected 6-item core set measures) at 6 and 12 months after PM/DM diagnosis onset (baseline).

Methods: 72 patients, 40 with PM and 32 with DM, diagnosed 2003–2010 who performed the FI-2 and the MMT at baseline were included. They had median age md (Q1-Q3) 55 (41–70) years and md diagnosis duration 0 (0–1) months. 44 were women and 28 were men, 34 patients had md 50 (30–60) mg of prednisone/day, 38 were without medication. Mixed Linear Model with time as fixed variable was used with the Bonferroni after test to compare genders and diagnosis at different time points. Individually patients were identified as responders improving > 20% or worsening > 20% in the FI-2/MMT at follow-ups compared to baseline. Significance level was set to 0.05.

Results: The group had md 27 (8–60) % of FI-2 maximal score and md 94 (83–99) % of MMT maximal score at baseline (p<0.000) with no significant change at 6 or 12 months compared to baseline. Men had higher FI-2 scores md 50% (22–84) of maximal score at baseline, 84% (17–88) at 6 months, 61% (27–90) than women md 13% (5–42) at baseline, 19% (6–47) at 6 months and 18% (10–46) at 12 months (p<0.000) and men improved more over time in FI-2 than women (p<0.000). 44% of 41 patients were responders and 22% worsened in FI-2 score at 6 months and 49% of 45 patients were responders and 29% worsened at 12 months. 19 % of 37 patients were responders in MMT score at 6

months and 15% of 33 patients were responders at 12 months, no patient worsened. PM and DM patients improved in VAS physician global disease activity at 6 and 12 months compared to baseline (p<0.034, p<0.002) but patients with PM had significantly higher scores 10 (5–30) mm at 12 months compared to DM md 6 (4–15) mm (p<0.043). The men had significantly reduced global extra-muscular VAS scores at 6 and 12 months compared to baseline (p<0.011, 0.021) and women remained unchanged. Patients with DM had reduced extra-muscular disease activity at 6 and 12 months (p<0.022, p<0.021) while there was no change in PM.

Conclusion: Male patients seem to improve more over time than women in muscle endurance and improve in extra-muscular disease activity while women do not. Patients with DM seem to have lower disease activity compared to PM and DM patients improve in extra-muscular disease activity while patients with PM do not. Between 44–49 % were responders and 22–29 % worsened in muscle endurance while 15–19% were responders and none worsened in muscle strength.

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Clinical Study of Determination of Myositis-Associated Autoantibodies in Japanese Patients with Connective Tissue Diseases except Autoimmune Myositis.

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Background/Purpose: Anti-Jo-1 antibody is detected in the sera of patients with polymyositis/dermatomyositis (PM/DM). The antigen to which this antibody is directed is histidyl-tRNA synthase, an aminoacyl-tRNA synthase (ARS) which occurs in the cytoplasm of eukaryotes, and various anti-ARSs have been identified depending on differences of corresponding amino acids. In addition, other autoantibodies detected in patients with myositis include anti-Ku antibody, anti-Mi-2 antibody, anti-SRP antibody, and anti-PM-Scl antibody. This study was performed to evaluate the clinical characteristics and usefulness of determining the serum levels of these antibodies in patients with connective tissue diseases (CTD) other than PM/DM.

Methods: The study included 337 patients with CTD who had been followed up at the outpatient service of this hospital. Of them, 63 had PM/DM, 86 had systemic lupus erythematosus (SLE), 86 had rheumatoid arthritis (RA), 29 had Sjögren's syndrome (SjS), 11 had mixed connective tissue disease (MCTD), 14 had progressive systemic sclerosis (SSc), 12 had ANCA-associated vasculitis, 5 had Behçet's disease, 6 had aortitis syndrome, 7 had adult-onset Still's disease, and 18 had other diseases. Serum levels of antibodies were determined using Myositis Profile 3 Euroline Blot Test Kit commercially available from EURO-IMMUN (Lubeck, Germany).Clinical features were assessed for cases found to be positive for these autoantibodies.

Results: The analysis revealed that 12 patients were positive for anti-PL7 antibody, among other anti-ARS antibodies, and 6 of these patients had CTD other than PM/DM. Similarly, anti-PL12 antibody was detected in 4 patients including those with SLE, RA or MCTD. Anti-EJ antibody and anti-Jo-1 antibody were also detected frequently in RA and other non-myositis CTD. As for other myositis-associated autoantibodies, anti-PM-Scl75 antibody was detected in 7 patients with SLE and 2 patients with RA, while anti-Ku antibody was demonstrated in 3 patients with PM/DM, 4 patients with SLE and 3 patients with MCTD.

Regarding the relationship between the autoantibodies detected and clinical manifestations, concurrent interstitial pneumonia (IP) was high in incidence irrespective of underlying disorders among anti-ARS antibody-positive patients with CTD other than PM/DM. Anti-Ku antibody, anti-SRP antibody and anti-Mi-2 antibody, on the other hand, were detected also in non-myositis connective tissue diseases; however, there was no definite correlation between these antibodies and clinical manifestations including IP. The data obtained were reviewed also with respect to arthritis and Raynaud's phenomenon.

Conclusion: Serum levels of antibodies associated with myositis were determined in 337 patients, and anti-ARS antibodies were detected in a number of patients with CTD other than PM/DM. These autoantibodies detected were strongly correlated with IP, which tended to be intractable. The present results indicate that it is clinically useful to determine the serum levels of anti-ARS antibodies and other myositis-associated autoantibodies in patients with CTD complicated by IP even when their underlying diseases are not myositis.

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An Analysis of Metabolic Syndrome in Adult Dermatomyositis with a Focus On Cardiovascular Disease. Mariana T. Moraes, Fernando H.C. Souza, Thiago B. M. Barros and Samuel K. Shinjo. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: Metabolic syndrome (MetS) is a cluster of metabolic abnormalities associated with increased cardiovascular risk. MetS has been systematically evaluated in all systemic autoimmune rheumatic diseases except for dermatomyositis (DM). Hence, we evaluated the frequency of MetS in DM patients and analyzed the possible association of MetS with traditional cardiovascular disease (CVD) risk factors and DM-related clinical and laboratorial features.

Methods: The present cross-sectional single center study included 84 consecutive DM patients (Bohan & Peter, 1975) and 105 healthy control individuals. MetS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III.

Results: The median age was similar in both the DM and control groups (aged 41.5 *vs.* aged 42.0, respectively; $p=0.378$) with a comparable predominance of the female gender ($p=0.904$) and white race ($p=0.654$) in both groups. The median disease duration was 4 years (range: 1–7). The DM patients had a higher prevalence of MetS (41.7 *vs.* 7.0%, $p<0.001$), diabetes mellitus (17.9 *vs.* 1.0%, $p<0.001$), ischemic stroke (4.8 *vs.* 0%, $p=0.024$), and a family history of premature CVD (32.8 *vs.* 8.6%, $p=0.004$). However, the frequency of sedentarism, hypothyroidism, smoking habit and alcohol intake were similar in both groups ($p>0.05$). Further analysis of the DM patients with ($n=35$) and without MetS ($n=49$) revealed that the patients with this complication were older (50.0±14.5 vs. 40.9±14.6, $p=0.006$) and had a similar disease duration ($p=0.925$) and a higher incidence of systemic arterial hypertension prior to the disease (54.3 *vs.* 10.2%, $p=0.001$). The frequency of other comorbidities, previously mentioned lifestyle contributing factors, clinical and laboratory disease features, and therapy schemes were similar in both groups ($p>0.05$). In a multivariate analysis, only hypertension diagnosed prior to the disease was associated with MetS (odds ratio 10.47, 95% confidence interval 2.62–44.81).

Conclusion: MetS is highly prevalent in DM and prior hypertension seems to be a major determinant of its development while disease and therapy related factors do not appear to play a relevant role.

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Efficacy and Safety of Disease Modifying Drugs, Biologic Therapies and Immunoglobulin in Patients with Polymyositis and Dermatomyositis: A Systematic Literature Review. JA Martinez-Lopez Sr.[1], J. Graña Sr.[2], Santiago Muñoz-Fernandez[3], I. Rua-Figueroa[4], José M. Pego-Reigosa[5], Estíbaliz Loza Sr.[6] and SER group for the study of systemic autoimmune diseases[7]. [1]Fundacion Jimenez Diaz, Madrid, Spain, [2]Hospital Juan Canalejo, Spain, [3]Hospital Infanta Sofía, Madrid, Spain, [4]Hospital de GC Dr Negrin, Las Palmas GC, Spain, [5]Hospital do Meixoeiro, Vigo, Spain, [6]Research Unit. Sociedad Española de Reumatología, Madrid, Spain, [7]Madrid

Background/Purpose: The aim of this study was to systematically review the efficacy and safety of available drugs in patients with polymyositis (PM) or dermatomyositis (DM)

Methods: We systematically searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials up to October 2011 using a comprehensive search strategy for disease modifying drugs (DMARD), biologic therapies, intravenous immunoglobulins (IVIG), primary PMS and DPM, efficacy and safety (mesh terms and text words). Selection criteria were predefined by protocol. We selected meta-analysis, systematic literature reviews, clinical trials (CT), that included >18 year-old patients primary PMS and DM on the selected drugs, English, Spanish and French languages. Studies including patients with secondary PMS or DM, and basic science studies were excluded. Title and abstract selection and subsequent detailed review of selected articles were independently performed by two reviewers. A hand search of the selected articles was performed. The included studies quality was graded using the Oxford Levels of Evidence Scale, and results expressed as level of evidence (LE), recommendation grade (RG).

Results: The search strategy identified 2,442 potentially relevant articles, of which 114 were selected for full paper review. Twenty articles were eventually included in the analysis. The selection included 7 randomized CT, 13 open trials, which analyzed 334 patients. Main characteristics and results are shown in the table.

Table 1. Main results of the systematic literature review

Study	Efficacy
Amato (2011), RCT (n=16 DM), 52 w, Oxford 1c ETA vs PCB	-Improvement on IMACS: ETA/PCB 55%/60% -Prednisone stop: ETN/PCB 73%/20%, p<0,001 -Median time to treatment failure: ETA/PCB 358 d/148 d, p<0,001
Bunch (1978), RCT (n=14 PM), 12 w, Oxford 2b AZA vs PCB	-Muscle biopsy: AZA/PCB improvement, p>0,050 -MMT: improvement, AZA/PCB improvement, p>0,050
Bunch (1980), RCT (n=16 PM), 12 w, Oxford 2b AZA vs PCB	-CPK levels: AZA/PCB improvement, p>0,050 -Muscular strength AZA/PCB improvement, p=0,580 -Muscle biopsy: AZA/PCB improvement, p>0,050
Dalakas (1993) RCT (n=15 DM), 24 w, Oxford 1c IVIG (1 infusion) vs PCB	-Neuromuscular symptoms and scores of muscular strength: IG more improvement than PCB, p<0,018 p<0,035 -Muscle biopsy of IG patients: clear improvement
Fries (1973) RCT (n=8 PM), 16 w, Oxford 2b CYC vs PDN	-Disease activity: CYC 5/5 worsened; PDN 3/3 improvement
Miyasaka (2011) RCT (n=26 PM/DM), 26 w, Oxford 1b IVIG vs PCB	-MMT: IG/PCB improvement 92%/57%, p>0,050 -Dysphagia: IVIG ceased 5/7 (71%), PCB no improvement 2/2 (100%), p=0.167 -ADL score: IG/PCB improvement p>0,050 -CPK levels: IG/PCB improvement p>0,050
Vencovsky (2000) RCT (n=36 PM/DM), 24 w, Oxford 1c MTX vs CyA	-Muscle endurance and functional test: MTX/CyA improvement 29%/47%, p>0,050 -Clinical assessment: MTX/CyA improvement 65%/58%, p>0,050 -Global patient assessment: MTX/CyA improvement 59%/68%, p>0,050 -Muscle MRI: MTX/CyA improvement, p>0,050 -CPK levels: MTX normal levels, CyA elevated -ANA +: MTX/CyA 76%/68%, p>0,050
Cherin (2002) OT (n=35 PM), 3 yr, Oxford 2b IVIG	-Muscle power: improvement 25/35 (71%) -Muscle disability scale score: improvement 28/35 (80%) -Esophageal disorders: ceased 8/11 (27%) -Relapses: 7/25 (28%) -Steroids reduction: 22/35 (63%) -CPK levels: normal 19/33 (58%), improvement 14/33 (42%)
Cherin (1994) OT (n=11), 16 w, Oxford 2b IVIG	-British Medical Council Research grading system: improvement 3/11 (27%) -CPK levels: reduction 8/11 (73%)
Chung (2007) OT (n=8 DM), 24 w, Oxford 2b RTX	-Partial remission: 3/8 (38%) -Muscle enzyme levels and skin scores: not significantly changed from those at baseline
Dastmalchi (2008) OT (n=13 PM/DM), 16 w, Oxford 2b IFX	-IMACS: improvement 3/9 (33%), worsened 3/9 (33%) -MMT: no improvements -Muscle MRI: worsened 5 patients -Muscle biopsy: no changes from baseline
García Hernán. (2010), OT (n=14 PM/DM), 1 yr, Oxford 2b RTX + CYC	-Comlete or partial remission 1 m/6 m/1yr: 65%/100%/64% -British Medical Research Council grading system: improvement 100% -5 relapses, median of time to relapse: 11 m -Significant decreased: EGS, CPK, Mb, LDH -Pulmonary function: improvement 75%
Hara (2003) OT (n=11), 12 w, Oxford 2b IVIG	-MMT: improvement 7/8 (88%) -ADL score: improvement 7/8 (88%) -CPK levels: improvement 7/8 (88%)
Hengstman (2008) OT (n=6 PM/DM), 26 w, Oxford 2b IFX + MTX	-Patient and physician disease activity assessment, MMT, handheld dynamometry: improved -CPK levels: improved 2/6 (33%)
Kameda (2005) OT (n=10 DM + interstitial pneumonia), Oxford 2b Prednisolone + CYC + CyA	-5 survived for > 2 yr well
Levine (2005) OT (n=7 DM), 52 w, Oxford 2b RTX	-MMT: improvement 6/7 (86%) -Rash, alopecia, and reduced forced vital capacity, improved markedly -4 relapses
Mastaglia (1998) OT (n=7 PM/DM), Oxford 2b IVIG	-Complete or partial remission: 5/7 (71%) -Fuerza muscular: improvement 5/7 (71%) -CPK levels: normalization 5/7 (71%)
Mok (2007) OT (n=4 PM), 28 w, Oxford 2b RTX	-Promimal muscle power scores: improved 100% -CPK levels: improvement 100%, 2 normalization -HAQ: improvement 100% -Disability scores, SF-36: trend to improvement
Saito (2008) OT (n=15 PM/DM), 12 w, Oxford IGIV	-MMT: improvement 14/15 (93%) -ADL score: improvement 12/15 (80%) -CPK levels: improvement 15/15 (100%)
Tokano (2002) OT (n=11 DM/PM), 24 w, Oxford 2b CyA	-Respiratory symphoms improveement, ↑ PaO$_2$>10 mmHg, ↑ %DLCO, improvement chest radiology/TACAR, ↓ steroids doses >10%, ↓ LDH>25%: 7/11 (64%) maintained improvement

Abbreviations: PM=polymyositis; DM=dermtomyositis; w=week; m=month; yr=year; ETA=etanercept; PCB=placebo; AZA= azathioprine; CPK=creatine phosphokinase; CYC=cyclophosphamide; PDN=prednisone; CyA= cyclosporine A; MTX= methotrexate; IVIG=intravenous immunoglobulins; RTX=rituximab; IFX=infliximab; MMT=Manual muscle tests; ADL= activities of daily living; EGS= erythrocyte globular sedimentation; LDH= L-lactate dehydrogenase; IMACS=International Myositis Assessmenet Clinical Studies; HAQ=health assessment questionnaire.

Conclusion: Rituximab is effective to achieve remission in patients with PM/DM refractory to standard therapy (high dose prednisone and DMARD), (LE 2b; GR B-C). There is no current evidence on the efficacy of infliximab in patients with PM/DM (LE 2b; GR B-C). The addition of etanercept to steroids does not increase response rate or decreased adverse events (LE 1c, GR B), but could be useful as steroids sparring in DM patients (LE 1c, GR B). The addition of azathioprine to steroids does not increase response rate or decreased adverse events in DM patients (LE 2b; GR B-C). IVIG are effective to achieve remission in patients with PM/DM refractory to DMARD (LE 2b, GR B-C).

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Distinctive Characteristics of Anti-Mi-2 and –p155/140 Autoantibody Production in Two Cohorts of Mexican Patients with Dermatomyositis.

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Background/Purpose: Various autoantibodies associated with a unique subset of polymyositis/dermatomyositis (PM/DM), including antibodies to Jo-1 and other synthetases, SRP, Mi-2, PM-Scl and others, have been described. Specificities of autoantibodies and associated clinical manifestations in PM/DM are known to be affected by both genetic and environmental factors. In particular high prevalence of DM and anti-Mi-2 in Central America is thought to be associated with high UV index of the area. Prevalence of autoantibodies and clinical manifestation in PM/DM patients were evaluated comparing two cohorts in Mexico

Methods: Ninety-five Mexican patients with PM/DM (66 DM, 29 PM; 67 Mexico City, 28 Guadalajara) were studied. Autoantibodies recognized by sera were characterized based on protein analysis by immunoprecipitation using ^{35}S-methionine labeled K562 cell extract and RNA analysis in immunoprecipitates by urea-PAGE and silver staining. Clinical information was from database and chart review.

Results:

DM was 69% in Mexican PM/DM and anti-Mi-2 was the most common autoantibody specificity (35%), followed by anti-p155/140 (11%); however, anti-Jo-1 that is the most common in most PM/DM studies was only 4%. DM was more common and comparable in both Mexico City and Guadalajara (69% and 71%, respectively). However, autoantibody profile in DM of Mexico City vs Guadalajara showed striking difference; anti-Mi-2 was 59% vs 15% (P = 0.001) whereas anti-p155/140 was 9% vs 30% (P = 0.05), respectively. Thus, despite comparable DM dominance and similar UV index in two areas, prevalence of anti-Mi-2 was very high (59%) in Mexico City but not in Guadalajara (15%), suggesting a role of factors other than UV. Reported differences in genetic background of Mexican-Mestizo in these two areas (higher percentage of Amerindian derived genes in Mexico City vs European derived gene dominance in Guadalajara area) may be related to the difference in prevalence of autoantibodies. Clinical feature of anti-Mi-2(+) DM (n = 30) vs anti-Mi-2(−) DM (n = 36) was compared. Male was more common in anti-Mi-2(+) vs (−) (37% vs 22%,P=0.27). Shawl sign (86% vs 62%, p=0.0002) and weight loss (59% vs 45%, p=0.30) were more common in anti-Mi-2(+) DM than anti-Mi-2(−) DM. High CPK (> 2000) (88% vs 35%, p= 0.0001) was more common in anti-Mi-2(+) and levels of muscle enzymes were higher in anti-Mi-2(+) group than anti-Mi-2(−) group (CPK p = 0.0001, LDH p = 0.001).

N=	PM/DM 95	DM 66	DM Mexico City 46	DM Guadalajara 20	PM 29
Autoantibodies					
Mi-2	35%	45%	59%[1]	15%[1]	10%
p155/140	11%	15%	9%[2]	30%[2]	0%
Jo-1	4%	3%	4%	0%	7%
Myositis specific antibodies negative	36%	21%	15%	35%	69%

1, p=0.001; 2, p=0.056 by Fisher exact test

Conclusion: Anti-Mi-2 is at high prevalence in Mexican DM and associated with male, shawl sign, and high CPK. Prevalence of anti-Mi-2 and anti-p155/140 was significantly different in Mexico City vs Guadalajara, suggesting roles of factors other than UV in DM autoantibody production. Significant difference in clinical features of DM within a same country need to be carefully evaluated and the role of environmental and genetic factors will need further studies.

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Nsaids Suppress the Inflammatory Reaction Related to Muscle Soreness but May Delay Recovery.

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Background/Purpose: Eccentric muscle contraction causes an inflammatory reaction with pain peaking 24 to 48 hours after exercise–delayed onset of muscle soreness (DOMS). NSAIDs are used frequently for treatment or even prevention of DOMS. But evidence for treatment effects of NSAIDs is controversial. Timing of intervention and pharmacological properties of the specific NSAID tested might explain the controversial results. In two previous studies using a daily life oriented model of DOMS induced by walking down stairs we found for 200 mg celecoxib when given about 16 h after exercise a modest, insignificant reduction in pain [Phys Med Rehab Kuror 2012; 22: 57–63]. Ketoprofen (100 mg bid), a higher potent anti-inflammatory drug, caused a delay in recovery from DOMS when given immediately after exercise [Phys Med Rehab Kuror 2012; accepted for publication].This study investigated the effects of a Cox-2 inhibitor (90 mg qd etoricoxib) on markers of inflammation, pain and muscle force after eccentric exercise.

Methods: Randomized, double-blind, placebo-controlled, cross over study in 50 healthy subjects exposed to equipment based, eccentric exercise of the lower limb ("extrafit Beinstrecker", extrafit INVESTMENT GmbH, Germany). Subjects with pain during muscle contraction of at least 5 on an 0–10 point categorical scale at 16±2 h after exercise were eligible for randomization. Pain at rest and during contraction, muscle force, pain threshold at tender point and markers of inflammation (high sensitive C-reactive Protein (hsCrP), sedimentation rate, leucocyte number) were evaluated at various time points during the treatment period of 7 days.

Results: There is a non significant trend for reduction of pain at rest with etoricoxib treatment for the first 24 h of treatment (etoricoxib: 10.4±9.7, placebo: 11.5±9.9). For peak torque and pain threshold at the tender point, there is a trend of delayed recovery with etoricoxib treatment. HsCrP is increased due to DOMS and showed significant cross-over effects (p=0.0089). The carry-over effect might be due to anti-inflammatory effects of etoricoxib in period I (p=0.0341) carried over into period II. This is in line with the overall result indicating a significant long term anti-inflammatory effect evident through a reduction in hsCrP as compared to placebo (p=0.0203). Overall, also a trend of reduction in model induced increase of leucocytes (p=0.0981) was shown. Sedimentation rate was insensitive to the model and treatment effects.

Conclusion: Equipment based eccentric exercise of the lower limbs appears to be a robust model of muscle pain. This approach allows the design of cross-over studies since the exercise load can be individualized and adapted to differences in muscle force of the dominant vs. non-dominant limb. Treatment related effects are in line with previous studies indicating a modest analgesic effect but evidence for delayed recovery. This supports the concept that the inflammatory reaction is an essential part of the recovery process.

Anti-inflammatory treatment might cause a delay in recovery. Caution should be used when using NSAIDs for the treatment of exercise induced muscle pain.

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Inflammatory Muscle Disease Associated Pulmonary Hypertension - Clinical Features and Survival At a National Referral Centre. Matthew Webber[1], D. Dobarro[1], Clive Handler[2], Christopher P. Denton[3], Benjamin E. Schreiber[2] and John G. Coghlan[2]. [1]Royal Free Hospital, London, United Kingdom, [2]Royal Free Hospital, London, London, United Kingdom, [3]UCL, London, United Kingdom

Background/Purpose: The association between connective tissue disease (CTD) and pulmonary hypertension (PH) is well known, especially in the scleroderma population. However, the association between inflammatory muscle disease (IMD) and PH has not been described in detail.

Methods: We searched our prospectively collected database of patients undergoing diagnostic right heart catheterization (RHC) from January 2000 to December 2011 for patients with a diagnosis of IMD who had been investigated at the Pulmonary Hypertension Unit, Royal Free Hospital, London (a national tertiary centre). Patient data was sourced from written notes and electronic medical records.

Results: Of the twenty patients with IMD who underwent RHC at the unit, 17 were diagnosed with PH. Mean age was 61 years and 76% were female with 11 patients diagnosed as dermatomyositis (DM) and 6 as polymyositis (PM). Mean pulmonary artery pressure (mPAP) was 41.2 mmHg with a pulmonary vascular resistance (PVR) of 730.7 (dynes.s.cm^{-5}). Mean 6 minute walk test (6MWT) result was 215 meters and mean NTproBNP values were 176.5 pmol/l. On HRCT scan 70% of patients had evidence of extensive interstitial lung disease (ILD), 24% had limited fibrosis and 1 patient showed no prior evidence of ILD.

Eleven patients went on to receive vasodilator therapies. Of these, 9 underwent repeat RHC at 3–6 months. There was a trend towards improvement: mPAP fell from 40 to 34.2 mmHg (p=0.20) and PVR fell from 704 to 375 dynes.s.cm-5 (p=0.10).

In the 6MWT there was a mean increase of 65.9 meters from baseline to 3–6 months post therapy start date and this improvement was maintained with a mean final result of 380 meters. NTproBNP values showed a weak trend towards reduction, with a fall from 189 to 143 pmol/l (p=0.29) 3–6 months post treatment.

Amongst all 17 patients diagnosed with PH the overall median survival was 41.6 months. In the 12 patients with extensive ILD associated DM/PM the 1, 3 and 5 year survival rates were 75%, 42% and 28% respectively compared to 100%, 75% and 37% for the 5 patients with limited/no ILD (p=0.19 for difference).

Conclusion: This analysis is the largest of its kind to assess hemodynamic characteristics and functional response to treatment in this rare group of patients. Patients with IMD who develop PH have shown an improvement in mPAP, PVR, 6MWT and NTproBNP although statistical significance was not reached.

There was no significant difference between outcomes in patients with or without extensive ILD and the survival rates in patients with extensive ILD were higher when compared to a similar group of patients in a regional scleroderma population. Given the young age of some of these patients and the poor prognosis it may be beneficial to consider them for lung transplantation at an early stage in their diagnosis. Despite the poor prognosis however, this observed response to treatment may buy time for pulmonary rehabilitation and the use of combination therapies in patients who are either not eligible or waiting for transplant.

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Abnormal Videofluoroscopy Swallow Study Finding in Inflammatory Myopathy Patient with Dysphagia As Predictor of Prognosis. Hye Won Kim, Hwang Kim, Sung Hae Chang, Hye Jin Oh, Myeong Jae Yoon, Bong Seung Ku, Byeong Mo Oh and Eun Young Lee. Seoul National University College of Medicine, Seoul, South Korea

Background/Purpose: Previous reports of dysphagia in patients with inflammatory myopathy (IM) have been focused on detection, intervention and rehabilitation. However, whether dysphagia with abnormal videofluoroscopy swallow study (VFSS) findings is in relation to clinical manifestations and treatment response is not known. We hypothesized that clinical entities in IM patients with dysphagia would be distinct from non-dysphagia patients and abnormal VFSS finding could be a predictor of prognosis.

Methods: Total 236 patients with IM were reviewed in this study. Of them, the patients with dysphagia were evaluated with clinical functional scale, VFS scale, new VFSS scale, and American Speech-Language-Hearing Association National Outcome Measurement System swallowing scale. VFSS score was categorized into oral, pharyngeal and esophageal phase based on modified Logemann's methods. Association between VFSS scale and serum creatinine kinase (CK), clinical findings, or treatment response were analyzed.

Results: Among 236 IM patients, 28 patients had IM related dysphagia (26 with dermatomyositis, 1 polymyositis and 1 inclusion body myositis). Ten male and 18 female with mean age of 42.7 were included. Dysphagia was a presenting symptom in 5 patients (17.9%) and rest of patients developed dysphagia in average 221 days later. The VFSS results showed more prevalent abnormalities in pharyngeal phase than oral phase (n=26 vs. n=9). Baseline CK level was higher in delayed laryngeal elevation and epiglottic closure (LEEC) patients than in normal LEEC patients (473.8 ± 415.6 mg/dl vs 3931.7 ± 5532.3 mg/dl, p=0.008) (Figure). There was no correlation in total VFSS score with baseline CK level. Intravenous immunoglobulin were significantly more prescribed in delayed LEEC patients than in normal LEEC patients (OR=10.7, p=0.047). Frequency of pulmonary involvement and malignancy were significantly different between patients with dysphagia and patients without dysphagia (7.1% vs 40.4%, p<0.001, 35.7% vs 9.6%, p=0001, respectively) (Table 1).

Table 1. Comparison of clinical characteristics between IM patients with dysphagia versus without dysphagia

Baseline characteristics	Dysphagia (n=28)	Nondysphagia (n=208)	p-value
Male/female (n, %)	10/18 (35.7/64.3)	47/161 (22.6/77.4)	0.157
Age (mean ± SD)	42.7 ± 21.6	46.3 ± 14.5	0.244
DM/PM/IBM (n, %)	26/1/1 (92.9/3.6/3.6)	156/51/1 (75.0/24.5/0.5)	0.013
Creatinine kinase	**3869.8 ± 5916.3**	**1546.3 ± 3529.9**	**0.004**
Interstitial lung disease (n, %)	**2 (7.1)**	**84 (40.4)**	**<0.001**
Malignancy (n, %)	**10 (35.7)**	**20 (9.6)**	**0.001**
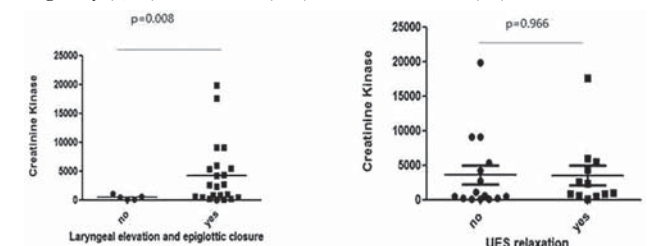
Conclusion: Abnormal VFSS findings in IM Patients with dysphagia were more prominent in pharyngeal phases than oral phases. Delayed LEEC was associated with higher baseline CK level and use of intravenous immunoglobulin. IM patients with dysphagia showed lower pulmonary involvement and higher malignancy. These results indicate that dysphagia in IM is not only a localized symptom or disabling condition, but also a predictor of prognosis.

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Clinical and Serological Associations of Malignancy in Adult Patients with Polymyositis and Dermatomyositis. Yuji Hosono, Ran Nakashima, Yoshitaka Imura, Naoichiro Yukawa, Hajime Yoshifuji, Motomu Hashimoto, Koichiro Ohmura, Takao Fujii and Tsuneyo Mimori. Graduate School of Medicine, Kyoto University, Kyoto, Japan

Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are systemic connective tissue disorders, which are often associated with internal malignancy. Several studies have reported the association between

autoantibodies (Abs) and clinical manifestations of the disease. In adult PM/DM, the association of malignancy with anti-p155/140 Ab is reported. However, background of association of malignancy in whole IIM patients is currently unclear. Here, we intended to analyze the clinical and serological associations of malignancy in adult IIM patients.

Methods: Clinical data and serum samples were collected from 207 adult Japanese patients with PM/DM (119 with DM and 88 with PM). Myositis-specific Abs were screened using the RNA immunoprecipitation assay (anti-ARS and anti-SRP) and immunoprecipitation with [^{35}S] methionine-labelled HeLa cells (anti-p155/140 and anti-CADM-140).

Results: 30 patients (14.5%,15 females and 15 males) had history of malignancies.20 patients (66.7%) were DM and 10 patients were PM (33.3%).No certain common cancer types were not recognized.In comparison with malignancy-negative patients, the average age at IIM onset was higher in malignancy-positive IIM patients (52.3 vs 59.6 years). Among malignancy-positive IIM patients, anti-p155/140 (N = 10,33.3%) and anti-ARS (N = 13,43.3%) predominated.2 (6.7%) were anti-SRP positive,1 (3.3%) was anti-CADM140 positive, and other 3 (10%) patients were positive for unknown Ab that immunoprecipitated a 120kDa protein.Anti-p155/140 showed the strong association with the onset of myositis and malignancy.All anti-p155/140-positive patients were diagnosised progressive malignancies at the same time of DM onset, while the onset of myositis proceeded 6.1 years at average before malignancy in 9 (69%) anti-ARS-positive patients. In addition, all anti-p155/140-positive patients were DM,whereas 46.2% (N=6) of anti-ARS-positive patients were PM. Onset age of patients with anti-p155/140 Ab were higher than that of patients with other Abs (65.7 vs 56.6).

Conclusion: Anti-p155/140 Ab and anti-ARS Abs were predominantly found among PM/DM patients associated with malignancy.Malignancies in PM/DM patients with anti-p155/140 were all diagnosed at the onset of DM,whereas the onset of malignancies in patients with anti-ARS did not coincide with myositis.These results suggest that different mechanisms maybe present in the association with malignancy and myositis between the two antoantibody-positive patient groups. Screening of autoantibodies and work up of malignancy are recommended in advanced age patients with a new diagnosis of DM.

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Myositis-Associated Usual Interstitial Pneumonia Has Better Survival Than Idiopathic Pulmonary Fibrosis.

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Background/Purpose: Usual interstitial pneumonia associated with idiopathic pulmonary fibrosis (IPF-UIP) has a poor prognosis with a median survival of 3 years. It is unknown whether myositis-associated UIP (MA-UIP) has an improved survival compared to IPF-UIP patients (pts). Our objective was to compare the cumulative and pulmonary event-free survival between MA-UIP and IPF-UIP.

Methods: Adult MA-UIP and IPF-UIP pts were identified using prospective registries. Pts with myositis (PM/DM/overlap) or the antisynthetase syndrome and radiographic UIP on HRCT scan (verified by a thoracic radiologist) or a lung biopsy revealing UIP histology were included. IPF pts met ATS criteria and had UIP pathology. Death status and date were verified with the Social Security Death Index. Kaplan-Meier survival curves and the log rank test compared cumulative and pulmonary event free survival (event = transplant or death) between a) all MA-UIP and IPF-UIP pts, b) MA-UIP pts with biopsy proven UIP (n=25) vs. IPF-UIP pts matched for age, gender and baseline FVC (±10%). Cox proportional hazards ratios compared overall and event free survival controlling for co-variates.

Results: IPF-UIP pts (n=81) had a mean age of 63 (±8.4), 73% male, 98% Caucasian, baseline FVC% 65 (±15.3) and DLCO% 47 (±17.3). The MA-UIP patients (n=43) had a mean age of 46 (±11.0), 35% male, 83% Caucasian, baseline FVC% 60 (±19.6) and DLCO% 47 (±18.3).

Median cumulative and event free survival time from diagnosis in IPF vs. MA-UIP was 5.2/1.8 years vs. 16.1/10.8 years, respectively. The 5 and 10 year % unadjusted event-free (graph 1) and cumulative survival was significantly worse in IPF-UIP vs. MA-UIP (25/0 vs. 80/50 and 59/32 vs. 80/65)

($p < 0.001$). The hazard ratio (HR) of IPF-UIP vs. MA-UIP pts was 2.86 (95% CI 1.45–5.61) for cumulative and 5.0 (95% CI 2.8–8.7) ($p<0.001$) for event-free survival. IPF-UIP event-free survival (but NOT cumulative survival) remained significantly worse than MA-UIP with a HR of 6.4 (95% CI 3.0–13.8) after controlling for age at ILD diagnosis, gender and baseline FVC%.

Out of 81 IPF-UIP, 36 died (mean age 68) and 45 had transplant (mean age 65) compared to 16 deaths (mean age 54) and 10 transplants (mean age of 54) in 43 MA-UIP. Respiratory failure was the most common cause of death in both groups, followed by infection.

25 biopsy-proven MA-UIP pts showed significantly better event free survival compared to matched IPF-UIP pts.

Graph 1. Kaplan-Meier curve for event free survival of MA-UIP and IPF-UIP
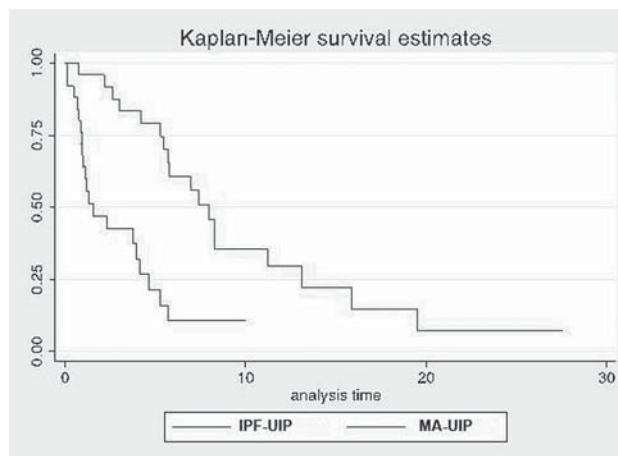
Conclusion: MA-UIP pts demonstrated a significant survival advantage over a matched IPF cohort, suggesting that despite similar histologic and radiographic findings at presentation, the prognosis of MA-UIP is superior to that of IPF-UIP. Thus, in pts with a radiographic or pathologic UIP picture, it is critical to distinguish those with an underlying autoimmune etiology as their course and response to therapies may differ from pts with true IPF.

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Proteomics Study of a Phase 1b Trial with an Anti-IFN-α Monoclonal Antibody Indicates Association of Soluble Interleukin 2 Receptor with Type I Interferon Activity in Patients with Dermatomyositis or Polymyositis.

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Background/Purpose: To evaluate downstream effects of an anti-IFN-α monoclonal antibody (mAb) in adult dermatomyositis (DM) and polymyositis (PM) patients using serum proteomics and gene expression profiling from patient blood and muscle samples.

Methods: A phase 1b randomized, double-blinded, placebo-controlled, multicenter clinical trial was conducted in adult patients with DM or PM. Whole blood, serum, and muscle specimens were procured both pre and 98 days post administration with an anti-IFN-α mAb, sifalimumab. Affymetrix whole genome arrays were used to measure transcript expression in whole blood and muscle, while a multiplex luminex immunoassay was used to measure serum levels of more than 130 proteins. Target modulation of type I IFN activity was measured using a 13 gene type I IFN gene signature in patients following administration with either sifalimumab or placebo.

Results: Serum levels of soluble interleukin-2 receptor (sIL-2R) were significantly higher at baseline in 19 DM and 18 PM patients showing an elevated blood type I IFN signature than in 6 DM and 5 PM patients without an elevated signature and 20 normal controls. Among patients with high baseline type I IFN gene signature, those expressing high levels of sIL-2R had lower manual muscle testing (MMT8) scores at baseline, compared to patients with only an elevated baseline type I IFN gene signature. Following administration with sifalimumab, whole genome transcript profiling identified

the IL2 signaling pathway as among the top ten most suppressed pathway, along with several T cell-related signaling pathways. This result was not identified in placebo-dosed patients. Sifalimumab also down-regulated sIL-2R levels by more than 30% in 3 DM and 4 PM patients, with no significant change in 11 placebo dosed patients. Further, patients showing strong sIL-2R down-regulation post dosing of sifalimumab, also exhibited suppression of the type I IFN gene signature (target suppression > 80% in the blood).

Conclusion: Our results demonstrate that sIL-2R levels in the serum of myositis patients, in combination with a blood type I IFN gene signature, may correlate with disease activity in a patient subset better than a type I IFN gene signature alone. Sifalimumab down-regulated serum sIL-2R levels in a subset of myositis patients that also showed strong suppression of the type I IFN gene signature in blood. These results suggest the possibility to combine sIL-2R and type I IFN gene signature as a prognostic marker for myositis patients.

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Significant Functional Improvement Using Aggressive Immunomodulatory Therapy in Patients with Inflammatory Myopathy and Interstitial Lung Disease. Ramona Mihu[1], Roger D. Rossen[1], Jovan Popovich[2] and Sandra L. Sessoms[1]. [1]Baylor College of Medicine, Houston, TX, [2]The Methodist Hospital, Houston, TX

Background/Purpose: Pulmonary disease in patients with idiopathic inflammatory myopathies, polymyositis (PM), dermatomyositis (DM), and clinically amyopathic dermatomyositis (CADM) is a major cause of morbidity. Approximately 35–40% of patients with PM/DM/CADM develop interstitial lung disease (ILD) during the course of their illness. Mortality ranges from 45–71% in those with ILD. Treatment of ILD in patients with inflammatory myopathies remains a challenge. In the absence of evidence-based data from randomized control trials, corticosteroids are regarded as the mainstay of therapy, although their effect is variable.

Methods: We retrospectively evaluated 62 patients with idiopathic inflammatory myopathies treated during the past ten years.

Results: Of the 62 patients reviewed, 22 developed ILD with varying degrees of functional impairment; 11 of the 22 had PM, 8 had DM and 3 had CADM. Three eventually died of causes unrelated to their lung disease. Pulmonary disease severity was judged by measuring blood oxygen saturation, dyspnea and tachypnea at rest, and following exercise, radiographic evidence of pulmonary infiltration and signs of pulmonary restriction and impaired diffusion capacity by pulmonary function testing. Patients were followed for at least 24 months, with an average length of follow up of 121 months. All ILD patients received combination therapy with an average number of 3 immune modulating agents plus corticosteroids. Four out of the 7 patients with severe ILD received concomitant combination therapy with IVIG, cyclophosphamide and cyclosporine for up to 6 months; 7 other moderate to severely affected patients received IVIG plus cyclosporine in addition to corticosteroids. Patients' functional capacity before and after treatment was evaluated according to the NYHA criteria developed for the assessment of patients with heart failure. The table (below) demonstrates that immunomodulatory therapy resulted in a statistically significant improvement, (Chi Square = 10.3, Df = 3 p < 0.02). One patient developed *Candida* pneumonia and 3 who were treated with cyclosporine and other agents had reversible declines in renal function during therapy. Four patients developed Herpes Zoster during the follow up period, but long after the aggressive immunomodulatory therapy was finished. Treatment was otherwise well tolerated.

Change in function

Functional class	1	2	3	4
before treatment	3*	8	5	6
after treatment	10	9	3	0

Worse

Better

*No. patients in each functional class

Conclusion: Our results support the early use of aggressive immunomodulatory therapy with a combination of agents designed to interfere with T cell recruitment, activation and replication in patients with idiopathic inflammatory myopathies and ILD.

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Efficacy of Rituximab for the Treatment of Refractory Inflammatory Myopathies Associated with Anti-Histidyl-tRNA Synthetase Antibodies (the FORCE Jo1 Study). Yves Allenbach[1], Aude Rigolet[1], Marguerite Guiguet[2], Isabelle Marie[3], Eric Hachulla[4], Dominique Farge[5], Kuberaka Mariampillai[1], Serge Jacquot[6], Fabienne Jouen[7], Olivier Boyer[8], Lucile Musset[9], Serge Herson[1] and Olivier Benveniste[1]. [1]Pitie-Salpetriere Hospital, Paris, France, [2]Paris, France, [3]Service de médecine interne, CHU de Rouen, Rouen, France., Rouen, France, [4]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [5]EBMT, Paris, France, [6]INSERM U905, Université de Rouen, Rouen, France, [7]Rouen University Hospital, Rouen Cedex, France, [8]INSERM U905, University of Rouen, Rouen, France, [9]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: anti-histidyl-tRNA synthetase (anti-Jo1) antibodies are found in approximately 25–30% of patients with idiopathic inflammatory myopathies, frequently in the frame of an anti-synthetase syndrome characterized (in addition to the myositis) by the association of interstitial lung disease (ILD, one of the main prognostic factor), arthritis, Raynaud's phenomenon and mechanic's hands. The recommended treatment is high dose corticosteroids in association with an immunosuppressant. Nevertheless, some patients remain refractory. We tested the efficacy of rituximab in this situation.

Methods: we conducted a prospective, multicenter, open, phase II study (ClinicalTrials.gov: NCT00774462) of rituximab (1g at day 0 (D0), 15 and month 6). Inclusion criteria were myositis as defined by the 119th ENMC workshop (Hoogendijk JE, et al. Neuromuscul Disord 2004;14:337–45) with anti-Jo1 antibodies, refractory to conventional treatments (i.e. failure, lack of efficacy or major side effects of prednisone and at least two immunosuppressants, leading the physician to a DMARD decision). Endpoints were evaluated at month 12 (M12).

Results: 12 patients were enrolled (8 men, median (IQR) age 50 (32 to 59)). The delay between diagnosis/first treatment and inclusion was 23 months (12 to 45). Patients already received in average 3 lines of treatments (2 to 4). Associated treatments with rituximab were prednisone (n=12), methotrexate (n=1), azathioprine (n=6), intravenous immunoglobulins (n=4), mycophenolate mofetil (n=2) and cyclophosphamide (n=1). Eleven patients completed the study and one was lost of follow-up after 3 weeks. No particular side effects due to rituximab were observed.

Muscle weakness evaluated by the manual testing (Kendall's test on 10 muscles,) was 94.5 (range 75 to 100) at D0. Only 1 patient had normal strength (=100) at DO, and 6 patients at M12. Median creatine kinase (CK) was 1331 U/l (range 32 to 11718) at D0. Only 1 patient had normal CK level (< 190 U/l) at D0, and 9 patients at M12. Effort dyspnea was noticed in 7/12 patients at D0 and 4/11 at M12. At DO, pulmonary tests showed, median FVC: 72% (46 to 117), FEV1: 69% (46 to 104) and DLCO/VA ratio: 73 (43 to 127). At M12, on the 6 patients who completed functional respiratory tests, 3 presented an increase by more than 10% of their FVC, FEV1 or DLCO/VA. Arthritis were observed in 9/12 patients at D0 vs. 4/11 at M12. Anti-Jo1 antibody titers remained stable over time, with no seronegativation. Finally, at M12 on 11 patients, the burden of associated treatments was unchanged (n=1) or even increased (n=4) in 5 patients but was slimmed-down for 6 patients.

Conclusion: in the difficult situation of long past history of refractory anti-synthetase syndrome with anti-Jo1 antibodies, rituximab seems effective in 50% of the cases permitting a reduction of immunosuppressants. This effect is observed on muscle strength, ILD and arthritis. Rituximab should now be evaluated in a phase III trials in this homogenous group of patients.

Expanding the Clinical and Serological Spectrum of MDA5-Associated Dermatomyositis. John C. Hall[1], Livia Casciola Rosen[1], Sonye K. Danoff[2], Lesly-Anne Samedy[1] and Lisa Christopher-Stine[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins School of Medicine, Baltimore, MD

Background/Purpose: Dermatomyositis (DM) is a heterogeneous systemic disease with specific autoantibodies (Abs) which correlate with unique clinical phenotypes. Melanoma differentiation-associated gene 5 (MDA5) Abs have been described (in several Japanese DM patient cohorts and one US DM cohort) in conjunction with amyopathic DM and rapidly progressive interstitial lung disease (ILD). Given the widening spectrum of associated clinical findings, we sought to determine prevalence of Abs to MDA5, associated clinical findings and whether Ab titers correlated with clinical course in a longitudinal cohort of myositis patients.

Methods: This is a retrospective case series review of clinical and serologic features of eleven DM patients with MDA5 Abs who were evaluated at the JHU Myositis Center. In addition, six MDA5 + patients with longitudinal data and banked serologic samples were evaluated for clinical correlations (MRC scale strength, cutaneous features, arthritis, ILD) with Ab titers.

All patients were evaluated as part of routine clinical care between 2006 and 2012. Informed consent was obtained, and 165 consecutive DM patients (for whom banked serum samples were available) were tested for the presence of MDA5 Abs. Patient sera were screened for autoantibodies by immunoprecipitation (IP) of *in vitro* transcribed/translated (IVTT), radiolabeled MDA5. When multiple serum samples were available from the same patient, IPs were performed simultaneously and run on the same gel for comparison. Patient sera were further screened for antibodies against Jo-1 and Ro52 by ELISA, and Mi-2 and NXP2 by IP of IVTT generated protein.

Results: MDA5 was targeted in 11/165 (6.7%) patients with DM. In our cohort of 11 MDA5+ patients, 82% (9/11) presented with a symmetric polyarthropathy; 5% (5/11) demonstrated overt clinical myopathy; and only 64% (7/11) had ILD. The majority of ILD stabilized with immunosuppression. Only two patients had progressive ILD, and both were anti-Ro 52 positive. All MDA5+ positive patients remained Ab positive over the entire course of follow-up. Longitudinal MDA5 antibody titers were assessed in 6 patients; with the exception of one patient, titers did not vary significantly over time, nor did they track with clinical course. Jo-1 was negative in all MDA5+ patients, while anti-Ro52, frequently found in Jo-1 positive patients, was seen in 3 of 11 patients.

Conclusion: This report adds to our growing understanding of the expanding phenotype of MDA5+ DM. The MDA 5 phenotype can overlap with the antisynthetase syndrome (e.g. mechanics hands, arthritis, myositis, fever and ILD),; however autoantibodies to Jo-1 were not found concomitantly. Many patients presented initially with an inflammatory arthritis that looked clinically similar to RA, and many patients had an overt myopathy. While MDA5 autoantibodies remained positive throughout disease course and relative titer did not correlated with clinical course, even patients with a relatively fulminant clinical course of disease with regard to ILD, myositis, cutaneous disease, and arthritis were often able to attain sustained clinical remission, in some cases even after discontinuation of immunosuppression.

Disclosure: J. C. Hall, None; **L. Casciola Rosen**, None; **S. K. Danoff**, None; **L. A. Samedy**, None; **L. Christopher-Stine**, None.

Lung Nodules in Patients with Idiopathic Inflammatory Myopathies. Laura C. Cappelli[1], Andrew L. Mammen[2], Sonye K. Danoff[3], Grant H. Louie[1], Thomas E. Lloyd[2] and Lisa Christopher-Stine[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins, Baltimore, MD, [3]Johns Hopkins School of Medicine, Baltimore, MD

Background/Purpose: The idiopathic inflammatory myopathies are associated with an increased incidence of malignancy, and interstitial lung disease (ILD) has been reported in as many as 20–78% of patients with polymyositis and dermatomyositis when followed from diagnosis. As a result of these associations, patients often receive CT scans of the chest where lung nodules are incidentally discovered. The radiographic nature of these lung nodules and whether they tend to increase in size, regress, or remain stable in size has not been described. The aim of this study was to define the prevalence of lung nodules in patients with inflammatory myopathies in a large clinical cohort evaluated at a Myositis Center, the clinical features associated with the presence of lung nodules, and whether the nodules changed in size over time.

Methods: Data was obtained from the cohort of 976 patients referred to the Myositis Center at Johns Hopkins. Only patients with confirmed inflammatory myopathies and at least one chest CT scan performed at our Center for clinical purposes were included in the study. For patients with more than one CT, all CTs were reviewed. The presence of interstitial lung disease was defined by decreased total lung capacity (TLC) or diffusion capacity (DLCO) on pulmonary function testing and/or presence of ground glass opacities on chest CT.

Results: 298 of the 976 patients had at least one chest CT performed at our Center. The prevalence of lung nodules in these patients was 25.5% (76/298). Only 5 patients had a nodule > 10 mm, and in those patients with follow up CTs, none of these nodules increased in size. Interstitial lung disease was present in 34.9% of the total cohort. The prevalence of nodules was not significantly different in those who had interstitial lung disease and those who did not (26.9% and 24.7% respectively, p=0.68). Of the 76 patients with lung nodules, 39.4 % (30/76) had a follow-up chest CT. The interval for follow-up was variable and ranged from 3 to 19 months. On subsequent CTs, none of the nodules had progressed in size by more than.2 cm and 51.6% (16/31) had regressed entirely.

Conclusion: Lung nodules are frequently observed in patients with inflammatory myopathies, but not greatly increased in prevalence over healthy adults where they are reported in 18% of patients. Lung nodules were no more common in patients with ILD than those patients without ILD. The lung nodules do not likely represent malignancy as they do not progress when followed over time. In fact, about half of patients had regression of the nodules,

Disclosure: L. C. Cappelli, None; **A. L. Mammen**, anti-HMGCR antibody test,; **S. K. Danoff**, None; **G. H. Louie**, UCB, 5; **T. E. Lloyd**, None; **L. Christopher-Stine**, None.

High Prevalence and Clustering Over Time of Anti-PL-7 Autoantibody-Positive Idiopathic Inflammatory Myopathies. Yoshioki Yamasaki[1], Minoru Satoh[2], Hidehiro Yamada[1], Machiko Mizushima[1], Takahiro Okazaki[1], Hiroko Nagafuchi[1], Seido Ooka[1], Tomohiko Shibata[1], Hiromasa Nakano[1], Hitoshi Ogawa[1], Kohei Azuma[1], Akihiko Maeda[1], Hirofumi Mitomi[1], Tomofumi Kiyokawa[1], Kosei Tsuchida[1], Hidenori Mikage[1], Jason Y.F. Chan[2] and Shoichi Ozaki[1]. [1]St. Marianna University School of Medicine, Kawasaki, Japan, [2]University of Florida, Gainesville, FL

Background/Purpose: Unusually high prevalence of autoantibodies to threonyl tRNA (PL-7) [17% in polymyositis/dermatomyositis (PM/DM) associated with lower levels of serum creatine kinase (CK) and milder muscle weakness (vs. anti-Jo-1 positive patients)] was found in our study 8 years ago. We extended and analyzed a larger population of patients with PM/DM to further clarify the clinical characteristics of patients with anti-PL-7 antibodies.

Methods: The diagnosis of PM/DM and clinically amyopathic DM (cADM) was based on the Bohan and Peter criteria and modified Sontheimer's criteria, respectively. Autoantibodies in sera from 97 Japanese patients with PM/DM (36PM/57DM/4cADM) were characterized by immunoprecipitation of K562 cell extract. Antibodies to Jo-1, melanoma differentiation-associated gene (MDA) 5, and Mi-2 also were tested by ELISA. Clinical and laboratory data were retrospectively collected.

Results: The prevalence of autoantibodies to aminoacyl tRNA synthetases (ARS) such as histidyl (Jo-1) (22%), glycyl (EJ) (4%), isoleucyl (OJ) (1%), and alanyl tRNA synthetase (PL-12) (1%), and autoantibodies to Ku (7%), p155/140 (5%), SRP (4%), and Mi-2 (3%) was similar to other studies. However, prevalence of anti-PL-7 was unusually high (12%, 12/97) in contrast to other studies showing a prevalence of up to 4% ($p < 0.05$ by Fisher exact test) consistent with our previous report. Notably, disease onset of patients with anti-PL-7 was either before 1993 or after 2002 and none between 1994–2001 whereas onset years of patients with anti-Jo-1 was distributed throughout (Table 1).

Table 1. Prevalence of autoantibodies to PL-7 and Jo-1 according to year of onset.

Year	90–93	94–97	98–01	02–05	06–09	10–12
n	6	5	13	19	39	15
Anti-PL-7 (%)	50	0	0	16	10	13
Anti-Jo-1 (%)	17	60	23	11	23	20

Interstitial lung disease (ILD) was common in all anti-ARS-positive patients. Manual muscle testing (MMT) (total score of 90) <80 was only in

10% of anti-PL-7 group vs. 35% in anti-Jo-1 group, CK >3000 IU/l was 17% in anti-PL-7 vs. 57% in anti-Jo-1 (*p* <0.05 by Fisher exact test) (Table 2).

Table 2. Frequency of ILD and severity of muscle involvement in patients with anti-ARS antibodies (vs. patients with no anti-ARS antibodies).

Autoantibodies (n)	PL-7 (12)	EJ (4)	Jo-1 (21)	ARS (−) (57)	P
ILD (%)	92[a]	100[a]	100[a]	49	[a]<0.05 vs. ARS (−)
MMT (max 90) (SD) <80 (%)	85 (5) 10[b]	90 (0) 0	81 (10) 35	81 (10) 40	[b]<0.1 vs. ARS (−)
Serum CK IU/l (IQR) <200 IU/l (%) >3000 IU/l (%)	942 (360–2679) 8 16	715 (246–1308) 25 0	3726[c] (756–5534) 5[d] 57[e]	606 (181–1807) 25 14	[c]<0.1 vs. PL-7[c] <0.05 vs. ARS (−)[d] <0.1 vs. ARS (−)[e] <0.05 vs. PL-7[e] <0.1 vs. EJ

Conclusion: Persistently high prevalence of anti-PL-7 antibodies was observed in this cohort, however, there was a 10 year period when anti-PL-7 was not observed, suggesting roles of environmental factors. Muscle involvement was milder in patients with anti-PL-7 and EJ vs. anti-Jo-1.

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Standardized Incidence Ratios and Predictors of Malignancies in 215 Southern Chinese Patients with Inflammatory Myopathies. Chi Chiu Mok[1], Chi Hung To[1], ML Yip[2] and King Yee Ying[3]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Kwong Wah Hospital, Kowloon, Hong Kong, [3]Princess Margaret Hospital, Hong Kong, Hong Kong

Background/Purpose: To examine the standardized incidence ratios (SIRs) and predictive factors for malignancy in a cohort of southern Chinese patients with inflammatory myopathies (IM).

Methods: Patients with polymyositis (PM), dermatomyositis (DM) or amyotrophic dermatomyositis (ADM) diagnosed between 2000 and 2010 in the three regional hospitals were studied. Diagnosis was made according to the Peter and Bohan criteria. Demographic data, clinical presentation, time of diagnosis of malignancies since diagnosis and the nature of malignancies were retrieved. Patients with malignancies diagnosed more than 1 year before the onset of IM were excluded. The age- and sex-adjusted standardized incidence ratios (SIRs) of malignancies in comparison to those of the general population obtained from the cancer registry of Hong Kong within the same study period were calculated. Demographic data, types of IM (DM vs ADM vs PM), creatine kinase (CK), presence of concomitant rheumatic diseases, extra-muscular manifestations were analyzed as predictors for malignancy in Cox regression models.

Results: 215 patients (65% women) with IM were studied (125 DM, 75 PM, 15 ADM) with a mean follow-up of 4.7±4.6 years. The mean age of disease onset was 51.5±16.3 years. Concomitant rheumatic diseases were diagnosed in 39 (18.1%) patients. 52 patients (24.2%) (44 DM, 6 PM, 1 ADM) were diagnosed to have malignancies. 13 (25%) and 14 (26.9%) malignancies, respectively, were identified within the preceding 1 year and at the same time of IM diagnosis. The mean time interval between the diagnoses of IM and malignancies was 1.29±1.56 years. The age- and sex-adjusted SIRs for malignancies for DM and PM were 3.9 [2.8–5.5] and 1.1 [0.5–2.6], respectively. The most frequently associated malignancies were: nasopharyngeal cancer 21 (40%), gastrointestinal cancer 10 (19%), lung cancer 10 (19%), breast cancer 4 (7.6%), cervical cancer 3 (5.7%), and the corresponding age- and sex-adjusted SIRs were 26.8 [16.5–41.5], 1.3[0.7–2.5], 1.8[0.9–3.5], 1.9[0.7–5.2], 8.4[2.6–26.5], respectively. On univariate analysis, the age at IM diagnosis (HR 1.03[1.02–1.05]), male gender (HR 3.88[1.95–7.74]), history of smoking (HR 3.86[1.95–7.65]), the diagnosis of DM (HR 3.37[1.39–8.14]), oropharyngeal muscle involvement (HR 2.55[1.28–5.07]) were associated with malignancies whereas the presence of concomitant rheumatic diseases (HR 0.23[0.05–0.95]), presence of interstitial lung disease (HR 0.37[0.16–0.85]) and use of azathioprine (HR 0.35[0.18–0.68]) were protective. Cox regression analysis revealed that a history of smoking (HR 2.7[1.12–6.56]), and oropharyngeal muscle involvement (HR 2.65[1.22–5.75]) were independently associated with malignancies.

Conclusion: DM, but not PM, was associated with an increased risk of malignancies compared to general population. DM patients in southern Chinese were particularly at risk of carcinoma of nasopharynx, lung and cervix.

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Polymyositis in HIV+ Patients Is Associated to Uncontrolled Viral Load. Yves Allenbach[1], Odile Dubourg[1], Thierry Maisonobe[1], Anthony Behin[2], Charles Duyckaerts[1], Guillaume Breton[1], Olivier Fain[3], Marie-Caroline Meyhoas[4], Catherine Leport[5], Marc-Antoine Valentin[6], Daniel Vittecoq[7], Jean-François Bergmann[8], Thomas Anslik[9], Marie-Paule Chauveheid[10], Zahir Amoura[11], Thomas de Broucker[12], Pierre Bourgeois[1], Bruno Eymard[2], Serge Herson[1] and Olivier Benveniste[1]. [1]Pitie-Salpetriere Hospital, Paris, France, [2]Institute of Myology, Pitie-Salpetriere Hospital, Paris, France, [3]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [4]Department of Infectious Diseases, Saint Antoine Hospital, Paris, France, [5]Paris, France, [6]Department of Infectious Diseases, Pitié-Salpetriere Hospital, Paris, France, [7]Department of Infectious Diseases, K Bicetre Hospital, Kremlin-Bicetre, France, [8]Internal Medicine, Lariboisiere Hospital, Paris, France, [9]Internal Medicine, Ambroise Pare Hospital, Boulogne Billancourt, France, [10]Internal Medicine, Bichat Hospital, Paris, France, [11]CHU Pitié-Salpêtrière, Paris, France, [12]Department of Neurology, Delafontaine Hospital, Saint Denis, France

Background/Purpose: Different myopathies can be observed in HIV-infected patients, such as idiopathic inflammatory myopathies (inclusion-body myositis or polymyositis) or toxic mitochondrial myopathies secondary to antiretroviral therapy. The frequency and the evolution of those different myopathies is not precisely known, thus we aimed to describe all HIV patients from our center who presented a myopathy.

Methods: We conducted a systematic review of computerised database of the department of pathology to select HIV infected patients who underwent a muscle biopsy during the 2005–2011 periods. For each biopsies, morphological (hematein eosin staining), mitochondrial (Gomori trichrome, succinic dehydrogenase and cytochrome oxidase staining) and immunological (HLA1, lymphocytes subclasses staining) analyses were performed.

Results: During the studied period, 2880 muscle biopsies were performed. Fifty biopsies (1.7%) were realised in 45 HIV+ patients (mean age: 50.1 years [39–61,2]).

Among the 50 biopsies, 43 were abnormal. The most frequently observed myopathy was polymyositis (60%). Among pathologically diagnosed polymyositis during this period of time (n=161), 23 (14%) were diagnosed in HIV+ patients. After polymyositis, mitochondrial abnormalities were the most frequently observed lesions (54%, myositis and mitochondrial abnormalities beeing observed concomitantly in some patients). Five cases (13%) of inclusion body myositis were also pathologically diagnosed.

Compared to a cohort of 50 anti-synthetase syndrome patients (with anti-Jo1 Abs), HIV polymyositis patients had a less severe weakness (MRC manual testing ≥ 4/5 83% in HIV+ vs. 54% for Jo1+ patients p<0.05) and lower CK levels (1677 vs. 4975 IU/L, p<0.05). Muscle weakness disappeared within six months after steroid treatments and/or highly active antiretroviral therapy introduction or modification. HIV viral load was detectable (125.186±21.295 copies/ml) for 80% of polymyositis patients whereas it was undetectable for all patients with isolated mitochondrial abnormalities (p<0.01). For the 7 patients with isolated mitochondrial abnormalities (suggesting mitochondrial toxicity), nucleoside-analogue reverse-transcriptase inhibitors were stopped for another highly active antiretroviral therapy combination, in the frame of an interventional study (the Myotox trial). Two years latter, no significant change concerning either muscular symptoms, CK level or pathological features of mitochondrial abnormalities were observed after this intervention.

Conclusion: This retrospective study showed that polymyositis is the most frequent HIV associated myopathy, and suggested that a HIV test must be proposed to every patient presenting a polymyositis. Polymyositis in HIV patients seemed not severe, and is associated with uncontrolled HIV replication. HIV patients with isolated mitochondriopathy did not improve after nucleoside-analogue reverse-transcriptase inhibitors withdrawal.

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Autoantibodies to Small Ubiquitin-Like Modifier Activating Enzymes in Japanese Patients with Dermatomyositis. Manabu Fujimoto, Takashi Matsushita, Yasuhito Hamaguchi, Kenzo Kaji, Minoru Hasegawa and Kazuhiko Takehara. Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

Background/Purpose: Myositis-specific autoantibodies (MSAs) are closely associated with distinct clinical subsets within idiopathic inflammatory myopaties, and thus serve as useful diagnostic tools. Recently, anti-small ubiquitin-like modifier activating enzyme (SAE) autoantibody has been reported as a novel MSA in dermatomyositis (DM) patients. In this study, we detected this autoantibody in a Japanese DM cohort and assessed its clinical correlations.

Methods: In this study, 456 consecutive Japanese patients with DM (11 children, 455 adults) including 373 with classic DM and 83 with clinically amyopathic DM (CADM) were examined. Controls included 62 patients with polymyositis, 108 with systemic lupus erythematosus, 433 with systemic sclerosis, and 124 with interstitial lung disease (ILD) alone. Autoantibodies were detected by immunoprecipitation assays using ^{35}S-methionine-labeled or unlabeled K562 cell extracts and western blotting using anti-SAE1/2 antibodies.

Results: Sera from 7 (1.5%) DM patients immunoprecipitated 90 and 40 kDa proteins, and were confirmed to react with SAE by western blotting. One patient had juvenile DM, while the other 6 had adult DM (median age of onset, 67 years). None of the control sera had this antibody. Heliotrope rash, Gottrons papules, periungual lesions, V signs, and Shawl signs were observed in 57%, 86%, 100%, 57%, and 86%, respectively. Consistent with a UK cohort study[1], skin manifestations preceded muscle involvement in 86% patients with anti-SAE antibodies. Systemic features were present in 57% of patients inbcluding 2 patients with severe dysphagia. In addition, chronic ILD was substantially higher in anti-SAE-positive DM patients (71%) than those negative (34%).

Conclusion: Consisitent with the UK cohort study, this study confirmed that anti-SAE antibody is specific for DM and that anti-SAE antibody characteristically occur in patients who present with CADM first and then progress to develop myositis with a high frequency of systemic features, including dysphagia. Our study also revealed a high frequency of ILD in Japanese DM patients with anti-SAE antibody.

1) Betteridge ZE et al. Ann Rheum Dis. 2009;68:1621–5.

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Long Term Outcome of Interstitial Lung Disease in Idiopathic Inflammatory Myopathies and Amyopathic Dermatomyositis. Machiko Mizushima[1], Hidehiro Yamada[2], Yoshioki Yamasaki[1], Masaomi Yamasaki[3], Minoru Satoh[4] and Shoichi Ozaki[5]. [1]St. Marianna University School of Medicine, Kawasaki, Japan, [2]St. Marianna University, Kawasaki, Japan, [3]St Marianna University, Yokohama City Seibu Hospital, Yokohama, Japan, [4]University of Florida, Gainesville, FL, [5]St. Marianna University School of Medicine., Kawasaki, Japan

Background/Purpose: The aim of this study was to assess the long term clinical course and outcome of interstitial lung disease (ILD) in polymyositis/dermatomyositis (PM/DM) and to determine predictive factors for the outcome of PM/DM-associated ILD.

Methods: Among 228 patients with IIM and clinically amyopathic dermatomyositis (cADM), 140 patients with ILD were identified by medical records search at our hospital. Pulmonary high-resolution computed tomography (HRCT) scan was available in 93 patients and their clinical features were analyzed.

Results: Mean follow up period (SD) of the 93 patients was 68 (55) months. Clinical course of ILD was monophasic resolution in 24 patients (25.8%), chronic stable in 30 (32.3%), relapsing in 32 (34.4%) and fatal progressive within one year in 7 (7.5%) (Table 1). Univariate analysis indicated older age (p =0.444), dermatomyositis (p =0.0393), cough (p =0.0167), periungual erythema (p =0.0123), lower values of aldolase

(p =0.047) and AST (p =0.031) were associated with the fatal ILD. Female (p =0.0045), concurrent malignancy (p =0.0037), and the absence of anti-aminoacyl-tRNA synthetase (ARS) antibodies (p =0.0292) were associated with the monophasic resolving ILD. Overall 5-years survival rate of PM/DM-associated ILD was 84%. anti-ARS antibodies positivity was associated with chronic & relapsing course of ILD. HRCT findings and its extension were not associated with the clinical course.

Table 1. Clinical characteristics in cADM/PM/DM patients according to clinical course of ILD.

	resolved (n=24)	chronic stable (n=30)	chronic relpsing (n=32)	fatal (n=7)
Female (%)	91.7	63.3	50.0	85.7
age at onsea of ILD (SD)	54 (12)	51 (15)	49 (10)	60 (7)
cADM/DM/PM (%)	12.5/62.5/25	10/50/40	6.3/59.4/34.4	0/100/0
periungual erythema (%)	58.3	46.7	37.5	100
malignancy (%)	33.3	6.7	6.3	14.3
anti-ARS antibody positive (%)	20.8	50	56.3	0
CK (SD)	891.7 (1233)	2063.6 (3779)	2314 (2129)	552.6 (414)
aldolase (SD)	17.6 (22)	48.3 (78)	50.2 (49)	7 (1)
KL-6 (SD)	1152.5 (1819)	1956.7 (794)	1133.5 (976)	907.4 (526)
%VC (SD)	77.1 (15)	86.1 (21)	73.2 (15)	79.1 (20)
alveolar to arterial PO2 difference (SD)	18 (13)	30.1 (41.5)	29.4 (31.2)	50.8 (27.1)
Groud-glass opacities (%)	50	63.3	53.1	71.4
consolidation (%)	66.7	26.7	53.1	71.4
traction bronchiectasis (%)	95.8	93.3	62.5	71.4
linear opacity (%)	87.5	80	87.5	85.7
honeycombing (%)	0	3.3	93.8	0
follow up period months (SD)	94.3 (52.9)	46.4 (36.7)	90.5 (56.1)	1.9 (1.6)

Conclusion: Patients with IIM-associated ILD presenting with predictive factors for poor outcome may require more aggressive therap.

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Simultaneous Initiating of Glucocorticoids and disease-Modifying Antirheumatic Drug Therapy in Polymyositis and Dermatomyositis Patients Results in the Opportunity to Taper Dosage of Glucocorticoids Early. Kavish J. Bhansing[1], Piet LCM Van Riel[1], Sigrid Pillen[2], Baziel G.M. van Engelen[1] and Madelon C. Vonk[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Catharina Wilhemina Hospital, Nijmegen, Netherlands

Background/Purpose: Glucocorticoids are the cornerstone of therapy in patients with polymyositis (PM) and dermatomyositis (DM). However, side effects are common. Furthermore, glucocorticoids exhibits an potential inhibitory effects on skeletal muscle regeneration. Therefore disease-modifying antirheumatic drugs (DMARDs) are used as glucocorticoids sparing agents. To date limited studies are available in which the glucocorticoids sparing effects of DMARDs are evaluated. The aim of this study is to analyze whether an early start of DMARDs in patients with PM or DM leads to the opportunity to taper dosage of glucocorticoids early.

Methods: All available patients with PM and DM of the Nijmegen Myositis inception cohort which was started in 2009 were included. The data available of this cohort consist of clinical features at diagnosis combined with follow up information on treatment and complications. All patient fulfilled the Bohan and Peter diagnostic criteria.

Early start of DMARD was defined as start of methotrexate, azathioprine, hydrochloroquine, mycophenolate, tacrolimus or sulfasalazine within 3 months after diagnosis. Dosage of less than 15 mg of prednisone was regarded as clinical relevant tapering. Two subgroups (early DMARD and non-early DMARD) were compared to analyze for time to reach the dosage of 15 mg prednisone with a follow-up of 1 year using a multivariate cox proportional hazards model.

Results: In the early DMARD starters group 36 patients were included and 25 patients as non-early DMARD starters. The mean age in early DMARD starters was 46 (SD 17) and 37 years (SD 17) in the non-early DMARD starters group. Clinical features and serology revealed no significant differences (Table 1).

Table 1. Study population characteristics

Characteristics	Early DMARD starters (n = 36)	Non-early DMARD starters (n = 25)	Significance (p-value)
Age, mean±SD (years)	46 ± 17	38 ± 17	NS
Gender (male/female)	15/21	7/18	NS
Type of myositis (PM/DM)	23/13	15/10	NS
Serum CK at diagnosis, median (Units/liter)	2467 (386–7370)	1523 (400–7275)	NS
ANA	21/32 (66%)	19/24 (79.2%)	NS
Anti-SSA	10/33 (30%)	8/24 (33%)	NS
Anti-SSB	1/33 (3%)	1/24 (4%)	NS
Anti-Jo1	9/33 (27%)	9/24 (38%)	NS
Interstitial lung disease*	8/36 (22%)	4/25 (16%)	NS

Interstitial lung disease, defined as fibrosis on HRCT-scan or < 70 % vital capacity on pulmonary function within 1 year after diagnosis; NS: not significant

In a Cox regression analysis, early start of DMARD therapy was found to be an independent predictor of tapering dosage of prednisone to less than 15mg (hazard ratio, 2.3; 95% CI, 1.1–4.8; p = 0.03) (fig.1).
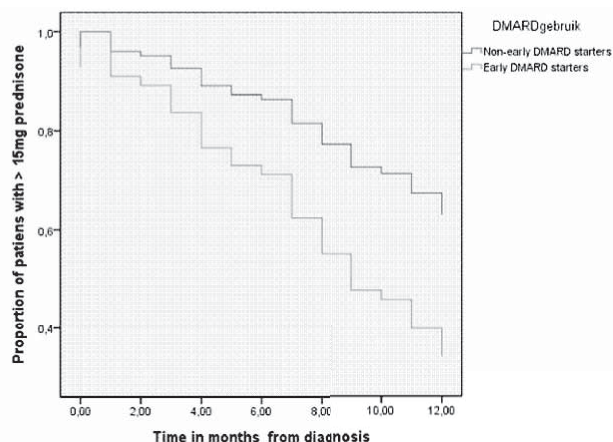
Figure 1. Survival curve of early and non-early DMARD starters for time to reach < 15 mg of prednisone use.

Conclusion: Simultaneous start of DMARD therapy with glucocorticoids leads to the opportunity to taper glucocorticoids to clinical significant lower dosages within 1 year after diagnosis in patients with PM and DM compared to adding DMARDs later or glucocorticoids alone in the course of the disease.

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Clinical Differences Between Adult and Juvenile Dermatomyositis Associated with Anti-NXP2 Autoantibodies.
Sarah Tansley[1], Zoe Betteridge[1], Harsha Gunawardena[2], Lucy R. Wedderburn[3], Hector Chinoy[4], Robert G. Cooper[5], Jiri Vencovsky[6], Lenka Plestilova[7], Ingrid E. Lundberg[8], Katalin Danko[9], Melinda Vincze[9], Neil McHugh[1], UK JDRG[10] and EuMyoNet[11]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]North Bristol NHS Trust, Bristol, United Kingdom, [3]University College London (UCL), London, United Kingdom, [4]The University of Manchester, Manchester, United Kingdom, [5]Hope Hospital, Salford, United Kingdom, [6]Institute of Rheumatology, Prague, Czech Republic, [7]Institute of Rheumatology, Prague 2, Czech Republic, [8]Karolinska Institutet, Stockholm, Sweden, [9]University of Debrecen, Debrecen, Hungary, Debrecan, Hungary, [10]London, United Kingdom, [11]Stockholm, Sweden

Background/Purpose: Myositis specific antibodies (MSA) can divide dermatomyositis patients into distinct clinical subsets and help predict the risk of disease complications such as interstitial lung disease and malignancy. Anti-NXP2 antibodies are one of the commonest MSA found in juvenile dermatomyositis (JDM) and can be identified in 18–25% cases. They have been associated with calcinosis and a severe disease course with more persistent disease activity. Anti-NXP2 antibodies have been found in adult myositis cohorts at a much lower frequency of 1.6%. A possible association with malignancy has been described in adults.

In this study we identified anti-NXP2 antibodies in a cohort of 172 juvenile and 1331 adult patients with idiopathic inflammatory myopathy and compared the clinical disease characteristics of both groups.

Methods: Serum samples were obtained from EuMyoNet and UK JDRG repositories. Immunoprecipitation of radio-labelled K562 cells was performed on all samples. Those with a band in the 140kDa region were further assessed by western blot using an NXP2 overexpression cell lysate (Abnova).

Results: Anti-NXP2 antibodies were identified in 20 children (11.6%) and 10 adults (0.8%). All children with anti-NXP2 antibodies had dermatomyositis. There was a strong association with calcinosis in children which was seen in 55% (p<0.0009). Of the adults nine had dermatomyositis and one polymyositis. One adult patient had calcinosis. An additional diagnosis of malignancy was present in three adults (breast, uterine, pancreatic) (p=0.051). When patients with anti-TIF1γ antibodies, (which are already known to be strongly associated with malignancy) were excluded this association became statistically significant (p=0.027).

Conclusion: Anti-NXP2 antibodies are associated with an increased frequency of calcinosis in JDM. Calcinosis is a common cause of morbidity in JDM but is rarely seen in adult disease. It is interesting therefore that one adult patient with anti-NXP2 antibodies also had calcinosis. In JDM calcinosis is associated with delayed diagnosis, a chronic disease course and inadequately treated disease. Anti-NXP2 in JDM have previously been shown to be associated with a more severe disease course with worse functional status and persistent disease activity. The increased risk of calcinosis may therefore reflect more aggressive disease in anti-NXP2 positive children.

Consistent with previous findings there is an association with malignancy in our anti-NXP2 positive adult population. Whilst malignancy in JDM is rarely seen it is an important disease association in adults and associated with a poorer prognosis. Identification of anti-NXP2 in adult myositis patients may have important prognostic implications, particularly in older adults and should warrant a high level of suspicion for additional malignant disease. Whilst the same MSA are found in adult and juvenile dermatomyositis and define clinical subsets, important clinical differences are seen depending on patient age. Whether this reflects differences in aetiology, pathogenesis or age-specific disease modifiers is yet to be established.

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Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMGCoR) Antibody in Necrotizing Myopathy and the Role of Statins.
Ashima Malik[1], Rohit Aggarwal[1], Zengbiao Qi[1], Noreen Fertig[1], Diane Koontz[1], Rufus W. Burlingame[2], David Lacomis[3] and Chester V. Oddis[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]INOVA Diagnostics, Inc., San Diego, CA, [3]University of Pittsburgh Medical Ctr, Pittsburgh, PA

Background/Purpose: Statin use is associated with myalgias, muscle weakness and elevated muscle enzymes, but recent reports of a statin-induced immune-mediated necrotizing myopathy (IMNM) have been intriguing. Of particular interest is the recently reported hydroxy-3-methylglutaryl-coenzyme A reductase antibody (anti-HMGCoR). Our Aim is to evaluate anti-HMGCoR antibody positivity and statin exposure in antibody negative necrotizing myopathy patients.

Methods: Using a large prospective computerized database we identified 48 patients with antibody negative Necrotizing Myopathy from 1980–2011, confirmed by a pathologist- review of all biopsies. As a comparison cohort we had SRP positive myositis patients (32), a subset known to have necrotizing myopathy with poor prognosis. Other controls were Non-SRP non-necrotizing myositis patients (73), non-myositis controls (21), antibody positive necrotizing myopathy controls (13). A validated anti-HMGCoR ELISA assay was done on all cases and controls with values (units/ml) as negative < 20, low positive 20–39, medium positive 40–59, high positive at ≥ 60. Computerized database and clinical chart review was done for history of statin use and other clinical parameters. Chi square test was used to compare between cases and various controls for statin use and anti-HMGCoR positivity. All myositis specific autoantibody testing was done in a research lab using ELISA and immunoprecipitation.

Results: 256 biopsies were reviewed and 48 identified as antibody negative necrotizing myositis. Anti-HMGCoR positivity was significantly (p<0.001) associated with antibody negative necrotizing myopathy 47.9% (23/48) as compared to a) all myositis and non-myositis controls 7.2% (10/139), b) SRP control alone 0% (0/32), c) Non-SRP non-necrotizing myositis controls 5.5% (4/73), but not when compared alone to antibody positive necrotizing myopathy (4/13) (with 2 on statin), P =0.54).

Higher titer anti-HMGCoR levels were seen in antibody negative (17/48) and antibody positive necrotizing myopathy (4/13) but not in other controls (2/126). Statin use was more common (p<0.001) in antibody negative necrotizing myopathy (23/48) as compared to all myositis and non-myositis control (17/127), b) SRP control alone (2/26), c) Non-SRP non-necrotizing myositis control (11/70) but only trend compared alone to antibody positive necrotizing myopathy (3/13 (with 2 anti-HMGCoR +) P =0.06).

Within patients with necrotizing myopathy: anti-HMGCoR was associated with patients on statin (19/24) as compared to patients without statin (7/27), p <0.01). Anti-HMGCoR antibodies were more common in any patients on statin (20/34) as compared to patients without statin (20/138), p < 0.001).

Conclusion: Anti-HMGCoR is strongly associated with antibody (−) necrotizing myopathy vs. anti-SRP (+) myositis. Moreover, anti-HMGCoR is more common in necrotizing myopathy pts with history of statin use vs. no statin use.

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Pulmonary Hypertension in the Antisynthetase Syndrome. Helena Andersson[1]. T. Mogens Aalokken[2], Torhild Garen[3], Oyvind Molberg[4] and Jan Tore Gran[1], [1]Oslo University Hospital, Oslo, Norway, [2]Oslo, Norway, [3]Oslo University Hospital Rikshospitalet, Oslo, Norway, [4]Department of Rhematology, Oslo University hospital, Rikshospitalet, Oslo, Norway

Background/Purpose: To describe the frequency and clinical characteristics of pulmonary hypertension (PH) in a cohort of Antisynthetase Syndrome (ASS) patients.

Methods: Patients from a single referral center diagnosed between 1994–2010 with a positive serologic test (immuno-blot) of antisynthetase antibodies, interstitial lung disease (ILD) and/or myositis were defined as ASS (N=90). All data were retrospectively collected from medical reports. A diameter of the Pulmonal artery >29 mm, measured by CT-scans, was defined as pathological. PH was suspected with an estimated pulmonary arterial pressure (PAP) of >45mmHg at transthoracal eccocardiography (TTE), and defined as a mean PAP >25 mmHg measured by right heart catheterization (RHC). The ratio between forced vital capacity and diffusion capacity of the lungs (FVC/DLCO) was considered pathological, indicating PH, at values > 1.6. All examinations were done within 3 months for each patient.

Fisher's exact test was used to evaluate statistical significance (p<0.05)

Results: The cohort consisted of 75 anti-Jo1 positive, seven PL-7 positive and eight PL-12 positive patients with mean age at ASS diagnosis of 48 years (range 12–82 yrs) and median disease duration of seven years (range 0.25–34 yrs). Fourteen patients were referred to RHC due to clinical suspicion of PH. Ten out of 14 were diagnosed with PH, with a median PAP of 38 mmHg (range 26–55). Eight out of 10 patients had a pre-capillary type of PH, defined as pulmonal capillary wedge pressure (PCWP) < 15mmHg. Over all frequency of PH was 11 % (10/90). Twelve of 14 patients had available TTE-exams, all but one indicating PH with estimated PAP of >45mmHg. The Pulmonal artery was pathological enlarged in 9/10 patients with PH, median diameter 40 mm (range 33–45). Although not statistic significant (p<0.07), the result indicates a correlation between enlarged pulmonary artery and PH. Seven of nine patients with PH had pathological FVC/DLCO ratios. All 10 PH patients had manifest ILD at time of PH diagnosis. 2/10 patients with PH had co-existing rheumatic disease, both systemic sclerosis. The diagnosis of PH was made 36–336 months after ASS onset. Five of 10 patients with PH died during the observation-period.

Clinical characteristics of ASS patients with performed RHC

PATIENT	SEX/ AGE	ANTIBODY	SS-A	FVC/ DLCO	DLCO	DIA A PULM	ECCO mmHg	RHC mmHg	PCWP/ mmHg	DEATH
PH										
1	M 61	Jo-1	+	2,12	17	45	60	33	2	+
2	F 63	Jo-1		NA	NA	36	55	35	14	
3	M 44	Jo-1	+	1,52	38	42	40	26	9	
4	F 43	Jo-1	+	1,91	45	42	70	44	7	
5	F 54	Jo-1	+	3	15	33	70	38	10	+
6	F 18	Jo-1	+	2,5	12	40	NA	50	8	+
7	M 33	Jo-1	+	2,23	26	38	60	38	16	
8	F 21	Jo-1		1,62	17	NA	76	55	18	+
9	M 43	Jo-1	+	1,8	41	41	60	26	7	
10	F 55	Jo-1	+	0,82	56	33	98	50	15	+
No PH										
11	M 60	Jo-1	+	1,87	56	28	60	23	11	
12	F 12	PL-12	+	1,17	47	33	45	18	2	
13	F 19	Jo-1		1,45	33	27	NA	15	4	
14	F 31	PL-12	+	2,09	31	33	70	24	6	

Conclusion: In this cohort of 90 ASS patients and with a median disease duration of seven years, a PH frequency of 11 % diagnosed by RHC was observed. The study indicated a correlation between enlarged Pulmonal artery and PH. In spite of small series, the results indicate PH as an important complication of ASS and should be given further notice.

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The Natural History of Sporadic Inclusion Body Myositis–an Observational Longitudinal Study. Pedro Machado[1], Andrea Cortese[1], Jasper Morrow[1], Liz Dewar[1], Andy Hiscock[1], Adrian Miller[1], Stefen Brady[2], David Hilton-Jones[2], Matt Parton[1] and Michael G. Hanna[1]. [1]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom, [2]Oxford Muscle and Nerve Centre, John Radcliffe Hospital, Oxford, United Kingdom

Background/Purpose: Our aim was to assess prospectively the clinical features and functional impact of inclusion body myositis (IBM), to identify reliable outcome measures for future trials and to identify prognostic factors of this condition.

Methods: Patients were classified with either probable or definite IBM, according to the Griggs' criteria (Griggs RC, et al. Ann Neurol 1995;38:705–713) or with clinically defined IBM, according to the Medical Research Council criteria (Hilton-Jones D, et al. Neuromuscul Disord 2010;20:142–147). Clinical data, manual muscle testing (MMT), quantitative muscle testing (QMT) of quadriceps extensors with HUMAC Norm CSMi™ dynamometer and IBM functional rating scale (IBM-FRS) were collected according to a standardised protocol (IBM-Net) at baseline (n=51) and one-year follow-up (n=23, QMT performed in a subgroup of 13 patients). The responsiveness to change of MMT, QMT and IBM-FRS was assessed by calculating the standardized response mean (SRM). Cox-regression analysis was performed to estimate the effect of sex, age at disease onset and previous or current treatment with steroids or immunosuppressants on the time to using a walking stick. Time to using a walking stick was modelled using a Kaplan-Meier curve.

Results: Mean age at disease onset was 58 years (16% before the age of 50). Weakness of quadriceps and finger flexors with sparing of proximal upper limb muscles was the most common presentation. After a median time of 7 years of disease, 63% of patients had lost independent walking ability and needed assistive devices. Twenty-seven patients (53%) reported difficulties with swallowing. IBM was initially misdiagnosed in 50% of cases, the commonest misdiagnosis being polymyositis. MMT, IBM-FRS and quadriceps QMT significantly declined after one year (by 5.2%, 13.8% and 27.9% respectively). QMT of the quadriceps muscle (SRM=1.8) and IBM-FRS (SRM=1.3) were the most sensitive measures of disease progression. Disease onset after 55 years of age (HR=4.1; 95% CI=1.7, 9.8; p=0.001), but not sex or treatment, was predictive of a shorter time to requirement of a walking stick (figure). We detected no differences in disease presentation and progression between clinically and pathologically defined IBM patients.
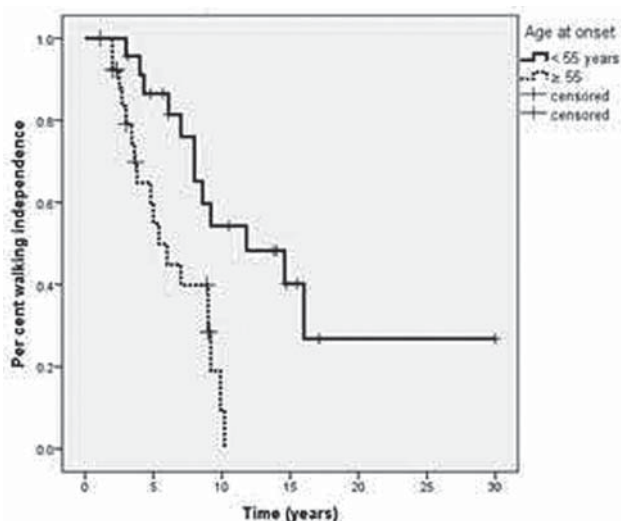
Conclusion: IBM is a disabling myopathy with prominent involvement of specific muscle groups, particularly quadriceps femoris and finger flexors, which are essential for activities of daily living. IBM is still probably an underrecognised and misdiagnosed disease. During one year follow-up, the responsiveness of QMT of quadriceps femoris and of IBM-FRS were greater than MMT, which makes the former two measures more sensitive markers of disease progression. Onset of the disease after 55 years of age was predictive of a shorter time to using a walking stick.

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IFN Signature Is Associated with Autoantibody Profiles in Patients with Idiopathic Inflammatory Myopathies. Saskia Vosslamber[1], Louise Ekholm[2], Anna Tjarnlund[3], Clio P. Mavragani[4], Lenka Plestilova[5], Martin Klein[5], Mary K. Crow[6], Peter J. Charles[7], Leonid Padyukov[8], Jiri Vencovsky[5], Ingrid E. Lundberg[3] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]1Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Sweden, Stockholm, Sweden, [4]School of Medicine, University of Athens, Athens, Greece, Athens, Greece, [5]Institute of Rheumatology, Prague, Czech Republic, [6]Hospital for Special Surgery, New York, NY, [7]Oxford University, London, United Kingdom, [8]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are rare autoimmune diseases characterized by the presence of autoantibodies, proximal muscle weakness and muscle inflammation. Recent studies showed an activated type I IFN activity (IFN signature) in a subset of patients and suggest a pathogenic role for type I interferon (IFN) in IIM patients. The extent of this signature appears to be related to disease activity, however, the relevance to disease or the underlying mechanism resulting in such a signature has not been revealed yet.

The aim of this study was to examine if the type I IFN activity in whole blood and sera from IIM patients correlates to disease activity, clinical manifestations or autoantibody profile.

Methods: Clinical data were collected from 94 polymyositis, dermatomyositis and inclusion body myositis patients recruited from the Karolinska University Hospital and Prague University. Serological data was obtained using lineblot assay. RNA samples, obtained from whole blood were assessed for expression levels of 9 IFN related genes using BioMark™Dynamic Arrays. IFN score was determined as the average gene expression level of these genes. Median IFN score was used to define the presence of an IFN signature.

Sera were assessed for IFN activity using a bioassay where expression of 3 type I IFN-inducible genes were quantified using real-time PCR. Two groups of patients, IFN+; IFN-, were categorized based on the sum of individual gene expression scores. Differences between these groups were assessed for clinical and serological data, as well as correlation between IFN signature and variables.

Results: The IFN signature in peripheral blood was present in a subgroup of patients with myositis. No significant difference in the presence and extent of the IFN signature was observed between ANA negative and ANA positive patients. Comparison of the IFN signature in patients positive for myositis associated or specific autoantibodies revealed that the highest IFN score was found in U1RNP positive patients (mean IFN score = 23.66), followed by La positive patients (mean IFN score = 11.94) and Ro60 positive patients (..). Comparable results were found in patients with multiple autoantibody specificity and those only positive for one of these antibodies. In addition, a majority of Jo-1 and Ro-52 positive patients were characterized by the presence of an IFN signature, although most of these patients appear to be positive for multiple autoantibody specificities. Detailed analysis revealed that presence of an IFN signature was related to multi-autoantibody specificity, i.e. 17 out of 23 patients positive for 2 or more autoantibodies (70%) versus 30 out of 71 of the patients positive for 1 or none of the specific autoantibodies (45%) displayed an IFN signature (Pearson Chi square p=0.008).

Significantly more IFN+ patients were positive for ANA compared to IFN- patients (p=0.001). No correlation between IFN activity in sera and disease activity was found.

Conclusion: These data reveal a preferential presence of the IFN signature in IIM patients that are characterized by multiple autoantibody specificities. These findings suggest a role for autoantibodies in the induction of type I IFN activity in IIM.

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ACR Poster Session A
Osteoarthritis - Clinical Aspects
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Central Sensitization Is Associated with Spontaneous Pain in Knee Osteoarthritis. Anisha B. Dua[1], Tuhina Neogi[2], Rachel A. Mikolaitis[3], Joel A. Block[3] and Najia Shakoor[3]. [1]Rush Universtiy Medical Center, Chicago, IL, [2]Boston Univ School of Medicine, Boston, MA, [3]Rush University Medical Center, Chicago, IL

Background/Purpose: Osteoarthritis (OA) is a chronic, prevalent disease that is a major cause of pain and disability. Pain is the primary symptom of OA, however its characteristics and pathophysiology remain poorly understood. Studies suggest that patients with knee OA have increased central sensitization, measured by pressure pain thresholds (PPTs) and temporal summation (TS) to repeated non-nociceptive stimulation. Here we evaluated the relationship between central sensitization (TS and PPTs) and pain magnitude in symptomatic knee OA.

Methods: Persons with moderate to severe radiographic (Kellgren-Lawrence (KL) grade $\geq$2) and symptomatic (at least 30mm on WOMAC visual analog scale) knee OA were compared with age matched controls without knee pain or OA (radiographic KL grade of 0–1, pain <20 on WOMAC VAS), and no history of diabetes, arthroplasty, or chronic widespread pain. In subjects with bilateral knee OA, the most symptomatic side was considered the "affected" side. Participants answered questionnaires regarding knee pain and function including the question "do you feel spontaneous pain in your knee?" Temporal summation (TS) was measured by application of a 60g Von Frey monofilament repeatedly (30 times) to pre-determined anatomic sites. Participants answered the question "do you consider this painful?" (yes/no) and rated their pain on a scale of 1–10. Pain pressure thresholds (PPT) were measured using a pressure algometer applied to pre-determined anatomic sites with steadily increasing pressure and recordings were taken at the first sensation of pain.

Results: 42 OA participants (mean age 54.1 ± 8.1 years) and 12 controls (mean age 52.9 ± 11.1 years) were evaluated. Significantly more OA subjects demonstrated TS compared with controls at the ipsilateral (54.8% vs 16.6%, p=0.02) and contralateral knee (49% vs 0%, p=0.005). PPTs were lower in the OA group but did not reach significance. KOOS and WOMAC pain scores did not correlate with PPT or TS at any of the several sites evaluated (rho= −0.115 to −0.139 and 0.150 to 0.286 respectively, p >0.05).

Spontaneous pain in the knee was reported by those with knee OA more frequently than controls (74.3% vs 0%, p=0.001) and those with spontaneous knee pain had lower PPTs than those without spontaneous knee pain (Table 1). In patients with OA, spontaneous knee pain was also associated with the presence and pain rating of TS at the ipsilateral and contralateral tibial tuberosities (Table 1).

Table 1. Relationship Between Spontaneous pain, Pain Pressure Thresholds and Temporal Summation

Spontaneous Pain	Yes	No	P value
Pain Pressure Threshold Radial Styloid (kgf)*, (Mean ± SD)	2.42 ± 1.07	4.39 ± 1.25	0.001
Pain Pressure Threshold Medial Joint Line (kgf), (Mean ± SD)	2.05 ± 1.08	3.98 ± 1.61	0.001
Pain Pressure Threshold Tibial Tuberosity (kgf), (Mean ± SD)	3.52 ± 1.44	5.01 ± 1.11	0.005
Presence of Temporal Summation Ipsilateral Tibial Tuberosity	69.20%	30.70%	0.012
Pain rating post-stimulus for eliciting Temporal Summation Ipsilateral Tibial Tuberosity Scale (Mean ± SD)	4.3 ± 2.6	1.6 ± 1.7	0.003
Presence of Temporal Summation Contralateral Tibial Tuberosity	65.40%	11.10%	0.007
Pain rating post-stimulus for eliciting Temporal Summation Contralateral Tibial Tuberosity Scale (Mean ± SD)	3.7 ± 2.3	1.4 ± 1.3	0.001

*kgf = kilograms of force

Conclusion: Conventional pain scales do not correlate well with measures of central sensitization. However, the presence of spontaneous pain is more frequent in OA patients than controls, and those who have spontaneous pain have generalized decreases in thresholds to pain sensation (lower PPTs) and also are more likely to demonstrate temporal summation.

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Peripheral and Central Sensitization in Patients with Different Degree of Knee Osteoarthritis. Lars Arendt-Nielsen[1], Thomas Navndrup Eskehave[2], Morten Asser Karsdal[3], Anne C. Bay-Jensen[3], Hans Christian Hoeck[4] and Ole Simonsen[5]. [1]Aalborg University, Aalborg, Denmark, [2]Ålborg University, Ålborg, Denmark, [3]Nordic Bioscience A/S, Herlev, Denmark, [4]C4Pain, Ålborg, Denmark, [5]Frederikshavn Hospital, Frederikshavn, Denmark

Background/Purpose: Though pain is the cardinal symptom of osteoarthritis (OA) the underlying causes are not fully understood. However, peripheral and central sensitization has been suggested to play an important role in OA pain. The aim of this study was to investigate associations between mechanism based pain assessment parameters associated with peripheral and central sensitisation in painful knee OA and clinical manifestations (K&L, Pain intensity, WOMAC).

Methods: 217 patients with different degrees of OA pain (rated on a visual analog scale (VAS) from 0 to 100) and 36 healthy controls participated in the study. Patients were allocated into: controls (VAS 0–9), Group A (VAS 10–39), Group B (VAS 40–69) and Group C (VAS 70–100). Pressure pain thresholds (PPT′s) were measured in the peripatellar region, tibialis anterior and extensor carpi radialis muscle before, during and after conditioning pain modulation (CPM). Temporal summation to repeated mechanical stimulation was measured at all sites. A sensitization index was constructed based on PPT′s, temporal summation and CPM. Pain and soreness areas were obtained. The radiologic assessment of OA was made by specialists using Kellgren & Lawrence grading scale (0–4).

Results: All patient groups had significantly lower PPT′s compared to controls. Patients showed facilitated temporal summation and reduced CPM function compared to controls. Significant correlations were found between CPM effect (r=0.23, p<0.01), degree of temporal summation (r=−0.36, p<0.01) and PPT (r=0.22, p<0.01) and clinical Vas ratings. The index of pain sensitization revealed that 37.3 % of the patients were twice as pain sensitive as controls. The pain sensitization score was significantly was correlated with VAS ratings (0.36, p<0.01) and pain/soreness areas (r=0.14, p<0.05 and r=0.15, p<0.05)

Conclusion: Patients with mild, moderate and severe pain had significantly lower PPT′s compared to controls. Furthermore, patients with OA had significantly more central sensitization (decreased CPM effect and increased temporal summation) compared to controls. This study is the first to demonstrate a tool for OA patient stratification into sensitized and non-sensitized based on relevant pain assessment parameters. This stratification can be useful for diagnosis and future treatment of OA patients and for monitoring the effects of new drugs under the development for OA pain.

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The Relationship Between Vibratory Sense and Somatosensory Pain Measures in Knee Osteoarthritis. Anisha B. Dua[1], Rachel A. Mikolaitis[2], Tuhina Neogi[3], Joel A. Block[2] and Najia Shakoor[2]. [1]Rush Universtiy Medical Center, Chicago, IL, [2]Rush University Medical Center, Chicago, IL, [3]Boston Univ School of Medicine, Boston, MA

Background/Purpose: Osteoarthritis is the most common form of arthritis, and is a major cause of pain and disability. Continuous nociceptive input can influence somatosensory processing, and studies suggest that patients with knee OA have altered somatosensory findings, demonstrated by decreased vibration perception threshold (VPT), pressure pain thresholds (PPTs), and temporal summation (TS) elicited by repeated non-nociceptive stimulation. Here, we further characterize the relationship between these somatosensory measures in knee OA.

Methods: Persons with moderate to severe radiographic (Kellgren-Lawrence (KL) grade ≥2) and symptomatic (at least 20mm on WOMAC visual analog scale) knee OA were evaluated. In subjects with bilateral OA, the most symptomatic side was considered the "affected" side. VPT was measured using a biothesiometer (Bio-Medical Instrument Co., Newberry, Ohio) that provided vibratory stimulation at multiple predetermined anatomic sites. VPT was recorded as the first sensation of vibration (volts). TS was assessed by application of a 60g Von Frey monofilament repeatedly (30 times) to various sites. Participants answered the question "do you consider this painful?" (yes/no) and rated the extent of their pain on a scale of 0–10, immediately and after 10 seconds. PPT's were measured using a pressure algometer applied to pre-defined sites with steadily increasing pressure. Recordings were taken at the first sensation of pain.

Results: 42 OA participants (mean age 54.1 ± 8.1 years) were evaluated. Subjects who demonstrated TS at the ipsilateral tibial tuberosity had significantly lower PPTs at multiple sites compared to those without TS (Table 1). VPT and PPTs were directly correlated at several anatomic sites (Table 2). VPT was lower at the first metatarsophalangeal joint (MTP) in those that demonstrated TS at the ipsilateral tibial tuberosity vs those that did not (8.2±3.3 vs 12.1±4.8 volts, p=0.005). VPT was also lower at the first MTP in those that sensed/rated pain at the ipsilateral tibial tuberosity 10 seconds post-stimulation (for TS) vs those that did not (7.6±4.2 vs 11.3±4.2 volts, p=0.011).

Table 1. Relationship between Temporal Summation and Pain Pressure Threshold

Pain Pressure Threshold (kilograms of force), (Mean ± SD)	Presence of Temporal Summation at Ipsilateral tibial tuberosity		P-value
	Yes	No	
Ipsilateral radial styloid	2.56 ± 1.19	3.71 ± 1.53	0.01
Contralateral radial styloid	2.51 ± 1.26	3.75 ± 1.50	0.007
Ipsilateral tibial tuberosity	3.16 ± 1.56	4.59 ± 1.39	0.003
Contralateral tibial tuberosity	3.57 ± 1.61	4.48 ± 1.32	0.052
Ipsilateral medial joint line	2.16 ± 1.23	3.44 ± 1.64	0.008
Contralateral medial joint line	2.54 ± 1.46	3.77 ± 11.81	0.02

Table 2. Correlation between VPT at Multiple Sites with PPT at the Ispilateral Tibial Tuberosity and Medial Joint Line

	PPT Ipsilateral tibial tuberosity Spearman's rho (p value)	PPT Ipsilateral medial joint line Spearman's rho (p value)
VPT Ipsilateral medial ankle	0.416 (0.006)	0.476 (0.001)
VPT Ipsilateral lateral knee	0.432 (0.004)	0.405 (0.008)
VPT Ipsilateral tibial tuberosity	0.350 (0.02)	0.268 (0.09)
VPT Ipsilateral medial knee	0.338 (0.03)	0.389 (0.01)

Conclusion: Key measures of central sensitization appear to be well correlated in this group, with lower pain thresholds (PPT) in those that demonstrate TS. Higher pain thresholds and the absence of TS were both associated with decreased vibratory sense acuity (higher VPT). Thus, the well documented loss of vibratory acuity in patients with knee OA may also be part of an inhibitory pathway reflected in higher pain thresholds and lack of temporal summation.

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Association Between Pain Threshold, Symptoms and Radiographic Knee and Hip Osteoarthritis: The Johnston County Osteoarthritis Project. Adam P. Goode[1], Xiaoyan A. Shi[2], Jordan Renner[3], Richard Gracely[4], Mehrnaz Maleki-Fischbach[5] and Joanne M. Jordan[6]. [1]Duke University, Durham, NC, [2]SAS Institute, Inc, Cary, NC, [3]University of North Carolina, Chapel Hill, NC, [4]Chapel Hill, NC, [5]National Jewish Health, Denver, CO, [6]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC

Background/Purpose: Little is known of the association between pain threshold and knee/hip symptoms as well as radiographic knee/hip osteoarthritis (rOA). These analyses: 1) determined the association between pain threshold and presence of knee/hip symptoms or knee/hip rOA, 2) determined the association between pain threshold and the number of joints with knee/hip symptoms or rOA and 3) determined if associations differed by demographic or clinical characteristics.

Methods: Dolorimeter measurements for pain threshold were available for 1,602 participants returning for second follow-up (2008–11) in the Johnston County Osteoarthritis Project. Participants mean age was 67.9 (SD 9.0), 67.2% female, 31.0% African American, mean body mass index (BMI) 31.5 (SD 7.1) and a mean Center for Epidemiologic Studies Depression (CES-D) Scale score of 31.5 (SD 7.1). Pain threshold measurements were averaged (mean of 3.6kg ((SD 0.7)) over three trials from left and right trapezius muscles. Knee and hip OA were both defined by a Kellgren-Lawrence score of 2–4. Knee and hip symptoms were obtained at clinical interview with "on most days do you have pain, aching or stiffness in at least one knee/hip?". Associations were determined with logistic regression while adjusting for age, race, BMI, CES-D scores and presence of hip or knee rOA. Interactions between pain threshold and clinical and demographic characteristics were tested at p<0.05.

Results: Knee and hip rOA were present in 45.7% and 40.3% of participants, respectfully. Knee and hip symptoms were present in 38.4% and 29.3% of participants, respectfully. A 1-unit increase in pain threshold was significantly associated with symptoms in the knee (adjusted odds ratio [aOR] 0.64 ((95% CI 0.54, 0.76)) and hip (aOR 0.67 ((95% CI 0.57, 0.79)). The figure illustrates the associations between pain threshold and number of knees and hips with symptoms. Compared to those without knee or hip symptoms, those with higher pain threshold were 20% less likely to have 1 joint with symptoms and 50% less likely to have 4 joints with symptoms. No significant associations were found with increased pain threshold and presence of knee or hip rOA or number of joints with knee and hip rOA. No significant interactions were found between pain threshold and demographic or clinical characteristics.
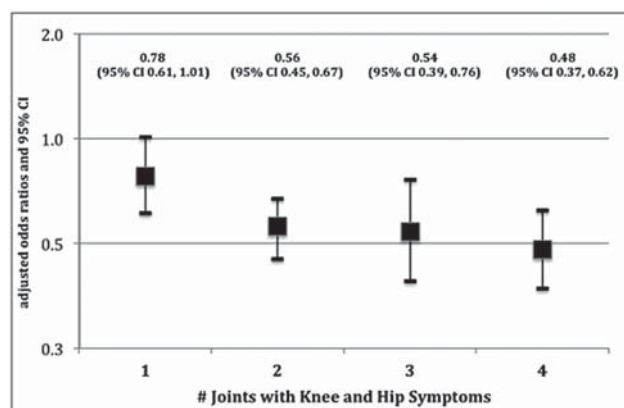
Figure. Associations between pain threshold and number of knees and hips with symptoms*.

* referent = those with no knees or hips with symptoms

Conclusion: Participants with higher pain threshold were less likely to report knee and hip symptoms, an association that strengthened with the number of symptomatic joints. In contrast, no association was found with increased pain threshold and knee or hip rOA. These findings suggest the presence of knee or hip rOA may not be informative in understanding an individual's knee or hip symptoms or useful for evaluating the efficacy of treatments targeting symptoms.

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Inevitable Deterioration? Trajectories and Risk Profiles of Pain in Patients with Radiographic, Symptomatic Knee Osteoarthritis. Jamie E. Collins[1], William M. Reichmann[2], Jeffrey N. Katz[1] and Elena Losina[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA

Background/Purpose: Knee pain is the primary reason that patients with OA seek medical care. The goal of this study is to describe pain trajectory over three years in a cohort of patients with radiographic, symptomatic knee OA.

Methods: We used data from the Osteoarthritis Initiative (OAI), a multi-center, longitudinal, prospective observational study of knee OA. Pain assessments were done at baseline and at yearly visits for 4 years. We defined patients with symptomatic knee OA as those with central reader Kellgren/Lawrence (KL) score >2 and a WOMAC pain score >0. We used group-based trajectory modeling to identify distinct patterns of pain progression. To minimize the impact of baseline flare effect we restricted our analysis to visits occurring in months 12 through 48. We also built multivariable generalized linear models to determine factors affecting change in pain severity over time. Factors examined included sex, race, education, baseline comorbidities, 12-month age, BMI, alignment, KL grade, and depression.

Results: We used the data from 1,447 OAI study participants with radiographic, symptomatic knee OA at month 12. The average WOMAC pain at month 12 was 24 (0–100 scale with 100 = worst) with standard deviation 17.6. Individual pain reports varied markedly over time. For example, at 48 months, 51% reported a *lower* pain score than at 12 months and 36% reported a *highe*r score. Also, 32% of all patients reported having no pain at one or more subsequent follow-up visits. Group based trajectory modeling identified 4 distinct pain trajectories [Figure]. Two-thirds of patients (groups 2 and 3 in Figure) started with moderate pain and showed little change on average over three years. The 12.6% in the highest pain trajectory tended to increase in pain by an average of 6 points over 3 years of follow-up, while patients in the first category (lowest pain at 12 months) decreased by an average of 9 points. Higher BMI, depression, and KL grade at the beginning of observation were associated with pain worsening over time in multivariable models.

Figure: WOMAC Pain Trajectories
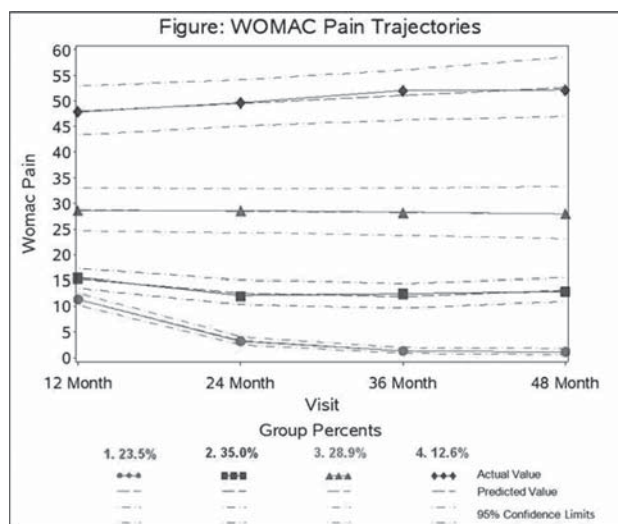
Conclusion: We found that knee pain is highly variable over time and that pain neither worsens nor improves, on average, over three years in a majority of patients. Just 12.6% of patients demonstrate progressive worsening. These observations of highly variable pain reports with relatively little change on average over time contrast with the frequent clinical teaching that osteoarthritis symptoms progressively worsen over time.

Knee Osteoarthritis Symptom Assessments That Combine Pain and Physical Activity Are Superior to Pain Alone. Grace H. Lo[1], Timothy E. McAlindon[2], Gillian A. Hawker[3], Jeffrey B. Driban[2], Lori Lyn Price[2], Jing Song[4], Charles Eaton[5], Marc C. Hochberg[6], Rebecca D. Jackson[7], C. Kent Kwoh[8], Michael C. Nevitt[9] and Dorothy D. Dunlop[4]. [1]Michael E. DeBakey Veterans Affairs Medical Center/Baylor College of Medicine, Houston, TX, [2]Tufts Medical Center, Boston, MA, [3]Women's College Research Institute, University of Toronto, Toronto, ON, [4]Northwestern University, Chicago, IL, [5]Warren Alpert Medical School at Brown University, RI, [6]University of Maryland, Baltimore, MD, [7]Ohio State University, Columbus, OH, [8]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [9]University of California-San Francisco, San Francisco, CA

Background/Purpose: Symptom assessment in knee osteoarthritis (OA) is challenging. Knee pain does not always correlate well with radiographic severity, perhaps because people modify/avoid activities to reduce symptoms. Accelerometers/pedometers can inexpensively and easily quantify physical activity. We hypothesize that symptom assessment accounting for pain intensity in the context of physical activity will improve discrimination across OA radiographic severity levels.

Methods: We studied Osteoarthritis Initiative (OAI) participants with ≥ 4 days accelerometer monitoring, knee-specific WOMAC pain data, *and* knee x-rays from the 48-month visit. Accelerometer data included average daily step count and average daily activity counts (i.e., weighted sum of activity frequency and intensity). Four composite knee pain and activity scores (KPAS) were calculated:

KPAS1 = daily step count/(Total WOMAC Pain Score + **1**)
KPAS2 = daily activity count/(Total WOMAC Pain Score + **1**)
KPAS3 = daily step count/(WOMAC Walking Pain Score + **1**)
KPAS4 = daily activity count/(WOMAC Walking Pain Score + **1**)
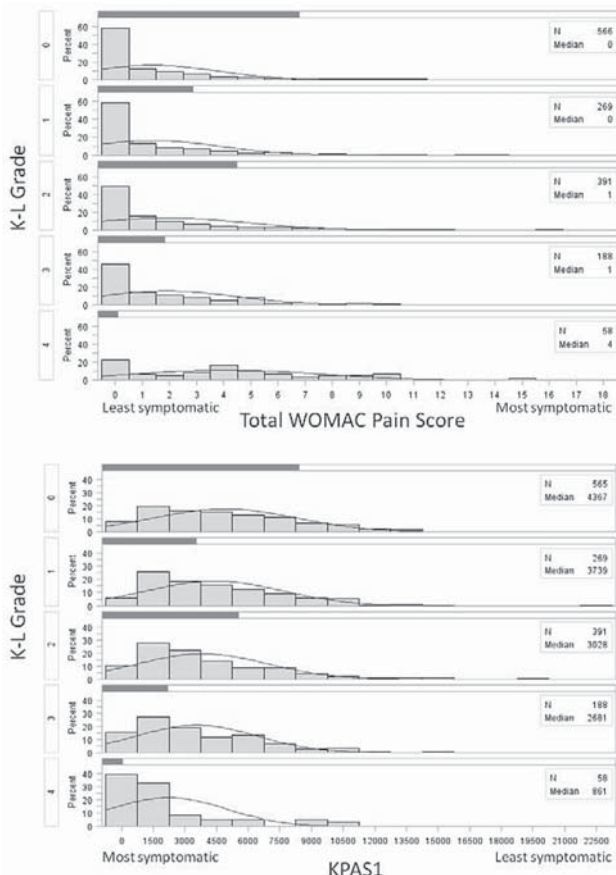
Figure 1. Histograms stratified by K-L Grade of the Total WOMAC Pain Score and KPAS1.

Lower KPAS values reflect greater symptoms, consistent with less activity and/or greater pain. X-rays were read for Kellgren and Lawrence (K-L) grade

(0–4). For each participant, only right knee data were evaluated. Total WOMAC pain score, WOMAC walking pain score, accelerometer data, and KPAS scores were tested for normality, and score discrimination by K-L grades using stratified histograms, Kruskal–Wallis testing, and quantile regression analyses (excluding WOMAC walking pain) unadjusted and adjusted for age, sex and BMI.

Results: 1472 participants, mean age 64.9 ($\pm$ 9.1), mean BMI 28.1 ($\pm$ 4.8), 43% male, were included. No symptom score was normally distributed, with pain assessments being the most skewed.

Table 1. Kruskal–Wallis testing of symptom assessments across adjacent K-L grades.

	Symptom Assessments							
K-L Grade Comparisons	WOMAC	WOMAC Walk	Step Count	Activity Count	KPAS1	KPAS2	KPAS3	KPAS4
0 v. 1			X	X			X	
1 v. 2	X	X			X	X	X	X
2 v. 3				X				
3 v. 4	X	X			X	X	X	X

"X" denotes statistically significant differences.

Table 2. Quantile regression: Differences in <u>median</u> symptom scores across K-L grade groups.

Outcome	Adjustment Factors	Median Scores KL 0 (Referent)	Differences in Median Scores from Referent Group				P for trend
			KL 1	KL 2	KL 3	KL 4	
WOMAC Total Pain	Unadjusted	0	0	1	1	4	*p=.006*
	Adjusted[a]	0	0	1	1	4	*p<.001*
Step count	Unadjusted	6253	−763*	−774*	−930*	−1957*	*p<.001*
	Adjusted[a]	18436	−286*	−242	−222	−299	p=0.20
Activity count	Unadjusted	211358	−13429	−20681*	−30746*	−51700*	*p<.001*
	Adjusted[a]	647624	−1920	732	7038	−3197	p=0.79
KPAS1	Unadjusted	4367	−627*	−1338*	−1674*	−3499*	*p<.001*
	Adjusted[a]	11709	−387	−1116*	−1245*	−2912*	*p<.001*
KPAS2	Unadjusted	146556	−14023	−40866*	−46057*	−110077*	*p<.001*
	Adjusted[a]	448042	−6880	−28642*	−29064*	−88068*	*p<.001*
KPAS3	Unadjusted	5560	−500*	−1088*	−1024*	−2842*	*p<.001*
	Adjusted[a]	16208	−179	−334	−271	−2226*	*p<.001*
KPAS4	Unadjusted	183218	−5603	−25181*	−23770*	−85471*	*p<.001*
	Adjusted[a]	614784	−892	−7509	−5994	−56155*	*p=.003*

[a] Adjusted for age, sex, and BMI
* Statistical difference of group median compared to the referent (KL score of 0) median; p<0.05.
Referent group is K-L grade 0. For WOMAC score, higher score = greater symptoms. For all other scores, lower score = greater symptoms.

Conclusion: Symptom assessments incorporating pain intensity and physical activity improved discrimination across radiographic OA severity. Pain better discriminates high disease severity while physical activity better distinguishes low severity. Relationships of KPAS measures with x-ray severity were robust to adjustment for traditional OA risk factors. To improve sensitivity, physical activity should be routinely assessed in studies of knee OA symptoms.

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Degenerative Changes in Patients with Knee Pain: A Comparative Study Between Ultrasound and Conventional Radiology. Santiago Ruta[1], Erika Catay[2], Javier Rosa[2], David A. Navarta[2], Ricardo Garcia-Monaco[3] and Enrique R. Soriano[4]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, [4]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina

Background/Purpose: Knee osteoarthritis (OA) is one of the most common rheumatologic joint diseases and causes an important disability in the elderly population. To date the gold standard for the diagnosis of knee OA is radiographic. However, these findings might not be useful in early stages.

Objectives: to investigate the ability of ultrasound (US) to detect abnormal findings related to OA in patients complaining of knee pain in comparison with conventional radiology (CR).

Methods: Consecutive patients over 50 years of age complaining of knee pain without a previous diagnosis of knee OA (ACR criteria) and no other known rheumatologic disease were included. US examination was performed by an experienced rheumatologist, blinded to clinical data, using a My Lab 70 machine (Esaote) provided with a multi-frequency linear transducer (4–13 MHz). A standardized scanning method was adopted in order to investigate the following US abnormal findings (presence/absence):

- osteophytes: defined as cortical protrusions at the joint margin seen in two planes and visualized as either proximal or distal to the joint
- degenerative femoral hyaline cartilage involvement: defined as loss of sharpness of the cartilage margins, loss of homogeneity of the cartilage layer and/or cartilage thinning (focal or extend to the entire cartilaginous layer)

Weight-bearing anteroposterior (AP) and lateral knee radiographs were read by an experienced rheumatologist, blinded to the clinical date and US findings, who assessed the presence or absence of osteophytes and degenerative femoral hyaline cartilage involvement, defined as the presence of femorotibial (FT) joint space narrowing. The FT space width was measured at the most peripheral site and at the mid-point of the medial compartment and lateral compartment. Frequency of each feature was calculated and compared between groups by chi2 test. A p value < 0.05 was considered significant.

Results: 84 patients (mean age 69 ± 10 years, 66 female/18 male) were included for a total of 116 knees evaluated (32 patients complained of bilateral knee pain). Both the presence of osteophytes and degenerative femoral hyaline cartilage involvement were significantly more frequently detected by US than CR (Table). The presence of at least one of these degenerative changes was found in 81/116 knees in 56 patients by US and in 64/116 knees in 42 patients by CR ($p < 0.05$ for both comparisons) (Table).

Table. US and CR features among patients with knee pain

		Ultrasound	Conventional radiology	p
Degenerative femoral hyaline cartilage involvement	Patients, n° (%)	41/84 (48.8)	26/84 (30.9)	0.0181
	Knees, n° (%)	70/116 (60.3)	46/116 (39.6)	0.0016
Osteophytes	Patients, n° (%)	52/84 (61.9)	26/84 (30.9)	0.0001
	Knees, n° (%)	77/116 (66.4)	41/116 (35.3)	<0.0001
Degenerative changes¶	Patients, n° (%)	56/84 (66.6)	42/84 (50)	0.0285
	Knees, n° (%)	81/116 (69.9)	64/116 (55.2)	0.0211

¶defined as the presence of at least one of the other findings: degenerative femoral hyaline cartilage involvement and/or osteophytes

Conclusion: US had the ability to detect more degenerative changes compared with CR in patients > 50 years old complaining of knee pain and without a previous diagnosis of knee OA. The use of US in patients with knee pain and normal CR might be useful in the diagnosis of early stage OA.

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Excess Body Weight and 4-Year Function Outcomes: Comparison of African-Americans and Caucasians in the Osteoarthritis Initiative. Carmelita J. Colbert, Orit Almagor, Joan S. Chmiel, Jing Song, Dorothy D. Dunlop, Karen W. Hayes and Leena Sharma. Northwestern University, Chicago, IL

Background/Purpose: Given the heterogeneity of knee OA impact, it is important to identify persons at risk for poor outcome. A better understanding of differences between risk groups may lead to development of more effective prevention strategies. Losina et al recently demonstrated losses in quality-adjusted life years due to knee OA and obesity, disproportionately high in black and Hispanic women (Ann Intern Med 2011). The impact within racial groups of greater than healthy body weight on more proximal outcomes is not well understood. We tested the hypothesis that African-Americans have a greater risk (vs. Caucasians) of poor baseline-to-4-year function outcome within each strata: women with high BMI, women with large waist circumference, men with high BMI, and men with large waist circumference. The OAI cohort study, enriched with individuals above a healthy body weight, provided an ideal setting.

Methods: Using WOMAC function, 20 meter walk, and chair stand performance, poor outcome was defined as moving into a worse function group or remaining in the 2 worst groups over 4 years. Logistic regression was used to evaluate the hypothesized relationships between racial groups and outcomes within each stratum, adjusting for age, education, and income, and then further adjusting for BMI, comorbidity, depressive symptoms, physical activity, knee pain, and OA severity.

Results: In 3,695 persons with or at higher risk for knee OA, high BMI and large waist circumference were each associated with poor outcome. As shown in the table, among women with high BMI and among women with large waist circumference, African-Americans were at greater risk for poor outcome by every measure, adjusting for age, education, and income. From fully adjusted models (not shown), potential explanatory factors included income, comorbidity, depressive symptoms, pain, and disease severity. Findings were less consistent for men (see table), emerging for the 20 meter walk or chair stand outcomes, and potentially explained by age and knee pain.

Table. Odds of poor 4-year outcome associated with race by gender, BMI and waist circumference groups, adjusting for age, education, and income (AA = African-American, C = Caucasian, significant results bolded)

	Poor WOMAC outcome adjusted OR (95% CI)	Poor 20 meter walk outcome adjusted OR (95% CI)	Poor chair stand outcome adjusted OR (95% CI)
AA vs. C women (in women with high BMI, ≥ 25 kg/m²)	*1.54 (1.19, 1.98)*	*1.43 (1.07, 1.91)*	*1.81 (1.37, 2.39)*
AA vs. C women (in women with large waist circumference, > 88 cm)	*1.55 (1.21, 1.99)*	*1.57 (1.18, 2.07)*	*2.02 (1.54, 2.65)*
AA vs. C men (in men with high BMI, ≥ 25 kg/m²)	1.26 (0.87, 1.81)	*1.94 (1.31, 2.87)*	*1.56 (1.07, 2.28)*
AA vs. C men (in men with large waist circumference, > 102 cm)	1.53 (0.93, 2.52)	*2.24 (1.30, 3.85)*	1.34 (0.80, 2.23)

Conclusion: Among women with high BMI and among women with large waist circumference, African-Americans were at greater risk than Caucasians for poor 4-year outcome by each measure evaluated, adjusting for age, education, and income. Modifiable factors that may in part explain these findings in women in the OAI include comorbidity, depressive symptoms, and knee pain. Targeting such factors, while supporting weight loss, may help to lessen the outcome disparity between African-American and Caucasian women.

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Relationship of Objective to Self-Reported Physical Activity Measures Among Adults in the Osteoarthritis Initiative. Grace E. Ahn[1], Jing Song[1], Jungwha Lee[1], Pamela A. Semanik[1], Rowland W. Chang[1], Leena Sharma[1], Charles Eaton[2], Rebecca Jackson[3], Alex Mysiw[4] and Dorothy D. Dunlop[1]. [1]Northwestern University, Chicago, IL, [2]Warren Alpert Medical School at Brown University, RI, [3]Ohio State University, Columbus, OH, [4]Denison University, Granville

Background/Purpose: Physical activity conveys health benefits for people with osteoarthritis (OA). Public health activity guidelines are tied to time spent in bouts of moderate/vigorous physical activity (MVPA) lasting 10 minutes or more. This study compares objective accelerometer measures of MVPA with self-reported Physical Activity Scale in the Elderly (PASE) scores and their association with function in adults with and without radiographic knee OA.

Methods: The Osteoarthritis Initiative accelerometer ancillary study includes 586 adults without and 969 with radiographic knee OA (Kellgren-Lawrence score ≥2 in one or both knees), aged 55 and above. Participants' response to the PASE questionnaire was followed by 7 days of accelerometer monitoring. Accelerometer measures included average daily MVPA minutes and MVPA minutes acquired in bouts. Function measures included gait speed averaged from two 20 meter walks, WOMAC (Western Ontario MacMaster) function, and SF12 (12-Item Short Form Health Survey) physical function. Nonparametric Spearman correlations were used to assess associations.

Results: Adults with and without knee OA had mean (SD) PASE scores: 149.82 (78.5), 154.5 (79.0); mean accelerometer MVPA minutes/day: 15.6 (17.2), 19.2 (20.5) and mean MVPA bouted minutes/day: 7.2 (12.4), 9.3

(15.8), respectively. PASE score correlations with accelerometer measures are shown below. In this sample, PASE was correlated most strongly with total activity counts followed by MVPA minutes and had weakest association with MVPA minutes accumulated in bouts. Further analysis shows all objective accelerometer measures had stronger associations with function than PASE (e.g., correlations from overall sample of gait speed function with self-reported PASE: r=0.16, accelerometer counts: r=0.29, MVPA: r=0.34, MVPA bouts: r=0.28). These findings were true of both adults with and without radiographic OA.

Table. Spearman Correlation Coefficients (r) between Self-Reported PASE Scores and Objective Physical Activity Accelerometer Measures

	Accelerometer Physical Activity Measures		
OAI Radiographic Subgroups	**Average Daily Counts of Total Activity**	**Average Daily Moderate/Vigorous Activity Minutes**	**Average Daily Moderate/Vigorous Activity Minutes in Sessions of 10 Minutes or More**
All n = 1555	0.38 (0.34, 0.42)	0.33 (0.28, 0.37)	0.20 (0.15, 0.24)
With Radiographic OA (n = 969) r (95% CI)	0.35 (0.30, 0.41)	0.31 (0.25, 0.37)	0.21 (0.15, 0.27)
Without Radiographic OA (n = 586) r (95% CI)	0.42 (0.36, 0.49)	0.35 (0.28, 0.42)	0.18 (0.10, 0.26)

Conclusion: In this sample with and without radiographic knee OA, the self-reported PASE score had stronger although modest correlations with objective measures of total activity than with MVPA minutes or MVPA bouted minutes. Objective physical activity measures compared to self report had stronger relationships with function. The choice of PASE, a recall measure of various activity types, and/or objective measurement for future epidemiologic studies must take into account the purpose for which physical activity is being measured.

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Relationship of Physical Activity with Health Utility in the Osteoarthritis Initiative. Dorothy D. Dunlop[1], Jing Song[1], Rowland W. Chang[1], Jungwha Lee[1], Pamela A. Semanik[2], Linda S. Ehrlich-Jones[3], Kai Sun[1], Leena Sharma[1], C. Kent Kwoh[4], Charles Eaton[5] and Larry Manheim[1]. [1]Northwestern University, Chicago, IL, [2]Rehabilitation Institute Chicago, Oak Park, IL, [3]Rehabilitation Institute Chicago, Chicago, IL, [4]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [5]Warren Alpert Medical School at Brown University, RI

Background/Purpose: Cost effectiveness analyses of arthritis interventions require utility measurements to evaluate their relative effectiveness. Clinical guidelines for knee osteoarthritis (KOA) treatment include a substantial role for physical activity. Recognizing the importance of physical activity, there are federal recommendations for US adults that now include persons with arthritis. To investigate if attainment of these guidelines translates into better health-related utility in adults with KOA, we analyzed data from the Osteoarthritis Initiative (OAI).

Methods: Physical activity was measured by accelerometers on 1154 OAI participants aged 49 to 84 years with radiographic KOA (KL grade ≥2 from central lab) in at least one knee at the 48 month follow-up visit. Activity intensity was determined from established accelerometer cutpoints for moderate-to-vigorous [MV] intensity (counts ≥ 2020/minute). Physical activity was classified as 1) inactive (no bouts of MV activity lasting 10 minutes over the week); 2) insufficient activity (bouts of MV activity/week < 150 minutes), or 3) met the 2008 Physical Activity Guidelines aerobic component (≥150 MV minutes/week acquired in bouts ≥10 minutes). An SF6-D utility score (0=worst to 1=best possibility utility) was derived from participant responses to the SF-12 questionnaire collected at the 48 month visit. The relationship of physical activity levels to average health utility controlled for demographics (age, gender, race, education, income), knee factors (KL grade, knee symptoms, WOMAC knee pain, knee injury history) and general health (BMI, comorbidity, depression, smoking, hip pain, ankle pain, foot pain) using multiple linear regression.

Results: Almost half (48%) of adults with KOA were inactive; another 40% failed to meet recommended Guidelines. Average utility scores consistently increased with better levels of physical activity: 0.772 for inactive,

0.797 for insufficient and 0.835 for meeting guidelines groups (p trend<.0001). To determine if higher physical activity levels consistently correspond to better health utility among people with similar demographics and measured health we examined utility differences controlling for these factors. These results (Table) showed a strong cross-sectional relationship and a statistically significant linear trend.

	Differences in mean utility between physical activity levels adjusted for demographic, knee health and general health factors		
Adjustment Factors n=1154	**Insufficient vs Inactive(95% CI)**	**Meet Guideline vs Inactive (95% CI)**	**Trend Test**
Unadjusted	0.025 (0.010, 0.040)	0.063 (0.039, 0.086)	p<.001
Demographic	0.020 (0.005, 0.036)	0.053 (0.029, 0.077)	p<.001
Demographic+ Knee+ General Health Factors	0.011 (−0.002, 0.024)	0.023 (0.003, 0.044)	p=.018

Conclusion: Despite known benefits of physical activity, most adults with KOA were inactive. Inactive adults with KOA had significantly lower health-related utility levels than persons who were insufficiently active as well as those who met Guidelines. These findings show a strong relationship between greater physical levels and better health utility. These findings support interventions to improve health-related utility for adults with KA by increasing physical activity, even if recommended levels are not attained

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Minimal Clinically Important Difference and Patient Acceptable Symptom State for the Oarsi -Omeract Intermittent and Constant OA Pain (ICOAP) Measure. Z. Anna Liu, Tetyana Kendzerska, Joy Elkayam, Shefali Ram and Gillian A. Hawker, Women's College Research Institute, University of Toronto, Toronto, ON

Background/Purpose: The Intermittent and Constant Osteoarthritis Pain (ICOAP) measure was developed to evaluate the OA pain experience, independent of the effect of pain on physical activity. ICOAP has been shown to be reliable, valid and responsive to treatment in knee OA. This study sought to establish for ICOAP the Minimal Clinically Important Difference (MCID) for improvement and worsening, and the Patient Acceptable Symptom State (PASS).

Methods: In subjects with painful knee OA, the ICOAP was administered twice by telephone, two-weeks apart. The ICOAP is comprised of two subscales (constant and intermittent pain); the total score (range 0–100) is the sum of subscale scores, with higher scores indicating worse pain. At both time points, participants were asked to report their knee pain in the past 48 hours and the acceptability of their current knee pain state (acceptable or unacceptable). At second interview, participants were asked to report the degree to which their knee pain had changed (5-point scale from much worse to much better). MCID was calculated as the mean absolute change in ICOAP scores (Time 2−Time 1) for those who reported 'slightly better' or 'slightly worse' versus 'no change'. PASS was defined as the threshold ICOAP score at or above which participants considered their pain as 'unacceptable'. Logistic regression was used to assess the ability of ICOAP change scores to predict reported improvement or worsening, and the relationship between scores and pain state acceptability.

Results: 136 participants completed the study; 66 (54%) were female with a mean age of 73.9 years (SD 9.5). Median ICOAP constant, intermittent and total scores were 0/100 (range 0–90), 37.5 (0–87.5) and 25 (4.6–88.6), respectively, at Time 1 and 0 (0–95), 37.5 (0–95.8), and 23.9 (4.6–95.5) at Time 2. 'Slight improvement' was associated with a mean decrease of 2 and 7 points for the ICOAP constant and intermittent scales, respectively, while 'slight worsening' was associated with a mean increase of 4 points for both scales. The threshold ICOAP subscale scores associated with an unacceptable symptom state were: 20/100 (constant pain); 40/100 (intermittent pain); and 30/100 (total score). Changes in ICOAP subscale and total scores had good discriminative validity for self-reported improvement versus no change/worsening (Figure 1; AUC = 0.60–0.75) and for reported worsening (AUC 0.73–0.82). Absolute ICOAP scores were highly predictive of the acceptability of symptom state (AUC 0.71–0.84).

ROC Curves for Comparisons

ROC Curve (Area)
— Change in ICOAP, intermittent subscale, AUC (0.7482)
– – Change in ICOAP, constant subscale, AUC (0.6001)
– · – Change in ICOAP, total score, AUC (0.7484)
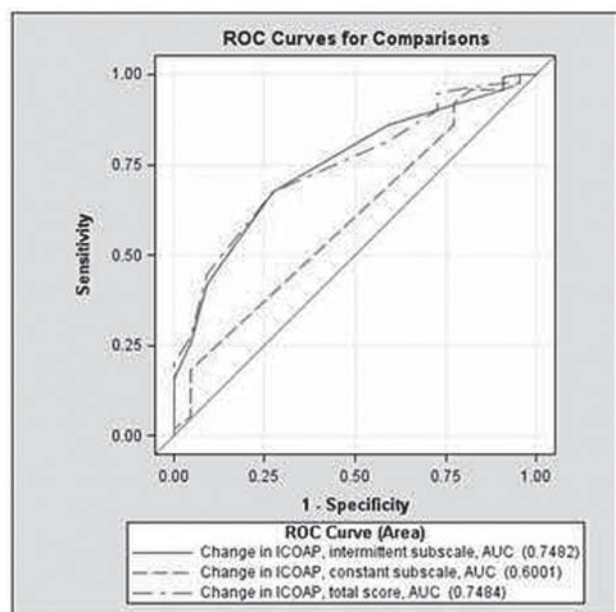
Conclusion: In an observational cohort, we determined the MCID and PASS for ICOAP total and subscale scores. These findings will assist clinicians and researchers in interpreting the clinical meaning of ICOAP scores for pain in knee OA. Future work will determine whether ICOAP MCID values differ across settings, including with clinical interventions.

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Similarities of Patient Self-Report Scores From a Multidimensional Health Assessment Questionnaire (MDHAQ), Laboratory Tests, Physician Global Assessment, and Polyarticular Involvement in Patients with Osteoarthritis and Rheumatoid Arthritis. Isabel Castrejón, Yusuf Yazici and Theodore Pincus. NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Rheumatoid arthritis (RA) and osteoarthritis (OA) are distinct diagnoses, based on widely differing pathogenetic mechanisms and treatments. However, OA patients may experience functional disability, pain and global distress at levels similar to RA patients. Furthermore, although differences may have been more pronounced in the past, at this time many OA patients have polyarthritis and levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) similar to RA patients. A systematic comparison of patients with RA vs OA, including patient self-report scores, involvement of specific joints, laboratory tests, and physician global assessment, appeared of value.

Methods: All patients seen at an academic rheumatology center complete a multidimensional health assessment questionnaire (MDHAQ) at each visit to assess physical function, pain, patient global estimate (all 0–10), routine assessment of patient index data (RAPID3)–a composite of these 3 measures (0–30), and a rheumatoid arthritis disease activity index (RADAI) self-report of painful joints. RADAI is scored 0–3 for 16 joint groups (8 right, 8 left): fingers, wrist, elbow, shoulder, hip, knee, ankle, toes (total 0–48). A binary scoring of 0 or 1 (to mimic a physician joint count) was also computed. All patients are assigned a physician global estimate. ESR and CRP are assessed in many patients. Measures were compared in 174 RA vs 113 OA consecutive patients: normally distributed variables by means and *t* tests, non-normally distributed variables by medians and Mann-Whitney tests, and categorical variables by chi-square tests; *p* values were adjusted for 23 comparisons.

Results: Mean age was 49.3 in RA patients vs 62.8 years in OA patients ($p < 0.0002$, adjusted for 23 comparisons). Median values for physical function, pain, patient global estimate, RAPID3, ESR, CRP, and mean physician global estimate did not differ in RA vs OA. Median total RADAI and binary scores were slightly higher in RA than OA (not statistically significant). More than 4 involved joint groups were self-reported by 64% of RA and 58% of OA patients. Involvement of wrists was higher in RA vs OA

(51% vs 32%, adjusted $p = 0.023$); no other differences in specific joint group involvement were statistically significant, adjusted for 23 comparisons.

	RA patients N = 174	OA patients N = 113	P	Adj. P*
DEMOGRAPHIC VARIABLES				
Age, years: mean (SD)	49.3 (15.1)	62.8 (12.5)	<0.00001	<0.002
Gender, % female	80%	73%	0.18	NA
Ethnicity, %			0.10	NA
● White	49%	65%		
● African American	14%	8%		
● Hispanic	27%	21%		
● Asian	8%	3%		
● Other	2%	3%		
Educational, years: median (IQR)	16 (12–18)	16 (12–18)	0.40	NA
CLINICAL AND LABORATORY VARIABLES				
Disease duration, years: mean (SD)	7.5 (6.2)	6.6 (5.2)	0.34	NA
ESR, mm/h, median (IQR)	14 (9–28)	12 (8–24)	0.87	NA
CRP, median (IQR)	1.6 (0.4–5)	5 (0.3–6)	0.36	NA
Physician global estimate (0–10): mean (SD)	2.9 (1.8)	2.9 (1.5)	0.97	NA
PATIENT SELF-REPORT MEASURES				
Physical function (0–10): median (IQR)	2.3 (0.6–4.3)	1.7 (0.7–3.3)	0.24	NA
Pain (0–10): median (IQR)	5 (2–8)	5 (3.5–7.5)	0.26	NA
Patient global estimate (0–10): median (IQR)	4 (1.5–7.5)	5 (2.5–6.5)	0.85	NA
RAPID3 (0–30): median (IQR)	11.7 (4.9–19.2)	11.8 (6.8–16.7)	0.80	NA
RADAI SELF-REPORT JOINT COUNT DATA				
Total RADAI (0–48): median (IQR)	9 (2–20)	7 (4–13)	0.75	NA
Binary RADAI (0–16): median (IQR)	6 (2–12)	4 (3–8)	0.33	NA
Number (%) scoring ≥4 joint groups	111 (64%)	66 (58%)	0.36	NA
INVOLVEMENT OF SPECIFIC JOINT GROUPS				
Fingers	98 (56%)	47 (42%)	0.01	0.23
Wrist	89 (51%)	36 (32%)	0.001	0.023
Elbow	53 (30%)	27 (24%)	0.22	NA
Shoulder	75 (43%)	46 (41%)	0.68	NA
Hip	62 (36%)	43 (38%)	0.67	NA
Knee	88 (51%)	77 (69%)	0.003	0.069
Ankle	70 (40%)	31 (28%)	0.02	0.46
Toes	71 (41%)	30 (27%)	0.01	0.23

*Adjusted for 23 comparisons. NA = not applicable (unadjusted $P > 0.05$).

Conclusion: OA and RA result in similar patient self-report MDHAQ scores. Further, physician global estimate, ESR, CRP and polyarticular involvement are similar in OA and RA at this time. RA and OA may have been more distinct in the past, when RA patients were younger, had much more severe clinical status, and less effective treatments. The data emphasize the need for careful evaluation by a knowledgeable physician to distinguish OA from RA, and may improve understanding of the concerns of OA patients, most of whom have polyarticular disease, functional disability and pain scores similar to patients with RA.

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Routine Assessment of Patient Index Data 3 (RAPID3) Is a Valid Index for Routine Care in Patients with Osteoarthritis. Alfredomaria Lurati[1], Luca Bertani[1], Daniela Bompane[1], Mariagrazia Marrazza[1], Katia Angela Re[1] and Magda Scarpellini[2]. [1]Rheumatology Unit, Magenta, Italy, [2]Ospedale Fornaroli, Magenta, Italy

Background/Purpose: RAPID3 (routine assessment of patient index data) is an arithmetic composite index of three Core Data Set, patient self-report, measures: physical function (0–3 converted to 0–10), pain (0–10), and patient global estimate (0–10) for a total of 0–30. It can be completed in the waiting room and can be calculated in only few seconds. Aim of this study was to compare RAPID3 with the Western Ontario and Mc-Master Universities Osteoarthritis Index (WOMAC) in patients with knee or hip osteoarthritis (OA)

Methods: patients with symptomatic knee or hip osteoarthritis as main rheumatologic diagnosis (VAS pain > 50 on a visual scale 0–100mm) according to the ACR (American College of Rheumatology) criteria and with stage 2 or 3 according to the Kellgren-Lawrence radiographic criteria were eligible. All subjects were clinically evaluated individually by an experienced rheumatologist and were asked to complete the self-report questionnaires (the original version of the WOMAC for hip or knee osteoarthritis and the RAPID3). There was no specific order in which the tests were completed; rather, each participant selected the order. Agreement between WOMAC and RAPID3 scores was estimated with rho Spearman correlation statistic and Cohen's kappa.

Results: 478 patients (155 males, 323 females) with hip (n=38) or knee (n=70) osteoarthritis were enrolled in daily practice clinical care during

2010–2012. Mean age ($\pm$SD) was 63 ± 14.4 years old. Mean score was 67 ± 9.1 for WOMAC and 6.5 ± 2.1 for RAPID3. RAPID3 and WOMAC have shown a global correlation rho index of 0.72 (p<0.01) and a Cohen's kappa of 0.7. Computing analysis for diagnosis, the means of WOMAC and RAPID3 weren't significantly different between patients with hip or knee osteoarthritis ($67\pm$ 9.9 vs 68 ± 6.8 and 6.4 ± 2.1 vs 6.6 ± 2.1, respectively. p>0.05). The Spearman's rho was 0.63 for hip osteoarthritis (p<0.01) and 0.78 for knee osteoarthritis. Cohen's kappa was 0.68 for hip osteoarthritis (p<0.01) and 0.78 for knee osteoarthritis, respectively.

Conclusion: Up to date there's not literature about the use of RAPID3 in patients with OA. In our study we found a strong correlation between RAPID3 and WOMAC in patients with either hip and knee OA, confirmed by a linear regression model developed using all variables collected. RAPID3 provide informative quantitative data for patient status from one visit to the next comparable to other self-reported questionnaire as WOMAC in a time sparing manner.

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Meager Depression Screening and Mental Health Referral Rates for Patients with Arthritis in a National Sample. Mary Margaretten, Patricia P. Katz, Laura Trupin, Gabriela Schmajuk, Jennifer Barton, Jinoos Yazdany and Edward Yelin. UCSF, San Francisco, CA

Background/Purpose: Depression in patients with arthritis is common and leads to poor health outcomes. While it has been shown that rheumatologists rarely communicate about depression to their patients with arthritis, there are no data about screening practices for depression in this population. Our objectives were to describe national rates of depression screening in patients with arthritis and real-world practices for mental health referrals for patients with arthritis and prevalent depression.

Methods: In 2005 the National Ambulatory Medical Care Survey, an annual visit-based cross-sectional survey conducted in physicians' offices, began collecting data about depression screening practices. Using 2005–2009 data, we compared office visits coded for current arthritis with other office visits to assess the rate of pre-existing depression, depression screening, and mental health referrals. Of 102,050 adult visits, we identified 14,611 coded for current arthritis (osteoarthritis and/or inflammatory arthritis) over the five-year study period. Multivariate logistic regression adjusted for age, race, and gender determined the independent association of depression and arthritis. Patients with a current diagnosis of depression were excluded from analyses of depression screening practices leaving 12,457 patient visits without depression. The chi-square test of association was used to compare depression screening practices, provider characteristics, and referral rates for mental health services between patients with and without arthritis. Patients with and without arthritis who had a current diagnosis of depression (n=11,664) were included in analyses for mental health referrals.

Results: The odds ratio for comorbid depression in patients with arthritis was 1.5 (95% CI 1.4, 1.6) controlling for age, race, and gender. Depression screening occurred in 77 (0.6%) of the eligible 12,457 visits associated with arthritis. Patients with arthritis were less likely to have depression screening services at their office visit compared to patients without arthritis (OR.69; 95% CI.54,.87). No rheumatologists screened their patients with arthritis for depression. Patients with arthritis and depression were less likely to receive referrals for psychotherapy (OR.43; 95% CI.38,.51), mental health providers (OR.25; 95% CI.15,.42), or other mental health services (OR.41; 95% CI.33,.51) compared to patients without arthritis.

Conclusion: Ambulatory physicians in the United States, whether they are rheumatologists or primary care providers, rarely screen for depression in patients with arthritis. Furthermore, identified depressed patients with arthritis are less likely to receive referrals for mental health services. Both recognition and treatment practices need to be improved for patients with arthritis and depression in order to improve health outcomes.

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Synovial Fluid Leptin Level Is Associated with Residual Pain and Functional Disability One Year After Total Joint Arthroplasty. Anne Lübbeke[1], Gabor J. Puskas[1], Axel Finckh[2], Domizio Suva[1], Sylvette Bas[3], Cem Gabay[1], Daniel Fritschy[1] and Pierre Hoffmeyer[1]. [1]Geneva University Hospitals, Geneva, Switzerland, [2]Geneva University Hospitals, Geneva 14, Switzerland, [3]Geneva University Hospitals, Switzerland

Background/Purpose: A sizeable number of patients continue to suffer from pain, functional disability and reduced quality of life after total joint arthroplasty (TJA). The etiology of post-TJA pain is not well established and the presence of chronic pain of neuropathic origin has been suggested. Leptin has been identified as a mediator of the immuno-inflammatory response in osteoarthritis (OA), and its pro-inflammatory functions could explain its role in peripheral pain sensitization. We previously demonstrated that high synovial fluid (SF) leptin concentrations correlate with increased preoperative pain in hip and knee OA patients. In addition, animal models have suggested the involvement of leptin in the pathogenesis of pain at the spinal level and in the development of neuropathic pain. Our objective was to assess pain, function, patient satisfaction and general health in patients undergoing TJA according to SF leptin concentration.

Methods: Prospective cohort study of patients with primary OA undergoing total hip or knee arthroplasty between January and December 2010. On the day of intervention, SF was sampled and leptin concentrations were assessed using an ELISA kit. Exposure was SF leptin concentration ($\leq$19.6 ng/ml vs. >19.6 ng/ml= highest quartile). Outcomes were: joint pain, function and general health measured pre- and at 1 year postoperative with WOMAC, VAS for pain, and SF-12, and patient satisfaction at 1 year measured on 5-item Likert scale.

Results: 167 TJAs were included, 88 total hip and 79 total knee arthroplasties. Mean age was 72 years, mean BMI 28 kg/m^2, 58% were women. High intra-operative SF leptin concentrations (>19.6 ng/ml) were found in 39 (23.4%) joints. Compared to leptin levels <19.6 ng/ml their presence was associated with significantly higher pain levels on both WOMAC and VAS pain scales, with lower function and worse physical and mental health scores both pre- and 1 year postoperative (effect sizes ranging from 0.4 to 0.7) and with lower satisfaction (see Table). Residual pain of $\geq$5 on the VAS was present in 33% of TJAs with high leptin concentration compared to 13% in the other group (RR 2.5, 95% CI 1.3; 4.7). The degree of improvement in all domains (difference pre- to postoperative) was not significantly modified by SF leptin levels.

Table 1. Preoperative and 1-year postoperative assessment of pain, function and general health according to leptin concentration

	Leptin 1–3rd quartile $\leq$ 19.6 ng/ml	n	Leptin 4th quartile > 19.6 ng/ml	n	4th vs. 1–3rd quartile Unadjusted mean difference (95% CI)	4th vs. 1–3rd quartile Adjusted mean difference (95% CI)*
WOMAC pain, mean (SD)		116		36		
Preoperative	42.2 ($\pm$18.3)		32.5 ($\pm$15.5)		9.7 (3.1; 16.4)	9.1 (2.6; 15.5)
At 1 year	71.8 ($\pm$24.1)		61.5 ($\pm$21.1)		10.2 (1.4; 19.1)	9.8 (0.8; 18.8)
Difference	*29.5 ($\pm$23.8)*		*29.0 ($\pm$21.2)*		*0.5 ($-$8.2; 9.2)*	*0.7 ($-$8.2; 9.6)*
WOMAC function, mean (SD)		116		36		
Preoperative	44.6 ($\pm$19.9)		37.6 ($\pm$15.4)		7.0 (0.8; 13.3)	7.4 (0.5; 14.2)
At 1 year	71.1 ($\pm$24.4)		62.5 ($\pm$20.4)		8.6 ($-$0.3; 17.5)	8.7 ($-$0.3; 17.8)
Difference	*26.5 ($\pm$25.2)*		*24.9 ($\pm$23.1)*		*1.6 ($-$7.7; 10.9)*	*1.3 ($-$8.1; 10.8)*
VAS pain, mean (SD)		122		37		
Preoperative	5.8 ($\pm$1.8)		6.5 ($\pm$1.7)		0.7 (0; 1.3)	0.6 (0; 1.2)
At 1 year	1.9 ($\pm$2.1)		3.3 ($\pm$2.4)		1.4 (0.5; 2.1)	1.2 (0.4; 2.0)
Difference	*3.9 ($\pm$2.3)*		*3.2 ($\pm$2.6)*		*0.7 ($-$0.2; 1.6)*	*0.6 ($-$0.3; 1.5)*
SF-12 physical component, mean (SD)		112		34		
Preoperative	35.7 ($\pm$8.4)		32.0 ($\pm$7.1)		3.7 (0.5; 6.8)	4.0 (0.8; 7.1)
At 1 year	42.3 ($\pm$9.4)		36.4 ($\pm$9.2)		5.9 (2.3; 9.5)	5.9 (2.2; 9.5)
Difference	*6.6 ($\pm$9.9)*		*4.4 ($\pm$8.8)*		*2.2 ($-$1.5; 6.0)*	*1.9 ($-$1.9; 5.7)*
SF-12 mental component, mean (SD)		112		34		
Preoperative	44.8 ($\pm$11.0)		39.3 ($\pm$11.0)		5.5 (1.2; 9.8)	5.8 (1.5; 9.9)
At 1 year	47.5 ($\pm$10.1)		41.0 ($\pm$9.7)		6.5 (2.7; 10.4)	6.7 (2.9; 10.5)
Difference	*2.8 ($\pm$11.1)*		*1.7 ($\pm$11.3)*		*1.1 ($-$3.3.; 5.4)*	*1.0 ($-$3.4; 5.4)*
Satisfaction (%)		126		39		
Very satisfied	82 (64.1)		12 (30.8)			
Satisfied	20 (15.6)		18 (46.2)			
<> Somewhat satisfied	12 (9.4)		5 (12.8)			
<> Dissatisfied	12 (9.4)		4 (10.3)		p=0.002	

*Adjusted for age, ASA score, OA site (hip vs. knee) and Charnley disability grade with use of multivariable linear regression

Conclusion: High intra-articular leptin were strongly associated with more residual pain and functional disability 1 year after arthroplasty. However, the degree of improvement was independent of leptin concentration. With respect to pain these results lend support to the hypothesis that high intra-articular leptin levels could favor spinal pain sensitization and the development of neuropathic pain earlier in the disease process.

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Medial Subchondral Bone Marrow Lesions Increase the Odds of Knee Joint Replacement–Data From the Osteoarthritis Initative. Frank Roemer[1], C. Kent Kwoh[2], David Hunter[3], Michael J. Hannon[4], Robert M. Boudreau[5], Felix Eckstein[6], Zhijie Wang[4], Markus R. John[7] and Ali Guermazi[8]. [1]Klinikum Augsburg, Augsburg, Germany, [2]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [3]University of Sydney, Sydney, Australia, [4]University of Pittsburgh School of Medicine, Pittsburgh, PA, [5]University of Pittsburgh, Pittsburgh, PA, [6]Paracelsus Medical University, Salzburg, Austria, [7]Novartis Pharma AG, Basel, Switzerland, [8]Boston University School of Medicine, Boston, MA

Background/Purpose: Knee joint replacement (KR) is a cost-effective procedure with good long-term outcomes. However, there is no clear consensus on indications for KR. Subchondral bone marrow lesions (BMLs) have been identified as important structural features relevant to clinical manifestation (e.g.pain) as well as structural progression (e.g. cartilage loss). Thus, BMLs are promising biomarkers for structural progression to important clinical outcomes such as KR. The aims of this study were therefore to test whether presence and size of BMLs increased odds of KR, and whether worsening of BMLs over time increased odds of KR.

Methods: We studied 121 knees from OAI participants that underwent KR before the 48 month visit at two time points (T0 and T-1) prior to KR, (i.e. for a KR reported at the 48 month (M) visit, T0 = 36M and T-1 = 24M). These were matched with 121 control knees that did not undergo KR based on radiographic disease stage, sex, and age ($+/-$ 5y). 3Tesla MRIs were read for subchondral BMLs in 14 articular subregions using the semiquantitative MOAKS system. Only BML size, which is scored from 0–3, was considered in this study. Analyses were performed on a plate (medial tibia, medial femur, lateral tibia, lateral femur, trochlea, patella) and compartmental level (medial tibio-femoral joint [TFJ], lateral TFJ and patello-femoral joint–[PFJ]). Conditional logistic regression was applied to assess the risk of KR relative to the maximum BML size per plate at T0. In addition, the number of subregions per compartment showing BML worsening from the time point prior T0 (=T-1) to T0 was analyzed relative to the odds of KR following T0.

Results: Subjects were on average 65.3 years old (SD $\pm$ 8.6), predominantly female (58.1%) and overweight (mean BMI 29.6 SD $\pm$ 4.9). The odds of KR were significantly greater for knees exhibiting large (i.e. grade 3) BMLs in the medial compartment when compared to the knees without BMLs at T0 (Table 1). Further, the odds for KR were significantly greater for knees with '3 subregions exhibiting increase in BML size in the medial TF compartment from T-1 to T0 compared to knees with no subregions showing worsening (OR 3.35, 95%CI 1.14–9.82). No significant associations were found for smaller lesions, the lateral TFJ and PFJ and respective plates cross-sectionally or longitudinally.

Conclusion: On a plate-level analysis, presence of large BMLs in the medial femur and/or tibia at the time point prior to KR was associated with increased odds of KR, while presence of large BMLs in the lateral TFJ or in the PFJ was not. Worsening of BML size in ≥3 subregions in the medial TF compartment from T-1 to T0 was associated with increased odds of KR when compared to knees without worsening in any subregion in the same compartment.

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Incident and Worsening Cartilage Damage in the Lateral Compartment and Multiple Subregions Worsening in the Medial Compartment Increase the Risk for Knee Replacement - Data From the Osteoarthritis Initiative. Frank Roemer[1], C. Kent Kwoh[2], Michael J. Hannon[3], Robert M. Boudreau[4], Felix Eckstein[5], David J. Hunter[6], Zhijie Wang[3], Markus R. John[7] and Ali Guermazi[8]. [1]Klinikum Augsburg, Augsburg, Germany, [2]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA, [5]Paracelsus Medical University, Salzburg, Austria, [6]University of Sydney, Sydney, Australia, [7]Novartis Pharma AG, Basel, Switzerland, [8]Boston University School of Medicine, Boston, MA

Background/Purpose: Knee joint replacement (KR) is a cost-effective procedure with good long-term outcomes. However, at present there is no clear consensus on indications for KR. Imaging biomarkers capable of predicting KR therefore are urgently needed and may be helpful in clinical studies and trials that utilize KR as an outcome. Specific MRI-based quantitative measures of cartilage morphology have recently been described to be associated with an increased risk of KR. The aim of the present study was to determine whether longitudinal changes in semi-quantitative MRI-based measures of cartilage differ between knees undergoing KR and control knees not undergoing KR. We used a compartment-based analysis (i.e., medial tibio-femoral (MTF), lateral tibio-femora (LTF) or patello-femoral (PF)0.

Methods: We studied 127 knees from OAI participants (age 46–81 years) that underwent KR before the 60 month visit at two time points prior to KR, (e.g. for a KR reported at the 48 month (M) visit, T0 = 36M and T-1 = 24M).127 control knees that did not undergo KR were matched for KL grade (0/1, 2, 3, 4), gender, and age ($+/-$ 5y) and were assessed at the same T0 and T-1 visits. 3 T MRIs were read for cartilage morphology using the semiquantitative MOAKS system in 14 articular subregions, which scores cartilage from 0 to 3 in regard to proportion of the area of the subregion involved and from 0 to 3 in regard to percentage of subregion involved by full thickness loss. Within-grade coding was used to score definite visual changes that do not fulfill criteria of a full grade change. Conditional logistic regression was applied to assess compartmental changes in cartilage morphology from T-1 to T0 with respect to risk for KR following T0.

Results: Subjects were on average 65.7 years old (SD $\pm$ 8.8), predominantly female (59.8%) and overweight (mean BMI 29.7 SD $\pm$ 4.82). The K/L distribution was: KL0: 8 (3.15%) KL1: 8 (3.15%), KL2: 57(22.44%), KL3:146 87(34.25%) and KL4: 94 (37.01%).

Development of full thickness cartilage damage and full grade worsening in the LTF, but not MTF compartment from T-1 to T0 was associated with greater odds for KR (OR 2.8, 95% CI 1.01–7.78 and 4.5 95% CI 1.52–13.30, respectively). More than 3 subregions exhibiting worsening in the MTF compartment was associated with increased odds for KR (OR 14.5, 95% CI 1.90–110.93), while this was not observed for the LTF or PF compartments.

Conclusion: Development of full thickness cartilage damage and worsening in the LTF compartment as well as multiple subregions showing worsening cartilage damage in the MTF compartment increase odds for TKR. Presence and change of these imaging biomarkers may be important prognostic markers when KR is used as a long-term outcome.

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Smaller Baseline and Follow-up Quadriceps Muscle Cross-Sectional Area Increases the Odds of Knee Replacement in Knee Osteoarthritis. Serter Gumus[1], Michael J. Hannon[2], Diana Kaya[1], C. Kent Kwoh[3] and Kyongtae Ty Bae[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA

Background/Purpose: Knee osteoarthritis (OA) is one of the major causes of disability among elderly. Knee replacement (KR) is the final effective treatment of OA after other treatment attempts fails to provide pain relief. Quadriceps muscle is the major stabilizer of knee joint. Our purpose was to evaluate the relationship between quadriceps muscle quality and total knee replacement incidence in patients having OA.

Methods: Cases were defined as the participants who had a KR between 36 to 60 months visit. Controls were matched by age (within 5 years), sex and baseline central Kellgren-Lawrence grade (0/1, 2, 3 and 4). Participants who had available mid-thigh MR imaging scans (15 contiguous slices, 5mm slice thickness) at baseline and 24 month follow-up were evaluated. Femoral insertion point of oblique tendon of adductor magnus muscle was determined as a landmark for each thigh for matching purposes to account for differences thigh length and body surface area (BSA). This slice was chosen for segmentation and cross-sectional area (CSA) measurements of quadriceps, hamstring muscles and intramuscular, subcutaneous fat (QM, HM, IMF, SCF). Segmentation was done by a radiologist who was blinded to TKR status. A second radiologist segmented 20 legs for reliability measurements.

Muscle quality (MQ) was defined as the peak muscle strength divided by muscle CSA. Four pairs were excluded for baseline and four additional pairs were excluded for follow-up MQ measurements because the peak strength values were not available. Conditional logistic regression analysis was used for statistical evaluation.

Results: There were 46 case-control pairs of thighs and knees (54 right, 38 left) from Osteoarthritis Initiative (OAI) database that were included in this case-control study. The mean ± SD age and BSA were 63.3 ± 8.9, 1.99 ± 0.23 respectively. Fifty percent of the participants were female and 7.6% were African American. Inter and intraobserver ICC was 0.997 and 0.999 respectively. In adjusted models, QMCSA was smaller in case group both in baseline and follow-up images (p=0.17, p=0.24 respectively). Baseline and follow up QM quality (QMQ) was not significantly different between cases and controls. HMCSA, HMQ, SCFCSA and IMFCSA measurements did not show any significant differences between case and controls.

Descriptive information of quadriceps muscle in participants with and without KR

	Knee Replacement(−)		Knee Replacement(+)		
	Number of patients	Mean ± Std. Deviation	Number of patients	Mean±Std. Deviation	p value
Baseline Quadriceps Muscle Cross-sectional Area, cm²	46	48 ± 13.9	46	44 ± 13.3	0.017
Follow-up Quadriceps Muscle Cross-sectional Area, cm²	46	47.3 ± 14.1	46	43.9 ± 13.1	0.024
Baseline Quadriceps Muscle Quality	42	7.4 ± 1.9	42	7.5 ± 2.1	0.66
Follow-up Quadriceps Muscle Quality	38	7.1 ± 2	38	7 ± 2	0.8

Conclusion: QMCSA seems to be significantly smaller in case group even the QMQ is not significantly different. We think that QMCSA has a potential of being one of the biomarkers for predicting future TKR candidates. Future studies may address the importance of increasing QMCSA by life style modifications and its effects on progression of disease.

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Presence of Severe Medial Mensical Pathology Increases the Odds for Knee Replacement: Data From the Osteoarthritis Initiative. Frank Roemer[1], C. Kent Kwoh[2], David J. Hunter[3], Robert M. Boudreau[4], Michael J. Hannon[5], Markus R. John[6], Felix Eckstein[7], Michel Crema[8], Zhijie Wang[5] and Ali Guermazi[9]. [1]Klinikum Augsburg, Augsburg, Germany, [2]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [3]University of Sydney, Sydney, Australia, [4]University of Pittsburgh, Pittsburgh, PA, [5]University of Pittsburgh School of Medicine, Pittsburgh, PA, [6]Novartis Pharma AG, Basel, Switzerland, [7]Paracelsus Medical University, Salzburg, Austria, [8]Boston University, Boston, MA, [9]Boston University School of Medicine, Boston, MA

Background/Purpose: Knee joint replacement (KR) is a cost-effective procedure with good long-term outcome. However, at present there is no clear consensus on indications for KR. Imaging biomarkers capable of predicting KR therefore are urgently needed and will aid in the decision making process on a patient level as well as in clinical studies and trials. The aim of the study was to assess if presence and severity of meniscal damage and extrusion at the time point prior to KR increases for the odds of KR, using a matched case-control study design.

Methods: Participants were drawn from the Osteoarthritis Initiative (OAI), a multicenter observational study, including 4796 participants with, or at risk of knee osteoarthritis. 120 knees from 113 OAI participants that received KR before the 48 month visit were studied at the time point prior to KR ((e.g. for a KR reported at the 48 month (M) visit, T0 = 36M). These were matched with the same number of control knees for radiographic disease stage, gender, and age (+/− 5 y). 3Tesla MRIs were read for medial and lateral meniscal morphology and extrusion using the semiquantitative MOAKS system, which scores meniscal morphology from 0 to 8 and for the following locations: anterior horn, body, posterior horn, medial and lateral. Grades 0 and 1 are considered the reference as a grade 1 lesion depicts intrameniscal signal changes of unknown relevance. Grades 2–5 code different types of meniscal tears while grades 6–8 code different grades of

meniscal maceration. Extrusion was graded from 0–3 at the medial and lateral joint lines on the coronal images.

Conditional logistic regression was applied to assess the odds of KR at T0 considering different measures of meniscal morphology.

Results: 240 knees;one knee per subject from 120 cases of KR and 120 matched controls that had available T0 data were included. Subjects were on average 65.5 ears old (SD ± 8.6), predominantly female (58.1%) and overweight (mean BMI 29.5 SD ± 4.88). Odds of KR was significantly greater for the subgroup exhibiting any type of maceration of the medial meniscal body and the medial posterior horn at T0 compared to knees without any meniscal pathology in these locations as the reference. Knees with a maximum grade of any meniscal maceration (i.e., grades 6–8) in any of the 3 medial compartment locations had an greater odds for KR when compared to knees with a maximum of zero or one (Figure 1).No significant associations were observed for the lateral compartment or for mensical extrusion

Conclusion: Presence of any medial meniscal pathology of the body and any type of maceration of the medial posterior horn at T0 increases the odds for KR compared to knees without relevant meniscal alterations. Further, the odds of KR is greater when a maximum grade of mensical maceration is present in any of the medial meniscal locations. Meniscal extrusion or pathology in the lateral compartment did not increase the odds of KR.

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Incidence of Osteoarthritis-Related Knee and Hip Joint Surgery in Southern Sweden. Aleksandra Turkiewicz, Ingemar F. Petersson, Leif E. Dahlberg and Martin Englund. Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden

Background/Purpose: To estimate the incidence and age and sex patterns of subjects having had osteoarthritis (OA)-related surgical treatment.

Methods: The Skåne Health Care Register (SHCR) is a legislative, mandatory register based on physicians' International Classification of Diseases (ICD) 10 diagnostic codes and the classification of health care procedures and surgical codes according to KKÅ97. The register covers all in- and outpatient health care in southern Sweden (total population 1.3 million). For the year 2011 we identified patients ≥35 years of age having had the hip replacement and a main diagnosis of hip OA (M16) or having the knee replacement or other knee surgery (arthroscopic or endoscopic exploration of the joint, synovectomy, excision of meniscus or articular cartilage or other surgery of synovial membrane of the knee) in conjunction with the main diagnosis of knee OA (M17) or derangement of meniscus due to old tear or injury (M23.2), which we consider probable OA. We obtained annual cumulative incidence of OA-related surgery in 2011 by cross referencing with the population register to include all residents (aged ≥35) of Skåne by the 31st Dec 2010. To obtain estimates of the annual cumulative incidence of OA-related knee or hip surgery among all known knee or hip OA patients we used the point prevalence of knee and hip OA by the 31st Dec 2011 based on the SHCR register data from years 1999–2011.

Results: The annual incidence of OA-related knee replacement in the population aged ≥35 was 18.6 per 10,000 persons (95%CI: 17.6; 19.6), 16.1 for men and 21.0 for women. The annual incidence of other OA-related knee surgery in the population was 11.8 per 10,000 persons (95%CI: 11.0; 12.6), 14.6 for men and 9.2 for women. The 2011 incidence of OA-related hip replacement in the population was 19.3 per 10,000 persons (95%CI 18.3; 20.3), 11.7 for men and 16.1 for women. The annual incidence of OA-related knee and hip replacement in the population ≥65 years of age was 35 and 37 per 10,000 persons respectively.

The incidence of OA-related knee replacement surgery among known prevalent knee OA patients aged ≥35 was 156 per 10,000 cases and peaked at age 65–74 years. The incidence of OA-related hip replacement among known prevalent hip OA patients was 359 per 10,000 cases and peaked at age 35–44 years (Figure).
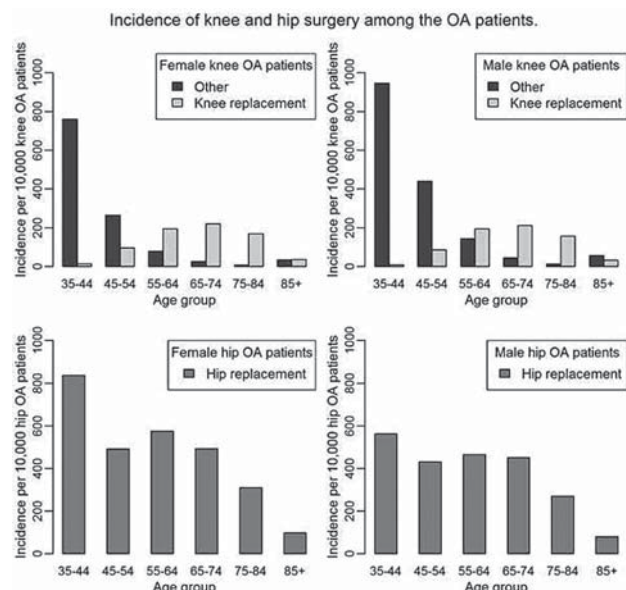
Figure. The annual incidence of osteoarthritis-related knee and hip joint surgery among the OA-cases.

Conclusion: The present high incidence of OA-related surgeries in those aged ≥65 together with the estimated increased prevalence of hip and knee OA in next decades warrants great concerns for the future burden on the health care system. Efficient conservative treatment options should be sought.

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Effects of Strontium Ranelate On Knee Osteoarthritis Pain: A Responder Analysis. JY. Reginster[1], Roland Chapurlat[2], N. Bellamy[3], E. Czerwinski[4], JP Devogelaer[5], L. March[6], K. Pavelka[7] and Cyrus Cooper[8]. [1]University of Liège, Liège, Belgium, [2]Hôpital Edouard Herriot, Lyon, France, [3]CONROD. The University of Queensland, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia, [4]Krakow Medical Centre, Kraków, Poland, [5]Cliniques Universitaires St. Luc, Brussels, Belgium, [6]University of Sydney, Insitute of Bone and Joint Research, Royal North Shore Hospital, St Leonards - Sydney, Australia, [7]Institute of Rheumatology, Prague 2, Czech Republic, [8]University of Oxford; Southampton General Hospital, Southampton, United Kingdom

Background/Purpose: In a large, randomised, placebo-controlled, double-blind phase-III 3-year study (SEKOIA), strontium ranelate 2g/day (SrRan) has demonstrated structure-modifying activity associated with statistically significant symptomatic improvement in patients with knee OA. In clinical trials, results for symptom improvement are usually reported as mean change in score which may not be directly clinically meaningful. The objective of this analysis was to describe, at an individual level, the effects of strontium ranelate on pain in patients with knee OA compared to placebo.

Methods: The main objective of the SEKOIA study was to demonstrate the effects of strontium ranelate on radiographic progression of knee osteoarthritis. Included patients were men and women over 50 years old, with symptomatic primary knee OA (at least 40 on a 100 mm visual analog scale (VAS) on most days of the previous month i.e. 1/2 days, Kellgren and Lawrence [KL] grade 2 or 3, and joint space width [JSW] 2.5–5 mm). Symptoms were assessed every 6 months over 3 years using the WOMAC questionnaire and a 100 mm VAS ("How would you rate the pain you have felt in the studied knee within the last 48 hours?"). Proportions of patients with an improvement of at least 20% or 50% from baseline of their WOMAC pain subscore[1] or pain VAS and proportion of OMERACT-OARSI-like responders[2] (calculated using improvement in pain and function but not

patient's global assessment as it was not assessed in this study) were compared using a chi^2 test.

Results: The ITT population included 1371 (82%) patients. At baseline, the mean, age was 63±7 years, BMI was 30±5 kg/m^2, VAS was 54±22 mm, and WOMAC was 132±62 mm. 61% were KL grade II and 69% were female. There were no differences between groups at baseline. Over 3 years, a significantly greater percentage of strontium ranelate 2g-treated patients had 20% improvement in WOMAC pain compared with placebo (72% vs 64%, p= 0.010) and a trend was seen with 50% improvement (51% vs 45%, p = 0.078). Similar results were confirmed on the VAS, with a greater number of patients having an improvement in global knee pain of at least 20% (76% vs 70%, p = 0.034) or at least 50% (60% vs 53%, p = 0.065) compared to placebo. When combining improvement in pain with improvement in function (OMERACT-OARSI-like responders) the percentage of responders was significantly greater in the strontium ranelate 2g group (54% vs 47%, p = 0.035) than in the placebo group.

Conclusion: Strontium ranelate 2g/day is associated with a greater number of patients having a clinically relevant decrease in their pain level over 3 years compared to placebo-treated patients. Strontium ranelate treated patients were also more likely to be OMERACT-OARSI-like responders.

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Clinically Meaningful Effect of Strontium Ranelate On Knee Osteoarthritis Symptoms. O. Bruyere[1], N. Bellamy[2], J. Brown[3], P. Richette[4], L. Punzi[5], X. Chevalier[6], Cyrus Cooper[7] and Jean-Yves Reginster[1]. [1]University of Liège, Liège, Belgium, [2]CONROD. The University of Queensland, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia, [3]Rheumatology Centre, Quebec City, QC, [4]Hôpital Lariboisière, Paris, France, [5]Azienda Ospedaliera di Padova, Padova, Italy, [6]Hôpital Henri-Mondor, Creteil, France, [7]University of Oxford; Southampton General Hospital, Southampton, United Kingdom

Background/Purpose: In the SEKOIA study, strontium ranelate 2g/day has been demonstrated to reduce total WOMAC score, pain subscore and global knee pain assessed using a visual analog scale (VAS) in comparison to placebo in patients with symptomatic primary knee osteoarthritis. The aim of these complementary analyses was to determine the number of patients considered as responders in terms of MPCI (Minimal Perceptible Clinical Improvement) and MCII (Minimal Clinical Important Improvement).

Methods: SEKOIA is a double-blind, placebo-controlled, randomized, international 3-year study aiming to demonstrate the effects of strontium ranelate on the radiographic progression of knee osteoarthritis. Clinical symptoms were assessed every 6 months over 3 years by the WOMAC questionnaire and a VAS. Percentages of patients reaching MPCI or MCII published values (1,2) were compared using a chi^2 test.

Results: ITT set included 1371 (82%) patients. In mean, age was 63±7 years, BMI was 30±5 kg/m^2, VAS was 54±22 mm, and WOMAC was 132±62 mm. 61% were KL II and 69% were female. Over 3 years, SrRan was associated with a greater number of MPCI and MCII responders as described in the table hereafter. This suggests that a greater number of patients reaches a threshold of improvement of their knee OA symptoms considered as clinically relevant with strontium ranelate treatment over 3 years compared to placebo.

	Placebo (N = 472) n (%)	Strontium ranelate 2 g (N = 454) n (%)	Difference relative to placebo [95% CI]	p-value
WOMAC Pain subscore				
Patients above MPCI threshold (9.7mm)	255 (55)	289 (65.5)	10.6 [4.2;16.9]	**0.001**
WOMAC Stiffness subscore				
Patients above MPCI threshold (10mm)	247 (52.8)	270 (60.1)	7.4 [0.9;13.8]	**0.025**
WOMAC Physical function subscore				
Patients above MPCI threshold (9.3mm)	229 (49.1)	257 (57.9)	8.7 [2.3;15.2]	**0.008**
Patients above MCII threshold (−9.1mm)	231 (49.6)	257 (57.9)	8.3 [1.9;14.8]	**0.012**
Knee pain by VAS				
Patients above MCII threshold (−19.9mm)	277 (59.4)	302 (67.7)	8.27 [2.05;14.49]	**0.010**

MPCI responders were statistically significantly greater from M18 (pain and function WOMAC subscores, p = 0.003 and p = 0.013, respectively) compared to the placebo group. Interestingly, after 2 years of treatment a significantly greater number of MPCI responders were observed for the WOMAC stiffness subscore (p = 0.008) in the strontium ranelate group. An earlier effect, close to statistical significance (p = 0.051) was also detectable for physical function MPCI responders.

Conclusion: This study demonstrates that positive effects of Strontium Ranelate on pain and physical function in patients with knee OA are clinically meaningful. Effect is early with a greater number of MPCI responders observed as soon as 18 months of treatment.

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Strontium Ranelate Decreases the Level of Urinary CTX-II in Patients with Knee Osteoarthritis. Julien Collette[1], Olivier Bruyere[2] and Jean-Yves Reginster[3]. [1]Labo Ria Chu Sart Tilman, Liege, Belgium, [2]Universite De Liege, Liege, Belgium, [3]University of Liège, Liège, Belgium

Background/Purpose: Knee osteoarthritis is a chronic disease affecting the global joint and characterized by cartilage degradation as well as subchondral bone remodelling. Effects of strontium ranelate (SrRan) on urinary CTX-II, an osteoarthritis-related biomarker, and on serum CTX-I and b-ALP, two markers of bone metabolism, were investigated.

Methods: The urinary level of collagen type II C-telopeptide fragments (uCTX-II), the serum levels of collagen type I C-telopeptide fragments (sCTX-I) and bone phosphatase alkaline (sb-ALP) were assessed in all patients included in the SEKOIA study at baseline and after 3, 6, 12, 24 and 36 months of treatment. 1683 patients have been included in this double-blind, placebo-controlled, randomized, international 3-year phase III study aiming to demonstrate the effects of SrRan on the radiographic progression of knee osteoarthritis and have been allocated to SrRan 1g or 2g per day or placebo. Analyses were performed by SUPREME (Liège) using ELISA (uCTX-II and sCTX-I) or a chemiluminescent immunoenzymatic assay (sb-ALP). CTX-II was corrected for urinary creatinine level. Group comparisons were assessed in the ITT (1371 patients) using a Mann-Whitney-Wilcoxon test for uCTX-II or a general linear model with sex, baseline and centre as covariates for sb-ALP and sCTX-I.

Results: At baseline, no significant difference was observed between the groups on uCTX-II, sCTX-I and sb-ALP levels. At the last visit, uCTX-II was significantly lower in the SrRan 1g and 2g groups than in the placebo group with an estimated mean difference of −0.04 and −0.03 μg/mmol respectively (p=0.003 for SrRan 1g group and p=0.021 for SrRan 2g group). Early differences between the treatment groups were demonstrated at 3 months, uCTX-II was significantly lower in the SrRan 1g and 2g groups than in the placebo group with an estimated mean difference of −0.04 and −0.07 μg/mmol creatinine (p<0.0001) respectively.

The results on bone markers sb-ALP and sCTX-I are those expected with SrRan, the level of sb-ALP was higher in SrRan 2g group compared to placebo and the level of sCTX I was lower in both SrRan groups compared to placebo at all visits from 3 months.

Conclusion: Treatment with strontium ranelate significantly decreases the level of urinary CTX-II compared to placebo in patients suffering from knee osteoarthritis, suggesting that strontium ranelate slows the evolution of knee osteoarthritis.

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Meta-Analysis of Four 12-Week Phase III Clinical Trials Investigating the Effect of TDT 064, a Transdermal Gel, in Osteoarthritis of the Knee. Matthias Rother[1], Johannes C. Vester[2], Wolfgang W. Bolten[3] and Philip G. Conaghan[4]. [1]IMR Partner GmbH, Graefelfing, Germany, [2]IDV Data Analysis and Study Planning, Krailling, Germany, [3]Klaus-Miehlke-Klink, Wiesbaden, Germany, [4]University of Leeds, Leeds, United Kingdom

Background/Purpose: A transfersome is an ultradeformable lipid vesicle originally developed to deliver high concentrations of drug (eg NSAIDs) transdermally. Large interventional trials in osteoarthritis (OA) of the knee comparing ketoprofen-containing vesicles (IDEA-033) to vesicles without active drug (called Sequessome, TDT 064) showed conflicting results for IDEA-033[1–3] but all demonstrated pronounced treatment effects of the vehicle itself (TDT 064) that, in one study,[4] were comparable to 100 mg b.i.d. celecoxib and statistically significantly superior to oral placebo.[4] Objectives were to investigate how the treatment effects seen with TDT 064 compare with the results reported for the placebo arm of other OA interventional studies using a meta-analytic approach.

Methods: The efficacy of TDT 064 gel has been evaluated in four randomized, double-blind, parallel-group multicenter, 12-week Phase III studies of IDEA-033 in knee OA that included TDT 064 as a drug-free vesicle control group. The meta-analysis combines the results of the WOMAC pain subscales from the studies which were standardized to a 0–100 scale. The resulting pre-post effect size (ES) is the standardized difference (Cohen)[5] of the changes from baseline of the WOMAC pain subscale score at Week 12 (based on the standard deviation of the changes of the corresponding TDT 064 group). Effect sizes of 0.2, 0.5, and 0.8 are used to represent small, medium, and large effect sizes, respectively.[5] The results of the meta-analysis are presented as two-sided tests with two-sided 95.0% confidence intervals (CIs; Hedges'g). The results of this analysis are compared with those of a meta-analysis of placebo responses from other conventional trials as published by Zhang et al.[6]

Results: The ES calculated for a total of 1061 patients with OA of the knee treated with TDT 064 gel was 1.15 (CI: 1.09–1.21). The respective values for the individual 4 studies were 1.33 (CI: 1.18–1.47)[1], 1.12 (CI: 1.03–1.21)[2], 1.05 (CI: 0.87–1.24)[3], and 1.12 (CI: 1.00–1.24)[4]. The results were comparable irrespective of whether 2.2 g or 4.4 g of TDT 064 gel was used (ES 2.2 g: 1.17 [CI: 1.07–1.28]; ES 4.4 g: 1.12 [CI: 1.04–1.20]). This compares to an ES of 0.51 (CI: 0.46–0.55) reported for all placebo applications and an ES of 0.63 (CI: 0.47–0.80) for the topical placebo arm investigated with topical formulations in the meta-analysis of Zhang et al.[6]

Conclusion: Pain reduction reported in 4 comparative, double-blind studies in knee OA using TDT 064 is substantially higher than the reduction reported for the topical placebo arm of other interventional trials. The magnitude of the difference indicates that this effect is unlikely to be due to a placebo response alone.

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Efficacy and Safety of the Chinese Herbal Compound Hou-Lou-Xiao-Ling Dan in Patients with Osteoarthritis of the Knee: Results of a Phase II International Study. Marc C. Hochberg[1], Lixing Lao[1], Patricia Langenberg[1], Harry H. S. Fong[2], David Y-W. Lee[3] and Brian Berman[1]. [1]University of Maryland, Baltimore, MD, [2]University of Illinois at Chicago, Chicago, IL, [3]Harvard Medical School, Boston, MA

Background/Purpose: Traditional Chinese Medicine (TCM), which includes the use of herbal medicines, is widely used to treat osteoarthritis (OA) of the knee in Asian societies; furthermore, many persons with OA in the United States use TCM therapies. The scientific basis for the use of TCM in the treatment of OA, however, is relatively sparse. Huo-Luo-Xiao-Ling (HLXL) Dan is a Chinese herbal compound that is used for the treatment of arthritis and Bi syndrome in Asia and has been shown to have anti-inflammatory and immunomodulatory properties in preclinical models of rheumatoid arthritis. The primary objective of this study was to examine the efficacy and safety of a proprietary formulation of HLXL Dan in patients with osteoarthritis (OA) of the knee who continued to have symptoms despite receiving standard analgesic and/or anti-inflammatory treatment.

Methods: A randomized, double-blind, placebo-controlled phase II clinical trial was conducted at two sites: the University of Maryland Center for Integrative Medicine and the Chinese University of Hong Kong. Patients with symptomatic radiographic knee OA who fulfilled ACR classification criteria and had moderate or greater frequent knee pain in one or both knees despite receiving background analgesic and/or anti-inflammatory medicines were randomized to receive either HLXL Dan at a dose of 5,180 mg/day (15 capsules in 3 divided doses) or matching placebo for 8 weeks. Clinical assessments were performed at baseline and weeks 2 and 8 including measurement of knee pain and function with the WOMAC OA Index, patient global assessment (PGA) and PGA of response to therapy (PGART) at end of study. Safety assessments were performed at each visit. Data were analyzed using an intent-to-treat protocol; statistical significance was inferred if $P <= 0.05$.

Results: A total of 92 patients were enrolled: 53 in the U.S. and 39 in Hong Kong. Overall, the mean age was 60 years, 65 (71%) were women and 64 (70%) were of Asian ethnicity. Mean (SD) baseline WOMAC pain and function score was 4.3 (1.5) and 4.2 (1.6), respectively, and PGA was 2.2 (0.8). There were no significant differences between HLXL- and placebo-treated groups in baseline variables. While both groups had significant improvement in all outcome measures after 8 weeks, there were no significant differences between the HLXL- and placebo-treated groups. At 8 weeks, about two-thirds of subjects noted that they were better based on PGART responses; there was no difference between treatment groups. In mixed models repeated measures analysis, there were no significant differences in WOMAC pain or function scores or PGA between groups; furthermore, there was no interaction between clinical site and degree of improvement. Average adherence exceeded 80 percent and was similar between clinical sites. Finally, there was a significantly greater rise in mean ALT levels in the HLXL-treated group compared with the placebo-treated group (3.8 [10.4] vs 0.1 [5.8] U/l) but no significant difference in either AST or γGT levels.

Conclusion: These data fail to demonstrate that a proprietary form of the Chinese herbal compound HLXL Dan is efficacious for treating the symptoms of knee OA.

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Long-Term Tanezumab Treatment for Osteoarthritis: Efficacy and Safety Results. Alfonso E. Bello[1], Evan F. Ekman[2], David Radin[3], Isabelle Davignon[4], Michael D. Smith[4], Mark T. Brown[4], Christine R. West[5] and Kenneth M. Verburg[4]. [1]Illinois Bone & Joint Institute, Glenview, IL, [2]Southern Orthopaedic Sports Medicine, Columbia, SC, [3]Stamford Therapeutics Consortium, Stamford, CT, [4]Pfizer, Groton, CT, [5]Pfizer, Williamston, MI

Background/Purpose: Nerve growth factor (NGF) levels are associated with increased pain perception and are elevated in joints of arthritis patients. Tanezumab, a humanized monoclonal antibody, inhibits NGF with high specificity and affinity. A non-controlled, randomized, dose-blinded extension study (NCT00809783) following placebo-controlled and active comparator, multiple-dose, Phase III parent studies was conducted to evaluate long-term efficacy and safety of tanezumab in patients with osteoarthritis (OA) of the knee or hip.

Methods: Patients were eligible to enroll up to 12 weeks after their last dose of study medication in the parent study. Patients (N=2142) received tanezumab 2.5 mg (n=522), 5 mg (n=832), or 10 mg (n=788) IV every 8 weeks up to 80 weeks. Safety assessments included adverse event documentation, physical and neurological examinations and laboratory tests. Efficacy analyses included change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Physical Function subscales and Patient's Global Assessment of OA.

Results: Demographic characteristics were similar across treatments. Mean duration of combined parent and extension study treatment for tanezumab 2.5, 5, and 10 mg was 353, 345, and 335 days, respectively. The most frequently reported treatment-related adverse events were paresthesia, arthralgia and hypoesthesia. Osteonecrosis was reported for 28 (1.3%) patients, only one event subsequently was adjudicated as osteonecrosis. Concomitant non-steroidal anti-inflammatory drugs (NSAIDs) use was associated with increased incidence of rapidly progressive osteoarthritis. A total of 187 patients (8.7%) underwent total joint replacements (TJR). All-cause TJR frequency was 5.2% in those not taking NSAIDs (n=1173) vs.13.0% in the concomitant NSAID cohort (n=969). Patients from tanezumab groups in the parent studies reported sustained improvement in WOMAC pain in the extension study (Figure). Few patients (7.2%) discontinued due to lack of efficacy indicating that treatment had a persistent beneficial effect. Similar results were observed for other efficacy endpoints.

Note: Figure represents the subset of patients who received tanezumab in the parent study
* Gap between last parent study dose and BL ≥8 weeks
Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; BL, baseline
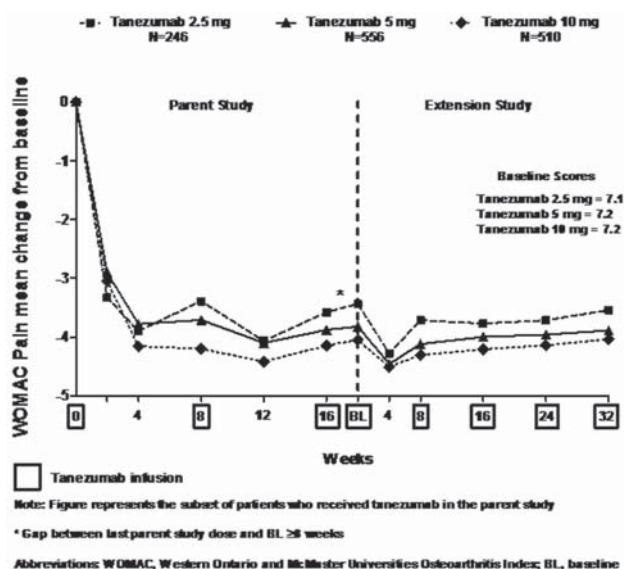
Conclusion: Repeated doses of tanezumab 2.5 mg, 5 mg, and 10 mg every 8 weeks were efficacious and generally safe with no new safety signals identified. Persistent beneficial efficacy similar to that observed in the parent studies was demonstrated and maintained in OA patients over the long term.

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Adjudication of Reported Serious Adverse Joint Events in the Tanezumab Clinical Development Program. Marc C. Hochberg[1], Steven B. Abramson[2], David S. Hungerford[3], Edward McCarthy[4], Eric P. Vignon[5], Michael D. Smith[6], Leslie Tive[7], Kenneth M. Verburg[6] and Christine R. West[8]. [1]University of Maryland, Baltimore, MD, [2]NYU Hospital for Joint Diseases, New York, NY, [3]Johns Hopkins University, Baltimore, MD, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, [5]Centre Hospitalier, Pierre Benite, France, [6]Pfizer, Groton, CT, [7]Pfizer Inc, New York, NY, [8]Pfizer, Williamston, MI

Background/Purpose: Tanezumab (TNZ) has been shown to be efficacious for pain and function in patients with hip and knee osteoarthritis (OA). Unexpected reports of adverse events described as osteonecrosis (ON) developed in patients enrolled in clinical trials in the TNZ development program. These reports led the FDA to impose a temporary clinical hold on the program.

Methods: Patients with reported adverse events of ON (N = 87) and reported total joint replacement (TJR) unrelated to ON (N = 299) were identified. Source documents were requested from site investigators; documents from 87 (100%) and 162 (54.2%) of patients with ON or TJR unrelated to ON, respectively, were obtained. All available source documents were reviewed by an independent adjudication committee (IAC) comprised of 3 rheumatologists, 1 orthopedic surgeon and 1 bone pathologist who were blinded to treatment assignment. Consensus was reached on all but 7 cases.

Results: The IAC classified the 249 cases into four categories: Primary ON; Rapidly progressive OA (RPOA; type 1 = loss of joint space width ≥ 1 mm over approx. 1 year, or type 2 = abnormal loss/destruction of bone uncommon for end-stage OA); Normal progression of OA (NPOA); Not enough information to distinguish between RPOA and NPOA; Other joint condition/diagnosis; or Not enough information to distinguish between primary ON, worsening OA or another diagnosis. Results of the adjudication are shown in Table 1. Of the 87 patients with an adverse event reported as ON, only 2 were adjudicated with primary ON; 34 (39.1%) were adjudicated with RPOA while the majority of others were adjudicated with NPOA or subchondral insufficiency fracture. The remaining 34 patients adjudicated with RPOA had a TJR unrelated to an adverse event of ON.

There was a significant dose-response relationship between incidence of RPOA and increasing dose of TNZ when given as monotherapy (0, 6 and 11 per 1000 person-years at doses of 2.5, 5 and 10 mg, respectively [P = 0.0124]) (see Figure 1). There was also an increased incidence of RPOA when TNZ was given in combination with NSAIDs as compared to montherapy (P < 0.001). Incidence was increased in all combination treatments compared to placebo, TZB monotherapy, and active comparator treatments. The highest rate of RPOA occurred in the TNZ 10 mg in combination with NSAIDs group (30 per 1000 person-years).

Table 1. Adjudication Results

Final diagnosis, n(%)	Total patients (N = 249)	Total joints (N = 282)
Primary osteonecrosis	2 (0.8)	2 (0.7)
Rapidly progressive OA	68 (27.3)	71 (25.2)
Normal progression OA	119 (47.8)	142 (50.4)
Other condition	29 (11.6)	33 (11.7)
Insufficient information	31 (12.5)	34 (12.1)

Rapidly Progressive OA
Phase 3 OA Studies, Event Rate by Dose
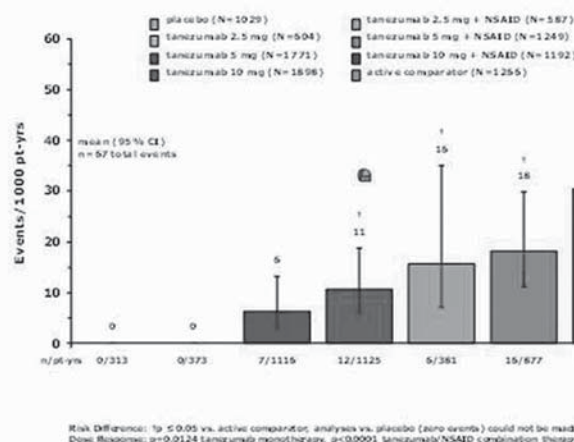
Conclusion: The rate of RPOA was greatest in patients who received TNZ with NSAIDs or TNZ alone at doses >= 10 mg. The mechanism for this association remains unclear. These results support the continued study of TNZ alone at doses below 10 mg for treatment of OA.

Disclosure: M. C. Hochberg, Abbott Laboratories, Astra-Zeneca, Bioiberica S.A., Eli Lilly Inc., Genentech/Roche, Merck Inc., Novartis Pharma A.G., Pfizer Inc., Stryker LLC, Xoma., 5; **S. B. Abramson**, Pfizer Inc., 5; **D. S. Hungerford**, Pfizer Inc., 5; **E. McCarthy**, Pfizer Inc., 5; **E. P. Vignon**, Pfizer Inc., 5; **M. D. Smith**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Tive**, Pfizer Inc., 3; **K. M. Verburg**, Pfizer Inc, 1, Pfizer Inc, 3; **C. R. West**, Pfizer Inc, 1, Pfizer Inc, 3.

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Effect of Advancing Age On the Gastrointestinal Safety of Celecoxib Versus Nonselective Nonsteroidal Anti-Inflammatory Drugs: A Post Hoc Analysis of GI-Reasons. Lee S. Simon[1], Byron Cryer[2], Gurkirpal Singh[3], Chunming Li[4] and Margaret Noyes Essex[5]. [1]SDG LLC Consulting, West Newton, MA, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]Stanford University School of Medicine, Palo Alto, CA, [4]Pfizer Inc, New York, NY, [5]Pfizer, Inc, New York, NY

Background/Purpose: Celecoxib use was associated with a lower risk of clinically relevant upper and lower GI events than nonselective (ns)NSAIDs in patients (≥ 55 years) with osteoarthritis (OA) at moderate GI risk, in standard US clinical practice, in the GI Randomized Event and Safety Open-Label NSAID Study (GI-REASONS).[1]Age has been identified as a factor for increasing patient risk for a GI adverse event when using NSAIDs. The objective was to assess whether the observed decreased GI risk with celecoxib compared to nsNSAIDs varies with advancing age in 8067 patients from the GI-REASONS trial.

Methods: A post hoc analysis of a prospective, randomized, open-label, blinded end point study[1] where patients were randomized (1:1) and stratified by *H pylori* status to receive celecoxib or any nsNSAID for 6 months. Patients randomized to the nsNSAID arm could switch between nsNSAIDS; crossover between treatment arms was not allowed. The primary end point, a composite of investigator and blinded adjudicated clinically significant upper and lower GI events, was assessed according to age (< 60 years, 60–69 years, and ≥ 70 years). Analyses were performed on the intention-to-treat (ITT) population controlling for *H pylori*status.

Results: 4035 celecoxib and 4032 nsNSAID patients with OA were included in the ITT population. 1344 (33.3%) and 1363 (33.8%) were aged < 60 years, 1997 (49.5%) and 1949 (48.3%) were aged 60–69 years, and 688 (17.1%) and 714 (17.7%) were aged ≥ 70 years in the celecoxib and nsNSAID groups, respectively. Age was not specified in 6 patients in both treatment groups. Significantly more patients aged < 60 years and ≥ 70 years in the nsNSAIDs group than in the celecoxib group met the primary end point at 6 months (Table 1). Consistent with the primary results, the most commonly used nsNSAID in each age group was meloxicam. The number of patients using gastric protective agents in the

celecoxib and nsNSAID groups were 310 (25.5%) and 335 (27.4%) aged < 60 years, 525 (28.4%) and 517 (28.5%) aged 60–69 years, and 169 (25.8%) and 223 (32.7%) aged ≥ 70 years, respectively. The number of patients who experienced moderate to severe abdominal symptoms in the celecoxib and nsNSAID groups were 37 (2.8%) and 49 (3.6%) aged < 60 years, 40 (2%) and 72 (3.7%) aged 60–69 years, and 17 (2.5%) and 17 (2.4%) aged ≥ 70 years, respectively.

Table 1. Clinically Significant Upper and Lower GI Events

| | Celecoxib | | nsNSAID | | OR (95% CI) | P Value |
	N	Patients With Event n (%)	N	Patients With Event n (%)		
< 60 years	1344	13 (1.0)	1363	30 (2.2)	2.3 (1.2–4.3)	0.0120
60–69 years	1997	35 (1.8)	1949	47 (2.4)	1.4 (0.9–2.1)	0.1570
≥ 70 years	688	6 (0.9)	714	21 (2.9)	3.7 (1.5–9.2)	0.0035

Conclusion: Celecoxib use had a lower risk of clinically significant upper and lower GI events than nsNSAIDs in patients < 60 and ≥ 70 years in the GI-REASONS trial. These data should be considered when prescribing NSAIDs for patients with OA.

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Flexible Footwear Reduces Dynamic Joint Loads in Knee Osteoarthritis: Results of a 6 Month Randomized Controlled Trial. Najia Shakoor[1], Roy H. Lidtke[1], Louis F. Fogg[2], Rachel A. Mikolaitis[1], Markus A. Wimmer[1], Kharma C. Foucher[1], Laura E. Thorp[1] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center

Background/Purpose: Dynamic joint loads are important in the pathophysiology of knee OA and biomechanical interventions aim to reduce these loads in hopes of improving symptoms and delaying disease progression. Recent evidence suggests that footwear can influence dynamic knee loading and that flat, flexible shoes may result in lower knee loads compared to more supportive, stiff-soled shoes. Here, we evaluate the longitudinal effects of flexible footwear ("mobility" shoe) compared to a control shoe on knee loading over 6 months.

Methods: Subjects with radiographic (KL grades ≥ 2) and symptomatic (at least 30mm pain of 100mm scale while walking) medial compartment knee OA were recruited and randomized to receive a flexible soled shoe (mobility shoe) or identical appearing "control" shoe with stiffer sole. The stiffness of the soles was evaluated using a biomaterial testing system and was substantially different between the shoes. Investigators and participants were blinded to shoe assignment. Baseline gait analyses were performed using an optoelectronic camera system and multi-component force plate in subjects' "own shoes", study shoes, and barefoot. Subjects were instructed to wear the study shoes at least 6 hours/day for 6 days/week. Gait analysis was repeated at 6, 12 and 24 weeks. The peak knee adduction moment (KAM), a validated marker of medial compartment loading, was evaluated. An intent-to-treat analysis was performed with imputation of missing data using a hot deck method. Repeated measures analysis of variance compared the two arms and planned contrasts were used to further analyze the data and load reductions at various time points.

Results: 22 participants (13 women, mean age 55±7 years) were assigned to the mobility shoe and 28 (21 women, mean age 55±8 years) to the control shoe. When evaluating the different walking conditions (study shoe, barefoot, own shoes), there were differences over time in the mobility group vs control. Compared to their own shoes at baseline, the mobility group experienced a 20% reduction in the KAM by 24 weeks (3.06±1.22 to 2.44±0.72 %BW*ht, p=0.002) while the control group experienced no significant reduction (3.13±0.81 to 3.00±0.66 %BW*ht, p=0.361). Furthermore, as previously described with use of the mobility shoe, there was a trend for a gait adaptation with reduction in loading during the own shoe condition (7.5%, p=0.154) and barefoot gait (13%, p=0.111) in the mobility shoe group from baseline to 24 weeks (Figure).
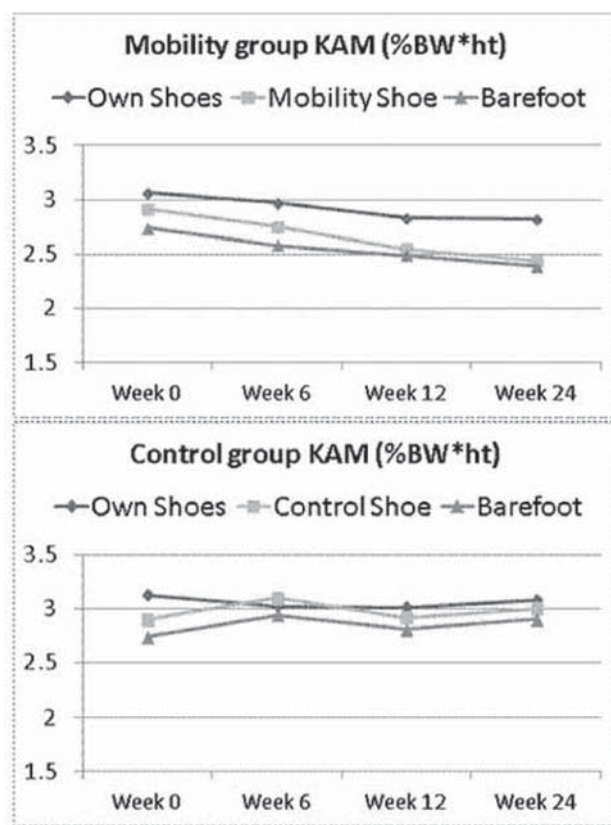
Figure. KAM over 24 weeks in Mobility and Control groups.

Conclusion: This double-blind randomized controlled trial suggests that use of flat, flexible footwear, in this case the mobility shoe, over 6 months results in significant reductions in medial knee loading compared to a stiff-soled control shoe. Thus, the use of flexible footwear may be an effective biomechanical intervention for the management of knee OA.

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Efficacy of Ketoprofen Vs Ibuprofen and Diclofenac: A Systematic Review of the Literature and Meta-Analysis. Fabiola Atzeni[1], Pier Carlo Sarzi-Puttini[1], Luigi Lanata[2] and Michela Bagnasco[2]. [1]University Hospital L Sacco, Milan, Italy, [2]Dompé SpA, Milan, Italy

Background/Purpose: The management of mild-to-moderate pain has traditionally been based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the synthetic non-opioid analgesic paracetamol (acetaminophen), both of which are effective, widely recommended, and extensively used. Among the NSAIDs, ketoprofen, ibuprofen and diclofenac have been used for the last 30 years. The published placebo-controlled randomised clinical trials (RCTs) do not allow direct comparisons of the various NSAIDs, but meta-analyses can be used to make indirect comparisons that can demonstrate similar (but not identical) drug efficacy.

The aim of this systematic review of the literature and meta-analysis of randomised controlled trials (RCTs) was to compare the efficacy of orally administered ketoprofen vs ibuprofen and/or diclofenac.

Methods: The literature was systematically reviewed and search was restricted to randomised clinical trials comparing the efficacy of oral ketoprofen (50–200 mg/day) vs ibuprofen (600–1800 mg/day) or diclofenac (75–150 mg/day) published until June 2011 in the Medline, Cochrane Central and Embase databases. The study selection was made independently by two rheumatologists in accordance with the Cochrane Collaboration guidelines.

Results: A total of 13 RCTs involving 898 patients met the inclusion criteria: eight ketoprofen vs ibuprofen and five comparing ketoprofen vs diclofenac. Nine of the 13 RCTs included 544 patients with systemic

rheumatic diseases such as RA, OA, ankylosing spondylitis (AS), low back pain or painful shoulder. The difference in efficacy between ketoprofen and ibuprofen/diclofenac was statistically significant (0.459, 95% CI 0.33–0.58; P=0.00) at all point-estimates of the mean weighted size effect (Fig 1). The test of heterogeneity for the efficacy outcome was not statistically significant ($c^2 = 18.07 - df= 12 - P = 0.1136$). Concerning the estimated efficacy outcomes, ketoprofen was superior to ibuprofen/diclofenac in all of the 13 RCTs, reaching a statistically significant difference ($P < 0.05$) in nine studies. The heterogeneity for the efficacy outcome was not different across the studies and this guaratees that the compared trials are homogeneous and the meta-analysis results reliable and valid. The meta-analysis showed that the effect of therapeutic doses of ketoprofen was strongly greater than the effect of therapeutic doses of ibuprofen or diclofenac.
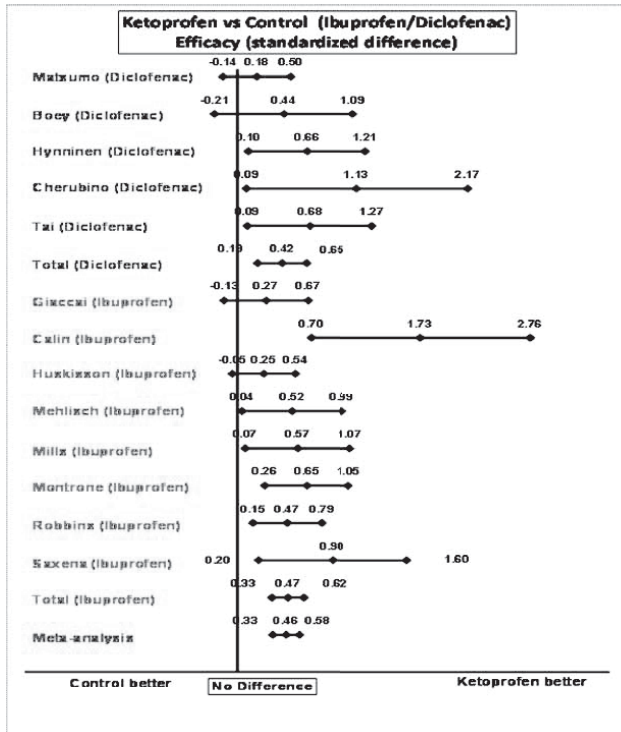
Figure 1. The size effect of ketoprofen and ibuprofen/diclofenac.

Conclusion: Findings of this meta-analysis support strong recommendation that the efficacy of orally administered ketoprofen in relieving moderate-severe rheumatic pain and in improving functional status and general conditions is significantly better than that of diclofenac/ibuprofen.

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Specialized Footwear Decreases Medial Tibial Bone Mineral Density Over 48 Weeks in Knee Osteoarthritis. Justin B. Gan, Laura E. Thorp, Roy H. Lidtke, Rachel A. Mikolaitis, Louis F. Fogg, Joel A. Block and Najia Shakoor. Rush University Medical Center, Chicago, IL

Background/Purpose: Osteoarthritis (OA) is characterized by increased subchondral bone mineral density at affected joints. In the knee, proximal tibial bone mineral density (BMD) is associated with dynamic joint loading (Thorp et al, *Bone*, 2006), and thereby serves as a marker for structural consequences of sustained altered joint loading. Biomechanical interventions such as specialized footwear (the mobility shoe) have been shown to reduce joint load in knee OA. We hypothesized that load reduction with use of the mobility shoe would yield appreciable reductions in proximal tibial BMD over 48 weeks.

Methods: Subjects with mild to moderate medial compartment radiographic knee OA were randomized to wear either the mobility shoe or "non-flexible" control shoe. All participants and investigators were blind to treatment group allocation. Participants were asked to wear the shoes 6 hours per day at least 6 days per week. Subjects underwent DXA scanning of bilateral knees at baseline and at 24 and 48 weeks after starting the intervention. These scans were evaluated in a blinded manner by a trained investigator using a previously validated method. The BMD of the medial and lateral regions of the tibial plateau were measured in each knee. Repeated measures ANOVA (rm-ANOVA) was used to evaluate changes in BMD over time in each group.

Results: Nine subjects in the mobility shoe group and 13 subjects in the control group had BMD data available at all three time points (0, 24, and 48 weeks). The mobility shoe group demonstrated a significant reduction in the medial proximal tibial BMD of the affected knee from 0 to 24 to 48 weeks (p=0.01, see Table). The control shoe group did not demonstrate a statistically significant reduction in medial proximal tibial BMD over this time (see Table). There were no significant changes in lateral tibial BMD in either group from 0 to 24 to 48 weeks (see Table).

	Control Shoe (n=13)	Mobility Shoe (n=9)
Medial Tibial BMD (g/cm^2)*		
Week 0	0.850 ± 0.138	0.836 ± 0.116
Week 24	0.848 ± 0.183	0.818 ± 0.121
Week 48	0.851 ± 0.137	0.790 ± 0.092
rm-ANOVA, p-value	p=0.979	p=0.01
Lateral Tibial BMD (g/cm^2)*		
Week 0	0.669 ± 0.119	0.681 ± 0.132
Week 24	0.688 ± 0.091	0.690 ± 0.133
Week 48	0.699 ± 0.116	0.691 ± 0.145
rm-ANOVA, p-value	p=0.267	p=0.466

*Values are the mean ± SD unless otherwise indicated; BMD, bone mineral density; rm-ANOVA, repeated measures ANOVA.

Conclusion: The mobility shoe yielded a significant reduction in medial tibial BMD over 48 weeks of use. A control walking shoe did not yield similar BMD changes. These results suggest that use of the mobility shoe can lead to potentially beneficial structural changes in subchondral bone as the result of a dynamic load reducing intervention.

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Reducing Loads in the Contralateral Side in Medial Knee Osteoarthritis; A 3-Year Follow-up Study. Roy H. Lidtke and Joel A. Block. Rush University Medical Center, Chicago, IL

Background/Purpose: No strategies have been shown to prevent Medial knee osteoarthritis (MKOA). For those with symptomatic unilateral MKOA, the contralateral knee may be at risk for developing MKOA. Early adaptation of load reducing strategies may reduce the development of the disease in the contralateral knee.

Methods: 90 subjects (69F 21M, Age 60±8, BMI 28.3±4.0) with radiographic and symptomatic medial knee OA (K-L grade 2–3, ambulatory pain >30 mm on a 100 mm VAS) were randomized into a control group fitted with bilateral neutral foot orthosis or a treatment group fitted with 7 degree valgus posted foot orthosis. The knee joint with greater pain was labeled as the index side. Subjects underwent gait analyses using an optoelectronic camera system and multi-component force plate. Subjects walked at their normal speed, and comparisons were performed after matching for speed. The peak external knee Adduction Moment (KAddM) (%body weight * height, %BW*Ht) was calculated and used as the primary endpoint. Subjects were evaluated at baseline and again at 36 months with and without the orthosis. Changes in the peak KAddM between conditions and time variable were calculated and expressed as a percentage change in the control condition. Nonparametric confidence intervals were calculated with the binomial method around the percentage of change to assess statistical significance with significance set at p<0.05.

Results: After 3 years the contralateral knee showed a 5.01±0.09% (Median±IQR) increase in medial knee load when the control orthosis was added while there was a (−)5.29±0.72% (Median±IQR) decrease in the medial knee load with the addition of the wedge orthosis in the treatment group. In the wedge treatment group the median drop in knee adduction moments between baseline and 36 months was (−)7.61±0.84% in the contralateral knee and (−)6.49±0.13% on the index side (Median±IQR). Interestingly After 3 years in the control treatment group there was a 10.66±0.52% increase in the medial knee loads on the index side while there was a (−)11.29±0.74% decrease in the medial knee loads on the contralateral side (Median±IQR).

Conclusion: The contralateral knee may be at risk in subjects with MKOA. These data suggest that the contralateral knee may get better benefit using load reducing strategies such as valgus wedge foot orthosis. The greatest sustained reduction of knee loads was seen in the contralateral knee of the control group. Since the control group was wearing custom foot orthosis posted to perpendicular to the ground it may be that a non-valgus posted custom foot orthosis on the contralateral side may be of benefit for reducing the progression of knee osteoarthritis.

Disclosure: **R. H. Lidtke**, None; **J. A. Block**, None.

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Knee Joint Stabilization Therapy in Patients with Osteoarthritis of the Knee: A Randomized, Controlled Trial. Jesper Knoop[1], Joost Dekker[2], Marike van der Leeden[3], Martin van der Esch[1], Carina A. Thorstensson[4], Martijn Gerritsen[1], Ramon E. Voorneman[1], Wilfred FH Peter[1], Mariette de Rooij[1], Suzanne Romviel[1], Willem F. Lems[5], Leo D. Roorda[3] and Martijn P.M. Steultjens[6]. [1]Reade, centre for rehabilitation and rheumatology, Amsterdam, Netherlands, [2]VU University Medical Centre, Department of Rehabilitation Medicine, EMGO Institute and Department of Psychiatry, Amsterdam, Netherlands, [3]Reade, Amsterdam, Netherlands, [4]University of Gothenburg, Institute of Neuroscience and Physiology, Gothenburg, Sweden, [5]VU University Medical Center, Amsterdam, Netherlands, [6]Glasgow Caledonian University, Glasgow, Scotland

Background/Purpose: Patients with knee osteoarthritis (OA) and instability of the knee joint may not benefit optimally from regular strengthening training. Therefore, we evaluated the effectiveness of a newly developed exercise program which initially focused on knee joint stabilization, before starting with muscle strengthening exercises and training of daily activities in knee OA patients and instability of the knee joint, compared to muscle strengthening exercises and training of daily activities only.

Methods: A single-blind, randomized, controlled trial involving 159 patients with knee OA and knee joint instability, randomly assigned to two treatment groups. Both groups received a supervised exercise program for 12 weeks, consisting of muscle strengthening exercises and training of daily activities, but only in the experimental group exercises initially focused on knee joint stabilization. Outcome measures included activity limitations (WOMAC physical function, primary outcome), pain and knee stability.

Results: Both treatment groups demonstrated large (20–40%) and clinically relevant reductions in activity limitations, pain and knee instability, which were sustained six months post treatment. No differences in effectiveness between experimental and control treatment were found on WOMAC physical function (B (95% CI) = −0.36 (−2.85–2.12)) or any secondary outcome measure.

Conclusion: Both exercise programs were effective in reducing activity limitations and pain and restoring knee stability in knee OA patients with instability of the knee. Against this background, no additional effect of initial knee joint stabilization training, before starting muscle strengthening exercises and training of daily activities could be demonstrated, emphasizing a dominant role of muscle function in stabilizing the knee joint.

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Osteopontin in Patients with Primary Knee Osteoarthritis: Relation to Disease Severity. Ramy Abdelnaby. Ain Shams University, Cairo, Egypt

Background/Purpose: To investigate the role of plasma and synovial fluid Osteopontin in primary knee osteoarthritis in relation to disease severity grading.

Methods: Forty patients aged 52–85 years with knee osteoarthritis and 15 healthy controls were enrolled in this study. The radiographic grading of knee osteoarthritis was performed by using the Kellgren-Lawrence-criteria to determine the disease severity. Osteopontin levels were measured using enzyme-linked immunosorbent assay.

Results: Osteoarthritis patients had higher plasma Osteopontin concentrations compared to healthy controls (171.37±15.96 vs 15.6±3.41ng/mL, P<0.0001). There was a highly significant positive correlation between plasma levels of Osteopontin and severity of the disease (r=0.923, p=<.0001) and a positive correlation between synovial levels of Osteopontin and severity of the disease (r=0.627, p=<0.05). Through ROC curve, results showed that to determine Osteoarthritis cases through measuring plasma Osteopontin levels it should be equal to or higher than the cut-off value, 83±4.25 ng/ml. To identify K-L grade 2 osteoarthritis from plasma Osteopontin levels must be equal to or more than, 132.25±3.1 ng/ml, to identify K-L grade 3 osteoarthritis it must be equal to or more than, 159.25±1.5 ng/ml, to identify K-L grade 4 osteoarthritis it must be equal to or more than, 183±0.9 ng/ml, with sensitivity 100% at these values.

Conclusion: Measurements of plasma and/or synovial levels of Osteopontin could possibly serve as a biochemical parameter for determining grades of different disease severity and may be predictive of prognosis with respect to the progression of osteoarthritic disease process.

Disclosure: **R. Abdelnaby**, None;

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Knee Osteoarthritis and Serum Uric Acid Concentration: The Third National Health and Examination Survey. Tony Ning, Carl Pieper, Virginia B. Kraus, William E. Kraus and Kim M. Huffman. Duke University Medical Center, Durham, NC

Background/Purpose: Osteoarthritis (OA) is a disease that is thought to be the result of many factors, which includes inflammatory causes. A recent study examined the relation of knee OA, synovial uric acid levels, and how it relates to NLRP3 inflammasome activity. It was demonstrated that synovial uric acid concentration is strongly correlated with markers of inflammasome activity and knee osteoarthritis. In addition, baseline synovial TNF alpha and synovial IL-18 was associated with changes in the osteophyte scores in 3 year longitudinal models of knee. This main focus of our research project is to examine the relation of serum uric acid concentration (SUA) and the severity of radiographic knee osteoarthritis. We hypothesized that higher concentrations of SUA is positively associated with the severity of radiographic knee OA as measured by Kellgren/Lawrence grades.

Methods: We used the National Health and Nutrition Examination Survey (NHANES III) database to carry out our research. Patients over the age of 60 had bilateral, non weight bearing knee films done. Our database was created by merging variable datasets provided by the NHANES III, which included lab values, knee imaging, demographics, as well as physical exam findings. A total of 2188 survey participants were in our database after excluding patients who either had gout or were on allopurinol. We performed correlative analyses between serum uric acid concentrations and different measurements of knee osteoarthritis using SAS Enterprise Guide version 2.3. The correlation between serum uric acid concentration and knee osteoarthritis was examined with Pearson's score of correlation. Co-variates were taken into account using generalized linear modeling. The NHANEs survey design was taken into account by applying sampling weights to our variables.

Results: A statistically significant correlation was seen in univariate analyses between serum uric acid concentration and measurements of radiographic knee OA, which included the combined total KL score (R=0.086, p<0.001), the combined total medial tibial sclerosis score (R=0.053, p=.01), and the combined total osteophyte score (R=0.069, p=0.001). Linear regression modeling was then preformed between the measurements of knee osteoarthritis and serum uric acid concentration to account for age, gender, body mass index (BMI), serum creatinine (Cr). Statistical significance was lost when accounting for these covariates.

Conclusion: In conclusion, our study showed a statistically significant correlation between serum uric acid concentration and radiographic measurements of knee osteoarthritis. This relationship was lost while accounting for age, gender, BMI, and serum creatinine. It is likely that soluble uric acid acts locally in increasing risk for OA.

Disclosure: **T. Ning**, None; **C. Pieper**, None; **V. B. Kraus**, None; **W. E. Kraus**, None; **K. M. Huffman**, None.

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Differences Between Patients with Hip and Knee Osteoarthritis. Kim F. Le Marshall[1], Bradley Yee[2], Paul A. Dieppe[2], Albert Leung[1], Carolyn Page[3], Peter F. Choong[3], Michelle Dowsey[3] and Keith K. Lim[1]. [1]Western Hospital, Melbourne, Australia, [2]University of Plymouth Campus, Plymouth, United Kingdom, [3]St Vincent's Hospital, Melbourne, Australia

Background/Purpose: This observational study was designed to examine the hypothesis that patients with hip osteoarthritis (OA) have a shorter duration of symptoms but more advanced radiological changes and more severe symptoms at first presentation to our clinic than similar patients with knee OA.

Methods: This pilot case-comparison study compared 35 consecutive hip OA patients and 70 (age and sex matched) knee OA patients from a single tertiary osteoarthritis clinic from 2008 to 2011. BMI, total symptom duration, duration of presenting complaint, Multi-attribute Arthritis Prioritisation Tool (MAPT) scores and Modified Kellgren-Lawrence (MKL) scores were recorded for each patient's first presentation to the clinic, where available. The MAPT score, designed to prioritise and monitor patients who may require joint surgery, is a severity score (out of a total of 100) derived from a standardised patient questionnaire. Data for the two groups was compared by non-parametric Mann-Whitney U testing, performed by a statistician who was blinded to the study hypothesis.

Results: Both groups had similar age, sex and BMI. The hip MAPT score (median = 71.3, interquartile range 37.9–89.6) was significantly higher than the knee MAPT score (median = 36.9, IQR 11.4–74.8); mean rank for hip group was 64.8 and mean rank for knee group was 47.1 ($U = 1638$, p = 0.005). The hip MKL scores (median = 4, IQR 4–5) were significantly higher than the knee MKL scores (median 4, IQR 3–4); mean rank for hip group was 65.7 and mean rank for knee group was 46.7 ($U = 1669.5$, p = 0.002). The total duration of symptoms for the hip group (median = 30, IQR 12–54 months) was significantly less than the duration of symptom for the knee group (median = 48, IQR 24–108 months); mean rank for hip group was 33.6 and mean rank for knee group was 44.1 ($U = 545.5$, p = 0.045). The duration of presenting complaint for the hip group (median = 6, IQR 3.0–6.5 months) was significantly less than the duration of presenting complaint for the knee group (median = 9.5, IQR 5.5–12.0 months); mean rank for hip group was 32.1 and mean rank for knee group was 45.1 ($U = 500$, p = 0.012).

Conclusion: In this pilot case-comparison study, patients with hip OA presented after a shorter duration of symptoms with higher MAPT and MKL scores than their knee OA counterparts. In other words, hip OA patients were more likely to present earlier to our clinic but were conversely more likely to have more advanced radiological changes and worse symptoms (by MAPT score) than knee OA patients. These findings support our hypothesis and warrant a larger observational study.

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Use of Drug Combinations in Patients with Osteoarthritis: A Population-Based Cohort Study. Daniel Prieto-Alhambra[1] and Rosa Morros[2]. [1]URFOA-IMIM, Parc de Salut Mar; Idiap Jordi Gol; University of Oxford; University of Southampton, Barcelona, Spain, [2]IDIAP Jordi Gol; Institut Català de la Salut, Spain

Background/Purpose: Patients affected with osteoarthritis (OA) use different drugs in search for relief. We used a large database including medical records and pharmacy invoice data to explore use of drugs in OA patients in the period 2006–2010: non-steroidal anti-inflammatory drugs (NSAIDs), Symptomatic Slow Acting Drugs for OA (SYSADOA), COX-2 inhibitors (COX2i), opioids, and analgesics (paracetamol and metamizol).

Methods: We screened the SIDIAP Database (www.sidiap.org) to identify those aged 40 years or older with a new diagnosis of OA, and ascertained use of NSAIDs, COX2i, SYSADOA, opioids, and analgesics in the period 2006–2010. SIDIAP contains anonymised medical records and pharmacy invoice data of a representative >4.9 million people in Catalonia (North-East Spain). We estimated prevalence (and 99% Confidence Intervals) of use of these drugs and their combinations, and the incidence (and 99%CI) of new users among newly diagnosed OA patients in the study period assuming a Poisson distribution.

Results: We identified 238,536 patients with an incident clinical diagnosis of OA. Among these, 128,655(53.9%) were treated with 3 or more drugs, and 60,740(25.5%) with 2 drugs. The most common combinations among the latter were:1.oral NSAID+analgesic, 2.topical NSAID+analgesic, and 3.oral NSAID+SYSADOA. Besides, 34,802(14.6%) patients received only 1 drug (the 3 most common being, in descending order: oral NSAID, analgesic and SYSADOA), and 14,339(6.0%) were not on pharmacologic treatment. Incidence of use of oral and topical NSAIDs, SYSADOA and analgesics decreased slowly from 2006 to 2010, while opioids increased continuously in the same period [Figure]. Incidence of use of COX2i rose steeply in the period 2006–2008, and continued increasing slowly from then onwards [Figure].
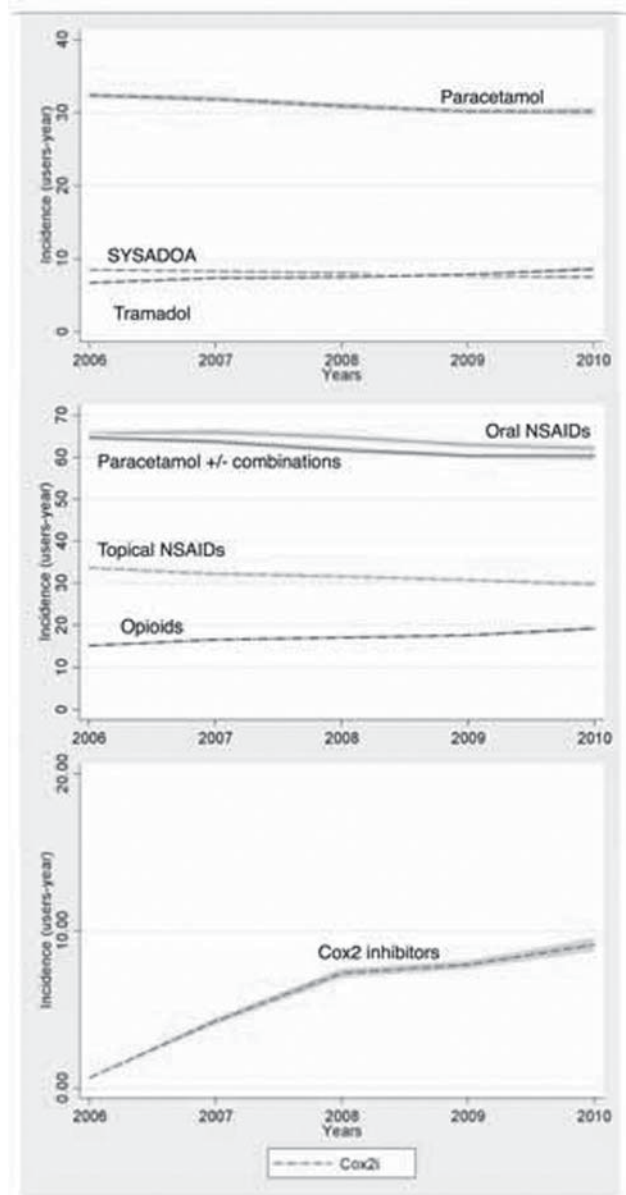
Figure. Incidence rates (and 99%CI) of newly indicated drugs for OA in the period 2006–2010: a) The most commonly used analgesic (Paracetamol), SYSADOAs and the most commonly prescribed opioid (tramadol) [top]; b) Topical and oral NSAIDs, Paracetamol (alone and combined with other drugs), and Opioids; c) Cox 2 inhibitors.

Conclusion: About 75% of OA patients are treated with at least 2 drugs, and more than half receive 3 or more. Incidence of use of commonly used drugs (such as analgesics and topical NSAIDs) is decreasing, whilst prescriptions of opioids increase. In addition, use of COX2i continues to grow, yet

more slowly after 2008, when warnings on the detrimental effects of COX2i on cardiovascular health were published. These data suggest that patients with OA are often polymedicated, and that current guidelines are poorly implemented in general practice. This has potential implications not only in terms of health care costs but also for patient safety.

Disclosure: D. Prieto-Alhambra, None; R. Morros, None.

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Bone Marrow Lesions in Knees with Osteoarthritis: Can Parameters From Dynamic Contrast Enhancement Predict Change in Bone Marrow Lesion Volume or Knee Pain Change? Andrew D. Gait[1], Timothy F. Cootes[1], Elizabeth J. Marjanovic[1], Matthew J. Parkes[1], Charles E. Hutchinson[2] and David T. Felson[1]. [1]University of Manchester, Manchester, United Kingdom, [2]University of Warwick, Coventry, United Kingdom

Background/Purpose: Dynamic contrast enhancement is a powerful tool for highlighting features of a medical image which may not otherwise be seen on "static" scans. While used extensively in other settings, it has not been used until now to study bone marrow lesions (BMLs) in osteoarthritis (OA), lesions which vary over time in volume and change with knee pain.

Methods: We studied 23 patients who had patellofemoral (PF) OA. All met ACR criteria for knee OA and were participating in a trial of PF knee braces. All patients had no treatment at baseline, were on brace at 12 weeks and acquired MRI's with a gadolinium(Gd)-enhanced dynamic image sequence at both times.

Within these knees, 40 PF or femoral BMLs were manually segmented at baseline and 12 weeks on sagittal Gd-enhanced images (TR 500ms, TE 17ms, FoV 16cm, 384×384). Knee osteoarthritis outcome score (KOOS) pain data was collected at each time.

We assessed dynamic parameters within BMLs in two steps: (1) transforming the segmented BML from the sagittal sequence to the axial dynamic sequence (TR 5.4ms, TE 1.9ms, FoV 14cm, 256×256); (2) using the extended Kety model (Tofts 1997) to calculate the parameters v_e (fractional extracellular volume), v_p (fractional blood plasma volume) and K^{trans} (transfer coefficient from v_p to v_e:a direct measure of perfusion) at each voxel. The mean of each parameter was calculated for each BML (one to three per patient), taking care to ensure that this was done consistently between the baseline and 12 week images. The distribution of K^{trans} within the BMLs was heterogeneous and limited to small volumes, so to avoid averaging of diverse values, we examined peak K^{trans} value in the BML also. To compare with KOOS, mean parameters and peak K^{trans} value were examined across all BMLs within a knee.

To evaluate the relation of the parameters to BML volumes and KOOS, we calculated Spearman rank correlation coefficients.

Results: After 12 weeks, change in mean values of the parameters K^{trans}, v_e and v_p did not correlate either with change in volume of the BML (K^{trans}: r=0.02; v_e: r=−0.07; v_p: r=0.02) or change in KOOS (K^{trans}: r=0.18; v_e: r=0.03; v_p: r=0.09). Change in the peak value of K^{trans} correlated better with change in volume of the BML (r=0.43: p=0.0056, see figure) but not with KOOS (r=−0.11).

Change in Ktrans max vs Change in BML volume
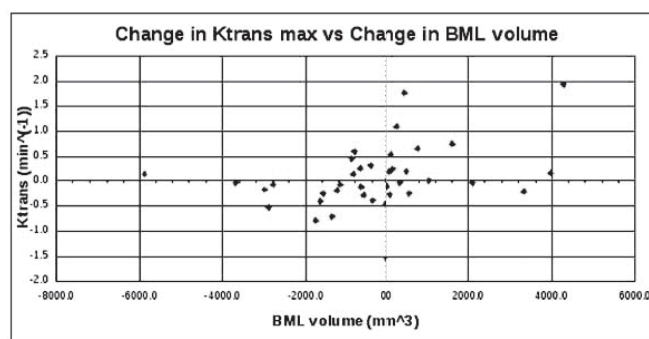
Conclusion: There are no clear correlations between the means of the parameters K^{trans}, v_e and v_p and change in BML volume or KOOS. The peak K^{trans} value of a BML may be related to its likelihood of undergoing change.

Disclosure: A. D. Gait, None; T. F. Cootes, None; E. J. Marjanovic, None; M. J. Parkes, None; C. E. Hutchinson, None; D. T. Felson, None.

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Interim Safety Analysis of a Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy Study of Apremilast (CC10004) in Subjects with Erosive Hand Osteoarthritis. Juergen Rech[1], Wolfgang Ochs[2], Wolfgang Spieler[3], Herbert Kellner[4], Ulf Müller-Ladner[5], Mathias Grunke[6], Matthias Schneider[7] and Georg Schett[8]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Rheumatology Practice, Bayreuth, Bayreuth, Germany, [3]Rheumatology Specialty Practice, Zerbst, Germany, [4]Centre for Inflammatory Joint Diseases, Munich, Germany, [5]Kerckhoff-Klinik GmbH, Bad Nauheim, Germany, [6]Medizinische Klinik und Poliklinik IV, University of Munich, Munich, Germany, [7]Heinrich-Heine-University, Duesseldorf, Germany, [8]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Apremilast is a small molecule, specific phospodiesterase4 inhibitor under investigation for a number of inflammatory conditions, including psoriasis and psoriatic arthritis. We report results of an interim safety analysis of a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 18 patients with erosive hand osteoarthritis (EHOA).

Methods: Subjects with a diagnosis of EHOA, fulfilling the classification criteria of the American College of Rheumatology with a disease duration of ≥6 months, were randomized to oral apremilast 20 mg BID or matching placebo. All subjects with at least the baseline visit reported were included in the analysis. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results: A total of 76 AEs were reported since the study started in 2010 (FPFV 29-Nov-2010, data lock for interim analysis 30-May-2012). Most AEs were mild to moderate in severity (93.5%); only 5 (6.6%) were grade 3 (severe). No grade 4 or 5 AEs were reported. The most commonly reported AEs were related to "Pain " 38% (Pain-Head/headache in 6/11 patients (55%) and Pain-Joint in 3/11 patients (27%) or "Gastrointestinal" (18%), with the most frequent AEs being headache (16%), fatigue (8%), diarrhea (7%), and joint pain (7%). Thirty-five AEs (46%) were considered possibly treatment related. Of these, 97% were mild to moderate and only 1 (3%) was grade 3 (hypotension). The most frequent treatment-related AEs were headache (9/35 [26%]), fatigue (3/35 [9%]), and diarrhea (3/35 [9%]). No serious AEs or deaths were reported during the study.

Conclusion: Given the lack of treatment options for patients with EHOA, there is an unmet need for an effective treatment to reduce the burden of this disease. Considering the pathophysiology of EHOA, mechanism of action of phosphodiesterase 4 inhibitors, and the reported AEs in earlier trials, we conclude that apremilast may also be well tolerated in patients with EHOA. Apremilast, if proven to be efficacious in ongoing investigations, will be an interesting treatment option for patients with EHOA.

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The Prevalence of Periarticular Lesions On Magnetic Resonance Imaging and Its Relation to Knee Pain in the Community Residents in Korea. In Je Kim[1], Kyeong Min Son[2], DH Kim[3], Yeong Wook Song[4], Ali Guermazi[5] and Hyun Ah Kim[6]. [1]Hallym University Kangdong Sacred Heart hospital, Seoul, South Korea, [2]Hallym university Chunchun sacred heart hospital, Chunchun, South Korea, [3]Chunchon, South Korea, [4]Seoul National University Hospital, Seoul, South Korea, [5]Boston University School of Medicine, Boston, MA, [6]Hallym University Sacred Heart Hospital, Kyunggi, South Korea

Background/Purpose: The purpose of this study was to investigate the prevalence of periarticular lesions detected by magnetic resonance imaging (MRI) and its association with knee pain and radiographic knee osteoarthritis (OA) in community residents in Korea.

Methods: Participants (n=357) were randomly chosen regardless of knee OA or knee pain from the population-based Hallym Aging Study. Demographic data and knee pain data including the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index were obtained by questionnaire.

We assessed periarticular lesions on 1.5-tesla MRI in the more symptomatic knee. Periarticular lesions included prepatellar or infrapatellar bursitis, anserine bursitis, Baker's cyst, and tibiofibular cyst. The association between each lesion and knee pain was examined by logistic regression analysis after adjustment of age, gender, body mass index, radiographic knee OA and other periarticular lesions.

Results: Radiographic knee OA was present in 34.5% of subjects. The most prevalent lesion was Baker's cyst (27.5%), followed by tibiofibular cyst (9.5%). Anserine bursitis was significantly associated with the presence of knee OA (OR 4.45, 95% CI [1.45–13.61]). Anserine bursitis among the subjects with OA was more common in the subjects with knee pain (21.8%) than in those without pain (7.1%). Anserine bursitis and Baker's cyst were significantly associated with knee pain (OR 3.47, 95% CI [1.18–10.21] and OR 2.03, 95% CI [1.19–3.45], respectively). Other periarticular lesions were not associated with knee pain or the presence of knee OA.

Conclusion: Incidental periarticular lesions on MRI of the knee are common in the middle- aged and elderly community residents in Korea. Anserine bursitis is related with knee pain and knee OA. Baker's cyst is associated with knee pain.

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ACR Poster Session A
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Systemic Lupus Erythematosus, Pediatric Vasculitis and Pediatric Myositis
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Childhood Onset Angiitis of the Central Nervous System: What Outcomes Can We Expect? Lena Das, Sook Fun Hoh, Terrence Thomas and Thaschawee Arkachaisri. KK Women's and Children's Hospital, Singapore, Singapore

Background/Purpose: Imaging findings in large-medium vessel Childhood Onset Primary and Secondary Angiitis of the Central Nervous System (cPACNS & cSACNS) are well described, however, structural changes of individual cerebral vessels after treatment has not been described. Our aim was to describe clinical outcomes and vessel progression using structural magnetic resonance angiography (MRA).

Methods: Children before age 16 with acute onset neuro-deficit and MRA findings suggestive of vasculitis-irregularity and/or narrowing of medium to large-sized cerebral vessels with repeated MRA studies, evaluated by pediatric rheumatologists and neurologists at KK Women's and Children's Hospital from January 2011–December 2012, were included. Patient demographic and clinical data were analysed. Median and interquartile range (IQR) were used for descriptive data.

Results: 7 patients were identified, 4 - cPACNS and 3–cSACNS (2–Takayasu Arteritis (TA), 1 - post-varicella CNS vasculitis). Median onset age was 9.0 years (IQR 6.4–14.0) with 5 males. Median follow-up duration was 21 months (IQR 7.0–31.0) with 3–6 months duration for repeated MRI/MRA (median numbers of MRI/MRA of 4 (IQR 2.0–6.0)). Motor deficits (hemiparesis) were present in 6/7, status epilepticus in 2/7 and aphasia and/or dysarthria in 4/7. Patient characteristics and distribution/sizes of cerebral vessels involved, along with the clinical outcomes and vessel progression after therapy is depicted in Table 1.

Upon a median follow-up of 21 months, all patients improved or had resolution of their initial motor deficits. They had also returned to school although 3/7 had continued cognitive impairment. None had clinical relapse despite further reduction of affected vessels (patient 3 at month 3, patient 1 at month 6 and patient 2 at month 9). All main arteries (MCA-M1, ACA-A1, ICA) were not recanalized at the end of the follow-up.

Table 1. Demographic, Clinical and Vessel Progression in Children with Angiitis of the CNS

Patient	Age (years)	Gender	Type*	Presentation	Treatment	Follow-up Time (months)	Initial MRA	MRA Outcome	Clinical Outcome**
1	6.4	M	P	R hemiparesis, GCS 15.	Aspirin, TCM	25	L MCA (M1)	L MCA (M1), ICA	No MD. No CI.
2	14	M	P	L hemiparesis, dysarthria, GCS 14.	Steroid pulses, CTX, MMF	17	R MCA (M1, M2)	R MCA (M1, M2), ICA	Improved MD. No CI.
3	9	M	P	R hemiparesis, aphasia, GCS 15.	Steroid pulses, CTX, MMF	21	L MCA, ACA (A1), ICA	No change	Improved MD. Improved CI. Mild aphasia.
4	8	F	S	R hemiparesis, aphasia, GCS 11.	Steroid pulses, CTX	7	L MCA (M1, M3, M4)	L MCA (M1)	No MD. No CI.
5	12	M	S	L hemiparesis, dysarthria, GCS 15.	Steroid pulses, CTX	3	R ICA, L ACA (A1)	Improved R ICA, L ACA	No MD. No CI.
6	1.75	M	S	Status epilepticus, GCS 12.	Acyclovir	54	L MCA (M1), ICA	L MCA (M1), ICA	Improved MD. Improved CI. Ongoing seizures.
7	14	F	P	L hemiparesis, status epilepticus, GCS 6.	Steroid pulses, CTX, MMF	31	L MCA (M1)	L MCA (M1)	No MD. Improved CI.

*Type: P Primary, S Secondary; GCS Glasgow Coma Scale; MCA Middle cerebral artery; ACA anterior cerebral artery; ICA internal carotid artery; TCM Traditional Chinese Medicine; CTX Cyclophosphamide; *Clinical Outcome: MD Motor Deficit; CI Cognitive Impairment

Conclusion: Despite our small cohort and regardless of the cause, after almost 2 years of follow-up, main arteries including MCA-M1 and ACA-A1, did not seem to recanalize. Interval improvements on MRA seemed to be limited to smaller M2 and M3 branches. Clinical outcomes, especially motor deficits may not follow the cerebral vessel course over time, however. Due to the rarity of diseases, multicenter with larger cohort studies are needed to confirm our initial observations and this is ongoing in our region.

Disclosure: **L. Das**, None; **S. F. Hoh**, None; **T. Thomas**, None; **T. Arkachaisri**, None.

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Pediatric Rheumatology Practitioners Experience with Biologics in Juvenile Dermatomyositis: Survey Results. Anjali Patwardhan[1], Kelly Rouster-Stevens[2], Harry L. Gewanter[3], Grant D. Syverson[4], Renee F. Modica[5], Kara M. Schmidt[6] and Charles H. Spencer[1]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]Emory-Children's Center, Atlanta, GA, [3]Pediatric & Adolescent HP, Midlothian, VA, [4]Medical College of Wisconsin, Wauwatosa, WI, [5]University of Florida, Gainesville, FL, [6]Univ of Louisville, Louisville, KY

Background/Purpose: Biologic therapy is increasingly prescribed in rheumatologic disorders. Juvenile dermatomyositis (JDM), the most common inflammatory myopathy in children, can be challenging to manage in a subset of patients. There are multiple reports of cytokine involvement in JDM. There is a paucity of information regarding the use of biologics for JDM among pediatric rheumatology practitioners, and only one clinical trial investigating a biologic in JDM. The purpose of the study is to examine pediatric rheumatology (PR) experience in North America with biologic therapy in children with JDM

Methods: The Childhood Arthritis and Rheumatology Research Alliance JDM Subcommittee on Biologics developed a 15-question on-line survey. Of the 231 pediatric rheumatology practitioners contacted, 105 (45%) participated between 2/17-3/20/2012

Results: Over half (57%) of the respondents currently managed 1–10 patients with JDM; 10% of respondents reported ≥20 patients with JDM in their practice. Sixty-one percent of respondents had used biologics in patients with JDM, with 32%, 5%, and 4% prescribing rituximab, etanercept and infliximab, respectively; 17% had prescribed more than one biologic. The majority of respondents (89%) had used biologics in combination with other therapies, while 11% had used biologics as monotherapy in JDM. The biologics used by the respondants were, rituximab, infliximab, etanercept and anakinra and abatacept. Among the respondents that used biologics, uncontrolled disease was the primary rationale for prescribing this medication. Over half of respondents used biologics after the patients failed other therapies; 11% of respondents used biologics for systemic (internal organ) involvement and 15% had used biologics for severe ulcerative disease. Seventy-three percent of respondents that used biologics noted improvement, while 10% reported worsening disease. Over half (53%) of respondents that used biologics noted improvement in calcinosis, while 64% reported side effects (common and uncommon). Among the respondents that had not used biologics (39%) in JDM, 88% would use this therapy if the opportunity arose; nearly half (47%) of these respondents had not used biologics because of

uncertainty regarding effectiveness in JDM. Seventy percent of practitioners recommended that biologics be formally studied in patients with JDM; 24% of respondents were unsure and 6% felt biologics should not be studied in patients with JDM

Conclusion: Several PR have used biologics in the management of pediatric patients with JDM. Among respondents that have not used biologics in this patient population, most would be interested in prescribing biologics. This survey supports the rationale for considering clinical trials and consensus protocols to elucidate the safety and effectiveness of biologics in children with JDM. Further information will be gathered by the CARRA JDM Subcommittee on Biologics through second survey to prioritize specific medications for investigation

Disclosure: **A. Patwardhan**, None; **K. Rouster-Stevens**, None; **H. L. Gewanter**, None; **G. D. Syverson**, None; **R. F. Modica**, None; **K. M. Schmidt**, None; **C. H. Spencer**, None.

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Development of a Longitudinal, Propective Cohort of Young Adults with Childhood-Onset Systemic Lupus Erythematosus. Aimee O. Hersh[1], Erica F. Lawson[2], Emily von Scheven[2], Edward Yelin[3] and John F. Bohnsack[1]. [1]University of Utah, Salt Lake City, UT, [2]UC San Francisco, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA

Background/Purpose: Data on the adult outcomes of childhood-onset systemic lupus erythematosus (cSLE) are lacking, and a feasible methodology is needed to obtain long-term follow-up on these patients after transition from pediatric to adult rheumatology care. The purpose of this study was to use established methodology to develop a prospective longitudinal cohort study of young adults with cSLE, in order to assess long-term clinical, socioeconomic and behavioral health outcomes.

Methods: Based on prior methodology utilized in the University of California San Francisco Lupus Outcomes Study (Yelin, 2007), a 45 minute baseline in-depth telephone interview survey was developed which includes patient-reported validated items pertaining to multiple domains including demographic and socioeconomic characteristics, cumulative disease manifestations, recent SLE activity and assessment of the transition from pediatric to adult rheumatology care. The survey was pilot tested and revised based on responses from the pilot testing. The initial cohort was developed by querying the clinical database from the University of Utah pediatric rheumatology clinic to identify patients diagnosed with cSLE (age <18 years at diagnosis) who are currently 18–30 years of age and met ACR criteria for SLE at diagnosis. Potential subjects were contacted by mail using their last known address in their medical record; interested subjects who received mailings returned a response card indicating their interest in study participation. These subjects were contacted by phone and completed the baseline interviews, and will be interviewed annually.

Results: 109 potential subjects were identified and contacted by mail, 50 subjects indicated an interest in participating; no response forms were returned which declined participation in the study. Twenty-six potential subjects were not reachable due to out of date contact information and 8 subjects were deceased. To date, 41 subjects have completed the baseline interview. Median age is 24 years (range 18–30), median disease duration is 11 years (range 4–20). The cohort is 95% female, ethnicities include Caucasian (78%), Hispanic (15%) and other (7%). Sixty-eight percent of subjects reported a history of renal disease; 51% had a history of renal biopsy and 2 subjects had a renal transplant. Nine subjects (22%) reported a lupus flare in the 3 months prior to the baseline interview. Eleven (26%) of subjects reported an emergency room visit for their SLE within the past year, nine (22%) subjects were hospitalized. Eight-five percent of subjects rated their health as "excellent/very good/good" and 15% rated their health as "fair/poor." Thirteen (32%) of subjects reported a lapse in insurance since turning 18, seven (17%) of subjects reported that this had a direct, negative impact on their health.

Conclusion: This abstract describes the successful establishment of a prospective longitudinal cohort of patients with cSLE as they enter adulthood. Such an inception cohort will permit the accurate estimation of the impact of biologic, socioeconomic, behavioral and access-to-care factors on disease outcomes over time.

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Dyslipidemia in Juvenile Dermatomyositis: The Role of Disease Activity. Katia T. Kozu[1], Clovis Artur Silva[2], Eloisa Bonfa[1], Adriana M. Sallum[3], Rosa M.R. Pereira[4], Vilma S. Viana[1], Eduardo F. Borba[5] and Lucia M. A. Campos[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo-SP, Brazil, [4]University of São Paulo, São Paulo, Brazil, [5]University of Sao Paulo, Sao Paulo, Brazil

Background/Purpose: Dyslipidemia has been infrequently investigated in pediatric population with autoimmune rheumatic diseases. However, lipid abnormalities in these diseases may occur due to multiple risk factors such as body composition, chronic inflammation, autoantibodies, lipodystrophy, sedentarism and therapy, especially glucocorticoid. The objectives of this study was to evaluate the presence of dyslipidemia in Juvenile Dermatomyositis (JDM) and its possible risk factors.

Methods: 25 JDM patients were compared to 25 healthy controls according to demographic data, body composition, fasting lipoproteins, glycemia, insulin, antibodies and muscle enzymes. The following JDM scores were assessed: Childhood Myositis Assessment Scale (CMAS), Manual Muscle Testing (MMT), Disease Activity Score (DAS), Myositis Disease Activity Assessment Analogue Scale (MYOACT) and Myositis Intention to Treat Activity Index (MYTAX).

Results: Abnormal lipid profile was found in nine patients and four controls (36% vs. 16%, p=0.196). JDM patients demonstrated significant higher levels of triglycerides (TG) [80 (31–340) vs. 61 (19–182) mg/dL, p=0.011] and higher frequency of abnormal levels of high density lipoproteins (HDL) (28% vs. 4%, p=0.04) when compared to controls. JDM patients with dyslipidemia demonstrated significant lower median of HDL levels compared to those without this condition [29 (0–49) vs. 50 (39–72) mg/dL, p=0.0005] and also had significant higher TG levels [128 (31–340) vs. 69 (46–138) mg/dL, p=0.011]. JDM with dyslipidemia demonstrated a higher frequency of low HDL levels (77% vs. 0%, p=0.0001), and also a higher frequency of increased levels of TG (44% vs. 0%, p=0.01), and TC (33% vs. 0%, p=0.03). Positive anti-LPL antibody was detected in just one JDM patient with abnormal lipid profile. JDM with dyslipidemia had higher ESR (26 vs. 14.5mm/1[st]hour, p=0.006), CRP (2.1 vs. 0.4mg/dL, p=0.01), DAS (6 vs. 2, p=0.008), MYOACT (0.13 vs. 0.01, p=0.012), MYTAX (0.06 vs. 0, p=0.018), and lower scores of CMAS (47 vs. 52, p=0.024) and MMT (78 vs. 80, p=0.001) compared to JDM without dyslipidemia. Positive correlations were detected between TG levels and CRP(r=0.697, p=0.001), DAS (r=0.610, p=0.001), MYOACT (r=0.661, p=0.001), MYTAX (r=0.511, p=0.008), and negative correlations with CMAS (r=−0.506, p=0.009) and MMT (r=−0.535, p=0.005). No differences were found between these groups regarding body composition, lipodystrophy, anti-LPL antibodies, and treatment (current and cumulative doses of prednisone, methotrexate and hydroxichloroquine) (p>0.05), except by higher frequency of cyclosporine current use in patients with dyslipidemia (33% vs. 0%, p=0.03).

Conclusion: Dyslipidemia in JDM patients was characterized by increased levels of TG and low levels of HDL, and disease activity and cyclosporine use were the mainly factors associated to these metabolic abnormalities.

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Evaluating Cardiovascular Risk Factors of Impaired Glucose Tolerance, Diabetes Mellitus, and Metabolic Syndrome in a Primarily Latino Population with Pediatric Rheumatic Diseases Associated with Vasculitis. Sara M. Stern, Jamie Wood, Katherine AB Marzan, Andreas Reiff, Bracha Shaham and Diane Brown. Children's Hospital Los Angeles, Los Angeles, CA

Background/Purpose: Pediatric (PED) systemic rheumatic diseases associated with vasculitis (DAV) such as Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD) and the various systemic vasculitides (SV) were previously largely fatal but are now chronic diseases (DZ). However, as adults these patients (pts) appear to have advanced cardiovascular disease (CV) with atherosclerosis that begins in childhood and is impacted by risk factors. The objective of this study was to evaluate PED

pts with DAV for risk factors of CV: diabetes mellitus (DM), impaired glucose tolerance (IGT), and metabolic syndrome (MS).

Methods: A prospective study of 14 PED pts with DAV at a tertiary care children's hospital. Each pt had 3 manual blood pressures (BP), a waist circumference, and a physical exam. After an overnight fast, a 2 hour oral glucose tolerance test (OGTT), fasting insulin level, fasting lipid panel, c-peptide, and hemoglobin A1c (HbA1c) were completed. Outcome measures included the OGTT, HDL and triglyceride (TG) levels, homeostatic model insulin resistance index (HOMA-IRI) and a diagnosis of MS. MS was established when 3 of 5 criteria (CR) were met: waist circumference ≥ 90% for age and gender (A&G), high TG (≥ 90% A&G), low HDL (≤10% A&G), high BP (systolic or diastolic BP > 90% for height, A&G or taking BP medication), and IGT (OGTT 2-h glucose ≥ 140 mg/dl). Insulin resistance (IR) was defined as a HOMA-IRI > 3.0.

Results: 14 pts (12F:2M) 11.5 to 16.9 yrs old were included; 10 pts with SLE, 2 with MCTD, 1 with granulomatosis with polyangiitis (GPA/WG), and 1 with microscopic polyangiitis (MPA). Mean age of DZ onset was 12 yrs with mean DZ duration of 2.6 years. 12/14pts were Latino. The majority of pts were Tanner (T) 3–5 (T3 29%, T4 29%, T5 21%) for pubic hair and T4–5 (T4 42%, T5 25%) for breast development. 10 pts had normal BMIs, 1 was < 5%ile, 2 were between 85th and 95th %ile, and 1 was > 95th %ile. All SLE pts had mild DZ activity by SLE Disease Activity Index (SLEDAI) and both pts with SV had a Birmingham Vasculitis Activity Scale of 1. All pts had a history of steroid use with 10 pts currently using steroids: 4 (1–5 mg), 2 (6–15 mg), 4 (16–30 mg) daily.

1 pt met 3 CR for MS (SLE), 2 pts met 2 CR (1 SLE, 1 MCTD), 7 pts met 1 CR (5 SLE, 1 MCTD, 1 SV). 5 (3SLE, 2MCTD) met criteria for HDL, 2 (2SLE) for TG, 5 for BP (3SLE, 1MCTD, 1SV), 1 (SLE) for waist circumference, and 1 (SLE) for IGT. Pts had a mean HbA1c of 5.3 ±0.25% and none met criteria for DM. 1 pt had a HOMA-IRI >3.0. 5 pts (SLE) had acanthosis nigracans, and 5 (3SLE, 1MCTD, 1SV) had high c-peptide levels (> 3.1 ng/mL). Of the 5 pts with elevated c-peptide, 3 (2SLE, 1 MCTD) had high fasting insulin (> 10 ulU/mL).

Conclusion: High rates of elevated c-peptide levels and low HDL levels were seen in PED pts with DAV. No pts met criteria for DM. While only 1 pt met formal criteria for MS, IGT, and IR, a majority of pts had components of MS and/or IR. Higher rates (71.4% vs 40.7%) of pts had ≥1 criteria of MS compared to the general adolescent Mexican-American population in the NHANES III study where a less stringent definition was used for MS (S. Cook et al). These findings illustrate that CV risk factors are prevalent in PED pts with DAV and screening should be routinely completed.

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Distribution of Vasculitides in Childhood Arthritis and Rheumatology Research Alliance-Affiliated Pediatric Rheumatology Centers in the United States. Melissa A. Lerman[1], Peter A. Merkel[2] and for the CARRA Registry Investigators[3]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Stanford

Background/Purpose: The epidemiology of pediatric vasculitis is poorly described. Two studies in the 1990s described the frequency in pediatric rheumatology centers in the United States and Canada (1.2–2.4% of rheumatologic diagnoses). Subsequently, consensus classification criteria for pediatric vasculitis were developed, yet disease patterns have not been reassessed. Although many immunomodulatory regimens are used, practice patterns for treatment of pediatric vasculitis are not known. Recently, the Childhood Arthritis and Rheumatology Research Alliance developed a registry of children treated at pediatric rheumatology centers in the United States (CARRAnet). The purpose of this study was to delineate the distribution and treatment of vasculitides within the first 24 months of CARRAnet.

Methods: This is a retrospective observational cohort study using CARRAnet. 55 centers submitted data on patients with defined rheumatologic disease (vasculitis, 35 centers) (May 2010-May, 2012). Not all patients with these diagnoses at each study site were included. Demographic, diagnostic evaluation, disease manifestation, and treatment data were collected using standardized forms and entered into an electronic database. This cohort includes children with vasculitis: granulomatosis with polyangiitis (GPA); Beh et's disease (BD); Takayasu arteritis (TAK); microscopic polyangiitis (MPA); central nervous system vasculitis (CNSV); systemic polyarteritis nodosa (PAN); cutaneous PAN; Churg-Strauss syndrome (CSS).

Results: 129 children, 1.8% of the registry, had vasculitis (Table 1). The median age of onset was 12.1 years; the median time to diagnosis was 2.8 years. There was a significant difference in the distribution of the age at onset (p<0.01), but not in the distribution of sex, race, or ethnicity (p=0.14, p=0.28, p=0.68), between vasculitides. Most children were treated with glucocorticoids (96%) and a non-biologic disease modifying anti-rheumatic drug (DMARD) (91%); 60% were treated with cyclophosphamide. 33% were treated with a biologic DMARD: tumor-necrosis factor inhibition (14%); CD20-depletion (15%).

Table 1.   Demographics and Treatment of Vasculitis in CARRAnet*

Disease	Number	% of CARRAnet**	
Vasculitis	129	1.8 (1.5, 2.1)	
	Number	**% of Vasculitis****	
Granulomatosis with Polyangiitis	64	49.6 (40.7–58.5)	
Behcet's Disease	18	14.0 (0.1–21.2)	
Takayasu Arteritis	16	12.4 (7.3–19.4)	
Microscopic Polyangiitis	11	8.5 (4.3–14.8)	
CNS Vasculitis	7	5.4 (2.2–10.9)	
Systemic PAN	7	5.4 (2.2–10.9)	
Cutaneous PAN	4	3.1 (0.9–7.7)	
Churg Strauss Syndrome	2	1.6 (0.2–5.5)	
Demographics	**Number**	**% of Vasculitis****	**p value†**
Sex (% Female)	77	59.7 (50.7–88.2)	0.14
Race (% Caucasian)	98	76.0 (67.7–83.1)	0.28
Ethnicity (% Hispanic)‡	14	10.9 (6.1–17.7)	0.69
		Median**	
Age Onset‡		12.1 (0.2–17.6)	<0.01
Time to Diagnosis§‡		2.8 (0.1–13.5)	0.03
Treatment	**Number**	**% of Vasculitis****	**p value†**
% Non-biologic DMARD	117	90.7 (84.3–95.1)	0.15
% Cyclophosphamide‡	77	59.7 (50.7–68.2)	<0.01
% Biologic DMARD	43	33.3 (25.3–42.2)	0.60
% TNF Inhibition	18	14.0 (8.5–21.2)	<0.01
% CD20 Depletion‡	19	14.7 (9.1–22.0)	—

*Abbreviations: CNS, central nervous system; PAN, polyarteritis nodosa; DMARD, disease modifying anti-rheumatic drug. TNF, Tumor Necrosis Factor.
**Percent (95% Confidence Interval); median in years (range), †Difference in distribution between vasculitides, significant p value ≤0.05. ‡Data not available on all 129 subjects. §Years from symptom onset to diagnosis.

Conclusion: While the frequency of vasculitis in CARRAnet is similar to that in earlier clinic-based registries, the distribution of diagnoses differs in that a greater percentage of children had GPA and TAK and a smaller percentage MPA. Compared to a recent pediatric GPA cohort, despite the increased use of CD20 depletion (15 vs. 1.5%), children were not spared exposure to cyclophosphamide (75 vs. 83%). Among pediatric rheumatology centers, treatment regimens for vasculitis vary considerably. This study demonstrates the usefulness of CARRAnet to study pediatric rheumatic conditions, especially rare vasculitides. Expanded enrollment of the cohort, and follow-up of cases, will provide important observational data not obtainable by single-center studies.

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Pediatric automated Neuropsychological Assessment Metrics As a Screening Tool for Neuropsychiatric Childhood-Onset Systemic Lupus Erythematosus. Patricia Vega-Fernandez[1], Eyal Muscal[2], Natasha M. Ruth[3], Frank Zelko[4], Andrea Vincent[5], Erin C. Thomas[6], Marisa S. Klein-Gitelman[7], Debra Canter[8], Alison Tian[9], Lisa Ravindra[10], HaiMei Liu[11], Jessica Hummel[12], Deborah M. Levy[9], Hermine Brunner[13] and Tresa Roebuck-Spencer[5]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Baylor College of Medicine, Houston, TX, [3]Medical University of South Carolina, Charleston, SC, [4]Children's Memorial Hospital, Chicago, IL, [5]University of Oklahoma, Norman, OK, [6]Anne and Robert C Lurie Hospital, Feinstein School of Medicine, Northwestern University, Chicago, IL, [7]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [8]Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [9]The Hospital for Sick Children, Toronto, ON, [10]University Hospital, Cincinnati, Cincinnati, OH, [11]Children's Hospital of Fundan University, Shanghai, China, [12]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [13]Cincinnati Children's Hospital Medical Center and PRSCG, Cincinnati, OH

Background/Purpose: Neuropsychiatric involvement appears to be common in childhood-onset systemic lupus erythematosus (cSLE), with

neurocognitive dysfunction (NCD) identified in as many as 59%. NCD is typically detected via formal neuropsychological testing but it is costly, time intensive, not readily available, and requires specialized advanced training. Recently, computerized tests have been explored as more feasible screening tools of NCD such as the Pediatric Automated Neuropsychological Assessment Metrics (PedANAM), a library of automated tasks assessing various aspects of cognitive status. The *objective* of this ongoing study is to determine the feasibility of the PedANAM to monitor cognitive status in cSLE in a clinical setting.

Methods: cSLE patients (pts) were recruited from 5 pediatric rheumatology centers. Demographic and disease relevant information was recorded. The 10 subtests of the PedANAM were administered to each patient. Pts were observed for at least part of the testing to document effort (motivation) and technical difficulties.

Results: Initial baseline data for 34 of an expected 200 pts were analyzed (94% females; mean age of 15.8 yrs; White 41%, Black 35%, Hispanic 18%, Asian 6%). Pts were mostly in high school; 2 pts repeated a grade, and 5 received special school services. PedANAM completion required 35–55 minutes. Mean reaction time for correct responses (MNc; in msec) and accuracy (AC; % of correct responses) were measured for each subtest. All pts completed testing. Six pts responded randomly and unusually quickly, which may indicate reduced motivation. Overall, pts had the greatest difficulty comprehending requirements on the continuous performance subtest (CPT) that measures working memory based on observation, self-report and poor performance patterns (e.g. low AC and high MNc scores). Pts were grouped by presence vs. absence of neuropsychiatric SLE (NPSLE) symptoms. Those with at least one symptom were significantly slower on a test of recognition memory (Code Substitution Delayed subtest or CDD) and less accurate on the CPT subtest (p's <.05). Using Pearson correlations, slower MNc and lower AC scores on the CDD were associated with disease activity measured by the SLEDAI (r= −.384; p =.036) (see Figure) and greater reported problems on the PCF-43 (r= −.463; p =.023).
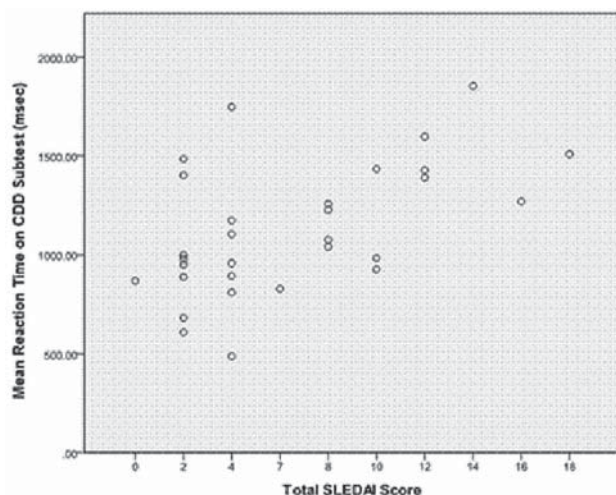
Conclusion: This study demonstrated acceptable feasibility of the PedANAM to monitor cognitive status in a clinical setting. A few pts had difficulty with comprehension of test directions, particularly on the CPT, which may warrant re-evaluation of current test directions. These data demonstrate that slower performance on the CDD and less accurate performance on the CPT are related to greater disease symptomatology. Further research is needed to explore the relationship between cognition and cSLE activity.

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The Pediatric Automated Neuropsychological Assessment Metrics - Reproducibility and Responsive to Change in Cognition in Childhood-Onset Lupus. Patricia Vega-Fernandez[1], Marisa S. Klein-Gitelman[2], Jessica Hummel[3], Erin C. Thomas[4], Jennifer L. Huggins[3], Frank Zelko[5], Tresa Roebuck-Spencer[6], Jun Ying[7] and Hermine Brunner[8]. [1]Cincinanti Children's Hospital Medical Center, Cincinnati, OH, [2]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Anne and Robert C Lurie Hospital, Feinstein School of Medicine, Northwestern University, Chicago, IL, [5]Children's Memorial Hospital, Chicago, IL, [6]University of Oklahoma, Norman, OK, [7]University of Cincinnati, Cincinnati, OH, [8]Cincinnati Children's Hospital Medical Center and PRSCG, Cincinnati, OH

Background/Purpose: The Childhood-onset Systemic Lupus Erythematosus (cSLE) *Neuropsychological Battery* (AC&R 2010; 62: 1029–33) was introduced to standardize neuropsychological testing (NPT), specifically probing the domains *Attention, Working Memory, Psychomotor Speed, Visuoconstructural Ability (VCA).* The Pediatric Automated Neuropsychological Assessment Metrics (PedANAM) software was developed to measure cognition in children ≥ 10 years. Performance on the PedANAM subtests is assessed by accuracy (AC = % of correct answers), mean reaction time for correct responses (MNc), & throughput (TP), the number of correct responses per minute. The *purpose of this study* was to (1) assess the reproducibility & (2) investigate the criterion validity of the PedANAM, using the *cSLE Neuropsychological Battery* as external standard.

Methods: cSLE patients and best-friend controls completed the PedANAM twice at baseline and then every 6 months. NPT was done at baseline and repeated after 18 month; Performance on Formal Neurocognitive Testing was standardized to age/gender/race-specific z-scores (mean 0, standard deviation 1) and then used to measure overall and domain-specific cognition (attention, processing-speed, working memory, VCA). Neurocognitive dysfunction (NCD) was graded as: no-NCD: all z-scores > −1; mild/moderate NCD: at most two z-scores < −1 but > −2 or one z-score < −2; moderate/severe: at least three z-scores < −1 or two z-scores < −2]. Intraclass and Spearman correlation coefficients were done to assess reproducibility and responsiveness to change.

Results: Among 40 cSLE & 40 controls (85% females), 13 (16.25%) had NCD at baseline and 18-month follow-up data were available for 24 cSLE and 16 control patients. Most subtests had good reproducibility in mean reaction time (MNc) and fair-good reproducibility in accuracy (AC) and consistency (CVc) (Table 1). Changes of AC scores were found positively related to changes of NCD domain scores. In particular, improved (worsening) NCD attention was found positively related to improved (or worsening) AC scores in Matching to Sample, Procedural Reaction Time, and Spatial Processing (r's >0.3, p's<0.05) over 18 months. Positive and negative relationships were also found between NCD domain scores and PedANAM MNc and CVc scores respectively (Table 2).

Table 1. Test-Retest reliability of the PedANAM of the PedANAM Scores

PedANAM Subtests	Mean reaction time for correct response (MNc)	Percentage of correct responses (AC)	Consistency (CVc = SD of MNc/MNc)
Code Substitution Delayed	0.58 (0.44, 0.71)	0.38 (0.21, 0.55)	0.21 (0.02, 0.40)
Code Substitution	0.80 (0.73, 0.88)	0.44 (0.27, 0.61)	0.43 (0.27, 0.60)
Continuous Performance Test	0.71 (0.61, 0.81)	0.78 (0.70, 0.86)	0.68 (0.57, 0.79)
Logical Relations	0.77 (0.69, 0.86)	0.23 (0.03, 0.43)	0.15 (0.00, 0.35)
Matching to Sample	0.64 (0.52, 0.76)	0.52 (0.37, 0.67)	0.57 (0.42, 0.72)
Matching Grids	0.77 (0.68, 0.85)	0.43 (0.25, 0.60)	0.38 (0.21, 0.56)
Mathematical Processing	0.91 (0.87, 0.95)	0.25 (0.05, 0.45)	0.62 (0.49, 0.75)
Procedural Reaction Time	0.47 (0.32, 0.62)	0.10 (0.00, 0.31)	0.16 (0.00, 0.38)
Spatial Processing	0.71 (0.61, 0.82)	0.26 (0.03, 0.49)	0.34 (0.17, 0.51)
Sternberg Memory Search	0.52 (0.38, 0.67)	0.55 (0.41, 0.69)	0.27 (0.10, 0.45)
Simple Reaction Time	0.68 (0.57, 0.79)	not estimable	not estimable

Values are intraclass correlation coefficients and 95% confidence intervals (in brackets).

Table 2. Relationship between changes of PedANAM score & changes of NCD domain scores*

PedANAM parameter	PedANAM Subtest*	ALL study participants (N=40)				
		Working Memory	Psychomotor Speed	Attention	Visuoconstructional Ability	All Domains
Percentage of correct responses (AC)	Code Substitution Delayed					
	Code Substitution					
	Continuous Performance Test					
	Logical Relations					
	Matching to Sample			0.35		0.30
	Matching Grids					
	Mathematical Processing					
	Procedural Reaction Time		0.36	0.34		0.39
	Spatial Processing			0.33	0.33	0.52
	Sternberg Memory Search					
Consistency (CVc = SD of MNc/MNc)	Code Substitution Delayed					
	Code Substitution					
	Continuous Performance Test			−0.32		
	Logical Relations					
	Matching to Sample		−0.35		−0.33	−0.41
	Matching Grids					
	Mathematical Processing					
	Procedural Reaction Time			−0.44		−0.38
	Spatial Processing					
	Sternberg Memory Search					
Mean reaction time for correct response (MNc)	Code Substitution Delayed				0.31	
	Code Substitution				0.40	
	Continuous Performance Test	0.31				
	Logical Relations					
	Matching to Sample		−0.36			
	Matching Grids					
	Mathematical Processing				0.39	
	Procedural Reaction Time				0.37	
	Spatial Processing				0.33	
	Sternberg Memory Search					

Conclusion: The PedANAM has good reproducibility especially for MNc measures. Changes cognitive domain scores were found significantly related to changes of performance scores of several PedANAM subtests over 18 months of follow up. These results are in line with our earlier research.

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Clinical and Laboratory Features Distinguishing Juvenile Polymyositis and Muscular Dystrophy in Children.

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Background/Purpose: We examined demographic, clinical and laboratory features of juvenile polymyositis (JPM) and muscular dystrophy in children to improve classification of these two conditions.

Methods: Thirty-nine patients with probable or definite JPM (31 JPM and 8 JPM overlapping with another connective tissue disease) by Bohan and Peter criteria and 9 patients with various muscular dystrophies (1 Duchenne's carrier, 8 limb girdle dystrophies) were examined. Differences in demographic and clinical features (including musculoskeletal, cutaneous, gastrointestinal, pulmonary, cardiac, constitutional signs and symptoms), muscle enzyme levels, Magnetic Resonance Imaging (MRI), electromyography (EMG), and muscle biopsy features between patients with JPM and dystrophies were evaluated by Fisher's exact and Rank sum tests. Backwards step-wise logistic regression modeling, followed by exact logistic regression, was performed to examine significant univariable differences between JPM and dystrophies in a multivariable model.

Results: Delay to diagnosis was longer in patients with dystrophies (median 12.0 months) compared with JPM (median 4.0 months, respectively, p=0.03). In addition, the following demographic, clinical and laboratory features distinguished JPM and dystrophies:

Features	JPM n/N (%)	Muscular dystrophies n/N (%)	P value
African-American Race	17/39 (43.6)	0/9 (0.0)	0.018
Insidious illness onset (○ 6 mo from first symptom to diagnosis)	11/31 (35.5)	7/9 (77.8)	0.05
Muscle atrophy on exam	17/37 (45.9)	8/9 (88.9)	0.027
Muscle atrophy on MRI	4/21 (19.0)	5/6 (83.3)	0.008
Increased insertional and spontaneous activity/fibrillation potentials on EMG	17/18 (94.4)	5/9 (55.6)	0.03
Complex repetitive discharge on EMG	16/23 (69.6)	2/9 (22.2)	0.02
Diffuse variation of myofiber size on muscle biopsy	20/38 (52.6)	9/9 (100.0)	0.008
Fiber hypertrophy on muscle biopsy	3/38 (7.9)	4/9 (44.4)	0.018
Myofiber fibrosis on muscle biopsy	4/38 (10.5)	5/9 (55.6)	0.007
Absence of response to treatment with prednisone	2/39 (5.1)	3/9 (33.3)	0.039
Absence of response to treatment with other immunosuppressive agents	2/39 (5.1)	4/9 (44.4)	0.008

Other features did not differ between JPM and dystrophies, including frequency of abnormal values and levels of serum muscle enzymes (CK, LDH, Aldolase, AST, and ALT); muscle edema and fatty replacement of muscle on MRI; inflammatory features on muscle biopsy; presence of short duration, small amplitude polyphasic motor units action potentials (MUAPS) and positive sharp waves on EMG; and demographic features (age at diagnosis, family history of autoimmune disease). Examining the 8 variables that were significant on univariate analysis in backwards selection stepwise logistic regression, followed by exact logistic regression, revealed less frequent myofiber fibrosis on muscle biopsy (OR = 0.1) and onset speed (OR = 0.16) to be significant predictors of JPM vs. muscular dystrophy. Because there were no African-American patients with dystrophies, a point estimate for race could not be obtained. The final multivariable model, including myofiber fibrosis, onset speed and race, provided a sensitivity of 55.6%, specificity of 97.2%, positive predictive value of 83.3%, and negative predictive value of 89.7%.

Conclusion: Muscular dystrophy can present similarly to patients with idiopathic inflammatory myopathy, particularly polymyositis. Selected demographic, clinical, and laboratory features may be helpful in distinguishing these patients, particularly the presence of myofiber fibrosis on muscle biopsy and a slower illness onset.

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Hospitalizations for Patients with Chilhood-Onset Systemic Lupus Erythematosus in the Pediatric Health Information System Databse.

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Background/Purpose: To describe patient demographics, admission characteristics and clinical care for hospitalized patients with childhood-onset systemic lupus erythematous (SLE).

Methods: Retrospective cohort study of the Pediatric Health Information System (PHIS) database, January 1, 2004 to December 31, 2010. The PHIS database was developed by the Children's Hospital Association and contains comprehensive administrative inpatient data from 43 independent, freestanding, pediatric hospitals in the United States. A total of 42 hospitals and 279.6 hospital-years of data were included in this analysis. The study cohort includes subjects with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis code for SLE (710.0) who had their first admission during the study period and were between 5–17 years old. Routine hospitalizations for intravenous (IV) cyclophosphamide were defined as hospitalizations with IV cyclophosphamide administration and a length of stay (LOS) of ≤ 2 days. ICD-9-CM and clinical transaction codes were used to identify commonly performed procedures and medications administered.

Results: We identified 11,647 admissions by 3,085 patients for childhood-onset SLE during the seven-year study period. Subjects had a median age (interquartile range (IQR)) of 14 (12–16) years, 81.7% were female, 36.3% African-American, 25.3% Hispanic, 21.8% White and 5.8% Asian. The median (IQR) and mean (SD) number of admissions per patient were 2 (1–4) and 3.8 (5.1) respectively. Fifty-one percent had a LOS of ≤ 2 days. Short-stay admissions associated with cyclophosphamide administration accounted for 2,108 (or 18.1%) of the total hospital admissions. Over the study period 25.5% of subjects had at least one admission to the intensive care unit. Table 1 summarizes the frequency of commonly performed procedures and administration of relevant medications. Fifty-nine (1.9%) subjects died during the study period resulting in an inpatient mortality per admission of 0.5%.

Table 1. Clinical care for childhood-onset SLE subjects in the PHIS database

	By Admission n= 11647	By Subject n=3085
Imaging, No. (%)		
Abdominal CT	607 (5.2)	475 (15.4)
Brain CT	714 (6.1)	529 (17.4)
Brain MRI	896 (7.7)	679 (22.0)
Brain MRA	515 (4.4)	418 (13.5)
Procedures, No. (%)		
Renal Biopsy	1080 (9.3)	932 (30.2)
Dialysis±	963 (8.3)	261 (8.5)
Electroencephalogram (EEG)	514 (4.4)	401 (13.0)
Ventilation Assistance	218 (1.9)	196 (6.4)
Immunosuppressive medications, No. (%)		
Any oral steroid	7206 (61.9)	2235 (72.4)
Methylprednisolone	5318 (45.7)	1992 (64.6)
Hydroxycholoroquine	5902 (50.7)	1767 (57.2)
Cyclophosphamide	3189 (27.4)	973 (31.5)
Mycophenolate Mofetil	2359 (20.3)	905 (29.3)
Azathioprine	613 (5.3)	298 (9.7)
Rituximab	580 (5.0)	288 (9.3)
Tacrolimus	285 (2.4)	127 (4.1)
Methotrexate	163 (1.4)	117 (3.8)
Immune Globulin (IVIG)	527 (4.5)	311 (10.1)

- CT = Computed Tomography
- MRI= Magnetic Resonance Imaging
- MRA= Magnetic Resonance Angiogram
- ± Includes hemodialysis and peritoneal dialysis

Conclusion: Utilizing the PHIS database, we identified a large cohort of hospitalized patients with childhood-onset SLE. Based on subject demographics and the expected frequency of commonly performed procedures and treatment, this cohort appears to be representative of the childhood-onset SLE population in the United States. Further work is needed to determine cause for admissions, subsequent treatment, and longitudinal outcomes for this cohort.

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Treatment and Outcome of ANCA-Associated Vasculitis in Children: A Pilot Study. Marinka Twilt[1], Audrey Bell-Peter[1], Ronald M. Laxer[1], Christian Pagnoux[2], Diane Hebert[3], Elizabeth Harvey[3], Shehla Sheikh[1] and Susanne M. Benseler[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]Hospital for Sick Children, Toronto, ON

Background/Purpose: Childhood ANCA vasculitides are rare, yet organ- or even life-threatening systemic vasculitides. Children most frequently present with rapidly evolving, severe disease such as pulmonary-renal syndrome. In 2009, evidence-based EULAR treatment recommendations were published. Treatment efficacy and safety data are largely derived from adult studies. The aim of this study was to report treatment efficacy and safety of the 2009 EULAR recommendations for severe-moderate disease onset in consecutive pediatric patients with newly diagnosed ANCA vasculitides.

Methods: A single-center cohort study of consecutive children newly diagnosed with ANCA vasculitis since July 2010 was performed. All children were treated according to the implemented EULAR recommendations. Baseline clinical and laboratory characteristics, treatment regimens and their efficacy and safety were analyzed. Disease activity was documented using the Pediatric Vasculitis Activity Score (PVAS). Adverse and serious adverse events and disease damage were captured.

Results: A total of 8 children (4 female, 4 male) were included, median age at diagnosis was 13.8 years (range 10.9–17.4 years); presenting clinical features were nephritis in 7 (including renal failure in 2) and lung disease in 4 (including pulmonary hemorrhage in 3), ENT involvement in 3 (including subglottic stenoses in 2), and eye disease in 3 (1 episcleritis). Laboratory investigation: median ESR was 72mm/h, CRP 99mg/dl. ANCA testing was positive in 7 children (6 c-ANCA, +PR3, 1 p-anca, +MPO). All patients were treated with high dose prednisone, with a tapering scheme, and iv cyclophosphamide pulses, 4/8 received additional plasmapheresis (PLEX) (3 for pulmonary renal syndrome - 1 for renal failure). Seven children completed the induction therapy and were commenced on Azathioprine, with low-dose prednisone for maintenance. Disease activity at diagnosis: median PVAS was 19 (14–29); Follow-up PVAS: 3 (1–5) at 3 month and 3 (1–3) at 6 months. One child remained in renal failure and remains on dialysis. Safety: 50% of the PLEX treated children developed a central line clot and subsequent pulmonary embolism requiring long-term anticoagulation. No clots were seen in patients not treated with PLEX. Clots are a known complication of central lines though. Pulmonary blastomycosis was confirmed in one child receiving PLEX and cyclophosphamide, who presented with a single lung nodule at 3 months of treatment. She responded rapidly to anti-fungal therapy. No early disease flares were noticed during the follow-up.

Conclusion: A significant decrease in disease activity was seen in all children with newly diagnosed, severe ANCA vasculitis treated according to the EULAR recommendations (PVAS 19 to 3). An increased risk of clots was seen in children treated with adjunctive plasmapheresis.

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Rituximab for Severe Disease Flares in Childhood ANCA Vasculitides. Marinka Twilt[1], Rayfel Schneider[1], Audrey Bell-Peter[1], Sharon Dell[2] and Susanne M. Benseler[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]the Hospital for Sick Children, Toronto, ON

Background/Purpose: Children with ANCA vasculitides frequently present with life-threatening organ manifestations including alveolar hemorrhage, critical subglottic stenosis and renal failure due to rapidly progressive glomerulonephritis (GN). The current initial management for adults includes high-dose steroids and cyclophosphamide. The majority of patients experience a serious disease flare. In adult studies, Rituximab is highly effective in the treatment of severe vasculitis flares. The aim of this study was to evaluate efficacy and safety of Rituximab for treatment of severe disease flare in children with ANCA vasculitides.

Methods: A single-center cohort study of consecutive children with ANCA vasculitis treated with Rituximab for severe disease flares was performed between January 2009 until July 2011. Children were managed according to a previously implemented protocol. Clinical, laboratory and imaging features, previous therapies, including efficacy and safety were documented in serial assessments. Disease activity was captured by Pediatric Vasculitis Activity Score (PVAS). Safety evaluation included adverse events and disease-related damage domains by Vasculitis Damage index (VDI).

Results: Six children (5 females, 1 male) were included, median age at diagnosis 7.8 years. Diagnosis: All children had lung involvement including 4 presenting with hemorrhage, 3 with renal disease and 3 with ENT involvement, including subglottic stenosis in 2. ANCAs: +c-ANCA +PR3 in 4 patients, + p-ANCA +MPO in 1 and -ANCA + MPO in 1. All children previously received high dose steroids and cyclophosphamide; previous maintenance treatment included: azathioprine in 1, MMF in 2 and MTX in 4 children. Two patients were still on MTX maintenance at time of flare. Disease flare: median disease duration until time to flare was 16 months (12–62 months); 5/6 had lung flares (hemorrhage, new nodules) and 1 child developed new GN. Treatment: All 6 children received Rituximab (500 mg/m2, 2 doses q2weeks) plus high dose prednisone (2 mg/kg/day, max 60 mg/day) and one patients continued on MTX maintenance. Plasmapheresis just prior to Rituximab was used in 2 children. Efficacy: The median PVAS at time of flare was 6; 4 children had no evidence of active disease at 3 months (PVAS=0), and 5 at 12 months. All patients completely depleted their B-cells. After Rituximab therapy, ANCAs were positive in 4 patients at 3 months and 2 patients after 12 months. Safety: Infusion reactions were uncommon. One child experienced itchiness, fever and myalgias during the 2nd cycle of infusions. One patient developed Pneumocystis Jiroveci pneumonia. Five children received a second course of Rituximab at 6–13 months postinitial course upon return of their B-cells.

Conclusion: A complete response (PVAS=0) was seen in 67% of

children with severe disease flares of ANCA vasculitis following treatment with Rituximab and high dose prednisone. This is a significantly higher response rate than with the current induction treatment for childhood ANCA vasculitides. Retreatment with Rituximab was required in the majority of children. Rituximab therapy was effective and safe; however long-term observations will determine the safety of repeated Rituximab treatment.

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The Association of *N*-Methyl-D-Aspartate Receptor Antibodies and Neurocognitive Dysfunction in Pediatric Lupus Patients and in the Offspring of Adult Patients with Lupus. Natasha M. Ruth[1], Mary C. Kral[2], Stephanie Slan[3], Tamara K. Nowling[1], Murray H. Passo[1] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC, [3]Medical University of South Carolina, Charlestons, SC

Background/Purpose: Approximately 1/5 of all systemic lupus erythematosus (SLE) starts in childhood and central nervous system (CNS) dysfunction is more common in childhood-onset SLE. CNS disease is second only to nephritis as a cause of morbidity and mortality in patients with SLE. Despite these findings, the diagnosis of CNS disease in SLE remains difficult. Anti-NMDA receptor antibodies are anti-double stranded DNA antibodies that cross react with the NMDA receptors NR2a and NR2b. The activation of the NMDA receptor is critical in learning and memory and is expressed on neurons throughout the hippocampus and cortex. The purpose of this study is to measure the prevalence of anti-NR2 glutamate receptor antibodies in patients with childhood onset SLE and JIA and to assess the association between elevated anti-NMDA-NR2 subunit receptor antibodies and neurocognitive dysfunction in pediatric patients with SLE and patients with JIA.

Methods: Patients diagnosed with SLE prior to age 18 were recruited along with a JIA control patient. Each patient underwent formal neurocognitive testing, assessing a range of cognitive domains. Serum NMDA receptor-NR-2 subunit antibody levels were measured in all subjects by ELISA.

Results: 17 lupus patients (16 female, 1 male, 9 African American, 5 Caucasian, 3 others), ages 10–20 and 7 JIA patients (5 female, 2 male, all Caucasian), ages 10–21 completed NMDA receptor antibody testing and of those all but one SLE patient completed formal neurocognitive testing. T-test comparison of the lupus cohort to the JIA cohort revealed that there were group differences for Full Scale IQ (p=.007), single word reading skills (p=.013), and math calculation skills (p=.039). The JIA patients performed better in these areas than did the SLE patients. The SLE patients also had higher NMDA receptor antibody levels and NMDA receptor antibodies correlated significantly (p=.005) with reaction time.
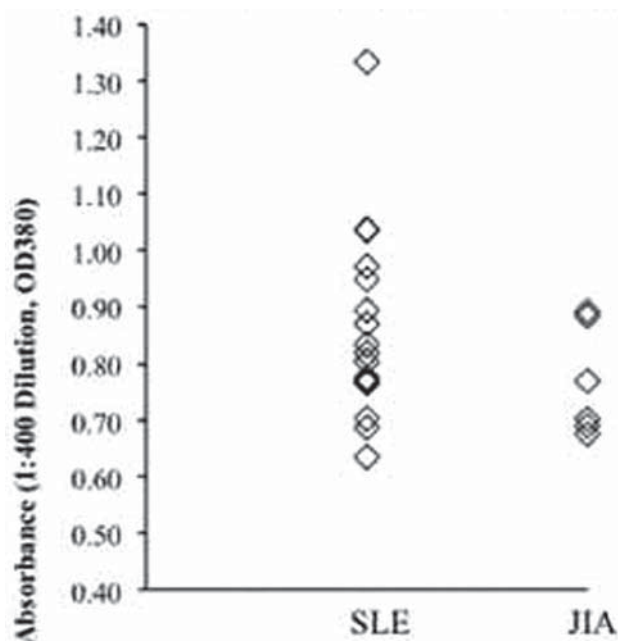
Conclusion: These findings suggest that pediatric patients with lupus have greater cognitive dysfunction than do patients with JIA. Patients with lupus also had higher NMDA receptor antibody levels than did the JIA controls. The higher antibody levels correlated with reaction time which has been a sensitive index of CNS injury in other diseases such as TBI. These preliminary results suggest that checking NMDA receptor antibody levels may be helpful in patients where there is concern for CNS lupus. Further research is necessary to study these antibody levels over time. We are also currently studying these antibody levels in children of mothers with SLE which will provide insight into the effects of fetal exposure during pregnancy.

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Variation in Healthcare Utilization by Region and Number of Rheumatologists Per State Among Pediatric Medicaid Patients with Lupus Nephritis Prior to End-Stage Renal Disease in the United States, 2000–2004. Linda T. Hiraki[1], Candace H. Feldman[2], Graciela S. Alarcon[3], Jun Liu[4], Michael A. Fischer[2], Wolfgang C. Winkelmayer[5] and Karen H. Costenbader[6]. [1]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [5]Stanford University School of Medicine, Stanford, CA, [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Unequal healthcare access and utilization may contribute to the striking sociodemographic disparities seen in outcomes for children with lupus nephritis. Medicaid is the U.S. federal-state program providing health insurance to low-income children and parents. We investigated variation in US nationwide frequencies of emergency department (ED), outpatient and inpatient visits among children with lupus nephritis enrolled in Medicaid, 2000–2004, in the months preceding the development of end-stage renal disease (ESRD).

Methods: We identified all children aged 3 to <18 years with SLE (≥3 ICD-9 codes of 710.0, each >30 days apart) in the Medicaid Analytic eXtract (MAX) from 2000–2004. This dataset contains all outpatient and inpatient Medicaid claims for enrollees in 47 U. S. states and the District of Columbia. These data were linked to those from the U.S. Renal Data System, which includes information on essentially all ESRD patients in the U.S., for the same years. We compared utilization of ED, outpatient and inpatient visits per year in the Medicaid enrolled time prior to development of ESRD for those in different categories according to: region of residence in the US, residence in a US designated Health Professional Shortage Area (HPSA), and quartiles of rheumatologist number in state of residence. Multivariable generalized linear models were adjusted for each of these variables along with enrollee age, race, sex, months of Medicaid enrollment and a validated measure of socioeconomic status combining seven US Census zip code level variables.

Results: Of the 254 pediatric lupus nephritis patients identified, the mean age was 14.2 (± 2.4) years; 72% were female, 61% were African American and 19% were Hispanic. Mean duration of Medicaid enrollment prior to the onset of ESRD was 28.5 (±16.4) months. Among all patients there was an average of 2.0 (± 2.4) ED visits per year, 10.8 (± 9.4) outpatient visits and 2.4 (± 2.6) inpatient visits. In multivariable adjusted models, children residing in areas with the lowest quartile of rheumatologists per state had on average 4.2 more ED visits per year (p=0.001) compared with those in the highest quartile of rheumatologists per state. Children residing in the West had on average 5.4 more outpatient visits per year (p= 0.03), and those in the South had 1.2 fewer inpatient visit per year (p= 0.03) than those in the Northeast. We did not observe statistically significant variation in utilization by HPSA.

Conclusion: We observed significant differences in health care utilization among children enrolled in Medicaid with lupus nephritis prior to the onset of ESRD. Low number of rheumatologists per state was the most important factor associated with more annual ED visits. This finding in addition to regional variation in annual inpatient and outpatient visits within this medically complex and low-income Medicaid population deserves further investigation.

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Validation of Promis Modules for Use in Childhood-Onset Lupus. Alexandria J. Greenler[1], Laura E. Schanberg[2], Michael P. Flannery[1], Shannen Nelson[1], Janet Wootton[2], Esi M. Morgan DeWitt[1] and Hermine I. Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Duke University Medical Center, Durham, NC

Background/Purpose: The impact of childhood-onset lupus (cSLE) and its treatment on quality of life (QoL) has not been systematically established. The *Patient Reported Outcomes Measurement Information System* (PROMIS™, http://nihpromis.org) is a publicly available system to measure patient reported outcomes that features electronic data collection. Although several legacy QoL measures have been validated for cSLE, each is longer than the *PROMIS™ Pediatric Short Forms* (Short Forms) which are ≤ 10 items each. The objective of this study was to investigate the feasibility and construct validity of the *Short Forms* in cSLE in a clinical setting.

Methods: As part of an ongoing project at two sites, 30 of 100 projected patients completed the *Pediatric PROMIS™ Short Forms* (Anger, Anxiety, Depression, Fatigue, Mobility, Upper Extremity, Pain Interference, Peer Relationships) and legacy QoL measures (Pediatric Quality of Life Inventory™ Generic Core [GC] & Rheumatology Modules [RM], Simple Measure of Impact of Lupus Erythematosus in Youngsters [SMILEY], Childhood Health Assessment Questionnaire [CHAQ], Child Health Questionnaire [CHQ], pain and well-being visual analog scales [VAS]). Questionnaire scores were compared and Pearson correlation analysis was performed in support of the construct validity of the Short Forms when used in cSLE.

Results: Participants (80% female; 48% White, 52% Black or Asian) had a mean age of 15.8 yrs (SD 2.1) and mean SLEDAI score of 5.8 (SD 4.57). No problems were encountered with completion of all PROMIS™ Short Forms (mean score = 50, clinically relevant score difference = 10) which required 5–10 minutes in total (legacy QoL tools >15 min each). On average, cSLE patients showed clinically relevant decrease in the Short Form assessing upper extremity function compared to healthy children, while the other QoL domains were less affected (Table 1). This is also supported by the scores of the CHQ-PHS and GC. Concurrent validity of the Short Forms is supported by moderate correlations with the scores of various legacy measures. Comparison to cohorts of healthy children and those with juvenile arthritis will be provided.

Table 1. Comparative scores of QoL Scores in cSLE*

PROMIS Short forms		CHAQ		PedsQL-GC		PedsQL-RM		SMILEY		CHQ-P5O	
Anger	49.5 (10.3)									Behavior (BE)	74.9 (11.3)
Anxiety	45.8 (11.6)					Worry	69.0 (22.7)				
				Emotional	74.6 (21.6)			Effect	67.3 (16.6)		
Depression	45.3 (10.1)									Mental Health (MH)	74.4 (10.8)
						Treatment	79.9 (16.2)	Burden	61.9 (15.8)	Self-esteem (SE)	18.1 (16.8)
Fatigue	49.9 (13.7)									Role/Social Limits-Physical (RP)	84.7 (26.0)
		Walk	0.3 (0.6)								
Mobility	47.5 (10.9)	Arise	0.5 (0.7)							Physical function (PF)	82.4 (21.2)
		Hygiene	0.2 (0.6)								
		Play	0.9 (0.8)								
		Dress & Grooming	0.3 (0.7)	Physical	68.2 (25.4)	Activity	86.9 (17.9)	Limitations	61.2 (21.4)		
Upperextremity function	34.4 (4.5)	Eat	0.3 (0.7)							Physical Summary (PHS)	40.3 (7.7)
		Reach	0.6 (0.8)								
		Grip	0.4 (0.8)								
Pain Interference	52.3 (12.0)					Pain	59.9 (33.8)			Bodily pain/discomfort (BP)	37.9 (29.8)
										Social & Emot Limits (REB)	88.4 (22.1)
Peer relationships	52.4 (14.3)			Social	79.2 (22.2)			Social	81.7 (19.1)		
										Gen. health percept (GH)	45.4 (11.4)
				School	63.9 (22.8)	Communic.	75.6 (22.6)			Psychosoc. Summary (PSS)	39.6 (3.1)
Completed by: Child										Completed by: Parent	

‡Values are means (standard deviations). ‡The PROMIS™ short form T score distributions are standardized such that a 50 represents the average for the US general population, and the standard deviation around that mean is 10 points. A high score always represents more of the concept being measured (for symptoms and other negatively-worded concepts like pain, fatigue, and anxiety, a 60 is one standard deviation worse than averages for functional scores and other positively-worded concepts like physical or peer relationships, a 60 is one standard deviation better than average).

Table 2. Construct validity of the PROMIS Short Forms

PROMIS SHORT FORMS	Anger	Anxiety	Depression	Fatigue	Mobility	Upper extremity function	Pain Interference	Peer relationships
Quality of Life Legacy measures & SLE measures								
SLEDAI	.06	−.02	−.17	.11	−.12	−.31	.19	.31
Physician global of disease activity	−.05	.05	.07	.11	−.01	.01	.12	.23
Pain VAS	.55*	.53*	.52*	.73**	−.70**	−.40*	.75**	−.24
Patient assessment of well being	−.49*	−.55*	−.62**	−.68**	.69**	.37	−.64**	.25
CHQ-Psychosocial Summary Score (PSS)	.17	.32	.26	−.04	−.13	.17	−.06	−.27
CHQ-Physical Summary Score (PHS)	−.13	−.18	−.24	−.48*	.57*	.26	−.34	.01
CHAQ-child	.32	.48*	.24	.64**	−.73**	−.82**	.73**	−.15
PedsQL GC-parent	−.27	−.32	−.33	−.52*	.67**	.43*	−.63**	.06
PedsQL RM-parent	−.40*	−.36	−.30	−.56*	.69**	.56*	−.63**	.001
PedsQL GC-patient	−.62**	−.75**	−.71**	−.79**	.80**	.50*	−.87**	.35
PedsQL RM-patient	−.62**	−.79**	−.62**	−.73**	.70**	.58*	−.79**	.31
SMILEY-parent	−.41*	−.27	−.42*	−.51*	.58*	.33	−.46*	.26
SMILEY-patient	−.57*	−.60**	−.65**	−.67**	.52*	.26	−.70**	.22

Values are correlation coefficients
*denotes moderately significant (p < 0.050)
**denotes strongly significant (p < 0.001)

Conclusion: Preliminary analysis supports QoL measurement using the PROMIS™ Short Forms as feasible and concurrently valid. If confirmed in the larger sample, clinicians treating cSLE will be able to utilize PROMIS™ measures for a more efficient patient self-report of health outcomes, taking advantage of easy interpretation of scores and changes in scores, thereby, reducing respondent burden and making QoL assessment feasible in both research and clinical care settings.

Disclosure: A. J. Greenler, None; **L. E. Schanberg**, None; **M. P. Flannery**, None; **S. Nelson**, None; **J. Wootton**, None; **E. M. Morgan DeWitt**, None; **H. I. Brunner**, None.

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Mycophenolate Mofetil and Abatacept Combination Therapy in Refractory Pediatric Systemic Lupus Erythematosus Nephritis. Rhina Castillo[1], Suhas M. Radhakrishna[2], Andreas O. Reiff[1] and Katherine AB Marzan[1]. [1]Children's Hospital Los Angeles, Los Angeles, CA, [2]Kaiser Permananete Medical Group, Oakland, CA

Background/Purpose: Nephritis (LN) in pediatric systemic lupus erythematosus (pSLE) requires treatment (tx) with corticosteroids (CS) and other agents such as mycophenolate mofetil (MMF) or cyclophosphamide (CYC). However, some patients (pts) fail standard therapy leaving physicians with few options. Although a recent phase II randomized controlled combination trial of abatacept and MMF (ABA+MMF) in adult SLE did not meet its endpoints, we examined if this combination therapy may have a therapeutic benefit in pSLE pts with refractory LN.

Methods: We performed a retrospective observational study in 5 pSLE pts with class IV and V lupus nephritis. All pts were treated with ABA+MMF after previous treatment and failure or intolerance to CYC and MMF with concomitant CS. Data collected included demographics, disease duration, renal histology and medications used. SLE Disease Activity score (SLEDAI) including parameters of systemic and renal disease activity were assessed at baseline and after 12 weeks of each tx.

Results: Pt age at diagnosis was 9–15years (mean 12.6 ± 2.3). Average disease duration was 22–97 months (mo) (mean 52.8 ± 30.8), before ABA+MMF therapy was started. Two pts had class IV, 1 pt had class V and 2 pts had class IV/V LN.

All 5 pts had a statistically significant decrease in their SLEDAI scores and successfully had their steroid dose reduced while on ABA+MMF. One pt achieved complete remission and 3 pts were completely weaned off steroids after an average of 9 mo (3–16mo). Repeated ANOVA analyses comparing SLEDAI scores at baseline and after 12 weeks of CYC, MMF and ABA+MMF respectively, showed a statistically significant pattern of change from the baseline score with each change in therapy (P<0.0001). Paired comparison of SLEDAI scores on each drug to baseline scores showed the most significant improvement with combination therapy (MMF+ABA p=0.0001, CYC p=0.0199, MMF p=0.0520).

C3 levels

Urine Protein

DsDNA

Total Daily Pr
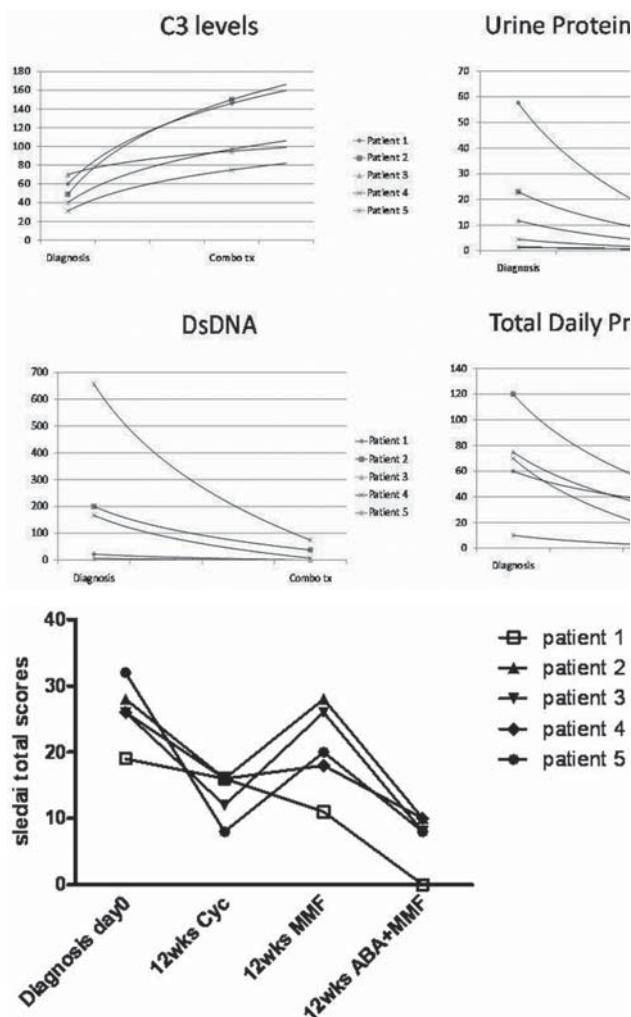
Conclusion: The above data suggests that combination therapy with ABA+ MMF can be superior to MMF alone and may be an effective option in refractory pSLE nephritis, raising the possibility of a synergistic effect between the two drugs. Additional studies are needed in pSLE to further assess the efficacy of this combo tx.

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Long-Term Outcomes in Neonatal Lupus. Amit Saxena[1], Peter M. Izmirly[2], Deborah Friedman[3] and Jill P. Buyon[2]. [1]New York University School of Medicine, New York, NY, [2]NYU School of Medicine, New York, NY, [3]New York Medical College, Valhalla, NY

Background/Purpose: Several studies have evaluated mortality and short-term morbidity in neonatal lupus (NL), however there have been no substantive descriptions of the long term cardiac, rheumatologic, or neurodevelopmental outcomes in children exposed to maternal anti-Ro antibodies. This study was initiated to ascertain the prevalence of these outcomes in NL children and their unaffected siblings, and to evaluate whether certain fetal echocardiographic risk factors or pacemaker placement associates with long term morbidity.

Methods: The study utilizes a retrospective cohort of family members from the Research Registry for Neonatal Lupus (RRNL). Follow-up questionnaires were completed for 75 cardiac NL children, 35 cutaneous NL children, and 74 unaffected siblings. The questionnaires focus on symptoms associated with rheumatic and cardiac diseases, and information on pacemakers, developmental milestones, medical diagnoses and medications. Records from the RRNL were reviewed for fetal echocardiographic data.

Results: Of 184 total respondents, 52 children (28%) were age 0–5, 45 (24%) were 5–10, 30 (16%) were 10–15, 32 (17%) were 15–20, and 25 (14%) were > 20 years old. Among the 75 cardiac NL cases, 64 (85%) had 3rd degree heart block, 3 (4%) 2nd degree, 5 (7%) 1st degree, and 3 (4%) isolated cardiomyopathy. 53 (79%) of the 67 with advanced block were paced, 43% of whom had at least one replacement. 15 (20%) cardiac NL cases were reported as ever having "heart failure" and 31 (41%) "an enlarged heart." Median age was significantly higher in those reporting an enlarged heart (p=0.016), and those needing a pacemaker and replacement (p=.001 and 0.003, respectively). Of 37 cardiac NL children > 10 yrs, 19% required cardiac medications (digoxin, ACE inhibitor, or beta blocker), vs. 5% < 10 yrs (p=0.086). Fetal echocardiographic dilated cardiomyopathy and valvular disease were positively associated with number of pacemaker replacements (p=0.044 and 0.008). Of the total 110 NL patients, 1 developed JIA, 1 psoriasis/iritis, 1 IBD, and 3 thyroid disease. Of the 74 unaffected siblings, 1 developed 1 RA, and 1 sarcoidosis. Autism was diagnosed in 3 (3%) NL children and 2 (3%) healthy siblings. 5 (5%) and 6 (8%) NL and unaffected children respectively were taking medications for ADHD. Hydrocephalus was diagnosed after birth in 6 (5%) NL children, 3 requiring shunts. In 13 (12%) and 2 (3%) NL and unaffected children, delays in motor milestones were reported (p=0.027). 41 (37%) NL children had ever been considered small in height or weight for age vs. 14 (19%) healthy siblings (p=0.005). However, only 12 (11%) NL children were still considered small at the time of the questionnaire vs. 9 (12%) of the unaffected siblings.

Conclusion: Older age is associated with a reported history of heart enlargement, greater need for pacing, and cardiac medications. This supports the requirement for continued intensive long term cardiac evaluation in affected children. Risks exist in NL for delayed motor milestones, and transient failure to thrive. This further suggests the need for comprehensive surveillance, perhaps with a multidisciplinary protocol at a center familiar with these children.

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Illness Features Associated with an Increased Risk of Mortality in Children with Juvenile Idiopathic Inflammatory Myopathies. Adam M. Huber[1], Gulnara Mamyrova[2], Julia A. Lee[3], Peter A. Lachenbruch[4], Ira N. Targoff[5], Frederick W. Miller[4], Lisa G. Rider[4] and Childhood Myositis Heterogeneity Study Group[6]. [1]Dalhousie University, Halifax, NS, [2]George Washington University, Washington, DC, [3]NIEHS, Bethesda, MD, [4]NIEHS, NIH, Bethesda, MD, [5]Oklahoma Medical Research Foun, Oklahoma City, OK, [6]Bethesda

Background/Purpose: Juvenile idiopathic inflammatory myopathies (JIIM) are potentially life-threatening systemic autoimmune diseases but little in known regarding factors associated with mortality.

Methods: Patients enrolled in a nationwide registry which included demographics, clinical and laboratory features, and outcomes. Timing of features (at diagnosis, after diagnosis or ever) was recorded. Mortality status was available for 419/441 (95%) patients (342 juvenile dermatomyositis (JDM), 30 juvenile polymyositis (JPM) and 47 juvenile connective tissue disease associated myositis (JCTM)), based on the Social Security Death Index or physician report. Poisson regression was used to assess univariable associations with mortality. Random survival forest classification followed by Poisson regression was used to assess multivariable associations.

Results: The cohort was 74% female, 69% white, median diagnosis age 7.6 years and median follow-up 4.3 years. There were 17 deaths (4%): 7 pulmonary (interstitial lung disease [ILD]), 3 gastrointestinal (perforation or hemorrhage), 3 multisystem (sepsis, multi-organ failure) and 4 unknown.

For univariable analysis, features present at diagnosis associated with an increased risk of death (P<0.05) were disease subgroup (mortality 2.3% JDM, 6.7% JPM, 14.9% JCTM), hospitalization, onset severity, younger age at diagnosis, anti-synthetase, anti-Ku or -La autoantibodies, dysphagia, abdominal perforation, Raynaud's phenomenon, ILD, shawl sign rash, gastroesophageal reflux and dysphonia. Features present after diagnosis associated with an increased risk of death were wheelchair use at last assessment, ILD, fever, pneumothorax or pneumomediastinum, abdominal perforation and number of hospitalizations. For features present at any time, including unknown timing, additional features associated with increased risk of death included syncope, dyspnea, sclerodactyly, weight loss, and decreased risk: fatigue, Gottron's papules and linear extensor erythema. Multivariable analyses revealed the following:

MULTIVARIABLE ANALYSIS		Incidence Rate Ratio	P-value
Features present at time of diagnosis			
	Raynaud's phenomenon	10.2	0.000
	Onset severity	3.8	0.01
Features present after diagnosis			
	Wheelchair use at last assessment	11.3	0.000
	ILD	5.1	0.004
	Any anti-synthetase autoantibody	4.4	0.02
Features present at any time			
	Fatigue	0.02	0.000
	ILD	12.8	0.001
	Weight loss	5.9	0.04

Conclusion: We have identified illness features associated with an increased risk of death in a large JIIM cohort. Some, such as ILD, anti-synthetase autoantibodies and Raynaud's, extend to JIIM the factors that have been associated with mortality in adult disease. Others, such weight loss, severity at onset, and fatigue (protective) are novel to this JIIM cohort. These results warrant further study in additional cohorts to confirm their predictive value.

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Clinical Utility of Anti-CADM-140/Melanoma Differentiation-Associated Gene 5 Autoantibody Titers in Patients with Juvenile Dermatomyositis and Rapidly Progressive Interstitial Lung Disease. Shinji Sato[1], Norimoto Kobayashi[2], Kazuko Yamazaki[3] and Yasuo Suzuki[1]. [1]Tokai University School of Medicine, Isehara, Japan, [2]Shinshu University School of Medicine, Matsumoto, Japan, [3]Yokohama City University Hospital, Yokohama, Japan

Background/Purpose: The presence of anti-CADM-140/(Melanoma Differentiation-Associated Gene 5: MDA5) autoantibody is specific for adult dermatomyositis (DM), especially in patients with little or no muscle manifestations (clinically amyopathic dermatomyositis: CADM). Its presence is known to have a strong association with rapidly progressive interstitial lung disease (RP-ILD). Recently, it was reported that anti-CADM-140/MDA5 antibody titers measured by an enzyme-linked immunosorbent assay (ELISA) were useful for predicting outcomes of RP-ILD as well as for monitoring disease activity in patients with adult DM and RP-ILD. However, despite its diagnostic utility in adult DM, its clinical significance in juvenile DM (JDM) is still unclear. Here, we have examined this issue using anti-CADM-140/MDA5 ELISA.

Methods: Serum samples from 35 patients diagnosed with JDM (26 with classical JDM and 9 with juvenile CADM) were screened for autoantibody using a previously established anti-CADM-140/MDA5 ELISA. Associations between anti-CADM-140/MDA5 titer and clinical course and outcome were analyzed.

Results: Sera from 11 of 35 patients (31%) with JDM were found to contain anti-CADM-140/MDA5 antibody (6 with classical JDM and 5 with juvenile CADM). All 11 patients who possessed anti-CADM-140/MDA5 antibody had ILD, of whom 6 developed RP-ILD. JDM patients with anti-CADM-140/MDA5 antibody were significantly more likely to have RP-ILD compared with those without this antibody (P=0.0017). In anti-CADM-140/MDA5-positive patients, the mean antibody titer before treatment was significantly higher in those with RP-ILD than in those without (166.7 units vs. 57.4 units, P= 0.048). Four of 6 patients with RP-ILD died despite intensive therapy. In a patient who responded to therapy and survived, the titer of anti-CADM-140/MDA5 antibody decreased to the cut-off level, in parallel with improved respiratory symptoms. In contrast, the mean anti-CADM-140/MDA5 titer in patients who failed to respond to therapy and died did not decrease significantly, being maintained at a high level over the disease course as also observed in patients with adult DM (197.2 units vs. 76.2 units, P=0.17, n=3).

Conclusion: These results illustrate the clinical utility of establishing anti-CADM-140/MDA5 antibody titers in patients with JDM and RP-ILD as well as in patients with adult DM and RP-ILD.

Disclosure: **S. Sato**, Holding a patent on anti-CADM-140/MDA5 antibody-measuring kit, 7; **N. Kobayashi**, None; **K. Yamazaki**, None; **Y. Suzuki**, None.

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Usefulness of Cardiac Magnetic Resonance in the Assessment of Myocardial Inflammation and Fibrosis in Children Born to Mothers with Anti-SSA/Ro Antibodies: A Prospective Study of 23 Cases and 6 Controls. Nathalie Costedoat-Chalumeau[1], Alice Maltret[2], Kateri Levesque[1], Shelby Kutty[3], Elisabeth Villain[2], Phalla Ou[2] and Gaëlle Guettrot-Imbert[4]. [1]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [2]Groupe Hospitalier Necker - Enfants Malades, Paris, France, [3]Division of Pediatric Cardiology, university of Nebraska Medical Center and Children's Hospital ans Medical Center, Omaha, NE, USA, Omaha, [4]Hopital Gabriel Montpied, Clermont-Ferrand, France

Background/Purpose: Besides congenital heart blocks (CHB), others manifestations of cardiac neonatal lupus erythematosus syndrome (NLES) include endocardial fibroelastosis (EFE), and dilated cardiomyopathy. Recently, autopsy of fetuses and children with cardiac NLES showed that EFE was under-diagnosed by echocardiography. We investigated the utility of cardiac magnetic resonance (CMR) for myocardial characterization, in children exposed *in utero* to anti-SSA/Ro antibodies (Ab), with focus on inflammation and fibrosis.

Methods: Children born to mothers with anti-SSA/Ro Ab were enrolled in a prospective study performed from December 2011 to June 2012. The control group consisted of 6 healthy children born to mothers without anti-SSA Ab. All the children had a complete cardiac testing with electrocardiogram, echocardiography and a CMR assessments (T2-weighted sequence for myocardial edema, T1-weighted sequence before and after intravenous administration of gadolinium for hyperemia, and late gadolinium enhancement). Positive findings in 2 of 3 sequences were considered diagnostic of myocarditis, and positive late gadolinium enhancement indicative of fibrosis.

Results: 23 children with (n=15, group 1) and without (n=8, group 2) cardiac NLES were included. Cardiac manifestations in group 1 were complete CHB (n=10), 2nd degree CHB (n=2), 1st degree CHB (n=1), supraventricular tachycardia (n=2). EFE was present on the *in utero* echocardiography in 7.

Group 2 included 3 children with cutaneous manifestations of NLES, and 5 symptom free children (2 had siblings with NLES manifestations).

11 children (10 in group 1 and 1 in group 2) had abnormal CMR whereas only 3 (all in group 1) had abnormal postnatal echocardiography (table1). Interestingly, no myocardial inflammation was observed after 3 months of life. The 6 children of the control group (anti-SSA-) had normal CMR.

CMR was performed twice in 3 children (2 with CHB and 1 with supraventricular tachycardia and EFE). In 2 children, the second MRI showed stability or an improvement of inflammation after 5 and 11 days respectively. In the third child (with CHB), an extension of fibrosis was observed after 9 months. This child died of heart failure at 2.8 years old despite cardiac pacing.

	Normal CMR	Normal but incomplete CMR (without injection)	Inflammation	Inflammation and fibrosis	Fibrosis
Children	11	2	2	2	6
Median age of children at CMR (years)	1.75 [0.01–8.54]	0.93	0.17	0.14	2.14 [0.01–7.6]
Number of children					
- group 1 (SSA+, cardiac NLES)	4	2	2	1	6
- group 2 (SSA+, no cardiac NLES)	7			1	
In utero echocardiography					
- normal	11	1		1	2
- EFE		1	2	1	3
- Not available					1
Post natal echocardiography					
- normal	11	2	1	1	5
- EFE			1	1	1

Conclusion: CMR is more sensitive than echocardiography to show myocarditis and/or fibrosis associated to anti-SSA antibodies. Further studies are needed to correlate CMR characteristics with late onset dilated cardiomyopathy.

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Effects of Obesity On Health-Related Quality of Life in Childhood-Onset Systemic Lupus Erythematosus. Rina Mina[1], Marisa S. Klein-Gitelman[2], Shannen Nelson[3], Lori B. Tucker[4], B. Anne Eberhard[5], Nora G. Singer[6], Deborah M. Levy[7], Kathleen A. Haines[8], Karen Onel[9], Marilynn G. Punaro[10], Kathleen M. O'Neil[11], Michael Henrickson[12], Jun Ying[13] and Hermine I. Brunner[3]. [1]Cincinnati Children's Hospital Medical Center/University of Cincinnati, Cincinnati, OH, [2]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]BC Childrens Hospital, Vancouver, BC, [5]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [6]Director, Division of Rheumatology, Metro-Health Medical Center, Case Western Reserve University, Cleveland, OH, [7]The Hospital for Sick Children, Toronto, ON, [8]Hackensack Univ Med Ctr, Hackensack, NJ, [9]University of Chicago, Chicago, IL, [10]Texas Scottish Rite Hospital, Dallas, TX, [11]Riley Hospital for Children, Indianapolis, IN, [12]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [13]University of Cincinnati, Cincinnati, OH

Background/Purpose: Obesity in adults with Systemic Lupus Erythematosus (SLE) is associated with an added risk of cardiovascular disease, decreased health-related quality of life (HRQOL), and increased disability. While cross-sectional studies report the prevalence of obesity in adult SLE cohorts at 27–29%, there are no studies that address the frequency of obesity in childhood-onset SLE (cSLE) or its impact on patient well-being. Patients with cSLE are more often treated with corticosteroids than adults with SLE, putting them likely at a higher risk for obesity. The purpose of this study is to estimate the frequency of obesity in our cSLE cohort and evaluate the effect of obesity on HRQOL measures in cSLE.

Methods: Obesity was defined as a body mass index $\geq 95^{th\%}$ of the sex-specific CDC 2000 BMI-for-age growth charts. In a prospective cSLE cohort (n=202), we compared the domain and summary scores of the generic and rheumatology modules of the Pediatric Quality of Life Questionnaire Inventory (PedsQL) and Child Health Questionnaire (CHQ) between obese cSLE patients and three comparison groups: 1) non-obese cSLE; 2) non-obese healthy children; and 3) obese controls without cSLE. Using mixed-effects models that adjusted for important predictors, we evaluated the independent contribution of obesity on HRQOL measures.

Results: Twenty five percent (n=51) of the cSLE patients in the cohort were classified as obese. We found a significant negative impact of obesity on overall HRQOL which persists even after adjustment for corticosteroid use, disease activity, disease damage, gender, and race of the patients *(Table 1)*. Obese cSLE patients had significantly lower physical and school functioning, and more pain compared to all three comparator groups (p-values<0.0001–0.05). There was also poorer emotional functioning in obese cSLE patients compared to their non-obese counterparts and healthy children (p-values <0.0001–0.04). Parents of obese cSLE patient worry more and perceive more physical limitations and limited family activities (p-values <0.0001–0.01).

Table 1. Difference in scores of health related quality of life (HRQOL) measures in cSLE according to presence of obesity*

Health Related Quality of Life Measures	cSLE			Historical controls without cSLE			
	(A) Obese	(B) Non-obese	P-value (A vs. B)**	(C) Non-obese†	P-value (A vs. C)††	(D) Obese¶	P-value (A vs. D)¶¶
	(N=51)	(N=151)				(N=63)	
Pediatric Quality of Life Questionnaire							
Generic Module: Parent-report	69.2 ± 2.8	81.7 ± 2.3	<0.0001	82.7 ± 0.2	<0.0001	75.0 ± 1.8	<0.0001
Physical Functioning	66.6 ± 3.9	81.6 ± 3.1	0.0004	84.5 ± 0.2	<0.0001	76.3 ± 2.2	<0.0001
Emotional Functioning	70.6 ± 3.2	80.4 ± 2.6	0.005	81.3 ± 0.2	<0.0001	72.6 ± 2.2	0.0001
Social Functioning	77.2 ± 3.2	87.7 ± 2.6	0.003	83.7 ± 0.2	<0.0001	73.5 ± 2.2	<0.0001
School Functioning	64.3 ± 3.3	77.4 ± 2.7	0.0003	78.8 ± 0.2	<0.0001	76.6 ± 2.1	<0.0001
Generic Module: Self-report	74.0 ± 2.6	81.4 ± 2.2	0.003	87.5 ± 0.1	<0.0001	74.0 ± 1.8	NS
Physical Functioning	68.6 ± 3.5	80.9 ± 3.0	0.0003	83.8 ± 0.1	<0.0001	77.5 ± 2.3	<0.0001
Emotional Functioning	75.8 ± 3.1	82.3 ± 2.7	0.04	79.3 ± 0.2	<0.0001	68.6 ± 2.3	<0.0001
Social Functioning	81.7 ± 2.5	89.0 ± 2.2	0.003	85.2 ± 0.2	<0.0001	72.1 ± 1.8	<0.0001
School Functioning	71.6 ± 3.1	74.6 ± 2.7	NS	81.1 ± 0.2	<0.0001	75.0 ± 1.8	<0.0001
Rheumatology Module: Parent-report	79.5 ± 2.1	85.6 ± 1.7	0.007	82.0 ± 1.5	NS	ND	
Pain and Hurt	65.2 ± 4.1	77.5 ± 3.3	0.005	73.1 ± 1.9	0.053		
Daily Activities	92.0 ± 2.4	94.0 ± 1.9	NS	88.5 ± 1.4	0.028		
Treatment	82.0 ± 2.2	85.9 ± 1.8	NS	70.8 ± 1.6	<0.0001		
Worry	70.3 ± 3.6	80.0 ± 2.9	0.013	89.6 ± 1.2	0.002		
Communication	81.1 ± 3.0	84.0 ± 2.5	NS	87.9 ± 1.4	0.022		
Rheumatology Module: Self-report	81.2 ± 2.1	86.0 ± 1.8	0.005	84.4 ± 1.5	<0.0001	ND	
Pain and Hurt	65.6 ± 3.9	80.7 ± 3.3	<0.0001	77.8 ± 2.0	<0.0001		
Daily Activities	92.2 ± 2.0	95.9 ± 1.7	NS	95.6 ± 0.9	<0.0001		
Treatment	85.7 ± 2.2	89.4 ± 1.9	NS	82.1 ± 1.4	<0.0001		
Worry	65.6 ± 3.7	69.9 ± 3.2	NS	83.6 ± 1.6	<0.0001		
Communication	78.7 ± 3.2	80.6 ± 2.8	NS	82.9 ± 1.7	<0.0001		
Childhood Health Questionnaire							
Physical Functioning	67.4 ± 3.5	76.3 ± 3.1	0.02	96.1 ± 0.7	<0.0001	ND	
Role/Social Limitations–Emotional/Behavioral	81.0 ± 3.4	87.1 ± 3.0	NS	92.5 ± 0.9	<0.0001		
Role/Social Limitations–Physical	84.7 ± 2.8	91.0 ± 2.5	0.044	93.6 ± 0.9	<0.0001		
Bodily Pain	51.9 ± 2.0	47.7 ± 1.8	NS	81.7 ± 1.0	<0.0001		
Behavior	67.5 ± 1.6	68.2 ± 1.4	NS	75.6 ± 0.8	<0.0001		
Generic Health Perceptions	52.7 ± 1.9	51.1 ± 1.6	NS	73.0 ± 0.9	<0.0001		
Mental Health	69.8 ± 1.7	72.9 ± 1.5	NS	78.5 ± 0.7	<0.0001		
Self Esteem	50.6 ± 3.8	52.3 ± 3.3	NS	79.8 ± 0.9	<0.0001		
Parent Impact–Emotional	56.1 ± 3.2	51.2 ± 2.6	NS	80.3 ± 1.0	<0.0001		
Parent Impact–Time	65.1 ± 3.7	57.5 ± 3.2	NS	87.8 ± 1.0	<0.0001		
Family Activities	69.7 ± 2.7	78.4 ± 2.4	0.004	89.7 ± 0.9	<0.0001		

*Values are mean ± standard error of the mean (SEM). For details, please refer to Table 1. NS-not significant; ND-not calculated (no comparison data).
** P-value from adjusted mixed effects models with summary and domain scores of HRQOL measures as dependent variable and presence of obesity (yes/no) as independent variable. Models adjusted for disease activity (SLEDAI scores ≤ 4 or not), daily prednisone dose (<0.2 mg/kg/day or not), race (African American or not), gender, and disease damage (total SLICC-DI scores ≤ 1 or not).
† P-value from 2-sided t-test comparing HRQOL scores from A (obese cSLE) vs. C (healthy controls).
†† P-value from 2-sided t-test comparing HRQOL scores from A (obese cSLE) vs. D (obese non-cSLE).
¶ Historical controls. For PedsQL-Generic Module: healthy pediatric patients with no chronic illness (N=9565) (1). For PedsQL-Rheumatology Module: healthy pediatric patients and JIA controls (N=141) (1). For CHQ: healthy pediatric controls (N=391).
¶¶ Historical controls. Obese pediatric patients without rheumatologic disease (N=63) *(Varni JW, et al. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007; 5:43).*

Conclusion: Our study demonstrates that about 25% of cSLE patients evaluated were obese. Obesity negatively impacts many aspects of HRQOL particularly physical functioning and pain/hurt domains. Given the adverse effects on HRQOL, there appears to be an urgent need to include weight management in the day-to-day management of children with cSLE.

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Brain Biopsy Diagnosis in Magnetic Resonance Imaging Negative Childhood Primary Angiitis of the Central Nervous System. Senq-J Lee, Cynthia Hawkins, Suzanne Laughlin, Shehla Sheikh and Susanne M. Benseler. The Hospital for Sick Children, Toronto, ON

Background/Purpose: Primary CNS vasculitis in childhood (cP-ACNS) is a devastating inflammatory brain disease mandating rapid and accurate diagnostic evaluation, in order to optimize neurologic outcomes. Traditional investigations including inflammatory markers are often abnormal, but not specific. Neuroimaging using MRI is considered the gold standard for detecting parenchymal inflammatory lesions, but is also not specific for cPACNS. We hypothesize that patients can still be diagnosed with cPACNS even if they have normal initial MRI studies, hence consideration of brain biopsy is vital. The aims of our study are: (1) To determine the proportion of children with confirmed cPACNS with normal initial MRI studies, and secondly, to calculate MRI sensitivity; (2) To report their presenting clinical, laboratory and brain histopathology findings, treatment response and long-term outcome.

Methods: We conducted a single centre cohort study of children diagnosed with cPACNS satisfying modified Calabrese criteria between 1990 and 2010. The study included all patients with normal MRI studies (defined as no evidence of an inflammatory or ischemic lesion at diagnosis) with subsequent confirmatory brain biopsy. Clinical, laboratory, histopathologic, treatment and patient outcome data was collected for these patients. MRI-studies were evaluated by a neuroradiologist, and histopathology by a neuropathologist.

Results: Out of 107 children diagnosed with cPACNS, 80 children were diagnosed with angiography-positive cPACNS; all had abnormal MRIs. 27 patients were diagnosed with angiography-negative cPACNS; 25 (93%) had abnormal MRIs. MRI sensitivity for the overall cohort was 98%, 100% for angiography-positive and 93% for angiography-negative cPACNS. Two children fulfilled inclusion criteria: previously healthy 11 and 13 year old males, both presenting with acute onset seizures progressing to refractory status epilepticus. Both patients had elevated serum inflammatory markers. One had a slightly raised WBC in CSF, the other had two normal CSF studies. Both patients had extensive workup for infection and rheumatologic disease, returning negative. Extensive imaging including CT, conventional angiogram, MRA, MRI, and MR spec-

troscopy returned normal. Treatment was with a standardized protocol of small vessel cPACNS, including corticosteroids, pulse IV cyclophosphamide for 6 months, followed by maintenance Mycophenolate Mofetil for 18 months. On last follow-up, one patient had mild residual neurologic deficits and intermittent seizures on anti-epileptics; the second had an excellent outcome with no neurologic deficit and seizure-free on Topiramate monotherapy.

Conclusion: Neuroimaging is a corner stone in the diagnostic evaluation of childhood CNS vasculitis. In our cohort, MRI was highly sensitive, however, a negative MRI does not rule out the diagnosis of cPACNS. In children presenting with refractory seizures, and/or if there is a high clinical suspicion, a brain biopsy should be considered despite repeatedly negative or non-diagnostic MRI studies.

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A Brazilian Multicenter Study of 71 Children and Adolescents with Takayasu's Arteritis.

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Background/Purpose: Takayasu's arteritis is a chronic granulomatous disease that affects the vascular wall of the large arteries and can result in end organ damage. It is more prevalent in young women, but can also occur in the childhood. The disease is rare and there are few reports about the clinical features at this age. Our aim was to describe the clinical features of Takayasu's arteritis in children and adolescents in our population.

Methods: In this Brazilian multicenter retrospective study including 10 pediatric rheumatology centers we identified 71 children and adolescents with Takayasu's arteritis. Patients' demographic, clinical, laboratory, angiographic, therapeutic data and disease outcome were recorded.

Results: Of the 71 patients, 51 (72%) were girls, with a mean age at onset of 9.2 years (range 4 months to 17.2 years); the average time to diagnosis was 1.2 years; and the mean follow-up time was 5.4 years. The most frequent angiographic type was type IV (41%) followed by type V (27%) and the abdominal aorta was the most affected vessel (63.4%). The main lesion was arterial stenosis (84.5% of patients). At initial presentation 80.6% of patients had increased acute phase reactants and 41% of patients had a positive Mantoux test. The predominant clinical symptoms at onset were constitutional (77.5%), followed by neurological (70.4%) and musculoskeletal symptoms (64.8%). The main cardiovascular manifestation was arterial hypertension (84.5%). At the final evaluation, neurological symptoms were predominant (22.7%) and decrease of peripheral pulses (66.7%) was the main cardiovascular manifestation. Sixty four (90.1%) patients were treated with corticosteroids, 30 patients (42.3%) with methotrexate as the first immunosuppressive treatment and 18 (25.4%) were treated with cyclophosphamide as initial therapy. Infliximab was used in only 4 patients throughout the follow-up. At the final evaluation, 55% of patients were in disease remission, 28% had active disease, 7% died and in 10% the outcome was unknown.

Conclusion: Takayasu's arteritis is a rare childhood disease. In this multicenter study we observed a high rate of disease remission, however prospective studies are needed in order to better define overall disease outcome.

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Effectiveness of Intravenous Cyclophosphamide in Severe or Refractory Juvenile Dermatomyositis - a National Cohort Study UK and Ireland.

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Background/Purpose: Juvenile dermatomyositis (JDM) is a rare autoimmune vasculopathy affecting primarily the muscle and skin, but can also involve other organs.

Early and aggressive treatment improves outcome and prevents complications. Cyclophosphamide has been used as a second-line agent in the treatment of severe or refractory JDM. The published literature on the effectiveness of cyclophosphamide in JDM is limited to a small case series and case reports.

The objective of the study is to describe the response to cyclophosphamide in the patients with severe or refractory JDM.

Methods: 56 patients treated with cyclophosphamide between years 2000–2011 were identified in the JDM National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies. 8 patients were excluded due to incomplete data or too short follow up. For the 48 patients included, demographics, myositis core outcome variables, skin measures, laboratory measures, steroid dose and other treatments were recorded at baseline, time 6, 12, 18, 24 months and last follow up post commencement of the drug.

Results: Indications for starting cyclophosphamide were ulcerative or severe skin disease, profound muscle weakness, lung disease, gastro-intestinal vasculopathy or refractory disease. Previous medications were steroids and Methotrexate for 47 patients and steroids and Cyclosporin for 1 patient.

All patients starting with muscle weakness (n=44) significantly improved at time12, and the gains were maintained at follow up (see table1). Physician VAS was available for 32 patients and these all improved by 12 and 24 months, and for 31 remained stable at follow up.

At last follow up 26/46(56%) had no rash, 32/46(69%) had normal nailfolds, 37/45(82%) had no Gottron's, and calcinosis improved in 9/14 (64%).

Table 1.
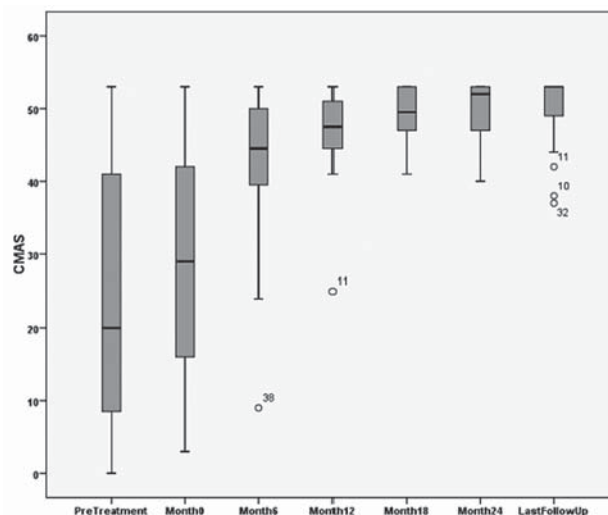
Table 2.
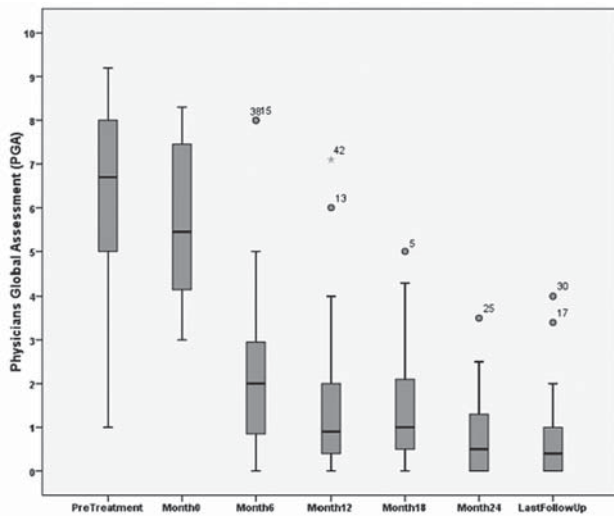
Conclusion: This study, the largest to date, demonstrated significant improvement in both muscle and skin domains in patients with JDM treated with intravenous cyclophosphamide.

Cyclophosphamide appears effective in the treatment of severe or refractory JDM.

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Childhood-Onset Predicts Increased Disease Damage and Steroid Toxicity in a Cohort of Adults with Systemic Lupus Erythematosus. Erica F. Lawson[1], Laura Trupin[1], Jinoos Yazdany[1], Aimee O. Hersh[2], Emily von Scheven[1] and Edward H. Yelin[1]. [1]University of California San Francisco, San Francisco, CA, [2]University of Utah, Salt Lake City, UT

Background/Purpose: While previous work has shown that adults with childhood-onset systemic lupus erythematosus (cSLE) have increased risk of mortality, renal disease and myocardial infarction as compared to individuals with adult-onset SLE (aSLE), little is known about differences in cumulative disease damage or steroid toxicity between adults with cSLE and aSLE. The goal of this study was to determine whether adults with cSLE are at increased risk for disease damage and steroid toxicity as compared to those with aSLE.

Methods: Data derive from the 2007–2011 cycles of the Lupus Outcomes Study (LOS), an annual longitudinal telephone survey of diverse English-speaking subjects with confirmed SLE. The Brief Index of Lupus Damage (BILD), a validated, patient-reported measure, was used to assess SLE-associated damage (Yazdany, 2011). Subjects age 18–63 were included in the analysis (N=823). Subjects were classified as childhood-onset if age at diagnosis was < 18 years (N=105). Outcome variables included BILD score and the presence of steroid-related damage. Steroid-related damage was defined as a self-reported history of cataracts, diabetes mellitus (DM), osteoporosis or avascular necrosis (AVN). We used negative binomial regression and logistic regression to compare cSLE and aSLE with and without adjustment for current age, gender and ethnicity. Disease duration was not included in the model due to colinearity with current age and category of age at onset.

Results: Mean age ($\pm$SD) was 46 years ($\pm$11), and 93% were female. Ethnicities included Caucasian (60%), Hispanic (10%), African American (12%), Asian (12%) and other (7%). Subjects with cSLE were more likely to be ethnic minorities (p<0.001). Mean age at diagnosis was 14 ($\pm$3) for subjects with cSLE and 33 ($\pm$10) for subjects with aSLE. Mean disease duration was 18 years ($\pm$8) for subjects with cSLE and 14 years ($\pm$10) for subjects with aSLE. Unadjusted mean BILD score was 1.8 (median 1, range 0–11) among subjects with cSLE and 2.0 (median 1, range 0–12) among subjects with aSLE. In adjusted analysis, there was greater SLE damage among subjects with cSLE (Table 1). There was no difference in unadjusted

frequency of steroid-related damage (cataracts, DM, osteoporosis or AVN) between cSLE and aSLE groups (30% vs. 33%). However, in adjusted analysis, subjects with cSLE were twice as likely to report steroid toxicity as compared to subjects with aSLE (odds ratio 1.9, 95% CI 1.1–3.3).

Table 1. Disease-related damage and steroid-related damage (osteoporosis, AVN, cataracts or DM) according to the BILD among subjects age 18–63 with SLE*

Variable	Mean BILD score (95% CI)†	Percent of subjects with steroid toxicity (95% CI)#
Childhood-onset SLE	2.63 (2.06–3.19)	46% (35–57%)
Adult-onset SLE	1.91 (1.77–2.04)	32% (28–35%)

*AVN = avascular necrosis; DM = diabetes mellitus, BILD = Brief Index of Lupus Damage; 95% CI = 95% confidence interval.
†Mean BILD score calculated from negative binomial regression results, adjusted for age, gender and ethnicity; P = 0.005
#Percent of subjects with steroid toxicity calculated from logistic regression results, adjusted for age, gender and ethnicity; P = 0.013

Conclusion: In this large cohort of adults with SLE, onset of lupus in childhood predicts increased disease damage. Childhood-onset SLE also predicts increased risk of steroid-related damage, which may be due to greater cumulative steroid exposure. Tight disease control and minimization of steroid use in childhood may be important to decrease long-term morbidity in cSLE.

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Reduction of Cerebral and Corpus Callosum Volumes in Childhood-Onset Systemic Lupus Erythematosus. A Volumetric Magnetic Resonance Imaging Analysis. Aline T. Lapa[1], Wesley G. Ferreira[1], Mariana Postal[1], Nailu A. Sinicato[1], Roberto Marini[2], Fernando Cendes[1] and Simone Appenzeller[3]. [1]State University of Campinas, Campinas, Brazil, [2]Universidade Estadual de Campinas, Sao Paulo, Brazil, [3]State University of Campinas, São Paulo, Brazil

Background/Purpose: Cerebral atrophy has been described to occur in SLE with variable frequency. Aging, systemic diseases, corticosteroid use and central nervous system (CNS) involvement may lead to cerebral atrophy. However, studies evaluating the prevalence of cerebral atrophy in childhood-onset systemic lupus erythematosus (cSLE) using magnetic resonance imaging (MRI) volumetric measurements are rare. Objectives: To determine the frequency of cerebral and corpus callosum atrophy in cSLE and to determine the possible relationships between atrophy and clinical, laboratory and treatment features of the disease.

Methods: A total of 51cSLE patients (48 female; mean age=17.0; SD=3.9) and 50 healthy age and sex matched volunteers (37 women; mean age=18.4; SD=5.7) followed at the pediatric rheumatology unit of the State University of Campinas were enrolled in this study. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory in all participants. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity (SLEDAI), damage (SDI) and current drug exposures. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated. MRI scans were performed in a 3T Phillips®scanner using a standardized protocol. Sagittal T1 weighted images were used for semiautomatic volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Non-parametric tests and correlation were used for statistical analysis.

Results: In cSLE, cerebral (mean volume=1077.1 cm^3; SD=94.5) and corpus callosum (mean volume=11.8 cm^3; SD=1.8) volumes were significantly smaller when compared to cerebral (mean volume=1191.7; SD=122.1; p<0.001) and corpus callosum (mean volumes=10.8; SD=1.6; p<0.005) volumes of healthy volunteers. Corpus callosum atrophy were identified in 4 (7.8%; p=0.005) and cerebral atrophy 7 (14%; p=0.003) cSLE and in none of the controls. The presence of corpus callosum atrophy was associated with positive anti-dsDNA antibodies (p=0.018). An indirect

correlation between age and corpus callosum volume (r=−0.88; p<0.001) was observed. The presence of cerebral atrophy was associated with the presence of depression (p=0.007), vasculitis (p<0.001) and disease activity (p=0.04). No relationships between cerebral and corpus callosum volume and disease duration, the presence of CNS manifestations, total corticosteroid dose, and the presence of antiphospholipid antibodies were observed.

Conclusion: Cerebral and corpus callosum atrophy is observed more frequently in cSLE when compared to controls. The presence of immunological and clinical features are associated with the presence of atrophy. Depression was the only neuropsiquiatric manifestation associated with cerebral atrophy.

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Prevalence and Clinical Significance of Hippocampal Atrophy in Childhood-Onset Systemic Lupus Erythematosus. Aline T. Lapa[1], Renata Brabosa[2], Mariana Postal[1], Nailu A. Sinicato[1], Roberto Marini[3], Fernando Cendes[1] and Simone Appenzeller[4]. [1]State University of Campinas, Campinas, Brazil, [2]Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, Germany, [3]Universidade Estadual de Campinas, Sao Paulo, Brazil, [4]State University of Campinas, São Paulo, Brazil

Background/Purpose: Hippocampal atrophy is associated with corticosteroid use and may be related to cognitive impairment in systemic lupus erythematosus (SLE).Objectives: To determine the prevalence of hippocampal atrophy in childhood-onset SLE (cSLE) using manual magnetic resonance imaging (MRI) volumetric measurements. To determine the possible relationship between hippocampal atrophy and disease duration, corticosteroid therapy, central nervous system (CNS) manifestations and the presence of antiphospholipid antibodies.

Methods: A total of 21 cSLE patients (21 female; mean age 17.28; SD=3.63) and 21 healthy age and sex matched volunteers (21 female; 20.57; SD=5.39) were enrolled in this study. A complete clinical, laboratory and neurological evaluation was performed. Neurological manifestations were analyzed according to the ACR classification criteria. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age and validated in Portuguese. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory in all participants. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. The cumulative dose of corticosteroids used was calculated by the sum of daily dosages versus time (days) of treatment. MRI scans were performed in a 3T Phillips scanner using a standardized protocol. Volumetric 1mm T1 weighted images were used for manual volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Non-parametric tests and correlation were used for statistical analysis.

Results: Right (mean volume=3.65cm^3; SD=0.49) and left (mean volume=3.64cm^3; SD=0.41) hippocampal volumes were significantly smaller in cSLE compared to healthy volunteers (right mean hippocampal volume=4.59cm^3; SD=0.44; p<0.001; and left mean hippocampal volume=3.94cm^3; SD=1.5; p<0.001). Hippocampal atrophy was observed in 13 (62%) cSLE patients and none of the controls. Hippocampal atrophy was associated with the presence of positive ANA (p=0.048), anticardiolipine antibodies (p=0.02), total corticosteroid dose (p=0.029), low complement (p=0.029) and vasculitis (p=0.03). Cognitive impairment was more frequently observed in patients with hippocampal atrophy (p=0.002). No relationships between hippocampal atrophy and age, disease duration, SLEDAI and SDI was observed.

Conclusion: Hippocampal atrophy is frequently observed in cSLE and associated with the presence of cognitive impairment. Immunological and clinical features and total dose of corticosteroids are associated with hippocampal atrophy.

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Decreased Frequency of Dystrophic Calcifications in Children with Juvenile Dermatomyositis: A 10-Year Study. Lauren M. Pachman[1], Gabrielle A. Morgan[2], Megan L. Curran[1], Lori J. Ferguson[2] and Chiang-Ching Huang[3]. [1]Division of Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Children's Hospital of Chicago Research Center, Cure JM Myositis Center, Chicago, IL, [3]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: In Juvenile Dermatomyositis (JDM), dystrophic calcifications, associated with increased morbidity and mortality, have been reported for 20–30% of patients. There are few laboratory indicators of disease activity, and a duration of untreated disease (DUD) greater than 4.5 months is associated with normalization of muscle enzymes (CK, Aldolase, LDH, SGOT), commonly used to guide response to therapy.

Objective: To determine the current frequency of dystrophic calcifications in children with JDM.

Methods: Patients with definite/probable JDM (overlap syndromes excluded) seen between 2000 and 2010 at the Ann and Robert H. Lurie Children's Hospital enrolled (IRB #2012–12858). At the first visit of 90 children, 52 were untreated and 38 were previously treated. Demographic data were obtained (Table), and their clinical inflammation assessed by disease activity scores (DAS) for skin and muscle. Diagnosis was confirmed by laboratory testing, and MRI directed muscle biopsy.

	Untreated (N=52)	Treated (N=38)	*P*-value
White/Hispanic (N, %)	46 (88%)	36 (95%)	0.51
Female (N, %)	40 (77%)	28 (74%)	0.91
Age at onset (year, mean±SD)	5.8±3.17	6.2±3.4	0.52
Disease duration (month, mean±SD)	10.4±16.2	9.6±13.4	0.79
DAS skin (mean±SD)	5.8±1.3	4.9±2.3	0.055
DAS muscle (mean±SD)	4.0±2.6	4.1±2.8	0.91

Results: Of the 52 untreated patients, 5 (9.6%) had calcinosis at presentation. The 52 children were initially treated with oral prednisone (47), IV prednisone (45), methotrexate (48), hydroxychloroquine (11), cyclosporin (1), mycophenolate (2), IVIG (0), and alendronate (0). During their disease course, the following medications were used: oral prednisone (50), IV methlyprednisone (45), methotrexate (48), hydroxychloroquine (21), cyclosporin (10), mycophenolate (29), IVIG (6), and alendronate (0). At follow-up 4/5 of the children's calcifications had resolved and the fifth one had diminished in size. None of the children with initially untreated JDM developed new calcifications. Of the 38 children previously treated, 7 (18%) had calcifications. Medications taken: oral prednisone (25), IV methylprednisone (5), methotrexate (25), hydroxychloroquine (20), cyclosporin (3), mycophenolate (2), IVIG (5), and alendronate (2). At follow-up, of the 7 children with calcifications: 2 improved in size (1 totally resolved), 3 remained the same, one developed more advanced calcification (from moderate to severe), and one developed 36 deposits months later.

Conclusion: In untreated JDM without calcifications, no deposits developed during a mean follow-up period of <4 years. Of the 5 untreated JDM with calcifications, 4/5 resolved and the one diminished. Of the seven treated JDM referred with calcifications, only one totally resolved, and one developed new calcifications after 36 months of therapy. These data suggest that early immunosuppressive therapy may impair the development of dystrophic calcifications in JDM, for only 7.0% of this total group had calcifications. None of the 52 initially untreated children without calcifications developed them at a later time. We speculate that dystrophic calcifications in JDM are preventable.

Accuracy of Systemic Lupus International Collaborating Clinics Classification Criteria Applied to Juvenile Systemic Lupus Erythematosus Patients. Marìa M. Katsicas[1], Ezequiel Borgia[2], Ileana Villarroel[2] and Ricardo Russo[3]. [1]MD, Buenos Aires, Argentina, [2]MD, Caba, Argentina, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototype autoimmune disease. The most widely used classification criteria for SLE were those developed by the American College of Rheumatology (ACR) in 1982 and revised by a committee in 1997, but not validated in that revision. The Systemic Lupus Collaborating Clinics (SLICC) revised the ACR SLE classification criteria and validated new criteria in order to improve clinical relevance and incorporate new knowledge in SLE immunology.

To assess sensitivity and specificity of revised and validated new SLICC SLE classification criteria in a cohort of Juvenile SLE patients.

Methods: The SLICC criteria rule for SLE classification requires: 1) four criteria, with at least one clinical criterion and one immunologic criterion or 2) lupus nephritis alone in the presence of ANA or anti-DNA antibodies. Seventeen criteria were identified. Cases were JSLE patients who were attending a single tertiary center in the past 10 years. JSLE had been diagnosed on clinical and immunological grounds by experienced pediatric rheumatologist. Controls were patients with rheumatic diseases other than SLE: Juvenile Idiopathic Arthritis (JIA); Juvenile Dermatomyositis (JDM), Autoimmune Hepatitis (AH) and Juvenile Systemic Sclerosis (JSS). Criteria were reviewed from prospectively developed databases and medical records by pediatric rheumatologists in order to establish the number and frequency of new criteria fulfilled by each patient. Descriptive statistics were used to characterize both patients groups. Summary statistics included overall sensitivity and specificity. McNemar's test was used to assess differences between ACR 1997 criteria and SLICC criteria with respect to accuracy.

Results: Cases: 107 patients with JSLE were included (F: 89 M: 18), age at onset: 12 (3–16) yo. Controls: 102 patients with JIA (36 patients, systemic 20, polyarticular 16); JDM (28), AH (28) and JSS (10), F:76 M: 26, age at onset: 11 (2–16) yo. SLICC SLE criteria sensitivity was 100 % vs 86% ACR 1997 criteria, while specificity was 98% vs 96% (p=0.009). Six patients with a clinical diagnosis of JSLE were correctly classified by SLICC but not by ACR criteria.

Table. lists the sensitivity and specificity of each criterion in SLICC SLE criteria

SLICC SLE criteria	Sensitivity %	Specificity %
Acute cutaneous lupus	61	100
Chronic cutaneous lupus	2	100
Oral ulcers	11	100
Nonscarring alopecia	14	98
Synovitis	65	68
Serositis	13	98
Renal	56	99
Neurologic	11	100
Hemolytic anemia	21	98
Leukopenia or Lymphopenia	34	95
Thrombocytopenia	31	92
ANA	100	60
Anti-DNA	63	100
Anti-Sm	30	100
Antiphospholipid antibodies	33	100
Low complement	91	90
Direct Coombs test	29	98

Conclusion: The SLICC new criteria performed better than the ACR 1997 criteria in a cohort of patients with JSLE. These new criteria allowed better accuracy than previous criteria in some variables such as low complement, anti-DNA, acute cutaneous lupus, ANA, and renal involvement.

Ancestral Group Differences in Pediatric SLE Early Disease Severity: An Analysis of the Carranet Registry. Jennifer M.P. Woo[1], Alice DC Hoftman[1], Emily von Scheven[2], Deborah K. McCurdy[1], Ornella J. Rullo[1] and CARRA Registry Investigators[3]. [1]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [2]UC San Francisco, San Francisco, CA, [3]Durham

Background/Purpose: Ancestral background may contribute to increased disease morbidity in patients with pediatric lupus systemic erythematosus (pSLE) of non-European descent; however, there exists a paucity of information describing the effects of ancestry on the early disease processes of pSLE. We recently identified that pSLE patients of not uniquely European ancestry (nonEA) at a tertiary care center in Los Angeles, California, were more likely to present with more active disease during the first 12 months of diagnosis. We aim to assess whether children and adolescents with pSLE of nonEA ancestry have a more severe early disease course than their European American counterparts.

Methods: CARRAnet Registry data was obtained for 665 subjects with pSLE (diagnosis <18 years); 130 were further identified as diagnosed within 12 months prior to their baseline visit between 2010 and 2012. Demographic and socioeconomic data, ACR SLE criteria, and SLE Disease Activity Index (SLEDAI) were evaluated at baseline, and any renal biopsy results were recorded. Cumulative steroid exposure and use of additional immunosuppressive agents was also documented. Impact of disease was assessed, using ACR functional class, health-related quality of life, Childhood Health Assessment Questionnaire (CHAQ), and physician global assessment (PGA). Comparison of these data between self-reported Hispanic- (HA), Asian- (A), African- (AA), non-European (nonEA; including all subjects of mixed ancestry or or of not uniquely European ancestry), and European- (EA) American patients with pSLE was conducted.

Results: Age at onset was slightly higher among HA, A, and nonEA patients when compared with EA pSLE (Table 1). All Non-EA pSLE groups were more likely to have renal involvement during year 1 than EA; similarly, HA, A, and nonEA were more likely to present with proteinuria than EA (22%, 30%, 17% vs. 12.5%). However, total ACR criteria and SLEDAI scores near diagnosis did not differ among all non-EA groups compared to EA (Table 1). HA, AA, and nonEA pSLE received more immunosuppressive agents in addition to steroids, and more A pSLE had >1 month of cumulative steroids compared to EA pSLE (Table 1). Furthermore, A pSLE patients had more active PGA scores than EA. Overall, the EA and all non-EA groups had comparable duration of symptoms prior to diagnosis despite lower rates of insurance coverage in HA and nonEA and more HA, AA, and nonEA subjects reporting poverty-level household incomes than EA (Table 1).

Table 1. Clinical and socio-economic characteristics of EA, nonEA, HA, AA, and A pSLE patients.

	EA	NonEA	*p**	HA	*p**	AA	*p**	A	*p**
Total pSLE Cohort, n	177	488		118		203		68	
Female:Male	149:28	410:78		100:18		166:37		60:10	
Age at diagnosis, Mean years (range)	12.6 (3–18)	12.7 (4–18)		12.3 (3–18)		12.8 (4–18)		12.8 (5–18)	
Early disease cohort, n	32	98		36		40		10	
Female:Male	30:2	118:12		33:3		37:3		9:1	
Age at onset, mean years	12.5	13.3	0.07	14.3	0.02	12.6	0.8	14.2	0.06
Duration of symptoms, mean‡	5.9	6.1	0.4	6.6	0.2	6.1	0.4	5.8	0.5
Duration of diagnosis, mean‡	3.7	5.6	0.3	4.3	0.2	4.1	0.3	3.1	0.3
Duration of symptoms prior to diagnosis, mean	2.3	2.3	0.5	2.3	0.5	2.2	0.4	3.1	0.1
Clinical									
ACR SLE Criteria, mean (range)	4.5 (1–8)	4.6 (1–8)	0.4	4.6 (1–6)	0.4	4.7 (2–8)	0.3	4.8 (2–7)	0.3
SLEDAI at baseline‡, median (range)	4 (0–32)	4 (0–34)	0.2	4 (0–26)	0.2	4 (0–34)	0.4	4 (0–17)	0.3
Arthritis, %	59	66	0.4	69	0.2	70	0.2	70	0.2
Renal involvement, %	38	52	0.03	47	0.2	50	0.07	70	<0.01
Cumulative steroid use, %†	88	82	0.4	81	0.3	75	0.03	100	<0.01
Immunosuppression, mean††	0.78	0.9	0.3	0.83	0.8	1.0	0.3	0.7	0.8
Quality of life									
PGA, mean	2.5	2.8	0.3	2.5	0.5	2.9	0.3	3.75	0.04
CHAQ, mean	0.22	0.29	0.2	0.33	0.2	0.30	0.2	0.25	0.2
Sociodemographic									
Household income <$25,000; %	0	20	<0.001	25	<0.001	23	<0.001	0	0.2
Insurance status, %	94	91	0.6	81	0.01	95	1	100	0.03

EA-European American; HA-Hispanic American; AA-African American; A-Asian American; nonEA-of mixed ancestry or not uniquely of EA descent, including HA, AA, and A groups; SLEDAI-SLE Disease Activity Index; PGA-physician Global Assessment; CHAQ-Childhood Health Assessment Questionnaire
*p-values taken in comparison to EA values and considered significant at $p< 0.05$
‡Values assessed at time of enrollment/baseline visit, which occurred within 12 months of symptom onset and 12 months of diagnosis
† % of patients requiring cumulative prednisone >1 month
††Number of immunosuppressive agents required in addition to steroids and/or hydroxychloroquine

Conclusion: CARRAnet Registry pSLE patients of not uniquely European ancestry present at a slightly older age and potentially reflect a more active and refractory disease during the initial 12 months compared to EA counterparts. As the CARRAnet Registry continues to grow and additional follow-up data is collected, trends may emerge to further support ancestry-related differences in disease severity in the early stages of pSLE.

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Burden of Childhood Central Nervous System Vasculitis: Identifying High Risk Factors for Poor Cognitive Outcome. Peter J. Gowdie, Marinka Twilt, Pascal N. Tyrrell, Robyn Westmacott, Tania Cellucci, Shehla Sheikh, Nick Blancette and Susanne M. Benseler. The Hospital for Sick Children, Toronto, ON

Background/Purpose: Childhood primary angiitis of the CNS (cPACNS) is an increasingly recognized, reversible cause of severe neurological and psychiatric deficit such as stroke, refractory seizures and hallucination in previously healthy children. Aggressive immunosuppression has significantly decreased the mortality, however little is known about the long-term neurocognitive burden of cPACNS. Objectives: To describe the neuropsychological outcome of children with cPACNS, compare the cognitive burden between distinct disease subtypes and identify risk factors for poor neurocognitive outcome.

Methods: A single-centre cohort study of children with cPACNS based on Calabrese criteria was performed. Children had to have completed a standard neurocognitive evaluation. Demographic characteristics, disease subtypes, clinical features, laboratory markers, neuroimaging studies, brain biopsy findings and treatment regimens were captured. Neurocognitive function was evaluated with a standardized battery of neuropsychological tests including domains of cognitive, social, emotional and adaptive function. The primary study outcome was the Full Scale IQ (FSIQ). Secondary outcomes included neurological function as defined by the Paediatric Stroke Outcome Measure PSOM, Health-related Quality of Life (PedsQL), disease activity and disease damage (VAS). Analysis: Univariate analysis compared variables between distinct disease subtypes; a multivariate prediction model for adverse cognitive outcome was used

Results: A total of 104 children were diagnosed with primary CNS vasculitis in the study interval, of whom 63 (61%) completed the neuropsychological assessment. Of these 19 had small vessel CNS vasculitis (SVcPACNS) and 44 angiography-positive CNS vasculitis (APcPACNS). The cohort included 28 girls (16 SVcPACNS, 12 APcPACNS) and 35 boys (3 SVcPACNS, 32 APcPACNS), median age at diagnosis was 8.1 years; SVcPACNS patients were older at diagnosis (9.8 vs. 7.5 years). At diagnosis, SVcPACNS patients present significantly more commonly with seizures(79%, p<0.05) and acute behaviour change (47% p<0.05), while hemiparesis was more frequently seen in APcPACNS (91%,p<0.05). Outcome: Overall, the mean FSIQ was 93 (52–132). The mean FSIQ in SVcPACNS was 82 (54–119) and was significantly lower than in APcPACNS, 97 (52–132) (p<0.05). Abnormal FSIQ scores (<85) were seen in 53% of the SVcPACNS and 27% of APcPACNS patients. Children with SVcPACNS had lower scores than APcPACNS in the subdomains of verbal comprehension, working memory and processing speed (p<0.05). Prediction model: Children with SVcPACNS and with seizures were at the highest risk of cognitive deficits.

Conclusion: Children with cPACNS carry significant disease burden. The inflammation causes drastically impaired cognitive functioning including comprehension, processing speed and memory deficits. Children with SVcPACNS and in particular those presenting with seizures are at the highest risk for adverse cognitive outcome. Early rehabilitation interventions have to be tailored to this high risk group.

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Clinicopathologic Correlates for Activity and Damage of Lupus Nephritis in Childhood-Onset Systemic Lupus Erythematosus. Ravi Nunna[1], Rina Mina[1], Michael Bennett[2], Shannen Nelson[3], Jessica Hummel[4], Prasad Devarajan[2], David Witte[3] and Hermine I. Brunner[3]. [1]Cincinnati Children's Hospital Medical Center/University of Cincinnati, Cincinnati, OH, [2]Cincinnati Children's Med Ctr, Cincinnati, OH, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: High AI activity (AI), tubulointerstitial (TI), and chronicity index (CI) scores from renal biopsy may predict poor renal outcomes in lupus nephritis (LN) in childhood-onset systemic lupus erythematosus (cSLE). Our aim is to evaluate the relationship between histologic evidence of renal disease activity and damage of LN with conventionally used biomarkers in cSLE.

Methods: Biopsy specimens of 18 cSLE patients were rated by a single nephropathologist for the AI, TI, and CI. Using logistic regression, the relationships between the biomarkers and high scores for AI (≥ 7), high CI (≥ 3), and high TI (≥ 4) were evaluated. Biomarkers evaluated include serum creatinine, creatinine clearance, urine sediment, proteinuria, albumin, blood pressure, anti-ds DNA antibody, C3, C4, sedimentation rate, and blood urea nitrogen (BUN); these were obtained on the day of renal biopsy to 30 days after.

Results: Patient's mean age $\pm$ SD was 14.1 $\pm$ 2.7 years. LN class distribution was as follows: II (28%), III (17%), IV (50%), and III plus IV (6%). All were positive for anti-ds DNA antibody. Only elevated BUN (odds ratio=14, 95% CI=1.2–156, p-value=0.05) was significantly associated with high TI score. None of the biomarkers were significantly associated with high AI and high CI scores using cut-offs as specified above (see Table).

Table. Relationship of high AI, high CI, and high TI scores with conventional biomarkers*

Biomarker	High AI Score N=12 Odds ratio	P-value	High CI Score N=4 Odds ratio	P-value	High TIAI Score N=10 Odds ratio	P-value
Systolic blood pressure	1.10 (0.98–1.17)	NS	1.03 (0.96–1.10)	NS	1.04 (0.97–1.12)	NS
Diastolic blood pressure	1.16 (0.99–1.36)	NS	1.02 (0.91–1.14)	NS	1.02 (0.92–1.13)	NS
Hematuria (> 5 RBC/ hpf)	0.67 (0.08–5.68)	NS	2.22 (0.25–20.17)	NS	1.29 (0.16–10.45)	NS
Pyuria (> 5 WBC/hpf)	1.00 (0.13–7.99)	NS	0.67 (0.08–5.68)	NS	1.40 (0.20–10.03)	NS
Urine protein to creatinine ratio	2.02 (0.88–4.78)	NS	27.03 (0.22–990)	NS	1.60 (0.87–2.95)	NS
Albumin	0.08 (0.01–1.07)	NS	0.85 (0.09–7.98)	NS	0.38 (0.07–2.11)	NS
C3	0.90 (0.12–6.78)	NS	0.55 (0.07–4.56)	NS	0.50 (0.07–3.68)	NS
C4	2.00 (0.11–37.83)	NS	0.29 (0.01–5.66)	NS	1.25 (0.07–23.26)	NS
Sedimentation rate	1.00 (0.97–1.03)	NS	1.00 (0.97–1.03)	NS	0.98 (0.94–1.01)	NS
Serum creatinine	1.09 (0.08–14.66)	NS	9.33 (0.62–139.51)	NS	1.78 (0.13–23.52)	NS
Creatinine clearance	0.99 (0.97–1.02)	NS	1.00 (0.98–1.02)	NS	0.99 (0.96–1.01)	NS
BUN	7.00 (0.65–75.74)	NS	3.00 (0.37–24.17)	NS	14.00 (1.25–156.61)	0.05

*High AI ($\geq 7/24$), high CI ($\geq 3/12$), and high TI ($\geq 4/21$) N-number of patients, Total N=18

Conclusion: Commonly used biomarkers are poorly associated with histological features for activity and damage of LN in cSLE highlighting the need for better biomarkers that can be used in clinical care.

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Children with Probable SLE by ACR Criteria May Need More Aggressive Lupus Treatment Early in the Disease Course. Anjali Patwardhan[1], Igor Dvorchik[2] and Charles H. Spencer[1]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]Nationwide Children's Hospital, Columbus, OH

Background/Purpose: This research explores whether delay of the childhood-onset SLE (cSLE) diagnosis until 4/11 ACR criteria are met affects patient outcome negatively

Methods: Institutional Review Board approval was obtained to retrospectively review the charts of 98 SLE patients seen in the rheumatology clinic at Nationwide Children's Hospital over the past 24 years. All the patients were divided in to two groups, 'definitive cSLE' - who met the minimum 4/11 or more ACR criteria at presentation in rheumatology clinic and the 'probable cSLE' who did not meet the minimum criteria. Both the groups were assessed for disease severity, damage and gradient of damage. Appropriate statistical tests were used, i.e. Chi-Square test, Fisher's Exact test, Univariate logistic regression and Wilcoxon two-sample test were utilized. All tests were conducted in SAS 9.2

Results: Out of 98 cSLE patients, 71 % were included in definitive cSLE (DcSLE) group while 29 % were included in probable cSLE (PcSLE) group. The mean time for PcSLE group to reach DcSLE status was 20.3 months There was no difference in the ethnic distribution (p=0.7370). PcSLE were more likely to have a higher male: female ratio (p=0.032), and were older at presentation that DcSLE (p=0.045). PcSLE patients were less likely to have internal organ involvement (7.1% vs. 25.7%), were less likely to be hospitalized and receive pulse steroids (P=0.0142) or oral steroids (0.0172) at presentation. PcSLE patients were less likely to be hospitalized to receive pulse steroids ever (p=0.0628), were less likely to have renal disease ever (p=0.0653) and nervous system disease ever (p=0.0182). PcSLE was more likely to receive hydroxychloroquine (p=0.050). The organ damage was assessed using SLICC/ACR damage index at 1, 5 and 10 years post diagnosis. The maximum damage was recorded within first 5 years of the diagnosis. Initial damage was predictive of later damage. D pSLE had higher disease damage scores at 5 and 10 years. We compared the gradient between the onsets of symptoms and the development of organ damage in the two groups. The PcSLE patients had significantly higher internal organ damage gradient as compared to DcSLE (p value=0.0169)

Conclusion: In our population, PcSLE patients had a significantly high gradient of damage than the DcSLE group. In spite of D pSLE being more severe diseases ever and more diseases damage, the disease damage progression was steeper and faster in PpSLE. This may be explained by the fact that PpSLE patients received a less intense treatment regimen at presentation than DcSLE group. It may be that PcSLE patients need just as early vigorous treatment as the children with DcSLE

Disclosure: A. Patwardhan, None; **I. Dvorchik**, None; **C. H. Spencer**, None.

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Risk Factors for Poor Outcomes in Hospitalized Patients with Pediatric Systemic Lupus Erythematosus. Mary Beth F. Son[1], Victor M. Johnson[2], Mindy S. Lo[2] and Karen H. Costenbader[3]. [1]Children Hospital Boston, Boston, MA, [2]Children's Hospital Boston, Boston, MA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Disparities in care among adults with SLE are well documented. We investigated associations of demographic factors and volume of annual inpatient hospital admissions with poor outcomes, including intensive care unit admission, renal failure and in-hospital mortality, among hospitalized patients with pediatric SLE.

Methods: The Pediatric Health Information System (PHIS) is an administrative database contributed to by >40 freestanding U.S. pediatric hospitals. We queried PHIS regarding all discharges for patients aged 3–21 years with at least one ICD-9 code for SLE from Jan 2006-Sept 2011. Patient demographics, medical insurance, hospital and ICU admissions, lengths of stay, renal failure (based on ICD-9 coding), and deaths were recorded. We classified hospitals according to the volume of inpatient admissions per year, in quartiles. We used summary statistics and univariable analyses to examine demographics of hospital admissions, readmissions, and lengths of stay. We employed multivariable logistic regression analyses, controlling for patient age, sex, race, ethnicity, insurance type (private, governmental, self-pay, or none), U.S. region (Northeast, South, Midwest and West), and hospital volume to examine risk factors for adverse outcomes, including ICU admission, renal failure and in-hospital mortality.

Results: A total of 3,389 patients with 14,631 admissions were identified in the study period. 2,781 patients (82%) were female and the median age at the time of the index admission was 16 years (IQR=14–18). White and African American race each comprised nearly 37% of the patients (n=1,250 and 1,252), while 5% (n=172) were Asian. Over a quarter of patients (n=888, 26%) were Hispanic or Latino. 87% of patients (n=2,953) had insurance, with over half supported by governmental insurance (n=1876, 55%). More than a third of patients had renal disease (n=1273, 38%); however, only 0.7% (n=24) had renal failure and 0.2% (n=8) required dialysis therapy. The high volume hospitals had shorter length of stay as compared to low volume hospitals (median 2 days, IQR=1–5, vs. 3 days, IQR=1–6, p<0.001), although readmissions per patient were more frequent in the higher volume hospitals (median 2, IQR= 1–6, vs. 2, IQR=1–3, p<0.001). Ten percent of admissions included an ICU stay. Overall in-hospital mortality was low at 0.4% (n=57). In multivariable models, ICU stays were associated with age <10 years at first admission (OR=1.61 [1.16 to 2.25], p<0.05). Poor outcome, defined as renal failure and death, was strongly associated with governmental insurance (OR=2.51 [1.47 to 4.29], p<0.05).

Conclusion: In our cohort of hospitalized children with SLE, hospital volume affected length of stay and number of readmissions, but not in-hospital mortality. Governmental insurance in this group of patients was associated with renal failure and in-hospital mortality. Further studies are needed to understand the relationships of medical insurance type and hospital volume with poor outcomes, in order to address modifiable barriers to care in pediatric SLE.

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ACR Poster Session A
Pediatric Rheumatology - Pathogenesis and Genetics
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Next-Generation Sequencing of Urinary Microrna in Human Lupus Nephritis. Beatrice Goilav[1], Iddo Z. Ben-Dov[2], Irene Blanco[3], Olivier Loudig[3], Dawn M. Wahezi[4] and Chaim Putterman[3]. [1]Children's Hospital at Montefiore, Bronx, NY, [2]The Rockefeller University, New York, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Children's Hospital Montefiore, Bronx, NY

Background/Purpose: Lupus nephritis (LN) is a common manifestation of SLE associated with significant morbidity and mortality. microRNAs (miRs) are small non-coding RNAs that regulate translation and mRNA stability. Preliminary studies have reported changes in miR expression in kidney tissue, urine, and PBMC that correlated with disease activity in LN. However, use of RNA deep-sequencing methods has not been previously described. We aimed at identifying miR expression patterns in LN by RNA sequencing.

Methods: Cell-free urine supernatants from adult (n=9) and pediatric (n=4) female patients with LN were obtained at the time of active disease and during remission. Total RNA was used to prepare small RNA cDNA libraries for Illumina sequencing. Multiplexing through sample-specific 3' adapters ("bar coding") was applied to limit batch effects, labor and cost. Sequenced reads were mapped to the human genome and small RNA databases, and miRs were quantified by relative read abundance. qRT-PCR was used for quantitative validation of sequencing results.

Results: We were able to obtain reproducible profiles of miRNA from the small RNA fraction. In a paired-sample analysis comparing the number of miR sequence reads in urine of active versus inactive LN, we found significant upregulation of multiple miRNAs, including −185, −328, −378, −874, and −423. In total, we found differential expression of 19 miRs during active nephritis. A subset analysis revealed 13 miRs that were upregulated by a 400-1,000 fold change during active disease in pediatric, but not in adult samples. Differential expression of several miRs was confirmed by miRNA qRT-PCR.

Conclusion: In summary, we detected a group of miRs (most of which have not been previously described in lupus) with significantly higher presence in the urine during active LN, particularly, in pediatric patients. These miRs may represent biomarkers for disease activity or indicators of specific histologic features. Several urine miRs were previously found to be differentially expressed in immune cells, which may imply that their presence in urine originates from infiltrating rather than kidney resident cells. Finally, upregulated miRs during active LN could imply that their "protective" target genes are repressed in relapse, and that identifying the latter may reveal novel therapeutic pathways in this challenging disease.

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Cell Type Specific Transcriptome Analysis in Patients with Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis (JIA-ERA). Amita Aggarwal, Arpita Myles and Priyanka Gaur. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Background/Purpose: Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis (JIA-ERA) is the most common category of JIA seen in Asian Indians. Transcriptome analysis is a useful tool to analyse pathways involved in disease pathogenesis. Peripheral blood and synovial fluid mononuclear cells (PBMC and SFMC) analysis showed involvement of innate immune cells in

JIA-ERA.However PBMC/SFMC have variable number of different cells and that can affect interpretation. No data is available on cell type specific transcriptome analysis of blood and synovial fluid in children with JIA-ERA.

Methods: Six samples each of peripheral blood and synovial fluid were collected from patients with JIA-ERA. Blood from 6 healthy controls was also collected. Mononuclear cells were separated by density gradient centrifugation. B cells, T cells and monocytes were separated using MACS columns and purity assessed by flow cytometry. After RNA extraction and checking the quality of RNA (RIN>8) microarray was done using Illumina chips WG 12 for whole PBMC/SFMC population, T cells, B cells and monocytes. Some of the significant genes were validated by qRT-PCR.

Results: Unsupervised hierarchical clustering revealed that cell subsets could be distinguished based on their gene expression profile.No significant differences were observed between PBMC of patients and healthy controls. Comparison of SFMC and PBMC reconfirmed the results seen earlier. Results obtained with monocytes, T cells and B cells are summarized below:

Groups compared	Genes up regulated	Genes down regulated	Number of dysregulated pathways [total (significant)]	Pathways of immunological relevance
EB vs EF	776	189	19 (12)	Cell adhesion, IgA production, antigen processing, lysosomal processing
CBMO vs EBMO	821	1251	21 (12)	Cytokine signaling, TLR signaling, antigen presentation, chemokinessignaling
EBMO vs EFMO	595	512	17 (9)	Complement cascade, cytokine signaling, antigen presentation
CBTC vs EBTC	497	477	20 (6)	Cell adhesion, cytokine signaling
EBTC vs EFTC	513	342	20 (13)	Cell adhesion, antigen processing, cytokine and chemokinessignaling
CBBC vs EBBC	648	900	26 (16)	Cell adhesion, BCR signaling, leukocyte migration, antigen processing, chemokinessignalling
EBBC vs EFBC	740	915	8 (0)	

EB: ERA blood mononuclear cells, CB: control blood mononuclear cells, EF: ERA Synovial fluid mononuclear cells, Mo: CD14+ monocytes, TC: CD3+ T cells, BC: CD3-CD14-CD19+B cells

The most prominent differences were found in monocyte subset. TLR pathway was one of the major pathway identified besides antigen presentation, cytokine and chemokine signalling

Conclusion: Monocyte probably play a major role in pathogenesis of JIA-ERA and TLR signalling may be the pathway involved.

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STAT3 Plays a Central Role in NLRP3 Inflammasome-Mediated IL-1β Production and Pyronecrosis. Jehad H. Edwan[1], Tri M. Tran[1], Mones Abu-Asab[2], Raphaela T. Goldbach-Mansky[3] and Robert A. Colbert[1]. [1]NIAMS NIH, Bethesda, MD, [2]NEI NIH, Bethesda, [3]Translational Autoinflammatory Diseases Section NIAMS NIH, Bethesda, MD

Background/Purpose: Gain of function mutations in *NLRP3* cause cryopyrin-associated periodic fever syndromes (CAPS), the most severe form of which is neonatal-onset multisystem inflammatory disease (NOMID), which is characterized by recurrent episodes of systemic and organ-specific inflammation. Mutations in *NLRP3* result in self-activation, promoting inflammasome-mediated IL-1beta processing and release, and can induce cell death through a process known as pyronecrosis. Many inflammatory disease manifestations are responsive to IL-1beta inhibitors, although patients often continue to have minor disease flares in the context of infections or other stressors. The hematopoietic cells that are the major producers of IL-1beta in NOMID and mechanisms mediating IL-1beta release and pyronecrosis have not been well elucidated.

Methods: Whole blood cells from NOMID patients and controls, THP-1 monocytic cells, and stably STAT3 knock down THP-1 cells were stimulated with LPS in the presence of cathepsin B and STAT3 inhibitors, followed by ATP treatment. Supernatants were collected and incubated with IL-1beta capturing beads. Cells were fixed and permeabilized and stained with IL-1beta, CD14, CD16 and CD83 antibodies, and cells and beads were evaluated by flowcytometry. LPS stimulated cells were also evaluated using immunofluorescent and electron microscopy and western blot assays.

Results: A sub-population of monocytes characterized by CD14hi/CD16low expression, produce the majority of IL-1beta in peripheral blood in response to LPS stimulation in NOMID and control PBMCs. In NOMID patients this subpopulation of monocytes also undergoes rapid cell death following LPS stimulation alone. The cell death is temporally associated with IL-1beta release, and is consistent with pyronecrosis. In contrast, CD14hi/CD16low cells from

healthy subjects only release IL-1beta after both LPS and ATP stimulation and are relatively resistant to cell death. IL-1beta release is partially inhibited in NOMID cells by caspase-1 inhibitors, and is blocked completely by inhibitors of cathepsin B. Cathepsin B inhibitors also prevent pyronecrosis. Similar to cathepsin, STAT3 inhibitors significantly abrogated cell death and IL-1beta release in NOMID cells. STAT3 inhibition also abolished all ATP-dependent IL-1beta release and cell death in monocytes from healthy subjects. Moreover, shRNA-mediated knockdown of STAT3 in THP-1 cells completely prevented ATP dependent IL-1b release and cell death. We confirm that STAT3 associates with mitochondria, and that inhibition of STAT3 but not cathepsin B, prevents mitochondrial damage suggesting that mitochondrial STAT3 activation may be upstream of cathepsin B activation.

Conclusion: These results identify the predominant IL-1beta-producing cell population in the peripheral blood of NOMID patients and healthy contorls, and identify a novel role for STAT3 in mediating *NLRP3* effects on pyronecrosis and IL-1beta release. We suggest that cell death may contribute to IL-1beta release.

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The DEK Autoantigen Regulates Formation of Neutrophil Extracellular Traps and Zymosan Induced Arthritis in Mice. Nirit Mor-Vaknin[1], Anjan K. Saha[1], Maureen Legendre[1], Marta J. Gonzalez-Hernandez[1], M. Asif Amin[2], Bradley J. Rabquer[2], Julie M. Jorns[3], Mariana J. Kaplan[1], Barbara S. Adams[4], David A. Fox[5], Alisa E. Koch[2] and David Markovitz[1]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI, [3]Ann Arbor, MI, [4]Univ of Michigan Health System, Ann Arbor, MI, [5]Univ of Michigan Med Ctr, Ann Arbor, MI

Background/Purpose: The nuclear oncoprotein DEK is a known autoantigen associated with juvenile idiopathic arthritis (JIA) and other autoimmune diseases. DEK is actively secreted by human macrophages and serves as chemoattractant for leukocytes, including neutrophils and T cells. We have previously demonstrated that DEK and anti-DEK autoantibodies are abundant in the inflamed synovia of JIA patients. Postranslational modification, particularly acetylation, of DEK markedly increases its autoantigenicity, suggesting an active role for DEK and DEK autoantibodies in the inflamed joint. Using zymosan induced arthritis (ZIA) mouse model, we demonstrate that DEK contributes to the development of inflammatory arthritis by recruiting neutrophils to the joint. Remarkably, DEK also appeared to be required for the formation of neutrophil extracellular traps (NETs) and is detected in association with known NET markers in human neutrophils from synovial fluids of JIA patients.

Methods: We investigated the role of DEK using the ZIA mouse model, comparing 129/B6 wild type (WT) to DEK knockout (DEK KO) mice. Zymosan A from *Saccharomyces cerevisiae*, or an equal amount of sterile saline, was injected through the suprapatellar ligament into the joint cavity of WT and DEK KO mice. Inflammatory cytokines in the joint tissue homogenates were detected by ELISA. Neutrophils from healthy volunteers were purified by centrifugation over a discontinuous Histopaque gradient. Synovial fluid neutrophils from JIA patients and mouse bone marrow neutrophils were isolated in a similar manner. The Transwell system was used for chemotaxis assays. The neutrophil markers Ly6G, elastase and DEK and were detected by immunoflorescence and confocal microscopy.

Results: Significant levels of DEK were found in NETs from JIA synovial neutrophils. In the ZIA mouse model, DEK KO mice displayed significantly less inflammation in the joints compare to WT. Substantially reduced levels of pro-inflammatory cytokines were detected in zymosan injected joints from DEK KO vs. WT mice. Neutrophil migration into the injected joints was markedly lower in DEK KO vs. WT mice and DEK KO neutrophils demonstrated defects in NETs formation in response to lipopolysaccharide (LPS) and *Escherichia coli.*

Conclusion: Extracellular DEK found in the supernatant of activated primary human neutrophils serves as a chemoattractant and is important for NET formation. DEK is also detected in NETs produced by synovial fluid neutrophils of JIA patients. These results demonstrate that the nuclear autoantigen DEK plays a major role in the development of inflammation in the joints, suggesting an active role for DEK in the development of JIA as well as other autoimmune diseases.

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Blood-Based Biomarkers of Neurocognitive Dysfunction in Childhood-Onset Systemic Lupus Erythematosus. Hermine I. Brunner[1], Jessica Hummel[1], Shannen Nelson[2], Erin C. Thomas[3], Jennifer L. Huggins[1], Megan L. Curran[4], Jun Ying[5] and Marisa S. Klein-Gitelman[6]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital, Cincinnati, OH, [3]Anne and Robert C Lurie Hospital, Feinstein School of Medicine, Northwestern University, Chicago, IL, [4]Division of Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]University of Cincinnati, Cincinnati, OH, [6]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

Background/Purpose: Several brain-reactive autoantibodies in the blood have been inconsistently associated with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) in adults but very little is known whether such findings are relevant to neurocognitive dysfunction (NCD) with childhood-onset systemic lupus erythematosus (cSLE). NCD with cSLE often impairs working memory, visuoconstructional (VC) ability, attention and working speed. The objective of this research was to examine the relationship between select candidate biomarkers in the serum for their usefulness in the identification of cSLE-associated NCD.

Methods: As part of a larger study, the cognitive ability of 38 patients with cSLE was studied using the *cSLE Battery of Neuropsychological Tests* (Ross et al; 2008) that probes cognitive domains typically impaired with cSLE, with overall cognitive performance expressed as the average z-scores of the standardized tests (mean in healthy reference population= 0; standard deviation= 1). Serum levels of neutrophil gelatinase associated lipocalin (NGAL; involved in blood-brain barrier integrity), as well as auto- antibodies to NR2 (involved in neuronal plasticity and apoptosis); phospholipids (aPL) (associated among others with white matter hyperdensities on magnetic resonance imaging and thrombosis), and ribosomal-P (associated with depression and seizure; proposed involvement in neuronal apoptosis) were measured using commercially available standard assays.

Results: The overall level of cognitive function was significantly worse in those with cSLE who tested positive for aPL-antibodies as compared to aPL-antibody negative cSLE patients [mean+SE; -2.44 ± 1.13 vs. -0.38 ± 0.61; p= 0.041]. We found aPL antibodies to be associated with a 5-fold increased risk of NCD (40% vs. 12%; p =0.08). We also found anti-ribosomal P antibodies present in 67% (24/38) of the cSLE patients. As shown in **Figure 1,** those who tested positive for anti-ribosomal P antibodies had a significantly lower overall cognitive functioning vs. cSLE patients without anti-ribosomal P antibodies (p= 0.0006). Conversely, we found serum levels of anti-NR2 antibodies to be unrelated to cognitive ability. The same was true for serum levels of NGAL.

Cognitive Ability with cSLE

y=sum of z-score with tests probing attention, working meory, processing speed and VC ability
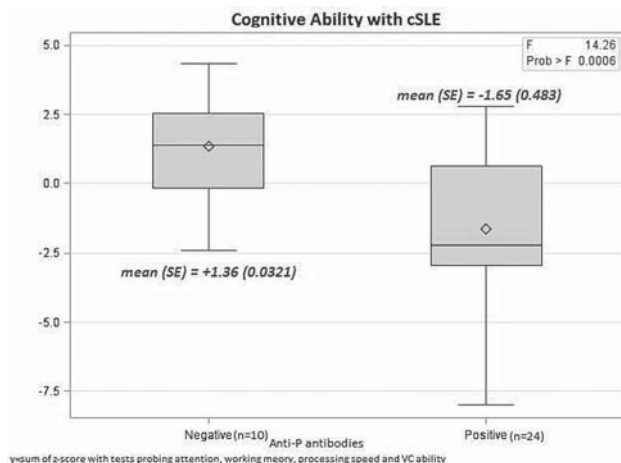
Conclusion: Presence of aPL and anti-ribosomal P antibodies in the serum is associated with the level of cognitive ability of children with cSLE, providing proof-of principle that discovery of biomarkers for NPSLE in the blood is feasible. Additional research is necessary to assess whether the duration of antibody exposure and/or the combination of antibodies are suited to reliably identify patients who suffer from cSLE-associated NCD or are at risk of developing it.

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Epigenetic Changes in Fibrosis and Myocyte Repair Genes May Contribute to Pathogenesis in Monozygotic Twins Discordant for Cardiac Manifestations of Neonatal Lupus. Paula S. Ramos[1], Timothy D. Howard[2], Miranda C. Marion[2], Satria Sajuthi[2], Robert M. Clancy[3], Jill P. Buyon[3] and Carl D. Langefeld[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]New York University School of Medicine, New York, NY

Background/Purpose: Cardiac manifestations of neonatal lupus (cardiac-NL) which comprise conduction defects and cardiomyopathy, occur in fetuses exposed to maternal anti-Ro antibodies and carry a case fatality rate of nearly 18%. The discordance rate for monozygotic (MZ) twins suggests a role for epigenetic factors in addition to maternal autoantibodies, genetic and environmental influences. Analysis of MZ twins represents the ideal design to dissect the role of epigenetic factors. Notably, the onset of cardiac-NL can occur within one week of a normal ultrasound and is most often detected between 18–24 wks gestation, and hence, there is very limited confounding due to environmental cues that might occur over decades, as for discordant MZ twins with other autoimmune diseases. As such, the analysis of these twins early in life has unprecedented value to test for disease-associated epigenomic variation and reveal potential metastable epialleles. This study examines an axis of heritable genetic information in human genomic DNA involving cytosine methylation and addresses the hypothesis that susceptibility to cardiac-NL is influenced by epigenetic variability.

Methods: Genomic DNA was extracted from two Caucasian monochorionic MZ male twin pairs who were discordant for cardiac-NL (advanced block). The source of one pair was umbilical cord blood and the other was saliva from 18-month-olds. DNA methylation profiling was performed using the Illumina Infinium HumanMethylation450 BeadChip. Probes with a detection P-value<1.0E-05 were excluded. A paired *t*-test on the probe-specific β-values was computed and significance was assessed as the intersection of meeting an FDR threshold and mean DNA methylation difference $(\Delta\beta)>|0.10|$.

Results: Significant hypomethylation in both affected twins was observed in genes with fibrosis and myocyte repair functions. With regard to fibrosis, these include protein phosphatase 1A (PPM1A; $\Delta\beta=-0.11$, P<1.E-15) a SMAD phosphatase, and a disintegrin and metalloproteinase domain 12 (ADAM12; $\Delta\beta=-0.13$, P<1.E-15), an enhancer of TGFb1 transcription. For myocyte repair, included are the LIM-protein 1 gene (FHL1; $\Delta\beta=-0.14$, P=1.2E-30) implicated in cardiomyopathy, the myocardin-like 2 gene (MKL2; $\Delta\beta=-0.13$, P<E-100) involved in cardiovascular morphogenesis, and the mitoferrin-2 gene (SLC25A28; $\Delta\beta=-0.33$, P=1.2E-78), implicated in hemoglobin biosynthesis. The most significant hypermethylated site is located in the membrane associated guanylate kinase gene MAGI2 $(\Delta\beta=0.40$, P=1.2E-39).

Conclusion: To our knowledge, this is the first study analyzing global disease-associated methylation patterns in early-life tissue of MZ discordant twins. The data support an epigenetic mechanism underpinning cardiac-NL discordance in MZ twins despite identical DNA sequence and exposure to maternal autoantibody via a shared placenta.

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Transcriptome and Surface Phenotype Analyses Suggest an Alternatively Activated (M2) Function for Hemophagocytes. Scott W. Canna[1], Ana Patrícia Costa Reis[2], William E. Bernal[3], Kathleen E. Sullivan[3], Michele E. Paessler[1] and Edward M. Behrens[1]. [1]Childrens Hospital of Philadelphia, Philadelphia, PA, [2]Childrenxs Hospital of Philadelphia, Philadelphia, PA, [3]Children's Hospital of Philadelphia, Philadelphia, PA

Background/Purpose: Hemophagocytes (HPCs) are activated macrophages identified in situ by having engulfed other hematopoietic cells. HPCs are rarely seen in normal bone marrow, but are abundant in a variety of cytokine storm syndromes. HPCs are the pathologic hallmarks of two related

diseases: Macrophage Activation Syndrome (MAS) and Hemophagocytic Lymphohistiocytosis (HLH). The function of the HPC is controversial. Some evidence suggests HPCs are inflammatory and pathogenic, while other evidence supports a housekeeping or anti-inflammatory role for these cells by pointing out their absence in some patients with overt MAS or HLH and their high expression of scavenger receptors like CD163. However, no study has yet attempted to directly phenotype these cells. Using two distinct approaches, we now show that HPCs display an M2, or anti-inflammatory phenotype.

Methods: Splenic HPCs induced in an animal model of MAS utilizing repeated Toll-like Receptor 9 (TLR9) stimulation in the context of IL-10 receptor blockade were isolated by single cell laser capture microdissection with the assistance of a board certified hematopathologist (MP). Gene expression levels of these cells were measured using microarray and compared to those of laser-captured resting splenic macrophages. Highly differentially expressed genes were verified using quantitative RT-PCR. Differential regulation of pre-determined gene sets was analyzed using a Gene Set Enrichment Analysis (GSEA). Additionally, bone marrow biopsies from patients with MAS or HLH noted to have excessive hemophagocytosis as part of their clinical evaluation were subjected to immunohistochemistry for markers of classical (M1) or alternative (M2) activation and scored by a blinded hematopathologist (MP).

Results: Of 6 treatment and 6 control samples, the RNA of 4 samples in each group were of sufficient quality for analysis. The gene sets meeting statistical significance for upregulation in HPCs were those related to the proteasome, M2 gene regulation, cytoskeleton regulation, and Nod-like receptor signaling. The gene set for M1 gene regulation was not found to be different between HPCs and resting macrophages. Human bone marrow biopsies stained for the mannose receptor and M2 marker CD206 showed HPCs with a membrane-bound staining pattern. HPCs with such staining for the M1 differentiation marker CD64 were very rarely identified.

Conclusion: For the first time, we have described the functional program of *in situ* HPCs as alternatively activated (M2) and potentially anti-inflammatory. This raises questions about elimination of HPCs as a therapeutic rationale, and supports future investigations into optimal treatment strategies for hemophagocytic diseases.

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Pediatric Lupus Nephritis: Micrornas–Macro Inflammation. Patrícia Costa Reis, Pierre Russo and Kathleen E. Sullivan. Children's Hospital of Philadelphia, Philadelphia, PA

Background/Purpose: New biomarkers to guide clinical management of lupus nephritis (LN) patients are highly desirable, since the histopathologic classification currently in use is an unreliable predictor of treatment response and disease outcome. MicroRNAs have emerged as a new class of biomarkers in several rheumatic diseases, but their role in LN is still unclear. These noncoding RNAs have a post-transcriptional regulatory effect, playing a key role in fundamental cellular processes and influencing immunologic function, especially in the maintenance of immunological tolerance. Perturbations in the microRNA expression patterns can, therefore, lead to pathological conditions, including autoimmune diseases, like systemic lupus erythematosus (SLE).

MicroRNA studies performed on serum, urine and peripheral blood mononuclear cells have revealed distinct profiles in SLE patients. Further studies are thus necessary to identify a specific LN microRNA signature, which will illuminate SLE pathogenesis and may lead to novel LN biomarkers.

The main aim of this study is to identify the microRNA signature in kidneys of children with LN. The ultimate goal is to find microRNAs associated with disease activity and prognosis that may guide clinical practice.

Methods: Paraffin-embedded tissue samples from children with LN, kidney biopsies performed on kidney donors, and post-streptococcal glomerulonephritis were used for microRNA extraction with Quiagen™ miRNeasy kit. Direct digital detection of microRNAs, through molecular barcodes, was performed with the nCounter® human miRNA assay kit.

Results: The microRNA signature can clearly differentiate samples from normal kidneys of those affected with LN. From over 700 human microRNAs analyzed, miR-26a and miR-30b were identified as being associated with pediatric LN. A significant decrease in the expression of these microRNAs

was found in LN class IV, when compared to normal tissue, post-streptococcal glomerulonephritis, LN class III or LN class V.

Conclusion: An altered microRNA signature can lead to the dysregulation of gene expression and broadly alter cell behavior. The study of microRNAs can, therefore, improve our understanding of the pathogenesis of several diseases. With this project, miR-26a and miR-30b were identified for the first time as components of the microRNA signature in kidneys of children with LN. These microRNAs are predicted to regulate the expression of genes that interfere with cell cycle, apoptosis and immune regulation, including IL18R1, which has been implicated in the pathogenesis of nephritis and tissue inflammation and HDAC9, which acts as an epigenetic switch in effector T cell-mediated systemic autoimmunity. This study has provided new insights for LN pathogenesis and for the development of new biomarkers.

Disclosure: **P. Costa Reis**, None; **P. Russo**, None; **K. E. Sullivan**, None.

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The Interleukin-10 (IL-10) Producing Regulatory B Cell ("B10 cell") Compartment Expands with Disease Activity in Juvenile Dermatomyositis (JDM) and Pediatric-Onset Systemic Lupus Erythematosus (pSLE). Ioannis Kalampokis, Jeffrey A. Dvergsten and Thomas Tedder. Duke University Medical Center, Durham, NC

Background/Purpose: pSLE and JDM are multisystem inflammatory diseases, whereas juvenile idiopathic arthritis (JIA) is typically an organ-limited disease. "B10 cells", a rare subset of human B cells with anti-inflammatory properties characterized by their functional capacity to produce IL-10, originate from a progenitor pool ("B10pro cells") and expand in response to inflammation. We conducted the first pediatric study of B10/B10pro cells with the primary objective of evaluating whether peripheral blood B10/B10pro cell frequencies expand and correlate with disease activity in the 3 most common pediatric autoimmune diseases.

Methods: Following institutional review board approval, pediatric (1–16 years old) subjects with JIA, JDM or pSLE were recruited from the outpatient pediatric rheumatology clinic and the inpatient unit at Duke Children's Hospital. Subjects with systemic-onset JIA, rituximab therapy within 1 year, current intercurrent illness, or major surgical procedure within 3 months were excluded. For analysis, two groups were defined (JDM/pSLE vs. JIA) and assessed for disease activity (inactive vs. active). After obtaining informed consent, a single blood sample from each subject was analyzed by flow cytometry. B10 and B10+B10pro cell numbers were determined by surface CD19 and intracellular IL-10 staining following *ex vivo* incubation with lipopolysaccharide (LPS) or CpG oligonucleotides in the absence (5 hour assay measuring B10 cells) or presence (48 hour assay measuring B10+B10pro cells) of recombinant CD40L. A visual analog scale (VAS) score was used to estimate disease activity. Non-parametric tests were used for statistical analysis due to small sample size. B10 and B10+B10pro frequencies were compared using the Mann-Whitney U test. VAS score correlations were performed by Spearman's rho. Due to multiple comparisons, significance was defined as $p<0.01$.

Results: 33 patients were recruited, 17 with JIA (8 inactive, 9 active) and 16 with JDM/pSLE (8 inactive, 8 active). No significant differences in the frequencies of B10 or B10+B10pro cells were observed in JIA between active and inactive subjects. Significant differences were observed during disease remission between JIA and JDM/pSLE, with the later group having lower frequencies of B10 ($p=0.0003$) and B10+B10pro ($p=0.0006$) cells in response to CpG. Within the JDM/pSLE group, there were significant differences in the frequencies of B10 cells in response to LPS ($p=0.0030$) and CpG ($p=0.0019$), and B10+B10pro cells in response to CpG ($p=0.0006$) between active and inactive subjects. Significant positive correlations with disease activity were observed in the JDM/pSLE group in the B10 responses to LPS ($p=0.0034$, rho=0.685) and CpG ($p=0.0036$, rho=0.682), and the B10+B10pro responses to CpG ($p=0.000001$, rho=0.915).

Conclusion: During disease remission, patients with JDM/pSLE have lower frequencies of B10 and B10+B10pro cells compared to patients with JIA. B10 and B10+B10pro cell frequencies increase with active disease in JDM/pSLE (but not in JIA); the magnitude of this expansion highly correlates with disease activity. Thereby, peripheral blood B10+B10pro cell expansion may represent a novel disease activity marker in patients with JDM/pSLE.

Disclosure: **I. Kalampokis**, None; **J. A. Dvergsten**, None; **T. Tedder**, None.

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Fatty Acid Profiling: Potential New Biomarkers in Juvenile Idiopathic Arthritis (pilot study). Weng Tarng Cham[1], Enzo Ranieri[2], Janice Fletcher[2] and Christina A. Boros[3]. [1]Women's and Children's Hospital, North Adelaide, SA 5006, Australia, [2]SA Pathology, North Adelaide, SA 5006, Australia, [3]University of Adelaide/Women's and Children's Hospital, Adelaide, Australia

Background/Purpose: The prostanoids are a family of biologically active lipids derived from the 20-carbon essential fatty acids (LCPUFA) all of which are involved in the inflammatory response. ω3-fatty acids, Eicosapentaenoic acid (EPA) and Docosapentaenoic acid (DPA), are anti-inflammatory, whilst the ω6-fatty acid, Arachidonic acid (AA), metabolites: 15-S-Hydroxyeicosatetraenoic acid [15(S)-HETE], Thromboxane B2 (TXB2), Prostaglandin F2α (PGF2α) and 6-Keto-Prostaglandin F1α (6-k-PGF1α) are pro-inflammatory. Liquid Chromatography Tandem Mass Spectrometry (LC-MSMS) allows contemporaneous analyses of multiple prostanoids with high accuracy using small blood samples. This method has never been used previously to measure these analytes in JIA and may find biomarkers which can help us predict disease activity and treatment response.

We aim to measure prostanoid profiles in patients with JIA using LC-MSMS.

Methods: Samples from 55 JIA patients (26 polyarthritis, 29 oligoarthritis) and 6 healthy siblings of JIA patients were collected onto specially prepared filter papers and analysed using LC-MSMS.

Results: The M:Fratio was 1:3, the average age at study entry (9.4 ± 5.0 y), average disease duration (44.7 ± 41.5 m), with 83.6% receiving treatment with NSAID, and 38.2% with Methotrexate (MTX).

15(S)-HETE levels were significantly higher in oligoarthritis than polyarthritis patients (Mann-Whitney U, p=0.046). Spearman rank correlations showed that MTX treatment correlated positively with 15(S)-HETE (p=0.01, R=0.493) but correlated negatively with TXB2 (p=0.004, R=−0.514), Leflunomide treatment correlated negatively with PGF2α (p=0.022, R=−0.448), Etanercept treatment correlated negatively with PGF2α, (p=0.013, R=−0.481) and correlated positively with 6-k-PGF1α (p=0.0216, R=0.451).

Stepwise linear regression showed TXB2 levels to be significantly higher in healthy controls compared to JIA patients (p=0.011) and JIA patients on MTX had significantly higher EPA levels (p=0.017) and lower AA:EPA ratios (p=0.011). 6-k-PGF1α level increased by 0.37nM in JIA patients with every extra month of disease (p=0.022) and DPA level reduced by 0.09nM with every point rise in Juvenile Arthritis Disease Activity Score (p=0.032).

Conclusion: We have been able to determine prostanoid profiles from whole blood using LC-MSMS in patients with JIA. Treatment with MTX increases the levels of anti-inflammatory prostanoids. This relationship has not been demonstrated previously.

NSAIDs are the mainstay of treatment in patients with JIA and resulted in lower TXB2 levels compared to healthy controls.

15(S)-HETE has been identified as a potential biomarker of disease activity in JIA

However, disease progression appears to continue in JIA despite treatment as shown by the elevation in 6-k-PGF1α levels. We are currently performing longitudinal analyses to elucidate the relationships between prostanoid profiles and disease subtype, activity and medication response.

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Replication Analysis of Non-HLA Gene Variants with Prior Evidence of Association with Juvenile Idiopathic Arthritis. Justine Ellis[1], Raul Chavez[1], Anne-Louise Ponsonby[1], Angela Pezic[1], Roger Allen[2], Jonathan Akikusa[2] and Jane Munro[2]. [1]Murdoch Childrens Research Institute, Parkville, Australia, [2]Royal Childrens Hospital, Parkville, Australia

Background/Purpose: Over the last few years, there have been numerous reports of associations of single nucleotide polymorphisms (SNPs) at various genetic loci with juvenile idiopathic arthritis (JIA). However, apart from a select few variants, the majority of these association findings would benefit from further replication in independent populations to confirm their involvement in disease risk. We examined a total of 60 SNPs in or around 44 genes previously examined by others for association with (total) JIA in the ChiLdhood Arthritis Risk factor Identification sTudY (CLARITY), a new Australian collection of cases and healthy child controls.

Methods: DNA from a total of 324 JIA cases (mean age 9.7 years, 67.3% female) and 568 controls (mean age 7.8 years, 40.7% female) was available for genotyping. Genes and SNPs were chosen based on reports by others over the last five years, and included *PTPN22* (rs 2476601), *IL2RA* (rs706778), *ATXN2* (rs653178), *C12orf30* (rs17696736), *C3orf1* (rs4688011), *JMJDC1* (rs12411988), *PTPN2* (rs7234029), *STAT4* (rs7574865), *TRAF1/C5* (rs2900180), and *VTCN1* (rs12046117). SNPs were genotyped using the Sequenom MassARRAY system. Allelic and genotypic association analyses were performed using PLINK. A p < 0.05, along with an odds ratio (OR) in the same direction as the original association report(s) was taken as evidence of replication of the prior findings.

Results: Following data QC, 292 cases and 497 controls were analysed. Evidence of replication was generated for *PTPN22* (Allelic OR = 1.67; 95% CI 1.16, 2.40; p (best test) = 0.006), *ATXN2* (OR = 1.54; 95% CI 1.25, 1.89; p = 3.8×10^{-5}), *C12orf30* (OR = 1.47; 95% CI 1.20, 1.81, p = 0.0002), *C3orf1* (OR = 1.32; 95% CI 1.03, 1.69; p = 0.030), *STAT4* (OR = 1.38; 95% CI 1.10, 1.74; p = 0.003), and *TRAF1/C5* (OR = 1.24; 95% CI 1.00, 1.53; p = 0.021). We were unable to confirm association with *IL2RA*, *PTPN2*, and *VTCN1*; however, this may reflect a lack of statistical power since ORs were directionally consistent with previous reports. Results for *JMJDC1* were neither statistically significant, nor were the ORs directionally consistent. Restriction of the dataset to 204 cases and 248 controls in whom Caucasian ancestry of all four grandparents could be confirmed did not materially alter these findings.

Conclusion: We have provided further confirmation of association of (total) JIA with a number of genes, adding to the growing international data that is clarifying the underlying genetic risk component of this serious childhood disease. Pooling of currently available candidate gene data for meta-analyses, and pooling of samples for large genome-wide association study efforts will likely provide further clarity. Future work to better define the overall JIA risk profile should also include an examination of gene-gene and gene-environment interactions.

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Gamma Interferon-Induced Protein-10 (IP-10) As a Potential Biomarker for Disease Activity in Pediatric Localized Scleroderma. Katherine Kurzinski[1], Carol A. Feghali-Bostwick[2], Christina Kelsey[1], Kelsey Magee[2] and Kathryn S. Torok[1]. [1]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Pediatric localized scleroderma (LS) is an autoimmune disease affecting the skin and underlying tissue. Cutaneous findings assist in categorizing the patients into active or inactive (predominately damage) disease states. The biopsies of those with active disease features demonstrate a lymphocytic infiltrate. T helper (Th) lymphocytes and their associated cytokines have been identified in the tissue and in the peripheral circulation of patients with scleroderma. This study was designed to evaluate the levels of Th-associated cytokines and chemokines at various stages of LS, with a particular focus on active disease and its clinical parameters.

Methods: Plasma samples were obtained from 69 pediatric LS patients and 71 healthy pediatric controls. Several cytokines and chemokines were evaluated using a Millipore luminex panel comparing LS to healthy controls, with additional analysis predetermined to be dedicated to LS patients with active disease. LS patient samples were categorized as either clinically "active" or "inactive" at the time of collection. Active disease was defined by the presence of new, enlarging, erythematous lesions and a Physician Global Assessment of Disease Activity (PGA-A) score greater than zero. Nonparametric statistics were employed comparing cytokine levels between LS and healthy groups and between active and inactive LS patients ($\alpha = 0.05$).

Results: IP-10 levels were significantly elevated in LS patients compared to healthy controls, $u = 4.785$, $p <.001$, as well as in LS patients with active disease compared to inactive disease, $u = 3.305$, $p =.001$ (Figure). Also, IP-10 levels were elevated in patients with new lesions, a variable strongly reflecting disease activity (trending toward significance, $p =.057$). IP-10 levels were also significantly correlated to two well accepted disease activity outcome measures, the modified Localized Scleroderma Skin Severity Index (mLoSSI) ($\rho = 0.343$, $p = 0.004$), a quantitative assessment of disease activity, and the PGA-A ($\rho = 0.450$, $p < 0.001$).

	Healthy	LS (overall)	Active LS	Inactive LS
	n = 71	n = 69	n = 30	n = 39
Median (pg/mL)	445.8	1140.34	2087.25	880.5
IQR (pg/mL)	246.0–833.5	497.9–2495.7	956.6–3099.0	447.8–1289.8
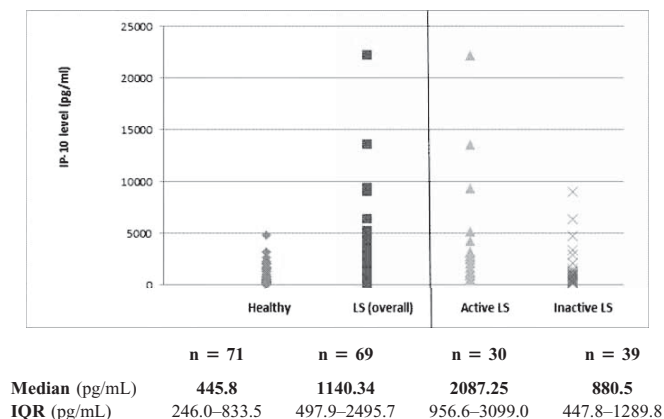
Conclusion: Our previous serologic analyses as well as studies in systemic sclerosis have identified gamma interferon-induced protein-10 (IP-10) as a potential molecule of interest in the pathogenesis of scleroderma. An elevation of plasma IP-10 levels in pediatric localized scleroderma (LS) when compared to those of healthy controls further supports these findings. Analyses demonstrating IP-10 elevation in patients with active disease and correlations with valid activity measures suggest that IP-10 may be a biomarker for disease activity in LS.

Disclosure: **K. Kurzinski**, None; **C. A. Feghali-Bostwick**, None; **C. Kelsey**, None; **K. Magee**, None; **K. S. Torok**, None.

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Evaluation of Anti-Citrullinated Type II Collagen and Anti-Citrullinated Vimentin Antibodies in Patients with Juvenile Idiopathic Arthritis. Brooke Gilliam, Anil K. Chauhan and Terry L. Moore. Saint Louis University, St. Louis, MO

Background/Purpose: Several studies have identified anti-cyclic citrullinated peptide (CCP) antibodies as an important indicator for destructive disease in patients with juvenile idiopathic arthritis (JIA). This is of particular significance in patients with IgM rheumatoid factor (RF)-positive polyarticular JIA, which closely resembles rheumatoid arthritis (RA). While the role of anti-CCP antibodies in RA and JIA is better understood, the identity of the target proteins of this modification remains undefined. We evaluated serum from patients with JIA to investigate the presence of anti-citrullinated type II collagen (CII) and anti-citrullinated vimentin antibodies, and their association with RF and anti-CCP antibody isotypes and previously measured anti-citrullinated fibrinogen and α-enolase antibodies. Our aim was to determine the prevalence and significance of previously identified target proteins for citrullination and elucidate their role in the disease process of JIA.

Methods: Sera were obtained from 96 patients with various JIA subtypes, 19 systemic lupus erythematous (SLE) patients, and 10 healthy children. All sera were measured for antibodies against citrullinated and native CII and vimentin (vim1–16, vim59–74) by ELISA. Results were compared to anti-CCP antibody and RF isotypes, and our previously measured anti-citrullinated fibrinogen antibodies and anti-citrullinated α-enolase antibodies, in addition to erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Results: Mean levels of all anti-citrullinated antibodies were significantly higher in JIA patients than in healthy children ($p<0.05$). The most commonly detected citrullinated autoantibodies were anti-citrullinated CII (33.3%) and anti-citrullinated fibrinogen antibodies (32.3%), with the least commonly detected being anti-citrullinated α-enolase antibodies (9.4%). One IgM RF-positive polyarthritis patient was positive for all tested anti-citrullinated autoantibodies. The most common combination of positivity was anti-citrullinated CII and anti-citrullinated fibrinogen antibodies in 7 patients. Twenty-two subsets of patients were identified based on their anti-citrullinated autoantibody profile, not including anti-CCP antibody isotypes. Anti-citrullinated CII antibodies correlated significantly with all other citrullinated autoantibodies ($p<0.05$). Anti-citrullinated vimentin 1–16 and 59–74 demonstrated strong correlation with each other, and both correlated significantly with anti-citrullinated fibrinogen and alpha-enolase antibodies ($p<0.05$). Anti-citrullinated vimentin 1–16 antibodies also correlated with ESR ($p<0.05$). When including the group of citrullinated autoantibodies in

logistic regression analysis, anti-citrullinated fibrinogen remained as the only autoantibody significantly correlated with joint damage ($p<0.05$).

Conclusion: This study demonstrates that multiple citrullinated epitopes can be detected in JIA patients, especially those patients with polyarticular disease. Anti-citrullinated fibrinogen antibodies remained as the single citrullinated autoantibody to correlate significantly with joint damage.

Disclosure: **B. Gilliam**, None; **A. K. Chauhan**, None; **T. L. Moore**, None.

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Glycosylation of Vitamin D Binding Protein Reduced in Juvenile Idiopathic Arthritis Patients At Risk of Disease Extension. David S. Gibson[1], Sorcha Finnegan[2], Gwen Manning[3], Mark Duncan[4], Stephen R. Pennington[5], Terry L. Moore[6] and Madeleine Rooney[7]. [1]Arthritis Research Group, Queens University Belfast, Belfast, United Kingdom, [2]Queen's University, Belfast, Belfast, United Kingdom, [3]Proteome Research Centre, University College Dublin, Dublin, Ireland, [4]Division of Endocrinology, University of Colorado, Denver, [5]UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin 4, Ireland, [6]Saint Louis University, St. Louis, MO, [7]Queens University Belfast, Belfast, United Kingdom

Background/Purpose: Juvenile idiopathic arthritis (JIA) comprises a poorly understood group of chronic, childhood onset, autoimmune diseases with variable clinical outcomes.We investigated whether profiling of the synovial fluid (SF) proteome by a fluorescent dye based, two-dimensional gel (DIGE) approach could distinguish the subset of patients in whom inflammation extends to affect a large number of joints, early in the disease process. The post-translational modifications to candidate protein markers were verified by a novel deglycosylation strategy.

Methods: SF samples from 57 patients were obtained around time of initial diagnosis of JIA. At 1 year from inclusion patients were categorized according to ILAR criteria as oligoarticular arthritis (n=26), extended oligoarticular (n=8) and polyarticular disease (n=18). SF samples were labeled with Cy dyes and separated by two-dimensional electrophoresis. Multivariate analyses were used to isolate a panel of proteins which distinguish patient subgroups. Proteins were identified using MALDI-TOF mass spectrometry with vitamin D binding protein (VDBP) expression and siaylation further verified by immunohistochemistry, ELISA test and immunoprecipitation. Candidate biomarkers were compared to conventional inflammation measure C-reactive protein (CRP). Sialic acid residues were enzymatically cleaved from immunopurified SF VDBP, enriched by hydrophilic interaction liquid chromatography (HILIC) and analysed by mass spectrometry.

Results: Hierarchical clustering based on the expression levels of a set of 23 proteins segregated the extended-to-be oligoarticular from the oligoarticular patients. A cleaved isoform of VDBP, spot 873, is present at significantly reduced levels in the SF of oligoarticular patients at risk of disease extension, relative to other subgroups ($p<0.05$). Conversely total levels of vitamin D binding protein are elevated in plasma and ROC curves indicate an improved diagnostic sensitivity to detect patients at risk of disease extension, over both spot 873 and CRP levels. Sialysed forms of intact immunopurified VDBP were more prevalent in persistent oligoarticular patient synovial fluids.

Conclusion: The data indicate that a subset of the synovial fluid proteome may be used to stratify patients to determine risk of disease extension. Reduced conversion of VDBP to a macrophage activation factor may represent a novel pathway contributing to increased risk of disease extension in JIA patients.

Disclosure: **D. S. Gibson**, None; **S. Finnegan**, None; **G. Manning**, None; **M. Duncan**, None; **S. R. Pennington**, None; **T. L. Moore**, None; **M. Rooney**, None.

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Immune Response to Porphyromonas Gingivalis Citrullinated α-Enolase Cross-Reacts with Human α-Enolase in Polyarticular JIA Patients. Peggy Lee[1], Rebecca Howsmon[2], Claire Murphy[2], Sarah Ringold[1] and Anne M. Stevens[1]. [1]University of Washington, Seattle, WA, [2]Seattle Children's Research Institute, Seattle, WA

Background/Purpose: Antibodies recognizing cyclic citrullinated peptides (CCP) are highly specific for rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (poly JIA), and may both predict and contribute to early onset and an aggressive disease course. Risk factors for RA, including the HLA-DRB1 shared epitope (SE) and smoking, are associated with higher levels of anti-CCP antibodies. It is unknown what the natural targets of

anti-CCP are, or how they are generated. P. gingivalis, associated with gingivitis and periodontitis, expresses a citrullinated protein, α-enolase, with homology to human α-enolase, and thus is a strong candidate for the autoantigen bound by anti-CCP antibodies. The P. gingivalis α-enolase may serve as a link between oral inflammation induced by P. gingivalis and arthritis. The pathogenesis of JIA may thus involve molecular mimicry between epitopes from citrullinated bacterial and human, triggering autoimmunity in genetically susceptible individuals.

Methods: Anti-citrullinated enolase peptide antibodies (anti-CEP) were quantified by ELISA in plasma from 20 RF+ poly JIA patients ages 7.1–18.5 years and 20 age- and sex-matched controls. Target peptides were selected based on previously identified immunodominant epitopes in adult RA patients, and included *P. gingivalis* CEP citrulline- versus arginine-containing sequences and the human CEP peptide homologs. Citrullinated vimentin and citrullinated non-immunogenic CEP were negative controls. Antibodies to CCP were assayed by QUANTA Lite CCP3.1 IgG/IgA ELISA.

Results: Antibodies to CCP were detected in all 20 RF+ JIA patients and in one of 20 controls, though at low titer. Antibodies to Hu-CEP were detected in 9 JIA patients (45%). All patients with anti-Hu-CEP antibodies also carried Abs to PG-CEP. A tight correlation was found between anti-PG CEP and anti-Hu CEP ($R^2=0.70$), suggesting cross-reactivity between antibodies. Patients with the DRB1 shared epitope (n=12) were no more likely to carry anti-Hu-CEP (50%) or anti-PG-CEP (58%) than those without the shared epitope (n=8, 38%, 50%). No differences were found between patients and controls in control peptide responses, which were all low. Only weak correlations were detected between anti-CEP and age of onset or disease activity as assessed by ESR, CRP, active joint count, loss of range of motion, MD assessment or CHAQ.

Conclusion: A high proportion of patients with RF+ poly JIA develop Abs to citrillinated proteins, which were not detected in healthy children. The coincidental occurrence of anti-Hu-CEP and anti-PG CEP suggest an etiologic role for P. gingivalis infection in poly JIA.

Disclosure: **P. Lee**, None; **R. Howsmon**, None; **C. Murphy**, None; **S. Ringold**, None; **A. M. Stevens**, None.

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Immunoprecipitation and Advanced Proteomics for the Discovery of Novel Antigenic Targets in Juvenile Idiopathic Arthritis.
Ginger L. Janow[1], Cristina Clement[2], Norman T. Ilowite[3], Laura Santambrogio[2] and Steven A. Porcelli[4]. [1]Children's Hospital at Montefiore, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Children's Hospital Montefiore, Bronx, NY, [4]Albert Eistein College of Medicine, Bronx, NY

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic condition seen by pediatric rheumatologists. The pathogenesis of disease is poorly understood, but is believed to be mediated by an adaptive immune response involving auto-reactive B-cells and T-cells. There are high concentrations of immune complexes in the joint but specificities of these immune complexes are unknown. We hypothesize that joint destruction is partly the result of an adaptive immune response mediated by antibodies, and that examination of peptides and proteins in the synovial fluid (SF) of children with JIA combined with the identification of antigens targeted by antibodies found in arthritic SF will help clarify the pathogenesis of JIA.

Methods: Subjects with JIA with active arthritis of the knee requiring intra-articular corticosteroid injection were recruited from our pediatric rheumatology clinic. Subjects seen by pediatric orthopedics requiring arthroscopic knee surgery for traumatic injuries were recruited as controls. SF was collected from the knee of 4 children with JIA and 2 orthopedic controls. Specimens were diluted, centrifuged, and filtered. Peptidome and proteome were separated with ultrafiltration spin columns and advanced MS/MS was carried out. Protein A&G was used to isolate IgG inclusive immune-complexes. Antigens were eluted with glycine and analyzed using trypsin restriction with MS/MS. Ingenuity pathway analysis was used to analyze the proteome.

Results: High concentrations of immune complexes were found in the joints of JIA patients, nearing 50% of the total sample. Pathway analysis of the proteomes revealed statistically significant overlap with 5 relevant canonical pathways in all patients: acute phase response signaling, complement activation, coagulation system, intrinsic prothrombin activation, and extrinsic prothrombin activation. Peptidome analysis revealed the breakdown products of structural components including multiple collagen subtypes. Antibody-targeted antigens present in three out of the 4 patients but absent in controls were alpha-1-antitrypsin precursor, hyaluronan binding protein, haptoglobin, and protein S100-A9.

Conclusion: Proteome analysis confirmed the validity of our methods, revealing significant overlap with 5 pathways already known to be important in the pathogenesis of JIA. Given the role of short peptides as antigenic targets of T cell responses, the composition of the peptidome in the synovial tissues and fluids of JIA patients is likely to contribute to disease associated adaptive immune responses. The preliminary finding of the breakdown products of structural components suggests a mechanism for amplification of the auto-immune process during inflammation. While the role of the identified antibody-targeted antigens in pathogenesis remains unclear, it is of interest that some of these proteins, including alpha-1-antitrypsin and protein S100-A9 have been implicated as biological markers in both adult RA and JIA. Future research will validate the presence of these antibodies in a larger sample. These antibodies could have potential roles as biomarkers for disease and as targets for treatment.

Disclosure: **G. L. Janow**, None; **C. Clement**, None; **N. T. Ilowite**, None; **L. Santambrogio**, None; **S. A. Porcelli**, None.

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Measurement and Evaluation of Isotypes of Anti-Citrullinated Fibrinogen and Anti-Citrullinated Alpha-Enolase Antibodies in Juvenile Idiopathic Arthritis Patients.
Brooke Gilliam, Sandra Crespo-Pagnussat, Anil K. Chauhan and Terry L. Moore. Saint Louis University, St. Louis, MO

Background/Purpose: Anti-cyclic citrullinated peptide (CCP) antibodies in juvenile idiopathic arthritis (JIA) have been identified as an important indicator for destructive disease, as is the case with rheumatoid arthritis (RA). Recently, studies have focused on identifying the target proteins of the citrulline modification in both RA and JIA. We found that both IgG anti-citrullinated fibrinogen and α-enolase antibodies were present in our JIA population. In this study, we evaluated serum from patients with various subtypes of JIA to further investigate the presence of isotypes (IgA, IgM) of anti-citrullinated fibrinogen and anti-citrullinated α-enolase, and their association with rheumatoid factor (RF) and anti-CCP antibody isotypes (IgA, IgM, IgG) and other clinical parameters.

Methods: Sera were obtained from 93 JIA patients, 17 systemic lupus erythematosus (SLE) patients, and 10 healthy children. All sera were measured for antibodies against citrullinated and native fibrinogen and α-enolase IgA and IgM by ELISA. Results were compared to anti-CCP antibody isotypes and RF isotypes, in addition to previously measured IgG anti-citrullinated fibrinogen and α-enolase antibodies. All results were also correlated with various clinical parameters.

Results: IgA anti-citrullinated α-enolase antibodies were positive in 14, IgG in 9, and IgM in 11 JIA patients. IgA anti-citrullinated fibrinogen antibodies were positive in 16, IgG in 31, and IgM in 17 JIA patients. Overall, the isotypes of anti-citrullinated fibrinogen and α-enolase appeared more frequently in the polyarticular subset of JIA. One IgM RF-positive polyarticular JIA patient was positive for all 3 isotypes of anti-citrullinated fibrinogen antibodies. IgM anti-citrullinated α-enolase antibodies correlated significantly with IgM anti-citrullinated fibrinogen antibodies (r=0.479, p<0.001), and IgM anti-citrullinated α-enolase antibodies correlated significantly with IgM anti-CCP antibodies (p<0.005). IgM anti-citrullinated fibrinogen antibodies correlated significantly with erythrocyte sedimentation rate (p<0.05). IgA anti-citrullinated α-enolase antibodies correlated significantly with IgA anti-citrullinated fibrinogen antibodies (p<0.05). IgA anti-citrullinated α-enolase antibodies also correlated significantly with IgA RF and IgM RF (p<0.05), and IgA anti-citrullinated fibrinogen antibodies correlated significantly with IgA anti-CCP antibodies and IgM RF (p<0.05). No significant differences were noted the levels of citrullinated autoantibody isotypes when comparing patients with and without joint damage.

Conclusion: Studies have suggested measuring anti-CCP antibody isotypes in both RA and JIA patients, and recent studies have identified target proteins of the citrulline modification. We found that isotypes of both anti-citrullinated fibrinogen and α-enolase antibodies are present in the serum of JIA patients. JIA patients with elevated isotypes of anti-citrullinated fibrinogen and α-enolase antibodies should be evaluated prospectively in comparison with JIA patients who exhibit a less diverse isotype pattern to further determine their role in the pathogenesis of JIA.

Disclosure: **B. Gilliam**, None; **S. Crespo-Pagnussat**, None; **A. K. Chauhan**, None; **T. L. Moore**, None.

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Anti-Cyclic Citrullinated Peptide Antibody Isotyping and Identification of Citrullinated Proteins in the Synovial Fluid of Juvenile Idiopathic Arthritis Patients. Brooke Gilliam, Sandra Crespo-Pagnussat, Anil K. Chauhan, Reema H. Syed and Terry L. Moore. Saint Louis University, St. Louis, MO

Background/Purpose: Several citrullinated proteins have been detected in the serum and synovial fluid (SF) of rheumatoid arthritis (RA) patients. However, few studies have evaluated citrullination of proteins in juvenile idiopathic arthritis (JIA). It has been proposed that anti-cyclic citrullinated peptide (anti-CCP) antibodies play a pathogenic role in the development of anti-CCP antibody positive arthritis, and it is expected that these antibodies would be present at higher concentrations at the site of inflammation. We evaluated SF from JIA patients to investigate the presence of anti-CCP antibody isotypes and identified specific citrullinated autoantibodies in JIA SF.

Methods: Anti-CCP antibody isotypes (IgA, IgG, IgM, IgA/IgG) were measured by ELISA in the SF of 47 JIA patients. As non-inflammatory controls, SF from 10 osteoarthritis (OA) patients was used. Twenty-four SF samples from patients with various diagnoses were treated and transferred to PVDF membranes and probed with antibodies to native-α enolase, native fibrinogen, and anti-modified citrulline (AMC). SF samples were immuno-precipitated with antibodies to fibrinogen and α-enolase, and citrullinated antibodies were then detected with AMC assay.

Results: Eleven of 47 (23%) JIA SF samples were positive for at least one anti-CCP antibody isotype. IgM anti-CCP antibodies were positive in 9 JIA patients, IgG anti-CCP antibodies were positive in 8 patients, and 2 were positive for IgA anti-CCP antibodies. Three JIA patients were positive for the combined IgA/IgG anti-CCP antibodies. Polyarthritis patients demonstrated significantly higher levels of all anti-CCP antibody isotypes compared to other JIA subtypes (p<0.05), and even higher levels when only evaluating IgM rheumatoid factor (RF)-positive polyarthritis patients. Serum-matched anti-CCP antibody data was available on 27 JIA patients and 5 controls. All IgM RF-positive polyarthritis patients were positive for IgG anti-CCP antibodies in both serum and SF. Two JIA patients positive for IgG anti-CCP antibodies in SF were negative in serum. More JIA patients were positive for IgA anti-CCP antibodies in serum than in SF, while SF showed increased positivity for IgM anti-CCP antibodies compared to serum.

Western blot analysis revealed multiple citrullinated proteins in JIA that were not detected in OA. Immunoprecipitation with α-enolase and fibrinogen, followed by AMC detection showed presence of these specific citrullinated proteins in JIA and no detection in OA

Conclusion: All anti-CCP antibodies were detected in the SF of JIA patients. The most commonly found anti-CCP antibody isotype in JIA SF was IgM, which may be partly indicative of defective B cell class switching in these patients. Measurement of only IgG anti-CCP antibodies would have overlooked 4 JIA patients with elevated levels of IgA and/or IgM anti-CCP antibodies, indicating the importance of measuring all 3 isotypes. The abundance of citrullinated proteins in JIA SF may be characteristic of inflammation, as seen in RA and spodyloarthritis. We have shown the detection of citrullinated proteins at the site of inflammation, specifically identifying citrullinated fibrinogen and α-enolase in SF.

Disclosure: B. Gilliam, None; **S. Crespo-Pagnussat**, None; **A. K. Chauhan**, None; **R. H. Syed**, None; **T. L. Moore**, None.

ACR Poster Session A
Rheumatoid Arthritis: Animal Models
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Silencing Intraarticular Snail Expression Ameliorates Rat Collagen-Induced Arthritis Through Induction of Mesenchymal-Epithelial Transition in Synovial Fibroblasts. Chrong-Reen Wang, Shih-Yao Chen, Ai-Li Shiau, Yuan-Tsung Li, Ming-Fei Liu and Chao-Liang Wu. College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background/Purpose: Morphological characteristics of rheumatoid arthritis (RA) synovial fibroblasts (SF) are similar to transformed cells. We hypothesized that epithelial-mesenchymal transition (EMT) of SF regulated by snail contributes to the progression of RA. The pathogenic role of EMT was studied, and the therapeutic effect on arthritis was evaluated by silencing intraarticular snail expression.

Methods: Expression of snail, mesenchymal markers including cadherin-11, epitheral markers and/or phospho-AKT was detected by RT-PCR, immunoblot and/or immunohistochemical analyses on RA synovium, and synovial tissues and SF from normal or collagen-induced arthritis (CIA) rats. Modulation of in vitro expression in SF and in vivo effect on normal or CIA joints was performed by lentivirus-mediated transfer of cDNA or shRNA specific to snail. In vivo responses were evaluated by clinical and histopathological assessments, and immunohistochemical staining on joints. In vitro cell viability and invasion were determined by colorimeric method and modified Boyden chamber, respectively. IL-6 concentrations in culture supernatants were quantified by enzyme-linked immunosorbent assay.

Results: Snail was expressed at high levels in synovial tissues of RA and CIA. Overexpression of snail in SF and joints of normal rats promoted EMT by down-regulation of epithelial markers, gain of mesenchymal markers and enhancement of invasive capacity. Moreover, silencing snail expression ameliorated CIA through the induction of mesenchymal-epithelial transition.

Conclusion: These data demonstrate that regulation of snail in SF alters cell morphology and gene expression between epithelial and mesenchymal phenotypes. These findings implicate that EMT regulated by snail might be explored as a novel therapeutic strategy targeting SF in RA.

Disclosure: C. R. Wang, None; **S. Y. Chen**, None; **A. L. Shiau**, None; **Y. T. Li**, None; **M. F. Liu**, None; **C. L. Wu**, None.

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Tolerogenic Dendritic Cells Ameliorates the Disease Severity of Murine Collagen-Induced Arthritis. Bin Ning[1], Shang-You Yang[2], Jianlu Wei[1], Weiming Gong[1] and Paul H. Wooley[2]. [1]Shandong University Jinan Central Hospital, Jinan, China, [2]Via Christi Wichita Hospitals, Wichita, KS

Background/Purpose: Rheumatoid arthritis (RA) is a common auto-immune disease characterized by synovial inflammation, cartilage breakdown and bone destruction with the involvement of various types of cells including dendritic cells (DCs). A subset of dendritic cells that induce tolerance is called tolerogenic DCs (tolDCs). They may represent a promising immunosuppressive therapeutic tool for the attenuation of pathogenic T cell responses in autoimmune arthritis. In this study, we examine a series of stable antigen-specific tolDCs with tracking green fluorescent protein (GFP) to investigate their influence in the murine collagen induced arthritis (CIA) model.

Methods: The DCs were isolated from bone marrow of DBA/1Lac/J mice, and stimulated with IL-10 (10ng/ml), TGF-β (10ng/ml), and type II Collagen (CII) to induce CII-specific tolerogenic dendritic cells (tolDCs). The cells were then infected with Lenti-GFP viral vectors for GFP transduction. The GFP-tolDCs were injected ip into CIA mice at the time of arthritis onset. Arthritic animals were clinically assessed 3 times a week. The arthritic paws and blood specimens were harvested at 8 weeks after onset for histological, immunological and molecular analyses.

Results: The phenotype of tolDCs was confirmed by flow cytometry and ELISA. Lymphocyte proliferation assays resulted in semi-matured, high IL-10 and TGF-β production, and low lymphocyte stimulatory capacity with low IFN-γ secretion. Both clinical and histological assessment on the animal studies indicated that the mice receiving tolDCs transfusion had a rapid and significant reduction in severity of arthritis compared to the controls (P<0.01). Fluorescent microscope observation showed aggregated green fluorescent cells in the inflamed synovial membrane where only sporadic presence in liver, spleen or lungs. Data also indicated the extended high expression levels of IL-10 and TGF-β at 4 weeks after the treatment, whereas the IL-17 expression was lower than controls (P < 0.01).

Conclusion: This study reports the successful establishment of a stable phenotype of CII-specific tolDCs and its potential therapeutic influence on collagen-induced arthritis in mice. Introduction of GFP-tolDCs significantly ameliorates the clinical and pathological progress of the experimental arthritis. TolDCs were cumulative at the inflammatory joints and the treatment diminished Th17 response (IL-17 expression). Further investigation is due to reveal the mechanism of tolDCs in regulation of the progression of rheumatoid arthritis.

Disclosure: B. Ning, None; **S. Y. Yang**, None; **J. Wei**, None; **W. Gong**, None; **P. H. Wooley**, None.

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IL-7; An Important Pro-Inflammatory Factor That Affects Myeloid Cell Function in RA and CIA. Nathan D. Chamberlain[1], Seung-jae Kim[1], Michael Volin[2], Anjali Mehta[1], Nadera J. Sweiss[1] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL

Background/Purpose: The aim of the study was to examine the role of IL-7 in the pathogenesis of rheumatoid arthritis (RA) as well as in collagen induced arthritis (CIA).

Methods: Linear regression analysis was employed to correlate expression of IL-7 and IL-7R with levels of DAS28 score in RA monocytes. Next, the contribution of IL-7/IL-7R to RA synovial fluid induced monocyte migration was examined by in vitro chemotaxis. Finally, CIA mice were treated therapeutically with IgG or anti-IL-7 antibodies and clinical parameters, joint proinflammatory factors, % spleen TH-1 and TH-17 cells as well as markers of bone destruction were quantified employing ELISA, FACS analysis or real-time RT-PCR.

Results: We show that patients with higher disease activity express elevated levels of IL-7 ($R^2=0.54$, $p=2.10\times10^{-14}$) and IL-7R ($R^2=0.56$, $p=6.59\times10^{-15}$) in 76 RA monocytes suggesting that ligation of IL-7 to IL-7R may be associated with disease progression. Next, experiments were performed to determine whether IL-7 and its receptor play a role in RA synovial fluid mediated monocyte migration. We found that neutralization of IL-7 in RA synovial fluid or blockade of IL-7R on monocytes greatly suppressed RA synovial fluid-mediated monocyte migration further documenting the importance of IL-7 and IL-7R function in myeloid cells. In order to evaluate whether IL-7 is a potential target in RA pathogenesis, CIA, a chronic murine model of RA was employed. We show that like in RA, IL-7R is significantly elevated in the lining and sublining macrophages as well as in sublining endothelial cells in CIA compared to PBS treated ankles. Additionally CIA mice produce 3 fold higher joint IL-7 levels compared to the control group. Hence to examine the role of IL-7/IL-7R in CIA pathology, CIA mice were therapeutically treated with anti-IL-7 antibody or IgG control starting on day 26 post CIA induction. These studies demonstrate that anti-IL-7 antibody treatment significantly reduced joint inflammation on days 33, 37, 40, 41 and 42 post CIA induction compared to the control group however there were no differences detected between the two treatment groups on days 28 and 30. We next found that joint TNF-a as well as ankle and serum levels of CCL2/MCP-1 were 2 fold higher in the IgG group compared to anti-IL-7 antibody treated CIA mice. We also demonstrate that anti-IL-7 treatment was capable of markedly reducing expression of markers for CIA bone erosion including RANKL (3 fold) and Cathepsin K (10 fold). In contrast the percentage of CD3, CD4, TH-1 and TH-17 positive cells was similar in anti-IL-7 and IgG treatment groups. Consistent with these findings joint IL-6 levels were unaffected by anti-IL-7 therapy while there was a trend towards lower levels of joint IL-1b and IL-17 however these values were not significantly different among the two treatment groups.

Conclusion: These novel results suggest for the first time that ligation of IL-7 to IL-7R can affect cell migration, production of proinflammatory factors and osteoclast differentiation from myeloid cells in RA as well as in experimental arthritis models.

Disclosure: N. D. Chamberlain, None; **S. J. Kim**, None; **M. Volin**, None; **A. Mehta**, None; **N. J. Sweiss**, None; **S. Shahrara**, None.

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The SYK Inhibitor, Fostamatinib, Administered Alone or in Combination with Methotrexate in Rat Collagen-Induced Arthritis, Reduces Bone Erosions, Biomarkers of Cartilage/Bone Destruction, and Synovial Osteoclastogenic Cytokines. Polly Pine[1], Ayodele Apatira[1], Betty Y. Chang[1], Nathan Schoettler[2], Elliott B. Grossbard[1] and Ernest Brahn[2]. [1]Rigel Pharmaceuticals, So San Francisco, CA, [2]UCLA School of Medicine, Los Angeles, CA

Background/Purpose: Spleen tyrosine kinase (SYK) is expressed in hematopoietic cells and is a major downstream regulator of signaling through Fcγ and immunoglobulin receptors as well as non-immunoglobulin receptors associated with adaptor proteins DAP12 and FcRg in osteoclasts. Inhibition of SYK has been shown to reduce the severity of collagen-induced arthritis (CIA). This provided the rationale for the development of the SYK inhibitor, fostamatinib (R788), as a potential treatment for rheumatoid arthritis (RA). In the present rat CIA study, we characterize the activity of fostamatinib alone or with co-administered methotrexate (MTX), on paw inflammation, bone erosion, serum biomarkers of bone destruction, and synovial proinflammatory cytokine expression.

Methods: Syngeneic LOU rats were immunized on day 0 with native type II collagen. At the onset of arthritis (day 10), a total of 59 rats were treated with either a vehicle control, fostamatinib at one of two dose levels (15 or 30 mg/kg q.d. by p.o. gavage), MTX alone (0.4 mg/kg s.c., q.w. for 3 weeks), or fostamatinib (15 or 30 mg/kg) in combination with s.c. MTX q.w. Hind limbs were scored daily for clinical arthritis severity using a standardized method based on the degree of joint inflammation. Serum and synovial tissue were harvested at sacrifice, and biomarker expression was assessed by ELISA. Blinded high resolution digital radiographs and micro3D-CT of hind limbs were obtained at the end of the study (day 28).

Results: Arthritis severity was significantly reduced within 7 days after initiation of fostamatinib therapy and continued to improve throughout the study. By day 28, the mean clinical score in the vehicle group was 7.4 compared with 4.1 and 2.4 in the fostamatinib groups (15 and 30 mg/kg, p< 0.0003 and 0.0001, respectively). Co-administration of MTX with fostamatinib further reduced the clinical scores to 3.6 and 2.1 (15 and 30 mg/kg, respectively, p< 0.0001 vs vehicle, p< 0.0001 vs MTX alone, p> 0.05 vs fostamatinib alone). Radiographs (day 28) demonstrated a significant reduction in joint damage: 5.1 (vehicle) vs. 0.6, 0.0, 0.5, and 0.08 (15 mg/kg and 30 mg/kg fostamatinib alone, 15 mg/kg and 30 mg/kg fostamatinib with MTX, respectively, p< 0.0001 for all groups vs vehicle). Treatment with MTX alone significantly reduced joint damage, although the response was not as robust as that seen with fostamatinib (mean radiographic score = 2.8, p< 0.02 vs vehicle). These findings were confirmed with micro3D-CT analysis. Serum RANKL and COMP were reduced in fostamatinib-treated rats, and combination treatment did not further reduce the level of bone biomarkers. Synovial IL-18, IL-6, and IL-1b were reduced (30 mg/kg fostamatinib with or without MTX vs vehicle). Fostamatinib and MTX treatment were well tolerated and had no overt adverse effects.

Conclusion: Fostamatinib significantly reduced the severity of established rat CIA, had modest additional improvement with co-administered MTX, and was superior to MTX alone. These results indicate that fostamatinib may have potential therapeutic benefits for both the inflammatory synovitis and bone erosions of CIA. Fostamatinib is currently in Phase III trials for RA.

Disclosure: P. Pine, Rigel Pharma, 3; **A. Apatira**, Rigel Pharma, 3; **B. Y. Chang**, None; **N. Schoettler**, None; **E. B. Grossbard**, Rigel Pharma, 3; **E. Brahn**, Rigel Pharma, 2.

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Fut1 Plays A Unique Role in K/BxN Serum Transfer Arthritis by Regulating Angiogenesis and Adhesion Molecule Expression. M. Asif Amin, Phillip L. Campbell, Takeo Isozaki, Jeffrey H. Ruth, Jonathan Vargo, Steven E. Domino and Alisa E. Koch. University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: Angiogenesis is important in rheumatoid arthritis (RA) synovial tissue proliferation and leukocyte ingress into the inflamed joints. Fucosyltransferases (Futs) are involved in the synthesis of glycoconjugates and blood group antigens and other Futs have been shown to be important in inflammatory pathways such as leukocyte homing. Hence, we examined the role of another Fut, Fut1, in angiogenesis and leukocyte recruitment in inflammatory arthritis.

Methods: Mouse lung endothelial cells (ECs) from Fut1 null and wild type (wt) mice were used to perform Matrigel tube formation assays in vitro. We performed Matrigel plug in vivo angiogenesis assays using Fut1 null and wt mice. Some of the plugs were homogenized for hemoglobin determination while others were sectioned to perform immunofluorescence to count the number of blood vessels. To determine the contribution of Fut1-mediated angiogenesis and leukocyte recruitment in an animal model of arthritis, we performed the serum transfer K/BxN arthritis model employing Fut1 null and wt mice. Mouse ankles were measured before induction of arthritis and then on alternate days. Ankles were harvested on day 9, the day of maximum arthritis. Some of the arthritic ankles were homogenized to determine hemoglobin (Hb) while others were sectioned for blood vessel counts. To determine the mechanism of decreased leukocyte recruitment, we performed immunofluorescence for adhesion molecule expression in wt and Fut1 null mouse ankle sections. We stimulated Fut1 null and wt ECs and performed quantitative PCR and enzyme linked immunosorbent assays for adhesion molecule expression.

Results: Fut1 null ECs formed significantly less tubes compared to wt ECs on Matrigel. In the Matrigel plug in vivo angiogenesis assays, we found

that Fut1 null mice had less Hb, an indirect measure of angiogenesis (four fold decrease) compared to wt mice. By immunofluorescence, wt mouse plugs formed significantly greater number of blood vessels. Fut 1 null mice were resistant to K/BxN arthritis showing a significant decrease in ankle circumference in comparison with wt mice. Fut1 null mouse arthritic ankle homogenates had less Hb, when compared to wt mice. Blood vessels formed in Fut1 null mouse ankle sections were four fold decreased compared to wt mouse ankle sections. This suggests that Fut1 plays a critical role in K/BxN arthritis development by modulating angiogenesis. Adhesion molecules are important in leukocyte recruitment into inflammatory sites. After finding decreased leukocytes in Fut1 null mouse sections, we examined the expression of adhesion molecules in arthritic mouse sections. By dual immunofluorescence, we found a marked decrease in intercellular adhesion molecule-1 (ICAM-1) in Fut1 null arthritic ankle sections. ICAM-1 expression was significantly decreased at both mRNA and protein levels in Fut1 null compared to wt mouse ECs, suggesting the mechanism of decreased leukocyte recruitment into the inflamed joint when Fut1 is absent.

Conclusion: These data suggest that Fut1 mediates inflammatory arthritis by modulating angiogenesis and may be a novel approach to treat angiogenesis-dependent diseases such as RA.

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PDL241, a Novel Humanized Monoclonal Antibody, Reveals CD319 As a Therapeutic Target for Rheumatoid Arthritis. Michel P.M. Vierboom[1], Jacky Woo[2], Hakju Kwon[2], Debra Chao[2], Shiming Ye[2], Jianmin Li[2], Karen Lin[2], Irene Tang[2], Nicole Belmar[2], Taymar Hartman[2], Elia Breedveld[1], Bert A. 't Hart[1] and Gary C. Starling[2]. [1]Biomedical Primate Research Centre, Rijswijk, Netherlands, [2]Abbott Biotherapeutics, Redwood City, CA

Background/Purpose: Current therapies have shown tremendous progress in the treatment of rheumatoïd arthritis (RA). However, a substantial group of RA patients are still refractory to these therapies or develop resistance. RA patients that are resistant to anti-CD20 therapy illustrate the need for therapies targeted against cells of the late B cell lineage. We identified CD319, a marker of differentiated B cells as a potential target for therapy of RA.

Methods: A humanized antibody PDL241 directed against CD319 was generated. The binding of PDL241 to human tissues was analyzed by immunohistochemistry and FACS analysis of PBMC. Functional activity of PDL241 on PBMC was demonstrated in vitro and in a HuSCID mouse model. PDL241 is a primate specific antibody and safety and efficacy was tested in a collagen-induced arthritis (CIA) model in the rhesus monkey. The rhesus CIA model is an autoimmune-mediated model of polyarthritis with inflammation and erosion of joints that shares several important cellular and histopathological features with RA.

Results: We found that CD319 was expressed on plasma cells, but not CD20 positive B cells, in rheumatoid arthritis synovial tissues. In cultures of PBMC, PDL241 bound plasmablasts and plasma cells but not naïve and memory B cells, and inhibited the production of immunoglobulins in an Fc-dependent manner in vitro by reducing the numbers of late stage B cell lineage cells. High levels of CD319 on plasmablasts and plasma cells rendered them susceptible to ADCC mediated by NK cells. PDL241 also was able to reduce production of human IgM in a PBMC-transfer HuSCID model. Finally, PDL241 showed a beneficial activity in a rhesus macaque model of collagen-induced arthritis (CIA). Treatment with PDL241 resulted in a reduction of collagen-specific IgG and IgM production in the early phase of the disease leading to a reduction in joint swelling and the subsequent destruction of cartilage and bone.

Conclusion: CD319 was identified as a potential therapeutic target in RA following analysis of expression and in functional assays of IgM production from PBMC. The functional activity of PDL241 in the rhesus CIA model further supported the promise of targeting CD319 in RA. Development of PDL241 was halted due to immunogenicity observed in non-human primate models; however, the current study demonstrated the strong potential of CD319 as a therapeutic target in a range of autoimmune diseases, including RA, where CD319-expressing cells have a role in the pathology.

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Blockade of CTGF Restores Aberrant Ostoclastgenesis in Collagen Induced Arthritis (CIA) Mice Through Inhibition of Th-17 Differentiation. Kazuhisa Nozawa[1], Maki Fujishiro[2], Ayako Yamaguchi[3], Mikiko Kawasaki[2], Shouzou Ichinose[2], Mitsuaki Yanagida[2], Kazuhisa Iwabuchi[2], Keigo Ikeda[4], Shinji Morimoto[5], Megumi Morioka[6], Yoshinari Takasaki[1] and Iwao Sekigawa[4]. [1]Juntendo University School of Medicine, Tokyo, Japan, [2]Juntendo University Graduate School of Medicine, Chiba, Japan, [3]Juntendo University Graduate School of Medicine, Tokyo, Japan, [4]Juntendo University Urayasu Hospital, Tomioka, Urayasu, Chiba, Japan, [5]Juntendo University Urayasu Hospital, Tokyo kyo, Japan, [6]Nihon Nosan Corporation, Kanagawa, Japan

Background/Purpose: Our previous study demonstrated changes in the profiles of serum protein biomarkers in infliximab-treated rheumatoid arthritis (RA) patients using a novel approach to proteomic research. Several proteins exhibited vast changes in expression after infliximab treatment, and we have reported connective tissue growth factor (CTGF) appeared to be a potent strong biomarker in infliximab-treated RA patients. Furthermore, we also found that CTGF was upregulated in both serum level and tissue expression of patients with RA, and that CTGF was related to disease progression of RA through abnormal activation of osteoclasts in vitro. To extend our research project, this study was conducted to clarify roles of CTGF for RA pathogenesis. To investigate more precise roles of CTGF for RA pathogenesis, we analyzed effects of blockade against CTGF pathway on the progression of arthritis in collagen induced arthritis (CIA) mouse.

Methods: CIA was introduced in DBA/1J mice by immunization in combination with typeIIcollagen and complete Freund's adjuvant (CFA). The efficacy and mechanisms for prevention of the arthritis were evaluated in the mice treated with or without neutralizing anti-CTGF monoclonal antibody (mAb).

Results: The blockade of CTGF by anti-CTGF mAb treatment significantly ameliorated the arthritis compared to the non-treated controls. Moreover, serum levels of C reactive protein (CRP) and matrix metalloproteinase (MMP)-3 reduced in the CTGF-treated mice. The blockade of CTGF decreased interleukin (IL)-17 and IL-21 production from purified CD4+ T lymphocytes. Although gene expression of retinoic-acid-receptor-related orphan receptors gamma t (RORgt) was not suppressed by anti-CTGF mAb treatment, those of interferon regulatory factor-4 (IRF-4) and IkappaBzeta, which are other important molecules for Th-17 differentiation, were suppressed. In addition, the blockade of CTGF inhibited pathological T lymphocytes proliferation against typeIIcollagen restimulation extra vivo. Moreover, aberrant sRANKL/MCSF-induced osteoclastgenesis of CD14+ progenitor cells in CIA was restored by anti-CTGF mAb treatment.

Conclusion: The present study demonstrated that the blockade of CTGF significantly prevented a progression of arthritis in CIA mice. The administration of anti-CTGF mAb had suppressive effects on aberrant pathological T cells proliferation and Th17 differentiation in CIA mice. In addition, the blockade of CTGF pathway might restore aberrant ostoclastgenesis of CIA through direct effect to CD14+ osteoclastic progenitor cells and indirect effects for Th-17 differentiation. CTGF may become a new target molecule for treatment of RA.

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Pressure and Blood Flow Measurements in Efferent Lymphatics As Biomarkers of Arthritic Flare. Echoe M. Bouta[1], Ronald Wood[2], Christopher T. Ritchlin[3], Lianping Xing[1] and Edward M. Schwarz[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester School of Medicine and Dentistry, Rochester, NY, [3]University of Rochester Medical Center, Rochester, NY

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease with episodic flares in affected joints. These flares are associated with decreased lymphatic drainage. In TNF-Tg mice, a model of inflammatory-erosive arthritis, the popliteal lymph node (PLN) expands in volume during the pre-arthritic "expanding" phase and then "collapses" during flare. Currently, the factors that cause PLN collapse are unknown. Local changes in physiology are reasonable explanations given the finding that PLN and iliac lymph node collapse occurs in series along the ipsilateral axis in the setting of unaltered chronic inflammation and systemic autoimmunity. Thus, we tested the hypothesis that PLN collapse and arthritic flare are associated with increased pressure and decreased blood flow within the efferent lymph node (PLN) of inflamed joints.

Methods: The PLNs of TNF-Tg mice (C57B6) were phenotyped as expanding or collapse with contrast-enhanced MRI. Pressure measurements

were performed by inserting a glass micropipette connected to a pressure transducer into the PLN of anesthetized WT and TNF-Tg mice. Blood flow within the lymph node and lymph node volume were measured by 3D power Doppler ultrasound and volumetric rendering in Amira.

Results: Lymph node pressure was significantly decreased in expanding PLN of TNF-Tg mice vs. that of WT mice (3.4 ± 0.4 vs 6.7 ± 0.6 cmH$_2$O; p<0.01). The pressure in collapsed PLN of TNF-Tg mice was significantly greater vs. expanding node in the same mice (8.6 ± 1.7 vs. 3.4 ± 0.4 cmH$_2$O; p<0.05), but similar to WT node. We also found that the volume of blood vessels positive for Doppler flow was significantly 6-fold less in collapsed vs. expanding PLN of TNF-Tg mice (0.050 ± 0.036 mm^3 vs. 0.3042 ± 0.08192 mm^3; p<0.05) (Figure).
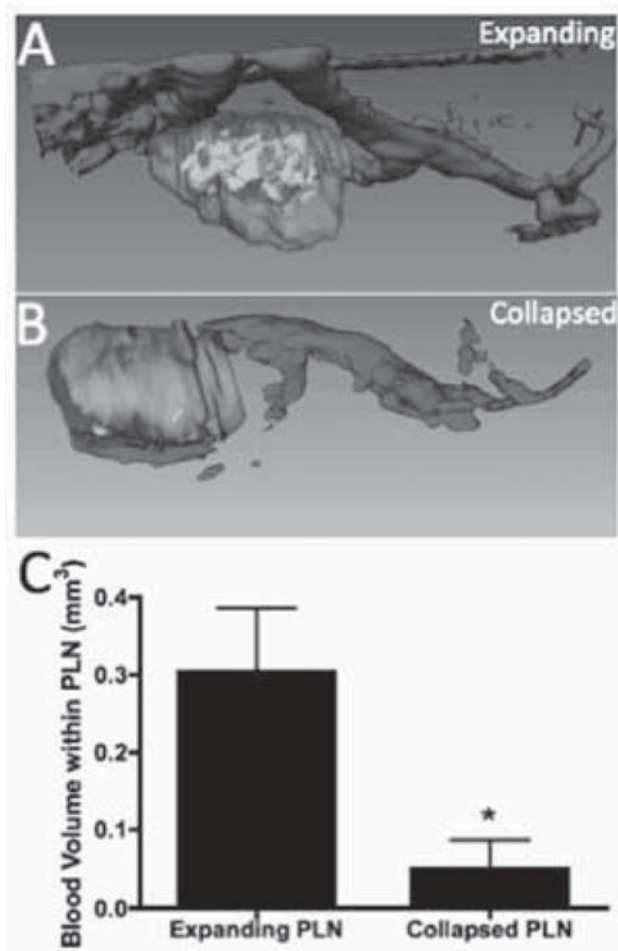
Conclusion: Here we describe a novel approach to quantify lymph node pressure and blood flow within PLNs of WT and TNF-Tg mice. Our finding of significantly decreased lymphatic pressure during the pre-arthritic stage is consistent with the theory that lymphangiogenesis is a compensatory mechanism to prevent synovitis and joint damage during RA pathogenesis. Furthermore, increased pressure and decreased vascular flow observed in collapsed PLN is also consistent with this theory, and suggest that lymphatic pressure and blood flow within the efferent lymph nodes are potential biomarkers to assess RA progression and response to therapy, with the later achieved using clinically relevant non-invasive ultrasound.

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Selective iNOS Inhibition Increases the Lymphatic Pulse and Drainage From Arthritic Joints in TNF-Tg Mice. Yawen Ju, Ronald Wood, Lianping Xing, Christopher T. Ritchlin and Edward M. Schwarz. University of Rochester Medical Center, Rochester, NY

Background/Purpose: Sufficient lymphatic drainage, which is partially controlled by an intrinsic lymphatic pulse, is an important mechanism to limit joint inflammation and destruction from arthritis. We reported recently that arthritic flare in TNF transgenic (TNF-Tg), a mouse model of inflammatory-erosive arthritis, coincides with the loss of the lymphatic pulse afferent to expanding draining lymph nodes, causing their collapse. From other models, the lymphatic pulse is known to be controlled by endothelia nitric oxide synthase (eNOS), and inhibited by inducible NOS (iNOS) expresses in Gr-1+ cells. To determine if this mechanism controls the lymphatic pulse and lymphatic drainage in inflammatory-erosive arthritis, we tested the hypotheses that: 1) Gr-1+/iNOS+ cells are present in the draining lymph nodes of flaring TNF-Tg mice; and 2) selective iNOS inhibition increases the lymphatic pulse and drainage from joints to draining lymph nodes.

Methods: Immunohistochemistry for Gr-1 and iNOS was performed on popliteal lymph node (PLN) frozen sections from WT and TNF-Tg mice. The lymphatic pulse and flow afferent to the PLN were quantified in TNF-Tg mice with collapsed PLN (>8-month-old) and WT controls (n=4 legs) via *in vivo* near infrared indocyanine green (NIR-ICG) imaging before and after saline (placebo), iNOS specific inhibitor L-NIL (4mg/kg), or general NOS inhibitor L-NAME (5mg/kg) was injected S.C. in footpad.

Results: Immunohistochemistry showed more iNOS expressing Gr-1+ cells in collapsed vs. expanding PLN (127 vs. 3 cells/mm^2), and undetectable numbers in WT PLN. Saline did not change the lymphatic pulse in either WT or TNF-Tg mice. However, L-NIL significantly increased the pulse in TNF-Tg mice (from $0.42 +/-0.84$ to $2.19 +/-0.77$ pulse/min; p<0.05), but not in age-matched WT mice ($0.96 +/-1.42$ to $3.13 +/-2.36$ pulse/min; p=0.08). Moreover, L-NIL significantly increase lymphatic flow in TNF-Tg vs. saline ($73.48 +/-8.9$ vs, $53.25 +/-12.72$ % ICG clearance; p<0.05). In contrast, L-NAME decreased the clearance rate in both WT ($27.77 +/-13.78\%$) and TNF-Tg ($9.07 +/-33.65\%$), but did not significantly change the pulse rate.

Conclusion: We demonstrated that large numbers of iNOS expressing Gr-1+ cells exist in collapsed PLN of TNF-Tg mice with flaring inflammatory-erosive arthritis, and that the specific iNOS inhibitor L-NIL increased the lymphatic pulse and afferent lymphatic drainage. These results suggest that selective iNOS inhibition may be effective in ameliorating arthritic flare by improving lymphatic drainage, which is currently being tested in a prospective study of flaring TNF-Tg mice treated for 6-weeks with L-NIL, L-NAME, or placebo. The effects of these treatments on knee and ankle synovitis and focal joint bone erosion determined by CE-MRI, micro-CT and histology will be presented.

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Treatment with Bgp-15, a Novel Insulin Sensitizer Attenuates Collagen-Induced Arthritis in DBA/1 Mice. Peter Mandl[1], Silvia Hayer[1], Stephan Blüml[1], Victoria Saferding[1], Despoina Sykoutri[1], Kurt Redlich[1] and Josef S. Smolen[2]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: BGP-15, a small synthetic hydroxylamine derivative is a member of a new class of insulin-sensitizing medications also known as chaperone-inducers. Beside its beneficial effects on glycemic control and insulin sensitivity in patients with Type 2 diabetes, BGP-15 is known to induce heat shock protein Hsp72 and heat shock transcription factor HSF1, which in turn are involved in joint inflammation. Moreover, BGP-15 also inhibits poly-ADP-ribose polymerase (PARP) and the phosphorylation of c-JUN N-terminal kinase via Hsp72 overexpression. Therefore it might also play a role in the regulation of inflammatory joint disease. Our objective was to evaluate the *in vivo* effects of BGP-15 on collagen-induced arthritis (CIA) in DBA/1 mice.

Methods: Arthritis was induced by intradermal injection of bovine type II collagen (bCII) and incomplete Freund's adjuvant (CFA) in male DBA/1 mice. BGP-15 was administered either one week prior to the first immunization (prophylactic experiment, n:14 in both groups) or upon the appearance of symptoms (therapeutic experiment, n:12 in both groups) in drinking water. Arthritis incidence and severity was assessed for 28 days following the second immunization (boost) with bCII and CFA on day 21. Histological evaluation was carried out on hind paws using Osteomeasure® software. Anticollagen antibodies were measured by enzyme-linked immunosorbent assay. The cellular composition of the draining lymph nodes was measured by flow cytometry. *In vitro* cytokine measurements were carried out on dendritic cells and macrophages differentiated from murine bone marrow macrophages.

Results: BGP-15 significantly reduced the incidence of CIA by 28% and also reduced both paw swelling (p≤0.01) and grip strength (p≤0.05) in the prophy-

lactic experiment. In the therapeutic experiment BGP-15 significantly attenuated both paw swelling (p≤0.01) and grip strength (p≤0.05). Histological evaluation of the hind paws demonstrated reduced area of inflammation (p≤0.05), area of erosion (p≤0.01) and number of osteoclasts (p≤0.05) in the BGP-15 treated group when compared to the control group. No significant differences were revealed between anticollagen antibody levels or in the distribution of T-cells, B-cells, dendritic cells and monocytes/macrophages harvested from draining lymph nodes, suggesting an effect predominantly involving the innate immune system. In line with these findings BGP-15 (1mM) inhibited the LPS-induced production of IL-12, IL-6 and TNF in both dendritic cells and macrophages.

Conclusion: Our results demonstrate that the novel chaperone-inducer BGP-15 has a profound prophylactic and therapeutic effect on autoimmune arthritis, mainly due to an effect on the effector phase.

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Preclinical Development of ALX-0061, an Anti-IL-6R Nanobody® for therapeutic Use in Rheumatoid Arthritis with a High in Vitro Affinity and Potency and a Competitive in Vivo Pharmacological Profile. Maarten Van Roy[1], Hans Ulrichts[1], Stefaan Rossenu[1], Sandy Jacobs[1], Sofie Poelmans[1], Gert Verheyden[1], Michel Vierboom[2], Bert 't Hart[2], Judith Baumeister[1] and Josefin-Beate Holz[1]. [1]Ablynx N.V., Zwijnaarde, Belgium, [2]Biomedical Primate Research Centre, Rijswijk, Netherlands

Background/Purpose: Interleukin-6 (IL-6) is a pleiotropic cytokine inducing a wide range of biological activities via its receptor IL-6R. IL-6 plays an important role in the pathogenesis of a variety of diseases, including rheumatoid arthritis (RA), and blocking of IL-6R results in clinical benefit as shown with tocilizumab (TCZ), a monoclonal antibody targeting IL-6R.

Nanobodies are therapeutic proteins based on the smallest functional fragments of heavy chain-only antibodies, naturally occurring in the *Camelidae* family. ALX-0061 is a bispecific anti-IL-6R Nanobody engineered to obtain an extended half-life *in vivo* by targeting human serum albumin, in combination with a high *in vitro* affinity and potency for the anti-IL-6R building block.

The presented work was aimed at determining the ALX-0061 *in vitro* and *in vivo* profile and at translating these results to a first-in-man (FIM) dose.

Methods: ALX-0061 was characterized extensively using *in vitro* systems: biological activity, specificity and affinity was assessed and compared to TCZ. Due to very tight target binding, the affinity of ALX-0061 for IL-6R could not be accurately determined via surface plasmon resonance and the new and more sensitive Gyrolab™ platform was used.

The PK/PD properties of ALX-0061 were examined in naive cynomolgus monkeys and in an human (h)IL-6-induced acute phase response model in the same species in which platelet numbers and plasma concentrations of CRP and fibrinogen were monitored as disease parameters.

In vivo efficacy of ALX-0061 was assessed in a collagen-induced arthritis (CIA) rhesus monkey model. In this model, inflammation of the joints was induced via sensitization with collagen type II, after which clinical endpoints were assessed in correlation to biomarker deregulation.

Results: ALX-0061 neutralized specifically both soluble and membrane IL-6R with a comparable *in vitro* potency to TCZ. However, affinity of ALX-0061 for IL-6R (0.19 pM ± 0.08 pM) was 2000-fold superior compared to TCZ (462 pM ± 138 pM).

In the cynomolgus monkey, ALX-0061 showed a dose-dependent and complete inhibition of three hIL-6-induced inflammation parameters. PK analysis in the same species demonstrated a half-life (5.7 to 7.4 days) similar to that reported for serum albumin which was predicted to translate into a convenient *iv* dosing regimen in humans. Measurement of total sIL-6R levels in these studies supported the calculation of the FIM dose.

Although emergence of neutralising anti-drug antibodies was observed in most of the ALX-0061- or TCZ-treated animals in the CIA disease study, both drugs demonstrated a clear biological effect as shown on CRP levels. A clinical effect was obvious in animals with active drug exposure throughout the course of the study.

Conclusion: ALX-0061 combines high *in vitro* affinity and potency with favorable PK/PD properties in non-human primates and has the potential to be an effective treatment for RA in humans. A Phase I/II clinical trial is ongoing. Interim analysis of the single ascending dose part were encouraging, results from the multiple dose part are expected in H2 2012.

Disclosure: **M. Van Roy**, Ablynx N.V., 3, Ablynx N.V., 1; **H. Ulrichts**, Ablynx N.V., 3, Ablynx N.V., 1; **S. Rossenu**, Ablynx N.V., 3; **S. Jacobs**, Ablynx N.V., 3, Ablynx N.V., 1; **S. Poelmans**, Ablynx N.V., 3; **G. Verheyden**, Ablynx N.V., 3, Ablynx N.V., 1; **M. Vierboom**, None; **B. 't Hart**, None; **J. Baumeister**, Ablynx N.V., 1, Ablynx N.V., 3; **J. B. Holz**, Ablynx N.V., 1, Ablynx N.V., 3, Ablynx N.V., 6.

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In Vivo Quantification of Joint Inflammation in a Murine Arthritis Model by Anato-Molecular Imaging. Smriti K. Raychaudhuri[1], Anupam Mitra[1], Kuang Gong[2], Jian Zhou[2], Jinyi Qi[2], Siba P. Raychaudhuri[1] and Abhijit J. Chaudhari[3]. [1]UC Davis School of Medicine/VA Sacramento Medical Center, Mather, CA, [2]University of California, Davis, Davis, CA, [3]UC Davis School of Medicine, Sacramento, CA

Background/Purpose: Positron Emission Tomography (PET) using the radiotracer 18F-fluorodeoxyglucose (FDG) with X-ray Computed Tomography (CT) has the ability of producing an in vivo, three-dimensional quantitative map of joint metabolism (hence inflammation) with co-registered anatomy. We report our experience on using 18F-FDG-microPET/CT as a quantitative marker for monitoring the pathogenesis of inflammatory arthritis in the collagen induced arthritis (CIA) mouse model.

Methods: CIA was induced in 8–12 weeks old male DBA/1 mice (n=10) by injecting 100mg bovine collagen type II in 100ml of complete Freund's adjuvant intradermally into the proximal tail followed by a second intradermal injection of collagen II with incomplete Freund's adjuvant on day 21. At baseline (1 day before the first injection), 5 randomly chosen animals underwent microPET/CT scan for assessment of baseline status. At days 28 and 56, 5 animals respectively were scanned using microPET/CT, clinical scoring was performed, and joint tissue was derived for histopathological analysis. Quantitative metrics derived from microPET/CT were correlated against clinical score and histopathology outcomes on a per joint and whole limb basis.

Results: Images from microPET showed a marked increase in metabolic activity at affected joints of the upper and/or lower extremity at follow-up compared to baseline values. microCT images provided detailed assessment of bone destruction. At the early time point (day 28), increase in metabolic activity by an average of 20% was observed in the limbs. This further increased to an average of 50% at day 56 as the disease progressed. Focal activity was visualized at individual affected joints by utilizing advanced resolution-recovery methods. microPET/CT metrics at the early and late time points seemed to broadly correlate with clinical and histopathology scores at the arthritic sites.
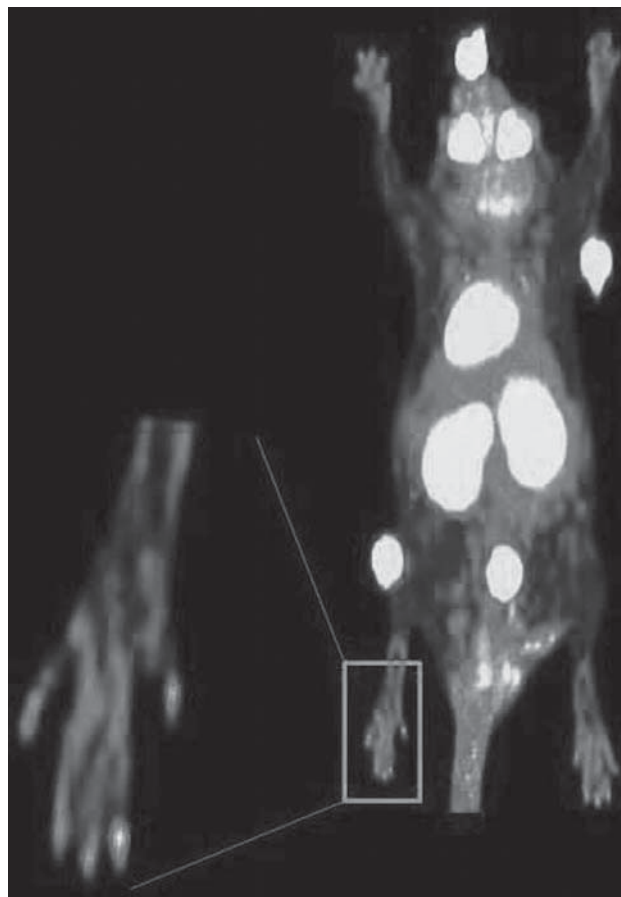
Figure 1. An 18F-FDG-microPET scan of the limb of an animal with collagen induced arthritis. Resolution recovery methods allow unparalleled visualization of the details of inflammatory activity.

Conclusion: Our study shows that quantitative metrics associated with disease pathogenesis can be derived from 18F-FDG-microPET/CT. Changes in clinical score and histopathology outcomes seem to correlate with microPET/CT metrics on both a per joint and whole limb basis. microPET/CT may provide a promising tool for understanding the pathogenesis of arthritis and for monitoring response to new treatments in experimental arthritic models.

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The Potent Phosphoinositide-3-Kinase-(δ,γ) Inhibitor IPI-145 Is Active in Preclinical Models of Arthritis and Well Tolerated in Healthy Adult Subjects. James R. Porter, Janid Ali, Jonathan P. DiNitto, Joi Dunbar, Kerrie Faia, Jennifer Hoyt, Brianne Leary, Alice R. Lim, Christian Martin, Charlotte McKee, Patrick O'Hearn, Melissa Pink, Jennifer Proctor, John Soglia, Bonnie Tillotson, Kerry White, David G. Winkler and Vito J. Palombella. Infinity Pharmaceuticals, Inc., Cambridge, MA

Background/Purpose: Phosphoinositide-3-kinases (PI3K) play pivotal roles in cell signaling and regulate a variety of cellular functions. PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity and are important mediators in inflammatory and autoimmune diseases. IPI-145 is a potent PI3K-δ,γ inhibitor in clinical development for patients with advanced hematologic malignancies and inflammatory/autoimmune disorders. The isoform selectivity and activity of IPI-145 were evaluated using *in vitro* and *in vivo* models, and a Phase 1 study was conducted in healthy adult subjects.

Methods: *In vitro* isoform selectivity and activity of IPI-145 was determined by measuring direct binding to PI3K isoforms, and via isoform-specific cell-based assays. Cell proliferation assays were performed by stimulating human peripheral blood CD19$^+$ B cells or CD3$^+$ T cells in the presence or absence of IPI-145. The PI3K-δ inhibitory activity of IPI-145 in human whole blood was measured in a basophil activation assay. The *in vivo* anti-inflammatory activity of IPI-145 was assessed in a rat collagen-induced arthritis model. Female Lewis rats with established type II collagen-induced arthritis were treated with IPI-145 (0.1 to 10 mg/kg) or vehicle once daily via oral gavage and paw swelling was assessed by plethysmometry.

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple ascending doses of IPI-145 was evaluated in a Phase 1 double-blind, placebo controlled, randomized clinical trial in healthy adult subjects. The *ex vivo* effect of IPI-145 on basophil activation in whole blood was assessed in both the single and multiple ascending dose portions of the study.

Results: IPI-145 potently inhibits PI3K-δ and PI3K-γ, with K_i values of 23 pM and 243 pM, respectively. IPI-145 is significantly less active against the PI3K-α isoform, with a K_i value of 25.9 nM, and inhibits PI3K-β with a K_i value of 1.6 nM. The IC_{50} of IPI-145 in a PI3K-δ-selective assay is 1 nM, and the IC_{50} in a PI3K-γ-selective assay is 32 nM. The IC_{50} values of IPI-145 in human B-cell and T-cell proliferation assays are 0.5 nM and 9.5 nM, respectively. In human whole blood, IPI-145 potently inhibits PI3K-δ specific basophil activation with an IC_{50} of 78 nM. In the rat collagen-induced arthritis model, the area under the ankle diameter versus time curve was reduced 25% to 89% relative to vehicle controls across the 0.1 to 10 mg/kg dose range evaluated.

In the Phase 1 clinical study there was a proportional increase in IPI-145 exposure following single ascending and repeat dose administration. A rapid onset and durable effect of IPI-145 in the *ex vivo* basophil assay was observed at all dose levels. In addition, IPI-145 is clinically well tolerated following single and repeat daily doses of IPI-145.

Conclusion: IPI-145 is a potent inhibitor of PI3K-δ,γ in biochemical and cellular assays and is active in B-cell and T-cell proliferation assays and the rat collagen-induced arthritis model. The preclinical activity and the favorable tolerability, PK, and PD profiles of IPI-145 in healthy human subjects support ongoing Phase 2 clinical trial plans in subjects with autoimmune and inflammatory disorders.

Disclosure: J. R. Porter, Infinity Pharmaceuticals, Inc., 3; **J. Ali**, Infinity Pharmaceuticals, Inc., 3; **J. P. DiNitto**, Infinity Pharmaceuticals, Inc., 3; **J. Dunbar**, Infinity Pharmaceuticals, Inc., 3; **K. Faia**, Infinity Pharmaceuticals, Inc., 3; **J. Hoyt**, Infinity Pharmaceuticals, Inc., 3; **B. Leary**, Infinity Pharmaceuticals, Inc., 3; **A. R. Lim**, Infinity Pharmaceuticals, Inc., 3; **C. Martin**, Infinity Pharmaceuticals, Inc., 3; **C. McKee**, Infinity Pharmaceuticals, Inc., 3; **P. O'Hearn**, Infinity Pharmaceuticals, Inc., 3; **M. Pink**, Infinity Pharmaceuticals, Inc., 3; **J. Proctor**, Infinity Pharmaceuticals, Inc., 3; **J. Soglia**, Infinity Pharmaceuticals, Inc., 3; **B. Tillotson**, Infinity Pharmaceuticals, Inc., 3;

K. White, Infinity Pharmaceuticals, Inc., 3; **D. G. Winkler**, Infinity Pharmaceuticals, Inc., 3; **V. J. Palombella**, Infinity Pharmaceuticals, Inc., 3.

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Differences Between Juvenile and Adult Rodents with Collagen Induced Arthritis. Tracy D. Wilson-Gerwing[1], Isaac V. Pratt[1], David M.L. Cooper[1], Tawni I. Silver[1] and Alan M. Rosenberg[2]. [1]University of Saskatchewan, Saskatoon, SK, [2]Royal University Hospital, Saskatoon, SK

Background/Purpose: Juvenile idiopathic arthritis (JIA) is among the most common chronic diseases of childhood. Arthritis is a potentially disabling disease that can result in ongoing pain and inflammation. Although chronic intra-articular inflammation is common to both children and adults with chronic arthritis there are, apart from onset age, clinical characteristics that further distinguish chronic arthritis in pediatric and adult populations. Collagen induced arthritis (CIA) is a model of inflammatory joint disease. For the first time, this project demonstrates that juvenile and adult rats respond differently to the inflammation and pain resulting from CIA.

Methods: Juvenile (5 wks old) and adult (13 wks old) male Wistar rats were immunized with an emulsion of bovine type II collagen and incomplete Freund's adjuvant. Naive juvenile and adult rats were included as controls. Paws were scored on a scale of 0 (normal paw) to 4 (disuse of paw). Animals were monitored for weight changes. Two weeks following development of arthritis, animals were euthanized and hindpaws were collected and imaged with micro-computed tomography (micro-CT), magnetic resonance imaging (MRI) and ultrasonography. Images were evaluated qualitatively for the degree of soft tissue swelling, joint changes and bone destruction.

Results: Juvenile rats developed arthritis significantly earlier than their adult counterparts (p=0.0126) and experienced less erythema and edema of the affected paws (p<0.0001). Micro-CT of affected hindpaws demonstrated that adult CIA rats exhibited widespread boney changes over the phalanges, metatarsals and tarsus while juveniles had more localized damage of phalanges and metatarsals. MRI of hindpaws confirmed extensive edema and inflammatory insult in the adult CIA rats compared to their juvenile counterparts. Ultrasound of distal phalanges of the juvenile CIA animals showed tissue edema not evident on inspection.
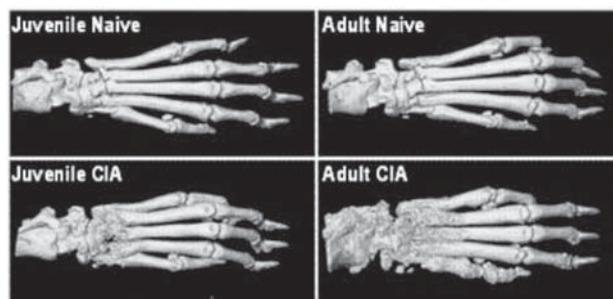
Conclusion: This research is the first to identify differences between juvenile and adult rats with CIA and provides evidence that the disease process may differ between the two age groups. This model will allow for studying arthritis pathogenesis and treatment interventions in juvenile versus adult populations.

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Myeloid Deletion of SIRT1 Aggravates Inflammatory Arthritis Via Nuclear Factor-Kappab Activation in Animal Model of Rheumatoid Arthritis. Sang-il Lee and Yun-Hong Cheon. Gyeongsang National University School of Medicine, Jinju, South Korea

Background/Purpose: The nuclear factor-kappaB (NF-kB) activation plays a pivotal role and macrophages are of central importance in the pathogenesis of rheumatoid arthritis (RA). The SirT1, which is a class III histone deacetylase, deacetylates acetyl group of various transcription factors including NF-kB and modulates their functions, suggesting that myeloid deletion of SirT1 may affect inflammatory arthritis such as RA. The study was performed to assess the function of SirT1 in inflammation and joint destruction in *in vivo* model of RA.

Methods: The mice with myeloid cells-specific deletion of SirT1 (M-SirT1 KO) were generated by using the loxP/Cre recombinase system. K/BxN serum transfer arthritis was induced in M-SirT1 KO mice and their age-matched littermate loxP controls (Sirt1$^{loxP/loxP}$LysM-Cre$^{-/-}$) by injection of K/BxN serum. Arthritis severity was assessed by clinical and histopathologic scoring. The levels of inflammatory cytokines in the joints and serum were measured by ELISA. The NF-kB acetylation, activation, and cytokine/chemokine expression were assessed by Western, EMSA, and ELISA, respectively, using bone marrow-derived macrophages (BMMs).

Results: M-SirT1 KO showed severe form of inflammatory arthritis accompanied by aggravated histopathologic findings including synovial inflammation, bone erosion, and cartilage damage. These effects were paralleled by increased F4/80+ macrophage infiltration into synovium and increased levels of IL-1, IL-6, and RANKL. TNF-α stimulated M-SirT1 KO BMMs displayed hyperacetylated p65 and increased NF-kB binding activity than controls, resulting in increased transcriptional activation of proinflammatory target genes.

Conclusion: This study demonstrates that SIRT1, in macrophages, functions to inhibit NF-kB-mediated transcription, implying that myeloid cell-specific modulation of SirT1 may be beneficial in the treatment of inflammation arthritis such as RA.

Disclosure: S. I. Lee, None; **Y. H. Cheon**, None.

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Oral Administration of a Novel Small Molecule BET Bromodomain Inhibitor, RVX-297, Reduces Disease Severity in a Rat Collagen-Induced Arthritis Model. R. Jahagirdar[1], S. Attwell[1], E.M. Gesner[1], K.G. McLure[1], H.C. Hansen[1], J. Chen[2], J. Wu[1], K. Norek[1], N. Shenoy[2], G.S. Wagner[1] and P. R. Young[1]. [1]Resverlogix Corporation, Calgary, AB, [2]Aravasc Inc., Sunnyvale, CA

Background/Purpose: BET (Bromodomain and Extra-Terminal) proteins have recently emerged as a key epigenetic regulator of genes at the transcriptional level and inhibition of their binding to select histone peptide sequences bearing acetylated lysines can suppress the production of some inflammatory cytokines. Here we determine the activity of a novel, orally bioavailable BET inhibitor, RVX-297, in an animal model of rheumatoid arthritis.

Methods: Binding of RVX-297 to purified bromodomains (BDs) was measured by competition with a tetra-acetylated peptide derived from the amino terminus of histone 4 using fluorescence resonance energy transfer (FRET) and by thermal denaturation of BDs. The effect of RVX-297 on inflammatory mediators in cellular assays was measured by quantitative RT-PCR. RVX-297 was dosed by oral gavage in the rat collagen-induced arthritis (CIA) model, an experimental model of polyarthritis that has been widely used for preclinical evaluation of anti-arthritic agents.

Results: RVX-297 selectively binds to BET bromodomains (e.g. IC$_{50}$s = 0.82 and 0.012mM for BRD4 BD1 and BD2, respectively), but not to other BDs tested. *In vitro*, RVX-297 dose dependently inhibited LPS-induced IL-6 in mouse bone marrow-derived macrophages, (IC50 = 0.3 mM) and T-cell receptor-induced IL-17 mRNA expression in human PBMCs (IC50 of 3.7 mM). Furthermore, in human primary synovial fibroblasts taken from patients with rheumatoid arthritis, RVX-297 inhibited TNFa-induced MMP1, MMP3, RANKL, VCAM-1 and IL-6 expression, all of which have been associated with diseased tissue. These observations suggested that RVX-297 might also show activity in an autoimmune disease model for rheumatoid arthritis.

Following administration of collagen, the rat collagen-induced arthritis model develops a measurable polyarticular inflammation, progressive destruction of cartilage and bone destruction in association with pannus formation. Therapeutic oral administration of RVX-297 from the onset of established arthritis significantly reduced the progression of disease severity in a dose-dependent manner (25 to 75 mg/kg b.i.d.). On day 7 of arthritis, RVX-297 (75 mg/kg b.i.d.) inhibited the increase in ankle diameter by 92% relative to disease controls. To further characterize the pharmacodynamic effects, histopathology of the ankle and knee joints was evaluated. At 50 mg/kg and 75 mg/kg, b.i.d., RVX-297 reduced the histopathology parameters in the in the ankle by 64% and in the knee by 86–94%.The expression of the inflammatory mediators IL-1b, MMP3, MMP13, RANKL, VCAM-1 and IL-6 were all reduced in the ankle joint at the mRNA or protein level.

Conclusion: These results demonstrate that the BET inhibitor RVX-297 significantly decreases clinical signs of disease in a rat model of rheumatoid arthritis, reflecting a decrease in production of a number of cytokine and inflammatory mediators. Therefore, BET inhibitors offer promise for the treatment of rheumatoid arthritis and other autoimmune diseases.

Disclosure: R. Jahagirdar, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **S. Attwell**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **E. M. Gesner**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **K. G. McLure**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **H. C. Hansen**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **J. Chen**, None; **J. Wu**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **K. Norek**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **N. Shenoy**, None; **G. S. Wagner**, Resverlogix Corporation, 3, Resverlogix Corporation, 1; **P. R. Young**, Resverlogix Corporation, 3, Resverlogix Corporation, 1.

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Novel Combination Therapy of Existing Repurposed Therapies, Designed by Predictive Software Modeling, Shows Profound Impact On Disease Progression in a Murine Collagen-Induced Arthritis Model. Shireen Vali[1], Canio Refino[2], Jay Dela Cruz[2], Robinson Vidva[1], Prashant Nair[1], Saumya Radhakrishnan[1], Pradeep Fernandes[1], Taher Abbasi[1] and Gurkirpal Singh[3]. [1]CellWorks Group, Saratoga, CA, [2]InTouch Bio, Alameda, CA, [3]Stanford University School of Medicine, Palo Alto, CA

Background/Purpose: Rheumatoid Arthritis (RA) involves a complex interaction of multiple cell systems, cytokines and mediators. We recently developed a predictive software-based mathematical model that emulates RA pathophysiology at cellular level by incorporating the interaction of known cell systems and associated signaling and metabolic pathways. For this study, this model was used to design a novel therapy for RA by screening more than one million in-vivo equivalent studies. CWG952 is an oral small molecule novel multi-targeted therapy, rationally designed to reduce signs, symptoms and radiologic progression of RA. It combines 3 FDA-approved drugs, repurposed from different indications, in a computer-generated specific ratio of individually sub-therapeutic dosages. We present results of this therapy on the murine collagen-induced arthritis (mCIA) model in an early therapeutic RA setting.

Methods: mCIA was induced in male DBA-1 mice by subcutaneously injecting 0.05 ml/mouse of Bovine Collagen in complete Freund's adjuvant (CFA) emulsion on day 0. A booster dose of collagen in incomplete Freund's adjuvant (IFA) emulsion was given via the same route three weeks later (day 21). On day 21, mice without clinical signs of RA were randomly assigned to 2 groups of 9 and subsequently orally gavaged with CWG952 or vehicle. Front and hind paws were evaluated every other day for clinical disease using a 0–4 scale with a maximum score of 16 per animal. After obtaining a terminal serum sample, mice were sacrificed on day 42. Hind paws were collected, processed and evaluated by a histopathologist blinded to group assignments. Scores (0 to 5), for synovitis, panus formation, cartilage destruction and bone erosion were assigned to each hind paw and mean scores for each mouse were calculated.

Results: Compared to the vehicle control, CWG952 treatment regimen significantly slowed disease progression and decreased the median total clinical disease by 72% and histological disease by 43% respectively. Liver enzyme and lipid assays conducted on the terminal serum samples showed no difference between the Vehicle and CWG952 treatment arms. Key efficacy results are summarized below.

	Vehicle control (n=9), Mean ± SEM	CWG952 (n=9), Mean ± SEM	P values (2-tailed t-test)
Day 39 Paw Scores	10.89±1.01	6.89±1.42	0.044
Paw Scores (mean day 25–41)	7.57±1.07	4.14±1.20	0.060
Synovitis Score	4.22±0.35	3.06±0.39	0.041
Cartilage Destruction	3.72±0.51	2.22±0.46	0.043
Bone Erosion	3.83±0.49	2.28±0.48	0.038

Conclusion: CWG952, an oral combination of 3 FDA-approved drugs, repurposed from other indications, and combined at sub-therapeutic dosages, shows profound impact on disease progression. These results suggest that CWG952 can be an effective therapeutic agent for treating RA.

Disclosure: S. Vali, CellWorks Group, 3; **C. Refino**, Cellworks group, 5; **J. D. Cruz**, CellWorks group, 5; **R. Vidva**, CellWorks Group, 3; **P. Nair**, CellWorks group, 3; **S. Radhakrishnan**, Cellworks group, 3; **P. Fernandes**, CellWorks Group, 3; **T. Abbasi**, CellWorks group, 3; **G. Singh**, None.

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Functional Impairment in an Animal Model for Rheumatoid Arthritis Assessed As Changes in Gait Is Due to Joint Destruction but Not Synovial Inflammation *Per Se.* Gregor Bauer[1], Constantin Aschauer[1], Birgit Niederreiter[1], Josef S. Smolen[2], Kurt Redlich[1] and Silvia Hayer[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: To investigate the individual impact of synovial inflammation, subchondral bone erosion or cartilage damage on functional impairment in an animal model of Rheumatoid Arthritis (RA).

Methods: We analysed gait profiles in human tumor necrosis factor transgene (hTNFtg) animals, using the video-based Catwalk gait analysis system (from Noldus, Netherlands). In this system, mice run along an illuminated glass plate. A digital camera measures light emissions resulting from the contact of paws on the glass plate. We evaluated gait profiles at different time points of disease (6, 10, 15 week of age) in hTNFtg animals. Wildtype littermates served as controls. Bodyweight and clinical signs of arthritis including paw swelling and grip strength were also evaluated. To investigate whether gait changes are pain related, we treated hTNFtg animals with diclofenac (50 mg/kg, i.p.) at week 10 and week 15 after birth and analysed gait profiles before, as well as 1h and 3h after treatment. To analyse inflammatory joint destruction, we quantitatively assessed the extend of synovial inflammation, subchondral bone erosion and cartilage damage on hematoxylin & eosine (H&E), tartrate-resistant acid phosphatase (TRAP) and toluidine-blue stained paw sections. We performed correlation studies between gait parameters and the histopathological components.

Results: We identified several gait parameters among them weight bearing, stride length and contact area of the paw to be significantly decreased in hTNFtg animals compared to sex- and age-matched wildtype animals. Moreover, we found a marked reduction in maximum intensity, an indicator for weight bearing, in week 10 and 15 compared to week 6 old hTNFtg mice. Similar effects were seen in print width, print area, print length, max contact max intensity and max contact area at different stages of disease. Interestingly, analgesic treatment with diclofenac (50 mg/kg, i.p.), resulted in a better improvement of weight-bearing parameters in 10 week old hTNFtg mice than in 15 week old hTNFtg animals indicating an pain independent, irreversible functional impairment in progressed disease. To further investigate to which extend synovial inflammation, subchondral bone erosion or cartilage damage are responsible for the functional impairment of joints, we correlated these components with changes in different gait parameters. We observed strong correlations of various gait parameters with the amount of cartilage damage, whereas subchondral bone erosions correlated to a lesser extend and synovial inflammation did not correlate at all.

Conclusion: Video-based Catwalk gait analysis is a useful tool for quantitative assessment of functional impairment in inflammatory, destructive arthritis. Joint destruction due to cartilage damage but not synovial inflammation *per se* is the most important component leading to functional impairment of hTNFtg mice.

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Non Classical Monocytes Are Required for Initiation Phase While Macrophages Are Necessary for the Resolution Phase in the K/BxN Murine of Inflammatory Arthritis. Alexander V. Misharin[1], G. Kenneth Haines III[2] and Harris R. Perlman[1]. [1]Northwestern University, Chicago, IL, [2]Yale University, New Haven, CT

Background/Purpose: Monocytes and macrophages play an essential function in the pathogenesis of rheumatoid arthritis. However, monocytes and macrophages are a heterogenous population and thus the role that the individual subsets play in the initiation, perpetuation and/or resolution phases of inflammatory arthritis is unknown. Here we utilized strategies to deplete selective populations of monocyte and macrophage subsets but not neutrophils, to uncover the role of these cells in the development and resolution phases of arthritis.

Methods: C57BL/6 and CD11b-DTR transgenic mice were used in the study. Conditional monocyte/macrophage ablation was induced by repetitive administration of diphtheria toxin (DT) into CD11b-DTR transgenic mice during initiation and resolution phases of inflammatory arthritis. Selective depletion of classic Ly6C+CCR2+ monocyte subset was achieved via administration of anti-CCR2 antibody during initiation and resolution phases

of inflammatory arthritis. Arthritis was induced using K/BxN serum transfer model and its severity was assessed using the clinical and histological scoring systems.

Results: Mice pretreated with DT and every three days for 14 days exhibited reduced numbers of peripheral blood monocytes but had no change in neutrophils. Subsequently, these mice initially developed K/BxN serum transfer induced arthritis but the arthritis was short lived and reached only a very moderate severity. An additional study was also performed, which entailed the administration of DT at day 7 and every 3 days until days 14–17 following the initial injection of K/BxN serum. Surprisingly, deletion of monocytes and synovial macrophages markedly delayed the resolution phase of the K/BxN serum transfer induced arthritis. In contrast, depletion of classic monocytes during both progressive phase and resolution of arthritis did not affect development or resolution of arthritis.

Conclusion: These data suggest a dual role for monocytes/macrophages in inflammatory arthritis that may be mediated by the local milieu. Thus, macrophages in the joint may initially function as one of central inflammatory mediators of the destructive arthritis, while their phenotype may be polarized to a wound healing or regulatory type macrophage during the resolution of arthritis. The fact that classic monocytes were dispensable for both initiation and resolution of arthritis is of special interest, since most of the macrophages in the arthritis joint are monocyte derived. Taken together, these data indicate that targeting monocytes and macrophages as single type of monocyte/ macrophage may not be therapeutically beneficial. Future therapies that identify the crucial type of macrophage at each stage of disease will lead to the development of novel therapeutics for RA.

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Predictive Software-Based Mathematical Modeling: A Novel Approach to Development of Oral Therapies for Rheumatoid Arthritis–Validation in a Murine Collagen Induced Arthritis Model. Gurkirpal Singh[1], Robinson Vidva[2], Prashant Nair[2], Saumya Radhakrishnan[2], Pradeep Fernandes[2], Taher Abbasi[2], Canio Refino[3], Jay Dela Cruz[3] and Shireen Vali[2]. [1]Stanford University School of Medicine, Palo Alto, CA, [2]CellWorks Group, Saratoga, CA, [3]InTouch Bio, Alameda, CA

Background/Purpose: Rheumatoid Arthritis (RA) involves complex interactions of multiple cell systems, cytokines and mediators, and interlinked signaling. While molecularly-targeted therapies manipulate specific interactions, it is possible that other, previously redundant, paths are subsequently activated, thus causing drug resistance. Ideal therapy design requires simultaneous modulation of multiple targets to achieve eventual convergence and synergy. A predictive software algorithm would tremendously increase the ability to identify such therapies.

Methods: A predictive in-vivo equivalent simulation technology emulating RA pathophysiology at cellular and molecular level was designed by assimilating information from 8928 publications over the past 8 years. The simulation platform is a co-culture of 8 cell systems representing RA phenotypes, associated signaling and metabolic networks and includes nearly 100000 cross-talks and interactions among approximately 31366 molecules. The platform was extensively validated using more than 4000 studies and correlated with retrospective human clinical drug data and animal experiments. A digital library representing 100 targeted drugs from different indications was screened in combinations of two's and three's translating to more than one million in-vivo studies. Automated analytics engine using the assay data from the studies generated a therapy candidate which is a combination of 3 oral FDA-approved drugs (CWG952), based on criteria of efficacy, synergy and PK/PD compatibility. For in-vivo validations, mCIA was induced in male DBA/1 mice and those with paw scores between 1 and 5 on day 19 were randomly assigned to treatment arms (9/group): CWG952 and anti-TNF with treatment started at 12hrs of enrollment.

Results: The RA predictive model was dynamically simulated to disease condition followed by application of CWG952 therapy. The simulations predicted a percentage reduction in TNF, IL6, IL1B, IL17a, RANKL and CRP by 81.8, 90.5, 85.9, 86.5, 85.1 and 95.5 respectively from disease condition with respect to control state. The model also predicted a 83.1 % reduction in bone and cartilage degradation and 85.1% inhibition of osteoclast activity. Anticipated effect on phenotypic disease markers were close to those seen in clinical trials of TNF-alfa inhibitors. The figure shows results from animal experiments (mCIA model) demonstrating a comparable efficacy to etanercept.
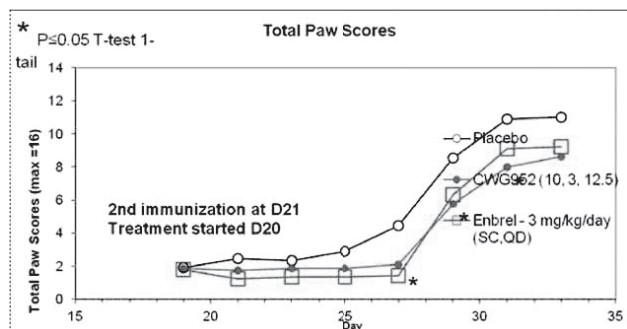
Conclusion: In-vivo validations of mathematically-designed CWG952 show results comparable to etanercept. These results, along with other previously published validations [1], suggest a robust validation of a software-based mathematical modeling approach that incorporates the complex interaction of immunomodulating molecules, and can potentially lead to the development of innovative therapies for immunological diseases.

1. Shanmugam MK et al. J Mol Med (Berl). 2011 Jul;89(7):713–27.

Disclosure: G. Singh, None; **R. Vidva**, CellWorks Group, 3; **P. Nair**, CellWorks Group, 3; **S. Radhakrishnan**, Cellworks group, 3; **P. Fernandes**, CellWorks Group, 3; **T. Abbasi**, CellWorks group, 3; **C. Refino**, Cellworks group, 5; **J. D. Cruz**, intouchbio, 5; **S. Vali**, CellWorks Group, 3.

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Sclerostin Protects Against Inflammatory Bone Loss by Regulating Tnfalpha Mediated p38-Mapkinase Activation. Corinna Wehmeyer[1], Christina Wunrau[1], Athanasios Stratis[1], Ina Kramer[2], Michaela Kneissel[2], Thomas Pap[1] and Berno Dankbar[1]. [1]University Hospital Muenster, Muenster, Germany, [2]CH-4056 Basel, Switzerland

Background/Purpose: Progressive loss of joint structure is a hallmark of rheumatoid arthritis (RA). TNFα has been shown to promote the destruction of bone by increasing the number of bone-resorbing osteoclasts and decreasing the number of bone-forming osteoblasts. The Wnt-Inhibitor sclerostin negatively regulates osteoblast differentiation and the disruption of this endogenous inhibitor increases the ability of Wnts to stabilize β-catenin and stimulate osteogenesis. Since it has been shown that sclerostin is upregulated in response to TNFα, we studied its role in inflammatory arthritis using the hTNF transgenic (hTNFtg) mice model of RA.

Methods: Sclerostin expression was assessed by immunohistochemistry, Western-blot-analysis, and RT-PCR. The localisation of β-catenin was determined by immunfluorescence staining. Western-blot-analysis was used to evaluate p38-MAPK phosphorylation. Sclerostin knockout (SOST$^{-/-}$) mice were crossed with hTNFtg mice to generate TNFα overexpressing mice that lack sclerostin (SOST$^{-/-}$hTNFtg). Clinical disease severity, bone erosion, cartilage destruction and synovial inflammation in SOST$^{-/-}$hTNFtg and hTNFtg mice were evaluated by histomorphometric, x-ray and micro-CT analysis. hTNFtg mice were treated with blocking antibodies against murine sclerostin or control-vehicle.

Results: Immunohistological staining revealed high expression of sclerostin in synovial tissue of hTNFtg ankle joints, especially in infiltrating synovial-like fibroblasts (SF). Only negligible staining was observed in wildtype animals. *In vitro,* hTNFtg SF expressed sclerostin whereas wildtype did not. Unexpectedly, radiographic, microCT and histopatological examination of hind paw joints of SOST$^{-/-}$hTNFtg mice demonstrated that the loss of sclerostin dramatically accelerated joint damage in this mouse model of RA. SOST$^{-/-}$hTNFtg mice displayed significantly more synovial hyperplasia, proteoglycan loss and bone erosion compared to hTNFtg mice. Moreover, injection of a neutralizing antibody to murine sclerostin in hTNFtg mice did not improve clinical signs of arthritis and but led to elevated inflammation as well as bone erosion. *In vitro,* upon stimulation of hTNFtg and SOST$^{-/-}$hTNFtg SF with recombinant Wnt3a, β-catenin translocated to the nucleus, but this was not affected by loss of sclerostin. Of note, recombinant sclerostin was able to inhibit the TNFα induced p38-MAPK activation of wildtype SF.

Conclusion: Since p38-MAPK signalling specifically regulates inflammation induced bone loss, our data strongly suggest a protective function of sclerostin against TNFα-mediated joint destruction by inhibition of TNFα induced p38-activation in synovial fibroblasts. The blockade of inflammatory cytokine action proposes a complete novel function of sclerostin.

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The Loss of S100A4 Prevents Induction of Experimental Arthritis in Human Tumour Necrosis Factor Transgenic Mouse Model. Michal Tomcik[1], Christine Boehm[2], Carina Scholtysek[3], Lucie Andres Cerezo[1], Wolfgang Baum[3], Clara Dees[3], Christian Beyer[3], Jerome Avouac[4], Pawel Zerr[3], Katrin Palumbo-Zerr[3], Alfiya Akhmetshina[3], Radim Becvar[1], Oliver Distler[5], Mariam Grigorian[6], Gerhard Kroenke[3], Georg A. Schett[3], Joerg HW Distler[3] and Ladislav Senolt[1]. [1]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Medical University of Vienna, Vienna, Austria, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [5]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [6]Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark

Background/Purpose: Our previous study demonstrated increased levels of S100A4 protein in sera, synovial fluid and synovial membrane of patients with rheumatoid arthritis (RA) compared to osteoarthritis. S100A4 regulates apoptosis and induces production of matrix metalloproteinases by synovial fibroblasts. Furthermore, S100A4 stimulates synthesis of tumour necrosis factor (TNF)-α by mononuclear cells and CD3 lymphocytes. The aim of this study was to investigate the effect of loss of S1004 in the induction of experimental arthritis in the human TNF transgenic (hTNFtg) mouse model.

Methods: We crossed the heterozygous hTNFtg mice with S100A4 knockout (S100A4$-/-$) mice. Following genotype determination, mice were clinically assessed for paw swelling, grip strength, leg movement and body weight every week from 6th to 14th week of age in a blinded manner. Sections of hind paws and tibias were histologically analyzed for synovial inflammation, cartilage loss, bone erosions, osteoclast numbers and bone formation parameters with the OsteoMeasure image analysis system.

Results: In the group of hTNFtg;S100A4$-/-$ mice, paw swelling and grip strength were significantly improved compared to hTNFtg;S100A4+/+ (p<0.05 for both parameters). Although not significant, body weight of hTNFtg;S100A4$-/-$ mice was slightly increased. Consistent with the clinical observations, histological analysis of the tarsal joints of hTNFtg; S100A4$-/-$ mice showed reduced pannus formation (area of inflammation decreased by 66±3%, p<0.01) and cartilage destruction (cartilage loss decreased by 63±6%, p<0.01) compared to hTNFtg;S100A4+/+ mice. Similarly, osteoclast numbers were decreased by 84±3%, (p<0.01) and bone erosions were less severe (area of bone erosion decreased by 81±4%, p<0.01) in hTNFtg;S100A4$-/-$ mice. Furthermore, hTNFtg;S100A4$-/-$ mice were protected from systemic bone loss. Absence of S100A4 completely reversed increased osteoclast formation and bone resorption in hTNFtg mice. hTNFtg; S100A4$-/-$ mice had an increased bone volume per total volume (BV/TV) by 78±20% (p<0.05), as well as a decrease in trabecular separation by 39±4% (p<0.05) compared to hTNFtg;S100A4+/+. The protection from systemic bone loss observed in hTNFtg;S100A4$-/-$ mice was further supported by decreased numbers of osteoclasts per bone perimeter (N.Oc/B.Pm decreased by 43±2%, p<0.01), decreased bone surface covered by osteoclasts (Oc.S/BS decreased by 52±3%, p<0.01), increased numbers of osteoblasts per bone perimeter (N.Ob/B.Pm increased by 129±20%, p<0.05) and increased bone formation rate per bone surface (BFR/BS increased by 112±18%, p<0.05).

Conclusion: These results suggest that the loss of S100A4 effectively prevented the induction of experimental arthritis via protecting against TNF-induced synovial inflammation, cartilage and bone destruction, and systemic bone loss. Thus, S100A4 might represent a novel therapeutic target in RA.

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Liver Fibrosis Evaluated by Shearwave Elastograpy Is Associated with Body Mass Index and Serum AST, but Not Methotrexate Cumulative Dose and Duration in Patients with Rheumatoid Arthritis. Tae Yeob Kim, So-Young Bang, Joo Hyun Sohn and Hye-Soon Lee. Hanyang University Guri Hospital, Guri, South Korea

Background/Purpose: Methotrexate (MTX) is a widely used drug for treatment of rheumatoid arthritis (RA), and a concern with drug-related liver fibrosis is an unsolved problem. ShearWave elastography (SWE) is a newly developed, repeatable and reproducible real-time elastography technique for the evaluation of liver fibrosis. This study aimed to detect the associated factors with liver stiffness (LS) in patients taking MTX with RA.

Methods: We prospectively analyzed a total of 171 patients (female 135, mean age 54.3 ± 9.4 years) with RA who underwent SWE, serum sample and arthropometric measurement on the same day (August 2011-February 2012). Also, we calculated MTX cumulative dose and duration. LS measured by SWE is expressed in kilo-Pascal (kPa) with mean value. Based on the previous our study, significant fibrosis defines as liver stiffness above 7.0 kPa. The factors associated with liver fibrosis were evaluated by univariate and multivariate analysis using SPSS 19.0 Statistical Software.

Results: Among 171 patients, 37 paients (21.6%) had SWE results suggesting significant fibrosis. In univariate analysis, body weight, body mass index (BMI), waist circumference, serum AST, ALT, HDL, glucose, and metabolic component were associated with liver fibrosis (p<0.05). Neither MTX cumulative dose (4768 ± 3145 mg vs. 4870 ± 3436 mg, p=0.87) nor MTX duration (330 ± 203 weeks vs. 338 ± 196 weeks, p=0.84) was associated with elevated liver stiffness. In multivariate analysis, only BMI $\geq 25 \text{kg/m}^2$ (odds ratio 18.9, 95% confidence interval 4.0–91.2, p<0.001) and serum AST levels (expB=1.198, 95%CI 1.008–1.251, p=0.036) were associated with significant fibrosis.

Conclusion: Significant fibrosis by SWE was detected in about 20% of patients taking MTX with RA, and was associated with only high BMI and serum AST levels, but not MTX cumulative dose and duration.

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Preliminary Results From a Controlled Study Assessing the Humoral Immune Response to Vaccines in Rheumatoid Arthritis Patients Treated with Tocilizumab. CO Bingham III[1], Warren C. Rizzo[2], Micki Klearman[3], Azra Hassanali[4], Ruchi Upmanyu[5] and Alan J. Kivitz[6]. [1]Johns Hopkins University, Baltimore, MD, [2]Advanced Arthritis Care & Research, Scottsdale, AZ, [3]Genentech Inc, South San Francisco, CA, [4]Genentech Inc, San Francisco, CA, [5]Roche, Welwyn Garden City, United Kingdom, [6]Altoona Center for Clinical Research, Duncansville, PA

Background/Purpose: Tocilizumab (TCZ) is an IL-6–receptor inhibitor for treatment of rheumatoid arthritis (RA) patients (pts). Because TCZ may impact how IL-6 modulates T-cell activation and regulates B-cell differentiation, response to vaccination in TCZ-treated pts is of interest. VISARA is the first randomized controlled study of the effects of TCZ on response to 23-valent pneumococcal polysaccharide vaccine (23VPPV) and tetanus toxoid vaccine (TTV) in RA pts on stable MTX. Preliminary analysis of study endpoints and post hoc analyses assessing impact of concomitant oral corticosteroids (OCS) are presented.

Methods: RA pts with inadequate response/intolerance to ≥ 1 anti-TNF agent were stratified by age and randomly assigned (2:1) to TCZ 8 mg/kg IV every 4 wks + MTX (TCZ) or MTX only (MTX). Baseline (BL) serology samples were collected 3 wks after the first infusion, just before 23VPPV and TTV vaccination. Anti-pneumococcal and anti-tetanus antibody titers were evaluated at wk 8, after which all pts received TCZ+MTX for 12 more wks. Endpoints were proportion of pts with positive response (2-fold or >1 mg/L increase in serum antibody titers) to ≥ 6 of 12 23VPPV serotypes (primary) and proportion with positive response (4-fold or ≥ 0.2 mg/L increase in serum antibody titers) to TTV (secondary) at wk 8 (5 wks postvaccination).

Results: Data are available for 74/91 enrolled pts and presented for 61 pts who met per-protocol criteria (ie, received ≥ 1 dose of study medication and both vaccines, had available BL and 8-wk titer samples and no protocol violations). At wk 8, 53.7% of TCZ+MTX and 65% of MTX pts responded to ≥ 6 of 12 23VPPV serotypes, a difference of 11.3% (not statistically significant at 95% CI level [CI: –37.3, 14.6]). When evaluated by age, the proportion of responders >50 y was lower by 10% in both arms. More MTX than TCZ+MTX pts responded to serotype combinations (from ≥ 1 to 12). However, the 95% CIs for the proportions of responders were wide and overlapping in both arms (Figure). A higher proportion of TCZ+MTX (43.9%) vs MTX pts (36.8%) responded to TTV, but the difference (7.1%) was not significant ([95% CI: –19.5%, 33.6%]). Two TCZ pts had nonprotective BL antibody titers (ie, <0.1 IU/mL); both achieved protective levels by wk 8. In pts taking OCS, the mean BL OCS dose was slightly higher in the responder than in the nonresponder MTX group, whereas the doses were similar in both TCZ+MTX groups (data not shown). Safety of TCZ was consistent with previous reports in RA pts.

Percentages of Pts Responding to Combinations of 12 23VPPV Serotypes (mean values and 95% CIs)
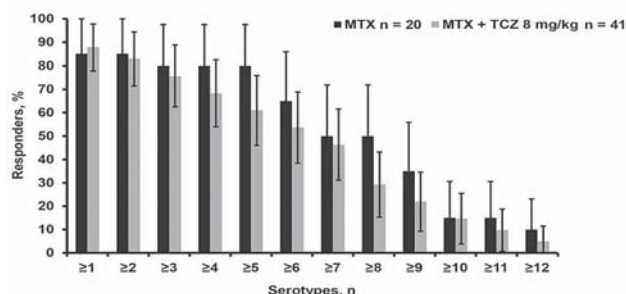
Conclusion: Based on the 95% CI for the difference in proportions of responders, TCZ does not appear to significantly attenuate responsiveness to 23VPPV or TTV compared with MTX. However, given the small study sample size and the short duration of TCZ treatment before vaccination, in line with current recommendations, pts should, if possible, be up to date with required immunizations before initiating TCZ to maximize the vaccine response.

Disclosure: **C. Bingham III**, Genentech, Roche Pharmaceuticals, 5; **W. C. Rizzo**, Advanced Arthritis Care, 2, UCB, Savient, 5, Amgen, Takeda, UCB, Roche Pharmaceuticals. Abbott, 8; **M. Klearman**, Genentech and Biogen IDEC Inc., 3; **A. Hassanali**, Genentech and Biogen IDEC Inc., 3; **R. Upmanyu**, Roche Pharmaceuticals, 3, Roche Pharmaceuticals, 1; **A. J. Kivitz**, Roche Pharmaceuticals, 8.

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Reduction of Inflammation with Abatacept and Tocilizumab Results in Lower N-Terminal Pro Brain Natriuretic Peptide Levels in Patients with Rheumatoid Arthritis: Results From Prospective Cohort Studies. Inge A.M. van den Oever and Mike T. Nurmohamed. Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) patients are at increased risk of heart failure (HF). The chronic inflammatory state in RA is associated with increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker for HF. Recently, a study demonstrated that NT-proBNP levels in RA patients decreased under TNF-blocking therapy. It is unknown whether this is also observed in biologics with other mode of actions. We evaluated the effects of abatacept and tocilizumab therapy on NT-proBNP levels.

Methods: In 34 RA consecutive patients starting with abatacept (10 mg/kg every 4 weeks) and 14 RA consecutive patients starting with tocilizumab (8 mg/kg every 4 weeks), disease activity parameters and serum samples were collected at baseline and after 12 weeks of therapy. Clinical response was assessed using EULAR response criteria. Responding patients comprised both good and moderate EULAR responders. NT-proBNP levels were measured by the Elecsys 2010 electrochemiluminescence method (Roche diagnostics). For statistical analyses t-tests, Mann-Whitney U tests and linear regression were used.

Results: NT-proBNP levels did not change significantly after 12 weeks (p=0.6) and there were no significant differences in NT-proBNP levels at baseline or after 12 weeks of treatment between the tocilizumab and abatacept group (p=0.16 and p=0.3, respectively). 34 patients (71%) were EULAR responders, (6=12% good, 28=88% moderate) and 14 patients (29%) were non-responders. Baseline DAS28, CRP and BSE were higher, though not significantly, in responders compared to non-responders (table). Baseline NT-proBNP levels were higher in responders versus non-responders (p=0.044). Change in NT-proBNP levels after 12 weeks of treatment was significantly different between responders and non-responders (p=0.002), with decreasing NT-proBNP levels in responders and increasing levels in non-responders.

Table 1. RA-related factors and NT-proBNP levels at baseline and after 12 weeks of treatment

	Baseline	12 weeks	p value
NT-proBNP (pg/ml)	7.5 (3.8–19.2)	7.8 (4.5–16.9)	0.599
Responders	8.1 (4.0–23.4)	6.7 (4.1–14.6)	0.013
non-responders	6.2 (2.9–8.5)	13.43 (4.9–17.3)	0.068
CRP (mg/l)	16.5 (2.8–42.5)	7.5 (1.0–13.5)	0.008
Responders	23.0 (4.3–44.8)	7.5 (1.0–12.8)	0.001
non-responders	7.5 (1.3–19.5)	7.5 (3.0–16.5)	0.760
ESR (mm/h)	37 (21–60)	17 (7–30)	<0.001
Responders	39 (27–63)	16 (6–24)	<0.001
non-responders	29 (10–50)	27 (16–46)	0.958
DAS28	5.72 (1.44)	4.34 (1.37)	<0.001
Responders	5.96 (1.15)	3.90 (1.07)	<0.001
non-responders	5.12 (1.88)	5.40 (1.47)	0.390

mean (SD) or median (IQR)

difference between EULAR responders versus non-responders in delta NT-proBNP after 12 weeks
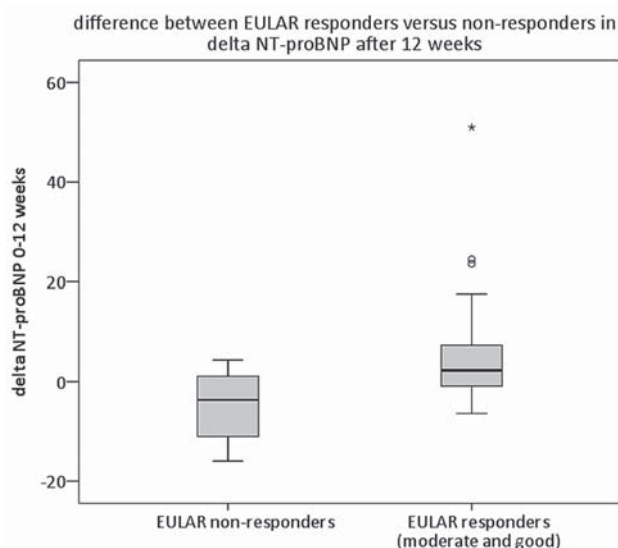
Conclusion: There was a remarkable difference in the course of NT-proBNP levels between EULAR responders and non-responders, as responders started with higher baseline levels which decreased significantly under both abatacept and tocilizumab treatment, while in contrast the NT-proBNP levels of non-responding patients increased. These findings indicate favourable effects of abatacept and tocilizumab on cardiac function in RA patients responding to treatment and underscore the importance of tight control of systemic inflammation in order to decrease CV risk.

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Prospective Follow-up of Tocilizumab Treatment in 764 Patients with Refractory Rheumatoid Arthritis: Tolerance and Efficacy Data From the French Registry Regate (REGistry –RoAcTEmra). Jacques Morel[1], Marie-Odile Duzanski[2], Thomas Bardin[3], Alain G. Cantagrel[4], Bernard Combe[1], Maxime Dougados[5], Rene-Marc Flipo[6], Jacques-Eric Gottenberg[7], Xavier Mariette[8], Martin Soubrier[9], Olivier Vittecoq[10], Alain Saraux[11], Thierry Schaeverbeke[12] and Jean Sibilia[13]. [1]Hopital Lapeyronie, Montpellier, France, [2]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [3]Hôpital Lariboisière, Paris, France, [4]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [5]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [6]Hopital R Salengro CHRU, Lille CEDEX, France, [7]Strasbourg University Hospital, Strasbourg, France, [8]Université Paris-Sud, Le Kremlin Bicetre, France, [9]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [10]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France, [11]CHU de la Cavale Blanche, Brest Cedex, France, [12]Groupe Hospitalier Pellegrin, Bordeaux, France, [13]CHU Hautepierre, Strasbourg, France

Background/Purpose: To assess tolerance and safety of rheumatoid arthritis (RA) treatment by tocilizumab (TCZ) in real life

Methods: The French Society of Rheumatology and the Club Rheumatism and Inflammation set up the REGATE registry to prospectively collect, every 6 months for 5 years, data from 1500 patients treated with TCZ for refractory rheumatoid arthritis.

Results: From January 13th 2011 to April 2nd 2012, RA patients treated by TCZ initiated after January 1st 2010 have been prospectively included from 76 French centres in the REGATE registry. Among the 764 included patients (women: 80.1%, mean age 57.2±13.4 years, mean disease duration: 14.1 years (9.57), mean number of prior DMARD: 2.6 (±1.6), 76.3% RF-positive, 77.9% ACPA positive), 5.4% of patients had a history of cancer and 6.15% of severe infection, 19.1% of cardiovascular events and 24.2% of dyslipidemia before TCZ. 16.2% had not received any anti-TNF prior to TCZ and the mean number of biologics before TCZ was 2.1±1.5. The last biologic prescribed before initiation of TCZ was an anti-TNF for 59.1% of patients, rituximab for 17.7%, abatacept for 22.2% and others (kineret, ocrelizumab) for 1%. The median time between the last dose of the previous biologic and the first infusion of TCZ was 1.83 months (0–120).

Before TCZ, mean DAS28 was 5.18±1.3. 68.7% of the patients received corticosteroids with a mean dose of 12.93 ± 41.4 mg/day. 38.3% of patients were treated with TCZ as monotherapy, and 61.7% with a concomitant DMARD mainly methotrexate (83%). After 1.3 years, the drug was stopped for 79 patients: 39 of them (51.9%) for non response and in 33 of them (44%) for safety reasons. 440 patients have already had at least 1 follow-up visit with mean current follow-up duration of 7.5 (±4.6) months corresponding to an exposure of 274 patients/year (PY). Ten patients discontinued TCZ for infusion-reactions (2.3%). Twenty two severe infections (11 soft tissues, 4 gastrointestinal, 3 articular, 3 respiratory tract and 1 genital) were reported in 20 patients corresponding to a rate of severe infections of 8.0/100 PY. The other SAE were 3 gut perforations (1/100 PY), 2 lymphoma (0.7/100 PY), 1 skin cancer (0.36 /100 PY), but no cardiovascular event and death were recorded.

Conclusion: These first and preliminary results of the REGATE registry show that a high proportion of patients treated with TCZ was previously treated by anti-TNF (87%) even though it can be prescribed as a first line biologic. In addition, TCZ is not infrequently prescribed in monotherapy in clinical practice (38%). Severe infections are in the higher range observed with biologics but deserve to be confirmed after longer exposure duration.

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Meta-Analysis: Influence of Methotrexate, Anti-TNF and Rituximab On the Immune Response to Influenza and Pneumococcal Vaccines in Patients with Rheumatoïd Arthritis. Charlotte Hua[1], Thomas Barnetche[2], Bernard Combe[3] and Jacques Morel[3]. [1]Hôpital Lapeyronie, Montpellier, France, [2]CHU Bordeaux Pellegrin, Bordeaux, France, [3]Hopital Lapeyronie, Montpellier, France

Background/Purpose: Vaccines against influenza and streptococcus pneumonia are currently recommended for patients with rheumatoid arthritis (RA). This meta-analysis assesses current literature data on the impact of methotrexate (MTX), anti-TNF or rituximab (RTX) on the humoral response to pneumococcal and influenza vaccines in RA patients.

Methods: Data sources were Medline, Embase and Cochrane databases and ACR 2011 abstracts. To be included, studies had to contain a group of RA patients treated with MTX, anti-TNF or RTX and a control group of RA patients without the treatment of interest. Both groups had to receive either pneumococcal or influenza vaccine. **Results** had to show rates of responders based on the antibody response ratio, corresponding to the level of antibodies measured at 1 month following vaccination as numerator and the level of antibodies at vaccination as denominator, for pneumococcal serotypes 6B and 23F or one of the 3 strains of influenza virus: H1N1, H3N2 and B. Out of 59 potentially relevant studies, 11 met inclusion criteria. Odds-ratios and their 95% confidence intervals were pooled using the generic inverse variance method. The heterogeneity between studies was assessed using the Cochran's Q-test and the I^2 value, and a random effect model was performed if necessary. All the analyses were realized with the RevMan software 5.1 version. A significant statistical threshold of 0.05 was used.

Results:

Following pneumococcal vaccination: response was reduced in patients treated with anti-TNF + MTX compared to those treated with anti-TNF not combined with MTX (pooled odds-ratio (OR) = 0.58; 95% confidence interval (CI) 0.36–0.94; p=0.03 for 23F and 0.33; 95% CI 0.20–0.54; p<0.0001 for 6B). Rates of responders were similar in patients under MTX alone and those treated with MTX +anti-TNF (OR = 1.21; 95% CI 0.83–1.75 for 23F and 0.96; 95% CI 0.57–1.59 for 6B). The immune response was lower in patients treated with RTX, combined in most cases with MTX, than in patients under MTX as monotherapy (OR = 0.22; 95% CI 0.11–0.47; p<0.0001 for 23F and 0.25; 95% CI 0.11–0.58; p=0,001 for 6B).

Following influenza vaccination: proportion of responders was not different between patients treated with MTX and those not treated with MTX (OR= 1.36; 95%CI 0.69–2.68 for H1N1, 1.33; 95%CI 0.70–2.53 for H3N2, 1.28; 95%CI 0.64–2.56 for B). Response was decreased in patients under PBO+MTX versus patients under PBO not combined with MTX (OR for responders to at least 2 strains = 0.35; 95% CI 0.18–0.66; p=0.001). Patients treated with anti-TNF with or without MTX had same responders rates than patients whose treatment did not include anti-TNF (OR for responders to at least 2 strains = 0.42; 95% CI 0.17–1.09). Patients under RTX in monotherapy or in combination with DMARDs had a diminished humoral response compared to patients treated with DMARDs without RTX, significance being reached for H3N2 and B (OR = 0.11; 95% CI 0.04–0.31; p<0.0001 and 0.29; 95% CI 0.10–0.81; p=0.02).

Conclusion: Immune response to both vaccines is reduced with RTX but not with anti-TNF. MTX decreased immunogenicity of pneumococcal vaccine whereas results about influenza vaccine are less homogeneous but suggest an impairment of the response due to MTX therapy.

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The Effect of Combination Therapy and Prednisolone On Haemostatic Markers in Rheumatoid Arthritis. Inge A.M. van den Oever[1], Danka J.F. Stuijver[2], Debby den Uyl[3], Bregje van Zaane[4], Marieke M. ter Wee[5], Willem F. Lems[5], D. van Schaardenburg[1], Joost C.M. Meijers[4], Victor E.A. Gerdes[4] and M. T. Nurmohamed[6]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]Academic Medical Center, Amsterdam, Netherlands, [3]VU University medical centre, Amsterdam, Netherlands, [4]Slotervaart Hospital, Amsterdam, Netherlands, [5]VU University Medical Center, Amsterdam, Netherlands, [6]VU University Medical Center/Jan van Bremen Research Institute, Amsterdam, Netherlands

Background/Purpose: There is accumulating evidence that rheumatoid arthritis (RA) should be considered as prothrombotic state, explaining the increased risk of thromboembolic events. Suppressing inflammation could reduce this hypercoagulability. COBRA, the combination of step-down prednisolone, methotrexate and sulfasalazine (SSZ) is an effective antirheumatic therapy. However, glucocorticoids have been identified as risk factor for the development of thromboembolism. In this study we evaluated the course of haemostatic markers in RA patients during strong anti-inflammatory therapy and the dose-dependent effect of prednisolone on coagulation and fibrinolysis.

Methods: 22 patients diagnosed with early RA, were randomised to either COBRA therapy or an attenuated form (COBRA-light) with halved initial prednisolone dose and no SSZ. At baseline and after 1, 4 and 26 weeks of treatment, 10 ml of citrated blood was collected for measurement of prothrombin time (PT), activated partial thromboplastin time (aPTT) and five haemostatic markers: prothrombin fragment 1+2 (F1+2), factor VIII (FVIII), von Willebrand factor (vWF), plasminogen activator inhibitor (PAI-1) and D-dimer. For statistical analyses t-tests and linear regression were used.

Results: Baseline characteristics were not significantly different between the 2 groups (each 11 patients). DAS44, CRP and ESR decreased significantly after 26 weeks (p<0.001). aPTT, D-dimer and F1+2 decreased during treatment in all patients (table). There was a significant positive association between decrease in CRP and BSE with D-dimer and decrease in CRP, BSE and DAS44 with F1+2 at all time points. There was no difference in the markers between the two groups, except for a stronger decrease in aPTT after 2 weeks (p=0.03) in the COBRA group. This difference was no longer seen at 4 weeks.

Table. Change in haemostatic factors in all 22 RA patients

	baseline	2 weeks	4 weeks	26 weeks
DAS44	3.9 (0.6)			1.6 (0.9)**
ESR (mm/h)	25 (12–43)			4 (3–7)**
CRP (mg/L)	13.0 (5.5–29.5)	2.5 (2.5–2.7)**	2.5 (2.5–4.5)**	2.5 (2.5–2.7)**
aPTT (sec)	29.9 (28.5–34.9)	26.2 (25.1–31.4)**	26.8 (25.5–29.9)**	27.9 (26.6–30.4)*
PT (sec)	11.2 (0.4)	11.3 (0.5)	11.1 (0.5)	11.2 (0.5)
FVIII (%)	142 (105–179)	151 (112–196)*	152 (123–193)	127 (111–170)
D-dimer (FEU/L)	1.18 (0.63–3.34)	0.55 (0.29–1.26)**	0.49 (0.26–0.84)**	0.25 (0.21–0.78)**
F1+2 (pmol/L)	342 (253–496)	192 (146–305)*	212 (160–285)**	213 (153–319)*
PAI-1 (ng/ml)	35 (25–49)	40 (19–63)	24 (16–53)	42 (17–73)
vWF (%)	115 (87–149)	121 (86–157)	138 (94–189)*	101 (86–143)

Values are mean (SD) or median (IQR) *p <0,05 and **p<0.001 change compared to baseline

Conclusion: Overall, both COBRA and COBRA-light therapy induced an improvement of inflammatory and procoagulant factors in RA. Prednisolone could have attenuated this effect, since the coagulation factors FVIII, vWF increased during the first weeks, when doses of prednisolone were highest. However, there were no remarkable differences in the haemostatic markers between the two groups, indicating that doses higher than 30 mg of prednisolone have no attributable effect on the procoagulant state in RA.

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Delayed Onset of Hepatitis and/or Neutropenia in Patients with Rheumatoid Arthritis Treated with Combination Therapy of Methotrexate and Leflunomide. Seung Won Choi[1], Ji Seon Oh[1], You Jae Kim[2], Bon San Koo[3], Min Wook So[3], Yong-Gil Kim[3], Chang-Keun Lee[3] and Bin Yoo[3]. [1]University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, South Korea, [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [3]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Background/Purpose: The adverse effects of combination therapy of methotrexate (MTX) and leflunomide (LEF) have been reported in many studies. Because combination of various doses of each drug is used in clinical practice, the reported incidence of hepatitis and neutropenia is variable. Currently, the incidence of such adverse events according to the duration of combination therapy has not been established. The purpose of this study is to evaluate the incidence of delayed onset of hepatitis or neutropenia in patients with rheumatoid arthritis (RA) treated with combination therapy of MTX and LEF.

Methods: We retrospectively reviewed medical records of 144 RA patients who had been treated with combination of fixed dose of MTX and 20mg of LEF, and who had been followed up with regular laboratory evaluation for longer than 6 months. We evaluated the incidence of hepatitis (serum aminotransferases greater than two times the upper limit of normal) and/or neutropenia (absolute neutrophil count < 1500/uL) according to the treatment duration.

Results: Mean age of patients was 55.3 ± 9.6 (range, 34–77; male: female, 27:117). Mean duration of combination therapy of MTX and LEF was 17.8 ± 13 months (range, 1.6–59.5 months; median 14 months). Mean doses of MTX was 9.8 ± 1.5 mg per week (range, 7.5–15 mg/week). The overall incidence of hepatitis was 19% (20/144). Of 144 patients, 14 (10%), 8 (6%), and 2 (1%) had delayed onset of hepatitis after 6, 12, and 24 months, respectively. Among patients with delayed onset of hepatitis after 6 months, mean duration of combination treatment was 14.5 ± 6.3 months (range, 8.3–26.0 months), and calculated cumulative doses of MTX and LEF, 628.7 ± 307.1 mg and 8.7 ± 6.0 g, respectively. The overall incidence of neutropenia was 6% (8/144). Of 144 patients, 7 (5%), 4 (3%), and 1 (1%) had delayed onset of neutropenia after 6, 12, and 24 months, respectively. Among patients with delayed onset of neutropenia after 6 months, mean duration of combination treatment was 18.0 ± 16.0 months (range, 6–52 months), and calculated cumulative doses of MTX and LEF, 774.0 ± 691.3 mg and 14.0 ± 10.9 g, respectively.

Conclusion: This study suggested that delayed onset of hepatitis and/or neutropenia in patients with combination treatment of MTX and LEF was relatively common during 6–12 months of treatment. In addition, regular monitoring for such adverse events should be required for cumulative toxicity of long-term combination therapy.

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Metaanalysis of 5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase (ATIC) 347C>G Polymorphism Affecting Methotrexate Efficacy and Toxicity in Rheumatoid Arthritis Patients. Fardina Malik[1] and Prabha Ranganathan[2]. [1]Alton Memorial Hospital, Alton, IL, [2]Washington Univ School of Med, St. Louis, MO

Background/Purpose: Methotrexate (MTX) exerts its effect in part by inhibiting 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC), a key enzyme in the purine biosynthetic pathway. Published data suggests an association between a non-synonymous single nucleotide polymorphism (SNP) in the ATIC gene (347C>G, Thr116Ser) with MTX efficacy and toxicity in patients with rheumatoid arthritis (RA); however this association has been inconsistent. The aim of this study was to investigate the effects of the ATIC 347C>G SNP on MTX efficacy and toxicity in patients with RA by performing a meta-analysis.

Methods: Studies examining the association of the ATIC 347C>G polymorphism with MTX efficacy and toxicity in RA patients were systematically identified from the Pubmed and Ovid Medline databases (from 1999 to May 31st 2012). Studies reporting genotypic or allelic distribution of ATIC 347C>G polymorphism in relation to MTX efficacy and/or toxicity were deemed eligible for the current analysis. Meta-analyses for both MTX efficacy and toxicity were separately performed to explore the composite effect of the ATIC 347C>G SNP on these outcomes. Fixed (Mantel-Haenszel) and random effects (DerSimonian and Laird) models were utillized based on the presence or absence of between-study heterogeneity. OpenMeta-Analyst software (beta version) was used for data entry and analysis.

Results: Five studies with sufficient data were included in the meta-analysis of the ATIC 347C>G SNP's association with MTX efficacy which represented 1100 RA patients. The meta-analysis did not demonstrate a significant association between the ATIC 347C>G polymorphism and MTX efficacy (Figure 1A). The pooled odds ratio (OR) using the fixed effects model was 1.194 (95% CI 0.915, 1.559; p = 0.193) with a trend towards between-study heterogeneity (p=0.091) and using the random effects model was 1.168 (95% CI 0.786, 1.736; p = 0.441). For the meta-analysis of the ATIC 347C>G SNP's association with MTX toxicity, five studies with sufficient data were included which represented 1055 patients. Meta-analysis using the fixed effects model demonstrated a significant association of the ATIC 347C>G SNP with MTX toxicity with an OR of 0.686 (95% CI 0.515, 0.915; p = 0.010) with no evidence of between-study heterogeneity (p=0.245) (Figure 1B).

A				
Studies	Estimate (95% C.I.)	CC	CG or GG	
Wessels et al. 2006	2.217 (1.261, 3.900)	51/97	36/108	
Takatori et al. 2006	0.679 (0.291, 1.582)	19/67	14/38	
Sharma et al. 2009	1.377 (0.729, 2.599)	61/77	144/196	
Grabar et al. 2010	0.842 (0.399, 1.774)	14/93	20/115	
Owen et al. 2012	0.993 (0.634, 1.556)	66/139	81/170	
Overall (I^2=50% , P=0.091)	1.168 (0.786, 1.736)	211/473	295/627	

B				
Studies	Estimate (95% C.I.)	CC	CG or GG	
Wessels et al. 2006	0.494 (0.264, 0.924)	21/94	39/106	
Takatori et al. 2006	0.708 (0.338, 1.483)	27/76	21/48	
Weisman et al. 2006	0.365 (0.165, 0.809)	52/185	15/29	
Grabar et al. 2010	0.881 (0.488, 1.592)	63/93	81/115	
Owen et al. 2012	0.949 (0.540, 1.667)	27/140	34/169	
Overall (I^2=27% , P=0.245)	0.686 (0.515, 0.915)	190/588	190/467	

Conclusion: Our meta-analysis suggests that the ATIC 347C>G polymorphism may be a predictor of MTX toxicity in patients with RA, with the C allele being protective and the G allele conferring a higher risk for toxicity.

Disclosure: F. Malik, None; **P. Ranganathan**, None.

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Safety of Abatacept in Rheumatoid Arthritis with Chronic Hepatitis B VIRUS Infection. Melissa Padovan[1], Elisabetta Lanciano[2], Oscar Epis[3], Alessandro Mathieu[4], Giulia Erba[5], Leopoldo Ciani[6], Sarah Giacuzzo[1] and Marcello Govoni[1]. [1]Section of Rheumatology, Ferrara, Italy, [2]Rheumatology Unit, Bari, Italy, [3]Rheumatology Unit, Milano, Italy, [4]Rheumatology Unit, Cagliari, Italy, [5]Medical Clinics, Monza, Italy, [6]Unit of Internal Medicine, Legnano, Italy

Background/Purpose: In patients with rheumatoid arthritis (RA) concomitant hepatitis B (HBV) represents a therapeutic challenge limiting, DMARD treatment options (conventional and biologics, especially anti-TNFa and rituximab) are limited. About abatacept there are unclear and scant data confined to isolated medical records review and anecdotal case reports. This observational multicenter retrospective study was planned to verify safety of abatacept in this particular setting in a group of italian patients.

Methods: Six rheumatologic centres in different geographical areas of Italy were invited to participate in the study and provided data from patients with RA and positive HBV serology treated with abatacept in recent years. HBV serological markers, RA clinical and laboratory data were assessed by retrieving information from clinical documentation (hospital records, patient folders and clinical charts) provided by each participating centre and stored in a dedicated database. Follow-up data at 3 months intervals, up to 24 months, were analysed. The dose of Abatacept was given according to the standard guidelines, every two weeks for the first month and then monthly.

Results: 33 patients were included, 5 male and 28 female, mean disease duration 12 ± 5 ys and baseline active disease (average DAS28 = 5.56 ± 1.5). 22 patients (66.6%) were RF positive and 19 (57%) ACPA positive. Prior biologics were tried unsuccessfully in 15 (2 biologics) and 5 patients (3 biologics) before starting abatacept. In combination with abatacept patients received methotrexate (18), leflunomide (4), sulphasalazine or hydroxicloroquine (1), corticosteroid alone (8). At baseline 27 patients were categorized as inactive carrier (one of these was also anti-HCV positive) and 4 patients as occult carries (anti-core positive) for HBV. Liver function tests were normal and HBV-DNA titer was low or undectable in all patients. Seven patients received antiviral prophylaxis, 5 with lamivudina e 1 with adefovir first and then tenofovir. In the follow-up assessment data were available in 14 patients ongoing at 12 months (DAS28 = 3.99±1.2) and in 5 patients ongoing at 24 months (DAS28 = 2.10 ±1.6) break point of follow-up. No patients experienced reactivation of hepatitis B; liver function tests remained normal and serologic HBV status remained the same as at baseline. Discontinuation of therapy was due to inefficacy (13 primary, 12 secondary), patient's decision (2), low compliance (1), lost to follow-up (1) and adverse events (4) none of them HBV related. The high rate of withdrawal can be justified by the particular characteristics of the included patients, being long-standing refractory RA with an high rate of previous treatment failure.

Conclusion: Our study–not designed to test efficacy - shows encouraging data about safety of abatacept in patients with concomitant HBV positive serology also in patients without any antiviral prophilaxys. More prospective data are needed to confirm these preliminary results.

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Is the Impact of Methotrexate On Mortality in Rheumatoid Arthritis Independent of Its Effect On Disease Activity? Dietmar MJ Krause[1], Bernadette Gabriel[2], Gertraud Herborn[3] and Rolf Rau[3]. [1]Internistische und rheumatologische Gemeinschaftspraxis, Gladbeck, Germany, [2]Private Practice, Gladbeck, Germany, [3]Evangelisches Fachkrankenhaus, Ratingen, Germany

Background/Purpose: Methotrexate (MTX) is the anchor drug in the treatment of rheumatoid arthritis (RA). MTX shows effects on disease activity, radiologic progression and mortality. These three effects are thought to be associated with each other. Therefore, MTX-treatment is often stopped in case of insufficient improvement of disease activity. However, this association is incompletely understood.

Methods: We analysed data of one of the earliest MTX-cohorts in Europe (Evangelisches Fachkrankenhaus Ratingen). From 1980 to 1987 all patients starting treatment with MTX (n=271) were enroled in a prospective observational study. One year after baseline, response to MTX-treatment was determined (improvement or no improvement of at least 20%). Nearly all patients continued MTX-treatment independent of this response (due to lack of alternative treatments). In 1995 and 2003, the follow-up of 250 patients could be determined. Cox regression was applied to estimate risks for increased mortality.

Results: Ten years after baseline, 88 patients were deceased, 64% of the patients alive were still on MTX-treatment. 59 patients died in the following eight years. A Cox model with age, gender, response to MTX-treatment after one year, number of swollen joints ten years after baseline and continuation of MTX-treatment as covariates showed independent positive effects of continued MTX-treatment on mortality (hazard ratio (HR): 0,63; 95%-confidence interval (CI): 0,44–0,89, p = 0,009). In the group of non-responders the HR was 0,41 (95% CI 0,14–1,16), significance was missed due to the small number of patients in this group (n=23)

Conclusion: In this cohort, there are hints of a mortality lowering effect of MTX that is independent of its effect on disease activity. This might have consequences for treatment decisions in RA patients with insufficient MTX-efficacy on disease activity.

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Six Months of an Attenuated Cobra Regimen ('COBRA-light') Is Clinically Noninferior to the Original Cobra Regimen: An Open-Label Randomized Trial in Early Rheumatoid Arthritis. Debby den Uyl[1], Marieke M. ter Wee[1], Maarten Boers[1], Alexandre Voskuyl[1], P.J.S.M. Kerstens[2], Mike T. Nurmohamed[3], Hennie G. Raterman[1], D. van Schaardenburg[3], N. van Dillen[2], B.A.C Dijkmans[1] and W.F. Lems[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Reade | Jan van Breemen Research Institute, Amsterdam, Netherlands, [3]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands

Background/Purpose: Early, intensive treatment of rheumatoid arthritis (RA) with combination therapy (COBRA therapy) considerably lowers disease activity and suppresses radiological progression. Although proven to be very effective, uptake of COBRA therapy among rheumatologists has been suboptimal, for reasons including fear of possible side-effects. A modified schedule of the COBRA therapy with a lower dose of prednisone ('COBRA-light'), might be equally effective and lessen concerns about side-effects. The purpose of this study was **to** investigate whether **COBRA-light therapy is non-inferior to** COBRA-therapy in patients with early, active RA. Trial duration: one year.

Methods: 164 patients with early, active RA were randomised to either COBRA therapy (MTX 7.5 mg/week, SSZ 2 g/day and prednisone 60 mg/d, tapered to 7.5 mg/day) (n=81) or COBRA-light therapy (MTX 25 mg/week and 30 mg prednisone, tapered to 7.5 mg/day) (n=83). Primary treatment goal was minimal disease activity, defined as DAS44 < 1.6. After 3 months

treatment, MTX dose could be **increased** up to 25mg/week, when DAS44 remained above 1.6. **A difference in change of** DAS44 **>** 0.5 between the groups after 6 months was considered clinically relevant, and set as the boundary of non-inferiority. Patients, physicians and assessors were aware of treatment allocation as this trial is an open label trial.

Results: At baseline, patients had moderately active disease: COBRA, mean (SD) DAS44 4.13 (0.81); COBRA-light, 3.95 (0.90). Two patients *(COBRA-light arm)* did not *initiate treatment and t*wo patients dropped-out of the study due *to adverse events (myocardial infarction in COBRA-arm and manic episode in COBRA-light arm). At 6 months DAS44* had significantly decreased in both groups: COBRA, –2.50 (1.21); COBRA-light, –2.18 (1.10) (Table). The difference between the groups in DAS44 change was 0.32 (95% CI: –0.03;0.68; p=0.08), i.e. within the noninferiority boundary. Minimal disease activity (DAS$_{44}$<1.6) was reached in almost half of patients in both groups (49% and 41% in COBRA and COBRA-light respectively). There were no significant differences between the treatment groups with respect to other measurements of disease activity including the EULAR and ACR response criteria and the HAQ-score.

Table 1. Outcome week 26

	COBRA (n=81)	COBRA-light (n=81)	P
Δ DAS44*	−2.50 (1.21)	−2.18 (1.10)	0.08
Absolute DAS44	1.63 (0.96)	1.77 (1.14)	NS
Minimal disease activity (DAS44<1.6)	49%	41%	NS
Δ HAQ	−0.8 (0.6)	−0.8 (0.7)	NS
Δ Tender joints	−14 (11)	−13 (11)	NS
Δ Swollen joints	−11 (6)	−10 (6)	NS
Δ ESR, mm/h	−21.5 (−37;−8)	−13.5 (−34;−4)	0.09
Δ CRP mg/L	−9.5 (−25;−1)	−8.5 (−29;−1)	NS
Δ Patient's global assessment disease activity, (0–100)	−34 (−59;−7)	−41 (−65;−17)	NS
Δ Physician's global assessment disease activity, (0–100)	−36 (−59;−9)	−31 (−54;−10)	NS
ACR 20 response	72%	72%	NS
ACR 50 response	56%	62%	NS
ACR 70 response	37%	49%	NS
EULAR good response	75%	65%	NS
EULAR non-response	6%	11%	NS
ACR/EULAR remission (Boolean)	15%	24%	NS
Intra-articular injections, n (%)	0%	4%	NS

* Δ: delta, difference between 0 and 26 weeks
Data are presented as mean (±SD) or median (interquartile range). Differences between groups were tested with independent T-test, Mann-Whitney U test or Chi square test. A p<0.05 was considered statistically significant.

Conclusion: Results at 6 months suggest that COBRA-light therapy is non-inferior to standard COBRA therapy: both strategies effectively lower disease activity in early, active RA patients. The clinical and radiological effects at one year are pending.

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Improved Radiological Outcome of Rheumatoid Arthritis: Early Treatment with methotrexate might be a key Prognostic Factor. Christoph Fiehn[1], Elisabeth Belke-Voss[1], Dietmar Krause[2], Siegfried Wassenberg[3] and Rolf Rau[4]. [1]ACURA Centre for Rheumatic Diseases, Baden-Baden, Germany, [2]Dept. for Medical Informatics, Biometry and Epidemiology, Ruhr University, Bochum, Germany, [3]Evangelisches Fachkrankenhaus Ratingen, Rheumazentrum, Ratingen, Germany, [4]Düsseldorf, Germany

Background/Purpose: To compare the rate of radiological progression in patients with rheumatoid arthritis (RA) diagnosed in the 1980s with those of the late 1990s until 2005 and to evaluate key factors for differences in prognosis.

Methods: 92 RA patients which were firstly seen in our clinic from 1997 to 2005 and in which baseline and at least one follow up radiograph of hands and feet were available were retrospectively identified. As a control group, 89 RA patients from 1986 to 1990 were matched for the criteria disease duration, age and number of x-ray controls. In both groups patients had a disease

duration of less than 5 years at first consultation (mean: 22 ±17 months). Radiologic damage was measured by the Ratingen score (RS).

Results: The baseline RS was significantly lower in the 1997–2005 group compared to the 1986–1990 group (mean 3.8 ±8.7 vs. 7.7 ±13.0 respectively, p<0.0001). This was also the case in the patients firstly seen before the approval of TNF-Inhibitors in 2000 (n=29, mean baseline RS 1997–2000: 2.7 ±4.9; p<0.001 in comparison to 1986–1990). Moreover, the 1997–2005 group showed significantly less radiologic progression than the 1986–1990 group during follow-up (ΔRS/year of 0.95 ±2.19 vs. 5.69 ±8.43; p<0.0001). In the later group more patients (73% vs. 28%; p=0.0001) received methotrexate (MTX), mainly early in the course of the disease. In contrast, the overall rate of DMARD treatment was not significantly different in both groups. Twenty one (23%) of the patients in the later group received biologic drugs, in the majority TNF-Inhibitors. Multivariate analysis showed that early start of MTX (before or directly after first consultation) was a significant predictor of low radiographic progression (p<0.005), as were low ESR at baseline and belonging to the later group. In contrast, neither treatment with glucocorticoids or biologic drugs nor the overall rate of MTX-use were predictive for a better outcome.
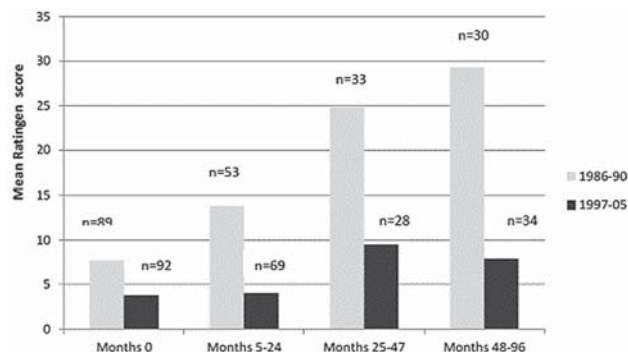
Fig. Mean Ratingen scores and radiologic progression in the different groups 1986–90 and 1997–2005 (grey and black). The results of the x-ray analysis were separated in dependence from the time after the first consultation (columns). The differences were statistically significant (p<0.0001) between the two groups at each time point.

Conclusion: Radiologic damage is markedly diminished in RA patients seen since the late 1990s. Early treatment with MTX may be the key factor for this improved prognosis. However, due to the retrospective design of the study, a bias cannot be completely excluded.

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Initial Introduction of Treat-to-Target Strategy in Patients with Recent Onset Rheumatoid Arthritis Is More Effective Than Delayed Introduction of Strategy with More Clinical and Functional Remission Achieved for 2-Years: Results of the Treating to Twine Targets (T-4) Study.
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Background/Purpose: To compare the clinical, radiological and functional efficacy of initial versus delayed introduction of strategy which is treat-to-target to patients with recent onset rheumatoid arthritis (RA) after 2-years follow up.

Methods: A post hoc analysis of the T-4 (treating to twine targets) study which is a multicenter, randomized and open trial in newly diagnosed RA patients (mean duration 1.4±1.1 yrs) who has not previously received disease-modifying anti-rheumatic drugs (DMARDs) was performed. In the T-4 study, a total of 243 RA patients were randomly allocated to one of four strategy groups: routine care (R group, n=62); disease activity score in 28 joints (DAS28)-driven therapy (D group, n=60); matrix metalloproteinase (MMP)-3-driven therapy (M group, n=60); or both DAS28- and MMP-3-driven therapy group (Twin; T group, n=61). Specifically, medication was started with sulfasalazine (1 g/day) in all intervention groups. Targets were DAS28 <2.6 for D group, MMP-3 normalisation for M group, and both DAS28 <2.6 and MMP-3 normalisation for T group. If the value in question did not fall below the previously measured level, we intensified medication

including methotrexate, other DMARDs and biologic agents. From 56 weeks all patients were allocated to T group, treatment was adjusted every three months if the value in question did not fall below the previously measured level. 61patinets in initial treat-to-target introduced group (T→Tgroup) were compared with 62 patients in delayed treat-to-target introduced group (R→Tgroup) for 2 years. Functional ability was measured by the Health Assessment Questionnaire (HAQ), radiological progression was measured by Sharp/van der Heijde scoring (SHS).

Results: Baseline differences between the two groups were not significant. Clinical (simplified disease activity index≤3.3) and functional (HAQ=0) remission at 2 years was achieved by more patients in initial treat-to-target introduced group (T→Tgroup) (51% and 74%) than in delayed group (R→T group) (18%; p<0.0001 and 50%; p=0.0063). There are no significant difference between initial and delayed group (52% versus 47%; p=0.5283) for radiographic remission (DSHS<0.5).

Conclusion: The results of post hoc analysis in T-4 study suggest that initial introduction of treat-to-target strategy in patients with recent onset RA is more effective than delayed introduction of strategy with more clinical and functional remission achieved for 2-years.

Disclosure: Y. Urata, None; **Y. Nakamura**, None; **K. I. Furukawa**, None.

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Impact of Tumour Necrosis Factor Inhibitor Treatment On Hand Bone Loss in Rheumatoid Arthritis Patients Treated in Clinical Practice. Results From the Nationwide Danish Danbio Registry.
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Background/Purpose: Rheumatoid arthritis (RA) is characterised by progressive joint destruction and periarticular bone loss. In RA patients with insufficient response to Disease-Modifying Anti-rheumatic drugs (DMARDs) treated in clinical practice tumour necrosis factor inhibitors(TNFi) retard the joint damage(1), but their impact on hand bone loss and predictors thereof are not known. The aim of this study was to compare hand bone changes during treatment with Disease-Modifying Anti-rheumatic drugs (DMARDs) and subsequent treatment with TNFi in RA patients in clinical practice, and investigate the association between radiographic progression and hand bone loss. Furthermore, to identify predictors of hand bone loss during TNFi treatment in clinical practice.

Methods: X-rays of hands were obtained 2 yrs before start of TNFi(pre-baseline), at the start of TNFi(baseline) and 2 yrs after(follow-up). Clinical data from the DANBIO registry and patient files were collected. Hand x-rays were scored blinded to chronology according to the Sharp/van der Heijde method. Hand bone mineral density (BMD) was estimated with Digital X-ray Radiogrammetry(DXR), a computerised method to measure cortical bone thickness of the 2nd–4th metacarpal. Annual (absolute and relative) hand BMD loss and radiographic progression rates during DMARD and TNFi treatment were calculated. Potential predictive baseline variables were investigated with univariate regression and significant variables included in a multiple linear regression analysis with annual BMD loss during TNFi treatment as the dependent variable.

Results: 136 RA patients (85% women, 71% rheumatoid factor positive, age 55(23–84) years(median (range)); disease duration 5(1–53) years) had three x-rays suitable for DXR. Pre-baseline 28 joint disease activity score-(DAS28) was 4.3(1.6–6.9). At baseline DAS28 was 5.3(1.4–8.2) and inflximab(74%), etanercept(13%), or adalimumab(13%) was started. At follow-up, 59% were on initial TNFi, 27% had switched to another TNFi and 14% had withdrawn. DAS28 was 3.1(1.4–7.7). Data on BMD loss and radiographic progression are shown in Table 1. Patients with radiographic progression (change in Total Sharp Score >0) had higher BMD loss than patients without radiographic progression in both the DMARD (−0.94 mg/cm^2 (median) vs. −0.54, p = 0.03, Wilcoxon) and TNFi period (−0.74 vs. 0.34, p = 0.004, Wilcoxon). Independent predictors of BMD loss during the TNFi period were: higher age (−0.2mg/cm^2/10 year increase) and 28 swollen joint count (SJC) (−0.4mg/cm^2/joint increase).

	BMD and radiographic status			Annual change in BMD and TSS		P-value (1)
	Prebaseline X-ray	Baseline X-ray	Follow-up X-ray	DMARD period	TNFi period	
TSS median (IQR), units	6 (0–21)	10 (1–29)	12 (2–31)	0.6 (0.0–2.5)	0.0 (0.0–0.8)	<0.0001
BMD median (IQR), g/cm²	0.55 (0.48–0.61)	0.53 (0.45–0.59)	0.52 (0.44–0.57)	−0.0079 (−0.017–002)	−0.0047 (−0.012 − −0.001)	0.001
BMD median (IQR), %				−1.55 (−3.45–0.44)	−1.11 (−2.52–0.15)	0.02
Correlation TSS vs. BMD (2)	−0.45	−0.45	−0.43	−0.23	−0.27	
P-value (2)	<0.0001	<0.0001	<0.0001	0.0007	0.001	

[1]Wilcoxon Signed Rank [2]Spearman. The DMARD period is the period between pre-baseline and baseline X-rays, while the TNFi period is the period between baseline and follow-up X-rays. TSS, Total Shap Score (of hands); BMD, Bone Mineral Density

Conclusion: In 136 established RA patients TNFi treatment reduced BMD loss and radiographic progression. High age and SJC predicted BMD loss during TNFi treatment. During DMARD- and TNFi treatment radiographic progression and BMD loss were moderately correlated.

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Response to Etanercept, but Not Infliximab or Adalimumab, Is Inversely Associated with Body Mass Index. James R. Maxwell[1], Darren Plant[2], Anne Barton[3], Kimme L. Hyrich[3], Ann W. Morgan[4], John Isaacs[5] and Anthony G. Wilson[6]. [1]University of Sheffield, Sheffield, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [5]Newcastle University, Newcastle upon Tyne, United Kingdom, [6]Section of Musculoskeletal Sciences, University of Sheffield, Sheffield, United Kingdom

Background/Purpose: Recent studies have demonstrated inverse association between BMI and radiographic severity in patients with Rheumatoid Arthritis (RA). There is also preliminary evidence that body mass index (BMI) may influence response to anti-TNF treatment. We hypothesized that BMI may affect response to the three most commonly used anti-TNF agents. The aim of this study was to determine if BMI is associated with response to individual anti-TNF agents in RA patients.

Methods: 2,160 patients were included, of whom 726 were treated with Infliximab, 737 Etanercept and 697 Adalimumab. Linear regression was used to investigate the influence of BMI, recorded at baseline on the change in DAS28 between baseline and 6 months of treatment, adjusted for gender, DMARD treatment, smoking, baseline DAS28 and HAQ score. Similar models were constructed to examine change in ESR and CRP. The proportion of patients achieving EULAR improvement criteria according to stratified BMI was compared using the Chi squared test. Analyses were performed separately according to individual anti-TNF agents.

Results: Mean disease duration was 13.7 years. BMI was not associated with change in DAS between baseline and 6 months and there was no statistical difference in the proportion of patients achieving EULAR response criteria according to BMI for any of the medications. For patients treated with Etanercept, but not Adalimumab or Infliximab, BMI was inversely associated with change in both ESR and CRP (p=0.003, and p<0.0001 respectively).

Conclusion: Change in inflammatory activity in response to Etanercept, but not Infliximab or Adalimumab, is inversely associated with BMI. Response to Infliximab has been reported to be reported to be inversely related to higher BMI in a study of 89 patients however our much larger study did not replicate this finding. Our data suggest that higher doses of Etanercept may be required in RA patient with high BMI. Studies are required to determine if lower doses of this agent could be used in patients with lower BMI.

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Risk Factors for Radiographic Progression During TNF-Inhibitor Treatment in 932 Rheumatoid Arthritis Patients Treated in Clinical Practice: Results From the Nationwide Danish Danbio Registry. Lykke Midtbøll Ørnbjerg[1], Mikkel Østergaard[1], Pernille Bøyesen[2], Anja Thormann[1], Ulrik Tarp[1], Wolfgang Bøhme[1], Ditte Dencker[1], Hanne M. Lindegaard[1], Uta Engling Poulsen[1], Annette Hansen[1], Vibeke Stevenius Ringsdal[1], Annette Schlemmer[1], Niels Graudal[1], Anne Rødgaard Andersen[1], Jakob Espesen[1], Gina Kollerup[1], Torben Grube Christensen[1], Randi Pelck[1], Bente Glintborg[1], Ole Rintek Madsen[1], Dorte Vendelbo Jensen[1], Ole Majgaard[1] and Merete L. Hetland[3]. [1]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Copenhagen, Denmark, [2]Diakonhjemmet Hospital, Olso, Norway, [3]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark

Background/Purpose: Despite treatment with tumour necrosis factor inhibitors (TNFi) some rheumatoid arthritis (RA) patients progress radiographically in randomised controlled trials and observational cohorts (1). Risk factors for radiographic progression during TNFi treatment in clinical practice have not been investigated. The aim of this study was to identify baseline risk factors for radiographic progression during 2 years follow-up of TNF-inhibitor treated RA patients in clinical practice.

Methods: X-rays of hands and wrists obtained at the start of TNFi (baseline) and approximately 2 years after (follow-up) were collected from 16 Danish departments, and linked with clinical data from the DANBIO registry. X-rays were blinded to chronology and scored according to the Sharp/van der Heijde method. Potential predictive baseline variables (28-joint Disease Activity Score(DAS28), C-reactive protein(CRP), 28 Swollen Joint Count(SJC), 28 Tender Joint Count(TJC), Health Assessment Questionnaire-(HAQ), Total Sharp Score (TSS), age, gender, IgM Rheumatoid Factor (IgM-RF), disease duration, number of previous Disease-Modifying Anti-Rheumatic Drugs (DMARDs), concomitant methotrexate (MTX), concomitant prednisolone, type of TNFi drug) were investigated with univariate regression and significant variables (p < 0.05) included in a logistic regression analysis with +/− radiographic progression (change in TSS> 0) as dependent variable.

Results: 932 patients (75% women, 79% IgM-RF positive, age 57(19–88) years (median(range)); disease duration 6(1–70) years), DAS28 5.4(4.6–6.1) (median(inter-quartile range(IQR)), TSS 30(38) (mean(SD)) 14(2–44)(median(IQR)) had available X-rays. At baseline 59% of patients started treatment with infliximab, 18% with etanercept and 23% with adalimumab. 15% of patients received TNFi monotherapy, 76% combination therapy with MTX and 9% with other DMARDs. At follow-up (median 526, IQR 392–735days), 59% were treated with the initial TNFi, 29% had switched to another TNFi and 12% had withdrawn from TNFi.

Yearly change in TSS was 0.6(2.4) units (mean(SD)), 0.0(0.0–0.5)(median(IQR)). 27% of patients progressed radiographically (change in TSS >0) during TNFi treatment. Independent risk factors for progression were baseline TSS, age, IgM-RF and concomitant treatment with prednisolone (Table).

Table. Final model of logistic regression analysis (n = 932)

Predictors of X-ray progression	Odds Ratio	P value
TSS (pr. unit increase)	1.004	0.049
Age (pr. year increase)	1.03	0.0002
IgM RF (if positive)	1.75	0.006
Concomitant prednisolone (if treated)	1.39	0.03

Conclusion: In this nationwide observational study of 932 RA patients, baseline TSS, age, IgM-RF and concomitant prednisolone were risk factors for radiographic progression during 2 years follow-up.

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Moderate Rheumatoid Arthritis Despite Methotrexate Treatment: Risk of Radiographic Progression. Bruno Fautrel[1], Gaia Gallo[2], Yves Brault[3] and Henk Nab[4]. [1]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [2]Pfizer, Rome, Italy, [3]Pfizer, Paris, France, [4]Pfizer Europe, Rome, Italy

Background/Purpose: Clinical remission or low disease activity are the main goals of rheumatoid arthritis (RA) treatment and European League Against Rheumatism guidelines recommend switching treatment after 3–6 months in patients who do not achieve these targets.[1] Despite this, in Europe the majority of patients have moderate disease activity and many of them remain on methotrexate (MTX) which may lead to disease progression and functional deterioration. Several risk matrix models have been already developed but always include a patient population with mostly severe RA and never in subjects with a stable moderate disease state. The objective of this study was to identify (a combination of) factors contributing to the risk of radiographic progression (RP) among moderate RA subjects despite MTX treatment.

Methods: Subjects from the MTX arm of the TEMPO trial[2] with sustained moderate RA (defined as $3.2 \leq$ mean disease activity score in 28 joints ≤ 5.1 during the last 6 months of the first year) were analyzed for radiographic progression after 2 and 3 years. Univariate logistic regression was performed to identify baseline predictors of RP. Predictor variables with $p < 0.10$ were selected for stepwise multivariate analysis. Receiver-Operating Characteristic (ROC) analysis was used to evaluate the performance of the final model to predict disease progression; the area under the ROC curve (AUC) was calculated as a measure of accuracy.

Results: During the last 6 months of the first year, 96 subjects had moderate RA, out of 187 patients that started MTX. Of these subjects, RP (change from baseline in modified Total Sharp Score [mTSS] ≥ 0.5) occurred in 48 (50%) and 54 (56%) at 2 and 3 years, respectively, with a subgroup of 25 (26%) and 33 (34%) subjects who experienced a higher degree of RP (change from baseline in mTSS >3.0) at 2 and 3 years, respectively. Univariate analysis showed erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) positivity, and C-reactive protein (CRP) levels were significantly predictive of mTSS change >3.0 at both 2 and 3 years ($p < 0.05$ for all; **Table**). Multivariate analysis of these variables showed ESR and RF positivity were predictive of mTSS change >3.0 after 2 and 3 years ($p < 0.05$ for all). ROC analysis found the AUC = 0.73 for both models, indicating a fair test of prediction.

Conclusion: Subjects with sustained moderate RA despite treatment with MTX are at risk of disease progression. Both ESR and RF positivity at baseline were strongly predictive of radiographic progression in these subjects.

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Improvement of Health-Related Quality of Life in RA Patients Treated with Biologics - One-Year Follow-up Data of the German Biologics Register Rabbit. Kerstin Gerhold[1], Adrian Richter[1], Matthias Schneider[2], Hans Joachim Bergerhausen[3], Winfried Demary[4], Anke Liebhaber[5], Joachim Listing[1], Angela Zink[1] and Anja Strangfeld[1]. [1]German Rheumatism Research Center, a Leipniz Institute, Berlin, Germany, [2]Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany, [3]Wedau Kliniken - Klinikum Duisburg, Duisburg, Germany, [4]Private Practice, Hildesheim, Germany, [5]Private Practice, Halle, Germany

Background/Purpose: Health related quality of life (HRQoL) has been increasingly recognized as a crucial indicator of disease burden in chronic diseases such as rheumatoid arthritis (RA). To measure the effectiveness of biologic disease modifying anti-rheumatic drugs (bDMARDs) on patient-assessed disease burden, we investigated the one-year course of HRQoL in a cohort of RA patients treated with bDMARDs or synthetic DMARDs (sDMARDs) after failure of at least one DMARD.

Methods: Patients enrolled in the German biologics register RABBIT from 2006 up to 2010 with a minimal observation period of one year were included. SF-36 questionnaire was used to capture patient-assessed mental and physical health at baseline and after one year of follow-up. Disease activity was measured by means of DAS28, patient-assessed functional capability by means of the FFbH (Funktionsfragebogen Hannover) score. We applied last-observation-carried-forward (LOCF) method for patients discontinuing initial therapy and patients who were lost to follow-up from the ITT-population. Level of statistical significance for differences between baseline and one-year follow-up values of physical and mental health subscales was set at a=0.00625 using Bonferroni correction for multiple testing of the 8 subscales (paired t-test for pre-treatment versus post-treatment comparisons, two-sided).

Results: Data of 804 patients treated with TNF inhibitors (anti-TNF), 234 patients treated with tocilizumab (TOC), 450 patients treated with rituximab (RTX), 124 patients treated with abatacept (ABA), and of 816 patients treated with sDMARDs were included in the analysis. LOCF was used in 226 anti-TNF patients, 58 TOC, 57 RTX, 43 ABA and 158 sDMARD patients. Mean disease duration at baseline was between 10.1 and 13.9 years in the bDMARD groups, and 6.0 years in the sDMARD group. At baseline all bDMARD groups showed higher disease activity, lower functional capacity and poorer values for all subscales of physical and mental health than the sDMARD group. At one-year follow-up, disease activity, functional capacity as well as all SF-36 scales had improved in all treatment groups. However, bDMARD patients developed greater improvement, especially in the mental health subscales, compared to sDMARD patients.

Table. Baseline predictors of mTSS change >3.0 in subjects with moderate RA

Univariate analysis Baseline Characteristic	At 2 years Odds ratio (95% CI) n = 96	p value	At 3 years Odds ratio (95% CI) n = 96	p value
ESR (mm/hour)	1.03 (1.01, 1.04)	0.005	1.03 (1.01, 1.05)	0.002
RF positive, Yes/No	5.68 (1.56, 20.73)	0.009	4.78 (1.63, 13.96)	0.004
CRP (mg/L)	1.02 (1.01, 1.04)	0.013	1.03 (1.01, 1.04)	0.008
Age, y	0.98 (0.95, 1.02)	0.295	0.98 (0.94, 1.01)	0.141
Gender, Female/Male	0.58 (0.19, 1.78)	0.341	0.70 (0.24, 2.05)	0.516
Duration of disease, y	0.97 (0.88, 1.05)	0.427	0.95 (0.87, 1.03)	0.193
Total swollen joints	0.99 (0.94, 1.03)	0.539	1.01 (0.96, 1.05)	0.800
Erosion score	1.00 (0.99, 1.02)	0.717	1.01 (0.99, 1.02)	0.461
Total tender joints	1.00 (0.96, 1.03)	0.815	1.01 (0.98, 1.04)	0.648
mTSS	1.00 (0.99, 1.01)	0.818	1.00 (1.00, 1.01)	0.391
HAQ	0.97 (0.57, 1.64)	0.897	0.99 (0.61, 1.62)	0.971
Multivariate analysis*				
ESR (mm/hour)	1.02 (1.00, 1.04)	0.039	1.02 (1.00, 1.04)	0.017
RF positive, Yes/No	3.89 (1.01, 14.96)	0.048	3.14 (1.00, 9.83)	0.049

*n = 95 (excluding one subject with missing ESR value).
HAQ, health assessment questionnaire.

Table 1. Mean values of SF36 scales and improvement after one year (D=mean$_{(1-year)}$-mean$_{(baseline)}$)

SF36 scales		Anti-TNF	TOC	RTX	ABA	s-DMARD	Anti-TNF	TOC	RTX	ABA	s-DMARD
		Mean values at baseline					Improvement [D]				
Physical Health Scales	Physical Function	45.1	39.7	37.5	37.5	55.0	5.9*	7.0*	4.6*	4.5	1.7
	Physical Role	24.4	19.6	18.1	17.9	33.7	11.8*	17.9*	10.9*	4.8	9.1*
	Body Pain	31.2	29.8	30.0	26.1	39.1	12.3*	13.9*	9.8*	8.8*	7.7*
	General Health	40.8	40.0	39.3	35.0	46.9	5.1*	7.6*	4.6*	3.4	2.3*
Mental Health Scales	Vitality	37.2	37.1	32.5	32.5	44.2	5.7*	7.0*	4.5*	4.3*	3.3*
	Social Function	61.9	56.9	56.9	55.5	68.3	6.1*	7.8*	6.1*	6.6*	2.8*
	Role Emotional	50.3	48.2	44.4	41.7	54.1	7.8*	9.2*	7.8*	9.4	4.0
	Mental Health	57.2	59.9	56.5	54.3	59.9	4.9*	4.4*	3.1*	5.2*	1.9*
Disease activity	DAS28 (ESR)	5.2	5.6	5.5	5.6	4.6	−1.4*	−2.1*	−1.2*	−1.2*	−1.0*
Functional capability	FFbH	65.1	60.0	53.5	53.8	72.1	4.4*	3.9*	7.1*	4.8*	2.8*

Conclusion: Patients treated with bDMARDs had a worse disease state due to disease activity and functional capacity at enrollment, compared to patients on sDMARDs, which reflects treatment choices in daily care. All bDMARDs improved patientsx HRQoL beyond control of disease activity and physical function. Benefit of treatment with bDMARDs was particularly noticeable in the mental health subscales of the SF-36.

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Efficacy of Methotrexate (MTX) According to Anti-Citrullinated Protein Antibody (ACPA) Status in an Early Inflammatory Arthritis Cohort.
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Background/Purpose: Data suggests patients with early, ACPA negative, rheumatoid (RA) and undifferentiated arthritis (UA) are less likely to achieve remission with MTX at 4 months in comparison to ACPA positive patients [1]. In patients with probable RA, MTX only delayed progression to RA in ACPA positive patients [2]. The objective was to determine whether response to MTX differs according to ACPA status in an early inflammatory arthritis cohort.

Methods: Patients with UA or RA (2010 ACR/EULAR criteria) initiated on MTX as first-line DMARD up to December 2011 were identified from the Inflammatory Arthritis disease CONtinuum (IACON) registry in Leeds. Outcome measures at 6 months were remission (DAS28-CRP<2.6) and EULAR response. Outcomes were analysed where complete response datasets were available using with last observations carried forward for patients who stopped MTX or escalated to combination DMARD therapy prior to 6 months. Logistic regression was used to compare the rate of DAS28 remission and EULAR good response at 6 months, adjusting for DAS28 at baseline.

Results: Of 78 patients commencing MTX monotherapy, 51 of 53 ACPA positive and 14 of 25 ACPA negative patients fulfilled 2010 RA criteria. Radiographic erosions were present in 6/35 (24%) ACPA negative and 11/53 (21%) ACPA positive patients. Table 1 displays baseline characteristics according to 2010 RA criteria and ACPA status. Over 6 months methotrexate was continued as monotherapy in 49 patients: alternative DMARD(s) were added (n=25), cessation (n=1), enrolment in clinical trial (n=1), death (n=1) and loss to follow-up (n=2). Patients escalating to combination DMARD therapy did so at a median time of 3 months on a median (IQR) weekly dose of MTX of 20 mg (20 to 25mg). This was similar to the weekly dose of MTX at 6 months in patients continuing monotherapy (median 20; IQR 15 to 25). Datasets were complete for analysis of response in 60 patients (Table 2). Rate of remission was higher in ACPA positive patients; odds ratio(OR) 8.9, 95% confidence interval (CI) 2.0 to 40. There was a trend towards a superior rate of EULAR good response in ACPA positive patients at 6 months (OR 2.1, 95% CI 0.6 to 7.7).

Table 1. Baseline Characteristics

	RA (2010 criteria)		UA	
	ACPA+ n= 51	ACPA− n= 14	ACPA+ n= 2	ACPA− n= 11
Age, mean (SEM)	53 (2)	60 (4)	58 (15)	44 (5)
Female, n (%)	36 (71)	8 (57)	1 (50)	9 (82)
Shared epitope, n positive/n tested (%)	20/22 (91)	4/6 (67)	Not recorded	8/9 (89)
RF positive, n (%)	44(86)	5 (36)	1 (50)	1 (9)
Symptom duration, median (IQR), wks	33 (17–77)	32 (11–62)	6, 77	28 (25–91)
Erosions, n (%)	11(22)	6(43)	0	0
Joint involvement (M=medium, L=large, S=small joints):	.	.	.	.
	0	0	1 (50)	0
1 M/L	0	0	0	0
2–10 M/L	11 (22)	3 (21)	1 (50)	3 (27)
1–3 S	14 (28)	1 (7)	0	8 (73)
4–10 S	26 (51)	10 (71)	0	0
>10 (at least 1 S)				

Table 2. Response at 6 months

ACPA Status	Escalation to combination DMARD therapy, n (%)	Weekly MTX dose in mg (IQR)	Baseline DAS28, median (IQR)	6 month DAS28, median (IQR)	Reduction in DAS28, median (IQR)	DAS28 Remission Baseline, n(%)	DAS28 Remission 6 months, n(%)	EULAR Response, n (%)		
								Good	Moderate	None
Positive (n=38)	13 (34)	20 (20 to 25)	3.9 (2.9 to 5.3)	2.5 (2.0 to 3.7)	1.1 (0.4 to 2.1)	8 (21)	20 (53)	13 (34)	12 (32)	13 (34)
Negative (n=22)	8 (36)	20 (15 to 25)	3.5 (3.0 to 4.6)	3.5 (2.5 to 4.2)	0.0 (−0.5 to 1.3)	5 (23)	5 (23)	4 (18)	4 (18)	14 (64)

Conclusion: Rate of remission was higher in ACPA positive vs ACPA negative patients, and there was a trend towards superior rate of eular response. Escalation of therapy was comparable between the groups. This data suggests that seronegative patients may be less responsive to MTX and may require a different treatment regimen.

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Improved Fatigue-Related Quality of Life in CAPRA-2, a 12 Week Study of 5-Mg Modified (Delayed) Release Prednisone in Rheumatoid Arthritis.
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Background/Purpose: Quality of life in rheumatoid arthritis (RA) patients can be improved by reducing the common symptom of fatigue caused by disease related factors such as pain and inflammation. Recent studies indicate that glucocorticoid treatment improves patient reported fatigue (Westoff et al, 2011). Chronotherapy with a modified (delayed) release (MR) prednisone tablet may also improve these symptoms. NP01 (Horizon Pharma, Deerfield IL) is a proprietary MR formulation of prednisone that results in a 4 hour delay in traditional pharmacokinetic parameters of prednisone. This formulation capitalizes on known cytokine and endogenous biologic rhythms. Here we report fatigue scores from the Circadian Administration of Prednisone in Rheumatoid Arthritis-2 (CAPRA-2) study which evaluated patients with active RA on stable disease-modifying antirheumatic drugs (DMARDs) given MR prednisone or placebo.

Methods: The study was a 12-week, double-blind, placebo-controlled study that randomized 350 RA patients to either 5 mg MR prednisone (n=231) or placebo (n=119) taken once daily at bedtime (eg, 10pm) in addition to their standard DMARD treatment (Buttgereit et al, 2012). The primary endpoint was the proportion of patients achieving ACR20 response after 12 weeks. A secondary objective was to compare treatment with 5 mg MR prednisone and placebo in the change from baseline on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire. This 13 item questionnaire assesses the effect of fatigue on daily activity and function on a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much), with a score range of 0 to 52.

Results: The mean baseline FACIT-F fatigue score was comparable in the 5 mg MR prednisone group and the placebo group (28.81 vs 28.73, Table 1). The least square mean (LSM) absolute increase from baseline to Week 12 was greater in the 5 mg MR prednisone group than in the placebo group (3.83 vs 1.59), indicating a reduction of fatigue (Table 1). The difference in FACIT-F score between baseline and Week 12 was clinically relevant for 5 mg MR prednisone but not for placebo (minimal clinically important difference [MCID]: 3–4; Cella et al, 2005). At Week 12, the LSM change from baseline was statistically significantly greater for 5 mg MR prednisone than for placebo, (LSM difference=2.24 [95% CI: 0.76, 3.72], p-value=0.0032) (Table 1). Similar results occurred for observed case data. These findings were consistent with improvement in ACR20 score.

Table 1. FACIT-F Fatigue Score at Each Visit (mITT Population, BOCF)

Visit		FACIT-F Fatigue Score		
		5 mg MR-Prednisone	Placebo	5 mg MR-Prednisone vs. Placebo
Baseline	n	231	119	–
	Mean (SD)	28.81 (10.443)	28.73 (10.725)	–
Week 12	n	231	119	–
	Mean (SD)	32.54 (10.893)	30.25 (10.465)	–
Absolute Change from Baseline to Week 12	LSM	3.83	1.59	–
	LSM Difference (SE)	–	–	2.24 (0.754)
	95% CI for LSM Difference	–	–	0.76, 3.72
	p-value	–	–	0.0032

Abbreviations: FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; mITT = modified intention-to-treat; BOCF = baseline observation carried forward; MR = modified-release; SD = standard deviation; LSM = least square mean; SE = standard error; CI = confidence interval.
Note: LSMs are from an analysis of covariance (ANCOVA) model with baseline results, treatment, and geographic region as factors. Model effects were from the Type III estimates.

Conclusion: Patients treated with 5 mg MR prednisone had significant improvement in FACIT-F scores compared with placebo, indicating a reduction in fatigue and improvement in an important aspect of quality of life. Chronotherapy with a MR prednisone formulation improves ACR scores and provides a potential new treatment option for patients with RA that can also improve symptoms of fatigue.

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Impact of Etanercept-Methotrexate Therapy On Patient-Reported Outcomes in Rheumatoid Arthritis Patients with up to 12 Months of Symptoms.

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Background/Purpose: Patient-reported outcomes (PROs) in patients with rheumatoid arthritis (RA) are critical in evaluating RA treatment effects on function and health-related quality of life (HR-QoL). Significant improvement in PROs has been reported in RA studies of biologic agents, including etanercept (ETN), but most studies have been conducted in patients with established disease. In addition to assessing treatment effects in early RA, there is interest in therapeutic strategies that allow dose reduction or withdrawal of biologic therapy (biologic-free) after induction of response. The PRIZE trial is an ongoing, 3-period study to evaluate the efficacy of combined ETN and methotrexate (MTX) therapy in patients with early, moderate-to-severe RA and to assess whether efficacy (remission) can be maintained with ETN dose reduction or biologic-free (Period 2) or drug-free (Period 3). Herein we report PROs associated with ETN 50 mg QW plus MTX (ETN50/MTX) therapy administered for 52 wks in Period 1 (induction) of the PRIZE trial.

Methods: In Period 1, MTX- and biologic-naïve patients with early, active RA (symptom onset ≤12 mo from enrollment; DAS28 >3.2) received open-label ETN50/MTX for 52 wks. The starting dose of MTX was 10 mg QW; at the discretion of the investigator, titration was permitted up to a maximum of 25 mg QW to achieve remission. Corticosteroid boosts were administered to patients not achieving low disease state at wks 13 and 26, unless contraindicated or not tolerated. PROs were assessed using the Health Assessment Questionnaire (HAQ) total score; Patient Acceptable Symptom State (PASS); EuroQol-5 Dimensions (EQ-5D) total index; Short Form Health Survey (SF-36); Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue; Work Instability Scale for Rheumatoid Arthritis (RA-WIS); and Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA).

Results: A total of 306 patients received treatment in Period 1 (mITT population); 222 (73%) patients completed the period. The majority of patients were female (70%), with a mean age of 50 y, mean DAS28 of 6.0 (median, 6.0), and duration of disease symptoms from onset of 6.5 months (median, 6.3 mo). Significant and clinically meaningful improvements in

PROs, including in HAQ, EQ-5D, SF-36, and FACIT-Fatigue, were demonstrated with ETN50/MTX therapy from baseline to the final on therapy visit (Table; $P<0.0001$). Similar improvements were observed in all dimensions of RA-WIS and WPAI:RA (Table; $P<0.0001$).

Table. Effects of ETN50/MTX on PROs in Early RA Patients in Period 1 of the PRIZE Study (N = 306)

Parameter	Baseline Mean (SD)	Final on Therapy Visit Mean (SD)	Δ from Baseline Mean (SD)
HAQ Disability Index	1.3 (0.7)	0.5 (0.6)	−0.8* (0.7)
EQ-5D Utility Score	0.5 (0.3)	0.8 (0.3)	0.3* (0.3)
EQ-5D VAS	50.9 (22.6)	77.2 (24.1)	27.4* (28.1)
SF-36 Physical Component Score	33.6 (8.0)	45.5 (9.7)	11.9* (9.6)
SF-36 Mental Component Score	42.9 (10.9)	50.6 (9.3)	7.5* (10.6)
FACIT-Fatigue	29.1 (12.6)	39.9 (11.4)	10.9* (12.2)
RA-WIS	13.5 (6.1)	4.8 (6.5)	−8.9* (6.6)
WPAI:RA, % activity impairment due to RA	57.2 (24.3)	21.5 (25.5)	−36.4* (29.4)

Endpoint	% Patients (95% CI), Final on Therapy Visit
Normal HAQ score (≤0.5)	66.6† (60.9, 71.9)
Clinically meaningful improvement in HAQ Disability Index (Δ ≥0.22)	80.2‡ (75.2, 84.6)
PASS	82.0† (77.2, 86.1)
RA-WIS High (>17)	7.7† (4.6, 11.9)
RA-WIS Low (0–9)	79.9† (74.2, 84.9)
RA-WIS Low/Medium (0–17)	92.3‡ (88.1, 95.4)

Note: Final on therapy visit and Δ values are for observed cases.
*$P < 0.0001$ vs baseline, paired t-test; †$P < 0.0001$ vs baseline, McNemar's test; ‡$P < 0.0001$ vs baseline, Binomial test; mITT population.
HAQ score: range, 0–3, 20 items; lower score = less functional disability; ≤0.5 = normal; Δ ≥0.22 = clinically meaningful.
EQ-5D: range, 0–1; higher scores = better QoL; Δ ≥0.05 = clinically meaningful.
FACIT-Fatigue: range, 0–52; higher scores = less fatigue; Δ ≥3.0 = clinically meaningful.
WPAI:RA: 0–100% work impairment; lower % = less work impairment.
RA-WIS >17 = high risk of work disability; RA-WIS 0–9 = low risk of work disability; and RA-WIS 0–17 = low or medium risk of work disability.

Conclusion: Combination therapy with ETN50/MTX for 52 wks in patients with <12 mo of symptomatic, active RA resulted in significant, clinically important improvements in measures of physical function, including normal HAQ (66.6% of patients), HR-QoL, fatigue, and work productivity. These outcomes are consistent with those reported in prior studies in patients with more established disease.

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Differences in Short-Term Radiographic Progression Following Early Response to Adalimumab Plus Methotrexate Vs. Methotrexate Alone.

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Background/Purpose: To prevent disease progression, treat-to-target recommendations for rheumatoid arthritis (RA) include the evaluation and adjustment of drug therapy at least every 3 months until a target level of remission or low disease activity is achieved. It is well established that anti-tumor necrosis factor (TNF) treatment modifies associations between disease activity and radiographic progression over periods of 1–2 years.[1] We aimed to assess whether TNF inhibition modifies this association over the initial 3–6 months of treatment for early RA.

Methods: Methotrexate (MTX)-naïve early RA patients randomized to double-blind treatment with adalimumab (ADA)+MTX combination therapy vs. MTX monotherapy were drawn from the Phase III PREMIER clinical trial. Associations between week 12 disease activity, assessed using DAS28-CRP(4), and changes in modified total sharp score (mTSS) from baseline to week 26 were compared between the ADA+MTX and MTX arms using generalized additive regression. mTSS progression was modeled as an absolute score change and as a worsening of ≥5 units.[2] Models were fit with and without adjustment for baseline mTSS, DAS28, numbers of tender and swollen joints, and RA duration.

Results: A total of 219 MTX-treated patients and 241 ADA+MTX-treated patients were included in the investigation. The mean age was 52 years, 73% were female, and the average RA duration was 9 months. In the

adjusted analyses, patients treated with ADA+MTX experienced limited mean increases in mTSS from baseline to week 26 that were numerically similar across all levels of week 12 DAS28, whereas patients treated with MTX showed a sharp increase in mTSS progression with increasing week 12 DAS28 (Figure). Compared to patients who were treated with MTX alone, those treated with ADA+MTX achieving a DAS28 ≤2.6 at week 12 had a significantly smaller change in mTSS (difference: −1.59; 95% CI: −2.74, −0.44) and a significantly lower risk of mTSS progression of ≥5 units (odds ratio [OR]: 0.19; 95% CI: 0.06, 0.61) at week 26. Results were similar for unadjusted analyses.

DAS-28 vs. Constant mTSS Change Adjusted
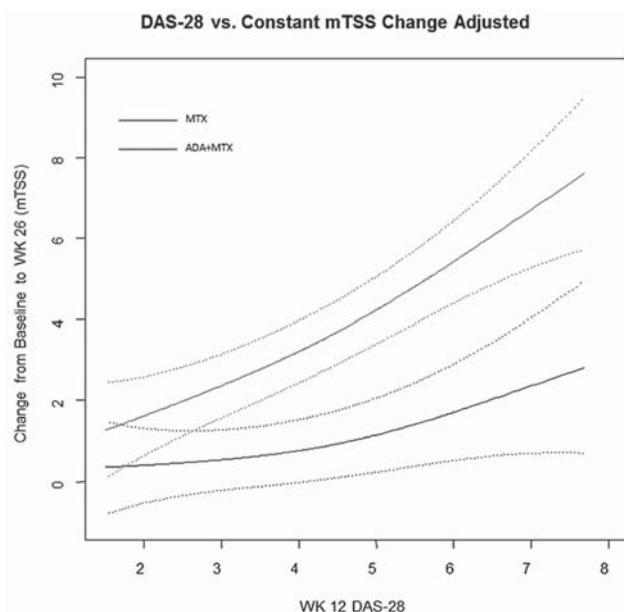
Conclusion: Early RA patients achieving a given disease activity level by week 12 with ADA+MTX experience less radiographic progression by week 26 than those achieving the same disease activity level with MTX alone. This could reflect the slower onset of response to MTX and/or a separate structure-protective effect for anti-TNF treatment. These aspects should be considered when setting disease activity targets with the goal of limiting radiographic progression.

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Characteristic of the Japanese Patients with Rheumatoid Arthritis (RA) of Rapid Radiographic Progression (RRP) Treated with Synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs) in Daily Practice: A Large-Scale Prospective Longitudinal Cohort Study (the 1st report of Apple Survey). Akitomo Okada[1], Atsushi Kawakami[1], Takaaki Fukuda[2], Toshihiko Hidaka[3], Tomonori Ishii[4], Yukitaka Ueki[5], Takao Kodera[6], Munetoshi Nakashima[7], Yuichi Takahashi[8], Seiyo Honda[9], Yoshiro Horai[1], Tomohiro Koga[1], Ryu Watanabe[10], Hiroshi Okuno[10] and Katsumi Eguchi[11]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Kurume University Medical Center, Kurume, Japan, [3]Zenjinkai Shimin-No-Mori-Hospital, Miyazaki, Japan, [4]Tohoku University, Sendai, Japan, [5]Sasebo, Japan, [6]Tohoku Kosei Nenkin Hospital, Sendai, Japan, [7]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasahi, Japan, [8]Yu Family Clinic, Sendai, Japan, [9]Kurume University School of Medicene, Kurume, Japan, [10]Tohoku University Hospital, Sendai, Japan, [11]Sasebo City General Hospital, Sasebo, Nagasaki, Japan

Background/Purpose: There has been few epidemiological report of longitudinal radiographic progression in rheumatoid arthritis (RA) patients captured in daily practice. In 20 related-centers of the Nagasaki University and Tohoku University in Japan we are conducting a large-scale prospective study (Apple Survey) to investigate extent of radiographic progression. We have tried to assess the extent of rapid radiographic progression (RRP) in synthetic disease modifying anti-rheumatic drugs (DMARDs)-treated RA patients.

Methods: We have selected the RA patients treated not by biologic DMARDs but by synthetic DMARDs for 1 year. One hundred fifty-three out of the 964 patients registered between May 09 and March 12 had evaluable data at present. Patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University, Tohoku University and related centers. DAS28-ESR was assessed every 3 months. Radiographs of the hands and feet were taken every 6 months. The images were scored by trained readers through modified total Sharp score (mTSS). RRP was defined as yearly progression of mTSS >3.0. We have examined what variables are associated with the development of RRP at 1 year.

Results: Ten variables including gender, disease duration at baseline, age, CRP at baseline (mg/dl), presence of autoantibodies (RF or anti-CCP Abs), DAS28-ESR at baseline, time-integrated DAS28-ESR during 1 year, mTSS at baseline, HAQ at baseline and the use of MTX or non-MTX DMARDs were evaluated through univariate and logistic regression analysis to explore the development of RRP at 1 year. RRP was found in 17 out of 153 patients (11.1%). Logistic regression analysis has found that short disease duration (p = 0.0061), younger age (p = 0.038), high time-integrated DAS28-ESR (p = 0.015) and high mTSS at baseline (p = 0.035) are independent variables to predict the development of RRP. There were the trend of presence of autoantibodies (p = 0.074) and non-MTX DMARDs use (p = 0.054) toward RRP at 1 year.

Conclusion: Our results have revealed the characteristic of synthetic DMARDs-treated Japanese RA patients who develop RRP. The treat-to-target strategy is particularly recommended in these patients.

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Treat-to-Target Strategy Aiming At Achievement of Structural and Functional Remission in Patients with Active Elderly-Onset Rheumatoid Arthritis. Takahiko Sugihara[1], Tatsuro Ishizaki[2], Tadashi Hosoya[1], Shoko Iga[1], Waka Yokoyama[1], Fumio Hirano[1], Nobuyuki Miyasaka[3] and Masayoshi Harigai[3]. [1]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan, [2]Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan, [3]Tokyo Medical and Dental University, Tokyo, Japan

Background/Purpose: Treat-to-target is the consensus treatment strategy for patients with rheumatoid arthritis (RA), but supporting evidence for treat-to-target strategy in elderly RA patients in clinical practice is insufficient. The objective of this study was to evaluate structural damage and physical disability of patients who developed RA at ≥60 y/o (elderly onset RA, EORA) and were treated aiming at low disease activity (LDA) in Choju registry of rheumatoid arthritis on non-biologic and biologic disease-modifying antirheumatic drugs (DMARDs) for elderly patients in Japan (CRANE), a prospective, mono-centric registry.

Methods: Of 150 Japanese elderly (≥60 years) patients with RA enrolled in the CRANE, we identified 106 methotrexate-naïve EORA patients with moderate to severe disease activity (disease activity score 28 joints (DAS28)≥ 3.2) and disease duration ≤ 3 years at the enrollment. We analyzed data from 84 patients who completed 12-month follow-up in this study. The treatment was adjusted every 3 months aiming at LDA (DAS28< 3.2). We started treatment with non-biologic DMARD monotherapy (methotrexate (MTX), tacrolimus, salazosulfapyridine, or bucillamine), followed by TNF inhibitors, then tocilizumab or abatacept. The co-primary outcomes were DAS28, Δtotal sharp score (TSS) and Health Assessment Questionnaire-Disability Index (HAQ-DI) at week52.

Results: Baseline characteristics of the 84 patients were as follows: mean age, 75.3 y/o; mean disease duration, 0.92 years; mean DAS 28, 6.33; mean HAQ, 1.23; anti-CCP antibody positive, 66.3%. Rates for comorbidity of the patients were 33.8% for chronic lung diseases, 12.8% for cardiovascular diseases and16.3% for diabetes mellitus. At week 12, 77.6% and 14.1% of the patients were receiving MTX at 7.3±1.8 mg/week and tacrolimus, respectively. At weeks 24 and 52, 16.9% and 33.3 % of the patients were treated with TNF inhibitors. LDA and functional remission (HAQ-DI≤0.5) were

achieved in 29.1% and 42.6% of the patients at week 24, respectively, and in 45.9% and 58.1% at week 52, respectively. Structural remission (ΔTSS/ year$\leq$ 0.5) were observed in 39.3 % and rapid radiographic progression (RRP,ΔTSS/year$>$3) in 32.6% of the patients. Triple (clinical, structural and functional) remission at week 52 was observed in 8.3% of the patients. Mean DAS28 at weeks 0, 12 and 24 and mean HAQ-DI at week 52 was significantly higher in the patients with RRP compared to those without RRP. The multiple logistic regression model involving the area under the curve (AUC) of DAS28 (accumulated DAS28) between week 0 and week 12, as well as age, sex, anti-CCP antibody status, HAQ-DI, and presence of bony erosions at week 0, predicted RRP at week 52 well with the C statistic of 0.897, and the AUC of DAS28 during the first 3 months predicted RRP better than those during the first 6 or 12 months (the C-statistic, 0.879 for 0–6 months, and 0.834 for 0–12 months).

Conclusion: Achieving LDA, structural remission and functional remission in daily clinical practice using non-biologic and biologic DMARDs in EORA patients were realistic goals. Rapid achievement and sustainment of clinical remission is indispensable to prevent RRP in the patients with EORA.

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TRAF1/C5 Locus Is Associated with Response to Anti-Tumor Necrosis Factor Therapy in Patients with Rheumatoid Arthritis. Helena Canhao[1], Ana M. Rodrigues[2], Maria José Santos[3], Diana Carmona-Fernandes[4], Bruno Bettencourt[5], Jing Cui[6], Fabiana Rocha[5], Jose canas Silva[3], Joaquim Polido Pereira[4], Jose Alberto Pereira Silva[7], José Antonio Costa[8], Domingos Araujo[9], Candida Silva[10], Helena Santos[11], Catia Duarte[12], Fernando Pimentel-Santos[13], Jaime C. Branco[13], Robert M. Plenge[6], Daniel H. Solomon[14], Jacome Bruges Armas[5], José A. P. Da Silva[15], João E. Fonseca[16] and Elizabeth W. Karlson[17]. [1]Instituto de Medicina Molecular, Lisbon, Portugal, [2]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Lisbon, Portugal, [3]Hospital Garcia de Orta, E.P.E., Almada, Portugal, [4]Instituto Medicina Molecular, Lisbon, Portugal, [5]Hospital de Santo Espirito da Ilha Terceira, Ilha Terceira, Portugal, [6]Brigham and Women's Hospital, Boston, MA, [7]Santa Maria Hospital, Lisbon, Portugal, [8]Centro Hospitalar do Alto Minho, Hospital de Ponte de Lima, Ponte de Lima, Portugal, [9]Unidade Local de Saude, Ponte de Lima, Portugal, [10]Instituto Portugues Reumatologia, Lisbon, Portugal, [11]Instituto Português de Reumatologia, Lisboa, Portugal, [12]Hospitais da Universidade de Coimbra, Coimbra, Portugal, [13]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [14]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA, [15]Centro Hospitalar e Universitário de Coimbra–Hospitais da Universidade de Coimbra, E.P.E., Coimbra, Portugal, [16]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal, [17]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Some of the allelic variants associated with rheumatoid arthritis (RA) susceptibility are related to tumor necrosis factor (TNF) signaling pathways. We hypothesized that they might influence the response to anti-TNF drugs. The primary aim of our work was to investigate potential associations between RA risk alleles specifically selected for their relevance on RA biologic pathways and the response to anti-TNF treatment in a Southern European population using a nationwide register.

Methods: We evaluated 383 RA patients for associations between anti-TNF treatment response, assessed by an absolute change in DAS28 at six months as the primary outcome, and single nucleotide polymorphisms (SNP) from _TRAF1/C5, TNFAIP3, REL, PADI4, PTPN22 and PTPRC_ loci and _HLA-DRB1*04_ high-resolution genotyping. We also studied the same association taking the proportion of EULAR good responders and non responders at six months as the outcome. Univariate and multivariate linear and logistic regression analyses were performed, adjusting for clinical variables known to influence treatment response.

Results: Our study sample included 383 Caucasian individuals with RA, 89.5% were women. 72.6% were seropositive. At six months, 119 (31.1%) patients were classified as good responders, 175 (45.7%) as moderate responders and 89 (23.2%) as non-responders according to the EULAR response criteria.

The minor allele (G), which is the risk allele for RA susceptibility, rs3761847 SNP in the _TRAF1/C5_ region was associated with a poor anti-TNF treatment response either in linear (coefficient −0.24; 95% confidence interval (CI) −0.43, −0.06; p-value 0.009) and in logistic univariate (odds ratio (OR) 0.61; CI 0.41, 0.92; p-value 0.018) and multivariate regression analyses. P-value of 0.009 for linear models either univariate and multivariate was very close to the level of significance set to 0.0083 after Bonferroni correction to multiple comparisons (Table 1).

Table 1. Association of the rs3761847 single nucleotide polymorphism of _TRAF1/C5_ locus with the response to anti-TNF treatment

Change in DAS	Absolute change in DAS n=383		EULAR good response vs non-response n=208 (good=119, non=89)	
	Linear regression models	Logistic regression models		
1.95 (1.26) 1.82 (1.31) 1.38 (1.19)	Univariate Coef. −0.24 CI −0.43,−0.06 P 0.009	Multivariate Coef. −0.23 CI −0.40,−0.06 P 0.009	Univariate OR 0.61 CI 0.41,0.92 P 0.018	Multivariate OR 0.58 CI 0.37,0.91 P 0.019

No significant associations were observed between _HLA-DRB1_ or the other allele variants with the response to anti-TNF treatment.

Conclusion: The rs3761847 _TRAF1/C5_ RA risk locus influenced the anti-TNF treatment response in the Southern European population assessed in this study. Additional studies in other populations are necessary to confirm the relevance of this finding.

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Patient-Reported Outcomes in Early Rheumatoid Arthritis Patients Failing to Achieve Stable Low Disease Activity: Comparing Addition of Adalimumab to Methotrexate Monotherapy with Maintenance On Adalimumab Plus Methotrexate. Arthur Kavanaugh[1], Ronald F. van Vollenhoven[2], Paul Emery[3], James W. Shaw[4], Mary A. Cifaldi[4], Stefan Florentinus[5] and Josef S. Smolen[6]. [1]UCSD School of Medicine, La Jolla, CA, [2]Karolinska Institute, Stockholm, Sweden, [3]University of Leeds, Leeds, United Kingdom, [4]Abbott Laboratories, Abbott Park, IL, [5]Abbott, Rungis, France, [6]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Treat-to-target guidelines for rheumatoid arthritis (RA) suggest adjusting therapy every 3–6 months for pts who fail to achieve a disease activity target. However, pts treated with adalimumab (ADA) plus methotrexate (MTX) can exhibit a delayed clinical response without radiographic damage.[1] Data from the Optimal Protocol for Treatment Initiation with MTX and ADA (OPTIMA) trial were used to evaluate differences in patient-reported outcomes (PROs) between pts maintained on ADA+MTX after failing to achieve a stable treatment target on that regimen compared to those treated with ADA+MTX after failing to respond to MTX monotherapy.

Methods: MTX-naïve pts ≥18 years of age with RA <1 year and active disease were randomized to ADA+MTX (N=515) or placebo (PBO) plus MTX (N=517) for 26 wks (Period 1). Those who failed to achieve stable low disease activity (LDA) (DAS28$_{CRP}$ <3.2 at wks 22 and 26) were offered open-label (OL) ADA+MTX for an additional 52 wks (Period 2). Pts completed the Work Productivity and Activity Impairment (WPAI) questionnaire, Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) subscale, Patient Acceptable Symptom State (PASS) classifier, and other PRO measures at wk 0 (baseline) and subsequent time points.

Results: At the end of Period 1, 259/466 (56%) ADA+MTX pts failed to achieve stable LDA (OL ADA carry-on arm) compared with 348/460 (76%) PBO+MTX pts (rescue ADA arm). Baseline characteristics for the OL ADA carry-on arm and rescue ADA arm were comparable, though pts in the former were less likely to be employed (46.8% vs. 55.7%, P=0.029) and were more fatigued (mean FACIT-F score: 23.6 vs. 25.8, P=0.022) than pts in the latter. Between wks 0 and 26, pts in the OL ADA carry-on arm had significantly greater improvements in physical functioning (mean HAQ-DI score change: −0.7 vs. −0.6, P=0.001), activity impairment (mean WPAI activity impairment score change: −24.6% vs. −18.3%, P=0.002), and health satisfaction (change in percent in PASS: 39.6% vs. 27.2%, P<0.001) than pts in the rescue ADA arm. Compared with pts in the OL ADA carry-on arm, pts in the

rescue ADA arm experienced significantly greater improvements in most PROs throughout Period 2. However, differences between the groups in improvements at wk 78 relative to wk 0 were statistically non-significant.

Mean Changes in PROs Relative to Wk 0 (Differences in Mean Changes Relative to Wk 26)

PRO	MCID	Treatment Arm	Wk 26	Wk 52	Wk 78
WPAI [range: 0–100]					
Absenteeism	7	OL ADA carry on	−11.9	−16.7	−18.4
		Rescue ADA	−11.9	−19.2 (−2.5)	−20.0 (−1.6)
Presenteeism	7	OL ADA carry on	−17.9	−24.0	−28.3
		Rescue ADA	−15.6	−29.8 (−8.0**)	−33.7 (−7.7**)
Overall work impairment	7	OL ADA carry on	−18.3	−26.7	−30.9
		Rescue ADA	−17.5	−33.4 (−7.5**)	−36.7 (−6.5)
Activity impairment	7	OL ADA carry on	−24.6	−31.2	−32.5
		Rescue ADA	−18.3*	−32.3 (−7.4**)	−32.9 (−6.7**)
WIS [range: 0–23]	NE	OL ADA carry on	−4.1	−5.3	−5.3
		Rescue ADA	−3.8	−7.6* (−2.6**)	−6.8 (−1.8**)
HAQ-DI [range: 0–3]	0.22	OL ADA carry on	−0.7	−0.8	−0.9
		Rescue ADA	−0.6*	−0.9 (−0.2**)	−0.9 (−0.2**)
FACIT-F [range: 0–52]	3–4	OL ADA carry on	8.7	10.7	11.1
		Rescue ADA	7.5	10.9 (1.3)	11.6 (1.6)
PASS [range: 0–100]	NA	OL ADA carry on	39.6	48.5	53.9
		Rescue ADA	27.2*	48.2 (12.2**)	60.1 (18.6**)

Notes: The FACIT-F and PASS were scored so that higher values indicated less fatigue and more satisfaction, respectively. Other outcomes were scored so that higher values indicated worse functioning or work productivity. Differences between groups in outcome trajectories were modeled using generalized estimating equations. Missing data were accounted for using multiple imputation. The MCID is the smallest change in measurement that signifies an important improvement or worsening.
Abbreviations: PRO, patient-reported outcome; MCID, minimum clinically important difference; OL, open label; ADA, adalimumab; WPAI, Work Productivity and Activity Impairment questionnaire; WIS, Work Instability Scale; HAQ-DI, Health Assessment Questionnaire Disability Index; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue subscale; PASS, Patient Acceptable Symptom State; NE, not established; NA, not applicable.
*P < 0.05, mean change relative to wk 0 different from OL ADA carry-on arm
**P < 0.05, mean change relative to wk 26 different between arms

Conclusion: The results of this study suggest that sustained treatment with ADA+MTX in the absence of an initial clinical response can yield substantial benefits beyond the inhibition of radiographic progression. In addition, for patients not achieving stable LDA with MTX alone, the introduction of ADA after six months of treatment allows for significant improvements in work productivity and other PROs.

Reference
[1]Keystone E et al. ACR/AHRP Scientific Meeting, Atlanta, GA, November 7–11, 2010. P1102.

Disclosure: A. Kavanaugh, Abbott Laboratories, 5; **R. F. van Vollenhoven**, Abbott Laboratories, 5, Abbott Laboratories, 2; **P. Emery**, Abbott Laboratories, 5; **J. W. Shaw**, Abbott Laboratories, 3; **M. A. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1; **S. Florentinus**, Abbott Laboratories, 1, Abbott Laboratories, 3; **J. S. Smolen**, Abbott Laboratories, 5, Abbott Laboratories, 2.

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Prevalence of Biologic Utilization Over Calendar Time Among Medicare Beneficiaries with Rheumatoid Arthritis. Jie Zhang[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Lang Chen[1], James Lewis[2], Kevin Haynes[3], Kenneth G. Saag[4] and Jeffrey Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Pennsylvania, [3]University of Pennsylvania., Philadelphia, PA, [4]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: The establishment of Medicare prescription drug coverage in 2006 and FDA approval of abatacept and rituximab for treatment of rheumatoid arthritis (RA) provided alternative biologics covered under Medicare for RA patients with fee for service coverage. Our objective was to examine the prevalence of biologic use among Medicare beneficiaries with RA from 2006 to 2009.

Methods: Using data from the 100% sample of U.S. Medicare beneficiaries with RA (>= 2 RA diagnoses from rheumatologist visit occurring between 7 and 365 days apart), we identified eligible RA patients with continuous Part A, B, and D coverage for each 3 months interval from July 1st, 2006 to December 31st, 2009; those who had at least one filled prescription or infusion during the 3 months were categorized as users. Among beneficiaries who initiated a biologic after at least 12 months without exposure to any biologic, we performed logistic regression to examine factors associated with the choice of an injection versus an infusion biologic, including demographics, concomitant glucocorticoids and non-biologic DMARDs, calendar year, physician preference, and receiving subsidy for Medicare part B premium from state of residence. Physician preference was measured by the percentage of patients treated with infusion biologics out of all patients treated with biologics in the preceding 6 months by each physician, grouped into quartiles.

Results: From 2006 to 2009, approximately 27% of all U.S. Medicare beneficiaries with RA treated by rheumatologists received biologics. The prevalence of infliximab use declined from 14.9% in the 3rd quarter of 2006 to 12.2% in the 4th quarter of 2009. In contrast, the prevalence of abatacept increased from 1.1% to 4.0% during this time. We did not observe an increase in the use of self-injectable biologics (Figure 1). After adjusting for covariates, we found that stronger physician preference for infusion biologic was associated with increased odds of infusion biologic use (odds ratio comparing highest quartile to the lowest quartile, 8.9; 95% CI, 8.0–10.0) and receiving subsidized Medicare coverage was associated with increased injection biologic use (odds ratio, 2.8; 95% CI, 2.6–3.0).
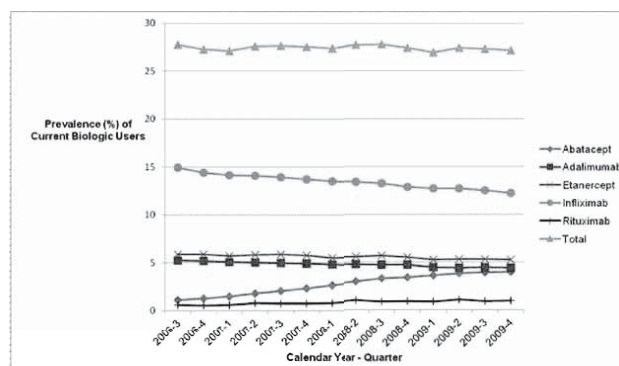
Figure 1. Prevalence of Biologics among Medicare Beneficiaries with Rheumatoid Arthritis

Conclusion: The prevalence of injection and infusion biologics remained stable from 2006 to 2009. The choice of infusion versus injection biologics appeared to be strongly driven by patients' financial considerations and physicians' preferences.

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Cell Phone Based Automated Monitoring of Patients with Early Rheumatoid Arthritis. Kari Puolakka[1], Tuulikki Sokka[2] and Hannu Kautiainen[3]. [1]Department of Medicine, South Karelia Central Hospital, Lappeenranta, Finland, [2]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [3]Orton Rehabilitation, Helsinki, Finland

Background/Purpose: Frequent monitoring improves patient compliance and outcomes of RA. Limited resources may hinder adherence to recommendations to frequent assessment. A remote assessment could be a solution with patient's global assessment (PtGA) as a measure.

Methods: A novel, cell-phone based monitoring system has been invented (SandRA).

Each incident patient with early RA is being registered in SandRA monitoring–with his or her informed consent. Baseline PtGA is recorded. Every 2 weeks during the following 6 months, SandRA sends automatically an SMS to the patient's cell phone, and patient answers by one push on keyboard. The first 2 SMSs concern medications ("Have you used the prescribed drug treatments?" Y/N) and adverse events ("Have you experienced any problems with the drug?" Y/N). From 6 weeks onwards, PtGAs is inquired: ("What is the severity of RA on scale 0 to 10, when 0 corresponds absence of RA symptoms and 10 as severe RA symptoms as you can imagine?"). Based on data from our previous early RA cohorts, a treatment target was set at 5-3/10 (figure 1).
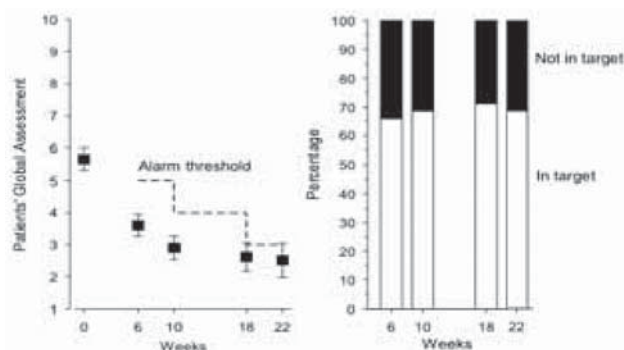
The patients' answers are recorded in SandRA database and automatically analyzed. If an answer does not indicate problems, patient receives an automatic SMS response of the answer being recorded. If an answer indicates problems, i.e., patient has not used the treatment, has experienced adverse events, or RA has not improved at the pace defined, the patient receives an SMS: "Your nurse will call you within 2 working days". At the same time, the nurse receives an e-mail about the patient's problem. If the problem cannot be solved on the phone, the patient is called for a visit for treatment adjustment.

Results: We analyzed 137 consecutive patients registered in SandRA. The patients' regular doctor appointments were scheduled at 3 and 6 months. Most patients achieved the treatment target, i.e., their PtGAs were under the alarm line (panel A). SandRA picked out 34%, 31%, 29%, and 31% of the patients at 6, 10, 18, and 22 weeks for assessment before regular appointments (panel B).

Conclusion: A novel automated cell phone based monitoring system may provide a feasible method to achieve treatment target in patients with early RA.

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Strategies for Use of Prednisolone in Rheumatoid Arthritis Have Changed Over the Past Decade: Data From the NOR-DMARD Register. Anna-Birgitte Aga, Elisabeth Lie, Till Uhlig, Tore K. Kvien and Espen A. Haavardsholm. Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: Focus on early aggressive treatment in patients with rheumatoid arthritis (RA) has increased during the past decade. There is evidence for the efficacy of prednisolone as bridging therapy awaiting the therapeutic effect of DMARDs as well as evidence for a disease-modifying effect of glucocorticoids. Our objective was to investigate pattern in prednisolone use in RA patients in the past decade.

Methods: Data for this study were provided by the NOR-DMARD register, including adult patients with inflammatory arthropathies starting a new DMARD regimen at 5 Norwegian centers. These analyses included Methotrexate (MTX) naïve RA patients starting MTX mono and biologics naïve RA patients starting TNF inhibitor (TNFi) + MTX between 2000 and 2010. Each group was divided into 2-year intervals according to date of treatment start. The proportion using prednisolone, and mean prednisolone doses at baseline and at 6 months were assessed. Comparisons between first vs. last time period were made by Chi^2-test and two-sample t-test. Possible linear effects of time were assessed by logistic and linear regression with year of treatment start as a continuous variable. 6-month DAS28 remission rates were calculated.

Results: 2573 pts were included–MTX mono n=1866 [70% female, 62% RF+, mean (SD) age 56.0 (13.7) years, time from diagnosis 3.6 (7.7) years] and TNFi+MTX n=707 [70% female, 75% RF+, age 52.1 (13.2) years, time from diagnosis 9.1 (9.3) years]. In patients starting MTX mono the proportion of patients using prednisolone at baseline increased over the years, while the proportion still using prednisolone at 6 months decreased (table). The differences between the first and the last period were statistically significant, but the effect of time was not linear. In the TNFi+MTX group the proportion of patients using prednisolone at baseline was stable during the decade, but the proportion at 6 months was significantly lower in the last vs. the first time period. The mean doses of prednisolone were stable throughout the decade in both groups. Proportions of patients reaching 6-month DAS28 remission increased gradually over the years in both groups (table).

Proportion of patients on prednisolone [%(n)]	2000–2002	2003–2004	2005–2006	2007–2008	2009–2010	p-value*
MTX mono (n=1866) Baseline [%(n)]	49.0 (172)	44.7 (207)	45.9 (181)	62.3 (223)	60.7 (182)	0.003
6 month [%(n)]	32.5 (114)	29.4 (136)	30.2 (119)	35.2 (126)	21.7 (65)	0.002
TNFi+MTX (n=707) Baseline [%(n)]	56.5 (48)	51.1 (94)	48.3 (69)	49.4 (79)	49.6 (67)	0.32
6 month [%(n)]	35.3 (30)	26.1 (48)	28.0 (40)	28.8 (46)	14.8 (20)	<0.001
Prednisolone dose mg/day [mean(SD)]						p-value**
MTX mono (n=1866) Baseline [mean(SD)]	8.9 (3.6)	9.1 (4.5)	8.9 (4.0)	8.9 (3.7)	9.2 (4.1)	0.37
6 month [mean(SD)]	6.0 (2.8)	5.6 (2.5)	5.7 (3.2)	5.4 (2.5)	5.6 (2.7)	0.44
TNFi+MTX (n=707) Baseline [mean(SD)]	8.0 (3.4)	7.2 (3.0)	7.5 (3.3)	7.9 (4.9)	7.1 (3.6)	0.17
6 month [mean(SD)]	5.8 (2.9)	5.5 (2.5)	5.3 (2.4)	5.7 (3.0)	7.6 (12.4)	0.45
DAS28 remission 6 month [%(n)]						p-value*
MTX mono (n=1866) 6 month [%(n)]	17.8 (43)	29.2 (95)	33.7 (89)	38.1 (80)	37.6 (44)	<0.001
TNFi+MTX (n=707) 6 month [%(n)]	16.9 (10)	29.3 (36)	34.5 (38)	31.4 (27)	46.3 (25)	0.003

* chi^2 –test first vs. last period, ** two sample t-test first vs. last period.

Conclusion: A higher proportion of RA patients used prednisolone when starting MTX in the recent years, and an increasing proportion of patients tapered and discontinued prednisolone. The observed increases in DAS28 remission rates likely reflects the implementation of modern DMARD treatment strategies including treatment earlier in the disease course and at lower levels of disease activity, but the changes in the use of prednisolone may be a contributing factor.

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Use and Long Term Use of Complementary and Alternative Medicine in Rheumatoid Arthritis Patients. Peri H. Pepmueller[1], Ramzy Jandali[1], Anu Sharma[2], Shannon Grant[3] and Katherine C. Saunders[4]. [1]Saint Louis University, St. Louis, MO, [2]Center for Rheumatic Diseases, Bethesda, MD, [3]Axio Research LLC, Seattle, WA, [4]CORRONA, Inc., Southborough, MA

Background/Purpose: Studies have identified widespread use of complementary and alternative medicine (CAM), particularly in patients with rheumatic disease. Most have reported results over short time frames, i.e. "used in last year" or "ever use"; few have evaluated long-term (LT) use of CAM. In addition, studies have often looked at all patients in a rheumatology practice rather than those with rheumatoid arthritis (RA) only. The purpose of this study was to quantify the frequency of ever and LT use of CAM in patients with RA and to identify characteristics associated with ever and LT CAM use.

Methods: Data from RA patients participating in the Consortium of Rheumatology Researchers of North America (CORRONA) registry, an independent prospective observational cohort with >30,000 RA patients enrolled from over 100 academic and private practices across the US, were examined. Patients provided data regarding the use of glucosamine/chondroitin, fish oil, borage seed oil, evening primrose oil, and flax seed oil at clinic visits. Other CAM use such as acupuncture, massage, or yoga was not collected. Patients with at least two years of follow-up and at least three visits were included in the analysis. Primary outcome was any CAM use within 2 years of first visit. LT use was defined as use of the same CAM at 3 consecutive visits or all visits in one year. Logistic regression was used to calculate odds ratios (ORs) of CAM use (ever or LT) by patient demographics, disease characteristics, and medication history.

Results: 11,970 patients were included in the analysis; 35.2% reported any CAM use, but only 10.8% reported LT use (p<0.0001). Fish oil was the most common CAM reported (27.3%). Without adjusting for other factors, patient demographics, medication history, and lower disease activity [Disease Activity Score (DAS28), tender/swollen joint count, modified Health Assessment Questionnaire (mHAQ), Clinical Disease Activity Index (CDAI), physician/patient assessments] were associated with ever and LT CAM use (Table 1). Separate multivariate models for ever and LT CAM use had the listed predictors in common (Table 1).

Table 1. Patient characteristics at first visit associated CAM use

Demographics	OR No Adjustment Ever CAM	LT CAM	OR (95% CI) With Adjustment[1] Ever CAM	LT CAM
Older age	1.005#	1.006#	N	N
White	1.160#	1.152*	1.25 (1.09 – 1.45)#	N
Current smoker	0.611*	0.556*	0.70 (0.62 – 0.79)*	0.71 (0.57 – 0.87)#
Education: high school or less vs any college	0.641*	0.523*	0.69 (0.63 – 0.75)*	0.58 (0.51 – 0.67)*
Married – vs windowed	0.732*	0.651*	0.72 (0.62 – 0.83)*	0.66 (0.52 – 0.84)#
- vs single	0.815*	0.718*	0.86 (0.74 – 1.00)*	0.68 (0.53 – 0.88)#
Region – Western vs Midwest	1.961*	2.269*	1.49 (1.29 – 1.72)*	1.67 (1.36 – 2.03)*
Northeast vs Midwest	0.817*	0.847* 1.141*	0.83 (0.74–0.93)*	0.85 (0.71–1.02)*
South vs Midwest	1.122*		0.88(0.79 – 0.997)*	0.80 (0.66–0.97)*
Part-time work vs full-time	1.159#	1.244#	1.17 (1.02 – 1.35)#	1.33 (1.08 – 1.64)#
More frequent visits (8+ vs 3 visits)	1.542*	2.024*	1.83 (1.53 – 2.19)*	2.63 (1.98 – 3.50)*
First visit in 2006 or later	2.014*	2.450*	1.83 (1.67 – 2.00)*	2.21 (1.90 – 2.56)*
Disease characteristics				
Duration of RA (years)	0.995#	0.994#	N	N
Older at RA onset(years)	1.007*	1.008*	1.01 (1.01 – 1.02)*	1.01 (1.01 – 1.02)*
Deformities present	0.900#	1.003	N	1.22 (1.06 – 1.41)#
Disease activity				
DAS 28	0.932#	0.873*	N	N
CDAI	0.994#	0.990*	N	N
Number of swollen joints	0.990#	0.992	N	N
Number of tender joints	0.995	0.981#	N	N
mHAQ	0.898#	0.784#	N	N
Physician assessed disease activity (scale 1–100)	0.997#	0.994*	N	N
Patient assessed disease activity (scale 0–100)	0.997#	0.994*	N	0.996 (0.993 – 0.999)#
Medical History				
NSAID use	1.274*	1.418*	1.31 (1.20 – 1.43)*	1.49 (1.29 – 1.72)*
Exposure to 3+ DMARDs vs 0	1.293#	1.131	1.30 (1.13 – 1.49)#	N
Patient report anxiety/ depression	1.188*	1.011	1.19 (1.09 – 1.31)#	N

[1]Multivariate models built separately for ever and LT CAM using stepwise logistic regression.
* p<0.0001, #p<0.05
N = not included in model

Conclusion: The results show significant differences in patient characteristics between CAM users and non-users, but clinical characteristics are similar suggesting that patient characteristics rather than disease severity are the driving force behind CAM use. CAM use with first visits after 2006 suggests that CAM use is increasing. Although "ever use" of CAM was 35.2%, the LT use was significantly lower, 10.8%, implying that patients may try complementary therapy, but few continue.

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Use of Anti-Tumor Necrosis Factor Monotherapy and Adherence with Non-Biologic Disease-Modifying Anti-Rheumatic Drugs in Combination with Anti-Tumor Necrosis Factor Therapy Among Rheumatoid Arthritis Patients in a Real-World Setting. Nicole M. Engel-Nitz[1], Sarika Ogale[2] and Mahesh Kulakodlu[1]. [1]OptumInsight, Eden Prairie, MN, [2]Genentech, South San Francisco, CA

Background/Purpose: Studies have shown better response for anti-TNFs (aTNF) when they are used in combination with non-biologic DMARDs (nbDMARD), than when used as monotherapies.[1] Therefore, non-adherence to nbDMARDs prescribed in combination with aTNFs may reduce the benefit obtained with these agents. This study examined the use of aTNF monotherapy in the real world, and adherence with nbDMARDs in patients receiving combination aTNF+nbDMARDs.

Methods: We conducted a claims analysis of adult RA patients in a US managed care plan, initiating an aTNF (etanercept; adalimumab; infliximab; golimumab; or certolizumab pegol) between Jan 2006 and Dec 2010. aTNF initiators were classified as 'biologic-naïve' or 'previously-exposed', based on prior biologic use. Patients were followed from aTNF initiation until discontinuation of that aTNF or plan disenrollment. The proportion of patients receiving aTNF as monotherapy (i.e. never received nbDMARD during aTNF follow-up) was determined; nbDMARDs included methotrexate (MTX), leflunomide, sulfasalazine, hydroxychloroquine, cyclophosphamide, gold salts, azathioprine, cyclosporine, and d-penicillamine. In patients receiving combination therapy (i.e. received nbDMARD at any time during aTNF follow-up), adherence to nbDMARDs was defined as the percent of days that patients received any nbDMARD while they were receiving the aTNF agent. Thus, 100% adherence indicates that the patient was on some nbDMARD 100% of the time during their aTNF follow-up based on filled prescriptions. Adherence with MTX was also assessed separately.

Results: Of 7,074 biologic-naive RA patients initiating an aTNF, 27% received it as monotherapy and 73% in combination with nbDMARDs. Of 2,690 aTNF patients previously exposed to biologics, 31% received monotherapy and 69% in combination with nbDMARDs. Only 42% of patients receiving aTNF monotherapy vs. 89% of combination therapy patients had filled a nbDMARD prescription during the 6 months prior to initiating the aTNF agent. Among biologic-naïve combination therapy patients, 52% of patients adhered with nbDMARD therapy less than 80% of the time while receiving aTNFs; 32% of the patients had less than 60% adherence. Of biologic-naïve patients who received aTNF combination therapy with methotrexate, 56% had less than 80% adherence with MTX and 35% had less than 60% adherence with MTX while receiving the aTNF. Results were similar for aTNF patients previously exposed to biologics. Adherence calculated here based on claims data may be an overestimate because we do not know if patients consumed the filled prescriptions.

Conclusion: This study found that up to 31% of patients receiving an aTNF agent for RA in the real-world received it as monotherapy, and a substantial proportion of those receiving combination therapy had less than 60% adherence with nbDMARDs. Some of these patients may have suboptimal outcomes, as suggested by evidence that RA patients receiving aTNFs in combination with nbDMARDs have better response.

[1]Nixon et al..Rheumatology 2007; 46: 1140–7.

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Persistency and Predictors of Persistency of Adalimumab Among Rheumatoid Arthritis (RA) Patients in a US Registry. Allan Gibofsky[1], Katherine C. Saunders[2], Arijit Ganguli[3], Mary Cifaldi[3], Shannon Grant[4], Jerry Clewell[3], Neelufar Mozaffarian[3], James Shaw[5], Reva McCaskill[3], George W. Reed[6] and Jeffrey D. Greenberg[7]. [1]Hospital for Special Surgery, New York, NY, [2]CORRONA, Inc., Southborough, MA, [3]Abbott Laboratories, Abbott Park, IL, [4]Axio Research LLC, Seattle, WA, [5]Abbott, Abbott Park, IL, [6]University of Massachusetts Medical School, Worcester, MA, [7]NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: There are limited observational data to guide physician decision-making when choosing to begin a patient on a new biologic treatment. Understanding real-world trends in persistency on therapy and factors related to persistency would aid in this process. We sought to identify predictors of persistence on adalimumab (time to discontinuation and change in treatment) in a large US registry of RA patients.

Methods: The CORRONA registry is a large, multicenter, longitudinal database of RA patients enrolled from > 90 academic and private practices across the USA. RA patients enrolled in CORRONA between March 2002 and September 2011 who initiated adalimumab and had at least one follow up visit post-initiation were included in this analysis. Discontinuation of adalimumab and treatment change were modeled separately. Discontinuation was defined as stoppage of adalimumab for any duration, while treatment change included discontinuation of adalimumab, change in adalimumab dose/ frequency, or adding /discontinuing a DMARD. Kaplan-Meier curves were used to estimate persistence quartiles. Associations between patient characteristics and persistence were estimated using univariate and multivariate proportional hazards (PH) regression models.

Results: 1639 patients initiated adalimumab and had at least one follow-up visit, 1003/1639 patients discontinued adalimumab, with a Kaplan-Meier estimate of median days to discontinuation: 632 (95% CI: 564.5–717). A multivariable model showed risk of discontinuation was associated with prior use of another biologic, number of swollen joints, duration of RA and prednisone use at initiation (Table 1). 1358/1639 patients experienced some form of treatment change. Median days to treatment change: 276 (95% CI: 258–298). Likelihood of treatment change increased with prior use of biologics, number of swollen joints and prednisone use at initiation; it decreased with concomitant use of MTX at initiation (Table 1). Hazard Ratios represent the baseline risk association.

Table 1.

	Hazard Ratio	(95% Confidence Interval)	P-value
Predictors of Discontinuation			
Use of previous biologic	1.532*	(1.259–1.864)	<0.0001
SJC at initiation	1.010+	(1.001–1.018)	0.0301
RA duration at initiation	1.005	(1.002–1.007)	0.0002
Prednisone use at initiation	1.279	(1.180–1.386)	<0.0001
Predictors of Change in Treatment			
Use of previous biologic	1.613*	(1.438–1.809)	<0.0001
SJC at initiation	1.015	(1.007–1.023)	0.0001
Prednisone use at initiation	1.116	(1.069–1.166)	<0.0001
MTX use at initiation	0.876	(0.835–0.919)	<0.0001

SJC, swollen joint count
*time varying association. HR estimates initial risk association; association decreases over time
+time varying association. HR estimates initial risk association; association increases over time

Conclusion: In the CORRONA registry, persistence on adalimumab was inversely correlated with factors suggestive of high disease severity. Patients using concurrent MTX with adalimumab at initiation were less likely to experience a change in their treatment compared to non-MTX users.

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DMARD and Biologic Use During Pregnancy Among Rheumatoid and Psoriatic Arthritis Patients in the Corrona Registry. John J. Cush[1], George Reed[2], Katherine C. Saunders[3], Joel M. Kremer[4], Jeffrey D. Greenberg[5] and Arthur Kavanaugh[6]. [1]Baylor Research Institute, Dallas, TX, [2]UMass Medical School, Worcester, MA, [3]CORRONA, Inc., Southborough, MA, [4]Albany Medical College, Albany, NY, [5]NYU Hospital for Joint Diseases, New York, NY, [6]UCSD School of Medicine, La Jolla, CA

Background/Purpose: CORRONA is a nationwide longitudinal disease-based registry that includes 32875 rheumatoid (RA) and 5462 psoriatic arthritis (PsA) patients. We sought to ascertain the frequency of pregnancy among 5377 women of childbearing age within the CORRONA registry and assess the impact of pregnancy on disease activity and medication use.

Methods: Females aged 18–45 yrs, diagnosed as RA or PsA with >12 mos follow-up were included. A preconception (PRE) visit < 12 mos of a self-reported pregnancy (PREG) was required. Disease activity and therapy were assessed at PRE and PREG visits and included CDAI, GAS, mHAQ, TJC, SJC and the % off all DMARDs or biologics (DMARD-free). We tallied those who flared or improved (defined: 20% change in TJC+SJC) and the percent moving to or from low activity (CDAI remission or LDAS) and high activity (CDAI moderate or severe). Therapies were classified as MTX, non-biologic DMARDs (NB-DMARD), TNF inhibitors (TNFi), other biologics (oBiologic) or all DMARDs (NB-DMARD or TNFi or oBiologic). The outcome of pregnancy was not the object of these analyses. While 251 total pregnancies (221 pts) were identified, 147 pregnancies (126 pts) met inclusion criteria. No differences were observed between included and excluded patients.

Results: 147 pregnancies (130 RA, 17 PsA) were found for a frequency of 2.3%. Mean age was 32.4 yrs and disease duration 7.3 yrs. Time span from PRE to PREG was 4.9 mos (RA) and 6.3 mos (PsA). Overall drug use and disease activity was less than that seen in nonpregnant CORRONA patients (data not shown). At the PRE visit TNFi were most often used (54%) with surprisingly less MTX (16%), oBiologic (4%), Pred (23%), NSAIDs (34%) use (Table). At PRE 69% were in CDAI remission or LDAS. PREG impact was modest with median change from PRE-PREG being zero for 8/10 activity measures. Joint counts improved in 31% and flared in 27% during PREG, with 36% having a 1–2 increase in joint count. From the PRE to PREG, only 13% of 101 low activity pts worsened to high activity. Conversely, 43% of those with high activity improved to low activity during

PREG. MTX and NB-DMARD decreased with PREG, yet some continued MTX (4%) or NB-DMARD (21%) at PREG. Biologic use was halved from 59% (PRE) to 29% (PREG) and DMARD-free rose from 28% to 61% during PREG. 61 patients were biologic free at PRE and only 2 (3.3%) started biologics during PREG. Conversely of 80 PRE patients who took TNFi, 42 (53%) stopped TNFi during PREG.

Comparison of Therapies and Activity Pre- and during Pregnancy

(n=147)	PRE	PREG
TJC	2.0	2.2
SJC	2.0	1.9
CDAI	7.8	7.7
GAS	5.9	6.0
Low Activity %	68.9	59.9
High Activity %	31.3	17.8
mHAQ	0.22	0.22
ESR mm/hr	20.5	22.4
MTX %	15.7	4.1
NB DMARD%	40.1	21.1
TNFi %	54.4	27.2
Other Biologics	4.1	2.0
DMARD Free %	27.9	61.2
Prednisone %	23.1	12.2
NSAID %	34.0	12.2

Conclusion: TNFi were most frequently used in those apparently planning to become pregnant and also during PREG. RA and PsA patients who become pregnant are likely to have low level disease activity and less commonly used MTX, NB-DMARD, Pred or NSAIDs. While the literature suggests up to 80% of RA patients improve during PREG, this large CORRONA cohort showed less disease activity change with 12% moving from low to high activity and only 43% moving from high to low activity during PREG.

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DAS Does Not Predict Increasing Treatment in Early Rheumatoid Arthritis: Results From the CATCH Study. Lonnie Pyne[1], Vivian P. Bykerk[2], Carol A. Hitchon[3], Edward Keystone[4], J. Carter Thorne[5], Boulos Haraoui[6], Ashley Bonner[7], Janet E. Pope[8] and CATCH Investigators[9]. [1]Western University, London, ON, [2]Hospital for Special Surgery, New York, NY, [3]University of Manitoba, Winnipeg, MB, [4]University of Toronto, Toronto, ON, [5]Southlake Regional Health Centre, Newmarket, ON, [6]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [7]McMaster University, Hamilton, ON, [8]Western University of Canada, St. Joseph's Health Care, London, ON, [9]Toronto, ON

Background/Purpose: The disease activity score (DAS) was developed in RA to guide therapy. Its utility in practice for early rheumatoid arthritis (ERA) has not been fully studied. The aim was to determine factors most strongly associated with an increase in therapy in ERA at 3 and 6 months.

Methods: Data were collected from Canadian Early Arthritis Cohort (CATCH) patients who were included if they had >2 visits and baseline and 6 months data. A regression analysis determined factors associated with treatment intensification.

Results: Of the 1,145 ERA patients, 790 met inclusion criteria. Mean age was 53.4 (SD 14.7), disease duration 6.1 months (SD 2.8), 75% were female, baseline DAS28 was 4.7 (SD 1.8) and 2.9 (SD 1.8) at 6 months. Factors most strongly associated with intensifying treatment in univariate analyses were MD global (assessment) (OR= 7.8 at 3 months and OR=7.4 at 6 months, P<0.0005) and SJC (OR= 4.7 and OR=7.3 at 3 and 6 months, P<0.0005). DAS did not affect treatment intensification as strongly in univariate analyses (OR= 3.0 at 3 months and OR=4.6 at 6 months, P<0.0005). In the logistic regression model only MD global was consistently associated with treatment intensification (OR= 1.5 and OR=1.2 at 3 and 6 months respectively, P<0.0005). DAS28 was not a consistent predictor of treatment intensification (OR= 1.0, P= 0.987 at 3 months and OR=1.2 P=0.023 at 6 months). If adjusting for multiple comparisons, only MD global was significant at both 3

and 6 months. When treatment was intensified; only 2% of physicians listed DAS28 as a reason for the treatment change, compared to 52%, 50% and 24% for SJC, TJC and MD global respectively. For the same SJC, larger joint involvement was more likely to influence treatment than small joint involvement at 3 months (OR=1.4, P=0.027). At 3 (but not 6) months for the same joint count, larger joint involvement was more associated with increasing therapy (P=0.027).

Table 1. Summary of variables in logistic regression model of increase therapy (strict definition) at 3 and 6 months. Model had a percent correct classification of 76.2% and P-value <0.0005 at 3 months and 79.3% and P-value <0.0005 at 6 months

	Age	TJC	SJC	ESR	CRP	Patient Global Assessment	HAQ-DI	Pain Today	MD Global Assessment	DAS28
Exp(B) (95% C.I.) 3 months	0.989 (0.975, 1.002)	1.019 (0.985, 1.055)	1.050 (0.998, 1.105)	1.008 (0.991, 1.024)	1.005 (0.984, 1.026)	1.007 (0.996, 1.017)	0.541 (0.357, 0.820)	1.116 (0.995, 1.251)	1.460 (1.316, 1.620)	0.999 (0.855, 1.167)
P-Value	0.089	0.273	0.061	0.372	0.638	0229	0.004	0.060	<0.0005	0.987
Exp(B) (95% C.I.)6 months	*	0.997 (0.962, 1.033)	1.098 (1.040, 1.160)	0.985 (0.968, 1.002)	**	1.015 (1.004, 1.027)	0.872 (0.569, 1.336)	0.996 (0.885, 1.122)	1.249 (1.106, 1.412)	1.235 (1.029, 1.481)
P-Value	—	0.868	0.001	0.083	—	0.007	0.529	0.952	<0.0005	0.023

Conclusion: Physician global assessment was independently associated with an increase in treatment at 3 and 6 months in ERA, whereas DAS28 was only significant at 6 months. SJC was also strongly related to treatment intensification at 6 months. Physicians rarely stated that DAS28 was the reason for increasing treatment and the data demonstrate that MD global assessment (which is not part of the DAS) is the main reason for treatment intensification in ERA.

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Does Biased Risk Perception Explain the Underuse of Disease Modifying Anti-Rheumatic Drugs?
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Background/Purpose: The prescription of a Disease Modifying Anti-rheumatic Drugs (DMARD) for patients with rheumatoid arthritis (RA) is considered a standard of effective care. However a recent study of Medicare managed care enrollees, only 63% received a DMARD. The explanation for underutilization is not fully known. In a sample of 144 patients, Constantinescu et al found compared to white adults with RA, African American patients assigned greater importance to the risks of treatment over the likelihood for benefit. The purpose of our study was to evaluate the determinants of risk perception (RP) in a large cohort of community RA patients and predictors of their willingness to take a proposed DMARD (DMARD willingness).

Methods: A single center, cross-sectional mail survey of RA patients in a community rheumatology practice. Patient characteristics including heath literacy screening index (HL), depression, RA duration, DMARD experience including bother from current DMARD side effects, satisfaction with RA control, Decision Regret Scale,TNFi knowledge, happiness, HAQ2, and CDAI were collected. Patients were presented a hypothetical decision scenario where they were asked to consider switching DMARDs. They evaluated how risky the proposed medication was and how likely they would be to take it. Predictors of RP and DMARD willingness were identified with hierarchical linear regression modeling.

Results: The completed sample included 1009 RA patients. The overall survey response rate was 71%. Patient characteristics: age 61.6 years (range 18–93), 75% female, minority 6.5%, low or marginal health literacy 8.8%, depression 15.0%, duration RA 13.1 years (range 0.5–68). A regression model evaluating predictors of RP demonstrated a $R^2 = 13.5$. The standardized regression coefficients show the strongest predictor of RP was HAQ2 disability (B=.152), followed by HL (B= −.149), and current or past experience of DMARD related bother(B=.146). Age, TNFi knowledge, happiness and depression, and other demographics did not significantly add to the predictive power of the model. A second model of predictors of DMARD willingness had a $R^2 = 12.7\%$. The standardized regression coefficients show the strongest predictors of DMARD willingness were satisfaction with control of RA (B=−1.67) and regret related to their previous DMARD choice (B=−1.60), and HL (B= 1.49). Age and other demographic characteristics, extent of past RA and general DMARD related experience, happiness and depression did not significantly add to the predictive power of the model.

Conclusion: RP was influenced by negative RA disease and treatment experience, while DMARD willingness was affected by perceived disease control. Health literacy, independent of low educational achievement or other demographic, was a predictor of both RP and DMARD willingness. When proposing to initiate a new DMARD, clinicians must be alert for cognitive impairment whether derived from educational, language, age related decline in information processing that could affect patient decision making. Time pressures increase cognitive load, which might justify extending the time of deliberation beyond the constraints of the office visit by using decision aids.

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2002-04 Vs. 2007-09: Initiation of Combination, and Tapering/ Discontinuation (DC) Patterns of TNFi and MTX in a US (RA) Patient Registry: Analysis with CDAI Scores.
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Background/Purpose: We compared patient (pt) characteristics, for initiating, tapering and DC of TNFi/MTX combination therapy (CT), among RA pts seen during 02–04 vs. 07–09 to detect changes in practice.

Methods: In the Consortium of Rheumatology Researchers of North America (CORRONA), a rheumatoid arthritis (RA) registry, the relationship between maximum CDAI(Clinical Disease Activity Index) and the use of CT during the 2 time intervals was compared using all RA pts in CORRONA and those with >=2 yrs of follow-up (f/u) (N=4955; N= 6847). DC'ing/tapering MTX, TNFi, or both and reasons for DC'ing were compared among the subset who initiated CT (n=315; n=697 respectively).

Results: Among pts receiving CT, age, gender and patterns of adding TNFi to MTX vs. MTX to TNFi were similar in the 2 time periods; The mean CDAI at CT initiation (for all pts and pts with >=2 yr f/u) was lower in 07–09 (18.6 and 18.3 vs. 14.6 and 14.0, p<0.001). 35% of all pts starting CT were on prednisone at initiation during the 02–04 interval vs. 30.4% during 07–09, p=0.084. Among all RA pts with 2 yrs of f/u a higher percentage of patients initiated CT in 07–09 than 02–04 in each maximum CDAI category. Although MTX DCing rates were similar between the 2 time periods, tapering was more frequent in the 07–09 (51%) vs 02–04 cohort (38.8%), p = 0.029. DCing (or switching) the TNFi occurred among 37% of pts initiating CT during 07–09 vs. 31.7% (02–04) p=0.105. Baseline CDAI did not predict DC patterns. The mean CDAI at time of DC was higher in the 02–04 cohort for MTX, TNFi or both with overall mean CDAIs (02–04 vs. 07–09) at the time of DC of CT of 19.4 vs. 13.2 p<0.001. The mean CDAI at time of DC of prednisone, was similar between the two time periods (15.2 vs. 15.0) p=NS.

Physician-recorded reasons for DC'ing MTX or TNFi were consistent across time intervals.

RA pts with 2 yr F/U after a visit in	2002–2004	2007–2009	Total
N	4955	6847	11,802
% of pts with a max CDAI during the 2 yr F/U who DID NOT receive CT anytime during the 2yr	p-value		
Max CDAI 10–22	80.8 %	74.3 %	<0.001
Max CDAI >22	74.2 %	71.1%	0.038
RA pts with 2 yr F/U after initiating CT	2002–2004	2007–2009	Total
N	315	697	1012
% of RA pts DCing CT during 2 yrs F/U	p-value		
DC only MTX (continuing TNFi)	15.2 %	13.1 %	0.350
DC only TNFi (continuing MTX)	31.7 %	37.0 %	0.105
DC both MTX + TNFi	7.9 %	6.5 %	0.390
DC Prednisone	33.6 %	43.5 %	0.085
CDAI (SD) at time of DC of RA pts who DC	p-value		
MTX only	14.2 (11.0)	10.6 (12.2)	0.088
TNFi only	20.5 (14.0)	14.5 (13.0)	<0.001
both MTX + TNFi	25.1 (17.2)	10.9 (10.1)	<0.001
DC Prednisone	15.2 (12.7)	15.0 (15.0)	0.951

Conclusion: We found lower CDAIs among those initiating CT between 07–09 and lower CDAIs among those weaning or stopping CT in 2 yrs of f/u, perhaps reflecting stricter definition and implementation of aggressive treatment goals in the later time periods.

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Treating Rheumatoid Arthritis to Target: A Canadian Patient Survey.
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Background/Purpose: Recently, many countries, including Canada, evaluated rheumatologists' acceptance and agreement with a set of 10 Treat to Target (T2T) recommendations for rheumatoid arthritis (RA), developed by an international task force.[1–3]In this study, the Canadian T2T steering committee evaluated how Canadian patients with RA perceive these recommendations. To assess the current state of RA management in Canada from a patient perspective and to assess whether, and to what extent, Canadians with RA agree with the 10 T2T recommendations.

Methods: Participating rheumatologists were asked to invite consecutive RA patients to complete a 20-question survey. The survey was designed to assess relevant socio-demographic variables, disease duration, current approach to RA management as seen from the patient perspective, and agreement with the T2T recommendations. Each T2T recommendation was re-phrased and/or re-worded in order to be easily understood by all RA patients, regardless of their level of education.[4]

Results: A total of 959 patients (77% females) were recruited by 22 participating rheumatologists from 6 Canadian provinces. Patients had a mean age of 59.1 yrs and a mean disease duration of 12.9 yrs. Approximately 72% of patients were on methotrexate (23.9% monotherapy, 76.1% combination therapy), 22.5% were treated with biologics (13.4% monotherapy, 86.6% combination therapy), and 17.5% were receiving corticosteroids. The patients' mean pain intensity over the week preceding the survey was 3.4 on a 10-point scale. The majority (88%) of patients was seen by their rheumatologist every 2–6 months; approximately 92% indicated having their joints examined and being asked about their daily activities at every visit. Over 89% of the patients rated ≥8 on a 10-point scale on the clarity of their rheumatologist's explanation. In Canada, agreement with the T2T recommendations was higher among patients than rheumatologists: For patients, the results ranged from 8.6 for recommendation #4 (frequency of adjustment of drug therapy) to 9.5 for recommendation #7 (consideration for making clinical decisions). The average rheumatologists' agreement scores ranged from 6.9 for recommendation #5 (the frequency of measures of disease activity) to 9.1 for recommendation #10 (the patient needs to be involved in

the decision-making process).[3]Among patients, agreement with recommendation #4 decreased with increasing age of the patient (from 9.1 for patients <43 yrs to 7.9 for patients >74 yrs). The agreement with recommendation #5 was significantly higher for patients in Quebec (9.4) and New Brunswick (9.3) compared to British Columbia (8.6)

Conclusion: The results of this survey shed some light on the management of RA in Canada and demonstrated a significant level of agreement with the T2T recommendations among Canadian patients. Additional efforts may be required to identify the reasons behind differences in agreement levels between patients and physicians in order to narrow certain gaps and improve RA management.

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The Wide Variation in Corticosteroid Use in Early Rheumatoid Arthritis - There Is Need for Guidelines.
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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease which causes significant pain and swelling in the joints. The early treatment of the disease mainly rests on two groups of agents; Disease modifying drugs and Corticosteroids. Steroids are very effective for the treatment of early disease, acutely controlling the disease activity and reducing the long-term damage They are used both as systemically (Oral or Intramuscular) or locally, however there is no consensus on the required dose, route of administration or duration of use in this condition.

The published data about adverse events of steroid usage in this situation is not clear and there is suggestion that quick aggressive control of inflammatory disease may actually outweigh the risk of damage.

Methods: A questionnaire was sent by post to all consultant Rheumatologists in England under 'Freedom of Information act (FOI)' to 131 NHS trusts. Questions were aimed to enquire about the initial steroid regime used by consultant rheumatologists in adult cases (≥ 18 yrs) of confirmed RA. The responses were received back by post and analysed.

Results: Total response received were 130 (92 % response rate), with 82.4 % agreeing on the early routine use of steroids in their practice. 53.6% used the Oral route, 48% used the intramuscular (IM) route and 45.6% of Consultants used the intra-articular route (either alone or in combination with other routes).

For those who used oral Prednisolone, the initial starting dose varied from 60mg (6.3%) to 7.5 mg (11.1% responses) per day with the majority using an initial dose of 15 mg (25.3%) or 20mg (23.8%) daily.

The duration of oral steroid use varied from 1 month (4.2%) to 2 yrs (4.2%) with the majority being for 4–6 months (72.3%).

The dose of IM Depomedrone varied from 40mg - 160 mg, with majority using 120 mg (86.2%), for a total duration that again varied from 2 months to 2 years, with the majority being 6 months (52.2%).

The dose of intraarticular injection for large joint also varied from 20 mg to 60 mg of Depomedrone with 40 mg used by majority (92%) of rheumatologist.

Conclusion: Majority of Rheumatologist use steroids for initial treatment of early Rheumatoid Arthritis. There is a wide variability in the use of steroids including its route, dose and duration of use. There is therefore an urgent need of scientifically proved guidelines on their initial use.

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Costs of Tumor Necrosis Factor Blockers Per Treated Rheumatoid Arthritis Patient Using Real-World Drug Data in a US Managed Care Population.
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Background/Purpose: Etanercept (ETN), adalimumab (ADA), and infliximab (INF) are FDA-approved tumor necrosis factor (TNF)-blocker treatments for moderate to severe rheumatoid arthritis (RA) and are commonly used first-line biologics. These agents have differing modes of

administration and dose ranges. It is important to understand the true cost of treatment with these agents including the effects of real-world dosing data, gaps in therapy, varying persistence, and switching. This study describes the annual TNF-blocker costs for patients treated with ETN, ADA, and INF, using data from a US managed care population.

Methods: The IMS LifeLink™ Health Plan Claims database was used to identify RA patients (18–64 years) with ≥ 1 claim for ETN, ADA, or INF between February 1, 2008 and July 5, 2010. Their first TNF-blocker claim after ≥ 6 months of continuous enrollment defined their index claim and medication. Patients were classified as "new" if they did not have a claim for the same agent in the previous 6 months (pre-index period) or "continuing" if they did. Patients were followed for 1 year after their index claim. Patients were excluded if they had a diagnosis in their pre-index period of psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, or juvenile idiopathic arthritis. Total annual TNF-blocker dose was computed and costs were calculated using the March 2012 wholesale acquisition costs and Medicare Physician Fee Schedule for TNF-blocker related administrations. For patients who switched agents in the first year, costs of other TNF blockers used were attributed to the patients' index medication.

Results: Overall, 16,280 patients with RA (7,754 [47.6%] ETN, 4,834 [29.7%] ADA, 3,692 [22.7%] INF) were identified. Mean age was 50.3 years and 76.5% were female. Overall, patient characteristics were similar. INF was more commonly given by a rheumatologist (63.3% vs 57.3% ADA and 53.5% ETN) and less likely to be a new agent (28.4% vs 39.1% ADA and 33.7% ETN). The majority of patients had commercial insurance (83.0%-86.0%) and the majority of plans were preferred provider organizations (65.0%-70.0%). The overall 1-year TNF-blocker cost per RA patient was lowest for patients on ETN ($16,787), followed by ADA ($19,308) then INF ($22,939). For patients new to TNF-blockers, 1-year cost per treated patient was $15,828 for ETN, $17,250 for ADA, and $19,397 for INF; 1-year cost per continuing patient was $17,275 for ETN, $20,626 for ADA, and $24,345 for INF.

Conclusion: Across new and continuing RA patients, ETN was the most frequently prescribed TNF-blocker and had the lowest cost per treated patient as observed in real-world drug utilization data.

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Medication Choices and Medication Survival in a National Multicentre Community Based Rheumatoid Arthritis Cohort. Lynden Roberts[1], Kathleen Tymms[2], Julien P. de Jager[3], Geoffrey O. Littlejohn[4], Hedley Griffiths[5], Dave Nicholls[6], Paul Bird[7], Julie Hill[8], Philip McCloud[8], James C. Scott[9], Jane Zochling[10] and OPAL Consortium[11]. [1]James Cook University, Townsville, Australia, [2]Canberra Rheumatology, Canberra, Australia, [3]Suite 2, Osler House, Southport, Australia, [4]Monash Medical Center, Melbourne, Australia, [5]Barwon Rheumatology Service, Geelong, Australia, [6]Coast Joint Care, Maroochydore, Australia, [7]Combined Rheumatology Practice, Sydney, Australia, [8]McCloud Consulting Group, Sydney, Australia, [9]Roche Products Pty Limited, Sydney, Australia, [10]Menzies Research Institute Tasmania, Hobart, Australia, [11]Melbourne, Australia

Background/Purpose: A sizeable body of high-quality research underpins our knowledge of the efficacy of various RA therapies. Outside the controlled environment of these clinical trials, however, in real world practice many additional factors may influence the use of DMARD/bDMARDs. There is little knowledge of whether the trial evidence is being implemented in real world settings, or whether the trial efficacy and safety translates into clinical effectiveness.

Methods: Point of care clinical software has been used to collect data since 2009 from 20 participating Australian rheumatology treatment centres. Patients with a rheumatologist diagnosis of RA were identified. Medication changes were analysed in 9 prespecified categories to permit the construction of population treatment algorithms. Medication survival was assessed using Kaplan Meier plots. The change in disease activity following a medication change was also assessed.

Results: RA patients numbered 9570, with 73% female, mean age 62, and median disease duration 7 years. Any DMARD was used in 87% overall, and 30% had used a biologic DMARD. The DMARD/bDMARD usage above 1% in the cohort included methotrexate 71%, Hydroxychloroquine 25%, Leflunomide 24%, Sulfasalazine 17%, Etanercept 12%, Adalimumab 11%, Tocilizumab 5%, Abatacept 3%, Golimumab 3%, Rituximab 2.5%, and Certolizumab 2%. Median DMARD survival ranged from 49 to 231 months for the

most common DMARDs and from 9 to 49 months for the most common biologic DMARDs. A tree diagram representing the observed treatment changes was constructed. Of the 2256 patients whose first RA medication was monotherapy Methotrexate and who required a change, 31% changed to greater than 1 conventional DMARD, 29% added Leflunomide, 17% added a bDMARD, and 16% ceased therapy. Of the 466 patients whose first change in RA medication was to Methotrexate plus Leflunomide and required a second change, 31% returned to monotherapy Methotrexate, 18% changed or added another conventional DMARD, 20% changed to monotherapy DMARD other than methotrexate, and 28% added a bDMARD.

Conclusion: Australian rheumatologists are making frequent changes in medications in their RA patients and appear to be implementing best evidence guidelines. Australian regulatory requirements for utilizing subsidised biologic therapy may also be affecting choices. The most commonly observed treatment algorithm in patients who required therapeutic escalation had patients starting with DMARD monotherapy followed by DMARD combination therapy followed by bDMARD combined with DMARD combination therapy. Shorter median survival of biologic therapies than traditional therapies may reflect the more refractory nature of the patients who are selected for these therapies. Analysis of the effect of a medication switch on disease activity will be of interest in this cohort.

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Retention Rate of the Anti-TNF Biologics in the Treatment of Rheumatic Diseases and Predictive Factors for Drug Withdrawal: Data From the Hong Kong Biologics Registry. Chi Chiu Mok[1], Cherry Kwan[1], Helen Chan[2], Ka Lai Lee[3] and Lai-Shan Tam[4]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Kowloon Hospital, Hong Kong, Hong Kong, Hong Kong, [3]Pamela Youde Eastern Hospital, Hong Kong, Hong Kong, [4]The Chinese University of Hong Kong, Hong Kong, China

Background/Purpose: To study the retention rate of the anti-TNF biologics in the treatment of rheumatic diseases and the associated factors for drug withdrawal

Methods: Data on the use of biological agents for the treatment of various rheumatological disorders in 14 public hospitals were collected prospectively. Efficacy data, serious adverse events, withdrawal of biologics and reasons for withdrawal were collected at regular time intervals. The cumulative retention rate of individual agent was studied by the Kaplan-Meier method and factors associated with drug withdrawal were studied by Cox regression.

Results: From 2005 to 2012, 1335 courses of anti-TNF biological agents in 991 patients with rheumatic diseases were used. There were 553 women and 438 men (mean age 44.9±13.9 years and duration of underlying disease 7.4±6.6 years). Underlying rheumatic diseases were: rheumatoid arthritis(RA) (50%), spondyloarthropathy (SpA)(37%), psoriatic arthritis(PSA) (11%) and others (2%). The initial choice of the anti-TNF biologics was: infliximab (IFX) (N=618, 46%), etanercept (ETN) (N=468, 35%), adalimumab (ADA) (N=208, 16%) and golimumab (GLM) (N=41, 3%). The dosages of the biologics used were: IFX (intravenous; 3–5mg/kg for RA, 5mg/kg for SpA and PSA), ETN (subcutaneous; 50mg/week or 25mg 2x/week), ADA (subcutaneous; 40mg every 2 weeks) and GLM (subcutaneous; 50mg every 4 weeks). The mean duration of administration per course of biologic was 20.1±19.7 months. 692 (52%) courses of anti-TNF agents were abbreviated because of the following reasons: 238 (34%) lack /loss of efficacy (primary or secondary failure); 185 (27%) serious adverse events; 123 (18%) financial reasons; and 146 (21%) other or unspecified reasons. The overall cumulative drug withdrawal rate (due to either lack /loss of efficacy or adverse events) at 12, 24 and 36 months was 28%, 39% and 46% for IFX, and 22%, 27% and 32% for ETN, and 23%, 27% and 34% for ADA, respectively (log rank test; p<0.005 between IFX and either ETN or ADA). When drug withdrawal was broken down into that due to loss of efficacy and adverse events, data remained significant in favor of ETN to IFX. The follow-up time of ADA users was significantly shorter than those of ETN, and there was no significantly difference in the withdrawal rates between ETN and ADA. The commonest reasons for drug withdrawal because of serious adverse events were: allergic skin reaction (3.6%), infusion/injection site reactions (2.1%) and tuberculous infection (1.9%). Among 26 patients who developed tuberculosis, 21 patients were IFX users, 4 were ETN users and 1 was GLM user. Patients with RA had significantly lower drug retention rate than SpA or PSA patients (log rank test; p<0.05). Cox regression analysis revealed that the anti-TNF agent used (IFX versus ETN/ADA/GLM; HR 1.46 [1.17–1.81];

p=0.001) and rheumatoid arthritis (vs other diagnoses; HR 1.47 [1.13–1.93]; p=0.005) was independent predictors for drug withdrawal due to inefficacy or serious adverse events after adjustment for age, sex and disease duration.

Conclusion: Our Registry data reveals that IFX is associated with a significantly higher withdrawal rate for both loss of efficacy over time and the development of serious adverse events, in particular tuberculosis.

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Oral Glucocorticoid Sparing Effects of Rituximab in Rheumatoid Arthritis Patients Who Have Switched from an Anti-TNF Therapy - an Administrative Claims Database Analysis. Stephen Johnston[1], Tripthi Kamath[2], Nianwen Shi[1], Robert Fowler[1], Bong-Chul Chu[1] and William Reiss[3]. [1]Truven Health Analytics, Washington, DC, [2]Genentech, Inc., South San Francisco, CA, [3]Genentech Inc., South San Francisco, CA

Background/Purpose: The current treatment paradigm in RA is to attempt to decrease concomitant use of oral glucocorticoids (OGC). This study examined the OGC-sparing effects of Rituximab in U.S. RA patients who had switched from an anti-TNF therapy.

Methods: Retrospective cohort study using a large U.S. administrative claims database. Patients selected for study were adults aged ≥18 years who had had been diagnosed with RA between 1/1/2004-3/31/2011 had initiated Rituximab treatment after treatment with anti-TNF therapy between 3/1/2006-3/31/2011, and had OGC use within 30 days prior to Rituximab initiation. Rituximab 'exposure periods' were constructed using Rituximab infusion dates and the recommended administration frequency schedule, equaling the duration of time from initiating Rituximab until the first occurrence of 1) switch to a different biologic disease modifying antirheumatic drug (BDMARD), 2) 90-day gap in treatment with Rituximab, 3) disenrollment from health insurance, 4) reaching 3/31/2011, or 5) reaching a maximum study follow-up of 36 months. Patients were excluded if within the 12-month period prior to Rituximab initiation they had been diagnosed with a non-RA indication for any BDMARD.

During the Rituximab exposure periods the study outcomes, proportion of patients using OGCs and average OGC dose expressed in prednisone equivalent, were measured in sequential 90-day intervals, the first of which commenced as of Rituximab initiation. A multilevel random coefficient model was used to test for statistically significant OGC-sparing effects over time.

Results: A total of 952 Rituximab exposure periods from 938 unique patients were included for study; average age 54.7 years, 79.2% female. Table displays the study results. The proportion of patients using OGCs decreased over time, with slight non-monotonic fluctuations, from 80.6% of patients in months 1–3 to 54.1% of patients remaining on therapy in months 34–36. The mean OGC dose also decreased over time, again with slight non-monotonic fluctuations, from 5.7 mg among patients in months 1–3 to 3.2 mg among patients remaining on therapy in months 34–36. The decreases in the proportion of patients using OGCs ($P<0.0001$) and the average OGC dose ($P<0.0001$) were both statistically significant. In sensitivity analysis subset to only patients remaining on therapy through months 34–36, the OGC use patterns were similar to those from among overall sample.

Table. OGC use over time since Rituximab initiation

Month range	Sample N	% using OGCs	OGC dose*	
			Mean	SD
1–3	952	80.6%	5.7	7.4
4–6	864	79.3%	5.5	6.1
7–9	715	73.6%	5.0	5.9
10–12	594	67.7%	5.0	6.3
13–15	381	69.0%	4.5	5.4
16–18	313	64.2%	4.4	5.8
19–21	242	59.1%	4.3	7.1
22–24	191	58.1%	3.4	4.6
25–27	162	56.2%	3.5	5.8
28–30	129	55.8%	4.0	9.2
31–33	98	57.1%	3.1	3.5
34–36	74	54.1%	3.2	4.1

*Average daily dose, expressed in prednisone equivalent (mg), calculated among all patients

Conclusion: In this study, statistically significant OGC-sparing effects were observed in RA patients who had switched to Rituximab after treatment with anti-TNF therapy. The clinical implications of such OGC-sparing effects warrant further investigation.

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Performance of Criteria for Remission in a Long-Term Observational Study of Patients with Early Rheumatoid Arthritis. Bjorn Svensson[1], Maria LE Andersson[2], Sidona-Valentina Bala[1], Kristina Forslind[3] and Ingiäld Hafström[4]. [1]Lund University, Lund, Sweden, [2]R&D Center, Spenshult Hospital, Oskarström, Sweden, [3]Helsingborgs Lasarett and Lund University Hospital, Helsingborg, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden

Background/Purpose: Remission is widely accepted as the goal of treatment in RA and has to be sustained to keep joint damage at a minimum (Smolen et al 2010). The DAS28<2.6 remission criterion is widely used but criticized for allowing remission to be present in spite of several swollen or tender joints. The recently proposed Boolean ACR/EULAR remission criteria are more stringent and do not have this bias but their utility in long-term observational studies needs to be evaluated. The present study addresses the performance of these criteria over 8 years in an observational study of patients with early RA.

Methods: 839 patients, included in 1992–1999, within one year from disease onset in the BARFOT observational study were followed for 8 years. The following remission criteria (RCr) were applied: The DAS28 RCr (DAS28<2.6) and the ACR/EULAR RCr (≤1 swollen joint, ≤1 tender joint, CRP ≤1 mg/dl and patient global assessment ≤1 (0–10 scale). Sustained remission was defined as remission at all four visits at 1, 2, 5 and 8 years. Radiographic joint damage was assessed by the Sharp van der Heijde method (SHS).

Results: Sustained remission was present in 79 patients (14%) by the DAS28 RCr and 16 (3%) by the ACR/EU RCr. In patients in sustained remission by the DAS28 RCr, radiological progression (RP) with SHS of >0 occurred in 31, 45, 57 and 65% and by the ACR/EU RCr in 21, 46, 46 and 62% at 1, 2, 5 and 8 years, respectively. The likelihood ratios for the ability of sustained remission by the the DAS28 criteria and the ACR/EU criteria, respectively, to identify patients with favorable radiographic outcome from baseline to 8 years was 2.2 vs 1.9 for a change in SHS of ≤0 (minimal RP), 1.5 vs 1.4 for a change of <5 (clinically relevant change) and 1.4 vs 1.3 for a change of <8 (<1 point per year). A small number of patients in sustained remission by DAS28 RCr had at some point in time more than one swollen or tender joint. More than one joint was found in 11 of 315 assessments (3.5%) of tender joint count (max 5 in one case) and in 28 of 315 assessments (9%) of swollen joint count (max. 6 in one case).

Conclusion: The new ACR/EU criteria appear too stringent to be feasible in long-term observational studies. Only a very small number of patients were identified and the ability to predict favorable radiographic outcome was not significantly superior. Sustained remission by the DAS28 criteria was more than four times as frequent and the frequency of possible false remissions was very low. Therefore, awaiting further development, the DAS28 remission criterion could be preferred in long-term observational studies.

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DAS28 Is Not a Sufficient Disease Activity Measure for Obese Rheumatoid Arthritis Patients - Don't Leave the Feet Behind. Vikram Garg[1], Paul Maranian[2], Mihaela B. Taylor[3], Harold E. Paulus[4], David Elashoff[4] and Veena K. Ranganath[5]. [1]UCLA David Geffen School of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA, [2]UCLA Medical School, Los Angeles, CA, [3]University of California Los Angeles, Los Angeles, CA, [4]University of California, Los Angeles, Los Angeles, CA, [5]University of California, Los Angeles, Western Consortium of Practicing Rheumatologists, Los Angeles, CA

Background/Purpose: Current literature suggests that obesity impacts disease activity in rheumatoid arthritis (RA) and the incidence of obesity is on

the rise. The objective of this study was to evaluate how obesity (BMI≥30) affects different composite disease activity measures in RA, specifically evaluating differences between 28 vs 44 joint counts measures.

Methods: We examined a long-term prospective observational cohort of early poor prognosis seropositive RA patients (within 15 months of symptom onset) from the Western Consortium of Practicing Rheumatologists. Patients included had a diagnosis of RA according to the ACR 1987 criteria, DMARD-naive, positive rheumatoid factor, ≥6 SJC, and ≥9 TJC. BMI was categorized above and below 30. The following baseline characteristics were collected: age, gender, BMI, disease duration, CCP status, prednisone use, sharp scores, and radiographic evidence of osteoarthritis (OA). Components needed to calculate DAS44/ESR-4 item, DAS28/ESR-4 item, and CDAI were also collected at baseline. Patients completed a comprehensive questionnaire at study entry including: demographics, health, medication, pain visual analog scale (VAS), patient global VAS, and the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Results: Significant difference between obese and non-obese patients were observed for baseline swelling of MCP, knees, ankles, and MTP joints, tender ankle joints, HAQ-DI and MD global. Consequently, DAS44/ESR-4item was significantly higher in the obese early RA patients, but DAS28/ESR4 item and CDAI were not significantly different. Other baseline measures were not different.

Table 1. Baseline Values

	BMI 20–30 (N=184)	BMI >30 (N=64)	
	mean (SD)	Mean (SD)	P-VALUE
Age	51.4 (13.1)	51.6 (11.4)	NS
Female	75.5%	78.1%	NS
Duration	8.16 (8.8)	6.57 (5.6)	NS
On MTX	54.4%	59%	NS
Nodules	0.18 (0.5)	0.08 (0.3)	NS
OA present	36.6%	37.7%	NS
ESR	40 (24.7)	42.7 (25.3)	NS
CRP	2.9 (6.9)	3.5 (4.1)	NS
On Pred	46.2%	45.9%	NS
CDAI	36.1 (14.4)	40.8 (16.3)	NS
HAQ-DI	1.1 (0.7)	1.4 (0.7)	0.005
das44esr4	4.6 (1.2)	5.1 (1.3)	0.01
das28esr4	6.1 (1.1)	6.4 (1.1)	NS
Pt global	54.5 (27.7)	57.9 (25.7)	NS
MD global	48.1 (21)	55.1 (20.3)	0.03
Tender28	13.5 (7.1)	14.5 (8.1)	NS
Tender44	20 (9.5)	21.7 (11.52)	NS
LE tender	6.9 (4.3)	7.2 (4.6)	NS
UE tender	13.2 (6.9)	14.4 (7.9)	NS
Ankle tender	0.9 (0.9)	1.3 (0.9)	0.004
Swell28	12.5 (6.6)	14.9 (7.3)	0.04
Swell44	17.4 (8.6)	22.2 (10.6)	0.003
LE swollen	5.5 (4.2)	8 (4.9)	<.001
UE swollen	11.6 (6.2)	14.4 (7)	0.008
MCP swollen	4.8 (3.2)	6.2 (3.3)	0.004
Knee swollen	0.8 (0.9)	1.2 (0.9)	0.001
Ankle swollen	0.8 (0.9)	1.4 (0.8)	<.001
MTP swollen	4 (3.7)	5.5 (4.1)	0.01

LE- lower extremity, UE- upper extremity

Conclusion: Our results suggest that in obese RA patients, swelling of the LE weight bearing joints may impact composite disease activity measures. DAS44/ESR-4 item (considered a gold standard measure) was significantly different between obese and non-obese RA patients, while the DAS28/ESR-4 item and CDAI were not. Several studies that examined the relationship between BMI and disease activity (Sahebari et al 2011, Klaasen et al 2011, Baker et al 2011), used DAS28 as their measure of disease activity. Our findings suggest that weight bearing joints should be included when assessing RA disease activity in obese patients, and future studies are needed to validate these results.

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Analysis of Factors Impact On Patient Global Assessment in Daily Practice Based On Observational Cohort IORRA (Institute of Rheumatology, Rheumatoid Arthritis).

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Background/Purpose: Patient global assessment (PtGA) is an element of the new ACR/EULAR remission criteria for rheumatoid arthritis (RA). This definition has been reported to better predict structural or functional outcomes than DAS28, and we have also reported the importance of maintaining stringent remission to avoid progressive functional damage (ACR 2011 #332). Boolean-based remission for clinical trials (Boolean trials) consists of 4 components: (tender [TJC28] and swollen joint counts [SJC28] as assessed by 28 joints, C-reactive protein [mg/dL], and PtGA (0–10 scale) values being ≤1). In most patients, whether Boolean trials remission is achieved or not depends on PtGA. It is therefore necessary to reveal what factors are significantly associated with PtGA.

Methods: The Institute of Rheumatology, Rheumatoid Arthritis (IORRA), is a hospital-based large observational cohort of RA patients. Clinical information and laboratory data have been collected biannually since 2000. Pain, PtGA, and physician global assessment (PhGA) scores were rated using a Visual Analogue Scale (0–10 cm). The validated Japanese versions of Health Assessment Questionnaire (J-HAQ) scores and European Quality of life 5 Dimensions (EQ-5D) ratings were used to evaluate physical function and quality of life (QOL), respectively. The subjects in this study were RA patients who participated in the IORRA survey during April 2011. Correlations between PtGA score and clinical parameters, including medications and pain VAS, J-HAQ, PhGA, and EQ-5D were examined by Spearman's correlation. Univariate and multivariate logistic regression models were used to evaluate the effect of clinical parameters on PtGA scores of >1 compared to PtGA scores of '1. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using the JMP 9.0. software package.

Results: We analyzed 5,276 Japanese RA patients from whom all 4 components of Boolean trials remission were available. TJC28, SJC28, and CRP were satisfied in 78.3%, 72.8% and 84.4% of them, respectively. By contrast, only 31.3% of the patients fulfilled PtGA scores of ≤1, but among them, Boolean trials remission was achieved in 76.9%. PtGA was closely correlated with J-HAQ (r = 0.54), EQ-5D (r = 0.66) and pain VAS (r = 0.86). In multivariate analyses, significant factors associated with a PtGA score >1 were J-HAQ (OR = 1.96; 95% CI, 1.61–2.40; p<0.001), non-steroidal anti-inflammatory drug (NSAID) use (OR = 1.40; 95% CI, 1.20–1.64; p<0.001), TJC28 (OR = 1.26; 95% CI, 1.17–1.36; p<0.001), SJC28 (OR = 1.11; 95% CI, 1.05–1.16; p<0.001), CRP (OR = 1.18; 95% CI, 1.06–1.33; p = 0.003), age (OR = 0.99; 95% CI, 0.98–0.99; p<0.001), and EQ-5D (OR = 0.001; 95% CI, 0.000–0.001; p<0.001).

Conclusion: In RA patients, a PtGA score of ≤1 was associated with not only joint involvements (TJC, SJC), inflammation (CRP), and physical dysfunction, but also impaired QOL, younger age, and NSAID use.

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Defining Criteria for Rheumatoid Arthritis Patient-Derived Disease Activity Score That Corrresponds to Disease Activity Score 28 and Clnical Disease Activity Index Based Statuses and Response Criteria.

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Background/Purpose: Patient-based disease activity score (PDAS1 [with ESR] & PDAS2 [without ESR]) in rheumatoid arthritis (RA) are

transformed for the linear regression analyses. EULAR good response and DAS28 remission were similarly assessed by logistic regression analysis.

Results: A total of 2573 patients were included: MTX mono n=1866 [69.9 % female, 62 % RF+, mean (SD) age 56.0 (13.7) years (yrs), time from diagnosis 3.6 (7.7) yrs] and TNFi + MTX n=707 [70.3 % female, 75 % RF+, mean (SD) age 52.1 (13.2) yrs, time from diagnosis 9.1 (9.3) yrs]. Significant time trends were found in both groups for baseline values of DAS28, 28-SJC and CRP (table). Significant time trends were also found for baseline disease duration, SDAI, MHAQ, 28-TJC, ESR, physician global, patient global and joint pain VAS (data not shown). Further, there was a trend towards increasing 6-month DAS28 remission rates over the years in both groups, whereas a gradual increase in the EULAR good response rate was only observed in patients starting MTX mono (table).

	2001–2002	2003–2004	2005–2006	2007–2008	2009–2010	p value
Baseline DAS28 [mean(SD)]						
MTX mono	5.17 (1.26)	5.06 (1.33)	4.85 (1.29)	4.62 (1.39)	4.75 (1.30)	<0.001
TNFi+MTX	5.88 (1.23)	5.25 (1.23)	5.21 (1.25)	4.87 (1.46)	4.64 (1.41)	<0.001
Baseline 28-SJC [mean(SD)]						
MTX mono	9 (6)	8 (6)	7 (6)	6 (5)	6 (5)	<0.001
TNFi+MTX	10 (5)	9 (6)	8 (5)	6 (5)	6 (4)	<0.001
Baseline CRP, mg/l [median(IQR)]						
MTX mono	22 (7–35)	13 (5–31)	10 (5–25)	8 (3–20)	7 (3–21)	<0.001
TNFi+MTX	27 (12–54)	19 (8–37)	12 (5–30)	9 (5–22)	7 (3–20)	<0.001
EULAR good response 6 months [%(n)]						
MTX mono	25.7 (59)	35.5 (105)	37.8 (90)	33.5 (65)	39.2 (40)	0.03
TNFi+MTX	29.3 (17)	44.6 (50)	46.5 (46)	43.6 (34)	38.0 (19)	0.47
DAS28 remission 6 months [%(n)]						
MTX mono	17.8 (43)	29.2 (95)	33.7 (89)	38.1 (80)	37.6 (44)	<0.001
TNFi+MTX	16.9 (10)	29.3 (36)	34.5 (38)	31.4 (27)	46.3 (25)	0.003

Conclusion: Mean baseline disease activity level for patients starting MTX treatment and for patients starting the first TNFi has decreased from high to moderate during the last decade. Mean disease duration also decreased significantly. These findings indicate that clinicians have implemented modern, more aggressive RA treatment strategies which will hopefully result in better long-term patient outcomes.

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Prevalence, Concordance and Predictors of Early and Sustained Remission Assessed by Various Indices in the French Early Arthritis Espoir Cohort. Cédric Lukas[1], Ihsane Hmamouchi[2], Xavier Le Loet[3], Bruno Fautrel[4] and Bernard Combe[5]. [1]Montpellier 1 University, Lapeyronie Hospital, Montpellier, France, [2]El Ayachi Hospital, Rabat, Morocco, [3]CHU de ROUEN, Rouen, France, [4]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [5]Hopital Lapeyronie, Montpellier, France

Background/Purpose: Clinical remission is the best achievable state in patients with rheumatoid arthritis (RA). The definition of remission, however, is still under debate. The aim of this study was to assess the prevalence of remission during the initial follow-up of a cohort of patients with early inflammatory arthritis, to evaluate the concordance across different criteria sets in defining this state, and to look for predictive factors for early- and sustained remission.

Methods: Patients from the French ESPOIR cohort, who had arthritis involving at least 2 joints for between 6 weeks and 6 months, and had not received any specific therapy before their inclusion, were followed-up every 6 months.Treatment was collected, but no specific strategy was imposed. We analyzed early remission (at 6 months follow-up) and sustained remission (remission state in both 6 months- and 1 year visits) in 3 different groups of patients: Patients who were diagnosed as having RA according to 2010 ACR/EULAR criteria (RA), undifferentiated arthritis (UA) after 1 year of follow-up, and the entire cohort (ESPOIR). Remission was defined according to 2011 ACR/EULAR criteria, 28 Joint Disease Activity Score (DAS28<2.6), and Simplified Disease Activity Index (SDAI<3.3). Agreement across available criteria sets was evaluated by k-coefficient. Predictive factors for sustained remission at 1 year in RA patients were analyzed by

logistic regression, with potential predictive factors tested from available clinical, biological and demographic data.

Results: 813 patients were included, mean age (SD) 48.1(12.6) years, 45.8% positive for rheumatoid factor (RF), 38.8% for anti-CCP test. Early remission rates in the RA/UA/ESPOIR groups were observed in respectively 29.2% (181/682), 51.4% (55/123) and 32.7% (239/813) of patients by DAS28; 15.7%, 29.1% and 18% by SDAI; and 11.2%, 29.1% and 12.8% by ACR/EULAR criteria. Agreement between classifications of remission by k-statistics was low for DAS28 vs ACR/EULAR (r=0.44 [0.38–0.51]), high for SDAI vs ACR/EULAR (r=0.78 [0.72-0-84]), and moderate for SDAI vs DAS28 (r=0.54 [0.48–0.61]). Lower baseline disease activity scores (DAS28<5.1), non-menopausal status and younger age (<50 years) were the best predictive factors for sustained remission at 1 year, with consistent results across the 3 definitions of remission.

Remission rates at 6 months
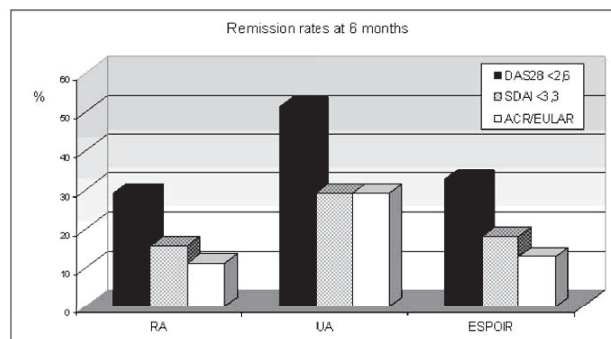
Conclusion: Our study showed that the rate of early (6 months) and sustained remission at 1 year in a cohort of early inflammatory arthritis is dependent on the definition used, with a variable degree of agreement across criteria sets, but with consistent predictive factors of favourable outcome at 1 year in patients finally diagnosed with RA: Younger age, lower baseline DAS28 and non-menopausal status.

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Assessment of Global Disease Activity in Rheumatoid Arthritis Patients Monitored in the Measurement of Efficacy of Treatment in the Era of Rheumatology Database: The patient's Versus the rheumatologist's Opinion. E. Gvozdenovic[1], R. Koevoets[1], R. Wolterbeek[1], Désirée van der Heijde[1], T.W.J. Huizinga[1], C.F. Allaart[1] and Robert B. M. Landewé[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands

Background/Purpose: Disagreement on disease activity between rheumatoid arthritis (RA) patients and rheumatologists may influence treatment decisions and compliance.

The aim is to compare the physician's (PhGDA) and patient's (PtGDA) assessment of global disease activity and to identify factors that might influence these differences over time, as well as factors that may influence the patients and the physicians score separately.

Methods: Anonymous data were used from 2118 Dutch patients included in the Measurement of efficacy of Treatment in the Era of Rheumatology (METEOR) database, a worldwide online tool for disease monitoring in RA. PhGDA and PtGDA were scored independently on a 100 mm visual analogue scale (VAS) with 0 and 100 as extremes. Intra-class correlation coefficients (ICC) were calculated as a measure of agreement and a Bland Altman plot was created to visualize the differences between PhGDA and PtGDA. Linear Mixed Model analysis was used to model PtGDA and PhGDA over time. Logistic repeated measurements were used to model the difference in PtGDA and PhGDA (PtGDA≥PhGDA vs. PtGDA<PhGDA) over time. Gender, age, swollen joint count, tender joint count, VAS pain, disease duration and ESR were considered as possible determinants in both models.

Results: Mean (SD) age was 57 (15) years and 67% of the patients were female. Agreement between PtGDA and PhGDA was moderate (ICC: 0.57). Patients scored on average 11 units higher (worse) than rheumatologists, 95% limits of agreement: −25.2 to 47.6. Patient's perception of pain (VAS) was positively associated with a PtGDA being

higher than PhGDA. Similarly, ESR and swollen joint counts were positively associated with a PhGDA being higher than a PtGDA (Table 1). Both PtGDA and PhGDA were independently associated with tender joint count, swollen joint count, disease duration, and pain (VAS) for pain.

Table 1. Clinical parameters associated to the difference between PtGDA and PhGDA as a binary dependent variable.*

Variable	PtGDA versus PhGDA* Estimate β, 95% CI	p-value
Male	0.16 −0.15, 0.47	0.30
Age	−0.00 −0.01, 0.01	0.46
Disease duration	0.01 −0.01, 0.02	0.23
ESR	−0.01 −0.02 −0.00	<0.01
SJC28	−0.29 −0.36, −0.21	<0.01
TJC28	−0.04 −0.10, 0.02	0.22
VAS pain patient	0.05 0.04, 0.06	<0.01

*1= patient scores equal or higher than the physician; 0= physician scores higher than the patient. (Reference category=0)

Conclusion: Patients rate global disease activity consistently higher than their rheumatologists. Patients base their judgment primarily on the level of pain; while physicians use SJC and ESR to rate global disease activity.

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Basal Metabolic Rate As an Indicator of Rheumatoid Arthritis Disease Activity and Predictor of Remission. Heather Jones[1], Annette Szumski[2] and Andrew S. Koenig[2]. [1]Pfizer Inc, Collegeville, PA, [2]Pfizer Inc., Collegeville, PA

Background/Purpose: The role of body mass index (BMI) in rheumatoid arthritis (RA) disease activity and response to treatment has been difficult to determine.[1] As a measure of physiologic function, basal metabolic rate (BMR) may be a better indicator than BMI for clinical assessment and treatment response in RA patients. In this posthoc analysis, the relationship between BMR, BMI, disease activity and responses to etanercept (ETN)-methotrexate (MTX) treatment were assessed in subjects with moderately active RA in the PRESERVE trial.[2]

Methods: Subjects with DAS28 >3.2 and ≤5.1 despite stable doses of oral MTX received open-label ETN 50 mg once weekly (QW) plus MTX (titration to ≤25 mg/week through week 28) for 36 weeks (Period 1). Posthoc analyses of disease activity and treatment response by BMR and BMI categories at baseline and Week 36 of treatment were conducted in subjects who received ≥1 treatment dose and had Week-36 assessments. The Mifflin-St Jeor[3] and revised Harris-Benedict[4] formulas were used to calculate BMR. Adjusted mean DAS28 scores were calculated using ANCOVA with BMR categories and weight as predictors at baseline and using weight and baseline scores as predictors at Week 36. Similar analysis performed on BMI categories but weight was excluded because it was not significant. Pearson correlations were used to determine overall associations between BMR/BMI and DAS28.

Results: Of 829 subjects analyzed, the proportions of patients with each category of BMR (Mifflin-St Jeor) were evenly distributed and half had a BMI in the low to normal range (table). At baseline, higher BMR was significantly associated with lower DAS28 scores after adjusting for weight (r=−0.127, p=0.008), and lower BMI was associated with lower DAS28 scores (r=0.124, p<0.001). At week 36, higher BMR was significantly associated with lower DAS28 scores (r=−0.233, p<0.001) and were also associated with a greater likelihood of remission (DAS28<2.6, p<0.001). Similar results were seen using the revised Harris-Benedict[6] formula. Higher BMI was significantly associated with higher week 36 DAS28 scores (p=0.002) and with decreased likelihood of remission (p=0.047).

Adjusted Mean DAS28 scores by Baseline BMR and BMI Category at Baseline and Week 36 of Treatment with ETN-MTX in Subjects With Moderate RA

		n (%)	Baseline Mean (95% CI)	Week 36 Mean (95% CI)
BMR	Very low (≤1188)	208 (25)	4.47 (4.40, 4.50)	2.90 (2.72, 3.07)
	Low (>1188 and ≤1305)	207 (25)	4.40 (4.34, 4.46)	2.65 (2.50, 2.80)
	High (>1305 and ≤1461)	209 (25)	4.38 (4.32, 4.44)	2.32 (2.17, 2.46)
	Very high (>1461)	205 (25)	4.25 (4.16, 4.33)	2.08 (1.88, 2.28)
BMI	Low to Normal (≤25)	418 (50)	4.33 (4.29, 4.38)*	2.42 (2.32, 2.52)
	Overweight (>25 and ≤30)	268 (32)	4.39 (4.34, 4.44)*	2.44 (2.32, 2.57)
	Obese (>30)	143 (17)	4.46 (4.39, 4.54)*	2.77 (2.59, 2.95)

*Means were calculated by 1-way ANOVA with BMI category as a predictor. DAS28 = Disease Activity Score based on a 28-joint count. Last observation carried forward imputation for missing data.

Conclusion: Subjects with moderate RA and higher BMRs demonstrated a better clinical response after 36 weeks of etanercept-MTX treatment compared to their counterparts with lower BMRs after adjusting for weight. Our data confirm previous research that BMI is suggestive of treatment outcomes in RA, but may not be clinically meaningful. In addition, the data suggest that BMR may be a more sensitive predictor than BMI. Further research is needed to evaluate the relationships between BMR, BMI, disease activity and treatment outcomes in RA.

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Can Sustained Remission of Rheumatoid Arthritis Be Predicted? an Analysis From the Japanese National Database of Rheumatic Disease (NinJa). Yoichiro Haji[1], Mitsumasa Kishimoto[1], Ryo Rokutanda[1], Sachiko Ohde[2], Gautam A. Deshpande[2], Yuri Ohara[1], Chisun Min[1], Yasuhiro Suyama[1], Hisanori Shimizu[1], Ken-ichi Yamaguchi[1], Akira Takeda[1], Yukio Matsui[1], Masato Okada[1] and Shigeto Tohma[3]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]St.Luke's Life of Science Institute, Tokyo, Japan, [3]Sagamihara National Hospital, Sagamihara City, Japan

Background/Purpose: Achievement of clinical remission in rheumatoid arthritis (RA) is now the goal of therapy to reduce joint damage and disability, and maintain or improve quality of life. Sustained remission is critical to attain these outcomes. Predictive factors for sustained remission of RA are not known. The purpose of this study is to identify prognostic factors of sustained remission and build a predictive model.

Methods: Data from RA patients registered in a nationwide Japanese cohort database (*NinJa:* National Database of Rheumatic Diseases by iR-net in Japan) in 2009 and 2010 were used to evaluate baseline characteristics, treatment profiles, and the following clinical outcomes: tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), ESR, patient Visual analog scale (VAS), physician VAS, and Modified Health Assessment Questionnaire (MHAQ). All patients with SDAI remission in 2009 were divided based on whether remission was maintained in 2010. A multivariate Cox regression model was constructed for predictive factors and a prognostic prediction model was constructed. Bootstrapping was used for internal model validation.

Results: Out of 4215 patients with RA in the 2009 cohort, 930 patients had SDAI remission, and 623 patients (67.0%) had sustained remission after 1 year. Compared to non-sustained remission group, duration of disease, SJC, CRP, ESR, patient VAS, physician VAS, and MHAQ were significantly lower in the sustained remission group (p<0.05). Mean SDAI score in the sustained remission group was 1.45 ± 0.92 versus 2.08 ± 0.86 in the non-sustained remission group (p<0.05). A prognostic prediction model with a total score of 6 points was constructed as follows: 2 points for MHAQ >1; 1 point each for SJC >1, ESR >20, patient VAS >0.5, and physician VAS >0.5. Area under the receiver operating characteristic (ROC) curve for this model was 68.8% (95% CI: 65.0–73.0%). Bootstrapped validation beta coefficients of predictors were identical to the original cohort data.

Conclusion: We found that duration of disease, SJC, CRP, ESR, patient VAS, physician VAS, and MHAQ are significantly lower in those with sustained remission after 1 year. A prediction model was successfully built and validated using clinically relevant parameters.

High Patient Global Assessment Scores Associate with the Residual Disease Activity Unidentified by a 28-Joint Examination in Rheumatoid Arthritis Patients Approaching Clinical Remission.
Yasushi Inoue, Eiichi Tanaka, Ayako Nakajima, Eisuke Inoue, Akiko Kobayashi, Daisuke Hoshi, Naoki Sugimoto, Kumi Shidara, Yohei Seto, Atsuo Taniguchi, Shigeki Momohara and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Patient global assessment (PtGA) is a component of the new ACR/EULAR remission criteria for rheumatoid arthritis (RA). It has been reported that >50% of patients who satisfied the other 3 components failed to achieve remission due to their higher PtGA score. Certain problems related to the higher PtGA among such patients may have been hidden. However, it remains to be clarified whether RA patients with a PtGA score ≤1 would essentially differ from those with a score >1, and whether significant differences would be found when comparing patients with a PtGA score ≤1 to those with a slightly higher score.

Methods: The Institute of Rheumatology, Rheumatoid Arthritis (IORRA), is a hospital-based large observational cohort of RA patients. Clinical information and laboratory data have been collected biannually. PtGA scores were rated using a Visual Analogue Scale (0–10 cm). Swollen and tender joint counts were recorded by examination of 45 joints. Components of DAS28 were documented as TJC28 and SJC28, and the other joint involvements in this study were described as "TJC45-28" and "SJC45-28." The validated Japanese versions of Health Assessment Questionnaire (J-HAQ) scores and European Quality of life 5 Dimensions (EQ-5D) ratings were used to evaluate physical function and quality of life (QOL), respectively. The subjects were 2,973 RA patients who participated in the IORRA survey in April 2011, and "fulfilled 3 other components" defined as TJC, SJC, and CRP being ≤1. Multivariate logistic regression analyses were performed to evaluate factors associated with PtGA in 2 models; model 1, patients with a PtGA >1 compared to those with a PtGA ≤1, and model 2, patients with a 1<PtGA ≤2 compared to those with a PtGA ≤1. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using the JMP 9.0 software package.

Results: Among patients fulfilling the other 3 components, only 42.8% achieved Boolean trials remission. Multivariate analysis showed that, whether Boolean trials remission was achieved or not was independently associated with age (OR = 0.99; 95% CI, 0.98–0.99; p<0.001), SJC28 (OR = 1.10; 95% CI, 1.04–1.16; p<0.001), TJC28 (OR = 1.26; 95% CI, 1.17–1.37; p<0.001), J-HAQ (OR = 1.97; 95% CI, 1.62–2.41; p<0.001), EQ-5D (OR 0.001; 95% CI, 0.000–0.001; p<0.001), and NSAID use (OR = 1.41; 95% CI, 1.20–1.65; p<0.001). Notably, "SJC45-28" was also strongly associated (OR = 1.18; 95% CI, 1.02–1.38; p<0.001) with achieving Boolean trials remission. When factors were analyzed in patients with a 1<PtGA ≤2 (n = 538) compared to those with a PtGA ≤1, significant associations were similarly found in age, SJC28, TJC28, J-HAQ, EQ-5D, NSAID use, and "SJC45-28", indicating that a slight increase of PtGA would reflect the hidden problems and residual disease activity.

Conclusion: Among patients fulfilling 3 other components, high PtGA scores (>1), even if only slightly higher, were closely related to impaired QOL, physical dysfunction, joints involvement, and NSAID use. Furthermore, any joint involvement unidentified by a 28-joint examination significantly influenced PtGA in the IORRA cohort. In clinical practice, a rheumatologist must pay attention to the other joints when the PtGA score is >1.

Can We Improve Outcomes in Early Rheumatoid Arthritis by Determining Best Practices? an Analysis of the Canadian Early Rheumatoid Arthritis Cohort (CATCH).
Jamie Harris[1], Vivian P. Bykerk[2], Carol A. Hitchon[3], Edward Keystone[4], J. Carter Thorne[5], Gilles Boire[6], Boulos Haraoui[7], Glen S. Hazlewood[4], Ashley Bonner[8], Janet E. Pope[9] and CATCH Investigators[10]. [1]Western University, London, ON, [2]Hospital for Special Surgery, New York, NY, [3]University of Manitoba, Winnipeg, MB, [4]University of Toronto, Toronto, ON, [5]Southlake Regional Health Centre, Newmarket, ON, [6]CHUS - Sherbrooke University, Sherbrooke, QC, [7]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [8]McMaster University, Hamilton, ON, [9]Western University of Canada, St. Joseph's Health Care, London, ON, [10]Toronto, ON

Background/Purpose: The goal of ERA treatment is remission but many patients do not achieve this state due to patient factors and perhaps differences in treating physicians. Studying treatment variation can lead to adopting best practices. Our objective was to investigate whether site differences occur and have an effect on outcome in ERA, and if so, to determine whether site size and/or differences in treatment explain the variability.

Methods: Sites from the CATCH database that had >40 patients at 6 months after enrolment were studied. Included sites were randomly renumbered and assigned a letter with investigators blinded. Patient data was used to calculate remission by several definitions (DAS28 < 2.6, SDAI ≤ 3.3, CDAI ≤ 2.8) and to determine treatment and treatment changes. Regression models included site as a variable and confounding baseline characteristics (HAQ, DAS28, serology, presence of erosions, cigarette smoking, age, gender, symptom duration, and SES) that had a p-value < 0.10 in univariate analyses.

Results: Of the 1138 baseline patients, 798 and 640 patients had data at 6 and 12 months respectively. Baseline descriptive statistics revealed that (mean (SD) or %): age 52(17) years; 72% female; 23% had erosions; 54% either were current or ever smokers; 37% anti-CCP positive; 51% RF positive; disease duration 187(203) days; HAQ 0.9(0.7); DAS28 4.5(1.4). Regression analyses showed that site is an important predictor for mean changes in DAS28 (p ≤ 0.000), increase in DAS28 (p ≤ 0.004), DAS28 remission (p ≤ 0.000), CDAI remission (p ≤ 0.000), and SDAI remission (p ' 0.022). Regression analyses including treatment showed that increases in medication was the strongest predictor of bad outcome (p < 0.05) and caused site to lessen some of its predictive ability.

Mean change in DAS28 from baseline to 6 months and baseline to 12 months by site arranged from smallest to largest
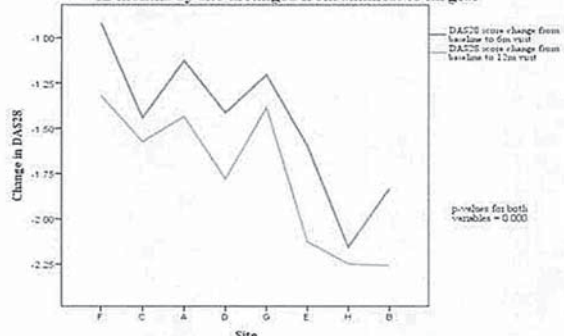
Proportion of patients ever on parenteral methotrexate by site arranged from smallest to largest, p-value = 0.000
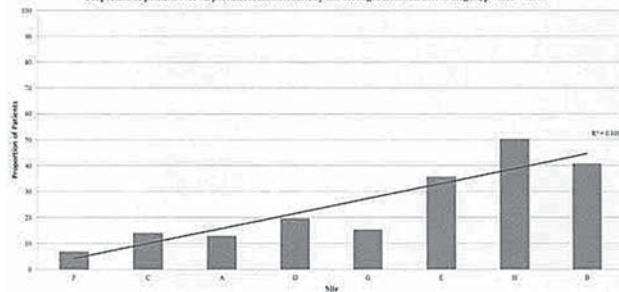
Conclusion: The two largest sites had the biggest mean changes in DAS at 6 and 12 months. Site is a predictor for ERA outcome. The fastest and best indicator for low DAS/remission was initial treatment with combination

DMARDs and for 12 months the latter approach or initial treatment with parenteral methotrexate at 20–25mg per week. We cannot say if an unmeasured factor accounted for better changes in DAS at the largest sites.

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Discordant Inflammatory Markers in Veterans with Rheumatoid Arthritis: Baseline Characteristics and Relationship with Disease Activity.
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Background/Purpose: Discrepancies between erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) elevations with clinical disease activity frequently occur in rheumatoid arthritis (RA) patients and may be due to comorbid factors other than RA disease activity. We hypothesize that common comorbidities such as current or prior tobacco use, congestive heart failure (CHF), coronary artery disease (CAD), and diabetes mellitus (DM) are associated with discrepancies in inflammatory marker elevations in RA patients.

Methods: We performed a cross-sectional analysis using data collected at the baseline visit in the Veterans Affairs Rheumatoid Arthritis (VARA) cohort. We obtained demographics and comorbidities (tobacco use, CHF, DM, CAD, sleep apnea, chronic obstructive pulmonary disease, malignancy, osteoarthritis, obesity) from linked Decision Support Services (DSS)-derived medical data. We used the following cutpoints to define normal laboratory values for ESR and CRP: 1)ESR for age over 50, 20mm/hr for men and 30 mm/hr for women; age under 50, 15mm/hr for both sexes 2) CRP of 0.8 mg/dL for both sexes. Concordant values were defined as both tests either being above or below these cutpoints. We analyzed the frequencies of comorbidities in patients with low disease activity by the clinical disease activity index (CDAI $\leq$ 10) in relation to: 1) concordant vs. discordant elevations in inflammatory markers and 2) low or moderate/high disease activity by DAS28-ESR ($<$3.2 or $\geq$3.2) and DAS28-CRP ($<$2.67 or $\geq$2.67). Finally, we documented the frequencies of comorbidities in patients who met all the current ACR/EULAR Boolean-based definition requirements and in those who met only the 3 clinical criteria but failed the CRP $\leq$ 1 criterion.

Results: We identified 1158 RA patients with baseline ESR and CRP values. There were 392 with concordantly normal, 368 with concordantly elevated, 205 with elevated ESR/normal CRP and 193 with elevated CRP/ normal ESR at baseline. Patients in low disease activity by the CDAI were equally likely to have an elevated CRP and normal ESR as they were to have a normal CRP and elevated ESR, irrespective of comorbidities. Fewer than 10% of patients with a low CDAI had moderate-high disease activity by DAS28-ESR and DAS28-CRP. There were 157 patients who met all ACR/EULAR Boolean remission criteria and 35 who met all criteria except for CRP $\leq$1. Among tobacco users, 20% who otherwise would have met ACR/EULAR remission criteria did not due to a CRP $>$ 1.

Conclusion: Common medical comorbidities are frequently associated with elevated ESR and/or CRP in patients with RA. ESR by itself or as part of the DAS28-ESR was as likely to be elevated and categorize patients in low disease activity as CRP by itself or as part of the DAS28-CRP. Despite potential concern that the presence of various comorbidities might significantly influence ESR and CRP and decrease the likelihood that patients meet current ACR/EULAR remission criteria, we did not observe strong evidence for this problem in veterans with RA.

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The Impact of Reaching Low Disease Activity in the First Year On Future Disability and Damage in Patients with Early Rheumatoid Arthritis.
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Background/Purpose: Remission has been proposed as the goal of treatment in patients with early rheumatoid arthritis (RA) by current clinical practice guidelines. Remission is ideal but rare and achieving a low disease activity state (LDA) may be a more realistic goal.The objective of this study was to assess the impact of LDAS at one year on patient function and x-ray progression.

Methods: We used data from The Study Of New Onset Rheumatoid Arthritis (SONORA), a North American prospective cohort of patients with early RA. Our analysis is based on 3 years of follow-up. The Simplified Disease Activity Index (SDAI) and patients' function (HAQ-DI) were measured at baseline, years 1, 2 and 3. Hand x-ray was performed yearly up to year 2; a modified sharp score of $\geq$3.5 indicated important x-ray progression[1].

Multivariate linear regression analysis was performed to assess the impact of reaching LDA (yes/no) at year 1 on future HAQ. Logistic regression was used to assess the impact of reaching LDA at year 1 on x-ray progression (yes/no) at year 2. Both analyses were adjusted for potential clinical confounders. Missing data were imputed using Multiple Imputation.

Results: Baseline characteristics of 984 eligible patients included: mean (sd) age 53 (14.8), disease duration 5.3 (3.1) months, swollen joint count (SJC) 9.4(7.1), tender joint count (TJC) 10.1 (8.0), CRP 1.4 (1.5), SDAI 30.5 (16.6) and median (IQR) HAQ 1.0 (0.37–1.63) and modified Sharp score 3.0 (0.0–7.0). Year 1 LDA was achieved in 37% of patients and x-ray progressed in 17%.Year 1 LDA was strongly associated with lower HAQ at 3 years (p=0.0003). Other predictors included higher baseline HAQ (p$<$.0001), older age (p=0.002), higher Joint space narrowing (JSN) score (p=0.03) and gender (female) (p=0.007) which were associated with higher HAQ. Complete case and imputed analyses showed similar results. Year 1 LDA was significantly *a*ssociated with less X-Ray progression at year 2 (OR 0.68, 95% CI 0.47–0.98; p=0.04) in the imputed case analysis (was not significant in complete case analysis). Baseline Sharp score (1.06, 1.01–1.12; 0.03), positive rheumatoid factor (1.98, 1.2–3.2; 0.01), positive anti-CCP (1.95, 1.1–3.4; 0.03), higher CRP 1.15 (1.01–1.30; 0.03) were also predictors of x-ray progression.

Conclusion: Reaching low disease activity is associated with improved long term outcomes in early RA. This provides strong supports for the current treat to target recommendations. An assessment of prognostic factors at baseline is essential and can help clinicians stratify patients and individualize RA treatment.

Reference:
1-K Bruynesteyn, M Boers, et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rhuem Dis.2005 Feb;64(2):179–82

Disclosure: P. Akhavan, None; **G. A. Tomlinson**, None; **P. R. Fortin**, None; **C. Bombardier**, None.

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Remission is a Difficult Target in Clinical Practice When RA Disease Is Established.
Till Uhlig[1], Elisabeth Lie[1], Cecillie Kaufmann[2], Erik Rødevand[3], Knut Mikkelsen[4], Synnøve Kalstad[5] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Vestre Viken, Drammen, Norway, [3]St. Olavs Hospital, Trondheim, Norway, [4]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [5]Tromsø, Norway

Background/Purpose: Clinical remission is the treatment target in rheumatoid arthritis (RA) and several composite indices are available for evaluation of remission and low disease activity (LDA) states. We currently have little information on how disease duration impacts remission and LDA

rates in daily clinical practice. We examined how often clinical remission and LDA is achieved in clinical practice using existing definitions in RA patients with variable disease duration.

Methods: Data were retrieved from the NOR-DMARD register. For the present analyses we used data from all 4568 patients starting with a synthetic (n=3095) or biological (n=1473) DMARD with available a 3-month follow-up data, and also from 3262 patients with available 6 months follow-up data. Mean (SD) age was 54.7 (13.7) yrs, disease duration was 8.5 (7.9) yrs, 72.7% of patients were females.

Applied definitions for clinical remission included the Disease Activity Score based on 28 joint counts (DAS28) <2.6, the Simplified Disease Activity Index (SDAI) <3.3, the Clinical Disease Activity Index (CDAI) <2.8, Routine Assessment of Patient Index Data (RAPID3, range 0–10) <1, and the ACR/EULAR remission definition (A/E) with tender joint count, swollen joint count, patient global assessment (scale 0–10), and CRP (mg/dL) all <1. We also explored a practical remission definition of A/E without CRP (A/E PRAC), and low disease activity for DAS28 (<3.2), SDAI (<11), CDAI (<10) and RAPID3 (<2). The four investigated categories for disease duration were: <1 year, 1<6 years, 6–10 years, and >10 years.

Results: The table shows percentages for patients according to disease duration periods who met different remission and LDA definitions after 3 months and 6 months of DMARD treatment.

While the new A/E remission criteria were most stringent, for all remission indices the likelihood of remission after 3 and 6 months of DMARD treatment decreased with increasing RA disease duration (Chi square test p<0.01 for all comparisons for 3 and 6 months follow-up). Remission and low disease activity rates after 3 and 6 months were clearly best in patients with up to one year disease duration. Only 6–9 percent of patients with disease duration over 1 year achieved after 3–6 months DMARD treatment a state of remission according to the A/E criteria.

Disease duration (yrs)	All	<1	1-<6	6-<10	>10	All	<1	1-<6	6-<10	>10
	Remission 3 months (%)					Remission 6 months (%)				
DAS28	21.2	26.3	19.9	16.9	18.1	24.7	31.7	20.8	23.5	19.6
SDAI	8.9	12.6	7.6	7.7	6.0	10.8	14.4	10.2	8.8	8.0
CDAI	9.5	12.9	8.2	8.4	6.8	11.4	15.4	10.3	9.7	8.4
RAPID3	19.4	25.5	17.0	19.2	14.0	20.1	26.0	20.0	18.0	14.2
A/E	8.0	11.0	6.8	6.5	5.7	9.4	11.6	9.0	8.0	7.7
A/E PRACT	9.5	12.9	8.6	7.9	6.9	11.3	14.3	10.1	9.8	9.1
	LDA 3 months (%)					LDA 6 months (%)				
DAS28	34.0	39.9	32.2	30.5	30.3	39.7	47.5	38.0	35.0	34.3
SDAI	40.5	46.9	38.3	37.2	36.4	46.7	55.1	45.1	42.7	40.3
CDAI	41.0	47.0	38.5	37.4	37.9	47.3	55.0	45.8	43.2	41.6
RAPID3	38.7	46.8	36.6	36.3	32.4	40.7	48.5	40.2	37.7	33.6

Conclusion: The target of remission varies in difficulty across different remission criteria and is less often achieved with increasing disease duration. These observations have implication for how treat-to-target can be managed in a realistic way in patients with established disease and may indicate that many patients with established disease will need an individualized target due to joint destruction, co-morbidities and other factors.

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Frequencies of Boolean and Index Based ACR-EULAR Remissions Differ Slightly Depending On the Method of Patient Global Assessment. Paul Studenic, Josef S. Smolen and Daniel Aletaha. Medical University Vienna, Vienna, Austria

Background/Purpose: Two definitions of remission have been put forward by the ACR and EULAR: a Boolean based, requiring swollen and tender joint counts (SJC, TJC), C-reactive protein (CRP in mg/dl) and patient global assessment (PGA on a 0–10cm scale, VAS) to be ≤1; and an index based definition, requiring the simplified disease activity index (SDAI) to be ≤3.3. The patient global has been shown to be crucial in fulfilling the criteria (1). In many settings a numerical rating scale (NRS) is preferred instead of a VAS. Here, we investigated whether the use of a NRS-like assessment would lead to different remission frequencies compared to a VAS.

Methods: We obtained data of a random cross-sectional visit of RA outpatients from a longitudinal observational database. We used simulated (s)-NRS values, in which VAS values were rounded to the closest integer, for calculation of the SDAI. We compared proportions of patients in Boolean and/or SDAI remission between PGA by VAS and sNRS, evaluating their difference or agreement descriptively by Kappa and receiver operating curve analyses (ROC).

Results: We identified 922 RA patients (80% female, 56% rheumatoid factor (RF) positive, mean disease duration 8 years). In the main analysis, 12.8% of patients were in Boolean remission using sNRS versus 11.3% using VAS (see table).

All patients in Boolean remission using VAS also were in remission by sNRS. Boolean remission using VAS and sNRS had a high agreement (κ of 0.93). SDAI remission frequencies were higher than Boolean remission frequencies with a good agreement (table), and showed a κ of 0.94 for the comparison of VAS and sNRS. In sensitivity analyses, in which we rounded all VAS values either up to the next higher integer, or down to the next lower integer to obtain the sNRS, confirmed the main analysis (table).

When using SDAI to test for Boolean remission in a ROC analysis, SDAI evaluated by VAS and by sNRS showed similar characteristics (AUC=0.99 for both), and sensitivity and specificity for the SDAI remission cutoff of 3.3 were 0.96 and 0.94 for VAS and 0.90 and 0.95 for sNRS.

. Frequencies of remission using different types of PGA

	VAS	sNRS – rounded arithmetically	sNRS – rounded up	sNRS – rounded down
% SDAI Remission	17.5	16.6	13.5	21.0
% Boolean Remission	11.3	12.8	11.3	15.2
% Boolean remitters within SDAI remitters	64.7	72.3	71.7	71.7
% SDAI remitters within Boolean remitters	97.1	90.7	82.7	95.7
Agreement SDAI/Boolean Remission (κ)	0.74	0.77	0.74	0.78

Conclusion: As expected SDAI remission rates were somewhat higher than Boolean remission rates. This was consistent regardless of the method used to assess the patient global. While Boolean remission was about 15% more frequent using sNRS than VAS, SDAI remission was numerically lower with sNRS than VAS. Thus, using a sNRS instead of a VAS for PGA assessment seems to have little impact regarding the achievement of both SDAI and Boolean remission so that sNRS may be a valid tool for PGA assessment in the new remission criteria. However, this assumption will have to be tested using true rather than simulated NRS.

1. Vermeer M, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology 2012;51: 1076–80.

Disclosure: P. Studenic, None; **J. S. Smolen**, None; **D. Aletaha**, None.

ACR Poster Session A
Rheumatoid Arthritis - Human Etiology and Pathogenisis
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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βig-h3 Regulates the Inflammatory Arthritis by Mediating Selective Recruitment of Effector/Memory T Cells. Keum Hee Sa, Jin Hee Kang, Mahmudul Md Alam, Kyung Hwa Lee, Churl Hyun Im, Eon Jeong Nam, In San Kim and Young Mo Kang. Kyungpook National University School of Medicine, Daegu, South Korea

Background/Purpose: Transforming growth factor-beta inducible gene-h3 (βig-h3) is abundantly expressed in synovial tissues of rheumatoid arthritis (RA) and has a regulatory role in growth, differentiation, adhesion, migration, and survival of cells. Previously, we found that βig-h3 regulates the adhesion and migration of T cells expressing a high level of $\alpha5\beta1$ integrin. Therefore, we sought to investigate whether βig-h3 regulates the adhesion of specific T cell subsets selectively and whether it recruits T cells into arthritic tissues differentially according to expression of βig-h3 in a soluble form or *in situ* within synovial tissues.

Methods: T cells were isolated using negative selection kit with MACS. T cell subsets were isolated with antibodies against CD4, CD45RO, and a5 integrin using FACS Aria™. Adhesion of T cell subsets was investigated on βig-h3-coated microtitre plates. βig-h3 overexpressing mice were generated

by the insertion of hβig-h3 transgene downstream of albumin promotor. βig-h3 deficient mice were also prepared by deleting βig-h3 gene using homologous recombination. Collagen antibody induced arthritis (CAIA) model was prepared. Recruitment of effector T cells was evaluated using in vivo homing assay.

Results: T cells isolated from SF of RA were mostly $\alpha5\beta1^{Hi}$, while most of those from PB of controls were $\alpha5\beta1^{Lo}$. Adhesion of SF T cells on the coated βig-h3 was enhanced compared with normal or RA PB T cells, which was inhibited by the function blocking antibody against $\alpha5\beta1$ integrin. RGD peptide, which also binds to $\alpha v\beta3$ integrin, did not block βig-h3-mediated adhesion of T cells, while dhfas-1, a fragment of the 4th fas-1 domain of βig-h3, blocked the adhesion in a dose-dependent manner. The proportion of CD45RO$^+$ cells among T cells was increased in the PB and SF of RA compared to PB of controls. Most of the CD45RO$^+$ T cells were $\alpha5\beta1^{Hi}$ population, while almost all the CD45RO$^-$ T cells were $\alpha5\beta1^{Lo}$ population. βig-h3-mediated adhesion were higher in the CD4$^+$CD45RO$^+\alpha5^{Hi}$ T cells compared with CD4$^+$CD45RO$^+\alpha5^{Lo}$ and CD4$^+$CD45RO$^-\alpha5^{Lo}$ T cells (0.40 ± 0.03 vs 0.19 ± 0.03 and 0.22 ± 0.02, respectively, $P < 0.01$). In βig-h3-trasgenic CAIA mice, arthritis severity was efficiently ameliorated compared with control ($P < 0.05$) and tissue sections revealed a decreased number of infiltrating T cells. In βig-h3 deficient mice, the severity of CAIA was significantly less severe compared to wild type C57BL6/J mice ($P < 0.05$), which was consistent with reduced histologic scores. To evaluate the role of βig-h3 in T cell recruitment into synovial tissues, in vivo homing of T cells was assessed after adoptive transfer of CSFE-labeled effector T cells. Homing of effector T cells into joint tissue was significantly reduced in βig-h3 deficient CAIA mice compared with that of wild type CAIA mice ($P < 0.05$).

Conclusion: The present data indicate that βig-h3 may play a critical role in the regulation of inflammation by the selective recruitment of memory/effector T cells into the synovial tissues of RA through the interaction with $\alpha5\beta1$ integrin. These results implicate a soluble βig-h3-based therapeutic strategy for the treatment of inflammatory arthritis.

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The I50V *IL4R* SNP Is Associated with Increased Th17 Cell Frequency and Poor Clinical Outcome in Rheumatoid Arthritis. Jan Leipe[1], Iryna Prots[2], Markus A. Schramm[1], Matthias Witt[1], Axel P. Nigg[1], Christiane S. Reindl[1], Claudia Dechant[1], Mathias Grunke[1], Hendrik Schulze-Koops[1] and Alla Skapenko[1]. [1]University of Munich, Munich, Germany, [2]Junior Research Group III, Interdisciplinary Center for Clinical Research Nikolaus-Fiebiger Center for Molecular Medicine, Erlangen

Background/Purpose: A single nucleotide polymorphism (SNP) in the IL4R gene (I50V, rs 1805010) has previously been associated with an aggressive destructive course of rheumatoid arthritis (RA). Patients homozygous for the V50 allele, which has been linked to diminished IL-4 signaling, develop more often bone erosions within the first two years of disease. On the other hand, Th17 cells and their cytokine IL-22 have also been associated with cartilage and bone destruction. Development of Th17 cells is negatively regulated by IL-4 signaling through the IL-4R. Because of the functional differences of the two *IL4R* alleles, we investigated a possible association between I50V *IL4R* SNP and Th17 cell frequencies in active RA.

Methods: *IL4R* genotypes were determined in well-defined cohorts of patients with early, treatment-naive RA (n=49) as well as in controls (healthy controls, [n=24] and patients with osteoarthritis [OA, n=15]) by TaqMan SNP assay. IL-17, IL-22 serum levels and *ex vivo* Th17 cell frequencies were analyzed by ELISA and flow cytometry. To assess the inhibitory effect of IL-4 on Th17 cell development, we primed CD4 T cells for 72 h in the presence or absence of IL-4 and determined Th17 cell frequencies. Clinical and radiographic data were evaluated at baseline and after one year after disease onset. Correlation of clinical data and radiographic progression was performed using Pearson rank correlation test or Chi square test.

Results: Gentotyping revealed 10 patients homozygous for the I50 alleles (I50I), 32 heterozygous patients (I50V), and 7 homozygous VV patients (V50V). Clinical activity was consistently higher in homozygous V50V RA patients during follow-up as compared to the i50V and I50I patients, despite similar treatment regimens. Moreover, the loss of functional *IL4R* alleles was associated with the presence of erosions. In all study cohorts T cells from V50V individuals responded weaker to IL-4 inhibition of Th17 cell development as compared to their I50I or I50V counterparts. The inhibitory effect of IL-4 on Th17 development in V50V cells was however even less prominent or even completely absent in RA patients as compared to controls. Accordingly, frequencies of Th17 cells were significantly increased in the V50V group of RA patients. RA patients homozygous for the V50 allele variant demonstrated significantly higher IL-17 and IL-22 serum levels as compared to I50I or I50V RA patients and healthy or OA controls.

Conclusion: Together, the data indicate that the V50 allele of the I50V *IL4R* SNP renders CD4 T cells from RA patients insensitive to IL-4. The V50 allele of the IL-4R might therefore contribute to the increased Th17 cell frequency, clinical activity and radiographic progression in RA.

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Alpha-Enolase Facilitates Migration of Fibroblast-Like Synoviocytes in Rheumatoid Arthritis. Kichul Shin[1], Ji Ah Park[2], Seyeon Bae[1], Jae Seung Kang[1] and Yeong Wook Song[3]. [1]College of Medicine, Seoul National University, Seoul, South Korea, [2]Seoul National Hospital, Seoul, South Korea, [3]Seoul National University Hospital, Seoul, South Korea

Background/Purpose: Alpha-enolase (ENO1) is a multifunctional glycolytic enzyme ubiquitously expressed in the cytoplasm. Citrullinated ENO1 is reported to be a candidate autoantigen in rheumatoid arthritis (RA), yet its specific biologic function remains unknown. Histologic analysis indicates that ENO1 is expressed in fibroblast-like synoviocytes (FLS), monocytes, and endothelial cells in the synovium. In pro-inflammatory conditions, ENO1 is translocated to the cell surface where it activates plasminogen. Its expression in monocytes mediates migration of the cells into inflamed lung tissues in animal models. Our aim was to investigate the role of surface-expressed ENO1 in RA FLS, the key constituent of pannus in RA synovium.

Methods: FLS from RA synovial tissues were isolated and cultured *in vitro*. ENO1 expression on the cell surface was assessed by confocal microscopy. Cell surface-expressed ENO1 was treated with a mouse anti-human ENO1-stimulating monoclonal antibody as well as an isotype control. Scratch test of cultured FLS and transwell experiments under platelet-derived growth factor (PDGF) were performed to assess FLS migration. Cytoskeletal rearrangement was analyzed after staining FLS with an anti-fillagrin antibody. Fluo-4 fluorophore was used for calcium-flux assays directly on discs plated with FLS.

Results: Cell surface ENO1 expression was low in (56 passages) cultured FLS under normal condtions. However, overnight TNF-alpha (as low as 0.1 ng/ml) treatment induced ENO1 translocation to the cell surface, which peaked at 24 hours (figure). Stimulation of cell surface-expressed ENO1 induced faster repopulation of FLS in the scratch test assay, and increased PDGF-induced transwell migration. Cytoplasmic actin filament rearrangement in FLS was markedly enhanced with ENO1 stimulation. Moreover, ENO1 stimulation induced a positive calcium flux response in FLS under intravital confocal microscopy.
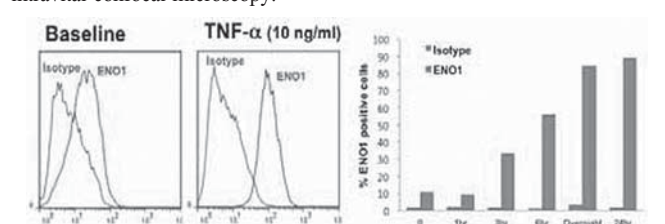
Conclusion: Translocation of cytoplasmic ENO1 to the cell surface in RA FLS is potentiated by TNF-alpha. Our results indicate that ENO1 can contribute to migration of RA FLS, especially under the pro-inflammatory milieu as in the RA synovium.

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Pathway Analysis of Genome-Wide Association Studies On Rheumatoid Arthritis. Young Ho Lee[1], Sung Jae Choi[1], Jong Dae Ji[1] and Gwan Gyu Song[2]. [1]Korea University Medical Center, Seoul, South Korea, [2]Korea Univ College of Med, Seoul

Background/Purpose: Genome-wide association studies (GWASs) have been successfully used to identify novel common genetic variants that contribute to susceptibility to complex diseases, but individual GWASs are limited in terms of identifying new loci. Thus, pathway-based analysis is required to identify further new loci that contribute to susceptibility to complex diseases. The aims of this study were to identify candidate causal single nucleotide polymorphisms (SNPs) and candidate causal mechanisms of rheumatoid arthritis (RA) and generate hypothesis for SNP à gene à pathways.

Methods: An meta-analysis dataset of RA GWASs was used that included 2,554,714 SNPs in 5,539 RA cases and 20,169 controls of European descent. ICSNPathway (Identify candidate Causal SNPs and Pathways) analysis was applied to meta-analysis results of the RA GWAS dataset.

Results: ICSNPathway analysis identified 49 candidate causal SNPs and 37 candidate causal pathways. The top 5 candidate causal SNPs, rs1063478 (p = 5.40E-09), rs375256 (p = 3.44E-09), rs365066 (p = 3.60E-30), rs2581 (p = 2.7E-25), and rs1059510 (p = 2.52E-06) were all at human leukocyte antigen (HLA) loci. These candidate causal SNPs and pathways provide 22 hypothetical biological mechanisms. The most strongly associated pathway concerned HLA: rs1063478 (nonsynonymous coding) à HLA-DMA à antigen processing and presentation of peptide antigen. ICSNPathway analysis identified two candidate causal non-HLA SNPs and ten candidate causal pathways, which provided two hypothetical biological mechanisms. First, rs2476601 (nonsynonymous coding [deleterious]) (p = 6.22E–71) à protein tyrosine phosphatase nonreceptor 22 (PTPN22) à immune response-activation cell surface receptor signaling pathway, and, rs2230926 (nonsynonymous coding) (p = 1.26E–07) à tumor necrosis factor-alpha-induced protein 3 (TNFAIP3) à the CD40L signaling pathway.

Conclusion: The application of ICSNPathway analysis to meta-analysis results of RA GWAS datasets resulted in the identification of candidate causal SNPs and pathways involving HLA-DMA, PTPN22, and TNAIP3 that might contribute to RA susceptibility.

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Early Growth Response-1 (EGR-1) Controls Synoviocyte Apoptosis, and Its Expression Is Regulated by the Direct Binding of Fibroblast Growth Factor-1 (FGF1) or Insulin-Like Growth Factor-1 (IGF1) to Integrin $\alpha v\beta 3$. Shino Tanaka[1], Jun Saegusa[1], Seiji Kawano[1], Yoshikazu Takada[2], Shunichi Kumagai[3] and Akio Morinobu[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]University of California, Davis, School of Medicine, Sacramento, CA, [3]Shinko Hospital, Kobe, Japan

Background/Purpose: Growth factors such as fibroblast growth factor (FGF) and insulin-like growth factor (IGF) are of interest in the initiation and development of rheumatoid arthritis (RA) synovial hyperplasia, because of their potent mitogenic and angiogenic activities. The traditional understanding of FGF and IGF signaling has held that their binding to their respective receptor (i.e., the FGF receptor [FGFR] or the IGF receptor [IGFR]) is sufficient to initiate signaling. We recently demonstrated that FGF1 binds directly to integrin $\alpha v\beta 3$, and that an integrin-binding-defective FGF1 mutant (FGF^{R50E}) cannot induce cell proliferation, even though the mutant still binds FGFR; this is also true for IGF1. In both cases, a ternary complex, FGF1-FGFR-integrin $\alpha v\beta 3$ or IGF1-IGFR-integrin $\alpha v\beta 3$, was formed. However, the mechanism underlying the cross-talk between growth-factor-receptor signaling and integrin signaling is unknown. Here we investigated how the growth factor-integrin $\alpha v\beta 3$ interaction is involved in growth-factor signaling in RA synoviocytes.

Methods: Several mutations were introduced at the interface of FGF1 or IGF1 with integrin $\alpha v\beta 3$, and integrin-binding-defective FGF1 and IGF1 mutants (FGF^{R50E} and IGF$^{R36E/R37E}$) were generated. RA synoviocytes were stimulated with FGF1 or FGF^{R50E}, and comprehensive gene-expression profiling was performed by cDNA microarray. Intracellular signaling in synoviocytes treated with FGF1, FGF^{R50E}, IGF1, and IGF$^{R36E/R37E}$was evaluated by real-time PCR and Western blot analyses. Synoviocytes transfected with scramble siRNA or early growth response-1 (EGR-1)-specific siRNA were treated with various apoptotic stimuli, and cell viability was measured by the WST-8 assay.

Results: The integrin-binding-defective mutants (FGF^{R50E} and IGF$^{R36E/R37E}$) showed a markedly reduced ability to induce the cell proliferation

of RA synoviocytes. The cDNA microarray analysis showed significantly reduced EGR-1 mRNA expression in the FGF^{R50E}-treated synoviocytes. Furthermore, EGR-1 mRNA and protein were rapidly induced in RA synoviocytes in response to FGF1 or IGF1, but the EGR-1 expression was significantly impaired in FGF^{R50E}- or IGF$^{R36E/R37E}$-treated synoviocytes. In addition, the down-regulation of EGR-1 by siRNA inhibited the apoptosis of synoviocytes treated with H_2O_2 or doxorubicin.

Conclusion: EGR-1 plays a pivotal role in synoviocyte apoptosis, and its expression is regulated by the direct binding of FGF1 or IGF1 to integrin $\alpha v\beta 3$. This integrin-growth factor interaction may be a novel therapeutic target for RA.

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Early Menopause, Smoking and Circulating Antibodies Against Citrullinated Peptides in the Pre-Clinical Phase of Rheumatoid Arthritis. Mitra Pikwer[1], Johan Rönnelid[2], Monika Hansson[3], Ulf Bergström[1], Lennart T.H. Jacobsson[1], Linda Mathsson[2], Per Johan Jakobsson[3], Guy B. Serre[4], Rikard Holmdahl[5], Lars Klareskog[6] and Carl Turesson[1]. [1]Lund University, Malmö, Sweden, [2]Uppsala University, Uppsala, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Centre National de la Recherche Scientifique - Université de Toulouse, Toulouse, France, [5]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [6]Karolinska Institute, Stockholm, Sweden

Background/Purpose: Previous studies indicate that anti-citrullinated peptide antibodies (ACPAs) may be detected in individuals who later develop rheumatoid arthritis (RA) years before onset, and that smoking and early menopause (before age 46) are risk factors for RA. Whereas smoking is a predictor of seropositive RA, early menopause has been associated with a milder, predominantly rheumatoid factor negative, phenotype. The objective of this study was to investigate circulating ACPAs and their relation to age at menopause and smoking before the onset of RA.

Methods: Incident cases of RA were identified among participants (n=30447; 18326 women) in a community based health survey, which was linked to local and national registers, followed by a structured review of the medical records. One control, matched for age, sex and year of inclusion in the health survey, was selected for each validated case. Using a multiplex assay system, sera from 131 female pre-RA cases and 131 controls were investigated for 12 different ACPA fine specificities. For all investigated antibodies, previous studies had shown good correlations between results obtained using this system and standard ELISAs. Corrected net values for ACPA specificity were calculated by subtracting values for arginine control peptides from the corresponding citrullinated peptides. Cut offs were set at the 98th percentile, based on investigation of sera from the matched controls. Analyses were stratified by time from inclusion in the health survey to RA diagnosis (1–4, 5–7 and 8–13 years, respectively), and by age at menopause (≤ 45 years vs > 46 years) or history of ever smoking.

Results: Serum was available from 131 women, who were diagnosed with RA a median of 5.5 years (IQR 3–8; range 1–13) after inclusion in the health survey. Seventy (53 %) of the pre-RA cases were positive for ≥ 1 ACPA. Significantly greater numbers of positive ACPA specificities were detected among pre-RA cases sampled closer to RA diagnosis (p for trend 0.03). A history of early menopause (p=0.001) and ever smoking (p=0.003) were both associated with subsequent development of RA. Ever smokers were more likely to be positive for most ACPAs and had higher numbers of positive ACPA specificities compared to never smokers (p=0.047). Ever smokers were more likely to be positive for ≥ 1 ACPA compared to never smokers, regardless of the time from inclusion to RA diagnosis. By contrast, women with a history of early menopause were less likely to be positive for ≥ 1 ACPA compared to those with normal or late menopause, in particular among cases included ≥ 8 years before RA diagnosis (29 % vs. 48 %).

Conclusion: The early occurrence of ACPA and the increase in ACPA specificities with a shorter time to diagnosis indicate that epitope spreading may precede disease onset. The immune phenotype in the pre-clinical phase of RA may differ between subsets depending on environmental exposures and associated disease mechanisms. The present results suggest that hormonal changes influence pathways in the pathogenesis of RA that are distinct from those associated with smoking.

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Single Nucleotide Polymorphisms within the HLA-DRB1 Gene in Relation to Antibodies Against Citrullinated Peptides in Individuals Prior to the Development of Rheumatoid Arthritis. Lisbeth Arlestig[1], Mikael Brink[2], Monika Hansson[3], Per Johan Jakobsson[3], Rikard Holmdahl[4], Linda Mathsson[5], Johan Ronnelid[5], Lars Klareskog[6] and Solbritt M. Rantapaa-Dahlqvist[7]. [1]Umeå University, Umea, Sweden, [2]Umea University, Umea, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [5]Uppsala University, Uppsala, Sweden, [6]Karolinska Institute, Stockholm, Sweden, [7]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umea, Sweden

Background/Purpose: Multiplex analysis has demonstrated the presence of several antibodies against cyclic citrullinated peptides (ACPA) preceding the development of rheumatoid arthritis (RA) by several years. Certain HLA-DRB1* alleles are strongly associated with RA.

To relate the presence of different ACPAs, in individuals before the onset of symptoms of RA, to single nucleotide polymorphisms (SNPs) within the HLA-DRB1 region in order to identify the SNPs most highly associated with the ACPAs analysed in the disease development.

Methods: The study group comprised 406 individuals, with 717 samples, who were identified before the onset of symptoms (median (IQR) 7.4 (9.3) years), as donors to the Medical Biobank of Northern Sweden. A total of 976 population controls were identified from the Medical Biobank for analysis of antibodies against 10 different citrullinated peptides in plasma using a microarray system developed in collaboration withPhadia AB/Thermofisher, Uppsala, based on their ISAC platform. In a previous study the highest frequencies of antibodies were found for fibrinogen (Fib) β36–52, α-enolase (CEP-1), and filaggrin. Anti-CCP2 antibodies were analysed using ELISA (Euro-Diagnostics). Samples from the same individuals were genotyped with the Immunochip custom array according to Illumina protocols (SNP&SEQ Technology Platform, Uppsala, Sweden). 81 SNPs covering the HLA-DRB1* to DQA1* region were analysed. The Haploview software version 4.2 was used for haplotype and association analysis with a permutation test.

Results: Thirty-seven of the SNPs were associated with the pre-diseased individuals compared with controls. After permutation test 22 of them and six haplotypes (7–16 SNPs) remained significantly associated. Anti-CEP-1 antibodies were associated with 15 SNPs although none remained significant after permutation tests. Anti-filaggrin antibodies were related to 4 SNPs, two of which were similar as for anti-CEP-1 (rs9271588 and rs9272363), none remained significant after permutation test. Anti-Fibβ36–52 antibodies were associated with 4 different SNPs compared with the other antibodies and none were significant after permutation test. Of the SNPs analysed 21 were associated with anti-CCP2 antibodies and two of them (rs9271588, rs9271850) and three haplotypes were significantly associated after a permutation test.

Conclusion: The presence of ACPAs is related to a number of SNPs within the HLA- region albeit with somewhat different patterns between the various antibodies.

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α(1,2)-Linked Fucosylated Cytokines Are Upregulated in Rheumatoid Arthritis. Takeo Isozaki[1], Jeffrey H. Ruth[1], M. Asif Amin[1], Phillip L. Campbell[1], Christine M. Ha[1] and Alisa E. Koch[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: Glycosylation is a common post-translational modification of proteins in eukaryotes. Fucosylated glycans are synthesized by fucosyltransferases (futs). We previously reported that sialyl Lewis[x], synthesized by futs, is involved in angiogenesis. Fucosyltransferase 1 (fut1) is an α(1,2)-fucosyltransferase responsible for synthesis of the H blood group and Lewis[y] antigens. We also reported that soluble H and Lewis[y] antigens are mediators of inflammatory cell adhesion and angiogenesis. However, a direct role of α(1,2)-linked fucose in rheumatoid arthritis (RA) has not been demonstrated.

Methods: Assay of total α(1,2)-linked fucosylated proteins in RA, osteoarthritis (OA) and normal (NL) synovial tissue (ST) homogenates were performed by enzyme-linked immunosorbent assay (ELISA). 2-fucosyl-

lactose bovine serum albumin (2'FL-BSA) was used as a standard. We previously showed that fut1 gene deficient mice in which KRN arthritis has been induced have less joint monocyte chemotactic protein (MCP)-1/CCL2 and interleukin (IL)-1β than wild type mice. Hence, we measured IL-1β and MCP-1/CCL2 in RA, OA and other inflammatory disease synovial fluids (SFs) by ELISA to determine if these cytokines have been modified. We also examined tumor necrosis factor (TNF)-α for fucosylation, as TNF-α is a central cytokine in RA pathology. To determine whether fut1 was expressed by NL and RA synovial fibroblasts, real time polymerase chain reaction (RT-PCR) was performed. To block the expression of fut1, RA synovial fibroblasts were transfected with fut1 small interfering RNA (siRNA). After treatment with fut1siRNA, RA synovial fibroblasts were stimulated with TNF-α for 1 hour. We then measured the expression of cytokines important in RA. MCP-1/CCL2, epithelial neutrophil-activating protein 78 (ENA-78)/CXCL5 and vascular endothelial growth factor (VEGF) mRNA were measured by RT-PCR.

Results: Total α(1,2)-linked fucosylated proteins in RA ST were significantly higher compared to OA STor NL ST [mean $\pm$ SEM 74 $\pm$ 21 ng/ml (n=5), 25 $\pm$ 4 ng/ml (n=7) and 29 $\pm$ 6 ng/ml (n=9), respectivel, p<0.05]. Specifically, α(1,2)-linked fucosylated IL-1β and MCP-1/CCL2 in RA synovial fluids were 6 $\pm$ 2% of total fucosylated proteins (n=9) and 20 $\pm$ 4% of total fucosylated proteins (n=12), respectively. In addition, α(1,2)-linked fucosylated TNF-α in RA synovial fluids was significantly higher than in OA and other inflammatory disease synovial fluids [950 $\pm$ 220 pg/ml (n=22), 150 $\pm$ 90 pg/ml (n=13) and 30 $\pm$ 20 pg/ml (n=11), respectively, p<0.05]. We also found that fut1 messenger RNA (mRNA) in cultured RA synovial fibroblasts was significantly elevated compared to NL synovial fibroblasts (p<0.05). Additionally, RA synovial fibroblasts transfected with fut1 siRNA had significantly lower mRNA expression for MCP-1/CCL2, ENA-78/CXCL5 and VEGF than did control siRNA transfected synovial fibroblasts.

Conclusion: These data show that α(1,2)-linked fucosylated proteins are upregulated in RA ST compared to other STs. We also show that fut1 in RA synovial cells is necessary for production of variety of cytokines. Targeting fut may be a novel way to alter joint cytokine production.

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First-Degree Relatives without Rheumatoid Arthritis Exhibit Reactivity to Multiple Anti-Citrullinated Protein Antibodies in Association with Rheumatoid Arthritis-Related Clinical Characteristics: Studies of the Etiology of Rheumatoid Arthritis. Kendra A. Young[1], Kevin D. Deane[2], Lezlie A. Derber[3], Jan M. Hughes-Austin[4], Michael H. Weisman[5], Jane H. Buckner[6], Ted R. Mikuls[7], James R. O'Dell[8], Richard M. Keating[9], Peter K. Gregersen[10], V. Michael Holers[2] and Jill M. Norris[1]. [1]Colorado School of Public Health, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]University of Colorado Anschutz Medical Campus, Aurora, CO, [4]Colorado School of Public Health/University of Colorado Anschutz Medical Campus, Aurora, CO, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]Benaroya Research Institute at Virginia Mason, Seattle, WA, [7]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [8]Univ of Nebraska Med Ctr, Omaha, NE, [9]University of Chicago, Chicago, IL, [10]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY

Background/Purpose: Prior to diagnosis of rheumatoid arthritis (RA), there are increases in the number of citrullinated proteins that anti-citrullinated protein antibodies (ACPA) target, suggesting an expansion of autoimmunity in early RA development that, if fully understood, may provide insight into the earliest antigenic targets important in disease pathogenesis. Anti-CCP assays are currently the most widely used ACPA assessments; however, the specific epitopes recognized by these commercial assays are unknown, thereby limiting the ability to make inferences about the type and expansion of ACPA responses. Our objective was to utilize multiplex technology to examine ACPA reactivity to specific citrullinated proteins and peptides in the pre-diagnosis period of RA development by performing this analysis in first-degree relatives (FDRs) of RA probands, who do not have RA, but are at increased risk of future RA.

Methods: We selected 113 FDRs (Ab+) who had been positive at $\geq$1 research visit for any of 5 Ab: rheumatoid factor (RF) by nephelometry; RF by ELISA for isotypes IgM, IgG, or IgA; or anti-CCP2; and 100 FDRs (Ab-) who had never been autoantibody positive. A panel of 18 ACPA was measured using a bead-based assay in serum from 397 visits by these FDRs. Cut-offs for positivity for each ACPA were determined using receiver

operating characteristic (ROC) curves of data from 200 patients with established RA (1987 ACR criteria), and 98 blood-bank controls, where we found that positivity for ≥ 9 ACPAs had 67% sensitivity and 92% specificity for RA, comparable to the 70% sensitivity and >95% specificity for anti-CCP2. In FDRs, we examined reactivity to ACPA and associations between ACPA (number positive and positivity for ≥ 9 ACPA) and RA-related characteristics including positivity for RF (nephelometry or isotypes) and swollen or tender joints on exam. While we had too few anti-CCP2 positive FDRs to test (n=8), associations were examined with the high-risk autoantibody profile (i.e., anti-CCP2 and/or ≥2 RF isotypes), which was shown to be highly specific (>96%) for future RA.

Results: Both Ab+ and Ab- FDRs showed reactivity to multiple ACPA, although Ab+ FDRs were positive for a greater number of ACPA than Ab- FDRs (mean 3.1 ± 4.3 vs. 2.1 ± 2.8, p=0.04). Of the 8 anti-CCP2 positive FDRs, 5 were positive for at least 9 ACPA, and 4 were positive for 16 or more ACPA. 76% of anti-CCP2 negative FDRs were positive for ≤ 2 ACPA, and 10% were positive ≥ 9 ACPA. Being positive for a greater number of ACPA is associated with being positive for RF (OR=1.22, 95%CI 1.09–1.35), with the IgM (OR=1.17, 95% CI 1.00–1.3) and IgA (OR=1.14, 95% CI 1.02–1.28) RF isotypes, and for those positive for anti-CCP2 and/or ≥2 RF isotypes (OR=1.22, 95%CI 1.09–1.35). FDRs positive for at least 9 ACPA had significantly greater odds of having least one tender joint on exam (OR=7.59, 95% CI 1.97–29.25). A similar association was observed for increasing number of ACPA (OR=1.21, 95% CI 1.05–1.39).

Conclusion: These results indicate that there may be RA-related autoimmunity and even early inflammatory arthritis in FDRs without 1987 ACR classified RA, even in FDRs negative for RF and anti-CCP2. Prospective follow-up is needed to further asses these findings.

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Hypoxia-Induced Endogenous Prostaglandin E2 Negatively Regulates Hypoxia-Enhanced Aberrant Overgrowth of Rheumatoid Synovial Tissue. Hirofumi Mitomi[1], Hidehiro Yamada[1], Toshiko Nozaki Shibata[1], Hiroshi Ito[1], Yoshioki Yamasaki[1], So Nomoto[2], Atsushi Kusaba[3], Hiroki Yamashita[3] and Shoichi Ozaki[1]. [1]St. Marianna University, Kawasaki, Japan, [2]Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan, [3]Ebina General Hospital, Ebina, Japan

Background/Purpose: During isometric exercise, the synovial joint tissue is prone to hypoxia, which is further enhanced in the presence of synovial inflammation. Hypoxia is also known to induce inflammatory cascades, suggesting that periodic hypoxia perpetuates synovitis in rheumatoid arthritis. We previously established an *ex vivo* cellular model of rheumatoid arthritis using the synovial tissue-derived inflammatory cells, which reproduced aberrant synovial overgrowth and pannus-like tissue development *in vitro*. Using this model, we investigated the regulatory mechanism of synovial cells against hypoxia in rheumatoid arthritis.

Methods: Inflammatory cells that infiltrated synovial tissue from patients with rheumatoid arthritis were collected without enzyme digestion, and designated as synovial tissue-derived inflammatory cells. Under normoxia or periodic hypoxia twice a week, their single-cell suspension was cultured in medium alone to observe an aberrant overgrowth of inflammatory tissue *in vitro*. Cytokines produced in the culture supernatants were measured by enzyme-linked immunosorbent assay (ELISA) kits.

Results: Primary culture of the synovial tissue-derived inflammatory cells under periodic hypoxia resulted in the attenuation of the spontaneous growth of inflammatory tissue *in vitro* compared to the culture under normoxia. Endogenous prostaglandin E2 (PGE2) production was enhanced under periodic hypoxia. When endogenous PGE2 was blocked by indomethacin, the aberrant tissue overgrowth was more enhanced under hypoxia than normoxia. Indomethacin also enhanced the production of TNF-alpha (TNF-α), macrophage colony-stimulating factor (M-CSF), matrix metalloproteinase-9 (MMP-9) under periodic hypoxia compared to normoxia. EP4-specific antagonist reproduced the effect of indomethacin. Exogenous PGE1 and EP4-specific agonist effectively inhibited the aberrant overgrowth and the production of the inflammatory mediators under periodic hypoxia as well as normoxia.

Conclusion: The enhancing effect of periodic hypoxia on the aberrant overgrowth of rheumatoid synovial tissue was effectively down-regulated by

the simultaneously induced endogenous PGE2. It is suggested that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) enhances hypoxia-induced synovial overgrowth in rheumatoid arthritis.

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Dyslipidaemia in Early Rheumatoid Arthritis Patients Is Common and Not Influenced by Two Years of Effective DMARD Therapy. the Opera Study. Torkell Ellingsen[1], Kim Horslev-Petersen[2], Merete L. Hetland[3], Peter Junker[4], Jan Podenphant[5], Mikkel Ostergaard[5] and Kristian Stengaard-Pedersen[6]. [1]Regional Hospital, Silkeborg, Denmark, [2]Southern University, Denmark, [3]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [4]Odense University Hospital, Denmark, [5]Copenhagen University Hospital at Glostrup, Denmark, [6]Arhus University Hospital, Denmark

Background/Purpose: In a cohort of early (<6 month duration) treatment-naïve rheumatoid arthritis (ERA) patients (the OPERA-study (1)) to measure lipid levels at baseline, year one and two. Further, to analyze for changes in lipid levels in relation to effective DMARD treatment during two years.

Methods: In 180 ERA patients total s-cholesterol, s-HDL, s-LDL, s-VLDL, s-triglyceride were measured by standardized techniques. All patients were treated with methotrexate (MTX) (20 mg/week) and triamcinolone intraarticularly in any swollen joint for 2 years and in addition randomized to receive adalimumab (ADA) or placebo (PLA)) during the first year. After year 1, ADA and PLA were withdrawn. If patients had DAS28 (CRP) > 3.2 during year 2, sulphasalazine (SZS) and hydroxychloroquine (HCQ) were added to MTX and if active disease persisted after withdrawel of ADA/PLA, ADA replaced SZS and HCQ in both treatment arms (1). Analysis was by ITT with last observation carried forward. Comparisons by Wilcoxon's test.

Results: Baseline characteristics and disease activity were similar in the MTX+PLA and MTX+ADA groups: age 54 vs 56 years; women 69% vs 63%; disease duration 83 vs 84 days; anti-CCP positive 70% vs 60%; IgM-RF positive 74% vs 70%; DAS28 (CRP) median 5.6 (range3.8–7.3) vs. 5.5 (3.8–7.8) respectively. The treatment had an excellent effect on inflammation but no effect on the dyslipidaemiae:

DAS28 Lipid levels mmol/L	Baseline Median (range)	Year 1 Median (range)	Year 2 Median (range)	Baseline % abnormal
DAS28(CRP)	5.6 (3.3–8.6)	2.0 (1.7–4.7)	2.0 (1.7–6.5)	–
Total s-cholesterol	4.8 (2.2–7.8)	5.1 (3.1–8.4)	5.1 (3.1–9.2)	50% >5.0
s-HDL	1.4 (0.7–2.7)	1.7 (0.8–3.6)	1.5 (0.7–2.8)	Male 53%>1.0 Female 84%>1.2
s-LDL	2.8 (0.8–6.1)	2.9 (0.9–6.1)	2.8 (0.9–5.9)	40%>3.0; 93%>1.8
S-VLDL	0.6 (0.1–1.7)	0.5 (0.2–1.6)	0.5 (0.2–1.7)	
s-triglyceride	1.3 (0.3–3.8)	0.9 (0.4–3.5)	1.1 (0.4–3.8)	27%>1.7
s-Cholesterol/ s-HDL	3.4 (1.7–9.8)	3.2 (1.3–7.2)	3.2 (1.8–7.3)	–

No effect of the efficient DMARD treatment strategy was observed after one or two years in any of the treatment arms regarding the levels of total s-cholesterol, s-HDL, s-LDL, s-VLDL or s-triglyceride (p-levels between 0.07–0.97). At baseline more than half of the 180 ERA patients had abnormal lipid concentrations compared to the reference levels.

Conclusion: In a Danish cohort of ERA patients (OPERA study) more than half of the patients had abnormal serum lipid concentrations at the time of diagnosis. Two years of effective synovitis suppression with MTX and glucocorticoid intraarticular and addition of ADA or PLA during the first year did not influence the dyslipidaemiae. (1) Horslev-Petersen, K et al: Adalimumab Added to Methotrexate and Intra-Articular Glucocorticoid Increases Remission Rates At One Year In Early, DMARD-Naive Patients with Rheumatoid Arthritis-An Investigator-Initiated Randomized, Controlled, Double-Blinded Study. ARTHRITIS AND RHEUMATISM Vol 63 (10) Supplement: S147 Meeting Abstract 2011

Disclosure: T. Ellingsen, None; **K. Horslev-Petersen**, Abbott Laboratories, 2; **M. L. Hetland**, None; **P. Junker**, None; **J. Podenphant**, None; **M. Ostergaard**, None; **K. Stengaard-Pedersen**, None.

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The Potential Role of *PTPRD* Gene Copy Number Variation in Susceptibility to Rheumatoid Arthritis. Seung Cheol Shim, Donghyuk Sheen, Mi Kyoung Lim and Hyo Park. Eulji University Hospital, Daejeon, South Korea

Background/Purpose: Since it is important to explore genetic variations associated with rheumatoid arthritis (RA), genome-wide association studies (GWAS) have led to the identification of RA genetic variants putatively associated with susceptibility. Recently, copy number variation (CNV) may also affect susceptibility to diseases, which have been already observed in diverse autoimmune diseases. Protein tyrosine phosphatase receptor D (PTPRD) is a member of the receptor-like PTP which expresses in the B cell lines and thymus and could be involved in the pathogenesis of autoimmune diseases. In this study, we investigated whether the variation of the *PTPRD* gene copy number related with susceptibility to RA.

Methods: To investigate whether the variation of the *PTPRD* gene copy number influence the pathogenesis to RA, blood samples and clinical records were obtained from 217 RA patients (184 females, 33 males) and 205 healthy controls. The genomic DNA of RA patients and healthy controls was extracted from leukocytes in peripheral blood using the Genomic DNA Extraction kit (iNtRON Biotechnology, Korea). To measuring the copy number of *PTPRD* gene, the quantitative real-time PCR (QPCR) was carried out using Mx3000P QPCR system (Stratagene, La Jolla, CA) and each sample for each gene was assayed in triplicate. Western blot was conducted to detect expression levels of *PTPRD*

Results: The copy number of *PTPRD* gene in RA patients was compared with that in healthy controls. The proportion of the individuals with <2 copy of *VPREB1* was significantly higher in patients than in controls, while that of the individuals with >2 copy was lower in patients than in controls. The average relative copy number of the *PTPRD* gene in RA patients (1.14, 95 % CI (1.12–1.16)) was significantly lower than that in healthy controls (1.65, 95 % CI (1.12–1.16), p < 0.0001) (Figure 1). Furthermore, we also investigated association between copy number of *PTPRD* and RA phenotype such as RF factor and anti-CCP levels, which showed no association between copy number of *PTPRD* and both RA phenotypes. Western blot showed the lower expression of *PTPRD* in patients with RA compared to control subjects (Figure 2).
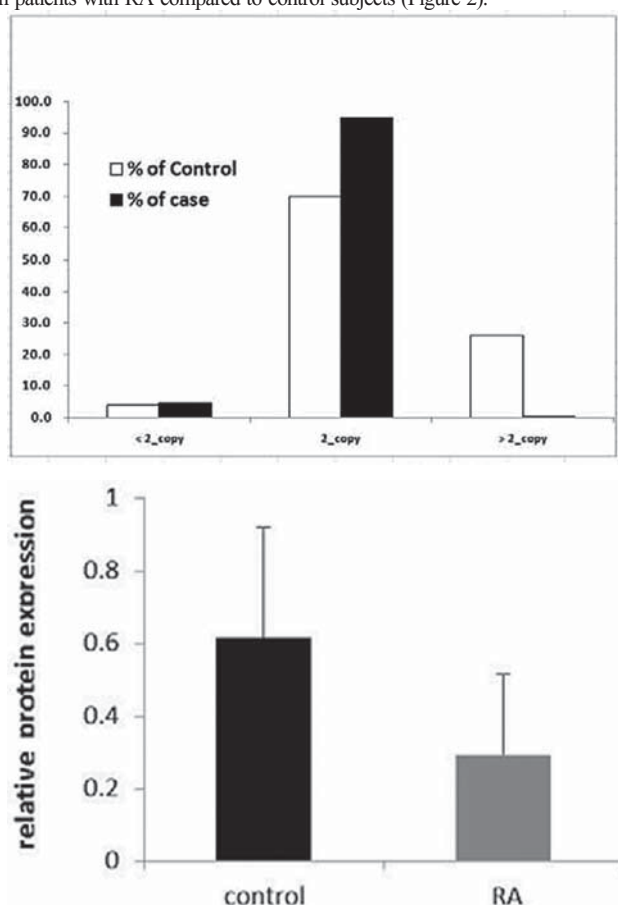
Conclusion: This is the first evidence showing the association between low copy number of the PTPRD gene and susceptibility to RA, which may help understanding the pathogenesis of RA and other autoimmune disorders like affecting maturation and differentiation of T cell and B cells.

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Immediate Early Response Gene X-1 Is Over-Expressed and Regulates Apoptosis and Cytokine Production in Rheumatoid Arthritis Synovial Fibroblasts. Akio Morinobu[1], Masaaki Fujita[2], Shino Tanaka[3], Jun Saegusa[2] and Shunichi Kumagai[4]. [1]Kobe university graduate school of medicine, Kobe 650-0017, Japan, [2]Kobe University Graduate School of Medicine, Kobe, Japan, [3]Rheumatology and Clinical Immunology, Kobe, Japan, [4]Shinko hospital, Kobe, Japan

Background/Purpose: Histone deacetylase inhibitors (HDACi) are potential therapeutic drugs for the treatment of rheumatoid arthritis (RA). We found that an HDACi up-regulates the gene expression of immediate early response gene X-1 (IEX-1) in rheumatoid arthritis synovial fibroblasts (RA-SF). IEX-1 is regulated by various stress stimuli and involved in apoptosis and cell growth. Since the role of IEX-1 has never been examined in RA, we examined the expression and function of the molecule in RA-SF.

Methods: Synovial fibroblasts from RA and OA patients were cultured and used between 2–4 passages. Gene and protein expression was determined by qPCR and Western blotting, respectively. Apoptosis was detected by annexin V staining using a flow cytometer. To examine the function of IEX-1, IEX-1 was knocked down by siRNA or over-expressed with lipofection.

Results: (1) IEX-1 mRNA levels were higher in RA-SF than in OA-SF. LPS and TNFa up-regulated the IEX-1 mRNA expression in RA-SF. (2)Over-expression of IEX-1 induced apoptosis and promoted anti-Fas mAb-mediated apoptosis in RA-SF, while knockdown of IEX-1 protected RA-SF from anti-Fas mAb-mediated apoptosis. Also, over-expression of IEX-1 augmented anti-Fas mAb-induced caspase-8 activation, while knockdown of IEX-1 suppressed it. Thus, IEX-1 promotes anti-Fas mAb-induced apoptosis through up-regulating caspase-8 activity. (3) IEX-1 was up-regulated by TSA, an HDACi. Interestingly, apoptosis induced by TSA plus anti-Fas mAb in RA-SF was partially inhibited by knockdown of IEX-1, indicating that TSA-induced apoptosis was mediated, at least in part, by the up-regulation of IEX-1. (3)When IEX-1 expression was down-regulated with siRNA, LPS-induced IL-6 production was decreased, showing that IEX-1 is also involved in cytokine production from RA-SF.
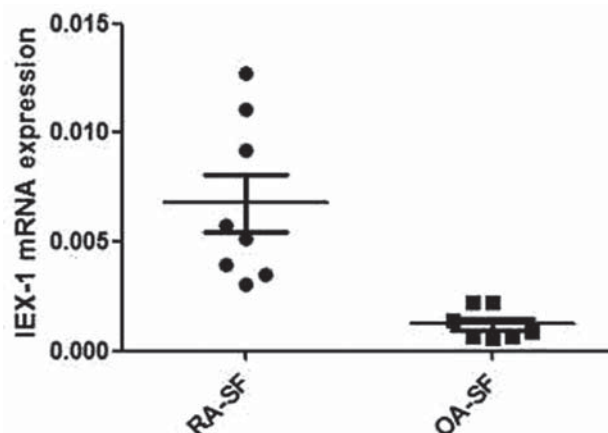
Conclusion: IEX-1 is over-expressed in RA-SF and further induced by TNFa. IEX-1 facilitates anti-Fas mAb-induced apoptosis by enhancing caspase activation, and regulates cytokine production. IEX-1 is likely to play an important role in RA pathogenesis.

Disclosure: A. Morinobu, None; M. Fujita, None; S. Tanaka, None; J. Saegusa, None; S. Kumagai, None.

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Epigenome Analysis of Rheumatoid Arthritis Synovial Fibroblasts Revealed TBX-5 As a Novel Transcription Factor in Chemokine Regulation. Emmanuel Karouzakis, Michelle Trenkmann, Renate E. Gay, Beat A. Michel, Steffen Gay and Michel Neidhart. Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Changes in DNA methylation and histone marks have been associated with diseases such as cancer, rheumatoid arthritis (RA) and systemic lupus erythematosus. Previously, we performed methylation immunoprecipitation (MeDIP) in combination with human promoter arrays and identified TBX5 as a differentially methylated gene in RA synovial fibroblasts (SF). Now, we want to further examine its role in the pathogenesis of RA and identify specific TBX5 gene targets.

Methods: Methylation immunoprecipitation assay was used to analyze DNA extracts from OASF (n=5) and RASF (n=7) cell cultures. Bisulfite sequencing was used to confirm the MeDIP results. Transient transfections were done in OASF cell cultures with a TBX5 overexpression vector. RNA and cDNA were prepared and used to hybridize an Affymetrix human microarray. The microarray expression array was confirmed by quantitative SYBR PCR in OASF cultures (n=7). DAVID bioinformatics software was used to functional annotate the microarray data.

Results: The TBX5 gene was significantly more methylated in OASF than RASF, as shown by MeDIP assay (OASF 17±2.9 and RASF 5±3.5 fold enrichment, p<0.04, n=6). The MeDIP results were confirmed by bisulfite sequencing of the TBX5 promoter. TBX5 transcripts were significantly more expressed in RASF than OASF (RASF dCt: 16.0 ± 0.6; OASF dCt: 19±0.3, p<0.005, n=8). In addition, Western blot showed that the TBX5 protein was expressed in RASF, but not in OASF. Overexpression of TBX5 in OASF revealed 640 genes commonly up regulated from 1.2 to 3-fold. Analysis of these genes by DAVID bioinformatics tool identified that the chemokines IL8, CXCL2 and CCL20 were common targets of TBX5 in OASF. The expression of chemokines was significantly upregulated in seven different OASF cell cultures (IL8: 2 fold change ±0.9, CXCL2: 1.97 fold change±0.9, CCL20:2.07±0.8, p<0.05).

Conclusion: Promoter specific DNA hypomethylation and an open chromatin are responsible for the intrinsically up-regulated TBX5 expression in RASF. TBX5 may be a novel regulator of chemotaxis thereby associated with the ability of RASF to attract inflammatory cells to the synovium.

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Loss-of-Co-Homozygosity Mapping and Exome Sequencing of a Syrian Pedigree Identified the Candidate Causal Mutation Associated with Rheumatoid Arthritis. Yukinori Okada[1], Namrata Gupta[2], Daniel Mirel[3], Stacey Gabriel[3], Thurayya Arayssi[4], Faten Mouassess[5], Walid AL Achkar[5], Layla Kazkaz[6] and Robert M. Plenge[7]. [1]1.Brigham and Women's Hospital, Harvard Medical School, 2.Program in Medical and Population Genetics, Broad Institute, Boston, MA, [2]The Broad Institute, Cambridge, [3]The Broad Institute, Cambridge, MA, [4]Weill Cornell Medical College-Qatar, Doha, Qatar, [5]Molecular Biology and Biotechnology, Damascus, Syria, [6]Tishreen Hospital and the Syrian Association for Rheumatology, Damascus, Syria, Damascus, Syria, [7]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Although there are >50 rheumatoid arthritis (RA) risk loci that contain common variants, there are no known genomic loci that harbor rare mutations that influence RA risk in a Mendelian fashion. Here, we perform whole exome sequencing to search for rare, causal mutations in a 4-generation, 48-person consanguineous Syrian pedigree in which 8 individuals were affected with seropositive rheumatoid arthritis (RA).

Methods: We performed GWAS genotyping on 16 family members (affected and unaffected) and genome-wide exome sequencing in 4 CCP+ RA cases. To search for rare causal mutations, we developed a novel non-parametric linkage analysis we term "Loss-of-co-Homozygosity" (LOcH) mapping that extends homozygosity mapping to include any type of inheritance mode. The fundamental principal underlying LOcH is that a disease-causing mutation in a pedigree resides on a single ancestral haplotype, and that affected individuals will carry at least one copy of the mutation – but are never homozygous for the non-mutated allele. We used LOcH mapping to search the genome for regional stretches that lose one or both homozygous genotypes (i.e., lose "co-homozygosity") in affected cases, which serve as candidate regions harboring rare causal mutations. Within the detected LOcH stretches, we performed imputation of mutations identified by exome sequencing. We evaluated the presence of the LOcH stretches in other non-exome-sequenced subjects, and calculated a P-value for association with case-control status using Fisher's exact test.

Results: Using GWAS data and LOcH mapping, we identified 12% of the genome in which the same ancestral haplotype was shared among all RA cases. Within these regions, we identified 13 nonsense or missense mutations shared among all cases but not observed in dbSNP, the 1000 Genomes Project, or the Exome Sequencing Project. We imputed these 13 candidate mutations in all unaffected family members, and found that 1 mutation preferentially segregated in cases compared to controls: all 4 RA cases inherited this mutation, but only 3/12 controls were heterozygous for the mutation (P = 0.02). The mutated gene is *phospholipase B1* (*PLB1*), which has been implicated in human epidermal barrier function but not yet implicated in RA or other autoimmune diseases.

Conclusion: While additional investigation of this mutation is required to confirm the association with risk of RA, the approach highlights a novel method of statistical analysis of genome-wide sequence data.

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Rheumatoid Factor, Not Antibodies to Citrullinated Proteins, Are Associated with High Disease Activity. Josef S. Smolen[1], Farideh Alasti[2] and Daniel Aletaha[2]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria

Background/Purpose: Autoantibodies in general, and rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) in particular, are a hallmark of RA. After their characterization, ACPA have been regarded as more specific than RF in relation to diagnostic and prognostic utility. However, these data have not been unequivocally shared throughout the literature and most of them have come from observational studies, often from a single or few centers. While it has been known for long that RF+ patients have more active and severe disease than RF- ones, it is not clear if this effect is due to RF, ACPA or both in the light of the high (usually >80%) overlap of RF and ACPA positivity and the above controversy. Here we compared the extent of disease activity in RF+ and/or ACPA+ patients to understand the impact of these autoantibodies on disease activity of RA.

Methods: We were kindly provided a large database of patient level data from an international multicenter clinical trial comparing methotrexate (MTX) and rituximab plus MTX in patients with early (<4 years) arthritis who had to be MTX-naïve and fulfill a predefined level of active disease (≥8 swollen and tender joints) and be RF+ or have erosive disease at entry (IMAGE trial)[1]. Core set variables as well as levels of RF (by nephelometry) and ACPA (by ELISA) were available from the database. For the purpose of this analysis, we focused on baseline data and pooled the patients of all three treatment groups. The following groups were formed four groups according to the presence/absence of RF and ACPA. We compared disease activity variables and indices (disease activity score, DAS28; simplified and clinical disease activity index, SDAI and CDAI) across these groups using the Kruskal Wallis test for overall assessment, and the Wilcoxon test for subsequent pairwise comparisons if appropriate. A main focus of the latter was the comparison of the RF+/ACPA- and RF-/ACPA+ populations compared to each other.

Results: At baseline, disease activity was 6.9, 7.1, 7.1 and 6.6 by the DAS28 for RF-/ACPA- (n=64); RF+/ACPA+ (n=611); RF+/ACPA- (n=40); RF-/ACPA+ (n=29), respectively; and 47.8, 49.8, 53.1, 42.3 for the SDAI, significantly different among the four groups for both measures. The lowest values of disease activity measures were seen for the RF-/ACPA+ population, and significantly lower than in the RF+/ACPA- group (p=0.014 for DAS28, and p=0.004 for SDAI). Similar findings were made for CDAI, swollen and tender joint counts, while for ESR and CRP there was a numerical trend in this direction (not shown). Interestingly, patients positive for both RF and ACPA tended to have slightly lower disease activity than RF+/ACPA-, and higher than RF-/ACPA+ ones. Importantly, similar findings were made for the baseline values of each of the three trial arms when assessed individually (not shown).

Conclusion: The data presented suggest that RF may contribute more strongly to disease activity than ACPA and, therefore, may have more direct pathogenetic implications. Confirmation of these findings in other trial databases would shed more light on this insight.

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1. Tak,P.P. et al. Ann Rheum Dis **70**, 39–46 (2011)

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Antibodies to Citrulline From Rheumatoid Arthritis Patients Also Bind Homocitrulline. Mathias Scinocca, Radha Joseph, David A. Bell, Ewa Cairns and Lillian J. Barra. Schulich School of Medicine and Dentistry, Western University, London, ON

Background/Purpose: Antibodies to citrullinated proteins/peptides (ACPA) are specific for Rheumatoid Arthritis (RA). One of ACPA's targets is citrullinated fibrinogen (citfib) and it is found in inflamed synovium. Recently, it has been reported that antibodies to homocitrullinated proteins/ peptides (AHPA) also occur in RA. Citrulline and homocitrulline are structurally similar. Both can be generated during inflammation, but by different processes. ACPA from RA patients, including those targeting citfib, are arthritogenic. However, the role of AHPA in RA is not known. The purpose of this study was to determine whether: **1)** RA patients have antibodies to homocitrullinated fibrinogen (AHFA) and **2)** ACPA and AHPA are cross-reactive.

Methods: Serum was obtained from patients who met ACR criteria for RA, Psoriatic Arthritis or Systemic Lupus Erythematosus and were compared to healthy controls. It was tested against the following antigens: fibrinogen (fib), citfib, homocitrullinated fibrinogen (homocitfib), JED (a proprietary synthetic citrullinated peptide) and homocitrullinated JED (homoJED). Citrullination was done *in vitro* using peptidyl arginine deiminase enzyme (PAD2) [1]. Homocitrullination was done using potassium isocyanate. Both modifications were confirmed by mass spectrometry using ESI-MSMS and MASCOT server analysis. Shared Epitope (SE) binding was predicted by a computer algorithm [2]. ACPA was purified by affinity chromatography using JED. Antibodies to the above antigens and cyclic citrullinated peptide 2 (CCP2) were detected by ELISA. Inhibition assays using fib and homocitfib were conducted by ELISA.

Results: Mass spectrometry of modified fibrinogen revealed 55/79 (70%) of arginines were citrullinated and 89/103 (86%) of lysines were homocitrullinated. Approximately 25% of MHCII-binding peptides were both citrullinated and homocitrullinated. Five of these peptides were predicted to bind to the SE. The majority of RA patients were anti-CCP2 positive (89%) and 50% expressed AHFA. None of the normal controls and <5% of PsA and SLE were AHFA positive. All AHFA positive patients were also anti-CCP2 positive. Reactivity to homocitrullinated sites on fibrinogen was confirmed by inhibition assays. Affinity purified ACPA using a citrullinated peptide (JED) had reactivity to JED, anti-CCP2, as well as the homocitrullinated peptides, homoJED and homocitfib.

Conclusion: Antibodies to homocitrullinated peptides/proteins are specific for RA. These antibodies bind citrullinated and homocitrullinated antigens, suggesting cross-reactivity and possible pathogenicity.

[1] Mydel *et al.* 2010. J Immunol 184(12):6882.
[2] Hammer *et al.* 1994. J Exp Med 180(6): 2353.

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Sputa Autoantibodies in Patients with Established Rheumatoid Arthritis and Subjects At-Risk for Future Clinically Apparent Disease. Van C. Willis[1], M. Kristen Demoruelle[1], Lezlie A. Derber[1], Catherine J. Chartier-Logan[1], Mark Parish[1], Isabel Pedraza[2], Michael H. Weisman[3], Jill M. Norris[4], V. Michael Holers[1] and Kevin D. Deane[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Cedars Sinai Med Ctr, Los Angeles, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Colorado School of Public Health, Aurora, CO

Background/Purpose: Elevations of rheumatoid arthritis (RA)-related autoantibodies (Abs) prior to the symptomatic onset of inflammatory arthritis (IA) suggest that autoimmunity in RA is initiated outside of the joints. Furthermore, emerging data suggest a potential site may be the lung, supported by the association of inhaled factors such as smoking with RA, our published findings that inflammatory airways abnormalities can precede the onset of symptomatic IA in RA, and known mechanisms for generation of autoimmunity in the lung such as bronchus-associated lymphatic tissue (BALT) (Rangel-Moreno et al 2006). Prior work suggests that comparison of sputa and sera can be used to identify lung generation of autoantibodies (Schiotz et al 1979); therefore, to investigate the role of the lung as a site of initial generation of RA-related autoimmunity, we tested RA-related Abs from sera and sputa from subjects with established RA and subjects at-risk for future RA due to a family history of RA.

Methods: Simultaneous collection of sera and induced sputa (5% nebulized saline) was performed in 17 healthy controls, 29 first-degree relatives (FDR) of RA probands without IA by clinical examination, and 12 subjects with early seropositive RA (1987 criteria; <1 year from diagnosis). Samples were tested for CCP2 (IgG), CCP3.1 (IgG/IgA), and IgM, IgG and IgA rheumatoid factors (RFs) using commercial ELISAs. In sera, CCP positivity was set from kit standards, and RF positivity was determined as a level elevated in <5% of 491 blood donors. Sputa positivity for each Ab was determined using the control mean plus 2 standard deviations. Chi-squared testing was used to compare groups, and matched-pair analyses were used to compare the frequency of Ab positivity in sputa and sera.

Results: There were no significant differences in age, sex, smoking status or history of lung disease between Early RA and FDR subjects. All of the Early RA and 8/29 (28%) of FDR subjects were positive in their sera for at least 1 Ab. Overall, a greater proportion of Early RA subjects were positive for each Ab in their sera vs. sputa. However, 8 of the 21 seronegative FDRs were positive in their sputa for at least 1 Ab. Specifically, the assays that detected IgA were elevated in significantly more FDR subjects' sputa than sera: CCP3.1 31% positive in sputa vs. 7% positive in sera, p=0.03; RF-IgA 14% vs. 0%, p=0.03).

Conclusion: Sputa elevations of RA-related Abs in seronegative FDRs without IA suggest that in some cases RA-related autoimmunity may be initially generated in the lung. Because sputum largely reflects airway responses, these findings also suggest that RA-related autoimmunity may be initially limited to the airways, and IgA predominant. However, the higher number of patients with RA with sera vs. sputa Ab positivity also suggests that after the symptomatic onset of RA the generation of Abs occurs at other sites, leading to autoantibodies in the circulation instead of sputa. These findings show the utility of sputa testing to assess RA-related autoimmunity in the lung, as well as demonstrate a need for prospective studies of subjects at-risk for future RA to determine the role of immunologic responses in the lung in the earliest phases of RA development.

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Influence of Pregnancy On Disease Activity-Associated Genes in Rheumatoid Arthritis. Erik J. Peterson[1], Shreyasee Amin[2], Hatice Bilgic[1], Emily Baechler Gillespie[1], Jane E. Salmon[3], Ann M. Reed[2], Weihua Guan[4] and Daniel L. Mueller[1]. [1]University of Minnesota Medical School, Minneapolis, MN, [2]Mayo Clinic, Rochester, MN, [3]Hospital for Special Surgery, New York, NY, [4]University of Minnesota School of Public Health, Minneapolis, MN

Background/Purpose: Rheumatoid arthritis (RA) disease activity can often quiesce during pregnancy. Nevertheless, most women will experience a disease flare postpartum (PP). We hypothesized that changes in blood immune cell gene expression patterns during healthy pregnancy, which promote fetal tolerance in order to protect against fetal loss, will also be relevant in regulating RA disease activity.

Methods: Whole-blood gene expression profiles (15,050 expressed; p<0.05) from 19 pregnant RA subjects and 13 pregnant age-matched healthy controls (CON) were assayed at first trimester of pregnancy (T1), T2, T3, and PP using Illumina HumanHT-12 v3 and v4 BeadChip arrays. At identical time points, disease activity in RA women was assessed using the DAS28-CRP. A Generalized Estimating Equations (GEE) approach was applied to model gene expression changes during pregnancy (T1-T3) and between pregnancy and PP, to take into account the correlation within samples. A version effect (v3 vs v4) was also included in the model.

Results: Within the CON samples, 581 blood cell genes demonstrated either a >20% change in mRNA expression between T1—>T2 or T2—>T3 of pregnancy, or a >20% change in expression between the average of T1—T3 and the PP period (BH q<0.05). Many of these genes mapped to Ingenuity Pathways associated with (p<0.01) hematopoietic system development and function (n=149 molecules), cell death (n=185), and immunological diseases (n=127). These 581 "pregnancy-related" genes were then selected for further study in the pregnant RA cohort. Of the 581 genes, 74 were found to be significantly associated with the DAS28-CRP score after correcting for multiple hypothesis tests (Bonferroni correction, $p<8.6\times10^{-5}$), with 11 of these demonstrating a >20% change in mRNA expression for every 1 unit change in DAS28-CRP score either during pregnancy or in the PP period. For the 50 pregnancy-related genes whose expression fell PP in association with rising DAS28-CRP, 7 genes (*CD247, CD5, CD6, FLT3LG, IL7R, RBM38, and TUBB*) were functionally associated with autoimmune diseases by Ingenuity Pathways Analysis; likewise, of the 24 genes whose expression directly correlated with DAS28-CRP PP, 5 genes (*IL1B, MYD88, NCF4, PFKFB3, and SLC22A4*) were associated with autoimmune diseases (p=0.0015).

Conclusion: Our experiments identify 74 RA disease activity-correlated blood cell genes whose expression is modulated during normal pregnancy. Insofar as these genes reflect alterations in immune cell reactivity normally associated with pregnancy and promotion of fetal tolerance, they may represent a window into processes and pathways with a capacity to regulate disease activity in RA patients. Pregnancy-modulated genes that fluctuate with RA disease activity may also have utility as disease activity biomarkers.

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Slug **Is Induced by Benzo(a)Pyrene and EGF Through PI3K/Akt/mTOR Pathway and Is Closely Involved in the Regulation of the Invasive Properties of FLS in Rheumatoid Arthritis.** Jaejoon Lee[1], Jiwon Hwang[2], Chan Hong Jeon[3], Joong Kyong Ahn[4], Hoon-Suk Cha[1] and Eun-Mi Koh[5]. [1]Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea, [4]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Seoul, South Korea

Background/Purpose: Slug, a Snail family of zinc finger transcription factor, plays a critical role in tumor proliferation, invasion and metastasis. We have previously shown that Slug is overexpressed in RA synovial tissue and suppression of Slug facilitates apoptosis of RA FLS. However, the precise mechanism through which Slug is induced in RA FLS remains unclear. Smoking is an important environmental risk factor for RA and influences RA disease susceptibility and severity. Benzo(a)pyrene (BaP) is a polycyclic aromatic hydrocarbon found in cigarette smoke. BaP can be metabolized to active compounds that induce the production of reactive oxygen species. The effect of Bap on Slug expression in RA FLS has not been studied thus far.

The present study was undertaken to investigate the biological effects of BaP on the expression of Slug, signaling pathway through which Slug is expressed, and the effect of BaP/Slug on the invasive properties of RA FLS.

Methods: Expression of Slug was measured by real-time PCR following stimulation of FLS with different concentrations of BaP, EGF, H_2O_2, TGF-β, and TNF-α (n=7, each). Phosphorylation of the key enzymes in the signal transduction pathway was analyzed by Western blot. Inhibitors targeting the PI3K/Akt/mTOR pathway were used to confirm critical signaling pathway for Slug expression (n=7). An in vitro cell invasion assay was performed using RA FLS treated with Slug siRNA or with control siRNA (n=4).

Results: Slug expression was significantly increased following treatment with BaP (4μM, p=0.0014), EGF (100ng/ml, p=0.027) and H_2O_2(0.25mM, p=0.029), but not with TGF-β and TNF-α. Stimulation with BaP and EGF induced phosphorylation of Akt kinase activity, but no significant change was observed in ERK, JNK and p38 activity. Slug mRNA expression by BaP and EGF decreased significantly following treatment with PI3K/Akt/mTOR inhibitors (p=0.026, p=0.002, respectively). Slug siRNA treatment induced a significant reduction in the invasive function of FLS compared to those treated with control siRNA (p=0.029). In addition, stimulation with BaP increased invasive function of control siRNA-treated FLS (p=0.01), but no such change was observed in Slug siRNA-treated FLS.

Conclusion: Our data show that BaP, one of major toxic components in cigarette smoke, induce Slug expression in RA FLS through PI3K/Akt/mTOR pathway, and may regulate invasive properties of RA FLS. This mechanism may provide a novel explanation for the increased RA susceptibility and severe clinical phenotype in those who smoke.

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Dickkopf-1 Stimulates Fibroblast-Like Synoviocyte Migration Through Janus Kinase Activation. Yubin Luo[1], Bryan Dieffenbach[2], Jung-Soo Song[3], Jinseok Kim[4], David L. Boyle[1], Michael Karin[1], Gary S. Firestein[1] and Maripat Corr[5]. [1]UCSD School of Medicine, La Jolla, CA, [2]UCSD School of Medicine, la Jolla, CA, [3]Chung-Ang University College of Medicine, Seoul, South Korea, [4]Jeju National University, Jeju, Korea, South Korea, [5]Univ of California-San Diego, La Jolla, CA

Background/Purpose: Wnt (wingless) pathway signaling has been implicated in patterning in embryogenesis and in adult wound healing and homeostasis. A canonical Wnt antagonist, Dickkopf-1 (DKK-1), has been described as an embryonic bone morphogen. DKK-1 expression is stimulated by TNF in inflammatory disease and is elevated in the sera of rheumatoid arthritis patients. This Wnt signaling antagonist has been linked to the depression osteoblast activity and bone loss. Here we examined a novel role for the pathogenic activity of this protein by virtue of its ability to activate JNK and increase migration of fibroblast-like synoviocytes (FLS).

Methods: Human and mouse FLS were cultured and the plates were scratched. Migration was measured by serial photography of a marked area and Image J quantification. **Results** were confirmed with an Oris™ stopper assay, and cell entry into the central clearing was measured by calcein AM fluorescence. FLS were treated with rDKK-1, rWnt5a, PDGF, SB216763 (a GSK3β inhibitor), SP600125 (a JNK inhibitor), and IWP-2 (a porcupine inhibitor). In some cases, FLS were lysed for Western blot and qPCR analyses.

Results: Human and mouse FLS exhibited faster migration in the scratch wound assay and the stopper assay when stimulated with DKK-1 (50, 100 or 150ng/ml). DKK-1 increased percent wound closure from 31+4to 46+5 (p<0.04) for human and 41+4 to 58+18 (p<0.04) for mouse FLS. DKK-1-induced migration was inhibited by the JNK inhibitor SP600125. On the other hand, SB216763 and IWP-2 had minimal or no effect, indicating that it is independent of endogenously produced Wnt. DKK-1 stimulated JNK phosphorylation in FLS within 10 minutes, which was also not abrogated by IWP-2. To determine which JNK isoform is responsible, JNK1 null and JNK2 null mouse FLS were studied in the migration assays. Unexpectedly, DKK-1 treatment still induced the migration of JNK1 deficient, but not JNK2 deficient cells. In association with increased migration, DKK-1 treated FLS increased expression of MMP-1 (1.4 fold), MMP2 (1.4 fold) and MMP13 (1.6 fold). In contrast, MMP9 and MMP3 expression was decreased.

Conclusion: DKK-1 stimulates migration of FLS, which is associated with JNK phosphorylation and increased expression of selected metalloproteinases. DKK-1-induced migration was mediated by JNK2 signaling, suggesting that this pathway plays a critical role in synoviocyte migration and cartilage damage in rheumatoid arthritis

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Epigenetic Features As Predictive Markers of Responsiveness to Epitope-Specific Therapy in Rheumatoid Arthritis. Roberto Spreafico, Maura Rossetti, Theodorus Van Der Broek, Olivia Morrow and Salvatore Albani. Sanford-Burnham Medical Research Institute, La Jolla, CA

Background/Purpose: The focus of current research for new therapeutic approaches in Rheumatoid arthritis (RA) is shifting from mere suppression to induction and maintenance of tolerance. Adaptive immunity, specifically the balance and functions of effector and regulatory CD4^{+} T cells, is central in this context. We have recently developed a protocol of oral tolerance induction to an epitope (dnaJP1) derived from a heat shock protein (HSP), a key component of the mechanism of perpetuation and amplification of chronic autoimmune inflammation. Phase II trial results showed clinical efficacy and an intriguing immune deviation of T cell immunity. In order to

dissect further the mechanism of action and also to identify biomarkers predictive of susceptibility to treatment, we employed here whole genome DNA methylation analysis, which can be correlated to gene expression and is relatively more stable compared to mRNA, the basis of the well-known whole transcriptome analysis.

Methods: Total CD4^{+} T cells from 12 patients taken at baseline, equally segregated in placebo responders/non-responders (R/NR) and HSP peptide R/NR, were sorted from PBMCs. DNA was extracted and bisulfite converted to analyze the cytosine methylation pattern. Converted DNA was analyzed using Illumina Infinium HumanMethylation450 BeadChip, yielding the methylation percentage of more than 485,000 CpG sites across the genome.

Results: A nearly perfect segregation of R and NR was observed when Principal Component Analysis (PCA) was applied to the whole dataset. When sites selected for discriminating R from NR (based on p-value and fold change) were used, PCA was also able to discriminate, based on average DAS-28 scores, weak responders from strong responders. Weak responders were more frequent among placebo treated subjects, while HSP peptide-treated subjects comprised stronger responders. In order to enrich for sites discriminating R and NR with high confidence without losing power due to the high number of CpG sites, pre-filtering of sites with low variance was performed. With this method, we found 51 sites differentially methylated between R and NR, clearly supporting the potential of the whole genome methylation analysis for discovery of new candidate biomarkers. As a control, mock comparisons, such as between all placebo against all HSP peptide-treated subjects irrespective of clinical outcome (which is not meaningful at baseline due to patient randomization) were run and consistently yielded fewer hits.

Conclusion: We found significant differences in the general pattern of DNA methylation between RA patients responding or not responding to an epitope-specific therapy. We have also identified a set of CpG sites with high predictive and prognostic power for discriminating the responsiveness to treatment, which may be developed as a screening tool. The functions of the genes found to be differentially methylated is currently under investigation.

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TNFα Modulates the Expression of Circadian Clock Gene, *Per2*, Via D-Box Motif in the Promoter Region in Rheumatoid Synovial Cells. Kohsuke Yoshida[1], Akira Hashiramoto[2], Takaichi Okano[3], Nao Shibanuma[4] and Shunichi Shiozawa[5]. [1]Hyogo Prefectural Rehabilitation Center at Nishi-harima, Tatsuno, Japan, [2]Department of Internal Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [3]Kobe University Hospital, Kobe, Japan, [4]The Center for Rheumatic Diseases, Kobe University Hospital/Departmant of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan, [5]Kyushu University Beppu Hospital, Beppu, Japan

Background/Purpose: The mammalian clock genes including *Clock* (circadian locomotor output cycles kaput), *Bmal1* (brain and muscle Arnt-like protein 1), *Per* (Period) and *Cry* (Cryptochrome) regulate the circadian rhythm. We previously showed that arthritis was significantly accelerated in $Cry1^{-/-}Cry2^{-/-}$ mice due to the activation of TNFα (tumor necrosis factor α) transcription, and TNFα inhibited the expression of *Per2* mRNA in primary cultured human rheumatoid synovial cells. Here, we tried to elucidate the effects of TNFα on the transcription of *Per2* gene in rheumatoid synovial cells.

Methods: Primary cultured rheumatoid synovial cells were synchronized upon incubation with 50% horse serum for 2 hours, and then stimulated with 10 ng/ml TNFα. Total RNA was extracted from synovial cells every 8 hrs until 32 hrs' culture period, and mRNA expression of D-box binding protein genes, including *Dbp* (D site of albumin promoter binding protein), *Hlf* (hepatic leukemia factor), *Tef* (thyrotroph embryonic factor) and *E4BP4* (E4-binding protein 4), were analyzed by real-time PCR. Synovial cells were transfected with the luciferase reporter vector containing the human *Per2* promoter to measure the transcriptional activity of *Per2* gene.

Results: The expression of *Dbp*, *Hlf*, and *Tef* mRNA were significantly inhibited ($P < 0.01$), while those of *E4bp4* mRNA was significantly increased ($P < 0.01$) upon incubation with TNFα in rheumatoid synovial cells. Since *Dbp*, *Hlf*, *Tef* and *E4bp4* genes could transactivate and suppress the expression of *Per2* gene, respectively, by binding to D-box motif in the promoter region, we next introduced site-directed mutations into the D-box 1 (TTATGTAA, −372 to −365) and/or D-box 2 (TTACGTAA, −47 to −40) motif in the promoter, and then transfected rheumatoid synovial cells with luciferase

reporter gene constructs driven by the *Per2* promoter. As results, TNFα inhibited the transcriptional activity of the wild type of *Per2* gene. However, when the promoter containing a mutated both D-box 1 and D-box 2 motif was transfected, TNFα-mediated transcriptional inhibition did not observed as compared with the wild type and the D-box 1 mutated promoter ($P < 0.05$ and $P < 0.05$, respectively).

Conclusion: TNFα significantly modulates the expression of *Per2* gene via D-box binding protein, DBP, HLF, TEF and E4BP4, in rheumatoid synovial cells, and thereby may contribute to the pathogenesis of RA.

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The Significance of the Apoptosis Level and the Apoptosis Related Signal Proteins of CD4^{+}t ACD4^{+}Foxp3^{+}t Cell in Patients with Rheumatoid Arthritis. Ning Li[1], Tianrui Ma[2], Jie Han[1], Jieru Zhou[1] and Songguo Zheng[3]. [1]Shanghai East Hospital, Shanghai, China, [2]Ningbo Pediatric Hospital, Ningbo, China, [3]Keck School of Medicine of the University of Southern California, Los Angeles, CA

Background/Purpose: To investigate the apoptosis of CD4^{+}T cell and Tregs in the pathogenesis and disease activity of rheumatoid arthritis patients.

Methods: Isolated lymphocytes from human peripheral blood, the expressive levels of Annexin V, Caspase-3/8, Fas and Bcl-2 of CD4^{+}T lymphocytes and Tregs in RA patients and controls were analysed by using flow cytometry. The correlation between the apoptosis level, the apoptosis signaling proteins expression of CD4^{+}T, Tregs and clinical activity parameters were analysed. The effects of IL-10 and anti-IL-10 were also observed.

Results:

1. Compared with the controls, the level of CD4^{+}T cells was higher in RA patients, while their apoptosis was lower ($p < 0.05$); the frequency of Tregs was lower in RA patients, while their apoptosis was higher ($p < 0.05$).

2. Compared with the controls, the expression of Fas ($p < 0.01$) and Caspase-8 ($p < 0.05$) by CD4^{+}T cells decreased in RA patients, the expression of Bcl-2 by CD4^{+} T cells ($p < 0.05$) increased; the expression of Fas ($p < 0.01$), Caspase-8 ($p < 0.05$) and Caspase-3 ($p < 0.05$) by Tregs elevated in RA patients.

3. The expression of AnnexinV and Fas by CD4^{+}T cells in RA patients were negatively correlated with DAS28 ($r = -0.84$, $p < 0.01$ and $r = -0.89$, $p < 0.05$, respectively), the expression of Bcl-2 by CD4^{+}T cells was positively correlated with DAS28 ($r = 0.91, p < 0.01$). There was positive correlation between the expression of Annexin V and Caspase-3 by Tregs and DAS28 in RA patients ($r = 0.82, p < 0.01$ and $r = 0.79, p < 0.05$, respectively).

4. After IL-10 treatment, the apoptosis of CD4^{+} T cells increased ($p < 0.05$), and that of Tregs decreased ($p < 0.05$); the apoptosis of CD4^{+} T cells in anti-IL-10 group decreased ($p < 0.05$), and that of Tregs increased ($p < 0.05$); the expression of Caspase-8 by CD4^{+} T cells in IL-10 group increased ($p < 0.05$), the expression of Bcl-2 by CD4^{+} T cells in IL-10 group decreased ($p < 0.05$); the expression of Caspase-8 by CD4^{+} T cells in anti-IL-10 group was lower than that of the blank group ($p < 0.05$), the expression of Bcl-2 by CD4^{+}T cells in anti-IL-10 group was higher ($p < 0.05$); the expression of Caspase-8/3 by Tregs in IL-10 group decreased ($p < 0.01$), while the expression of Caspase-8/3 by Tregs in anti-IL-10 group was significantly elevated than that of the blank group ($p < 0.01$).

Conclusion:

1. The higher level of CD4^{+} T cells and the lower frequency of Tregs may be caused by the decreased apoptosis of CD4^{+} T cells and the increased apoptosis of Tregs, which may be the reason of the abnormal autoimmune response in RA.

2. Fas, Caspase-8 and Bcl-2 may play a role in the the apoptosis of CD4^{+}T cells. The apoptosis of Tregs may be related to the higher expression of Fas, Caspase-8/3.

3. The expression of AnneinV, Fas and Bcl-2 by CD4^{+}T cells and the expression of AnnexinV and Caspase-3 by Tregs in RA patients might be sensitive indicators of the clinical activity of RA.

4. IL-10 has different immunoregulatory functions in different cells. It can downregulate the expression of Bcl-2, stimulate the expression of Caspase-8 in CD4^{+} T cells and inhibit the expression of Caspase-8/3 in Tregs of RA patients.

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Comprehensive Microrna Analysis Identifies Mir-24, Mir-26a, and Mir-125a-5p As Plasma Biomarkers for Rheumatoid Arthritis. Koichi Murata, Moritoshi Furu, Hiroyuki Yoshitomi, Masahiro Ishikawa, Hideyuki Shibuya, Hiromu Ito and Shuichi Matsuda. Kyoto University Graduate School of Medicine, Kyoto, Japan

Background/Purpose: MicroRNAs (miRNAs) are present in human plasma in a stable form despite the endogenous RNase activity. Plasma miRNAs are non-invasive biomarker for cancer detection and tissue injuries. We previously showed the potential ability of the plasma miRNAs as biomarkers for rheumatoid arthritis (RA) and designed this study to identify plasma miRNAs specific for RA by a comprehensive array approach.

Methods: We performed a systematic array-based miRNA expression analysis on plasma samples from patients with RA and healthy controls (HCs) (n=3, respectively). The expression of plasma miRNAs in the first comprehensive analysis with more than four times change or with significant (p<0.05) change between RA and HCs, or that of detectable plasma miRNAs only in RA plasma, were followed by confirmation analysis of eight patients with RA and eight HCs using real-time quantitative PCR (qPCR). Plasma miRNAs consistently detectable in our system and significantly different between RA and HC were chosen for further validation with 102 RA patients and 104 HCs. Receiver operation curves were generated, and correlations between miRNAs and other biomarkers of RA were statistically examined.

Results: The array analysis and the subsequent confirmation by qPCR in larger patient cohort identified eight RA-associated circulating miRNAs, including miR-24, miR-26a and miR-125a-5p (Table 1). The area under curve (AUCs) of each miRNA was 0.80, 0.81 and 0.83 respectively (Figure 1A). Logistic regression analysis provided a formula for estimated probability for RA by plasma miR-24, miR-30a-5p, miR-125-5p (ePRAM) with increased the diagnostic accuracy (AUC: 0.86, Figure 1B). The diagnostic ratio was not influenced by the antibody values against anti-citrullinated peptide. These miRNAs levels in OA patients were as low as in HC and these miRNA levels in RA patients showed no significant changes with the administration of biologics.

Figure 1.

Conclusion: Plasma levels of miR-24, miR-26a, miR-125a-5p, and ePRAM can be diagnostic biomarker for rheumatoid arthritis.

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miRNA	(nM)	P value	AUC
miR-24			0.80
RA	3.4 ± 3.2		
HC	0.91 ± 0.79	5.0×10^{-13}	
miR-26a			0.81
RA	3.5 ± 4.0		
HC	1.0 ± 3.7	7.3×10^{-6}	
miR-28-5p			0.59
RA	$4.9 \times 10^{-2} \pm 9.7 \times 10^{-2}$		
HC	$1.8 \times 10^{-2} \pm 2.6 \times 10^{-2}$	1.6×10^{-3}	
miR-28-3p			0.75
RA	8.9 ± 8.6		
HC	3.8 ± 4.6	5.6×10^{-7}	
miR-30a-5p			
RA	3.0 ± 3.4		
HC	3.4 ± 15	0.8	
miR-30c			0.71
RA	1.3 ± 1.4		
HC	0.54 ± 0.49	1.7×10^{-7}	
miR-30e-3p			
RA	15 ± 18		
HC	18 ± 12	0.76	
miR-125a-5p			0.83
RA	0.23 ± 0.30		
HC	0.10 ± 0.60	4.8×10^{-2}	
miR-126-3p			0.74
RA	8.1 ± 12		
HC	2.0 ± 2.7	7.2×10^{-7}	
miR-502-5p			0.70
RA	0.71 ± 0.13		
HC	0.24 ± 0.41	4.7×10^{-4}	

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Basic and Clinical Significance of Interleukin 6 (IL-6) in AA Amyloidosis with RA. Kazuyuki Yoshizaki, Prabha Tiwari, Lokesh P. Tripathi, Shandar Ahmad, Kenji Mizuguchi, Teppei Nishikawa-Matsumura, Tomoyasu Isobe and Soken-Nakazawa J. Song. Osaka University, Osaka, Japan

Background/Purpose: Cytokine-induced hepatic serum amyloid A (SAA) is associated with the pathogenesis of AA amylodosis, a fatal disease with deposition of AA amyloid fibril on systemic organs, especially on kidney, thyroid and intestine in chronic inflammatory disease such as rheumatoid arthritis (RA). This study was to provide our recent results on SAA activation by IL-6-induced STAT3 and clinical analysis of IL-6 blocking therapy in AA amyloidosis complicating RA.

Methods: STAT3 contributing to transcriptional activation of SAA by forming a complex with NF-kB was analyzed by using the super shift assay, ChIP assay, and DNA affinity choromatography systems. A set of candidates for non-consensus STAT3 binding sites on SAA promoter was identified by using a new mathematics calculation theory. The binding of STAT3 to the non-consensus STAT3 binding sites was also confirmed by means of Luciferas assay and DNA affinity choromatography assay.

Results: We demonstrated that IL-6 activated STAT3 is essential for inducing SAA mRNA expression, and that NF-kB p65 complementally augments SAA mRNA induction by IL-6 stimulation combined with IL-1or TNF-α.We found a non-consensus STAT3 response element (RE) at the 3'-down stream of NF-kB site on SAA promoter region for STAT3 binding. Anti-IL-6 receptor antibody can completely inhibit SAA expression and stat3-NF-kB complex formation induced by IL-6+IL-1+TNF-α.

Conclusion: We identified a non-consensus STAT3 binding site in SAA promoter based on a new statistical analysis method of protein-DNA complex structures, and confirmed that STAT3 binds to the predicted site followed for SAA expression induced by IL-6+IL-1. Our basic results may explain why IL-6 blockade completely inhibit the SAA production in AA amyloidosis patients with RA, and IL-6 is a pivotal cytokine for induction of SAA. Our results also indicated that STAT3 may activate more broad genes during inflammation through non-consensus RE, and IL-6 inhibition may inactivate more broad inflammatory genes.

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Identification and Characterization of Fibrinogen-Specific T Cells in Patients with Rheumatoid Arthritis. Laura Su and Mark M. Davis. Stanford University School of Medicine, Stanford, CA

Background/Purpose: Rheumatoid arthritis (RA) is a common, highly debilitating systemic inflammatory condition. To date, little is known about which autoantigens are involved in RA and how T cells which recognize self-proteins may become pathogenic in disease. Fibrinogen is a common target of autoantibodies in RA patients, and a putative T cell autoantigen involved in disease development. The goal of this study is to identify and characterize fibrinogen-specific CD4$^+$T cells.

Methods: Autoantigen-specific T cells were identified directly *ex vivo*using peptide-MHC tetramers. To identify individuals carrying the HLA-DRB1*0401 (DR4) allele, HLA typing was performed on healthy blood donors and RA patients using sequence-specific primer PCR. To identify antigen-specific T cells, tetramer staining was performed at room temperature for 1 hour using tetramers loaded with several fibrinogen peptides. Memory phenotyping was performed using antibodies against CD45RO and CCR7. Tetramer tagged cells were magnetically enriched and analyzed by flow cytometry. Single cell TCR amplification and sequencing was performed to trace T cell clonality.

Results: We identified several populations of T cells recognizing citrullinated and uncitrullinated fibrinogen peptides. The frequency of fibrinogen-specific T cells in RA patients ranges between 3 to 19 per million CD4$^+$T cells. Many of these lymphocytes express the memory marker CD45RO, particularly among cells that recognize citrullinated forms of the fibrinogen peptides. Examination of the same antigen-specificities in healthy people demonstrated that the frequency and memory characteristics of these cells appear similar in individuals without disease. Moreover, we also found in some healthy people the presence of clonally expanded T cells that recognize citrullinated fibrinogen.

Conclusion: T cells that recognize citrullinated fibrinogen can be detected in the peripheral blood of RA patients and healthy individuals. These fibrinogen-specific populations contain large numbers of antigen-experienced T cells with some showing evidence of clonal expansion.

Disclosure: L. Su, None; **M. M. Davis**, None.

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Genome Wide Association Analysis of Pain Reduction in Rheumatoid Arthritis Patients Treated with Anti-TNF Medication. Results of the DREAM and Danbio Registries. Marieke J.H. Coenen[1], Masha Umicevic-Mirkov[1], Hans Scheffer[1], Sophine B. Krintel[2], Sita H. Vermeulen[1], Julia S. Johansen[2], Wietske Kievit[1], Mart A.F.J. van de Laar[3], Piet L.C.M. van Riel[1], Barbara Franke[1] and Merete L. Hetland[4]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [3]Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [4]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark

Background/Purpose: Patients with rheumatoid arthritis (RA) rate pain relief as the highest priority in treatment outcome, and tumor necrosis factor inhibitors (anti-TNF) have proven very successful in pain reduction. Interestingly, recent research indicates that inflammation and pain pathways are important, but partly independent, targets of anti-TNF. Therefore the identification of genetic factors predicting pain relief is important in efforts to personalize treatment.

Objective: We aimed to identify and replicate genetic factors predicting pain reduction upon anti-TNF treatment in patients with RA using a genome-wide association approach.

Methods: We included 508 RA patients treated with anti-TNF agents from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Single nucleotide polymorphism (SNP) markers were genotyped using the Illumina HumanHap550-Duo or Human660W-Quad BeadChip. Association analysis using the change of Visual analogue scale of pain (VASpain) after 14 weeks of treatment initiation as outcome was performed on an imputed dataset under an additive genetic model with adjustment for baseline VASpain. SNPs demonstrating association with VASpain change with a p-value$<10^{-5}$were selected for replication in 207 RA patients treated with anti-TNF from the Danish DANBIO registry. We performed a meta-analysis using METAL. Pathway analysis was performed in Ingenuity.

Results: 2,557,253 SNPs and 406 patients passed quality control. No findings reached the threshold for genome-wide significance (p-

value $\leq 1 \times 10-8$) in the Dutch discovery cohort. 46 SNPs showed p-values$<10-5$, five of these (rs7921473, rs2237199, rs2237204, rs1424441, rs2615233) reached nominal significance (p<0.05) in the Danish DANBIO registry. Meta-analysis led to the identification of three SNPs with a p-value $<1 \times 10^{-7}$. These SNPs can be linked to functions that might involve pain processing in the brain. They are located within or nearby *ATXN1* (rs2237204, rs2237199), a gene involved in the pathology of spinocerebellar ataxia type 1, a neurodegenerative disorder characterized by progressive degeneration of cerebellum and *NRG3* (rs7921473) which influences neuroblast proliferation, migration and differentiation. Pathway analysis, including all SNPs with a p-value$<10^{-3}$ (n=2649) from the discovery cohort also point to the brain. The analysis shows that genes involved in neuritogenesis are overrepresented in our dataset (p=6.78×10^6). In addition, six SNPs map to the α-adrenergic signaling pathway (p=6.16×10^{-4}), an important target for pain medication.

Conclusion: Significant findings will be replicated in a third patient population. Confirmed biomarkers can be used to personalize medication for the individual patient.

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IL–22 Mediated Pannus Formation in Autoimmune Arthritis Is PI3K/Akt/mTOR Dependent. Siba P. Raychaudhuri[1], Anupam Mitra[1], Ananya Datta Mitra[2], Christine Abria[2] and Smriti K. Raychaudhuri[2]. [1]VA Sacramento Medical Center\UC Davis School of Medicine, Mather, CA, [2]VA Sacramento Medical Center, Mather, CA

Background/Purpose: IL-22, a Th17 cytokine plays a key role in the formation of "pannus" in autoimmune arthritis such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA), by inducing proliferation of synovial fibroblasts (FLS) [1, 2]. Among diverse functions of PI3K/Akt/mTOR signaling cascade, cell proliferation is an important one and is emerging as a potential therapeutic target for various malignant diseases. Here we are reporting that IL-22 induced FLS proliferation is PI3K/Akt/mTOR dependent.

Methods: FLS were derived from synovial tissues of PsA (n=5) and RA (n=5) patients. MTT assay in presence or absence of dual kinase (PI3K/mTOR) inhibitor, NVP-BEZ235 (BEZ) and mTOR inhibitor, Rapamycin were performed to determine the role of PI3K/Akt/mTOR in IL-22 induced FLS proliferation. Further we substantiate our findings by determining the expression of Akt/mTOR in presence or absence of IL-22, BEZ and Rapamycin with western blotting.

Results: IL-22 significantly increased proliferation of FLS (OD: 1.70 $\pm$ 0.09 vs. 0.86$\pm$0.04, p<0.0001, ANOVA) (Figure 1) derived from patients of autoimmune arthritis. Both Rapamycin and BEZ significantly inhibited IL-22 induced FLS proliferation. BEZ showed more inhibitory effect than rapamycin. In western blot, we observed that IL-22 significantly induced phosphorylation of Akt and mTOR in FLS (Figure 2). IL-22 induced phosphorylation of Akt and mTOR in FLS was significantly reduced by BEZ and Rapamycin respectively. This indicates that IL-22 induces FLS proliferation through the PI3K/Akt/mTOR pathway.
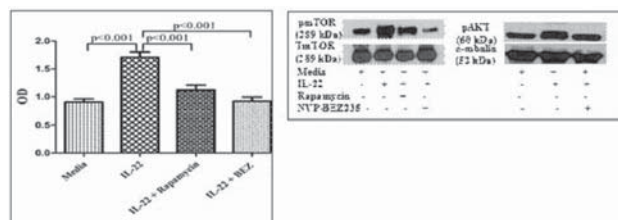
Conclusion: This is the first study showing the regulatory role of PI3K/Akt/mTOR signaling cascade in the IL-22 mediated FLS proliferation in autoimmune arthritis and thus provides a new insight in the signaling cascade of IL-22 in autoimmune arthritis.

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CIP2A Facilitates Apoptotic Resistance of Fibroblast-Like Synoviocytes in Rheumatoid Arthritis Independent of c-Myc Expression. Jaejoon Lee[1], Jiwon Hwang[2], Jinseok Kim[3], Joong Kyong Ahn[4], Hoon-Suk Cha[1] and Eun-Mi Koh[5]. [1]Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Jeju National University Hospital, Jeju, South Korea, [4]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Seoul, South Korea

Background/Purpose: Cancerous inhibitor of protein phosphatase 2A (CIP2A) is a recently identified oncoprotein that leads to cellular proliferation in cancer cells by stabilizing c-Myc protein. The effect of CIP2A in stabilizing c-Myc by inhibition of protein phosphatase 2A activity is a prerequisite step in tumor cell growth and in vivo tumor formation. We have previously shown that CIP2A is expressed in rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS), and that its expression is strongly associated with histopathological synovitis score and invasive function of RA FLS. The aim of this study is to investigate the effects of CIP2A on the apoptosis of RA FLS and to determine the signaling pathway through which dysfunctional apoptosis is facilitated.

Methods: Proliferation and apoptotic activity of RA FLS following treatment with CIP2A siRNA or control siRNA were analyzed using MTT assays and Cell Death Detection ELISA kit. RA FLS was treated with CIP2A siRNA or control siRNA in 3, 6, and 9 day intervals for a Western blot analysis to determine C-Myc expression. To evaluate the signal transduction pathways engaged in apoptosis, caspase-3 activity, caspase-9 activity, PARP, and phosphorylation of the Akt kinase were analyzed by Western blot analysis.

Results: Cell viability of RA FLS, as measured by MTT assay, was significantly lower in the CIP2A siRNA-treated group compared with the control after 7 days (p=0.022). Apoptosis of RA FLS, as measured by DNA fragmentation, was significantly higher in the CIP2A siRNA-treated group compared with the control when incubated for 3, 6 and 9 days (p= 0.029, p=0.021, p=0.043, respectively). Interestingly, c-Myc expression, as determined by Western blot analysis, did not change with the different incubation periods. CIP2A siRNA-treated FLS expressed higher level of activated caspase-3, caspase-9, and PARP (p=0.014, p=0.020, p=0.021, respectively) and lower level of phosphorylated Akt (p=0.001) compared with those treated with the control siRNA.

Conclusion: Our data show that CIP2A expression in RA FLS is an important mediator of dysfunctional apoptosis independent of c-Myc stabilization. Expression of CIP2A may contribute to apoptotic resistance of RA FLS through activation of Akt and deactivation of caspase-3, caspase-9, and PARP. Inhibition of CIP2A may therefore constitute a novel, promising therapeutic target in RA.

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Synthetic Anti-CCP Antibody Aggravated Severity of Animal Arthritis and Captured Citrullinated Antigen in the Serum of Patients with Rheumatoid Arthritis. Youngkyun Kim[1], Su-Jin Moon[1], Hyoju Yi[1] and Ji Hyeon Ju[2]. [1]College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]College of Medicine, The Catholic University of Korea & Stanford University, Seoul & Palo Alto, CA

Background/Purpose: Auto-antibodies against citrullinated protein antigens (ACPA) have shown their relevance for the prognosis and diagnosis of rheumatoid arthritis (RA), and have been implicated in disease pathogenesis. However, the exact pathologic relevance of these antibodies remains unclear. To obtain insight into this question, we tried to synthesize ACPA and then apply it to animal model and human samples.

Methods: Using hybridoma technology, an IgG monoclonal antibody (mAb), 12G1 was developed against a cyclic-citrullinated peptide (CCP). Clones were selected on the basis of not reacting with control peptide (CRP) which was included one arginine instead of citrulline on the same peptide sequence and structure, but reacting well with synthetic CCP. After successful establishment of hybridoma for anti-CCP Ab, we analyzed the characteristics

of this synthetic anti-CCP Ab. 12G1 was challenged to collagen induced arthritis (CIA) model. Western blot with 12G1 was done on the serum samples of RA patients (n=25) and non-RA control (n=23). Synovium of CIA and RA patients were immunostained with 12G1.

Results: Immunohistochmical analysis with 12G1 revealed positive staining result in CIA and RA patients in comparison with control samples of wild type mice and osteoarthritis. Western blot analysis of sera from RA patients had stronger 12G1-positive bands of citrullinated protein compared with non-RA controls. Average band density was four times higher in RA than non-RA (p=0.001). These western results showed the meaningful correlation with 2nd generation commercial Anti-CCP Ab diagnostic kit (n=48, p=0.02). Moreover, to evaluate the direct role of generated anti-CCP Ab, mice were immunized with CII and then injected with 12G1 instead of second boosting. Immunized mice with 12G1 demonstrated significantly increased disease severity and incidence compared with mice challenged with negative control.

Conclusion: In conclusion, we generated a synthetic monoclonal antibody against CCP. This antibody exacerbated arthritis in CIA model and had the potential to detect citrullinated Ag in human RA serum. Application of this anti-CCP Ab may contribute to understanding the pathophysiology of RA and developing synthetic Ab-driven diagnostic strategy.

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SIRT6 Regulates Cigarette Smoke Induced MMP1 Expression in Rheumatoid Arthritis Synovial Fibroblasts. Anna Engler, Renate E. Gay, Beat A. Michel, Steffen Gay and Caroline Ospelt. Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland

Background/Purpose: Cigarette smoking is the best-known environmental risk factor for the development of rheumatoid arthritis (RA). However, the molecular mechanisms involved in the association of smoking and progression of RA are not well investigated. Sirtuins (SIRTs) are recently discovered regulators of inflammation. The aim of the current study was to investigate the impact of cigarette smoke extract (CSE) on the expression of interleukins (ILs) and matrix metalloproteinases (MMPs), and the possible function of SIRTs in the cigarette smoke induced inflammatory response in RA synovial fibroblasts (RASF).

Methods: Synovial tissues were obtained from RA patients undergoing joint replacement surgery. RASF from non smokers (n=16) were stimulated with 5% CSE or 10 ng/ml TNFα for 24 hours. Expression of SIRTs, ILs and MMPs was measured at the mRNA level by Real-time TaqMan and SYBR green PCR. Protein levels of SIRTs were detected by immunoblot in cell lysates and of ILs and MMPs in cell culture supernatants by ELISA. For silencing of SIRT6, RASF (n=10) were transfected with siRNA targeting SIRT6 or control siRNA for 48h prior to stimulation.

Results: Stimulation of RASF with CSE significantly increased protein levels of IL8 (by 1.9-fold$\pm$0.26, p=0.03) and MMP1 (by 1.8-fold$\pm$0.13, p=0.01), but did not affect the protein expression of IL6 and MMP3. Also at the mRNA level IL8 was 4.1-fold$\pm$0.7 (p=0.03) and MMP1 was 5.8-fold$\pm$1.4 (p=0.02) increased in CSE stimulated RASF, indicating that cigarette smoke regulates the expression of IL8 and MMP1 at the transcriptional level. Analysing the expression of SIRTs 1–7 revealed that CSE increases significantly the expression of SIRT6. Furthermore, SIRT6 protein levels were elevated upon TNFα stimulation. Basal expression as well as induction of SIRT6 after stimulation was successfully blocked by transfection of RASF with SIRT6-specific siRNA. Basal production of MMP1 increased significantly by 31$\pm$6% (p=0.008) after silencing of SIRT6. After stimulation with CSE, silencing of SIRT6 enhanced the levels of MMP1 protein by 35$\pm$8.8% (p=0.01) compared to control transfected, CSE stimulated cells. Also stimulation with TNFα had a significantly stronger effect on MMP1 expression in SIRT6 silenced, compared to control transfected cells (control: 4.1-fold $\pm$1.4 induction, siSIRT6: 6.4-fold $\pm$2.1 induction; p=0.004). Expression of IL6, IL8 and MMP3 was not affected by silencing of SIRT6 under basal as well as in stimulated conditions.

Conclusion: In the current study we found that CSE increases the expression of IL8 and MMP1 in RASF. Most interestingly, we could show that both CSE and TNFα induced production of MMP1 is specifically regulated by SIRT6. Therefore, we conclude that SIRT6 acts as a protective regulator attenuating CSE as well as TNFα induced MMP1 production in

RASF. This protective function of SIRT6 must be considered in the development of therapies using pan sirtuin inhibitors that target also SIRT6 activities.

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Methyl Supplementation of Rheumatoid Arthritis Synovial Fibroblasts Regulates the Expression of Transcription Factors and Matrix Metalloproteinases. Edvardas Bagdonas, Emmanuel Karouzakis, Astrid Jungel, Caroline Ospelt, Renate E. Gay, Steffen Gay, Beat A. Michel and Michel Neidhart. Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Previously we reported that methyl supplementation can reverse the global hypomethylation of rheumatoid arthritis synovial fibroblasts (RASF) and attenuate their aggressive behaviour. Now we analysed the molecular changes occurring in matrix metalloproteinases (MMPs) and transcription factors after treatment with methyl supplementation.

Methods: RASF (n=6 patients) were cultured in DMEM/F12 + 10% FCS as a control and in medium supplemented with 10-fold excess amount of folic acid (70 μM), vitamin B12 (6 μM) and L-methionine (1,1 mM) (high supplementation - HS) for 10 days. After the treatment, cells were counted to determine doubling time, their RNA isolated and supernatants were tested using MMPs ELISA assays. The gene expression of MMPs and transcription factors was evaluated by real time-PCR and gene expression array (QIAGEN RT^2 Profiler PCR Human Transcription Factors Array), respectively. The untreated and treated RASF were implanted together with normal human cartilage into SCID mice. The cartilage sample slides were scored by three independent investigators.

Results: After 10 days of culturing in HS medium, the expression of MMP1 gene was significantly down regulated (p = 0.034) while changes in the mRNA level of MMP3 were not significant (p = 0.56). There was also a significant reduction in the level of MMP1 protein in RASF grown in HS medium (p = 0.027) and no significant reduction of MMP3 protein level (p = 0.49). The effect of HS on the state of DNA methylation and gene expression is dependent on cell proliferation. Indeed, MMP1 expression strongly correlated with the cell population doubling time – r = 0.9455, p = 0.0044. The expression of 6 out of 84 analyzed genes was significantly changed by methyl supplementation. ELK1, HDAC1, HSF1 were up regulated while JUN, NFATC3 and SMAD9 were down regulated (p < 0.05). Most interestingly, HS treated RASF showed reduced invasion and perichondrocytic degradation in the SCID mouse invasion model *in vivo* (invasion score: control 2.25±0.27; HS 1.26±0.26, p<0.03, n=5; perichondrocytic score: control 1.91±0.18; HS 1.17±0.23, p<0.01, n=5).

Conclusion: Methyl supplementation reduced the expression of MMP1, significantly altered expression pattern of 6 transcription factors and inhibited the invasive properties of RASF *in vivo*. Therefore, this supplementation might be used as a novel therapeutic approach to inhibit joint destruction in rheumatoid arthritis.

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Interaction of Antibodies Against Citrullinated Peptides with HLA Shared Epitope, PTPN22 1858T Variant, and Smoking in Individuals Prior to and After the Development of Rheumatoid Arthritis. Heidi Kokkonen[1], Mikael Brink[2], Monika Hansson[3], Linda Mathsson[4], Ewa Lassen[5], Per Johan Jakobsson[3], Rikard Holmdahl[6], Johan Rönnelid[4], Lars Klareskog[7] and Solbritt M. Rantapaa-Dahlqvist[8]. [1]Umeå University, Umea, Sweden, [2]Umea University, Umea, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Uppsala University, Uppsala, Sweden, [5]Umeå University, Umeå, Sweden, [6]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [7]Karolinska Institute, Stockholm, Sweden, [8]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umea, Sweden

Background/Purpose: The presence of antibodies against cyclic citrullinated peptides (ACPA) has been demonstrated to precede the development of rheumatoid arthritis (RA) by several years. The gene-environment interaction for these antibodies has not been elucidated.

The aim was to analyse for the development of reactivity against citrullinated peptides during the pre-disease phase of RA and after disease onset in relation to genetic and environmental factors.

Methods: This study comprised 406 individuals, providing 717 samples, who were identified before onset of symptoms of RA (median (IQR) 7.4 (9.3) years), as donors to the Medical Biobank of Northern Sweden. Among these, 204 were also sampled at the time of diagnosis. Population controls (1305) were identified from the Medical Biobank. Analysis of antibodies against 10 different citrullinated peptides; fibrinogen (Fib) β36–52, Fib α72, Fib α74, Fib α573, Fib α591, α-enolase (CEP-1), collagen citC1, filaggrin, vimentin (Vim) 2–17, and Vim 60–75 was performed using a microarray system developed in collaboration with Phadia AB/Thermofisher, Uppsala, based on their ISAC platform. All samples were also analysed for anti-CCP2 antibodies by ELISA (Euro-Diagnostica). HLA-DRB1 alleles were genotyped using polymerase chain reaction sequence-specific primers. Genotyping of the PTPN22 1858C/T polymorphism was performed using a Taqman instrument.

Results: The frequency of antibodies against Fibβ36–52, CEP-1, and filaggrin and anti-CCP2 increased significantly during the pre-dating time with the highest frequency of all antibodies before onset of symptoms. The number of positive antibodies against citrullinated peptides increased the closer to onset of symptoms and was significantly higher in individuals carrying HLA-SE or T-variant compared with those without. Individually antibodies against Fibβ36–52, CEP-1, and filaggrin were in combination with HLA-SE, PTPN22 T variant and smoking associated with the development of RA, even stronger than for anti-CCP2 antibodies. Development of antibodies against the various citrullinated peptides after disease onset in individuals who were negative for these antibodies prior to onset of symptoms was associated with the presence of HLA-SE and smoking e.g. antibodies against Fib β36–52, CEP-1, Fib α74, and Vim 60–75 were significantly associated with HLA-SE. Positivity for antibodies against Fib β36–52, CEP-1, Vim 60–75, collagen citC1, Fib α591, and Fib α573 was all significantly associated with smoking.

Conclusion: These results indicate that the development of an ACPA immune response is restricted to individuals carrying HLA-SE or the PTPN22 1858T variant, is strengthened by smoking and conversion to positivity for several of the antibodies is associated with the presence of HLA-SE and/or smoking

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Effects of Fetal Microchimerisms On Disease Onset and Severity in Women with Rheumatoid Arthritis and Systemic Lupus Erythematosus. Marianne Kekow[1], Sara Fill Malfertheiner[2], Maria Barleben[1], Susanne Drynda[3], Joern Kekow[3] and Thomas Brune[1]. [1]Univ of Magdeburg, Children's Hospital, Magdeburg, Germany, [2]Univ of Magdeburg, Department of Obstetrics and Gynecology, Magdeburg, Germany, [3]Univ of Magdeburg, Vogelsang-Gommern, Germany

Background/Purpose: The major source of naturally acquired microchimerisms (MC) is the transplacental traffic of fetal cells between a mother and the fetus during pregnancy. Fetal cells have been found to persist in maternal blood for many years post partum. It was the aim of this study to analyze the prevalence of fetal MC in patients with inflammatory rheumatic diseases and to investigate the association of MC with disease severity.

Methods: A total of 143 women who had delivered at least one male offspring were recruited: 73 women with rheumatoid arthritis (RA), 16 women with systemic lupus erythematosus (SLE) and 54 women as non-affected controls. The mean age was 62.5 years (RA), 56.2 years (SLE), and 40.5 years (control cohort). Women who had received a blood transfusion in the past were not included in this study.

For the analysis of fetal MC in DNA from maternal circulation a nested PCR was used to detect a male fetal sequence in the TSPY gene on the Y chromosome.

For both disease groups age at disease onset and markers for disease activity were compared for MC+ and MC- patients, this includes for RA patients anti-CCP-antibodies (anti-CCP), rheumatoid factor (RF) and radiographic progression (Steinbrocker score); and for SLE antinuclear antibody

(ANA) and anti-dsDNA antibody, serum C3, C4, CH50, and soluble interleukin 2 receptor (sIL2R) levels.

Results: The prevalence of fetal MC was 18% in RA patients and 31% in patients with SLE, which is significantly increased compared to 3.7% in non-affected controls (p=0.02 and p=0.006, resp.).

The mean age at disease onset was comparable in MC+ and MC- RA patients with about 43.3 years. Disease onset occurred 18.7 and 19.8 years post partum of the first son for MC+ and MC- patients, respectively. The presence of anti-CCP and RF did not differ significantly: anti-CCP were found in 75% of MC+ and 87% of MC- RA patients, RF in 75% of both MC+ and MC- patients. A higher mean Steinbrocker Score in MC+ patients (3.2 vs. 3.0) was associated with a longer disease duration: 19.4 years (MC+) vs. 16.5 years (MC-).

In SLE patients mean age at disease onset was 42.6 years in MC+ and 49.1 years in MC- patients. Disease onset occurred 24.0 and 26.4 years post partum of the first son for MC+ and MC- patients, respectively. The presence of ANA and anti-dsDNA antibodies, sIL2R, C3, C4, and CH50 did not differ significantly. In MC+ patients sicca symptoms were found most frequently (80%), followed by involvement of joints (60%), central nervous system (20%) and kidneys (20%). In contrast, in MC- patients joints were affected mostly (70%), followed by skin (60%), central nervous system (30%) and sicca symptoms (20%).

Conclusion: In a cohort of RA patients as well as in patients with SLE the prevalence of MC was significantly increased compared to a cohort of non-affected controls. The disease severity in patients with RA or SLE did not differ depending on the presence of MC.

In conclusion our results indicate that the long persistence of microchimerism as a marker of a pathologic clearance of semi-allogeneic DNA is associated with rheumatic diseases without effect on disease severity.

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Performance of Anti-Cyclic Citrullinated Peptide Assays Differs in Healthy Subjects At Elevated Risk for Future Rheumatoid Arthritis and Subjects with Established Disease.
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Background/Purpose: The 2010 ACR/EULAR RA criteria include autoantibodies to cyclic citrullinated peptides (CCP) that are highly specific for RA in the setting of inflammatory arthritis (IA). In addition, multiple studies demonstrate that CCP positivity can occur years prior to the onset of IA. Therefore, there is hope that CCP testing can be used to identify healthy subjects with sufficiently high risk for future RA who can be studied to understand the natural history of RA, as well as to identify subjects most likely to benefit from preventive interventions. However, while there are multiple types of CCP assays, there is limited data in subjects with and without RA comparing the performance of each assay or the ability of a positive test to predict future development of clinically-apparent RA.

Methods: CCP testing was performed using 2 commonly used ELISA assays [CCP2 (IgG) (Axis-Shield) and CCP3.1 (IgG, IgA) (INOVA)] in sera from the following: 1) RA cases from the Studies of the Etiology of RA (SERA) project, 2) RA cases from the Dept of Defense Serum Repository (DoDSR) with pre- and post-diagnosis samples available, 3) SERA first degree relatives (FDR) of probands with RA who are at elevated risk for future RA due to familial RA, and 4) controls (case-matched DoDSR subjects and randomly selected blood donors). The diagnostic accuracy of assays for established RA was calculated comparing cases (probands and DoDSR) and controls. Prevalence of positivity was compared using chi-squared/Fishers exact testing.

Results: For established RA, CCP2 was more specific but less sensitive than CCP3.1 (Table). As cut-off levels for positivity were increased, specificity increased. In all subjects, CCP3.1 was more prevalent than CCP2. In DoDSR samples prior to RA diagnosis, there was a strong association of CCP

levels >2× normal with a diagnosis of RA within 2 years [CCP2 OR 7, 95% CI 3–17, p<0.01; CCP3.1 OR 7, 95% CI 3–16, p<0.01]. Assay agreement was good in established RA (kappa 0.7), but poor in subjects without RA (k 0.2). However, agreement improved (k 0.5) in FDRs using cut-offs >2× normal suggesting the moderate range CCP titers encompass most of the discordant samples.

Results of CCP2 and CCP3.1 Assay Testing in Subjects with and without Rheumatoid Arthritis

	Sensitivity (or prevalence)			Specificity†		
	Standard kit cut-off‡	Cut-off >2× normal	Cut-off >3× normal	Standard kit cut-off‡	Cut-off >2× normal	Cut-off >3× normal
SERA RA (N = 340)						
CCP2 (95% CI)	57.4 (51.9–62.6)	54.1 (48.7–59.5)	52.4 (46.9–57.8)	99.0 (96.1–99.8)	99.5 (96.8–100)	99.5 (96.8–100)
CCP3.1 (95% CI)	66.2 (60.8–71.1)	61.8 (56.3–66.9)	59.1 (53.7–64.4)	94.0 (89.5–96.7)	96.5 (92.6–98.5)	97.0 (93.3–98.8)
CCP2 and/or CCP3.1 (95% CI)	67.6 (62.4–72.5)	—	—	93.5 (88.9–96.3)	—	—
DoDSR RA Post-diagnosis (N = 47)						
CCP2 (95% CI)	68.1 (52.7–80.5)	66.0 (50.6–78.7)	63.8 (48.5–76.9)	100 (90.6–100)	100 (90.6–100)	100 (90.6–100)
CCP3.1 (95% CI)	76.6 (61.6–87.2)	70.2 (54.9–82.2)	70.2 (54.9–82.2)	89.4 (76.1–96.0)	97.9 (87.3–99.9)	97.9 (87.3–99.9)
CCP2 and/or CCP3.1 (95% CI)	76.6 (61.6–87.2)	—	—	89.4 (76.1–96.0)	—	—
DoDSR RA Pre-diagnosis (N = 83)						
CCP2 (95% CI)	61.4 (50.1–71.7)	57.8 (46.5–68.4)	51.8 (40.6–62.8)	100 (94.5–100)	100 (94.5–100)	100 (94.5–100)
CCP3.1 (95% CI)	63.9 (52.5–73.9)	59 (47.7–69.5)	56.6 (45.3–67.3)	88.7 (77.5–95.0)	95.2 (87.5–98.4)	98.8 (92.5–100)
CCP2 and/or CCP3.1 (95% CI)	66.3 (55.0–76.0)	—	—	91.6 (82.9–96.3)	—	—
SERA FDRs (N = 681)*						
CCP2	2.2	1.6	1.5	—	—	—
CCP3.1	9.5	4.3	3.2	—	—	—

†Specificity calculated for SERA RA cases compared to random blood donor controls (N = 200); for DoDSR RA cases compared to DoDSR matched controls
‡standard kit cut-off levels used, for CCP2 >5 units and for CCP3.1 ≥20 units
*Prevalence of positivity; comparing CCP2 and CCP3.1, p-value <0.01 for all 3 cut-offs

Conclusion: CCP assays differ in established RA to an extent that may have a clinically meaningful impact on diagnosis. Also, as CCP3.1 is more often elevated in pre-RA DoDSR cases and in subjects at-risk for future RA, it may represent a more sensitive test, albeit less specific, to identify subjects for investigations into the pathogenesis of RA and potential candidates for preventive interventions. Furthermore, in DoDSR cases, the association of higher CCP levels with a shorter time to the onset of RA suggests that CCP levels can be used to predict the timing of future onset of RA in currently asymptomatic subjects. These findings, as well as potential mechanisms underlying the differences (such as isotype or antigen detections) in these 2 commonly-used tests need further investigation.

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Joint Effects of Known Genetic Markers of Rheumatoid Arthritis Risk and 25-Hydroxyvitamin D On Rheumatoid Arthritis Risk.
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Background/Purpose: Rheumatoid arthritis (RA) is a complex disease with both genetic and environmental risk factors. A number of susceptibility genes have been identified. Past studies have also observed an association between decreased levels of vitamin D and RA. We aimed to examine the joint effects of genetic markers of RA, and circulating vitamin D levels on RA risk.

Methods: We selected incident Caucasian RA cases (n=133) who contributed blood samples prior to first RA symptom and matched controls (n=134) from the Nurses' Health Study and Nurses' Health Study II cohorts. We genotyped 36 RA risk alleles identified by previous GWAS and meta-analysis, and 8 *HLA-DBR1* shared epitope (SE) genotypes at 4 digit resolution. We measured 25-hydroxyvitamin D (25(OH)D) levels by chemi-luminescence immunoassay. We used conditional logistic regression to examine the marginal genetic and 25(OH)D effects, as well as testing for

additive and multiplicative interaction between the genetic markers and 25(OH)D (sufficient vs. insufficient (^{2}20ng/mL)). We ran unconditional logistic regression analysis stratified by seropositive (n=66) and seronegative (n=67) RA phenotypes additionally adjusted for matching factors. We adjusted for multiple comparisons with Bonferroni correction.

Results: We found statistically significant main effects of *HLA-DBR1* SE and RA (p=0.0013) and seropositive RA (p=4×10^{-5}). There was no significant main effect association between vitamin D insufficiency and RA. Among all RA cases we observed a statistically significant additive interaction between *FCGR2A* (rs7552317) and insufficient 25(OH)D (p=0.004). For subjects with having any *FCGR2A* alleles and insufficient 25(OH)D there was an >2-fold odds of RA (2.18 (95% CI 1.11, 5.81)) when compared to those without *FCGR2A* alleles and sufficient 25(OH)D (Table). Among seropositive RA we observed a statistically significant additive interaction between *HLA-DRB*0101* and insufficient 25(OH)D (p= 0.0002) where having any *HLA-DRB*0101* and insufficient 25(OH)D was associated with an >2-fold increase in odds of RA (2.18 (95% CI 0.82, 5.79)).

Table. Gene-vitamin D interactions between *FCGR2A* and *HLA-DRB1*0101* polymorphisms and vitamin D insufficiency in relation to risk of all rheumatoid arthritis (RA) and seropositive RA.

RA phenotype	Genetic factors	Categories of 25(OH)D*	No. cases/ No. controls	OR (95% CI)	Attributable proportion (p-value)	Multiplicative p-value
All RA	*FCGR2A*	Sufficient vitamin D	28/14	1.0 (ref)	0.66 (0.0043)	0.07
	None		11/12	0.93 (0.51–1.70)		
	None	Insufficient vitamin D	61/72			
	Any	Sufficient vitamin D	25/25	0.94 (0.36–2.48)		
	Any	Insufficient vitamin D		2.54 (1.11–5.81)		
Seropositive RA	*HLA-DRB1*0101*	Sufficient vitamin D	15/11	1.0 (ref)	0.92 (0.0002)	0.03
		Insufficient vitamin D	3/8	0.55 (0.27–1.12)		
	None		27/81			
	None	Sufficient vitamin D	19/31	0.62 (0.14–2.67)		
	Any	Insufficient vitamin D		2.18 (0.82–5.79)		
	Any					

Conclusion: We observed significant gene-vitamin D interactions when assessing RA risk and seropositive RA risk. *FCGR2A* (Fc fragment of IgG, low affinity IIa, receptor) and *HLA-DRB1* play important roles in the immune system. *FCGR2A* has been associated with receptor aggregation, neutrophil activation, SLE and lupus nephritis. These results offer clues into the pathophysiology of RA and support a role for vitamin D in inflammatory pathways in pre-RA.

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Secreted Frizzled-Related Protein 5 Exerts the Anti-Inflammatory Role in Rheumatoid Arthritis Via Down-Regulation of c-Jun N-Terminal Kinase. Yong-Jin Kwon, Tae-Yeon Kim, Sang-Won Lee, Yong-Beom Park, Soo Kon Lee and Min-Chan Park. Yonse University College of Medicine, Seoul, South Korea

Background/Purpose: Secreted frizzled-related protein 5 (Sfrp5) is a novel adipokine that has beneficial effects on metabolic dysfunction by controlling inflammatory cells within adipose tissue. Sfrp5 acts as a soluble modulator that binds and sequesters Wnt proteins in the extracellular space and that prevents the activation of frizzled and attenuating non-canonical Wnt signaling. Consequentially, c-Jun N-terminal kinase (JNK), a downstream target of non-canonical Wnt signaling, is inhibited. The purposes of this study are to determine the expression of Sfrp5 in fibroblast-like synoviocyte (FLS) from rheumatoid arthritis (RA) patients and to investigate the correlation between the expression levels of Sfrp5 and that of pro-inflammatory genes in RA FLS.

Methods: FLS were isolated and cultured from synovial tissues obtained from patients with RA or osteoarthritis (OA) during total knee replacement surgery. The mRNA expressions of Sfrp5 in peripheral blood mononuclear cells (PBMCs) and FLS from patients with RA or OA were determined using real-time quantitative RT-PCR. Adenovirus containing Sfrp5 transcript was constructed and delivered into RA FLS to strengthen Sfrp5 expression, then, Sfrp5 RNAi plasmid was transfected to abrogate Sfrp5 expression in RA FLS.

The mRNA expressions of TNF-α, IL-1β, IL-6, CCL-2, CCL-7, COX-2 and MMP-9 were also determined using quantitative real-time PCR and western blot analysis was performed to assess MKK4, MKK-7, ATF-2, c-Jun and JNK activity in RA FLS.

Results: Expression of Sfrp5 mRNA in PMBCs from RA patients was significantly decreased compared to those from OA patients, and this decrease was more accentuated in RA FLS compared to OA FLS (more than 10-fold in OA FLS). The mRNA expressions of TNF-α, IL-1β, IL-6, CCL-2, CCL-7, COX-2 and MMP-9 were remarkably increased in Sfrp5 RNAi plasmid-transfected RA FLS, compared to non-silencing RNAi plasmid-transfected RA FLS. However, adenoviral vectors encoding Sfrp5 significantly reduced the mRNA levels of TNF-α, IL-1β, IL-6, CCL-2, CCL-7, COX-2 and MMP-9 as compared with control vector. The activity of MKK4, MKK-7, ATF-2, c-Jun and JNK were up-regulated in RA FLS with no Sfrp5 expression by Sfrp5 RNAi plasmid; and were down-regulated with strong Sfrp5 expression by adenoviral vectors encoding Sfrp5.

Conclusion: Sfrp5 suppressed various pro-inflammatory gene expressions via modulation of JNK. These findings suggest that Sfrp5 may have a certain role in RA pathogenesis and have an anti-inflammatory effect.

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ACR Poster Session A
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Tocilizumab Improves Bone Mineral Density Compared with Abatacept in Patients with TNF Blockers-Resistant Active Rheumatoid Arthritis. an Open Label Randomized Controlled Trial. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1], Kazuhiko Hatta[2], Kuniki Amano[3], Noriko Kuwaba[4] and Hiroyuki Ohta[5]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hatta Clinic, Kure, Japan, [3]Sky Clinic, Hiroshima, Japan, [4]Sanki Clinical Link, Hiroshima, Japan, [5]Hiroshima, Japan

Background/Purpose: To compare the effect of tocilizumab(TCZ) plus methotrexate (MTX), with the effect of abatacept(ABT) plus MTX on bone mineral density(BMD) in TNF blockers resistant active rheumatoid arthritis(RA; without osteoporosis) patients, in a prospective open label randomized study design.

Methods: RA patients were eligible if they had active disease despite treatment with MTX plus TNF blockers. All patients have no previous history of lumbar and hip fractures. Patients receiving or having received bisphosphonates or hormone replacement therapy, steroids, or any biologics were excluded. 52 patients with moderate to severe active RA patients (DAS28 >3.2) were randomly assigned to receive TCZ plus MTX (n=26) or ABT plus MTX (n=26). All patients with worsening disease activity at week 12, the patients were allowed to escape to another group (by clinician's judgment). The primary outcomes were changes in lumbar and femoral BMD by dual-energy X-ray absorptiometry, secondary outcome were changes in biomarkers of bone turnover (procollagen type I amino-terminal propeptide(P1NP) from baseline to 52 weeks. Clinical data were collected at regular visit. All patients were taking calcium (1 g/day) and vitamin D (800 IU/day).

Results: The characteristics of each group at baseline were not significantly different. 24 patients each in the TCZ and ABT groups completed 52 weeks. Lumbar and femoral BMD were attenuated significantly by TCZ (weeks 52-baseline: lumbar BMD: 0.09±0.011 g/cm^2, $p < 0.001$; femoral BMD: 0.08±0.01 g/cm^2, $p < 0.001$). On the other hand, lumbar and femoral BMD were not attenuated significantly by ABT (weeks 52-baseline: lumbar BMD: 0.01±0.039 g/cm^2, p =0.66; femoral BMD: $-$0.004±0.014 g/cm^2, p =0.87. The change (weeks 52-baseline) lumbar and femoral BMD of the TCZ group were significantly improvement than those of the ABT group (TCZ vs. ABT, lumbar BMD: p <0.05; femoral BMD: p <0.05).P1NP was significant increase by TCZ (weeks 52-baseline: 4.2 ±0.15μg/L, p <0.05), but was not attenuated significantly by ABT (weeks 52-baseline: 0.98 ±0.83μg/L, p=0.65).DAS28 and CRP improved significantly in both groups (weeks 52-baseline; DAS28, TCZ: $-$1.87±0.45, ABT: $-$1.81±0.42) (CRP, TCZ: $-$18.6±4.2 mg/l, ABT: $-$17.7±4.3mg/l) (p <0.05). They were no significant difference between groups.

Conclusion: TCZ plus MTX improves bone mineral density compared with ABT plus MTX in TNF blockers resistant RA. If RA patients were resist TNF blocker, we might think the patients were treated by TCZ than ABT.

Disclosure: **K. Kume**, None; **K. Amano**, None; **S. Yamada**, None; **K. Hatta**, None; **K. Amano**, None; **N. Kuwaba**, None; **H. Ohta**, None.

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Combination of Intra-Articular Steroid Injection and Infliximab More Effective Than Infliximab in Rapid Radiographic Progression Patients with Rheumatoid Arthritis: A Randomized, Open Label, x Ray Reader Blinded Study. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1], Kazuhiko Hatta[2], Kuniki Amano[3], Hiroyuki Ohta[4] and Noriko Kuwaba[5]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hatta Clinic, Kure, Japan, [3]Sky Clinic, Hiroshima, Japan, [4]Hiroshima, Japan, [5]Sanki Clinical Link, Hiroshima, Japan

Background/Purpose: Treatment of rheumatoid arthritis (RA) should aim at full remission. However, recent publications described rapid radiographic progression (RRP) existed despite initial biologics and methotrexate combination therapy in early RA. In RRP, initial biologics and methotrexate might be inadequate.To compare remission and radiographic non-progression in RRP patients treated with infliximab or with infliximab plus intra-articular steroid injection.

Methods: We designed a single-blind(X ray reader and assessment physician), randomized controlled trial. We screened 48 RRP (CRP> 35mg/L, RF +, and ACPA+) early (disease duration<6 months) RA patients for inclusion. 39 were randomly allocated infliximab group (I group) or infliximab plus intra-articular steroid injection group (I plus I group). All patients were taking methotrexate (from 14 to 22mg a week). For I plus I group, palpate examinations of both MP and PIP joints, wrists, elbows, shoulders, and knees were performed every 4 weeks. If swollen joints were existed, intra-articular steroid injections were intensified in each swollen joints. Co-primary endpoints were proportion of patients showing clinical remission (SDAI <3.3) and radiographic non-progression (Δ modified total Sharp score ≤0.5) at 52 weeks. Analysis was by intention-to-treat with last observation carried forward to missing data.

Results: The characteristics of each group at baseline were not significantly different. Clinical remission at 52weeks was achieved by more patients in the I plus I group (32%) than in the I group (19%) (p<0.05). Radiographic non-progression at 52 weeks was achieved by more patients in the I plus I group (37%) than in the C group (24%) (p<0.05).

Conclusion: Results of this reveal that combination of intra-articular steroid injection and infliximab can achieve a high clinical and radiological remission rate in early RRP RA.

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Clinical Remission and Rate of Relapse After Tocilizumab Withdrawal in Rheumatoid Arthritis Patients. Cesar Vargas-Serafin[1], Luis Aguilar-Lozano[1], Jorge Padilla-Ibarra[1], Carlos Sandoval-Castro[1], Jose Dionisio Castillo-Ortiz[1], Jorge Morales-Torres[2], Claudia Hernandez[2] and Cesar Ramos-Remus[1]. [1]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico, [2]Hospital Aranda de la Parra, Leon, Mexico

Background/Purpose: Although there is much discussion regarding when to initiate a biological agent in rheumatoid arthritis (RA) patients, data on when to stop these agents is scant. Disease activity outcomes after the ending of an industry sponsored clinical trials may provide useful information regarding the duration of drug-free remission for a given biological agent. The aim of this study was to assess the length of remission and rate of relapse of disease activity after ending the open label, long-term extension study (5 yrs) using tocilizumab in RA patients enrolled in the OPTION[1] trial.

Methods: Patients who no longer received tocilizumab because of the ending of the extension study (5 yrs) of the OPTION trial were analyzed. All patients were: a) in remission (DAS28 < 2.6, 0 swollen joints) at the time of the last tocilizumab administration (week 260), b) followed thereafter every 8 weeks until relapse (≥ 1 swollen joints), c) on a stable methotrexate dose during the follow-up.

Results: Forty-five patients were analyzed, 87% females with a mean age of 52 yrs and a mean disease duration of 14 yrs. During the first 12 months of follow-up, 26 (58%) patients maintained remission, and at the last visit (17 months) 17 (38%) patients continued in remission. Relapses occurred in 28 (62%) patients: 14 (50%) of them during the first three months after the last tocilizumab administration. No variables were identified to predict length of remission.

Conclusion: Long-term clinical remission is possible in a substantial number of RA patients after suspension of tocilizumab. Additional data are required to support recommendations for discontinuing a biological agent after achieving remission. These recommendations would impact in patients' safety and the economic burden imposed by these treatments.

Reference
[1]Smolen JS et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo controlled, randomized trial. Lancet 2008;371:989–97.

Disclosure: **C. Vargas-Serafin**, None; **L. Aguilar-Lozano**, None; **J. Padilla-Ibarra**, None; **C. Sandoval-Castro**, None; **J. D. Castillo-Ortiz**, None; **J. Morales-Torres**, None; **C. Hernandez**, None; **C. Ramos-Remus**, None.

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Long-Term Safety and Efficacy of Tabalumab, an Anti-B-Cell Activating Factor Monoclonal Antibody, in Patients with Rheumatoid Arthritis: A 52-Week, Open-Label Extension Study. Maria W. Greenwald[1], Leszek Szczepanski[2], Alastair C. Kennedy[3], Chin H. Lee[4], Emery Polasek[5], Melissa Veenhuizen[5], Rebecca Jones-Taha[6] and Pierre-Yves Berclaz[5]. [1]Desert Medical Advances, Palm Desert, CA, [2]Wydz. Fizjoterapii, Wyzsza Skola Spoleczno-Przyrodnicza, Poland, [3]Alastair C. Kennedy, MD, Vero Beach, FL, [4]Eli Lilly and Company, Indianapolis, IN, [5]Eli Lilly & Company, Indianapolis, IN, [6]PharmaNet/i3, Blue Bell, PA

Background/Purpose: Tabalumab, a monoclonal antibody that neutralizes membrane-bound and soluble B cell activating factor (BAFF), has been shown to reduce rheumatoid arthritis (RA) signs and symptoms[1]. This open-label study evaluated the long-term safety and efficacy of tabalumab in RA patients (pts).

Methods: This 52-week (wk), open-label, flexible-dose extension study enrolled pts who completed 24 wks of a randomized, controlled trial (RCT) of tabalumab vs placebo (pb) and received study drug for ≥6 or 12 wks. Pts remained on stable MTX doses throughout. In RCT 1, pts received pb or tabalumab 30 or 80 mg IV every 3 wks for 6 wks and followed-up for 18 wks. In RCT 2, pts received pb or tabalumab 1, 3, 10, 30, 60, or 120 mg SC every 4 wks (Q4W) for 24 wks. At extension study start, all pts received SC tabalumab 60 mg Q4W for 48 wks; a 1-time increase to tabalumab 120 mg Q4W (60/120 mg) and 1-time decrease to 60 mg Q4W per pt was allowed (60/120/60 mg).

Results: Of those who completed RCT 1 or 2, 98% (N=182, safety population) enrolled: tabalumab 60 mg (n=60), tabalumab 60/120 mg (n=121), and 1 pt after taking tabalumab 120 mg then returned to 60 mg. Baseline (pre-tabalumab) RA activity levels were generally higher for the 60/120 mg group. Overall, both groups appeared to maintain efficacy with long-term treatment (Table 1). One pt died due to myocardial infarction (60/120 mg). In each group, 5% discontinued due to an adverse event (AE). There was a higher frequency of serious AEs (SAEs) and treatment-emergent AEs (TEAEs, including severe events) as well as events of interest, including infections and injection-site reactions in the 60/120 mg group. Most infections involved the upper respiratory tract. One pt (60/120 mg) reported a fungal skin infection. No clinically significant differences in hematologic or chemistry values, vital signs, or ECGs were seen. Total B lymphocyte counts decreased by 40% from pre-tabalumab baseline for all groups. The incidence of treatment-emergent, anti-tabalumab antibodies was 4.4% (8/182). Table 2 shows more detailed safety data.

Table 1. Efficacy Outcomes In Extension Study

	Tabalumab (60 mg) N=59		Tabalumab (60/120 mg) N=120		All Patients N=180[b,c]	
	Week 24	Week 52[a]	Week 24	Week 52[a]	Week 24	Week 52[a]
ACR20 response, %	69.6	66.1	40.7	32.5	50.0	43.3
ACR50 response, %	35.7	33.9	20.4	13.3	25.3	20.0
ACR70 response, %	12.5	18.6	5.3	6.7	7.6	10.6
ACR-N, mean (SD)	28.7 (53.6)	31.9 (47.6)	−8.9 (126.7)	11.3 (46.4)	3.0 (109.8)	18.8 (47.7)
EULAR [good+moderate], %	88.5	83.9	56.0	55.6	66.0	64.9
Baseline DAS28, mean (SD)	5.5 (1.3)		6.0 (1.1)		5.8 (1.2)	
Change in DAS28, mean (SD)	−2.0 (1.5)	−2.1 (1.5)	−1.2 (1.4)	−1.3 (1.5)	−1.4 (1.5)	−1.5 (1.5)
Baseline HAQ, mean (SD)	1.54 (0.66)		1.72 (0.56)		.66 (0.60)	
Change in HAQ, mean (SD)	−0.25 (0.53)	−0.27 (0.53)	−0.26 (0.56)	−0.30 (0.62)	−0.26 (0.55)	−0.29 (0.59)

[a]For ACR measures, patients who discontinued from study prior to Week 52 are imputed as non-responders (n=34), for all other measures the LOCF approach was used.
[b]Only 1 patient received 60/120/60 mg tabalumab; this patient is included in All Patient data.
[c]Two patients were excluded from efficacy analyses: 1 patient had no post-baseline efficacy data (60 mg) and was lost to follow-up, and 1 patient was removed due to good clinical practice violations (60/120 mg).

Table 2. Safety and Pharmacodynamic Outcomes

	Tabalumab (60 mg) N=60 Week 52	Tabalumab (60/120 mg) n=121 Week 52	All Patients N=182[a] Week 52
Discontinued due to AEs, n (%)	3 (5.0)	6 (5.0)	9 (4.9)
Deaths, n (%)	0 (0.0)	1 (0.8)	1 (0.5)
Serious AEs, n (%)	4 (6.7)	16 (13.2)	21 (11.5)
Treatment-emergent AEs, n (%)	38 (63.3)	95 (78.5)	134 (73.6)
Infection	22 (36.7)	58 (47.9)	80 (44.0)
Infections of the upper respiratory tract[b]	16 (25.0)	32 (25.4)	47 (25.8)
Urinary tract infection	2 (3.3)	13 (10.7)	15 (8.2)
RA (eg, worsening, flare)	11 (18.3)	30 (24.8)	41 (22.5)
Injection-site reaction	2 (3.3)	13 (10.7)	15 (8.2)
Injection-site pain	2 (3.3)	12 (9.9)	14 (7.7)

[a]Only 1 patient received 60/120/60 mg tabalumab; this patient is included in All Patient data.
[b]Includes MedDRA High Level Terms of Upper Respiratory Tract Infections NEC; Laryngitis, nasopharyngitis, Pharyngitis, Pharyngotonsillitis, Rhinitis, Sinusitis, Upper Respiratory Tract Infection.

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Sustained and Cumulated Response Over Time in Rheumatoid Arthritis Patients Treated with Rituximab After Initial Failure of Anti Tumor Necrosis Factor Agents. Ioan Ancuta[1], Catalin Codreanu[2], Ruxandra Ionescu[3], Magda Parvu[4] and Mihai Bojinca[1]. [1]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [2]"Dr. I. Stoia" Center for Rheumatic Diseases, Bucharest, Romania, [3]Clinic Hospital "Sf. Maria", Bucharest, Romania, [4]"N.Gh. Lupu" Clinical Hospital, Bucharest, Romania

Background/Purpose: Although anti-TNF therapies moved forward the treatment of rheumatoid arthritis (RA), failure of the first anti-TNF medication is not uncommon. Many times modifying dosage/frequency of the initial drug or prescribing a different TNF inhibitor proves to be still inadequate. Using instead a biologic with a different mechanism of action, such as Rituximab (RTX), may be beneficial in terms of RA treatment to target.

Based on EULAR-T2T and ACR criteria we analysed response following each RTX course (2 g at every 24 weeks).

Methods: Longitudinal (2002 to date), observational, population-based, cohort study. The analysis was performed based on data from the National Health Insurance House (NHIH) for 400 out of 1126 patients treated with RTX for RA in October 2011 in the NHIH database. The patients' selection is statistically representative and homogenous at national level. All patients had an anti-TNF medication as first treatment stage for 2.5 years (average). In the second stage, 208 patients were switched to RTX after the initial anti-TNF failure. The remaining 192 patients followed one or two more anti-TNF therapy and only then continued with RTX. A total of 5 RTX courses were administered to both groups. Before each RTX course patient were monitored for DAS28 and EULAR response.

Results: Average DAS28 before RTX was 6.7 (N=400), reaching 4.5 (before C2), then 3.41 (before C3). At the time of this analysis 335 patients followed C3 and 211 C4. Before RTX start, 93% of the total number of patients was in HDA and 8% in MDA. After 2 RTX courses 38.25 % of the patients reached LDA or remission. After 18 months (before C4) 63.88 % patients were in LDA or remission, while before C5 86.73% of the 211 patients having C4 were in LDA or remission (48.82% in remission). In terms of EULAR response after 4 RTX cycles 84.36% had a good response and 15.64% a moderate response, compared to previous treatment with anti-TNF in the same interval (2 years): 5.03% good response and 91.82% moderate response.

	Baseline	W24	W48	W72	W96
DAS28	6.7	4.5	3.41	3	2.6
LDA %	0	5.25	26.25	37.91	37.91
Remission %	0	0.00	12.00	25.97	48.82
Eular Good Response %	0	2.00	32.25	60.90	84.36
Eular Moderate Response %	0	85.5	67.25	38.51	15.64

Conclusion: Each RTX course led to an increased and cumulative clinical DAS28 response compared to the previous one. With each following RTX course all patients registered consolidation of lower DAS28 response, and continuously growing LDA or remission percentage. Response was sustained and cumulated regardless their rheumatoid factor status. Introducing Rituximab to patients with no response or intolerance to anti-TNF agents proved to be an adequate choice, therefore we consider its prescription after the first anti-TNF failure as a preferred option in terms of clinical response.

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Rituximab After First Anti Tumor Necrosis Factor Failure Is More Efficient with High Impact in Reducing Time and Costs to Achieve Superior Rates of Low Disease Activity and Remission. Ioan Ancuta[1], Catalin Codreanu[2], Ruxandra Ionescu[3], Magda Parvu[4] and Mihai Bojinca[1]. [1]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [2]"Dr. I. Stoia" Center for Rheumatic Diseases, Bucharest, Romania, [3]Clinic Hospital Sf. Maria, Bucharest, Romania, [4]"N.Gh. Lupu" Clinical Hospital, Bucharest, Romania

Background/Purpose: Significant steps were done in creating new medications for treatment of rheumatoid arthritis (RA). As RA seriously affects the patients' quality of life, the effectiveness of selected approaches is a primary concern for the National Health Insurance House (NHIH). Also being a chronic disease and having finite budgets it is important to find also the best results/costs approach. In case of first anti-TNF medication failure, options are prescribing a different anti-TNF or switching to Rituximab (RTX).

Our objective was to identify the best results/costs ratio by comparing two RA therapeutic alternatives: (1) switch to RTX after first anti-TNF failure versus (2) switching after 2–3 anti-TNF failure.

Methods: Based on data from NHIH, we analysed clinical results and the corresponding costs for N=400 RA patients, within a longitudinal (2002–2011), observational, population-based, cohort study. All patients had an anti-TNF medication as first treatment stage for 2.5 years (average). In the second stage, 208 patients (Group 1) were switched to RTX after first anti-TNF failure, and 192 (Group 2) had one or two more anti-TNF before switched to RTX. We evaluated the clinical effectiveness of the 2 approaches using: DAS28 and EULAR response. For efficiency assessment we calculated in each set-up indicators like: average spending to obtain the treatment target (LDA or remission), average cost per decreased DAS28 point and duration of treatment versus target.

Results: In Group 1, after the first 2 RTX cycles (12 months) medium ΔDAS28 was -3.36 (compared to its value before the RTX switch). Group 2 evidenced first development of resistance to the anti-TNF medication, medium ΔDAS28 was $+0.26$ and after switch to RTX, ΔDAS28 decreased in 12 months with -2.72. By September 1st 2011 (four RTX cycles), 91% of Group 1 patients experienced LDA (36.1%) and remission (54.9%) vs. 80.8% of the patients in Group 2 (40.4% LDA, 40.4% remission). While the groups are comparable in size, with respect to the total expenditure for N=400 patients, Group 1 represents 38% while Group 2 is 62% of the total costs. In terms of treatment objectives 51% of the patients in Group 1 after 12 months achieved LDA or remission vs. 23.4% in Group 2. Considering the budget spent to obtain these results, NHIH spent in average 58% more per patient per DAS28 point with Group 2 vs. Group 1.

Conclusion: Switching on RTX after the first anti-TNF failure allows the achievement of a sooner and better EULAR response than RTX therapy after 2 or 3 anti TNF stages. DAS28 decreased consistently for all

RTX patients, irrespective of their group, but those in Group 1 achieved a lowest value faster. RTX after first anti-TNF is clearly more efficient, the costs to obtain superior clinical response being almost half of those involved in the second therapeutic option. The savings could be used for higher number of RA treated patients with the same budget and shortening the RA patient's waiting list. The balance cost-benefits being in favour of initiating a RTX medication after the first anti-TNF therapy (follow NICE recommendation) this is our recommendation for NHIH.

Disclosure: I. Ancuta, None; **C. Codreanu**, None; **R. Ionescu**, None; **M. Parvu**, None; **M. Bojinca**, None.

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Late Onset Neutropenia After Rituximab Treatment for Rheumato-logical Conditions. Gabriel S. Breuer[1], Michael Z. Ehrenfeld[2], Itzhak Rosner[3], Alexandra Balbir-Gurman[4], Devy Zisman[5] and Daphna Paran[6]. [1]Shaare Zedek Medical Center, Jerusalem, Israel, [2]Chaim Sheba Medical Center, Tel HaShomer, Israel, [3]Bnai Zion Medical Center/Technion Faculty of Medicine, Haifa, Israel, [4]Rambam Health Care Campus, Haifa, Israel, [5]Carmel Medical Center, Haifa, Israel, [6]Tel Aviv Sourasky Medical Ctr, Tel Aviv, Israel

Background/Purpose: Rituximab is a monoclonal chimeric antibody targeting the CD20 on the surface of normal and abnormal maturing B cells. Late onset neutropenia (LON) is defined as an unexplained absolute neutrophil count of $<1.5 \times 10^9$/liter occurring at a time point at least 4 weeks after therapy. LON following rituximab treatment has been described extensively in hematological malignancies. However it has been reported infrequently in association with rheumatological diseases. To the best of our knowledge only 29 such cases have been published so far in the English literature. The aim of this work is to review cases in Israel and to compare them to published cases in the literature thus adding to the body of knowledge regarding this unusual phenomenon.

Methods: Members of the Israeli Rheumatology Association were encountered by e-mail, requesting reports of cases of LON after therapy with rituximab. Submitted cases were reviewed, with demographics and clinical data collated and tabled. Current cases were compared to previously published rheumatology cases.

Results: Eight episodes in seven patients were reported throughout the country after encounting 150 Israeli rheumatologists. Five of the patients had RA, one SLE and one MCTD. The average neutrophil count was 0.275/cubic mm in compare to 0.380/cubic mm in previously published cases. One patient had cellulitis of the forearm and all other patients did not have any infection. Five patients were treated with G-CSF. All patients had complete recovery. In comparison to published cases, a larger percentage were RA patients reflecting current usage of the medication in Israel. The average time to LON diagnosis was 177 days as compared to 148 days in published cases.

Table 1. LON: current series compared to previous published cases

Age/Gender	Dg	No of tx	Additional tx	Days since tx	WBC (% neu)	Repeat tx	Infection	Action taken
32/F	RA	4	MTX PRED	151	1100 (10)	Yes	No	G-CSF
34/F	MCTD	1	CYC AZA PRED	105	1000 (42)	Yes	No	G-CSF
22/F	SLE	1	CYC	240	0	No	Cellulitis	G-CSF
38/F	RA	1	MTX PRED	120	0	No	No	G-CSF
68/F	RA	1	PRED ABITREN	330	1270 (50)	No	No	G-CSF
50/F	RA	1	MTX HCQ	138	2300 (47)	Yes	No	MTX D/C
51/F (same patient on following year)	RA	2	HCQ	180	2600 (45)	No	No	
78/F	RA	1	MTX PRED	150	1800 (39)	No	No	MTX D/C Increase PRED
Published cases average age: 52 17 (60%) Females8 (40%)Males	RA −12 GPA =12 SLE =3 VASCULITIS=1 JRA=1	n/a	MTX −8 MMF −4	148	380 neutrophiles	n/a	Sepsis −5 Fever − 3	G-CSF − 11

Conclusion: LON is a well described finding and should be taken into consideration when following rheumatological patients treated with rituximab. In most cases it can be managed with a single dose of G-CSF and does not put the patient in an additional risk. Periodic complete blood count monitoring is recommended.

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Pilot Study of Stimulation of the Cholinergic Anti-Inflammatory Pathway with an Implantable Vagus Nerve Stimulation Device in Patients with Rheumatoid Arthritis. Frieda A. Koopman[1], Sanda Miljko[2], Simeon Grazio[3], Sekib Sokolovic[4], Kevin Tracey[5], Yaakov Levine[6], Ralph Zitnik[6] and Paul-Peter Tak[7]. [1]Academic Medicalq Center/University of Amsterdam, Amsterdam, Netherlands, [2]University Clinical Hospital, Mostar, Bosnia, [3]Clinical Hospital Center Sestre Milosrdnice, Zagreb, Croatia, [4]University Clinical Center, Sarajevo, Bosnia, [5]Feinstein Institute for Medical Research, Manhasset, NY, [6]SetPoint Medical Corporation, Valencia, CA, [7]Academic Medical Center/GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: The inflammatory reflex regulates innate and adaptive immunity (Andersson O, Tracey K, Annu. Rev. Immunol. 2012; 30:313). Activation of its efferent arm (the Cholinergic Anti-inflammatory Pathway (CAP)), by electrical vagus nerve stimulation (VNS) reduces systemic inflammation and ameliorates disease in many acute and chronic animal models. We determined whether VNS could similarly improve clinical manifestations of rheumatoid arthritis (RA).

Methods: This is an open label study of patients with active RA ($>/=$ 4 tender and 4 swollen joints (28 joint scoring), and CRP of at least 7 mg/L) despite stable methotrexate dose for 3 months. Patients failing TNF antagonists (only for safety or tolerability reasons) could also be enrolled after washout. After a pre-implantation baseline visit, patients were surgically implanted with a Cyberonics VNS system. The device delivered the first VNS during its standard intraoperative diagnostic check sequence. Two weeks following implantation patients returned for initial in-clinic VNS. One week after the first clinic visit (day 7), patients began self-delivery of 60 second, once daily home stimulations, escalated in output current intensity as tolerated, through day 28. At day 28 patients without a EULAR good or moderate response were increased to four times daily VNS. Primary endpoint results at day 42 are reported.

Results: 8 patients (4 female, 7/8 RF+, 6/8 ACPA+, mean age 56 [range 39–70], mean disease duration 8 yrs [range 0.5–13]) were enrolled and implanted. Implantation and stimulation were generally well tolerated. Moderate postoperative hoarseness occurred in one patient. Pre implantation baseline values (mean, SD) were: DAS28-CRP: 6.06 (0.87), CRP: 17.5 mg/L (9.9), HAQ-DI: 1.63 (0.90). Changes at day 42 visit from pre-implantation values were: DAS28-CRP: −2.28 (1.65), CRP: −3.46 (17.95) mg/L, HAQ-DI: −0.44 (0.48). Similar levels of improvement were seen across all ACR core set assessments. ACR 20/50/70 response rates from pre-implantation baseline to day 42 were 75% (6/8), 50% (4/8), and 25% (2/8), respectively.

Conclusion: In this pilot study VNS was generally well tolerated and improved signs and symptoms of RA. This is the first demonstration in humans that stimulation of the CAP can favorably impact clinical manifestations of systemic inflammation. If efficacy and safety are confirmed in larger controlled studies, implantable medical devices may offer a feasible alternative approach to the treatment of RA and other chronic inflammatory diseases.

Disclosure: F. A. Koopman, None; **S. Miljko**, SetPoint Medical, 2; **S. Grazio**, SetPoint Medical, 2; **S. Sokolovic**, SetPoint Medical, 2; **K. Tracey**, SetPoint Medical, 1, SetPoint Medical, 5; **Y. Levine**, SetPoint Medical, 1, SetPoint Medical, 3; **R. Zitnik**, SetPoint Medical, 1, SetPoint Medical, 3; **P. P. Tak**, SetPoint Medical, 2, SetPoint Medical, 5.

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Effectiveness and Tolerance Infiltration Intraarticular Corticosteroid According to Dose. Daniele F. Pereira[1], Rita N.V. Furtado[2], Natalia P. Machado[3] and Jamil Natour[3]. [1]Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil, [2]Universidade Federal de São Paulo-UNIFESP, São Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: The optimal dose of corticosteroid to be used in intraarticular injection is not well established. The objective of this study is to compare the effectiveness and tolerance in the medium-term between small and large doses of triamcinolone hexacetonide (TH) used in intraarticular injection (IAI) of medium size joints of patients with rheumatoid arthritis (RA).

Methods: A controlled, randomized, prospective, double-blind study was carried out in patients with RA. It was evaluated 60 wrists joints (representing medium size joints) from the outpatient clinic at the Rheumatology Division UNIFESP, Brazil. Inclusion criteria were: patients with established RA, age between 18 and 65 years, disease modifying anti-rheumatic drugs (DMARDs) stable for at least 3 months, synovitis in wrist with pain visual analogic scale (VAS) between 4 and 8cm. Patients with overlap syndromes, polyarticular synovitis, diabetes mellitus or uncontrolled hypertension and those with suspected local or systemic infection were excluded. Patients were randomized (Clapboard randomization) in two groups of 30 patients each: group 1 (high dose) was injected with 40mg (2ml) of TH and group 2 (low dose) was injected 20mg (1ml). Only one joint was injected per patient (IAI blindly). Evaluation was conducted by a blinded observer at five times: baseline (T0), one week (T1), four (T4), eight (T8) and twelve (T12) weeks and the following assessment instruments were used: visual analogue scale for pain and swollen (swelling) (VAS 0–10cm); wrist goniometry; chronic disease activity index (CDAI). Side effects and related events were reported in a medical questionnaire. The level of statistical significance was 5%.

Results: A total of 60 patients were injected (50 women, 37 white). Mean age was 50.0 ($\pm$ 12.5) years old in the high dose group and 51.7 ($\pm$ 11.6) in the low dose group (p=0.586). No statistically significant difference between groups was observed for VAS for pain, VAS for swelling, CDAI, HAQ and goniometry. But all study variables improved over time in both groups and particularly T0 improved statistically significant from all other times for VAS for pain and swelling,CDAI and HAQ (all p<0.008). Wrist goniometry was statistically different in some periods and only in the high dose group was the improvement maintained until T12 (p<0.004). There was a significant increase of the use of nonsteroidal anti-inflamamatory (NA) and analgesics necessary to relieve pain soon after IAI, but this use decreased after T1 equally between groups (p<0.692). Very few adverse effects and related events were reported in both groups (p=0.195).

Conclusion: There is no difference in effectiveness of the intraarticular injection between high and low doses of TH used in medium size joints of patients with RA.

Disclosure: **D. F. Pereira**, None; **R. N. V. Furtado**, None; **N. P. Machado**, None; **J. Natour**, None.

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Fish Oil in Rheumatoid Arthritis: A Randomised, Double Blind Trial Comparing High Dose with Low Dose. Susanna Proudman[1], Llew Spargo[1], Cindy Hall[1], Leah McWilliams[1], Anita Lee[1], Maureen Rischmueller[2], Robert Gibson[3], Michael James[1] and Leslie G. Cleland[1]. [1]Royal Adelaide Hospital, Adelaide, Australia, [2]Queen Elizabeth Hospital, Adelaide, Australia, [3]University of Adelaide, Adelaide, Australia

Background/Purpose: The symptomatic benefit and NSAID-sparing effects of fish oil (FO) in RA are well known but effects on disease outcomes are less well established, especially in the context of contemporary treatment of early RA. The aim of this investigator-initiated randomized controlled trial was to assess the effects of high vs. low dose FO on disease outcomes in patients with early RA receiving a "treat-to-target" protocol of combination DMARDs.

Methods: Patients with RA according to ACR criteria with active polyarthritis of <12 months' duration and who were DMARD-naïve, received MTX, sulphasalazine and hydroxychloroquine. They were randomized 2:1 to fish oil at a high dose (FO) or low dose (control) providing 5.5 and 0.4 g/day respectively, of the marine omega-3 fats, EPA+DHA. DMARD doses were adjusted according to a pre-defined protocol taking disease activity and

toxicity into account. DAS28-ESR, mHAQ, remission and plasma phospholipids were assessed 3 monthly. In a novel study design, the primary outcome was DMARD use at 52 weeks, defined as the addition of leflunomide to triple therapy ("failure of triple therapy").

Results: After 52 weeks, there were no significant differences between treatment groups for the outcomes of MTX dose, DAS28 or mHAQ; but compared with controls (16/46, 35%), fewer FO patients (9/75, 12%) had commenced leflunomide (p= 0.005, Fisher's exact test). In FO patients, the rate of commencement of leflunomide was lower (Hazard Ratio 0.27, 95%CI 0.12–0.59) whereas the rate of achieving first ACR remission was higher (HR 2.22, 95%CI 1.18–4.18) compared with controls (Kaplan-Meier estimate).
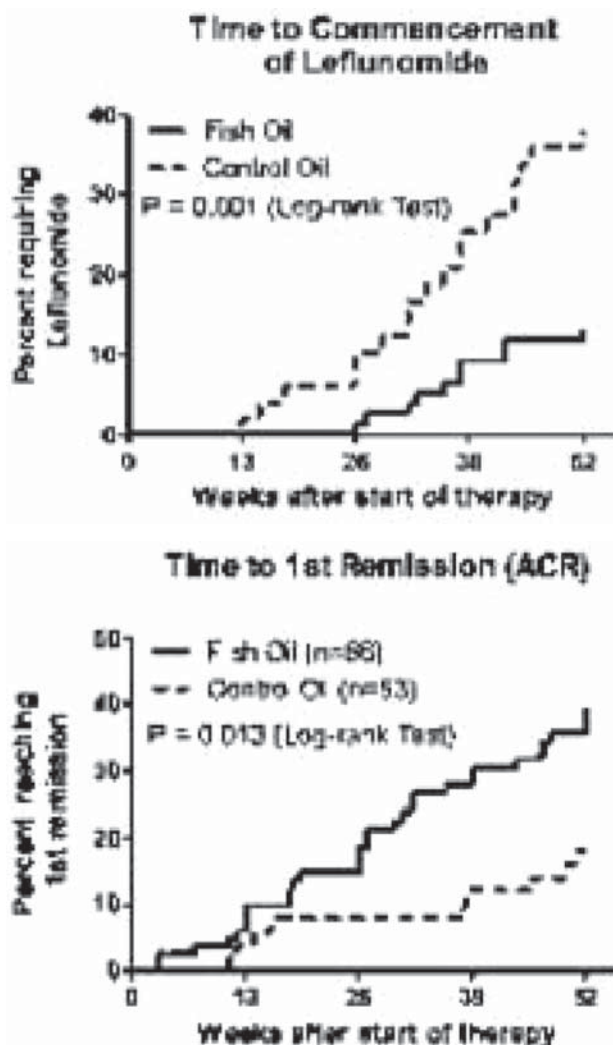
There was considerable overlap in plasma omega-3 levels between the FO and control groups. Results were analysed by plasma omega-3 quartiles (t12AUC/unit time). Compared with the lowest quartile, patients in the highest quartile had significantly higher odds of achieving remission, by either DAS28 or ACR criteria (respectively, OR =3.30, 95% CI; 1.13–9.71, OR = 3.53, 95%CI; 1.05–11.90).

Conclusion: FO was associated with benefits additional to those achieved by combination "treat-to-target" DMARDs with similar MTX use. The benefits included reduced likelihood of progression to leflunomide ("failure of triple therapy") and a higher rate of ACR remission. High plasma n-3 fatty acids were associated with higher odds of achieving remission.

Disclosure: **S. Proudman**, None; **L. Spargo**, None; **C. Hall**, None; **L. McWilliams**, None; **A. Lee**, None; **M. Rischmueller**, None; **R. Gibson**, None; **M. James**, None; **L. G. Cleland**, Melrose Laboratories, 9.

Long-Term Efficacy of Tocilizumab Monotherapy in Patients with Rheumatoid Arthritis Previously Methotrexate Naive or Methotrexate Free for 6 Months. Graeme Jones[1], Anthony Sebba[2], Denise Lepley[3], Jenny Devenport[3], Corrado Bernasconi[4], Devi Smart[5], Chiedzo Mpofu[4] and Juan J. Gomez-Reino[6]. [1]Menzies Research Institute Tasmania, Hobart, Australia, [2]University of South Florida, Tampa, FL, [3]Genentech, South San Francisco, CA, [4]Roche, Basel, Switzerland, [5]Roche Products Ltd, Welwyn Garden City, United Kingdom, [6]Hospital Clinico Universitario, Santiago, Spain

Background/Purpose: Treatment with tocilizumab (TCZ) monotherapy has been studied in 3 randomized clinical trials: AMBITION,[1] ACT-RAY,[2] and ADACTA.[3] AMBITION[1] was the first trial to demonstrate clinical superiority of a biologic monotherapy over methotrexate (MTX) monotherapy: in pts who were MTX naive or MTX free for 6 mos before entry, treatment with TCZ 8 mg/kg monotherapy resulted in statistically greater ACR 20/50/70 responses than MTX at 24 wks. Numeric differences favoring TCZ monotherapy were observed for other endpoints and pt-reported outcomes as early as 2 wks. TCZ was generally well tolerated. In this post hoc exploratory analysis, long-term efficacy was evaluated in pts from AMBITION who remained on TCZ monotherapy in the ongoing long-term extension (LTE) period up to 240 wks. The rate, timing, and nature of the addition of disease-modifying antirheumatic drug (DMARD) for TCZ pts who added DMARDs were also characterized.

Methods: Pts randomized to TCZ 8 mg/kg monotherapy in AMBITION (n=286) who entered the LTE (n=243) were included. During the LTE period, MTX/other allowable DMARD could be added according to the investigator's practice and as tolerated by the pt for those pts who did not achieve a 50% reduction in the number of tender and swollen joints from baseline of the core study. Efficacy assessments and DMARD status were evaluated up to 240 wks.

Results: Of 243 pts assigned to TCZ monotherapy who entered the LTE, 57.2% (n=139) remained on monotherapy in the LTE until withdrawal or data cut, 9.9% (n=24) added a DMARD before LTE entry, and 32.9% (n=80) added a DMARD after LTE entry (18.5% [n=45] ≤3 wks post-entry and 14.4% [n=35] >3 wks post-entry). Added DMARDs included MTX (93% [97/104]), hydroxychloroquine (3% [3/104]), leflunomide (2% [2/104]), and parenteral gold (2% [2/104]). Of the 139 pts who remained on TCZ monotherapy, 102 (73%) reached 240 wks of treatment for this data cut and 37 (27%) withdrew. Mean SJC, TJC, and DAS28 (data not shown) decreased sharply during the first 24 wks, and levels continued to decrease or were maintained thereafter (Table). Similar trends in improved disease state were observed, as shown by 40.1% and 16.7% of pts achieving DAS28 <2.6 and clinical disease activity index (CDAI) remission by wk 24, respectively; rates increased or were maintained thereafter; absolute numbers achieving these endpoints increased to wks 192 and 120 (Table). Absolute numbers of pts achieving DAS28 '3.2 and CDAI low disease activity increased to wks 120 and 96 (data not shown for wk 96), respectively.

Table. Efficacy over time in patients on TCZ monotherapy

Wk[a]	0[b] n = 139	24[c] n = 138	72 n = 126	120 n = 121	168 n = 113	192 n = 108	216 n = 102	240 n = 90
SJC (66 joints) mean (SD)	19.0 (10.36)	4.8 (6.04)	2.7 (4.68)	1.8 (3.09)	2.1 (3.74)	1.7 (3.36)	1.5 (3.13)	1.8 (3.37)
TJC (68 joints) mean (SD)	32.5 (14.39)	10.5 (12.48)	6.2 (8.40)	4.8 (7.47)	4.2 (5.38)	3.7 (5.34)	4.0 (5.61)	3.8 (6.70)
	n = 138	n = 137	n = 121	n = 115	n = 111	n = 107	n = 100	n = 87
DAS28 <2.6 n (%)	0 (0)	55 (40.1)	65 (53.7)	69 (60.0)	70 (63.1)	73 (68.2)	62 (62.0)	58 (66.7)
DAS28 ≤3.2 n (%)	0 (0)	74 (51.8)	90 (74.4)	89 (77.4)	84 (75.7)	82 (76.6)	76 (76.0)	68 (78.2)
	n = 138	n = 138	n = 124	n = 121	n = 112	n = 109	n = 103	n = 90
CDAI remission (≤2.8) n (%)	0 (0)	23 (16.7)	36 (29.0)	52 (43.0)	43 (38.4)	43 (39.4)	39 (37.9)	37 (41.1)
CDAI low disease activity (≤10), n (%)	0 (0)	66 (47.8)	77 (62.1)	85 (70.2)	77 (68.8)	84 (77.1)	80 (77.7)	72 (80.0)

For TJC and SJC, missing data were handled by using the last-observation-carried-forward method. For the physician and patient global assessments of disease activity, no imputation of missing post-baseline values was performed.
[a]Assessed numbers of patients decreased over time because some had not yet reached later assessments or had withdrawn. [b]Baseline in AMBITION. [c]LTE entry.

Conclusion: For the large proportion of pts continuing treatment in the LTE, TCZ monotherapy provided durable efficacy over time, as demonstrated by increasing proportions and/or numbers achieving low disease activity and remission thresholds.

References
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Lack of Additive Benefits of Concomitant Methotrexate Use to Tocilizumab Monotherapy for Rheumatoid Arthritis in Daily Clinical Practice. Keisuke Izumi[1], Yuko Kaneko[2], Hidekata Yasuoka[2], Noriyuki Seta[3], Hideto Kameda[1], Masataka Kuwana[1] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Keio Univ School of Medicine, Shinjuku-ku, Japan, [3]Keio university, Tokyo, Japan

Background/Purpose: To explore the benefit of concomitant use of methotrexate (MTX) for the effectiveness of TCZ in rheumatoid arthritis (RA) patients in daily clinical practice.

Methods: A total of consecutive 115 RA patients initiating TCZ treatment in KEIO university hospital from July 2008 to March 2011 were enrolled. They received 8 mg/kg of TCZ every 4 weeks, and were observed for 52 weeks to evaluate the clinical and structural outcomes as well as safety.

Results: Baseline patient characteristics were as follows: mean age of 55.6 years; mean disease duration of RA of 8.54 years; prior treatment with TNF inhibitors in 46.6%; concomitant use of methotrexate (MTX) in 57.3% and use of concomitant glucocorticoid was in 43.7%. Baseline patients' characteristics were comparable between the combination group of TCZ and MTX and the TCZ monotherapy group. TCZ improved disease activity measured by DAS28-ESR from 5.02 at baseline to 1.97 at week 52; 68.9% of patients achieved DAS28 remission (DAS28-ESR < 2.6 LOCF method), and 50.0% of patients achieved CDAI remission. Structural remission (DTSS≤0.5) was achieved in 60.9% of the patients. The percentages of DAS28 remission, CDAI remission and structural remission in patients who received TCZ as monotherapy were comparable to those in the patients who received TCZ in combination with MTX. The retention rate of TCZ at week 52 was 81.4% in TCZ monotherapy and 86.4% in TCZ plus MTX group. Safety data was comparable between the 2 groups and was as reported in previous study reports.

	TCZ combination with MTX (n=59)	TCZ monotherapy (n=44)	Total (n=103)	p
DAS28-ESR (mean ± SD, at week 52)	2.07 ± 1.18	1.99 ± 0.73	1.97 ± 0.93	0.937*
DAS28-ESR remission (%, at week 52)	62.7	77.3	68.9	0.114**
CDAI remission (%, at week 52)	43.2	57.9	50.0	0.184**
TSS (mean ± SD, at week 52)	0.73 ± 1.52	1.05 ± 3.15	0.87 ± 2.34	0.726*
No progression of joint damage (%, at week 52)	60.9	70.7	60.9	0.266**

* Wilcoxon test between TCZ+MTX and TCZ monotherapy
** Pearson's χ^2 test between TCZ+MTX and TCZ monotherapy

Conclusion: The efficacy of TCZ was observed in RA patients regardless of the concomitant use of methotrexate in real-world clinical practice.

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Factors Influencing Choice of Rituximab Versus an Alternative Tumor Necrosis Factor Inhibitor Following Tumor Necrosis Factor Inhibitor Failure in Patients with Rheumatoid Arthritis: Sub-Analysis of a Global, Observational Comparative Effectiveness Study. Axel Finckh[1], Jacques-Eric Gottenberg[2], Chiedzo Mpofu[3], William G. Bensen[4], Andrea Rubbert-Roth[5], Fedra Irazoque[6], Victor Martínez Taboada[7], Carol Chung[8], Lykke Hinsch-Gylvin[3], Clodoveo Ferri[9] and Paul Emery[10]. [1]University Hospital of Geneva, Geneva, Switzerland, [2]CHU Strasbourg, Strasbourg, France, [3]F Hoffmann-La Roche Ltd, Basel, Switzerland, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON, [5]University of Cologne, Cologne, Germany, [6]Hospital Angeles Mocel, Mexico City, Mexico, [7]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [8]Genentech Inc., South San Francisco, CA, [9]University of Modena and Reggio Emilia, Modena, Italy, [10]University of Leeds, Leeds, United Kingdom

Background/Purpose: SWITCH-RA is a global, observational study evaluating the effectiveness of switching to an alternative TNFi or rituximab (RTX) following initial TNFi failure in patients with RA. The study also assessed the reasons for discontinuation of initial TNFi therapy and factors that drive choice of RTX vs alternative TNFi as subsequent therapy.

Methods: Reasons for initial TNFi discontinuation and rationale for selection of subsequent therapy were recorded. The association between various factors and choice of RTX or alternative TNFi as second biologic were analyzed using logistic regression with a stepwise method for variable selection.

Results: A total of 1107 enrolled patients (mean age 55.5 yrs; mean disease duration 8.3 yrs) were analyzed. Reasons for discontinuing initial TNFi were: lack of efficacy (n=824 [74%]); intolerance (n=264 [24%]); other (n=19 [2%]). In all, 602 (54%) received RTX and 505 (46%) an alternative TNFi as second biologic. Factors associated with choice of RTX or alternative TNFi are shown in the Figure.

Factors associated with choice of RTX or alternative TNFi
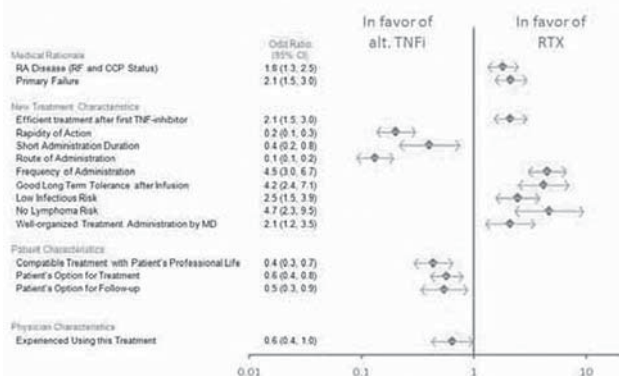
Factors most clearly associated with selection of RTX were generally associated with treatment characteristics related to the safety profile (no lymphoma risk, low infection risk, and good long-term tolerance after infusion) and frequency of administration. Factors most clearly associated with selection of an alternative TNFi were associated with treatment (route of administration, rapidity of action, short administration duration) and patient (treatment being compatible with patient's professional life) characteristics.

Conclusion: Lack of efficacy was the main reason for discontinuation of an initial TNFi. Factors associated with selection of RTX over an alternative TNFi tended to be associated with treatment characteristics related to the safety profile and frequency of administration, while those associated with selection of an alternative TNFi were associated with administration and patient characteristics.

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Biologic Disease-Modifying Anti-Rheumatic Drugs and the Risk of Non-Vertebral Osteoporotic Fractures in Patients with Rheumatoid Arthritis Aged 50 Years and Over. Jean-Pascal Roussy[1], Louis Bessette[2], Sasha Bernatsky[3], Elham Rahme[3] and Jean Lachaine[1]. [1]University of Montreal, Montreal, QC, [2]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC, [3]McGill University, Montreal, QC

Background/Purpose: Chronic inflammation in rheumatoid arthritis (RA) may interfere with bone remodelling. Inflammation mediators such as TNF-α stimulate osteoclast formation which favors bone destruction. Small prospective studies have suggested biologic DMARDs preserve bone mineral density at 6–12 months, but impact on fracture risk is yet to be characterized. Our objective was to determine the risk of non-vertebral osteoporotic fractures in RA subjects aged $\geq$50, comparing outcomes in patients who were exposed or unexposed to biologic DMARDs.

Methods: A population based, retrospective, nested case-control study from January 1 2002 to December 31 2008 was conducted, using Quebec physician billing and hospital discharge data. RA subjects were identified from ICD-9/10 codes in billing (2 RA codes, $\geq$2 weeks apart but within 2 years) and hospitalization (any RA code) data. Subjects were followed until the earliest of: 1) non-vertebral osteoporotic fracture (index date), 2) death, or 3) end of study period. A validated algorithm identified non-vertebral osteoporotic fractures from physician claims. Controls were selected with incidence density sampling, matched to cases (4 to 1 ratio) on age, sex, and date of study entry. Biologic DMARD exposure was defined as being on treatment for $\geq$180 days pre-index. Conditional logistic regression was used, adjusting for: RA duration, comorbidity, history of previous fracture/arthrosplasty, use of traditional DMARDs, osteoporosis medication, hormone replacement, corticosteroids, proton-pump inhibitors, anticonvulsants, opioids, non-steroidal anti-inflammatories, antidepressants, anxiolytics, antipsychotics, medical visits and hospitalizations.

Results: The cohort included 29,666 RA subjects aged $\geq$50. Over the study period, 1,963 fractures were captured (incidence rate: 13.4 per 1000 person-years). Of these, 160 were excluded because they either occurred during the first 180 days of follow-up (where by definition, one could not be exposed to biologic) or controls could not be found. The final number of cases was 1,803 (with 7,175 controls). The most frequent fracture site was hip/femur (43.7%). Cases and controls were mainly older women and most (n=1,233, 68.4%) had a RA duration $\geq$5 years at the index date. In total, 190 subjects (53 cases, 137 controls) were exposed to biologic DMARDs for $\geq$180 days. We were unable to demonstrate a statistically significant association between biologic DMARDs and fracture risk (Odds Ratio, OR [95% Confidence Interval, CI]: 1.16 [0.51–2.62]). RA duration had the strongest impact on fracture risk; for subjects of RA duration $\geq$10 years (vs. <5 years), the OR was 6.40 (95% CI 3.57–11.46), while those with RA duration 5–10 years (vs. <5 years) had an OR of 3.05 (95%CI 1.90–4.89). The inability to detect an effect remained when varying exposure definition, induction period, and definition of corticosteroid use, and when restricting by history of fracture, RA duration, or follow-up time.

Conclusion: Despite the positive impact of biologic DMARDs on bone remodelling observed in small prospective studies, we were unable to demonstrate a reduction in the risk of non-vertebral osteoporotic fractures in older adults with RA.

Disclosure: J. P. Roussy, Pfizer Inc, 1, Pfizer Inc, 3; **L. Bessette**, None; **S. Bernatsky**, None; **E. Rahme**, Pfizer Inc., Merck Inc., 5, Janssen Inc., Pfizer Inc., 2; **J. Lachaine**, None.

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Better Retention RATE At 5 YEARS of ANTI-TNF Agents USED in Conjonction with Methotrexate Over Time in Patients with Rheumatoid Arthritis: REAL-Life DATA From Rhumadata Computerized Database. Denis Choquette[1], Diane Sauvageau[2], Boulos Haraoui[2] and Jean-Pierre Raynauld[2]. [1]Institut de Rhumatologie De Montréal, Montreal, QC, [2]Institut de Rhumatologie de Montréal, Montreal, QC

Background/Purpose: Anti-TNF agents have been in used in Canada for the last ten years. Although a vast body of clinical experience has been accumulated since that time, there are still areas of uncertainty in their usage. One of them is whether usage in monotherapy has a similar clinical efficacy profile than usage in combination with a DMARDS. Products monograph actually disclosed that both usage are officially indicated base on short term Phase III and Phase IV trials results.

Methods: The primary objective of this study is to compare the survival rates of two different anti-TNF agents, adalimumab (ADA) and etanercept (ETA) used as first biologic agent with and without associated DMARDS in the treatment of rheumatoid arthritis (RA) using the data coming from the Rhumadata computarized database at the Institute of Rheumatology of Montreal.

The secondary objective is to evaluate the influence of baseline demographic and clinical data on the primary outcome.

Data for all patients with rheumatoid arthritis according to the ACR criteria included in the database since 2005 and exposed for the first time only to an anti-TNF agents were extracted. Only patients exposed to adalimumab and etanercept were included in this analysis to standardize route of administration. Demographics and baseline clinical data are: age, gender, disease duration, tender joint count (TJC), swollen joint count (SJC), disease activity score including DAS 28 ESR and CRP 3–4 variables, CDAI, SDAI, Rheumatoid Factor and Anti-CCP baseline status, ESR and CRP at baseline, HAQ score, VAS fatigue scale, VAS pain Scale, morning stiffness duration, Dmards and glucocorticoid usage.

Results: Data from 249 patients with rheumatoid arthritis are used. 95 and 154 patients were respectively using adalimumab or etanercept. All baseline demographic and clinical variables were comparable for both group (p≥0.05). There was slightly more usage of Dmards with ADA than ETA (89% vs 78%, p=0.02). TJC slightly lower for ETA than ADA (7.3 vs 9.5, p=0.04). There were more female patients in the monotherapy group than in the combination group (75% vs 90%, p=0.01). The 4 year survival rates (Kaplan-Meier survival proportion) for ADA+DMARDS vs ADA mono are respectively 56% and 11% (p=0.03 Log-rank statistic), for ETA+DMARDS vs ETA mono, 67% vs 47% (p=0.007), for combined ETA-ADA+DMARDS vs ETA-ADA MONO, 62% vs 40% (p=0.001) and for ADA or ETA both on MTX, 67% vs 57% (p=0.12).

Conclusion: Combination of etanercept or adalimumab with a traditional DMARDS agent such as methotrexate exhibit a far better survival rate at 5 years than adalimumab or etanercept used in monotherapy.

Disclosure: D. Choquette, None; **D. Sauvageau**, None; **B. Haraoui**, None; **J. P. Raynauld**, ArthroLab Inc., 4.

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Long-Term Safety of Rituximab: 10-Year Follow-up in the Rheumatoid Arthritis Global Clinical Trial Program. Ronald F. van Vollenhoven[1], Paul Emery[2], Clifton O. Bingham III[3], Edward Keystone[4], Roy M. Fleischmann[5], Daniel E. Furst[6], Nicola Tyson[7], Abdul Mehbob[7] and Patrica B. Lehane[7]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]University of Leeds, Leeds, United Kingdom, [3]Johns Hopkins University, Baltimore, MD, [4]Mount Sinai Hospital, Toronto, ON, [5]University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, TX, [6]UCLA, Los Angeles, CA, [7]Roche Products Limited, Welwyn Garden City, United Kingdom

Background/Purpose: This analysis evaluated the long-term safety of rituximab (RTX) in RA patients (pts) in a global clinical trial program.

Methods: Pooled observed case analysis of safety data from pts with moderate to severe active RA treated with RTX+MTX. Pts were retreated based on physician's determination of clinical need and evidence of active disease (defined as either SJC and TJC ≥8 or DAS28 ≥2.6). Subgroup analysis of pts with follow-up >5 yrs was undertaken. Pooled data from pts who received placebo during placebo-controlled study periods were also analyzed.

Results: As of Sep 2011, 3595 pts (All-Exposure population) had received ≤19 courses of RTX over the 10-yr observation period (14008 pt-yrs). Of these pts, 1145 had follow-up >5 yrs (7716 pt-yrs) (>5 yr). The placebo population comprised 818 pts (1107 pt-yrs) with a mean follow-up of 1–1.5 yrs. In the All-Exposure population, infusion-related reaction (IRR) was the most frequent adverse event (AE); most were grade 1 or 2, were rarely serious, and generally occurred following the 1st infusion of the 1st course (789/3595 pts; 22%). Rates of AEs, serious AEs (SAEs), and infections were comparable across analysis populations and generally remained stable over time and multiple courses (Table). Overall serious infection (SIE) rates in the RTX All-Exposure and >5 yr sub-population were comparable to that observed in the placebo population. Pneumonia was the most frequently reported SIE (2% of RTX pts). There were no cases of hepatitis B reactivation. Two cases of pulmonary tuberculosis (TB), treated with anti-TB medication, occurred in the All-Exposure population, as reported previously.[1] No cases of extra-pulmonary TB, atypical mycobacterial infection, or multidrug-resistant TB were reported. Serious opportunistic infections were rare (0.05/100 pt-yrs in RTX pts vs 0.09/100 pt-yrs in placebo). No further cases of PML in the RA clinical trial program have been reported other than the single case previously described.[2] No increased risk of malignancy over time or course was evident, and MI rates (0.40/100 pt-yrs) were consistent with rates in the general RA population (0.48–0.59/100 pt-yrs).[3]

	AE rates per 100 pt-yrs (95% CI)		
	RTX All-Exposure (n=3595) 14008 pt-yrs	RTX Long-term (>5 yrs) (n=1145) 7716 pt-yrs	Pooled placebo (n=818) 1107 pt-yrs
AEs	249.34 (246.74–251.97)	237.25 (233.83–240.71)	315.43 (305.14–326.06)
SAEs	14.03 (13.42–14.66)	12.25 (11.49–13.05)	13.82 (11.79–16.19)
Infections	78.60 (77.14–80.08)	75.10 (73.19–77.06)	90.39 (84.96–96.17)
Serious infections	3.80 (3.50–4.14)	2.76 (2.41–3.16)	3.79 (2.80–5.13)

Conclusion: These long-term data from 3595 pts treated with RTX over 10 yrs (14008 pt-yrs) of follow-up in clinical trials confirm that RTX remains well tolerated over time and multiple courses with a consistent safety profile. No new safety signals were observed with increasing duration of exposure, including within a subgroup of pts with >5 yrs' follow-up. Apart from IRRs, the overall safety profile of RTX remains similar to that of the pooled placebo population and is consistent with published data for moderate to severe RA and with previous analyses of this pt cohort.

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Real-World Efficacy and Safety of Abatacept Treatment for Rheumatoid Arthritis: 12-Month Interim Analysis of the Action Study. H. Nüβlein[1], R. Alten[2], M. Galeazzi[3], H. M. Lorenz[4], Dimitrios Boumpas[5], M. T. Nurmohamed[6], W. Bensen[7], G. R. Burmester[8], H.-H. Peter[9], F. Rainer[10], Karel Pavelka[11], M. Chartier[12], C. Poncet[13], C. Rauch[14] and M. Le Bars[15]. [1]University Erlangen, Nürnberg, Germany, [2]Schlosspark-Klinik, University Medicine, Berlin, Germany, [3]University of Siena, Siena, Italy, [4]University Hospital Heidelberg, Heidelberg, Germany, [5]Panepistimio Kritis, Rethymnon, Greece, [6]VU University Medical Center/Jan van Bremen Research Institute, Amsterdam, Netherlands, [7]St. Joseph's Hospital and McMaster University, Hamilton, ON, [8]Charité-Universitätsmedizin, Berlin, Germany, [9]University Medical Center Freiburg, Freiburg, Germany, [10]Hospital Barmherzige Brueder, Graz, Austria, [11]Institute of Rheumatology, Prague, Czech Republic, [12]Chiltern International, Neuilly, France, [13]Docs International, Sévres, France, [14]Bristol-Myers Squibb, Munich, Germany, [15]Bristol-Myers Squibb, Rueil Malmaison, France

Background/Purpose: Randomized controlled trials (RCTs) of abatacept (ABA) in patients (pts) with RA have demonstrated sustained, long-term efficacy, high pt retention, and consistent safety.[1] Data from the clinical setting can determine if benefits translate into the real world. We evaluate 1-yr retention, efficacy and safety of ABA in RA pts treated in routine clinical practice (according to label at time of enrollment) in Europe and Canada.

Methods: AbataCepT In rOutiNe clinical practice (ACTION) is an ongoing, non-interventional, prospective cohort of ABA-treated RA pts with inadequate response to MTX or anti-TNF therapy in Europe and

Canada, initiated Mar 2008.[2] At data cut-off in Feb 2012, all pts had reached 1-yr follow-up. Retention rate (Kaplan–Meier estimate) and disease activity (EULAR response) are reported over 12 mths for pts on treatment and with available data, according to whether pts received ABA as a first biologic, or after failure of 1 or ≥2 anti-TNFs. Safety is reported for all enrolled pts, up to data cut-off.

Results: 1138 pts were enrolled and 1120 were evaluable. 1000 (89.3%) had previously failed on biologic treatment, 982/1000 (98.2%) of whom failed ≥1 anti-TNF agent. 120 (10.7%) had not received biologic treatment prior to ABA initiation. Baseline characteristics for the three groups are shown in the Table. Retention rates, reasons for discontinuation and % moderate and good EULAR responders at Mth 12 are presented for ABA when used as the first biologic, first switch agent, and after ≥2 anti-TNFs, and suggest that earlier usage results in higher pt retention (Table). 106 serious adverse events were reported in 60/1138 (5.3%) pts (21 discontinuations). 11 deaths were reported, including 3 due to serious infections (sepsis [4 mths after last ABA infusion; pt was receiving tocilizumab]; *Pneumocystis jiroveci* [4 mths after last ABA infusion, pt had deep vein thrombosis]; and urosepsis) unrelated to ABA. 23 pts experienced serious infections; 9 malignancies; 5 serious cardiac disorders; and 3 serious vascular disorders. No TB occurred, two opportunistic infections were reported (*cytomegalovirus* and *P. jiroveci)*.

Baseline characteristics	ABA first biologic n=120	ABA first switch (1 previous anti-TNF) n=481	ABA after ≥2 previous anti-TNFs n=501
Mean age (SD), years	59.0 (13.8), n=120	56.2 (12.4), n=481	56.0 (12.4), n=501
Mean RA duration (SD), years	7.0 (7.8), n=118	9.8 (8.0), n=465	13.1 (9.4), n=484
≥1 CV risk or comorbidity, n (%)	86 (71.7%), n=120	336 (69.9%), n=481	365 (72.9%), n=501
Mth 12 outcomes			
Retention, Kaplan–Meier estimate (95% CI)	83.6% (74.9, 89.5)	73.2% (68.8, 77.2)	64.1% (59.5, 68.4)
Discontinuation for lack of efficacy, n (%)	11 (9.2%), n=120	75 (15.6%), n=481	101 (20.2%), n=501
Discontinuation for intolerance, n (%)	3 (2.5%), n=120	11 (2.3%), n=481	15 (3.0%), n=501
Good EULAR response	34.5%, n=29	34.5%, n=194	27.3%, n=165
Moderate EULAR response	37.9%, n=29	41.8%, n=194	45.5%, n=165

EULAR response criteria: Moderate/good=DAS28 improvement of ≥0.6 and a DAS28 of ≤5.1; Good=DAS28 improvement of >1.2 and a DAS28 of <3.2; Moderate=DAS28 improvement of >1.2 and a DAS28 of ≥3.2, or DAS28 improvement of 0.6–1.2 and a DAS28 of ≤5.1

Conclusion: This large-scale, international, observational real-life study showed that the use of ABA as the first biologic in MTX-inadequate responders, or after first or later switching from anti-TNFs, was associated with good pt retention over 12 mths, particularly when used earlier in the course of treatment. ABA was clinically effective and well tolerated. These data are consistent with previous RCT findings,[1,3] and national registry data for biologics.[4–6]

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Patterns of Tocilizumab Use, and Dosing Among Patients with Rheumatoid Arthritis in the Clinical Practice. Preliminary Analyses of ACT-Life Study.
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Background/Purpose: Currently, the available evidence about tocilizumab (TCZ) use for the treatment of rheumatoid arthritis (RA) in daily clinical practice is scarce. This study was devised to describe usage patterns of TCZ and reasons for dosage modification (reduction/interruption/discontinuation) in the routine clinical practice, as well as its effectiveness and safety profile under real conditions of use.

Methods: This is a 12-month prospective observational study in 40 Spanish centers. Patients with moderate or severe RA of ≥6 months duration initiated on treatment with TCZ after failure of at least one previous DMARD or TNF inhibitor were included. We present preliminary results at 6-month follow-up

Results: A total of 390 patients were evaluable with a median age of 57 years (47–66) and 83% female. At baseline, patients had mean RA duration of 11.4±8.3 years, 70% were positive for rheumatoid factor and 68% for anti-CCP. Mean DAS28, SDAI, HAQ scores and CRP levels were 5.4±1.2, 22.4±14.9, 1.6±0.7 and 5.8±12.9 mg/dL, respectively. Patients had previously received a mean of 3±1.5 DMARDs and a mean of 2.3±1.2 biological agents, and 97.7% of them initiated TCZ at dose of 8 mg/kg. At the 6-month follow-up, the mean DAS28 decreased significantly from baseline (5.5±1.2 *vs* 2.9±1.4; p<0.001, paired t-test, n=143), and disease remission (DAS28<2.6) was achieved in 48% of patients. Based on EULAR response criteria, 59.4% of patients were good responders, 31.5% moderate responders and 9.1% non-responders. Of all patients, premature withdrawal from the study during the first 6 months was reported in 34 (9%), 14 (41.2%) as a result of adverse events and 12 (35.3%) due to inadequate response. Grade 3/4 neutropenia occurred in 14 (3.6%) patients and grade 3/4 elevation of liver transaminases in 12 (3.1%). No cases of grade 3/4 thrombocytopenia were observed. One hundred and one (25.9%) patients required at least 1 dose reduction and 56 (14.4%) at least 1 temporary dose interruption. In patients intolerant or non-responders to DMARDs, delta DAS28 was significantly higher than in those previously treated with biological agents (3.2±1.2 *vs* 2.4±1.2; p<0.001). No differences in delta-DAS28 were found when TCZ was administered as monotherapy or in combination with DMARDs. Patients with intolerance or inadequate response to DMARDs showed significantly higher percentage of dose reduction than those intolerant or non-responders to biologic agents (36.7% *vs* 23.9%; p<0.05).

Conclusion: These results show that in daily clinical practice, tocilizumab is a safe and effective treatment for moderate or severe RA, with the majority of patients having a good EULAR response and a disease remission being achieved in approximately 50% of patients. Tocilizumab appears more effective when administered as a first-line biological agent. Additionally, TCZ proves to have a similar safety profile regardless of the use pattern as monotherapy or in combination, and the line-biological option may be used.

Subcutaneous Abatacept: Long-Term Data From the Acquire Trial.

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Background/Purpose: The Abatacept (ABA) Comparison of Sub-[QU]cutaneous (SC) versus Intravenous (IV) in Inadequate Responders to MethotrexatE (MTX) (ACQUIRE) study showed comparable efficacy and safety of SC vs IV ABA over 6 mths;[1] here, we present 32-mth data from the long-term extension (LTE), during which all patients (pts) received SC ABA.

Methods: ACQUIRE was a Phase IIIb, 6-mth, double-blind (DB) study of pts with active RA ($\geq$10 swollen and $\geq$12 tender joint count [TJC and SJC], C-reactive protein (CRP) $\geq$0.8 mg/dL) refractory to MTX. Pts were randomized to SC ABA (125 mg/wk) with IV ABA loading (10 mg/kg) on Day 1 or IV ABA (10 mg/kg every 4 weeks) for 6 mths, plus MTX. After 6 mths, pts could enter the open-label LTE to receive SC ABA 125 mg/wk. Safety and efficacy were assessed for pts treated in the LTE, with efficacy presented according to original DB treatment group (as observed). Not all pts had reached later time points at time of analysis, as a result of differential enrollment in the trial.

Results: Of 1372 pts entering the LTE, 1134 (82.7%) remained on therapy at time of reporting. Mean baseline RA duration was 8 yrs, TJC and SJC were 30 and 20, and HAQ-DI was 1.7. The median (range) ABA exposure was 33 (8–44) mths. The incidence rate (IR; events/100 pt-yrs) of serious adverse events for pts treated with SC ABA in the LTE (8.76 [95% CI: 7.71–9.95]) was comparable with that for SC ABA in the DB period (9.02 [6.31–12.90]) and did not increase with increasing exposure (not shown). The IR of overall and serious infections in the LTE (44.80 [41.81–48.01] and 1.72 [1.30–2.27], respectively) did not increase vs the DB period (84.62 [74.50–96.11] and 1.48 [0.62–3.56], respectively). Bacterial, viral and hospitalized infections occurred at IRs of 27.28 (25.16–29.57), 18.25 (16.61–20.06) and 1.55 (1.16–2.07) during the LTE. The IR of malignancy did not increase in the LTE (1.19 [0.86–1.66]) vs the DB period (0.59 [0.15–2.36]). Injection-site reactions occurred in 27 (2.0%) pts in the LTE (none serious) and 19 (2.6%) pts in the DB period. Overall, 139/1365 (10.2%) and 1/153 (0.7%) pts experienced immunogenicity (ECL) during the LTE and DB periods. ACR responses were maintained from Mth 6 to 32 and were comparable for original SC and IV groups (Figure). DAS28 (CRP) <2.6 rates (95% CIs) were 24 (21–27) [n=685] and 25 (22–28) [n=667] at Day 169 and 39 (33–44) [n=288] and 35 (29–40) [n=275] at Day 981 for the original SC and IV groups, respectively. HAQ-DI responses (change from baseline $\geq$0.3) were 73 (95% CI: 69–76) [n=691] and 68% (65–72) [n=672] at Day 169 and 74 (69–79) [n=313] and 70% (65–75) [n=303] at Day 981 for the original SC and IV groups, respectively.
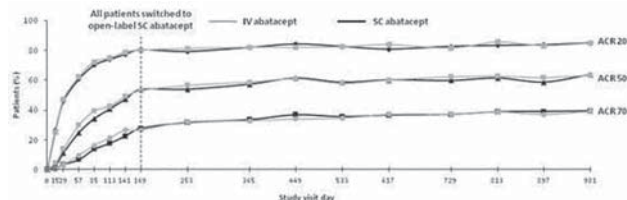
Conclusion: Over 32 months, SC abatacept showed consistent safety with high patient retention (82.7%). ACR, HAQ-DI responses and DAS28 remission rates were maintained through the long-term extension.

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Drug Survival, Efficacy and Predictors for Survival On Tocilizumab in Real-Life Patients with Rheumatoid Arthritis; Results From the Swedish Biologics Register.

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Background/Purpose: To evaluate drug survival, clinical response and predictors for drug survival for tocilizumab in patients with rheumatoid arthritis (RA) with inadequate response and/or adverse effects to previous treatment or contraindications to other medications in ordinary clinical practice, based on prospectively registered data from the Swedish biologics register, Anti-Rheumatic Therapies in Sweden (ARTIS).

Methods: All Swedish RA patients who had started treatment with tocilizumab from Sept, 2006 until March, 2012 were identified in ARTIS. Patients without DAS28 value at start and without known disease duration were excluded and were censored if the duration since the last follow-up extended 18 months. Clinical response was assessed by DAS28 and by EULAR response criteria. Kaplan Meier survival analyses with log-rank test and Cox Proportional Hazard Regression analyses were performed.

Results: 646 RA patients had started with tocilizumab of which 522, 81% were included in this report. 420 (80.5%) were females. The mean (SD) age, disease duration, HAQ, DAS28 and CRP at start was 57.8 (12.8) years, 14.2 (10.7) years, 1.4 (0.6) score, 5.4 (1.3) score and 27 (32) mg/L, respectively. 389 (75.5%) patients had seropositive RA. 185 (35.4%) were on monotherapy whereas 337 (64.6%) were treated with concomitant DMARDs of which 295 (56.5%) methotrexate (MTX). 325 (62.3%) were on corticosteroids. 63 (12%) patients were bionaïve, 278 (53.3%) were treated with $\geq$ 1 TNF-inhibitor, 126 (24.1%) $\geq$ 1 TNF-inhibitor and rituximab/abatacept and 49 (9.4%) with $\geq$ 1 TNF-inhibitor and rituximab and abatacept.

The overall 1 and 2-year estimated drug survival was 63% and 50%, respectively. 390 (74.7%) had $\geq$ 1 DAS28 value between 2.5 and 8 months follow-up, the first value was chosen. The percentages of EULAR Good/Moderate/No responders were 47.2/33.1/19.7%. 55% had DAS28 < 3.2 and 37% was in DAS28 remission. Univariate analyses revealed that men had significantly longer drug survival as compared to women (p=0.013). High CRP or ESR divided into quartiles were associated with longer drug survival, (p=0.0022 and p=0.013, respectively). Patients with HAQ <1.5 had longer drug survival compared to those with HAQ values $\geq$1.5 (p=0.014). Having been exposed to none or increasing number of biologics were associated with inverse drug survival (p=0.0002). Age, disease duration, seropositive RA, DAS28, being on MTX, on any DMARD or on steroids was not associated with drug survival. In the multivariate analysis with the above significant predictors as independent covariates, adjusted for age, the Hazard Ratios were: sex 0.79 (95% CI 0.52–1.19), HAQ 1.34 (95% CI 1.05–1.70), previous biologics 1.39 (95% CI 1.17–1.67) and CRP 0.80 (95% CI 0.69–0.91, per 1 SD change).

Conclusion: In this cohort of real-life patients with longstanding RA treated with tocilizumab the estimated 1-year drug survival was 63%, about 80% of the patients achieved a EULAR Good/Moderate response and drug survival was predicted by high CRP, low HAQ and no/low exposure of biologics. Treatment with concomitant MTX, DAS28, disease duration or age was not predictors for drug survival.

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Rituximab for Treatment of Rheumatoid Arthritis: Treatment Effectiveness in the Corrona Database. Leslie R. Harrold[1], George W. Reed[1], Robert P. Magner[1], Katherine C. Saunders[2], Jeffrey D. Greenberg[3], Joel M. Kremer[4], Ani John[5], William Reiss[5], Steve Zlotnick[5] and Ashwini Shewade[5]. [1]University of Massachusetts Medical School, Worcester, MA, [2]CORRONA, Inc., Southborough, MA, [3]New York University School of Medicine, New York, NY, [4]Albany Medical College, Albany, NY, [5]Genentech Inc., South San Francisco, CA

Background/Purpose: Rituximab (RTX) in combination with methotrexate is used for the treatment of adult RA with an inadequate response to TNF antagonists. We aimed to describe the real-world use and effectiveness of RTX in a large cohort of patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry.

Methods: All patients with RTX initiations in CORRONA between Feb 2006 and May 2011, with available clinical disease activity index (CDAI) score at baseline and at 12-months and not in remission (CDAI ≤2.8) at the time of RTX initiation, were included. Demographic and disease characteristics at baseline; change in CDAI at 12 months (overall and based on number of prior TNFs); and reported safety events were summarized.

Results: Overall, 615 patients (mean 2.3 previous non-biologic disease-modifying anti-rheumatic drugs [DMARDs] and 2.2 prior biologic DMARDS) initiated RTX. Lack of efficacy was most commonly (65%) reported reason for discontinuing prior biologic. Of these, 265 patients (80% female; median age 57 years; median disease duration 13 years) met the inclusion criteria. Approximately 43% of the patients had received 1 prior TNF and 57% had ≥2 prior TNFs. Approximately 77% patients started RTX in combination with DMARDs and 42% with concomitant prednisone. Mean change in CDAI was −8.1 (95% CI: −9.8; −6.4) for all RTX initiators not in remission, with similar results when stratified by number of prior TNFs. Among the subset of patients with active disease (moderate/high disease activity; CDAI >10) at baseline (Table), 8% went into remission and 29% achieved low disease activity (LDA). The mean change in CDAI in these patients was −10.3 (95% CI: −12.3; −8.4) with similar results when stratified by 1 or ≥2 prior TNFs. However, more patients with 1 prior TNF went into remission or achieved LDA versus patients with ≥2 prior TNFs. Patients with 1 prior TNF were more likely to achieve remission or LDA (unadjusted odds ratio 0.40 [95% CI: 0.22; 0.73]). Among patients who started RTX with concomitant prednisone, 43% decreased and 26% had no change in their prednisone dose at 12 months. Reported rates of all cardiovascular events, serious infections, and malignancies were 1.9 (95% CI: 0.6; 4.0), 1.6 (95% CI: 0.5; 4.9), and 1.5 (95% CI: 0.6; 4.0) per 100 person-years, respectively.

Change in disease activity in patients with moderate/high disease (CDAI >10) at baseline

CDAI at 12-months	All RTX initiators (n=218)	IR to 1 prior TNF (n=87)	IR to ≥2 prior TNFs (n=131)
Remission (CDAI ≤2.8) (n, %)	18 (8.3)	9 (10.3)	9 (6.9)
Low disease activity (2.8<CDAI ≤10) (n, %)	64 (29.4)	35 (40.2)	29 (22.1)
Mean change in CDAI (95% CI)	−10.3 (−12.2; −8.4)	−10.1 (−13.2; −7.0)	−10.5 (−12.9; −8.0)

Conclusion: RTX appeared effective in usual care in patients with previous exposure to one or more prior TNFs, with a safety profile comparable to randomized controlled trials of RTX. More patients with 1 prior TNF versus ≥2 prior TNFs appeared to achieve improvement in disease activity at 12 months after initiating RTX. The magnitude of response in CDAI seemed to be similar regardless of number of prior TNFs, even with ≥2 prior TNFs, suggesting good response in more refractory RA patients.

CDAI = clinical disease activity index; CI = confidence interval; TNF = tumor necrosis factor-α antagonist.

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The Comparative Effectiveness of Oral Methotrexate Versus Subcutaneous Methotrexate for the Treatment of Early Rheumatoid Arthritis. Glen S. Hazlewood[1], J. Carter Thorne[2], Janet Pope[3], Gilles Boire[4], Boulos Haraoui[5], Carol A. Hitchon[6], Edward Keystone[1], Diane Tin[2], CATCH Investigators[7] and Vivian P. Bykerk[8]. [1]University of Toronto, Toronto, ON, [2]Southlake Regional Health Centre, Newmarket, ON, [3]Schulich School of Medicine and Dentistry, Western University, London, ON, [4]CHUS - Sherbrooke University, Sherbrooke, QC, [5]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [6]University of Manitoba, Winnipeg, MB, [7]Toronto, ON, [8]Hospital for Special Surgery, New York, NY

Background/Purpose: To determine the comparative effectiveness of subcutaneous (sc) versus oral methotrexate (MTX) as initial therapy for patients with early rheumatoid arthritis (ERA) in routine clinical care.

Methods: Patients with early inflammatory arthritis initiating methotrexate therapy were included from the Canadian Early Arthritis Cohort (CATCH), a multicenter, prospective cohort study of patients with ERA. In CATCH patients are treated at the discretion of the rheumatologist and followed every 3 months over the first year according to a standardized protocol. For this study, all patients had an age >16 years, a diagnosis of RA by 2010 criteria, symptom duration < 1 year, used MTX within 3 months of study entry and were MTX-naïve or minimally exposed to MTX. The exposure was route of MTX (oral vs. sc) and the outcome was DAS-28 over the first year (3, 6, 9, 12 months). A multilevel random-effects linear regression model was used to account for repeated measures within patients while adjusting for potential confounders: age, gender, comorbidities, smoking, education, symptom duration, serological status, erosions, baseline DAS-28, functional status (HAQ-DI), and other concurrent DMARDs or corticosteroids. The analysis was performed with and without adjusting for the starting dose of MTX and clustering of patients by treatment center.

Results: 653 patients were included (442 oral MTX, 211 sc MTX); mean age 54 (SD 14), 72% female, mean symptom duration 5.3 (SD 2.7) months, mean baseline DAS-28 4.6 (SD 1.2). Patients treated with sc MTX were more likely to have erosions at baseline (35% vs. 25%, p=0.01), were less likely to receive other DMARDs (38% vs. 58%, p<0.01), and had a higher median starting dose of MTX (25 mg vs. 15 mg, p<0.01). Other characteristics were similar between groups. In the repeated measures model, after adjusting for all potential confounders except starting dose of MTX, sc MTX was associated with a reduction in the average DAS-28 score over the first year of 0.23 [(95%CI:0.08, 0.38), p<0.01]. After adjusting for starting dose, the route of MTX (oral/sc) was no longer significant (p=0.22), but for each additional mg of MTX, the average DAS-28 decreased by 0.02 [(95%CI:0.004, 0.03), p=0.02]. After controlling for treatment center, neither route nor starting dose was significantly associated with DAS28 at follow-up.
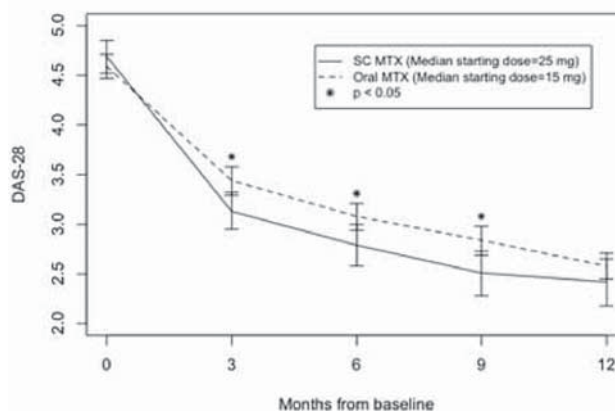
Conclusion: Sc MTX was associated with lower DAS28 scores over the first year of treatment, which may be mediated through the higher starting dose used in clinical practice. There was no relationship after adjusting for treatment center, suggesting caution in generalizing the results and highlighting the importance of considering a treatment center effect when reporting comparative effectiveness research from observational studies.

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Synovialitis Plus Articular Cartilage Monitoring Via Magnetic Resonance Imaging and Ultrasound Under Tocilizumab Therapy in Patients with Rheumatoid Arthritis. Maria Hoehle[1] and Michael Finkenstaedt[2]. [1]Rheumatology, Hamburg, Germany, [2]Private Practice for Radiology and Neuroradiology, Hamburg, Germany

Background/Purpose: To determine remission in RA, recent publications point out the importance of radiological parameters, besides scores like DAS28, TJC, SJC, CrP, patient global assessment, or the SDAI. [1] Inflammatory activity can remain despite clinical remission in RA.[2] This process can be monitored with modern imaging without radiation exposure – high-field MRI and colour and power Doppler sonography. These diagnostic methods are also valuable for the determination of an OFF therapy or an individual dose adaption.[3] The latest adaptions allow the precise monitoring of cartilage and subchondral bone under cytokine therapy in clinical practice.

The course of chronic active inflammation at affected joint structures can be quantitatively and qualitatively measured by aforementioned techniques. The aim is to optimize and control biologic therapy.

Methods: 22 RA-patients (12 men, 10 women, between 20 and 72 years of age) with high disease activity at baseline (DAS 28 over 3.3, CRP over 10, ESR over 20, fibrinogen over 470 mg/dl, RF positive, high erosion tendency (anti-CCP positive)) were treated 8mg TCZ/kg body weight from 08/2008 until now, data were analyzed retrospectively. 3 female patients from each group received TCZ (iv q4w) in combination with MTX, while all other patients received TCZ in monotherapy.

Examination criteria at baseline and before infusion administration were DAS 28, serum fibrinogen, colour and power Doppler ultrasound examination, and every 3 to 6 months high-field MRI (T1 T2 STIR KM 3.0 T; panorama image) of the affected joints' inflammation activity, the cartilage, or the subchondral bone. The evaluation was carried out using MRI (RAMRIS) and sonography score.

Results: Of the 22 patients observed 10 patients (6 men, 4 women) exhibited early or very early RA (group A); 5 patients (1 man, 4 women) established RA with low articular cartilage destruction and erosion (Sharp score of up to 2; group B); and 7 patients (3 men, 4 women) chronically established RA (Sharp Score 3; group C) at baseline.

After 12 week, all inflammation parameters, including DAS 28, were within the normal range. Inflammation activities could still be detected by Doppler ultrasound imaging and MRI. Cartilage imaging showed no erosions and changes in the subchondral bone in group A during the course of the therapy. In group B, the cartilage and bone erosion also stopped. In group C, the cartilage or subchondral bone destruction progressed, despite the decrease of inflammation parameters.

Conclusion: The cytokine therapy with tocilizumab leads to a rapid decrease in the inflammation parameters and hence to a normalization of DAS 28. The inflammation-verifying imaging such as the aforementioned Doppler sonography and the high-field MRI still registered inflammation activities during the course of the therapy. The use of TCZ as mono therapy for early and very early RA extensively decreases the inflammation process and prevents cartilage/bone destruction. In chronically established, advanced RA (Sharp score 3), the systemic inflammation can be inhibited, while the cartilage and subchondral bone destructions remained progressive during the course of the disease.

Disclosure: M. Hoehle, None; **M. Finkenstaedt**, None.

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Seropositive Rheumatoid Arthritis Patients with an Inadequate Response to Tumor Necrosis Factor Inhibitors Achieve Improved Clinical Effectiveness After Switching to Rituximab Versus Switching to an Alternative Tumor Necrosis Factor Inhibitor. Andrea Rubbert-Roth[1], Axel Finckh[2], Piercarlo Sarzi-Puttini[3], Jacques-Eric Gottenberg[4], Denis Choquette[5], Victor Martínez Taboada[6], Leonor Barile-Fabris[7], Carol Chung[8], Lykke Hinsch-Gylvin[9] and Paul Emery[10]. [1]University of Cologne, Cologne, Germany, [2]University Hospital of Geneva, Geneva 14, Switzerland, [3]L Sacco University Hospital, Milan, Italy, [4]CHU Strasbourg, Strasbourg, France, [5]University of Montreal, Notre-dame Hospital, Montreal, QC, [6]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [7]Hospital de Especialidades Centro Médico Nacional Siglo XXI, Mexico City, Mexico, [8]Genentech Inc., South San Francisco, CA, [9]F Hoffmann-La Roche Ltd, Basel, Switzerland, [10]University of Leeds, Leeds, United Kingdom

Background/Purpose: RA patients (pts) with an inadequate response (IR) to a tumor necrosis factor inhibitor (TNFi) may achieve greater benefit by switching to rituximab (RTX) than to an alternative TNFi.[1] Seropositive pts achieve greater clinical responses to RTX than seronegative pts.[2,3] SWITCH-RA, a global, multicenter, prospective, observational, clinical practice study, evaluated the relative effectiveness of RTX vs an alternative TNFi in pts with an IR to a single previous TNFi. The objective of this subanalysis was to compare the relative effectiveness of RTX vs an alternative TNFi according to serotype.

Methods: This was a prospective, observational cohort study, designed to evaluate in routine practice the relative clinical outcomes of RTX or a second TNFi to which pts were switched following a single TNFi failure. Primary endpoint was 6-month change from baseline in DAS28 based on DAS28(3)-ESR. Analysis of covariance adjusting for unbalanced baseline characteristics was used for treatment cohort comparisons, with missing DAS28(3)-ESR values imputed with nearest-timepoint values.

Results: Overall, 728 pts were included (RF+ and/or anti-CCP+ [seropositive], n=559; seronegative, n=169). Of seropositive pts, 331 and 228 received RTX or an alternative TNFi; corresponding numbers for seronegative pts were 74 and 95, respectively. In both seropositive and seronegative pts, at time of switch, baseline DAS28(3)-ESR (SD) scores were higher in the RTX than in the alternative TNFi group (5.2 [1.2] vs 4.8 [1.3] p<0.0001, and 5.3 [1.1] vs 4.7 [1.3] p=0.0019, respectively). After adjusting for baseline differences, in seropositive pts receiving RTX, DAS28(3)-ESR improved significantly at 6 months vs pts switching to an alternative TNFi (table). The relative benefit of RTX varied in seropositive pts according to the reason for interrupting the previous TNFi (inefficacy/intolerance). In seronegative pts, improvements in DAS28(3)-ESR at 6 months were not significantly different between RTX and alternative TNFi pts. At 6 months, greater decreases in ESR (LS mean [SE]) were observed in seropositive pts receiving RTX than in those receiving an alternative TNFi (−14.4 [4.5] vs −7.3 [4.8] p=0.006); corresponding results in seronegative pts did not reach statistical significance (−13.4 [8.3] vs −10.4 [9.0] p=0.582).

Changes in DAS28(3)-ESR at 6 months

LS mean (SE)	Seropositive patients (n=559)			Seronegative patients (n=169)		
	RTX	TNFi	p-value	RTX	TNFi	p-value
All patients	−1.6 (0.3)	−1.2 (0.3)	0.011	−1.3 (0.4)	−1.1 (0.4)	0.449
Inefficacy	−1.9 (0.3)	−1.5 (0.4)	0.021	−0.5 (0.6)	−0.2 (0.7)	0.472
Intolerance	−0.5 (0.5)	−0.5 (0.5)	0.997	−2.1 (1.2)	−1.9 (1.3)	0.815

Patient numbers (all/inefficacy/intolerance): seropositive RTX=331/253/74; TNFi=228/171/51; seronegative RTX=74/58/15; TNFi=95/65/28

Conclusion: Following discontinuation of a first TNFi, seropositive pts switching to RTX achieved significantly improved effectiveness over 6 months, in particular those interrupting therapy due to inefficacy, compared with pts switching to an alternative TNFi. These differences were not evident in seronegative pts.

References:
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Disclosure: A. Rubbert-Roth, Roche, Pfizer, 2, Roche, Chugai, Abbott, Pfizer, UCB, MSD, 5, Roche, UCB, Chugai. MSD, 6, Roche, UCB, Chugai, MSD, 8; **A. Finckh**, Roche, Pfizer, BMS, 2, Roche, Pfizer, BMS, 5; **P. Sarzi-Puttini**, Roche, Pfizer, UCB, Abbott, 2; **J. E. Gottenberg**, Roche, Pfizer, MSD, Abbott, 5; **D. Choquette**, Roche Pharmaceuticals, 8; **V. Martínez Taboada**, Schering-Plough, Wyeth-Pharma, Roche, 2, UCB-Pharma, Bristol Myers Squibb, Roche, Cellerix, Pfizer, 5; **L. Barile-Fabris**, Roche, 5; **C. Chung**, Genentech, Inc (full time), 3; **L. Hinsch-Gylvin**, F Hoffmann-La Roche Ltd, 3; **P. Emery**, Pfizer, Merck, Abbott, BMS, Roche, UCB, 5.

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Adalimumab Treatment Is Associated with Decreased Concomitant Rheumatoid Arthritis Medication Use Over 24 Months. Daniel E. Furst[1], Neelufar Mozaffarian[2], Shannon Grant[3], Mary Cifaldi[2], Jerry Clewell[2], Joel M. Kremer[4] and James Shaw[2]. [1]University of California at Los Angeles, Los Angeles, CA, [2]Abbott Laboratories, Abbott Park, IL, [3]Axio Research LLC, Seattle, WA, [4]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Adalimumab (ADA) is an effective medication in the treatment of rheumatoid arthritis (RA). However, it is not clear whether the use of ADA is associated with altered use of concomitant RA medications. A study was conducted to examine changes in the use of concomitant RA medications after initiation of ADA.

Methods: The Consortium of Rheumatology Researchers of North America, Inc. (CORRONA) registry is a multi-center, longitudinal rheuma-

tology database (for physical examination data, laboratory tests, and patient outcomes) from more than 90 academic and private sites across the US. We examined RA patients enrolled in CORRONA between March 2002-September 2011 who initiated ADA and had at least one follow-up visit. RA-related concomitant medications (methotrexate [MTX], prednisone, nonsteroidal anti-inflammatory drugs [NSAIDs], intra-articular joint injections [IAs]), antidepressant use, comorbidities (high blood pressure, cardiovascular disease, lymphoma, other cancers, liver disorders, asthma, chronic obstructive pulmonary disease, diabetes mellitus, psoriasis), and demographics (age, sex, disease duration, insurance status) were examined. Trends in medication use over time were estimated using random effects logistic regression adjusting for sex, age, the number of comorbidities at initiation, and the use of ADA at each time point. Analyses included all patients with follow-up at 6, 12, 18, or 24 months after ADA initiation.

Results: Of the 1,173 patients who initiated treatment with ADA, available follow-up decreased over time to 417 patients by 24 months. The mean (SD) age and disease duration were 54.2 (12.3) and 10.1 (9.2) years, respectively, and 79.3% of patients were female. At baseline, 67% of patients were treated concomitantly with MTX, 30% with prednisone, 61% with NSAIDs, 8% with IAs, and 30% with antidepressants. Multivariable trend analysis revealed MTX and prednisone use to decrease over 24 months following ADA initiation (table). Controlling for time of follow-up and other factors, patients with $\geq$2 comorbidities were less likely to use MTX and more likely to use antidepressants than those with no comorbidities. The number of comorbidities was unrelated to prednisone, NSAID, or IA usage.

Concomitant Medication	Multivariable Trend Analysis 24 Months vs. Initiation OR (95% CI)	P-Value	Influence of Comorbidities $\geq$2 vs. 0 Comorbidities OR (95% CI)	P-Value
MTX	0.68 (0.48 − 0.95)	0.05	0.48 (0.29 − 0.80)	0.01
Prednisone	0.61 (0.43 − 0.86)	0.003	0.90 (0.56 − 1.44)	NS
NSAIDs	0.77 (0.57 − 1.04)	NS	1.15 (0.75 − 1.76)	NS
Antidepressants	1.00 (0.71 − 1.40)	NS	2.45 (1.55 − 3.88)	<0.001
Intra-articular injections	1.05 (0.67 − 1.64)	NS	1.06 (0.63 − 1.77)	NS

Abbreviations: OR, odds ratio; CI, confidence interval; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; NS, not significant.

Conclusion: Among RA patients who initiated treatment with ADA, MTX and prednisone decreased over 24 months. This suggests the clinical efficacy of ADA in RA disease control across a medically diverse patient population.

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Intra Articular Injections in Patients with Rheumatoid Arthritis: Analyses From the Behandelstrategiën Study. E. Gvozdenovic[1], L. Dirven[1], M. van den Broek[1], Kh Han[2], T.H.E. Molenaar[3], R. Landewe[4], W.F. Lems[5] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Maasstad hospital, Rotterdam, Netherlands, [3]Groene Hart Hospital, Netherlands, [4]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [5]VU University medical center, Amsterdam, Netherlands

Background/Purpose: Intra articular (IA) corticosteroid injections aim at amelioration of symptoms of local inflammation in rheumatoid arthritis (RA). Some patients also report a systemic effect. In treat-to-target strategies IA injections may help to achieve low disease activity. Our aim was to investigate the immediate and late effects on pain, disease activity and functional ability over time of IA injections and to compare the subsequent disease course in injected versus non-IA injected RA patients.

Methods: In the BeSt study IA injections were allowed in all four treatment strategy arms at the discretion of the treating rheumatologist. We evaluated the effect of IA injections administered in large joints in the first year of treatment. We compared pain scores (Visual Analogue Scale (VAS)), Disease Activity Score (DAS) and local joint swelling and tenderness before and after injection. The subsequent disease course in IA injected versus non-IA injected patients was compared using a linear mixed model (LMM) to model the DAS and the Health Assessment Questionnaire (HAQ) score over time. Considered confounders were age, gender, DAS at baseline, treatment strategy, body mass index (BMI), anticitrullinated peptide antibodies

(ACPA), rheumatoid factor (RF) and DAS at time of outcome HAQ or HAQ at time of outcome DAS.

Results: 61 patients received >=1 IA injections in the large joints, mostly in shoulders (34%) and knees (31%). Pre-injection, local joint swelling was scored in 48% of injected joints, and local tenderness in 64%. Three months after the injection, 56% of the swollen joints were no longer swollen and 52% of the tender joints were no longer tender. Mean (SD) DAS before was 3.7 (1.3) and after was 3.3 (1.4) respectively (p<0.01), with a mean (SD) VAS for pain of 52 (26) before and 39 (26) after IA injection (p<0.01). Significantly more IA injections were given in the first year of treatment with initial methotrexate monotherapy than in the initial combination therapy arms (including either prednisone or infliximab), p<0.01. LMM showed a significantly higher DAS and HAQ in patients who received IA injections in year 0–1 compared to those who did not (mean DAS (SD) 3.07 (0.10) versus 2.75 (0.04), p<0.01) mean HAQ (SD) 0.90 (0.04) versus 0.82 (0.02), p=0.03), and no significant difference in subsequent years (table 1). Patients who were injected in year 0–1 had a similar number of treatment adjustments in subsequent years compared to patients who were not. Radiological damage after 8 years was present in 18% of the X-rays of injected joints, and in14% of the X-rays of non-injected joints.

Table 1. Mean DAS and mean HAQ in injected patients versus non injected patients

| | Injected in the first year (yes/no) | | |
	yes	No	P-value
Year 0–1			
Mean DAS (SE)	3.06 (0.10)	2.75 (0.04)	<0.01
Mean HAQ (SE)	0.90 (0.04)	0.82 (0.02)	0.03
Year 1–2			
Mean DAS (SE)	2.03 (0.10)	1.86 (0.04)	0.10
Mean HAQ (SE)	0.62 (0.05)	0.58 (0.02)	0.39
Year 1–8			
Mean DAS (SE)	1.81 (0.08)	1.68 (0.03)	0.13
Mean HAQ (SE)	0.64 (0.05)	0.58 (0.02)	0.3

Conclusion: Our data suggest that IA injections have moderate short term and limited long term efficacy in patients with early RA.

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Concomitant Assessment of Clinical and Ultrasound Efficacy and Safety of Tocilizumab in Patients with Moderate to Severe Rheumatoid Arthritis: The Torpedo Study. Thierry Schaeverbeke[1], Philippe Gaudin[2], Aleth Perdriger[3], Christian Roux[4], Muriel Vray[5], Stephanie Rouanet[6], Ghislaine Steinberg[6] and Fabien Etchepare[7]. [1]Groupe Hospitalier Pellegrin, Bordeaux, France, [2]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [3]Hôpital Sud, Rennes, France, [4]Paris Descartes University, Paris, France, [5]Paris, France, [6]Roche, Boulogne, France, [7]G.H. Pitié-Salpêtrière, Paris, France

Background/Purpose: The anti-IL6-R tocilizumab (TCZ), indicated for the treatment of moderate to severe rheumatoid arthritis (RA), has demonstrated its clinical and structural efficacy in phase III, but little information is available on concomitant ultrasound and clinical evolution.

Methods: 103 patients with moderate to severe RA were treated with TCZ 8 mg/kg+ methotrexate (MTX) in the Torpedo study every 4 weeks during 12 months. 40-joint ultrasound (US) examinations (B and Doppler (D) modes scores 0 to 120) were performed at baseline, 12, 24 and 48 weeks of treatment in parallel with usual clinical parameters assessments (DAS28, SJC, TJC). Doppler score was semi-quantitative, graded as 0(normal), 1, 2 or 3 (worst) for each joint and for each US mode following a pre-established coding guideline. Analysis was performed on the intent-to-treat population (patients with at least one TCZ infusion). Non-responder imputation was performed for DAS 28 and CDAI remissions.

Results: 103 patients main characteristics at baseline were: mean age 52±12, disease duration 4±3 years, 75% women, 66% DMARD IR*, 74% with concomitant steroid treatment, mean DAS 28 = 5.5±1.0. *Efficacy*: under TCZ + MTX, percentage of patients in DAS28 and CDAI remission increased in parallel with decrease in B and D modes ultrasound scores (table 1). Among the patients on DAS 28 remission at W48, 28 were on DAS28 remission for at least 6 months, and 15% of them had no synovitis in B mode

and 56 % had no Doppler signal (D mode). At week 48, 17% /39% of patients under steroids at baseline could discontinue/decrease steroid dose below 5mg equivalent prednisone/day at W 48. *Safety*: reported AE's** (97% of patients with at least one AE) and SAE's** (23% of patients with at least one SAE) were in accordance with the known safety profile of TCZ.

Table 1. Clinical and ultrasound evolution of patients

	Baseline	W12	W24	W48
Number of patients in the analysis	*103*	*103*	*103*	*103*
% patients in remission DAS 28	0	36	42	46
% patients in remission CDAI	0	8	16	22
Number of patients in the analysis	*103*	*94*	*87*	*77*
40-joint US D mode mean score±Sd	10.4±12.4	5.2±6.9	4.0±5.1	3.2±5.2
Median[Q1; Q3]	7[2; 14]	3[1; 7]	2[0; 6]	1[0; 5]
40-joint US B mode mean score±Sd	26.2±17.5	18.2±14.3	14.3±11.0	11.4±10.9
Median[Q1; Q3]	21[12; 37]	14[8; 25]	11[6; 21]	9[3; 18]

*IR = inadequate responder **AE = adverse event, SAE = serious adverse event

Conclusion: In this study, parallel efficacy was shown in RA patients treated with TCZ on clinical, ultrasound scores together with steroid sparing effect. However, long term clinical remission could be associated with persistence of Doppler signals and synovitis on ultrasound. Safety profile was consistent with the previously published data.

Disclosure: T. Schaeverbeke, Roche Pharmaceuticals, Pfizer, UCB, Abbott, BMS, 5, Roche Chugai, 2; **P. Gaudin**, Abbott, BMS, 5, Abbott, MSD, Pfizer, Chugai, Roche, 2; **A. Perdriger**, Roche-Chugai, 2; **C. Roux**, Roche-Chugai, Servier, Amgen, Lilly, Abbott, Novartis, 2; **M. Vray**, Roche-Chugai, 2, GSK, 5; **S. Rouanet**, Roche Pharmaceuticals, 3; **G. Steinberg**, Roche Pharmaceuticals, 3; **F. Etchepare**, Roche-Chugai, Abbott, Esaote, Pfizer, 5.

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Efficacy and Safety of Golimumab As Add-On Therapy to Disease-Modifying Antirheumatic Drugs. Bernard Combe[1], Bhaskar Dasgupta[2], Ingrid Louw[3], Sarvajeet Pal[4], Jürgen Wollenhaupt[5], Cristiano Zerbini[6], Andre D. Beaulieu[7], Hendrik Schulze-Koops[8], Patrick Durez[9], Ruji Yao[10], Nathan Vastesaeger[11] and Holly Weng[10]. [1]Hôpital Lapeyronie-Service d'Immuno-rhumatologie, Montpellier, France, [2]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [3]Panorama Medical Centre, Cape Town, South Africa, [4]Advance Rheumatology Clinic, Hyderabad, India, [5]Schön-Klinik, Hamburg, Germany, [6]Centro Paulista de Investigações, Sao Paulo, Brazil, [7]Centre de Rhumatologie, St. Louis, QC, [8]University of Munich, Munich, Germany, [9]UCL Saint-Luc, Brussels, Belgium, [10]Merck Sharp and Dohme, Kenilworth, NJ, [11]Merck Sharp and Dohme, Brussels, Belgium

Background/Purpose: This study evaluated golimumab (GLM) as add-on therapy in patients with active RA despite treatment with non-biologic DMARDs. Two GLM treatment strategies (subcutaneous [SC] vs intravenous [IV]/SC combination) for induction and maintenance of remission were evaluated.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients with active RA (DAS28-ESR ≥3.2). In Part I, patients received 50-mg SC GLM once monthly for 6 months. The primary outcome was the percentage of patients with good or moderate EULAR DAS28-ESR response at 6 months. Effects of several variables on response were evaluated: MTX dosage, type of concomitant DMARDs, corticosteroid (CS) use, and number of failed DMARDs. In Part II, patients who achieved good or moderate response but not remission at 6 months were eligible for random assignment to treatment up to month 12 with either continued 50-mg SC GLM once monthly or a combination of IV GLM and SC GLM. The coprimary efficacy endpoints in Part II were the percentage of patients with EULAR DAS28-ESR remission at the beginning of month 11 and the end of month 12. Treatment effects were evaluated with chi-square tests.

Results: At baseline of Part I, 3280 efficacy-evaluable patients had mean age 52.3 (SD=12.8) years, median disease duration 4.9 years, mean HAQ-DI 1.44 (SD= 0.67), and mean DAS28-ESR 5.97 (SD=1.10). Concomitant MTX was used by 81.1% of patients; concomitant CSs by 63.4% of patients. 34.4%, 35.9%, and 29.7% of patients failed 1, 2, and 3 DMARDs, respectively. At month 6, 82.07% (2692/3280) of patients achieved a good or moderate EULAR DAS28-ESR response and 23.90% (784/3280) achieved remission. No statistically or clinically significant differences were seen when treatment response was compared for patients who received concomitant MTX or CS vs those who did not, for high- vs low-dose MTX, or for patients who failed multiple vs only 1 DMARD. In Part II, 490 responders who were not in remission were evaluable for efficacy. The 2 treatment arms had similar

DAS28-ESR remission rates at the month-11 and -12 endpoints (ranging from 24% to 27%) and were similar in the time to first remission. GLM was generally well tolerated. Observed SAEs were consistent with those observed in RA patients treated with anti-TNF agents. In Part 1, SAEs occurred in 5.7% of patients and 10 deaths (0.2%) occurred. In Part II, SAEs occurred in 6.9% and 2.4% of patients in the IV/SC and SC arms, respectively, and 1 death occurred in the IV/SC arm.

Conclusion: In patients with active RA despite DMARD therapy, addition of GLM 50-mg once monthly resulted in moderate or good EULAR DAS28 response at 6 months for 82.07% of patients. Response to GLM was not impacted by use of concomitant MTX or CS, dose of concomitant MTX, or number of failed DMARDs. Of patients with response but not remission at month 6, approximately 25% achieved remission after 6 additional months of GLM treatment. The IV/SC regimen provided no additional efficacy over the SC regimen and was associated with a higher incidence of AEs. The safety profile for the SC regimen was consistent with previous studies of GLM.

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More Positive Expectations of Treatment with Golimumab for Rheumatoid Arthritis Are Associated with Greater Improvement in Clinical Outcomes. Bhaskar Dasgupta[1], Bernard Combe[2], Ingrid Louw[3], Sarvajeet Pal[4], Jürgen Wollenhaupt[5], Cristiano Zerbini[6], Andre D. Beaulieu[7], Hendrik Schulze-Koops[8], Patrick Durez[9], W. Bensen[10], V. Wolff[11], Ruji Yao[12], Holly Weng[12] and Nathan Vastesaeger[13]. [1]Southend University Hospital, Westcliff-on-Sea, United Kingdom, [2]Hôpital Lapeyronie-Service d'Immuno-rhumatologie, Montpellier, France, [3]Panorama Medical Centre, Cape Town, South Africa, [4]Advance Rheumatology Clinic, Hyderabad, India, [5]Schön-Klinik, Hamburg, Germany, [6]Centro Paulista de Investigações, Sao Paulo, Brazil, [7]Centre de Rhumatologie, St. Louis, QC, [8]University of Munich, Munich, Germany, [9]UCL Saint-Luc, Brussels, Belgium, [10]St. Joseph's Hospital and McMaster University, Hamilton, ON, [11]Hospital del Salvador, Santiago, Chile, [12]Merck Sharp and Dohme, Kenilworth, NJ, [13]Merck Sharp and Dohme, Brussels, Belgium

Background/Purpose: Little is known about how patient and physician expectations relate to clinical outcomes. This study investigated the expectations that patients and physicians have at the start and after 3 months of treatment with golimumab (GLM) for RA and evaluated the relationship between these expectations and treatment outcomes.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients who had active RA despite DMARD treatment. All patients received 50-mg subcutaneous GLM once monthly for 6 months. At baseline and after 3 months of treatment, patients rated their overall expectation of how well their treatment would control RA symptoms. They also rated the ability of the treatment to relieve specific symptoms and improve quality of life 3 months later using 5-point Likert scales (1=good outcome, 5=poor outcome). Patients were then divided into tertiles of expectation scores: high (≤1.5), medium (>1.5 to <1.86), or low (≥1.86). Patients indicated which attribute they wanted to improve most. Physicians were asked to predict patient disease state 3 months later and selected (from the same list used by patients), the attribute they thought patients most wanted to improve.

Results: At baseline, 3280 patients had mean age of 52.3 (SD=12.8) years, median disease duration of 4.9 years, mean HAQ-DI of 1.44 (SD=0.67) and had moderate (21.3%) or high disease activity (78.7%). Prior to starting treatment, 95.9% of patients expected GLM to be better than their

current DMARD treatment. After 3 months of treatment, 85.1% expected the treatment to be more effective still by month 6. The attributes patients wanted to improve most were pain and quality of life, with pain selected by most patients at baseline and quality of life selected by most following 3 months of treatment. Patients with more positive expectations about treatment had greater improvement in DAS28-ESR and HAQ scores and were more likely to show good EULAR response at month 6 than patients with less positive expectations (**Table 1**).

Table 1. Relationship Between Patients' Baseline Treatment Expectations and Improvement in Outcomes

Baseline Treatment Expectation	DAS28-ESR			HAQ			DAS28-CRP	
	Baseline, Mean (N)	Change at Month 6, Mean (SD)	P Value[a]	Baseline, Mean (N)	Change at Month 6, Mean (SD)	P Value[a]	Achieved EULAR Response, n/N (%)	P Value[a]
High (≤1.5)	6.03 (1212)	−2.43 (1.377)		1.40 (1211)	−0.65 (0.691)		1030/1212 (84.98)	
Medium (>1.5 to<1.86)	6.00 (1009)	−2.28 (1.386)	NS[b]	1.43 (1009)	−0.55 (0.610)	<0.0001	827/1009 (81.96)	NS[b]
Low (≥1.86)	5.86 (1054)	−2.04 (1.344)	<0.0001	1.48 (1053)	−0.44 (0.583)	<0.0001	805/1054 (76.38)	<0.0001

[a]P values are for pairwise comparison with high expectation group.
[b]P values >0.001 are considered to be nonsignificant.

At baseline, physicians expected 29.6% of patients to attain remission and 59.2% to attain low disease activity after 3 months of treatment. At the end of month 3, they expected 38.8% to attain remission and 53.1% to attain low disease activity by the end of month 6. Physicians identified pain and tender and swollen joints as the issues they thought their patients most wanted to improve.

Conclusion: Despite similar baseline scores, patients with more positive expectations about outcomes of GLM treatment demonstrated better outcomes than patients with less positive expectations.

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The Addition of Another Disease-Modifying Anti-Rheumatic Drug to Methotrexate in Place of Infliximab Reduces the Flare Rate During 2 Years After Infliximab Discontinuation in Patients with Rheumatoid Arthritis. Hideto Kameda[1], Takahiko Kurasawa[1], Hayato Nagasawa[2], Koichi Amano[3] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Saitama Medical Ctr, Kawagoe, Japan, [3]Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Background/Purpose: The treatment strategy for rheumatoid arthritis (RA) should be divided into remission-induction phase and its maintenance phase. To date, the usefulness of the combination therapy of disease-modifying anti-rheumatic drugs (DMARDs) has been exclusively examined in remission-induction phase. Therefore, we examined whether the addition of another conventional DMARD to methotrexate (MTX) in place of infliximab (IFX) could decrease the rate of disease flare after discontinuing IFX in well-controlled RA patients. The BuSHIDO (Bucillamine Study of Holding remission after Infliximab Dose-Off) trial is a prospective, randomized, controlled study comparing MTX monotherapy with MTX plus bucillamine (Buc), a DMARD structurally related to d-penicillamine, as to flare rate during the following 2 years.

Methods: RA patients who had been receiving 6 or more infusions of IFX, maintaining DAS28-CRP > 2.6 (or DAS28-ESR<3.2) for more than 6 months, were randomized to either the addition of Buc 200 mg/day to MTX (the group 1) or non-addition of bucillamine (the group 2) upon discontinuing IFX. Primary endpoint was the flare rate (DAS28-ESR>3.2 and DAS28-CRP>2.6) within 2 years. The proportions of patients who met given criteria were compared with Fisher's exact test.

Results: Finally, 24 and 31 patients, providing a written informed consent, were assigned to the group 1 and 2, respectively. Patients discontinuing MTX during the study period (2 in the group 1, and 4 in the group 2) had been excluded from the subsequent analyses. Seven patients experienced flares in the group 1, while 17 patients did in the group 2. Notably, Buc treatment was discontinued in seven patients because of rash (n=5), reversible proteinuria (n=1) and incompliance (n=1). Three of those seven patients experienced disease flare. The flare rates were 26.7% in Buc-continuing patients and 42.9% in Buc-discontinuing patients, respectively, in the group 1, while it was significantly higher in the group 2 (63.0% versus 31.8% in the whole group 1, p=0.045). Moreover, the flare rates sorted by the achievement of Boolean remission upon IFX discontinuation were significantly different in the group 2 (40.0% in patients achieving remission versus 91.7% in non-remission patients; p=0.014), while the flare rates were similarly reduced in the group 1 (29.4% versus 40.0% in remission and non-remission, respectively).

Conclusion: The combination therapy of non-biological DMARDs, such as bucillamine plus MTX, may be a better treatment strategy rather than MTX monotherapy for maintaining RA remission after the discontinuation of biological agents.

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Dose Reduction in Rituximab Retreatment May Delay Achievement of Optimal Responses. Mohammed I. Sharif[1], Sudipto Das[2], Paul Emery[3], Helen MacIver[1], Wendy Shingler[1], Philip S. Helliwell[2], Katharina Sokoll[1] and Edward M. Vital[2]. [1]Bradford Teaching Hospitals NHS Foundation Trust, Bradford, United Kingdom, [2]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom

Background/Purpose: The best long-term treatment strategy for rituximab has not been established. Retreatment at a fixed interval of 6 months maintains stable disease activity[1] and half-dose is equally effective in first-cycle responders[1]. In first-cycle non- or moderate responders, responses may improve further after a second cycle at full dose[2,3.]

We used a strategy of fixed 6-monthly retreatment at half-dose following an initial full dose cycle in responders and non-responders, and looked for changes in clinical response.

Methods: Patients received 2×1000mg rituximab at month 0 (C1), 2×500mg rituximab at month 6 (C2) and 2×500mg at month 12 (C3) regardless of C1 response. All patients were positive for RF and/or anti-CCP. 18/41 were taking concomitant MTX and 9/41 other DMARDs. 2 patients were taking concomitant oral prednisolone. DAS28 was measured at baseline and at 3–6 months after each cycle and compared to baseline of the first cycle.

Results: To date, 41 patients received C1, 34 C2, 17 C3 and 14 C4 with outcome data. For all patients, mean(SD) DAS28 at baseline and after C1, C2 and C3 were 6.15(0.74), 4.14(1.10), 3.82(1.14) and 3.13(1.06) respectively. EULAR Non/Moderate/Good responses were achieved by 5, 28 and 8/41 patients (12/68/20%) in C1; 5, 18 and 11/34 patients (15/53/33%) in C2; 1, 6, 10/17 patients (6/35/59%) in C3; and 1, 3 and 10/14 patients in C4 (7/21/71%). 3/5 patients with Non response in C1 responded to C2.

Proportions of patients with a change in EULAR response between C1-C2 and C2-C3 was compared for the 17 patients who received 3 cycles. For C1-C2: 53% patients maintained the same EULAR response, 18% improved and 29% worsened. For C2-C3, 47% maintained the same response, 41% improved and 12% worsened. DAS28 for these patients is shown in Figure 1. There was no significant difference between C1 and C2 and a trend to reduction in DAS28 after C3 (p=0.128, paired t-test).
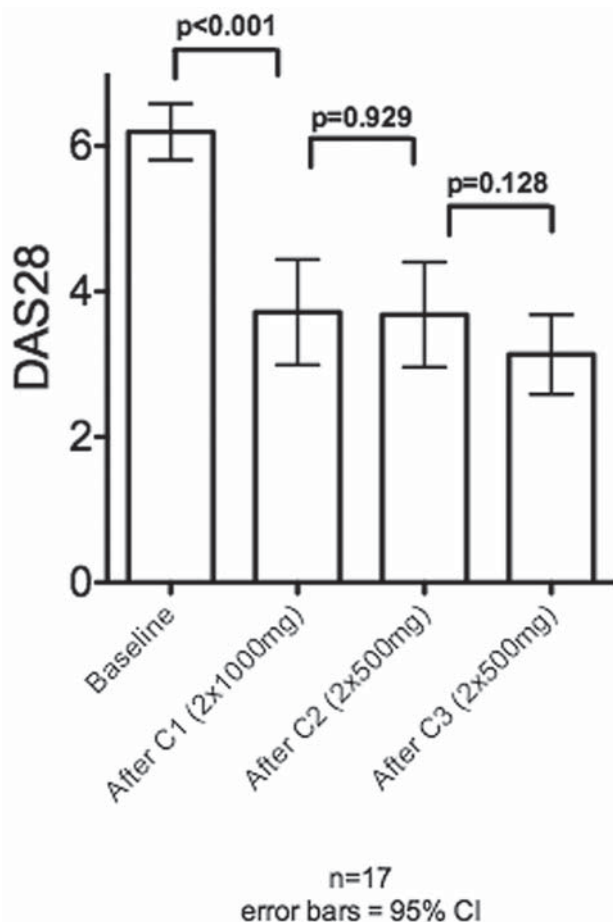
Figure 1. DAS28 at baseline and after C1(2×1000mg) and C2 and C3 (2×500mg).

Conclusion: Some C1 non-responders responded to retreatment with half-dose at 6 months, but response rate across all patients was similar. Incremental improvements in C1 non- or moderate responders were seen more frequently after a second half-dose retreatment. This suggests that dose reduction may delay achievement of optimal responses in C1 non- or moderate responders, and these patients should have 2 full-dose cycles before reducing doses. Future work will analyse B cell depletion in this cohort.

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Immunologic Responsiveness in Patients with Juvenile Idiopathic Arthritis On Methotrexate and Etanercept: 23 Valent Pneumococcal Vaccination. Ankur A. Kamdar[1], Patricia C. Giclas[2] and Barry L. Myones[3]. [1]University of Texas Medical School at Houston, Houston, TX, [2]National Jewish Health, Denver, CO, [3]Baylor College of Medicine, Houston, TX

Background/Purpose: There is a paucity of data regarding response to vaccinations in patients with juvenile idiopathic arthritis (JIA) treated with methotrexate (MTX). It is also unclear whether biologic agents affect vaccination response. Data was previously reported on the secondary response to protein vaccination with tetanus. This study investigates the primary response to polysaccharide vaccination in this same cohort.

Methods: Patients with a diagnosis of polyarticular JIA on stable doses of NSAIDS and/or MTX for a minimum of 3 months were enrolled into this prospective study. All patients were naïve to both Pneumovax and Prevnar (7-valent) vaccines. All patients received 0.5 cc Pneumovax (23-valent) subcutaneously. Serum was obtained at vaccination and after 4–6 weeks. 12 Pneumoccocal serotypes were measured (1, 3, 4, 6b, 7f, 8, 9n, 12f, 14, 18c, 19f, 23) by standard EIA. Positive response was considered a 2-fold increase in titer. 200 ng Ab N/mL was considered clinically protective by the clinical laboratory. Serum was subjected to C4 allotyping, immunoglobulin and complement levels to examine alternative causes for non-response. Statistical analysis was performed using parametric and non-parametric methods when appropriate.

Results: 50 patients were included for analysis. 3 additional patients were excluded because of reaction to vaccination requiring steroid treatment. Patients were subdivided into MTX and non-MTX groups for primary analysis. 38 patients were on MTX (n=16 on MTX + etanercept) & 12 patients were on NSAIDS. There was no statistical difference between the 2 groups in the 2-fold response for all serotypes. In addition, there was no difference in 2-fold response in the etanercept+MTX vs MTX vs non-MTX groups. The number of serotypes each group responded to was similar. 39 patients had a response to at least 1 serotype (36 to at least 2). In 11 patients who did not respond, there were no differences in proportion of patients on MTX or etanercept. For each serotype, the pre-dose geometric mean concentrations (GMC) were all greater than 200 ng Ab N/ml. Post immunization GMCs were similar in 9 of 12 serotypes between the MTX and non-MTX groups. Etanercept use did not influence this result. In the other 3 serotypes (1, 6b, 23), the MTX group had significantly higher post-GMCs. There were significant increases in post-GMCs for all serotypes. There was no difference in geometric mean ratio (GMR) for 10 of 12 serotypes between the 2 groups. Of interest, for the other serotypes (1, 18c), the MTX group had a significantly higher GMR when compared to the non-MTX group. Serotype 14 was the most immunogenic (GMR 2.57, 95% CI 1.92, 3.44) while serotype 3 was the least (GMR 1.37, 95% CI 1.08,1.74). Baseline age, MTX dose, or etanercept use did not predict response to pneumococcal vaccine.

Conclusion: In a non-immunized population of patients that were Prevnar naive, with only environmental exposure to Pneumoccocus, use of MTX and etanercept did not diminish humoral response to Pneumovax. All serotypes had post GMCs that were clinically protective. In addition, despite extended use of MTX and etanercept, most patients had protective pre-immunization titers. Future studies will address response to live virus vaccines.

Disclosure: A. A. Kamdar, None; **P. C. Giclas**, None; **B. L. Myones**, None.

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Effects of Vitamin D Repletion and Maintenance Therapy On Clinical Indicators of Disease Activity in Rheumatoid Arthritis. Uzma J. Haque[1], Clifton O. Bingham III[2] and Susan J. Bartlett[3]. [1]Johns Hopkins Hospital, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]McGill University, Montreal, QC

Background/Purpose: Low Vitamin D levels are prevalent in Rheumatoid Arthritis (RA). We have previously reported that low vitamin D levels are associated with higher disease activity indicators and poorer patient reported outcomes (PROs). Our goal was to investigate the effect of vitamin D repletion and maintenance therapy in vitamin D deficient patients on clinical indicators of disease activity.

Methods: 139 persons who met 1987 ACR RA criteria were enrolled in an RCT at routine clinic visits from 1/2009 – 4/2011. Exclusion criteria included hypercalcemia and hyperparathyroidism. Tender and swollen joint counts (TJC, SJC) and evaluator disease assessments were performed. 25(OH)D levels were assessed using the Diasorin radioimmunoassay. Patients with 25(OH)D levels < 30 ng/ml were randomly assigned to receive either standard intensive therapy [50,000 IU ergocalciferol/week for 8 or 16 weeks] till repletion (25(OH)D > 30 ng/ml was achieved] + 16 weeks of maintenance therapy (50,000 IU ergocalciferol /month) or placebo for 16 weeks, followed by the above vitamin D protocol. At baseline visit, 83 of 139 (60%) patients had 25(OH)D levels < 30 ng/ml. **Results** show the effects of vitamin D repletion and maintenance therapy (independent of original treatment assignment).

Results: Patients had a mean (SD) age of 52.5 (12.8) yr, RA duration of 9.8 (9.6) yr and BMI of 31.8 (6.8) kg/m2 and were mostly female (83%),

white (76%), well-educated (60% reported some college education) and non-smokers (61%). Of 73 who began repletion therapy, 58 were sufficient after 8 wks of therapy; 6 were sufficient after 16 weeks of therapy and 3 failed to achieve adequate levels. During maintenance, 62 people completed 8 wk and 61 completed 16 wk of therapy. Vitamin D increased an average of 71% (mean increase 17.3 [12.9]; range $-22.4 - +57.8$ ng/ml) during repletion then declined steady during maintenance (see Table). Increases in Vitamin D were inversely and moderately associated with baseline vitamin D (r=-.43; p<.001) but not with age, sex, minority status, BMI, RA duration or smoking status. Disease activity score (DAS) and TJC significantly (p<.05) increased during treatment and decreased during maintenance; other clinical indices were not significantly different at any time point.

	Repletion		Maintenance	
	Start	End	8 weeks	16 weeks
25(OH)D	24.0 ± 7.9	41.6 ± 11.7	33.9 ± 9.1	29.5 ± 6.7
DAS-28 CRP	**3.0 ± 1.4**	3.3 ± 1.4	–	3.0 ± 1.5
CDAI	11.9 ± 12.4	12.9 ± 13.5	13.3 ± 14.3	12.5 ± 12.4
Tender Joints	**5.3 ± 7.1**	6.4 ± 8.1	6.8 ± 8.8	5.3 ± 7.4
Swollen Joints	3.1 ± 4.1	3.4 ± 4.6	2.5 ± 4.1	3.1 ± 4.1
MD GAF	17.6 ± 19.4	15.1 ± 16.4	15.8 ± 17.3	15.2 ± 15.0

Conclusion: Intensive repletion therapy modestly increased vitamin D levels in RA patients with 25(OH)D < 30 ng/ml. However, patients were unable to maintain adequate levels over 16 weeks of maintenance therapy. With the exception of tender joints which increased during treatment then returned to baseline levels following maintenance, other clinical indices remained stable throughout treatment. Thus, in RA patients who are insufficient, standardized intensive vitamin D protocols appear to only modestly increase circulating levels of 25(OH)D and do not impact clinical indicators of RA disease activity.

Disclosure: U. J. Haque, None; **C. O. Bingham III**, None; **S. J. Bartlett**, None.

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Impact of Etanercept On Incident Cancer in Taiwanese Patients with Rheumatoid Arthritis. Jiunn Horng Chen[1] and Wen-Miin Liang[2]. [1]China Medical University Hospital, Taichung City, Taiwan, [2]China Medical University, Taichung, Taiwan

Background/Purpose: The recent Taiwanese report has indicated an elevated risk of malignancy in RA patients[1]. Etanercept, one of the tumor necrotic factor inhibitors (TNF-I) to treat severe rheumatoid arthritis (RA), has been approved in Taiwan for 10 years. Its effect in ameliorating inflammation in RA has been shown prominent. Although the potential risk of TNF-I on cancer in RA patients has been reported, the impact of TNF-I in Asian RA patients is still lacking. We used the National Health Insurance Database in Taiwan to investigate if etanercept impacts on incident cancer in RA patients.

Methods: A prospective one-to-one case-control study matched with age, gender, index day (prescription date of etanercept), RA duration (from the date of RA diagnosis to the index day), dosage and duration of methotrexate usage was conducted. Cancer incidence, including solid-tumor and hematological malignancy, was compared in RA patients between etanercept users and those who were naïve to the TNF-I. Cox proportional hazard model was used for analysis.

Results: Among the 1,931 matched pairs (3,180 women and 682 men with the mean age of 53.8 years) during a mean follow-up of 3.7 years, 36 subjects were found cancer in the case-cohort (31 solid-tumor and 5 hematologic malignancy), and 48 in the control-cohort (46 solid-tumor and 2 hematologic malignancy). The incidences of total cancer in subjects with RA duration within 1 year and 1–2 years were 37.0 x10^{-3} and 11.6 x10^{-3} person-years in the case-cohort, which were lower than those of 127.2 x10^{-3} and 27.9 x10^{-3} person-years in the control-cohort, respectively (the corresponding p=0.002 and 0.03). On the other hand, the incidences of total cancer in subjects with RA duration within 2–3 years and more than 3 years were 12.8 x10^{-3} and 2.8 x10^{-3} person-years in the case-cohort, which were higher than those of 6.7 x10^{-3} and 1.9 x10^{-3} person-years in the control-cohort, respectively (the corresponding p=0.15 and 0.35). The incidence of hematologic malignancy in the case-cohort was 0.95 x10^{-3} person-years, which was 2.5 times higher than that of 0.38 x10^{-3} person-years in the control-cohort (p=0.26). Although no statistically significant risk of etanercept was noted for total cancer after multivariate adjustment, hazard ratios for solid tumor and hematologic malignancy were 0.70 (95% confidence interval, 0.44–1.33) and 2.17 (0.42–11.23), respectively.

Conclusion: A potential benefit of etanercept was shown for patients with shorter RA duration by a trend of lower cancer incidence in the etanercept users compared with controls, which was contrasted to the findings noted for patients with RA duration more than 2 years. Although a trend of higher risk of hematologic malignancy for etanercept users than controls was noted in the current study, we may not conclude a significantly higher risk for RA patients received etanercept than those who received the convention treatment to develop cancer. Further investigation is needed in the future.

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Disclosure: J. H. Chen, None; **W. M. Liang**, None.

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Body Mass Index Negatively Influences the Response to Infliximab in Rheumatoid Arthritis. Sébastien Ottaviani[1], Anais Gardette[2], Emilie Quintin[2], Karen Dawidowicz[2], Ghislaine Gill[2], Elisabeth Palazzo[3], Olivier Meyer[3] and Philippe Dieude[2]. [1]APHP, Paris, France, [2]APHP, Hopital Bichat, Paris, France, [3]Hopital Bichat, Paris, France

Background/Purpose: The excess of adipose tissue in obese individuals may have immunomodulating properties and pharmacokinetics consequences. Adipose tissue is potentially involved in the regulation of inflammation in rheumatoid arthritis (RA). Recently, an exploratory study suggested that body mass index (BMI) could affect infliximab (IFX) treatment responses in RA patients (1)

The aim of this study was to investigate whether body mass index (BMI) affects the response to IFX in RA patients

Methods: In this retrospective study were included RA patients fulfilling the ACR 1987 criteria and receiving infliximab therapy. All individuals provided informed written consent as approved by the local ethic committee board. The BMI was assessed before the initiation of IFX treatment (3 mg/kg intravenously). After 6 months of treatment, changes in disease activity (DAS28) were assessed. The primary end point was the EULAR DAS28 response. The following covariates were included for the analysis: gender, anti-CCP antibodies and RF status, mean disease duration, erythrocyte sedimentation rate (ESR), CRP level, DAS28, concomitant DMARDS therapy and corticosteroids consummation.

Results: A total of 73 RA patients (age: 48.5 ± 10.5 years, 82% of females, disease duration: 8.8 ± 6.9 years, 77% RF+, 86% anti-CCP +) were included. At M0, BMI was 27.1 ± 6.9 kg/m^2. Patients were classified in 3 distinct groups according to their BMI: normal (BMI < 25 kg/m^2), overweight (BMI [25–30] kg/m^2) and obesity (BMI > 30 kg/m^2). At baseline no difference was observed between the 3 BMI subgroups according to the RA covariates, notably the DAS28. The EULAR non-response was found to be only influenced by 2 independent factors: a lower initial DAS28 (4.9 ± 1.4 *vs* 5.9 ± 1.0, $P = 0,012$) and a higher BMI (29.5 ± 8.7 vs 25.2 ± 3.9 kg/m^2, $P = 0.013$). When the 3 BMI subgroups were independently analyzed, the negative influence of BMI on response to IFX was only found in obese patients ($P = 0.008$, OR 5.2 [1.3–23.2]) in comparison to normal BMI group.

Conclusion: Our study supports the previously reported negative correlation between BMI and infliximab response in RA. Further prospective studies, including assessment of the fat mass, pharmacokinetics and adipokines dosages are mandatory to elucidate the role of obesity and the fat mass in modulating the RA IFX response.

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Active Immunization with TNF-Kinoid in Rheumatoid Arthritis Patients with Secondary Resistance to Tumor Necrosis Factor-Alpha Antagonists Is Safe and Immunogenic. Patrick Durez[1], Pedro Miranda[2], Antoaneta Toncheva[3], Alberto Berman Sr.[4], Oscar L. Rillo[5], Yves Boutsen[6], Tatjana Kehler[7], Eugenia Mociran[8], LiAn Soto Saez[9], Bruno Fautrel[10], Xavier Mariette[11], Panayot Solakov[12], Eleonora Lucero[13], Tonko Vlak[14], Simeon Grazio[15], Ksenija Mastrovic[16], Rodica Chiriac[17], Géraldine Grouard-Vogel[18], Olivier Dhellin[18], Stéphane Ouary[18], Pierre Vandepapeliere[18] and Marie-Christophe Boissier[19]. [1]Université Catholique de Louvain, Brussels, Belgium, [2]Centro de Estudios Reumatologicos, Santiago de Chile, Chile, [3]National Multiprofile Transport Hospital, Sofia, Bulgaria, [4]Hospital Padilla, Tucuman, Argentina, [5]Hospital Tornú, Buenos Aires, Argentina, [6]UCL Mont-Godinne, Godinne, Belgium, [7]Thalassotherapia Opatija, Opatija, Croatia, [8]Emergency County Hospital Dr Constantin Opis, Maramures, Romania, [9]Sociedad Medica del Aparato Locomotor SA, Santiago de Chile, Chile, [10]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [11]Université Paris-Sud, Le Kremlin Bicetre, France, [12]Diagnostic and Consulting Center, Plovdiv, Bulgaria, [13]Centro Investigaciones Reumatológicas, Tucumán, Argentina, [14]University Hospital Split, Split, Croatia, [15]Clinical Hospital Center Sestre Milosrdnice, Zagreb, Croatia, [16]Clinical Hospital Sveti Duh, Zagreb, Croatia, [17]Rehabilitation clinical Hospital Iasi, Iasi, Romania, [18]NEOVACS SA, Paris, France, [19]Hopital Avicenne, Bobigny, France

Background/Purpose: Blocking TNF alpha (TNFα) with monoclonal antibodies (mAbs) has been successful in the treatment of rheumatoid arthritis. However secondary resistances are frequent and impose treatment changes. Active immunization with a TNF-Kinoid that safely induces self polyclonal anti-TNFα antibodies (Abs) could be an alternative to anti-TNFα mAbs. We evaluated the immunogenicity and safety of TNF-K in patients with rheumatoid arthritis and secondary resistance to TNF blockers.

Methods: TNFα-Kinoid (TNF-K, Neovacs SA, Paris, France) is an immunotherapeutic composed of recombinant human TNFα conjugated to KLH, inactivated and adjuvanted with ISA-51 emulsion. 40 patients with active rheumatoid arthritis (DAS28$\geq$3.2) with history of positive clinical response to at least one TNF-blocker followed by secondary failure (35% IFX, 30 % ADA, 42.5% ETA) were enrolled in a double-blind, placebo-controlled, phase 2 study to evaluate three different intramuscular doses of TNF-K (90, 180, 360 mcg) and two immunization schedules (D0 and 28 or D0, 7 and 28). Humoral immune responses were evaluated through titration of anti-TNFα and anti-KLH Abs and neutralization assay. The T cell response was assessed by lymphoproliferative assay with tritiated thymidine incorporation. Clinical response was evaluated by the ACR and EULAR core set response.

Results: No related serious adverse event has been reported. Few minor transient local and systemic reactions have been recorded following immunization. Anti-TNFα Abs were induced in 50%, 75% and 91% of patients at 90 mcg, 180 mcg and 360 mcg, respectively. 100% of patients with three injections of 180 or 360 mcg had immunogenic response against TNF versus 67% in the groups receiving two injections. The anti-TNF antibody geometric mean titres were higher in patients who received 3 injections of 360 mcg. No lymphoproliferative response could be measured after stimulation with native TNF. Among the 21 patients who developed anti-TNF Abs, 48% present a moderate to good response according to EULAR score as opposed to only 31% of the 16 patients without Abs. A mean decrease of -14% of the C reactive protein level is measured in patients with Abs while in patients without Abs, the mean CRP level increased by 5%.

Conclusion: Active immunization with TNFα kinoid to induce a polyclonal, self-anti-TNFα antibody response is safe and immunogenic. A clear dose-response was observed for the dose of kinoid as well as for the number of administrations. Association of anti-TNF Abs induced by the kinoid with clinical and biological responses were observed in patients included in this preliminary phase 2 study. Further studies are needed to confirm this new approach in RA.

Etanercept Induces A Significant Decrease of Oxidative Stress and Osteoprotegerin Compared with Sdmard in Patients with Rheumatoid Arthritis. Claire I. Daien[1], Anne-Marie Dupuy Gorce[1], Edith Pinot[1], Thibault Mura[2], Jean-Paul Cristol[1], Bernard Combe[1] and Jacques Morel[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]Hopital Gui De Chauliac, Montpellier, France

Background/Purpose: TNF-inhibitors are known to decrease cardiovascular events in rheumatoid arthritis (RA) as compared with synthetic disease modifying anti-rheumatic drugs (sDMARD). However, mechanisms involved remain to be explored. Osteoprotegerin (OPG) is increased and independently associated with coronary-artery atherosclerosis in patients with RA. Adiponectine has cardioprotective functions and joint-destruction role in RA. Oxidative stress, especially urinary F(2) isoprostanes, predicts cardiovascular mortality and is increased in RA. We aimed to explore metabolic parameters changes after 6 months of anti-TNF therapy or sDMARD in patients with RA.

Methods: Twenty-four patients were included in the etanercept (ETN) group and 17 in the sDMARD group. Metabolic parameters were evaluated at baseline and at 6 months. HOMA was calculated as (insulin*glycemia)/22.5. Urinary F(2) isoprostanes were assessed using negative ion chemical ionization gas chromatography-mass spectrometry. OPG and total adiponectine levels were determined by enzyme linked immunosorbent assay. Changes were evaluated using paired-t-tests or Wilcoxon matched-pairs signed rank tests and correlations using spearman tests.

Results: Patients of the ETN group had a significantly longer RA duration, were more often RF and ACPA positive and had more often erosions and steroids. Patients had similar blood pressure, body mass index (BMI), glycemic and lipid parameters, homocystein, OPG and isoprostanes at baseline in both groups. Adiponectine tended to be higher in ETN group (196 [126–228] vs 136 [196–286] μg/ml, p=0.08).

Isoprostanes at baseline correlated with triglycerides (r=0.42, p<0.05) and inversely correlated with HDL (r=$-$0.37, p<0.05), HbA1c (r=$-$0.38, p<0.05).OPG at baseline correlated with age (r=0.48, p<0.01), DAS28 (r=0.38, p<0.05), CRP (r=0.53, p<0.01), HbA1c (r=0.51, p<0.01).

A significant decrease of BMI at 6 months was observed in the ETN group (-0.6 ± 1.4 kg/m^2, p<0.05 and 1.8 ± 0.62 kg/m^2 in ETN and sDMARD group respectively). The BMI variation was significantly different between the 2 groups (p=0.02). No correlation was found between BMI change and steroid changes. No change in mean blood pressure, HOMA, HbA1c, cholesterol and homocystein was observed after 6 months of either treatment. A significant decrease of OPG (-0.93 ± 1.64 pmol/l, p=0.03 vs 0.35 ± 2.05 pmol/l, NS; respectively in ETN and sDMARD groups), isoprostanes (-227 ± 243 pmol/mmol of urinary creatinine, p=0.01 vs -18 ± 141, NS) and a tendancy to adiponectine increase (62 ± 217 μg/ml, p=0.08 vs -13 ± 67 μg/ml, NS) was found in patients treated with ETN at 6 months whereas no change was observed in the sDMARD group. Variations were different between the 2 groups for isoprostanes (p<0.05), with a tendancy for OPG (p=0.06) and adiponectine (p=0.09). Isoprostanes and OPG changes were not correlated with DAS28 or CRP variations between baseline and 6 months.

Conclusion: ETN induced a decrease of oxidative stress and OPG which may partially explain the protective cardiovascular effect of TNF inhibitors.

Duration of Sustained Remission and Differences in Responce Between Medications, in Tumor Necrosis factor inhibitor Treated Rheumatoid Arthritis Patients. Jon T. Einarsson[1], Pierre Geborek[2], Tore Saxne[3] and Meliha C. Kapetanovic[4]. [1]Dept of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Sweden, Lund, Sweden, [2]Lund University, Lund, Sweden, [3]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [4]Dept of Clinical Sciences Lund, Lund, Sweden

Background/Purpose: Remission is increasingly becoming a treatment goal in rheumatoid arthritis (RA) patients and DAS28 remission criteria are widely used, despite their limitations.

The purpose of this study was to study frequency, duration, and timing of sustained remission (SR) defined as DAS<2.6 for at least 6 months, and to compare efficacy of different therapies, in patients with established RA treated with Tumor Necrosis Factor inhibitors (aTNF) in the observational setting of Southern Sweden.

Methods: aTNF treatments in RA patients registered in the SSATG register were eligible for this study. Remission time was defined as time between first visit after treatment initiation with DAS28<2.6 and subsequent visit with DAS28>2.6.

The comparison of the drugs was done using logistic regression analysis, adjusting for baseline variables, and the ORs for achieving SR 12 and 24 months were adjusted for baseline age, disease duration, DAS28, HAQ, concomitant MTX and prednisolone. Life-table techniques were used to estimate SR time, looking only on first biologic treatments.

Results: Of 3446 initiated treatments, 481 (14 %) fulfilled the criteria. Of those who reached SR 63.2% did so within the first year.

Among patients naïve to biologic treatments and after correction for baseline variables, the ORs for achieving SR within the first 12 months of treatment were 1.9 for etanercept and 1.7 for adalimumab, with infliximab as the reference drug, while etanercept and adalimumab were not significantly different, see figure 1.

Median estimated SR survival time was 3.9 years (etanercept 4.4y, adalimumab 4.8y and infliximab 3.0y). Estimated SR survival was significantly longer for etanercept and adalimumab compared to infliximab (p < 0.05), with no significant difference between etanercept and adalimumab. The estimated SR survival, at 12, 24, and 48 months was 94%, 68% and 48% respectively. After 120 months 11% remained in SR.
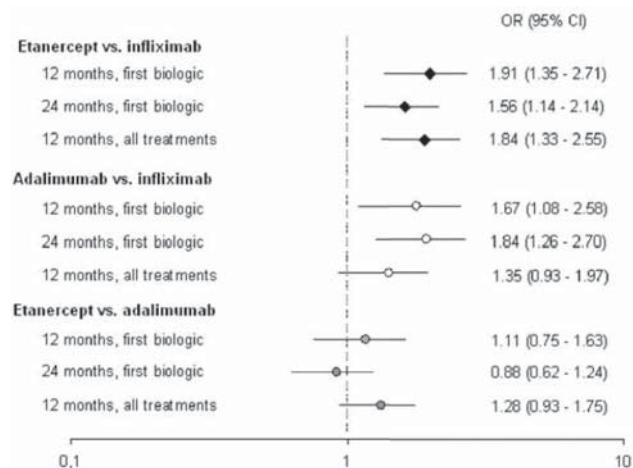
Figure 1. Odds of having achieving sustained remission on first biologic after 12 and 24 months, and for all treatments after 24 months. Drug on right the reference drug.

Adjusted for age, sex, disease duration, concomitant methotrexate and prednisolone treatment, CRP, DAS28 and HAQ score at baseline.

Conclusion: Differences were seen in remission rates and duration between different medications. Within 12 months etanercept and adalimumab had significantly higher likelihood of reaching remission than infliximab, and the estimated remission survival was significantly longer for etanercept and adalimumab compared to infliximab.

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B-Lymphocyte Count Is Not Associated with an Increased Risk of Infection in Patients Treated with Rituximab for Auto-Immune Diseases. Ilias Lazarou, Axel Finckh, Lara Fischer, Camillo Ribi, Joerg Seebach and Pierre A. Guerne. University Hospitals of Geneva, Geneva, Switzerland

Background/Purpose: B-Lymphocyte (B-Ly) depletion therapy with the monoclonal anti-CD20 antibody rituximab (RTX) is widely used in a variety of autoimmune (AI) diseases. The risk of severe infection related to RTX use in this population is estimated to be 5–14.1/100 patient-years. Additional risk factors for severe infection, such as low IgG levels, age, and concomitant immunosuppressive therapy, have been recognized.

In practice, many clinicians are reluctant to use RTX if B-Ly levels are decreased. Our aim was to examine whether B-Ly counts, the direct target of RTX, are associated with an increased risk of infection in patients with AI diseases.

Methods: We conducted an observational cohort study of all 161 patients treated with RTX between 2002 and 2012 in the Rheumatology and Immunology Divisions of the Geneva University Hospital. Primary outcome was severe (iv antibiotics, hospitalization, related death) and non-severe infection (requiring antibiotics). Primary predictor of interest was absolute B-Ly count, assessed by flow cytometry before RTX treatment. Time-to-infection was analyzed by Cox proportional hazard model, adjusting for potential confounders (glucocorticoid and other immunosuppressants use, diabetes and other chronic comorbidities, RA versus other AI diseases, age and sex).

Results: A total of 161 patients were included and followed for a mean period of 2.4 years; 85 (53%) had RA, and the remaining 76 (47%) mainly connective tissue disorders and vasculitides. During follow-up, 63 severe and 111 non-severe incident infections were observed. The incidence rate of severe infection was 15 /100 patients-years in non-RA patients compared to 3.5 in RA patients (p<0.001). The most recent B-Ly level before RTX treatment was not associated with subsequent infections (HR 0.999, p=0.78). Significant predictors of infection were an AI condition other than RA (HR 3.4, p<0.001), age (HR 1.03, p=0.03) and low IgG levels (HR 0.91, p=0.02).

Conclusion: In this population treated with RTX for AI diseases, B-Ly counts before RTX infusion were not associated with incidence of infections. This data does not support the common concern of infection with low B-Ly counts, and does not encourage assessing B-Ly before RTX treatment. We confirm the higher risk of infection conferred by low IgG levels, older age and AI disease other than RA.

Disclosure: **I. Lazarou**, Roche Pharmaceuticals, 2; **A. Finckh**, Roche, Pfizer, BMS, 2, Roche, Pfizer, BMS, 5; **L. Fischer**, None; **C. Ribi**, None; **J. Seebach**, None; **P. A. Guerne**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 6.

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An Evaluation of Literature On Discontinuation Rates of Biologics in Rheumatoid Arthritis. Setareh A. Williams[1], Victoria Porter[2], Victoria Zarotsky[3], Sujatha Sundaram[4], Elisabeth Nyman[5], Cassie K. Gregson[6] and Paul S. J. Miller[6]. [1]AstraZeneca LP, Wilmington, DE, [2]OptumInsight, Mastic Beach, NY, [3]OptumInsight, Calabasas, CA, [4]OptumInsight, Hanover, NH, [5]AstraZeneca, Mölndal, Sweden, [6]AstraZeneca, Macclesfield, United Kingdom

Background/Purpose: To assess reasons for biologic discontinuation or switching in the treatment of rheumatoid arthritis (RA).

Methods: A text mining strategy was developed to identify, from the biomedical information published through July 2011, data relevant to discontinuation or switching due to adverse events (AEs) or lack of efficacy or patient preference. Searches encompassed Medline, ACR and EULAR conference abstracts, and > 20,000 selected full-text documents. The abstracts of the identified documents were manually assessed to determine whether they reported on the incidence/duration of and/or reasons for discontinuing/switching therapy. Expert opinions including non-systematic reviews, case studies, and editorials and commentaries were excluded.

Results: 234 full-text articles and 45 meeting abstracts were identified as reporting on discontinuation due to AEs/lack of efficacy. Fourteen articles/abstracts reporting on discontinuation due to patient preference were identified. Sixty-one articles on discontinuation due to AEs/lack of efficacy met inclusion criteria (4 systematic reviews/meta-analyses, 17 randomized controlled trials, 7 registry studies, 21 prospective studies, and 12 observational studies), and 9 studies on patient preference met inclusion criteria (3 registry studies, 4 retrospective analyses, 1 cross-sectional, and 1 prospective study). AEs accounted for 5% to 40% of discontinuations within the 1st year of therapy. Injection/infusion site reactions were the most common discontinuation-related AE, most frequently reported with infliximab use and in patients with history of allergic reactions. Discontinuation due to lack of efficacy varied from 1% to 52% in studies with a 6-month follow-up duration and from 17% to 47% per year over a 10-year period. Patients were more

likely to start on a 2nd biologic if their 1st biologic was discontinued due to lack of efficacy than if discontinued due to AEs. Patient preference accounted for 4% to 29% of the total discontinuations. Infliximab, followed by etanercept, were the most widely evaluated biologics. Limited data on withdrawal rates were available for 2nd generation and non-TNF inhibitor biologics.

Conclusion: Despite the availability of 9 RA biologics, a substantial proportion of patients discontinue treatment largely due to AEs or lack of efficacy. Heterogeneity in RA disease is well-known; hence, new therapies with different mechanisms of action may help mitigate this issue. Treatments offering equivalent efficacy to that of currently available biologics that can be sustained over longer time periods would benefit RA patients with inadequate response to available treatments.

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Comparison of Rheumatoid Arthritis-Related Health Care Resource Use and Comorbidities Among Patients with Rheumatoid Arthritis Treated with Adalimumab Vs. Etanercept. Jipan Xie[1], Arijit Ganguli[2], Hongbo Yang[1], Kejal Parikh[1], Eric Q. Wu[1] and Mary Cifaldi[2]. [1]Analysis Group Inc., Boston, MA, [2]Abbott Laboratories, Abbott Park, IL

Background/Purpose: Adalimumab (ADA) and etanercept (ETN) are two commonly used tumor necrosis factor (TNF)-α antagonists for the treatment of rheumatoid arthritis (RA). The study is aimed to compare the rate of experiencing RA-related urgent care and surgery, and the risk of developing new comorbidities between ADA- and ETN-treated patients with RA.

Methods: Adult RA (ICD-9-CM: 714) patients who initiated ADA or ETN were identified from the Thomson MarketScan database (2005–2009). The date of the first prescription of ADA or ETN was defined as the index date. Patients were required to have continuous eligibility for at least 6 months prior to (baseline period) and 12 months after (study period) the index date. In addition, patients were required to be free of other medical conditions (e.g., Crohn's disease and psoriasis), for which ADA or ETN is indicated, during the baseline period. Baseline characteristics (demographics, comorbidities, prior treatments for RA and health care resource use) were compared between the ADA and ETN cohorts using Chi-square tests for categorical variables or Wilcoxon rank-sum tests for continuous variables. The rate of experiencing RA-related urgent care (i.e., inpatient or emergency room visits associated with RA diagnoses), RA-related surgery, and the risk of developing new comorbidities (including gastrointestinal disease, cardiovascular disease, diabetes, hypertension, osteoporosis) during the study period were compared between the two cohorts using Cox proportional hazards models, adjusting for the above baseline characteristics.

Results: A total of 3,109 ADA-treated RA patients and 3,972 ETN-treated RA patients met the study inclusion and exclusion criteria. Compared to ETN-treated patients, ADA-treated patients were older (50.2 vs. 49.4, p=0.006), and had a higher baseline use of methotrexate (62.9% vs. 58.7%, p<0.001). After adjusting for baseline characteristics, ADA was associated with a significant lower rate of experiencing RA-related urgent care (hazard ratio [HR]=0.82, 95% confidence interval [CI]=0.67–0.99) and RA-related surgery (HR=0.65; 95% CI=0.47–0.91). ADA was also associated with a lower risk of developing new gastrointestinal disease compared to ETN (HR =0.85; 95% CI: 0.76–0.95). The risks of developing other comorbidities including cardiovascular diseases, diabetes, hypertension, and osteoporosis were not significantly different between the two cohorts.

Conclusion: Compared to those treated with ETN, patients with RA treated with ADA, were less likely to experience an RA-related urgent care or RA-related surgery, and to develop new gastrointestinal disease.

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Immunogenicity of Infliximab Is Related to Reduction of Frequency of Infliximab Administration in Rheumatoid Arthritis and Spondyloarthritis Patients. Mathieu Verdet[1], Clément Guillou[2], Marie-Laure Potier[2], Martine Hiron[2], Fabienne Jouen[3], Olivier Boyer[4], Thierry Lequerré[5] and Olivier Vittecoq[6]. [1]Rouen University Hospital, Bois Guillaume, France, [2]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [3]Rouen University Hospital, Rouen Cedex, France, [4]INSERM U905, University of Rouen, Rouen, France, [5]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [6]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France

Background/Purpose: To analyze the clinical and biological characteristics associated with presence of antibodies to Infliximab, in rheumatoid arthritis (RA) and spondyloarthritis patients (SpA).

Methods: Sera from RA (n=22) or SpA (n=23) patients receiving Infliximab have been analyzed with a commercial multiplex enzyme-linked immunosorbent assay kit (LISA-Tracker Infliximab BMD®). Antibodies toward Infliximab (ATI) and Infliximab trough concentrations were measured in their serum. Result was considered positive if ATI concentrations were >10ng/mL. Clinical and biological data were retrospectively collected from the patient's medical file.

Results: Infliximab was given in association with methotrexate in 31 patients (69%). The time between two consecutive Infliximab adminstration was higher than 8 weeks in Fifteen patients (33%). Fifteen patients were in remission at time of analysis. Time between two Infliximab administration was significantly longer in patients who had obtained remission(9.27 weeks) compared to other patients(6.83 weeks; Mann-Whitney Test, p=0.0005).

Seven patients(15%) were ATI+. Time since beginning of Infliximab was not different between ATI+ and ATI- patients.

Posology of Infliximab at time of analysis was not different between ATI+ (4.29mg/kg) and ATI- patients(4.13mg/kg; Mann-Whitney Test, p=0.74).

Longer time between infliximab infusions was associated with presence of ATI(ATI +: 9.57 weeks; ATI -: 7.29 weeks; Mann-Whitney Test p=0.02). As expected, Infliximab concentration was significantly lower in ATI+ patients(0.18μg/mL) compared to ATI- patients(2.1μg/mL; Mann-Whitney Test, p=0.0005). There was a significant inverse correlation between ATI titer and Infliximab concentration in the serum(Spearman test, p=0.0001). In contrast, no association was found between the posology of Methotrexate and presence of ATI.

Conclusion: Immunogenicity against Infliximab was associated to a longer interval between infusions. This result could impact on treatment strategy for patients in clinical remission since decreasing the frequency of Infliximab administration may favor the development of ATI.

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Impact of Adalimumab Therapy On Laboratory Parameters of Interest in Patients with Early or Long-Standing Rheumatoid Arthritis. De Furst[1], Ana P. Lacerda[2], Nupun Andhivarothai[3], Jasmina Kalabic[4] and Neelufar Mozaffarian[3]. [1]University of California at Los Angeles, Los Angeles, CA, [2]Abbott Laboratories, São Paulo, Brazil, [3]Abbott Laboratories, Abbott Park, IL, [4]Abbott GmbH & Co. KG, Ludwigshafen, Germany

Background/Purpose: The systemic inflammation of rheumatoid arthritis (RA) can have detrimental effects on the hematopoietic and cardiovascular systems. Additionally, effective DMARD treatments for RA can be hemato- or hepatotoxic. The effects of adalimumab (ADA) in combination with methotrexate (MTX) therapy on these systems in patients with early or long-standing RA have not been previously summarized. This analysis evaluates the effects of ADA+MTX therapy compared to MTX monotherapy on laboratory and vital sign parameters relevant to hematopoietic, cardiovascular, and hepatic organ systems.

Methods: Clinical trials DE013 and OPTIMA (MTX-naïve patients, early RA, mean duration=0.8 yrs in DE013, 0.35 yrs in OPTIMA) and DE019 (MTX-incomplete responders, long-standing RA, mean duration=11 yrs) were double-blind studies that compared ADA+MTX therapy to MTX monotherapy for ≥6 months. This *post hoc* analysis determined the percentage of patients who developed neutropenia, lymphocytopenia, thrombocyto-

Conclusion: In these early RA patients, baseline disease activity resulted in substantial functional impairment. Patients who responded to early treatment with either ADA+MTX or PBO+MTX had low ACT-HAQ and DAM-HAQ values at wk 26 that were sustained through week 78. Patients with an inadequate response after 22 and 26 wks of PBO+MTX or ADA+MTX therapy showed significant improvement in HAQ even though not achieving LDA, and further improvement when treated with O-L ADA+MTX. Notably, even among initial inadequate responders, the disability at week 78 mostly consisted of ACT-HAQ, suggesting the potential for further improvement in these patients with further adjustment of treatment regimen.

Reference
Ann *Rheum Dis* 2010;69:1058–1064.

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Patient Preferences for Biologic Treatments in Rheumatoid Arthritis.
Beenish Nafees[1], Andrew Lloyd[1], Carol L. Gaich[2], Julie Birt[2] and Rodney A. Hughes[3]. [1]Oxford Outcomes, Oxford, United Kingdom, [2]Eli Lilly and Company, Indianapolis, IN, [3]St. Peters Hospital, Chertsey Surrey, United Kingdom

Background/Purpose: Patients with rheumatoid arthritis (RA) and their physicians face a range of treatment choices. The treatments that patients receive should be driven partly by their views and preferences regarding different aspects of the treatments. The present study was designed to elicit the treatment preferences of people with RA.

Methods: A stated preference survey was developed based on published literature, discussion with clinicians (n=4) and qualitative interviews with patients (n=5). The survey presented hypothetical treatments that varied in terms of six key attributes: *Mode of administration & frequency, Time medication stays in the body, Effectiveness in treating pain, Functional ability, Number of RA flares in next 12 months,* and *Out of pocket cost.* Socio-demographic, and clinical data were also collected. Participants (US n=150; UK n=150) completed the survey following IRB approval. Survey data were analysed using the conditional logit model whereby the attributes were the independent variables and patient choice data were the dependent variable. The coefficients obtained from the logit model provided an estimate of the (log) odds ratios (ORs) of preference for treatment attributes.

Results: 287 participants (143 patients in UK and 144 in US) completed all study questionnaires. Participants reported a median current pain VAS of 5.0 (0–10 scale) and poor quality of life (EQ-5D score = 0.41 (US) and 0.45 (UK) on a 0 (dead) to 1.0 (full health) scale. Over 90% of the sample reported experiencing at least 7 flares in the last 12 months. All attributes were significant predictors of choice where all or some levels were significantly more important than the reference case as shown by the ORs. The three most important drivers of preference were number of symptom flares per year, effectiveness in reducing pain and functional ability (Table 1). Treatments which reduced the number of symptom flares per year from 5 to 0 were of high importance to participants. Participants preferred treatments that reduced pain (assessed on a visual analogue scale) score by 80%. Avoiding functional difficulties was also very important to participants (Table 1). Oral (daily or twice-daily) and subcutaneous treatments (weekly or bi-weekly) were preferred to intravenous therapies (every 4 weeks or 8 weeks), but this was less important to participants; and time medication is in body was not important to participants. Cost was somewhat a significant predictor of choice, whereby participants were willing to pay more for improvements of therapy.

Table 1. Results of logit model by country

Attribute and level	Odds Ratios (Lower – Upper 95% Confidence intervals)	
	US	UK
Administration & Frequency – Sub-cutaneous weekly (reference)‡		
Oral daily	1.03 (0.78–1.36)	1.45 (1.11–1.90)
Oral twice daily	0.82 (0.56–1.18)	1.40 (0.99–2.0)
Intravenous-8 weeks	0.52 (0.35–0.77)	1.06 (0.73–1.55)
Intravenous-4 weeks	0.44 (0.29–0.66)	0.85 (0.58–1.26)
Sub-cutaneous-biweekly	0.95 (0.71–1.27)	0.93 (0.74–1.30)
Time in Body-8 weeks (reference)		
1 day	0.77 (0.65–0.09)	0.82 (0.70–0.96)
4 weeks	1.19 (1.01–1.41)	1.12 (0.95–1.32)
Level of pain while taking treatment–Current pain level reduced by 20% (reference)		
Current pain level reduced by 80%	6.25 (5.12–7.63)	4.44 (3.71–5.30)
Current pain level reduced by 40%	2.68 (2.24–3.20)	2.12 (1.80–2.49)
Functional Ability-Some difficulty & moderate discomfort (reference)		
No difficulty	2.29 (1.89–2.77)	2.20 (1.86–2.62)
Some difficulty & mild discomfort	1.73 (1.44–2.08)	1.37 (1.16–1.62)
Number of Flares-5 (reference)		
0	5.28 (4.32–6.46)	3.85 (3.22–4.60)
2	3.09 (2.55–3.74)	2.60 (2.19–3.09)
Cost		
Cost ($)	1.0 (1.0–1.0)	0.99 (0.99–0.99)

‡ - reference case is the base profile in each attribute.

Conclusion: The results show the relative importance of different features of RA treatments to patients. Improving pain control, functioning, and avoiding flares were the most important aspects of treatment. Participants were much less concerned about the mode or frequency of administration.

Disclosure: B. Nafees, Oxford Outcomes, 3; **A. Lloyd**, Oxford Outcomes, 3; **C. L. Gaich**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **J. Birt**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **R. A. Hughes**, None.

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The Comparative Effectiveness of Anti-TNF Medications Among Older and Disabled Rheumatoid Arthritis Patients in the U.S. Medicare Population.
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Background/Purpose: Evaluating the real world effectiveness of biologic DMARDs in rheumatoid arthritis (RA) patients using administrative claims data has previously not been feasible due to the lack of clinical information present in such databases. A novel, recently published, validated administrative data-based algorithm (Curtis et. al., Arthritis Res Ther 2011) provides the potential to compare the effectiveness of different biologics to one another, with focus on older and vulnerable populations that are sometimes excluded or not present in large numbers in clinical trials or registries.

Methods: We evaluated the effectiveness of etanercept, adalimumab, and infliximab in 100% of Medicare beneficiaries with RA and with >= 24 months of fee-for-service + drug coverage, 2006–2009. Patients included those eligible for Medicare on the basis of age >= 65 or disability. New users of anti-TNF agents had a 12 month baseline during which no prescription or infusion of any biologic medication was given. The outcome was effectiveness at 12 +− 2 months according to the algorithm, which required six dichotomous conditions be met (Table). We calculated the proportion meeting effectiveness criteria by anti-TNF medication and compared effectiveness between them using robust Poisson regression to compute risk ratios (RRs), adjusted for demographics, income, comorbidities and other medications.

Results: We identified 1,635, 2,077 and 3,181 new users of adalimumab, etanercept and infliximab, respectively. Overall, 35% of patients were disabled, almost all of whom were younger than age 65. The algorithm classified the medication as effective for 27% of adalimumab users, 31% of etanercept users, and 29% of infliximab users. After multivariable adjustment, the RRs for effectiveness were 0.99 (95% confidence interval (CI): 0.90–1.10) for adalimumab, and 1.11 (95% CI: 1.02–1.22) for etanercept compared to infliximab. Across all anti-TNFs, patients who were not disabled had

higher effectiveness for anti-TNF medications than patients who were disabled (RR=1.26, 95% CI: 1.15–1.39).

Table. Components of the effectiveness algorithm† for adalimumab, etanercept, and infliximab at 1 year*

	Adalimumab %	Etanercept %	Infliximab %
Effectiveness Criteria, %			
High adherence to the index drug	55	59	65
No switch to a different biologic	87	85	89
No addition of a new non-biologic DMARD	90	90	91
No biologic dose increase compared to starting dose	94	99	84
For patients not using glucocorticoids at baseline, no initiation of glucocorticoids; for patients using glucocorticoids at baseline, no increase in dose	84	88	84
No more than one joint injection on unique days after the 3 months of new treatments	89	90	88
Satisfied all 6 effectiveness criteria	**27**	**31**	**29**

† The gold standard outcome was low disease activity (Disease Activity Score using 28 joint counts (DAS28) <= 3.2) or improvement in DAS28 by >1.2 units at 12+2 months with high adherence to therapy. This newly published claims-based effectiveness algorithm was validated using the clinical information in Veterans affairs RA registry as the gold standard.
* assessed between the first exposure date and the outcome rheumatologist visit date (10–14 months later)

Conclusion: A recently-published claims-based effectiveness algorithm provides opportunities to assess the comparative effectiveness of RA medications using administrative data. Etanercept was associated with somewhat higher effectiveness among new anti-TNF users compared to infliximab. Effectiveness of all anti-TNF medications combined was significantly higher among older patients who were not disabled compared to younger, disabled RA patients.

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12- and 24-Week Patient-Reported Outcomes From a Phase 2b Dose-Ranging Study of Baricitinib, an Oral Janus Kinase 1/ Janus Kinase 2 Inhibitor, in Combination with Traditional Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis.
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Background/Purpose: Baricitinib (formerly, LY3009104/INCB028050) is a novel, oral inhibitor of the JAK1 and JAK2 in the JAK-STAT pathway known to be of importance in the pathobiology of rheumatoid arthritis (RA) and has previously been shown to improve the signs and symptoms of RA after 12 weeks of treatment.[1] This study evaluates the patient-reported outcomes (PROs) within a 24-week blinded phase 2b study for 1 mg, 2 mg, 4 mg, and 8 mg baricitinib once daily (QD) at 12 weeks, and 4 mg and 8 mg at 24 weeks.

Methods: Patients with active RA and on stable doses of methotrexate were randomized (2:1:1:1:1) to receive either placebo (PBO) or 1 of 4 QD baricitinib doses (1, 2, 4, or 8 mg) for 12 weeks. Patients assigned to placebo or 1 mg were reassigned to an exploratory 4 mg QD or 2 mg BID group between weeks 12 and 24 and were excluded from the primary 24-week analysis; patients initially assigned to 2 mg, 4 mg, or 8 mg remained on the same treatment. PROs included patient global assessment (PtGA) of disease activity (Visual Analog Scale [VAS]), pain (VAS), physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), health-related quality of life (Medical Outcomes Study [MOS] Short Form 36 [SF-36]), fatigue

(Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]), and duration of morning stiffness. Analyses were done using analysis of covariance (ANCOVA). Statistical comparisons of means were conducted for each active treatment group against the PBO group; p-values were not adjusted to correct for multiple comparisons.

Results: Of 301 randomized patients, those who received baricitinib experienced clinically meaningful improvements in most PROs as early as week 2 vs. PBO as well as at 12 weeks (Table 1). These improvements were maintained or continued to improve through 24 weeks (e.g., change from baseline for 4 and 8 mg groups, respectively, FACIT-F: 5.32 [SEM: 1.31], 5.00 [SEM: 1.52]; SF-36 PCS: 7.32 [SEM: 0.97], 7.67 [SEM: 1.23]).

Table 1. Patient-Reported Outcomes at 12 Weeks Showing Mean Change From Baseline (LOCF), (Mean [SEM])

Measure	PBO (N=98)	1 mg (N=49)	2 mg (N=52)	4 mg (N=52)	8 mg (N=50)
PtGA (VAS)	−10.3	−24.9*** (3.89)	−16.2 (3.11)	−25.4*** (3.03)	−29.8*** (3.00)
Pain (VAS)	−8.8	−22.8*** (3.91)	−14.2 (2.47)	−25.0*** (2.69)	−25.3*** (2.87)
Physical function (HAQ-DI)	−0.10	−0.35** (0.08)	−0.18 (0.07)	−0.33*** (0.06)	−0.39*** (0.07)
SF-36 Mental Component Score	0.88	2.54 (1.73)	1.89 (0.96)	2.39 (1.11)	3.03 (1.51)
SF-36 Physical Component Score	3.22	6.66* (1.17)	4.15 (1.08)	7.07*** (1.03)	7.00* (1.28)
Fatigue (FACIT-F)	2.02	4.48 (1.51)	3.80 (1.28)	4.41* (1.21)	4.11 (1.41)
Morning Stiffness Duration (minutes)	−33.9	−49.5* (10.51)	−30.7 (6.64)	−75.0*** (20.09)	−62.7*** (12.48)

* p≤0.05, ** p≤0.01, ***p≤0.001

Conclusion: In this phase 2b study in patients with RA, those who received baricitinib reported clinically meaningful improvements as early as week 2 in most PROs relative to PBO as well as at 12 weeks. These improvements were maintained or continued to improve through 24 weeks.

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Predictors of Initiating Biologic Monotherapy in Biologic Naïve Patients with Rheumatoid Arthritis (RA) in a US Registry Population.
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Background/Purpose: Published data have shown that approximately one-third of patients with RA are treated with biologic (Bio) monotherapy (MT) (without concomitant DMARD) and a considerable portion of these patients are previously Bio naïve (Yazici et al. 2008). The purpose of this analysis is to determine the predictors of initiating a biologic as MT versus in combination with a DMARD (CMB) in previously Bio naïve patients in the Consortium of Rheumatology Researchers of North America (CORRONA) Registry.

Methods: Data on patients previously Bio naïve and initiating their first biologic therapy were included in this analysis. Demographic and baseline clinical characteristics were evaluated and logistic regression models were used to assess potential predictors of Bio MT initiation. The following independent variables, selected for clinical relevance and significant in the univariate model, were entered in the models simultaneously as fixed effects in various combinations: a) medical history of neutropenia, hepatic disease and malignancy, b) swollen joints counts and presence of erosions, c) whether

the biologic is approved for MT in the US, and d) and if the biologic was initiated prior to 2006 which marks the increased availability of biologics approved for MT. A random effect of individual physician's prescribing patterns was also included in the model to estimate a median odds ratio (Larsen et al., 2000).

Results: Between October 2001 and April 2012, 3,923 previously Bio naïve patients initiated biologic therapy, of which 19% initiated as MT. Baseline characteristics of patients initiating Bio MT and Bio CMB were similar: age (years; mean±SD) 57±15 vs. 58±13, female 74% vs. 76%, duration of RA (years; mean±SD) 9±9 vs. 8±9, and CDAI (mean±SD) 19±14 vs. 19±14. A significantly higher proportion of patients initiating a Bio CMB had a history of non-biologic DMARDs (86% vs. 97%, p<0.0001) and specifically, a history of methotrexate (MTX) (72% vs. 92%, p<0.0001). The most frequently reported reason for discontinuing MTX was due to toxicity (Bio MT 45% vs. Bio CMB 36%, p = 0.05); similar results were seen for history of leflunomide.

Table 1. Adjusted Odds Ratios[a] for Biologic Monotherapy Versus Combination in Biologic Naïve Patients

	Model 1[b] N=3861[c]	Model 2[b] N=2823[c]	Model 3[b] N=644[c]
History of Hepatic Disease	6.5 [3.20, 13.07]	7.49 [3.19, 17.58]	5.20 [0.95, 28.49]
History of Malignancy	3.79 [1.64, 8.73]	2.78 [1.02, 7.59]	1.00 [0.19, 5.40]
Swollen Joint Count	0.97 [0.95, 0.99]	0.96 [0.95, 0.98]	0.98 [0.94, 1.02]
Use of Mono Approved Biologic	1.47 [1.20, 1.81]	1.45 [1.13, 1.86]	1.93 [1.08, 3.43]
Initiated after 2006	0.83 [0.68, 1.00]	0.79 [0.63, 0.99]	
Erosions		0.84 [0.68, 1.03]	0.96 [0.62, 1.49]
History of Neutropenia			4.89 [1.16, 20.59]
Random effect of individual physician's prescribing patterns	1.89 [1.66, 2.23]	1.86 [1.61, 2.25]	1.58 [1.23, 2.72]

Notes:
[a] OR > 1 implies monotherapy more likely.
[b] Three different models with various combinations of fixed effects from independent variables described above and a random effect of individual physician's prescribing patterns were fitted.
[c] Models fitted using available data among 3,923 previously Bio naïve patients initiating a biologic therapy.

Conclusion: Biologic approved for MT and effect of individual physician prescribing patterns consistently influenced the likelihood of Bio MT use along with significant effects in some instances of less severe disease, history of conditions potentially influencing use of concomitant DMARDs and year of initiation.

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Divergent Toxicity of TNF Inhibitors On Demyelinating Disorders and Neurological Events. Sergio Schwartzman[1], John Clark[2] and John J. Cush[3]. [1]Hosp for Special Surgery, New York, NY, [2]RiskBenefits LLC, Flourtown, PA, PA, [3]Baylor Research Institute, Dallas, TX

Background/Purpose: There are currently five anti-TNF agents that have been approved for various autoimmune illnesses. There is no convincing evidence that any one of these is superior to the others in terms of efficacy. However, some differences in safety, such as tuberculosis risk, have been described. There is no single source of information on the safety of these agents that is universally precise. The Adverse Event Reporting System (AERS) maintained by the US Food and Drug Administration (FDA) receives spontaneous reports of adverse reactions to approved medications licensed for use in the United States. These are submitted by health care professionals or through the manufacturer. It is widely accepted that this type of reporting underestimates the number of actual cases of toxicity that occur and at times may be biased. Therefore any comparisons should be approached with caution. We sought to evaluate the frequency and type of neurologic events seen with TNF inhibitor (TNFi) therapy.

Methods: The AERS database was queried to identify neurological toxicity events following TNFi use reported from date of approval to end 2011 for etanercept, infliximab, adalimumab, golimumab and certolizumab. The frequency of these events is influence by time and total market exposure for each agent. Groupings of preferred terms were used to retrieve the following adverse events: acoustic neuritis (AN), central demyelination other (CDO), chronic inflammatory demyelinating polyneuropathy (CIDP), demy-

elination NOS (DN), Guillain-Barre (GB), multiple sclerosis (MS), optic neuritis (ON), and peripheral neuropathy (PN). The results were calculated as report proportions, i.e. number of cumulative AE reports divided by number of cumulative total reports and expressed as percentages.

Results: The following cumulative report proportions were calculated from data received in AERS between the time of initial marketing through December 2011 (values in %).

Neurologic Event Reported	Etan	Infl	Adal	Goli	Cert
Acoustic Neuritis	0.00	0.00	0.00	0.00	0.00
Central Demyelination Other	0.00	0.00	0.00	0.00	0.00
Chronic Inflammatory Demyelinating Polyneuropathy	0.01	0.02	0.00	0.00	0.00
Demyelination NOS	0.12	0.36	0.10	0.00	0.07
Guillain Barre	0.04	0.17	0.06	0.00	0.01
Multiple Sclerosis	0.18	0.15	0.15	0.35	0.02
Optic Neuritis	0.08	0.14	0.06	0.12	0.08
Peripheral Neuropathy	0.20	0.41	0.17	0.00	0.20
Presumed Central Toxicity[1]	0.38	0.65	0.32	0.47	0.16
Presumed Peripheral Toxicity[2]	0.25	0.60	0.23	0.00	0.21

1. AN + CDO + DN + MS + ON 2. CIDP + GB + PN
* All adverse events were coded using MedDRA; **NOS=Not Otherwise Specified.

Conclusion: From initial marketing in 1998 until December 31 2011 patients treated with different anti-TNF agents exhibited differing patterns of neurological injury. Compared to other anti-TNF agents, presumed central demyelination and conditions such as multiple sclerosis were less likely to be reported in patients receiving certolizumab. The peripheral nerve events, Guillain-Barre and peripheral neuropathy, were more likely to be reported in patients receiving infliximab, as were non-specific terms that referred only to demyelination (DN). Golimumab had no peripheral neurological events, but had disproportionately more multiple sclerosis. Although spontaneously reported data does not allow conclusions regarding causality, these results suggest that different anti-TNF agents may be associated with different rates of adverse neurological effects and with different sites of neurotoxicity within the nervous system.

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Effect of Infliximab On Employment Status in Patients with Rheumatoid Arthritis or Ankylosing Spondylitis. W. Bensen[1], J. Carter Thorne[2], Saeed A. Shaikh[3], Maqbool K. Sheriff[4], Susan M. Otawa[5], Allen J. Lehman[6] and Hayssam Khalil[7]. [1]St. Joseph's Hospital and McMaster University, Hamilton, ON, [2]Southlake Regional Health Centre, Newmarket, ON, [3]McMaster University, St Catharines, ON, [4]Nanaimo Regional General Hospital, Nanaimo, BC, [5]Janssen Canada Inc, Mississauga, ON, [6]Janssen Inc, Toronto, ON, [7]Janssen Canada Inc, Toronto, ON

Background/Purpose: Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are associated with significant functional impairment and work disability. In the absence of treatment, approximately 80% of RA patients will show evidence of joint abnormalities or disability, while 50% will have work disability after 10 years (1). Similarly, the prevalence of work disability in AS ranges from 13% to 45% based on the patient population (2–4). The purpose of this analysis was to evaluate the prevalence of unemployment due to work disability and determine the effect of treatment with infliximab (IFX) in patients with RA and AS in a real-world, Canadian, routine clinical practice setting

Methods: BioTRAC is an ongoing, prospective, registry of patients initiated on treatment with IFX or golimumab as first biologics or after having been treated with a biologic for less than six months. A total of 798 RA patients and 290 AS patients initiated IFX between 2002 and 2012 and were included in this analysis.

Results: Among the total number of RA and AS patients, 179 (22.4%) and 57 (19.7%), respectively, reported being unemployed due to their disability, while 335 (42.0%) and 77 (26.6%) were unemployed due to other reasons.

Table 1 shows the baseline patient characteristics by employment status. Patients reporting being unemployed due to disability had significantly higher disease severity. Furthermore, patients unemployed due to disability had RA

for a longer period, while disease duration was comparable in AS patients across employment statuses.

Table 1. Patient Characteristics at Baseline by Employment Status

Diagnosis RA	Parameter: Mean (SD) or n (%)	Unemployed due to Disability n=179	Unemployed due to Other Reasons n=335	Employed n=284	P-value
	Female	138 (78.4%)	266 (82.4%)	184 (66.7%)	<0.001
	Age: years	53.8 (10.0)	64.5 (13.5)	49.0 (10.9)	<0.001
	Disease duration: years	11.2 (10.0)	11.4 (10.4)	7.7 (8.0)	0.008
	HAQ-DI	1.9 (0.5)	1.8 (0.7)	1.3 (0.7)	<0.001
	SJC-28	12.0 (7.1)	11.6 (7.1)	9.2 (6.4)	<0.001
	TJC-28	15.4 (8.0)	13.3 (7.9)	10.3 (7.5)	<0.001
	PtGA: VAS mm	67.4 (20.0)	62.1 (23.1)	55.6 (25.6)	<0.001
	Pain: VAS mm	64.7 (20.7)	58.7 (23.2)	52.1 (25.2)	<0.001
	DAS28-ESR	6.3 (1.3)	6.0 (1.4)	5.3 (1.5)	<0.001
	DAS28-CRP	5.9 (1.2)	5.5 (1.2)	5.1 (1.4)	<0.001
AS		n=57	n=77	n=156	
	Female	23 (42.6%)	32 (44.4%)	51 (33.3%)	0.205
	Age: years	49.4 (9.1)	50.4 (15.7)	43.9 (10.0)	<0.001
	Disease duration: years	9.0 (8.7)	11.7 (12.3)	9.2 (9.5)	0.318
	HAQ-DI	1.5 (0.6)	1.3 (0.6)	1.1 (0.5)	<0.001
	BASDAI	7.2 (2.1)	6.6 (2.1)	6.1 (2.0)	0.002
	ASDAS	4.0 (0.9)	4.0 (0.9)	3.9 (1.1)	0.859

By 6 months on IFX treatment, clinically meaningful and statistically significant (P<0.05) improvements in all parameters studied were observed in all three employment status groups in both RA and AS patients. No significant between-group differences in the absolute change of these disease parameters were observed upon adjustment for baseline values with the exception of BASDAI and ASDAS which showed a greater improvement in employed AS patients. Among the RA and AS patients unemployed due to disability, 10.6% and 14.0%, respectively, returned to full-time or part-time employment post baseline, the majority of whom (63.0%) within 6 months of treatment. The mean (SD) time to employment for this patient subpopulation was 10.8 (13.6) months in RA patients and 12.1 (6.6) months in AS patients.

Conclusion: At IFX initiation, patients with work disability had more severe disease compared to patients unemployed due to other reasons or employed patients. Furthermore, RA patients had longer disease duration before being treated with IFX. However, treatment with IFX was equally effective in reducing disease severity and symptoms regardless of employment status and most importantly enabled a portion of patients to return to employment.

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Are There Gender Specific Differences in Patient Characteristics At Initiation of Biologic Treatment in Rheumatoid Arthritis? William Bensen[1], Denis Choquette[2], Isabelle Fortin[3], Alice V. Klinkhoff[4], Susan M. Otawa[5] and Hayssam Khalil[6]. [1]St. Joseph's Hospital and McMaster University, Hamilton, ON, [2]University of Montreal, Notre-dame Hospital, Montreal, QC, [3]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [4]The Mary Pack Arthritis Ctr, Vancouver, BC, [5]Janssen Canada Inc, Mississauga, ON, [6]Janssen Canada Inc, Toronto, ON

Background/Purpose: The prevalence of rheumatoid arthritis (RA) is 2–4 times higher in women compared to men depending on age. Furthermore, in women RA incidence increases from the age of menarche peaking around menopause, while it is rare in men under the age of 45 years (1). Several studies have shown that treatment outcomes are worse in women (2). This analysis examined gender-specific differences with respect to patient and disease parameters at initiation of the first anti-TNF agent for the treatment of RA in a Canadian routine clinical practice setting.

Methods: BioTRAC is an ongoing Canadian registry of RA, AS or PsA patients initiating treatment with infliximab (IFX) or golimumab (GOL) as first biologics or after having been treated with a biologic for less than six months. This analysis is based on 781 biologic naive RA patients initiating infliximab treatment between 2002 and 2012.

Results: Among the 781 patients, 593 (75.9%) were female and 188 (24.1%) were male. Mean age and disease duration at initiation of infliximab treatment were comparable between groups.

Overall patient characteristics differed significantly between genders (Table 1). Mean morning (AM) stiffness, HAQ-DI, pain, patient global assessment of disease activity (PtGA), CDAI, and RAPID 3 were statistically significantly higher in female patients. Furthermore, a higher proportion of women were rheumatoid factor (RF) positive and unemployed. However, physician assessment of global disease activity (MDGA), TJC, SJC, CRP, DAS28-CRP, and SDAI were comparable between genders.

Table 1. Patient Characteristics at Baseline by Gender

Parameter Mean (SD)	Male (n=188)	Female (n=593)	P-Value
Age: years	54.3 (13.1)	55.6 (13.7)	0.228
Disease duration: years	7.9 (8.2)	9.0 (9.7)	0.557
AM stiffness: min	63.8 (44.2)	72.9 (43.4)	0.012
HAQ-DI	1.4 (0.7)	1.7 (0.7)	<0.001
Pain: VAS cm	5.4 (2.5)	5.9 (2.3)	0.019
CRP: mg/L	21.5 (27.8)	18.2 (22.7)	0.142
SJC-28	10.2 (7.4)	11.1 (6.9)	0.058
TJC-28	12.3 (8.5)	13.0 (7.9)	0.245
MDGA: VAS cm	6.3 (2.3)	6.6 (2)	0.137
PtGA: VAS cm	5.6 (2.6)	6.2 (2.3)	0.012
DAS28-CRP	5.2 (1.4)	5.5 (1.3)	0.068
SDAI	36.4 (18.5)	39.3 (16.6)	0.056
CDAI	34.5 (17.5)	37.2 (15.8)	0.035
RAPID 3	15.6 (6.7)	17.7 (6.0)	<0.001
RF-positive: n (%)	112 (67.1%)	425 (76.6%)	0.028
Employed: n (%)	92 (49.2%)	184 (31.3)	<0.001

Conclusion: Objective measures (SJC, TJC, MDGA, CRP) were similar for male and female patients at infliximab initiation. However, patient reported outcomes (HAQ-DI, Pain and PtGA) were worse at baseline for female patients at initiation of biologic treatment in this Canadian rheumatoid arthritis population.

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Comparison of Discontinuation Rates by Biologic Since 1998 in US Patients with Rheumatoid Arthritis. Sofia Ramiro[1], Frederick Wolfe[2], David J. Harrison[3], George Joseph[3], David H. Collier[3], Désirée van der Heijde[4], Robert Landewé[5] and Kaleb Michaud[6]. [1]Academic Medical Center, University of Amsterdam, The Netherlands and Hospital Garcia de Orta, Almada, Portugal, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Amgen Inc., Thousand Oaks, CA, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Academic Medical Center, University of Amsterdam and Atrium Medical Center, Heerlen, Netherlands, [6]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Since discontinuation may be a surrogate for ineffectiveness, we measured rates and reasons for biologic discontinuation in a real-world setting.

Methods: From 1998 to 2011, all medication use was measured every 6 months via questionnaire in a US-wide longitudinal study of RA patients. We limited our analysis to patients with a baseline observation immediately before initiating their first (1st) or second different (2nd) biologic and at least one observation after initiation. Patients reported their primary reason for discontinuation. Time-on-drug survival analyses were conducted for individual biologics and groups and annual rates reported. Survival of anti-TNFs and non-anti-TNFs was compared, in crude and adjusted in propensity score analyses.

Results: A total of 2,340 RA patients initiated their 1st biologic; 1,148 (49%) discontinued and 1,128 initiated their 2nd; 567 (50%) discontinued. The vast majority initiated one of the following: etanercept (1st 44%, 28% 2nd), infliximab (1st 37%, 38% 2nd), and adalimumab (1st 13%, 19% 2nd). The annual discontinuation rate of all 1st biologics was 18% (95% CI 17–19%) and 2nd was 21% (19–23%). Annual discontinuation rates for 1st and 2nd by drug was 15% (14–16%) and 16% (14–19%) for etanercept; 19% (17–21%) and 18% (16–20%) for infliximab; and 20% (17–23%) and 26% (22–32%) for adalimumab. Anakinra had the highest annual rates, 1st 59% (44–78%) and 2nd 106% (74–151%). Patients who started a biologic after 2005 had higher annual discontinuation rates, 1st 25% (22–29%) and 2nd 31% (27–35%). Anti-TNF had lower annual discontinuation rates vs non-anti-TNF (1st); crude HR 0.48 (0.34–0.69) and after propensity score adjustment, HR of 0.60 (0.40–0.90). For 2nd line, a crude HR of 0.64 (0.48–0.84) and adjusted HR of 0.81 (0.59–1.11) (see Figures). Reporting a side effect had the highest discontinuation rate, 1st 63% and 2nd =81%, followed by reporting the drug was "not working", 1st 49% and 2nd 60%.
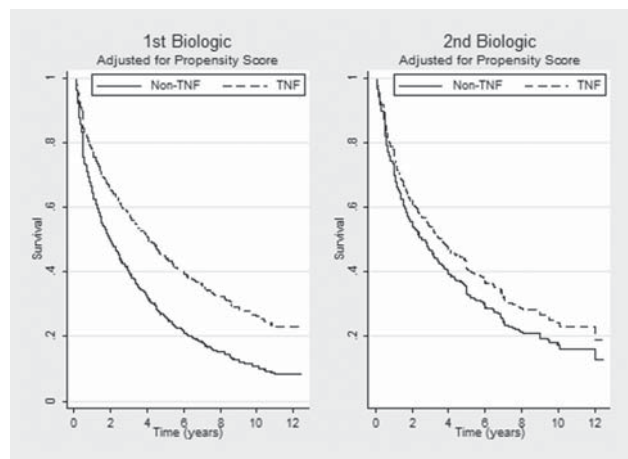
Conclusion: In this large cohort, RA patients tend to remain on their initial and second biologic for relatively long periods suggesting the drugs' effectiveness. Discontinuation rates were higher for non-anti-TNFs and in patients who initiated a biologic more recently when more treatment options were available. Contrary to recent findings, there was no statistically significant difference in discontinuation rates of anti-TNFs and non-anti TNFs as second biologic treatment.

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Real-World Effectiveness of Infliximab in Improving Routine Assessment of Patient Index Data 3 Outcomes: The Canadian Experience.
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Background/Purpose: The routine assessment of patient index data 3 (RAPID3) was recently designed as a pooled index of 3 patient-reported outcomes (PROs): physical function, pain and patient global estimate. Compared to other simplified disease activity scores RAPID3 may be more desirable in a clinical setting due to the shorter scoring time required. The study objective was to assess in a Canadian real-world setting the RAPID3 outcomes in rheumatoid arthritis (RA) patients treated with infliximab (IFX).

Methods: BioTRAC is an ongoing Canadian registry of RA, AS or PsA patients initiating treatment with IFX or golimumab (GOL) as first biologics or after having been treated with a biologic < 6 months. A total of 806 RA patients initiated IFX between 2002 and 2012 and were included in this analysis. RAPID3 was assessed both in continuous and categorical scales defining high activity (>12), moderate activity (6.1–12), low activity (3.1–6), and remission (≤3).

Results: Mean (SD) age of the patient cohort was 55.3 (13.5) yrs, and mean (SD) duration since diagnosis was 8.9 (9.3) yrs. Mean (SD) patient characteristics at baseline were: ESR = 32.5 (24.2) mm/hr; CRP = 19.0 (24.0) mg/L; SJC-28 = 10.8 (7.0); TJC-28 = 12.7 (8.0); HAQ-DI = 1.7 (0.7); DAS28-CRP = 5.4 (1.3); Pain-VAS= 5.8 (2.4); PGA-VAS = 6.6 (2.1); SGA-VAS = 6.1 (2.4) and CDAI = 36.4 (16.2). By 6 months of treatment, clinically meaningful and statistically significant (P<0.05) improvements were observed in all parameters which were sustained over 24 months. Similarly, the mean (SD) RAPID3 score significantly decreased from 17.3 (6.2) at baseline to 11.4 (6.9), 10.5 (7.0), and 9.3 (6.9) at 6, 12, and 24 months, respectively. Figure 1 shows the RAPID3 disease categories over time upon IFX treatment. The proportion of patients with high disease activity decreased from 80.6% at baseline to 34.2% at month 24. Furthermore, the proportion of patients with low activity or remission increased from 6.0% at baseline to 41.6% at month 24.
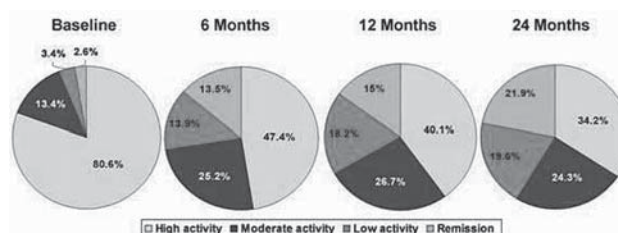
Figure 1. RAPID3 Disease Activity Categories Over Time

The positive correlation over time between DAS28-CRP and RAPID3 (rho=0.748; P<0.001) and between SDAI and RAPID3 (rho=0.743; P<0.001) further confirms the validity of the RAPID3 as disease activity score in real-life RA patients.
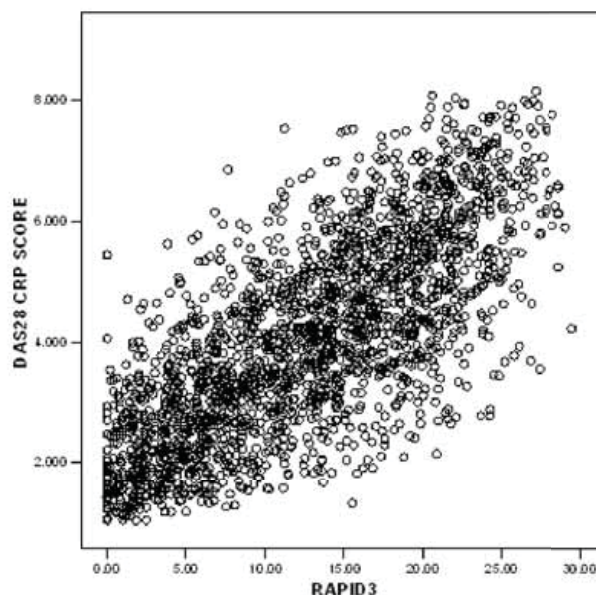
Figure 2. Correlation between RAPID3 and DAS28-CRP Over Time

Conclusion: The results of this Canadian real-world observational study demonstrate that, over 2 yrs of treatment, IFX is effective in reducing symptom severity and improving patient-reported outcomes in RA patients. Furthermore, the data from this registry confirmed the validity of the RAPID3 index as disease activity measure in a real-world RA cohort.

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Golimumab Drug Utilization Patterns in Canada – Higher Retention Rate in Golimumab Treated Rheumatoid Arthritis Patients Compared to Etanercept and Adalimumab. Hayssam Khalil[1] and Amir Tahami[2]. [1]Janssen Canada Inc, Toronto, ON, [2]Janssen Canada Inc., Toronto, ON

Background/Purpose: Golimumab is a monthly self-injected anti-tumor necrosis factor alpha therapy for patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). It was approved by Health Canada in April 2009 and this is the first Canadian report of golimumab's utilization in a real-world setting. The purpose of this project was to assess the utilization patterns of rheumatoid arthritis patients who received golimumab (GLM), etanercept (ETA) or adalimumab (ADA) in a large private drug plans database.

Methods: RA patients initiating therapy with GLM, ETA or ADA between January 1, 2009 and June 30, 2010 were selected from the IMS Brogan Canadian private drug plans database. Patients were included if they had ' 3 claims for GLM, ETA or ADA and were naïve to biologics prior to initiation of treatment. The 6-month period preceding the first GLM, ETA or ADA claim (index date) for each patient was used as a baseline to ensure that the patient were naïve to biologics. Patients were tracked for a maximum of 12 months after their index date to assess dosing patterns. The average dose in mg/week and the % of discontinuation (defined as the gap between 2 consecutive claims exceeding 60 days or switching to another drug) were evaluated.

Results: A total of 146, 1436 and 1171 RA patients receiving at least three prescriptions of GLM, ETA or ADA respectively were identified. Within the period of analysis, patients treated with ETA had a numerically higher discontinuation rate (44%) followed by ADA patients (41%) whereas patients treated with GLM had the lowest discontinuation rate (34%). The average dose of GLM, ETA or ADA were respectively 51.6 mg/month, 46.7 mg/week and 42 mg/q2weeks in accordance with their respective label in Canada for RA.
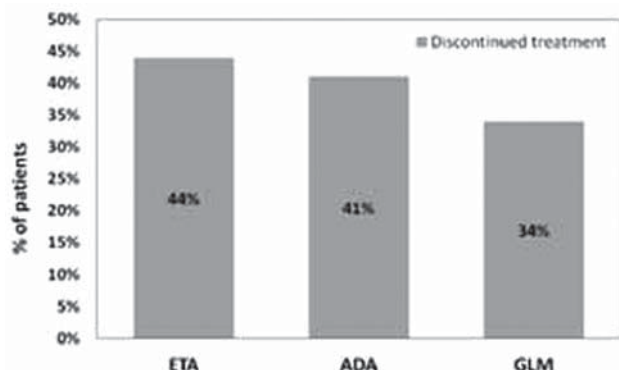
Figure 1. Treatment discontinuation rate within a period of 12 month following initiation (Bionaïve at initiation)

Conclusion: Results of these descriptive claims analyses show that in a real-world setting, the use of golimumab in RA patient's naïve to biologics is in accordance with the approved dose of 50 mg/month and that a numerically higher drug survival rate is observed for GLM (76%) compared to ETA and ADA 1 year after initiation of treatment. This is the first time that drug utilization patterns of GLM in comparison to ETA and ADA is reported in a real-world setting. Further research is needed to compare the relationship between drug utilization patterns on healthcare resource utilization and outcomes.

Disclosure: H. Khalil, Janssen Canada Inc, 3; **A. Tahami**, Janssen Canada Inc., 3.

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LIGHT (TNFSF14), Cathepsin-K, DKK-1 and Sclerostin in Rheumatoid Arthritis Patients: Effect of ANTI TNF-α Treatment in the WNT/β-Catenin Network Signaling. Alberto Cauli, Grazia Dessole, Giovanni Porru, Matteo Piga, Alessandra Vacca, Valentina Ibba, Pietro Garau and Alessandro Mathieu. University of Cagliari, Cagliari, Italy

Background/Purpose: We previously reported increased expression of cell membrane RANKL in PBMC of patients with active rheumathoid arthritis (RA) which was down-regulated by anti TNF-α treatment with adalimumab, while soluble RANKL and OPG were scarcely affected. We speculated that anti TNF-α induced down-regulation of membrane RANKL could be important in preventing articular damage in RA patients. Joint damage may also be mediated by the balance of other mediators involved in osteoclast functions such as LIGHT (TNFSF14) and cathepsin-K, while osteoblast functions are influenced by DKK-1 and sclerostin, although the data available is still contrasting and the significance under debate. The aim of this study was to investigate the impact of anti TNF-α treatment on the major soluble mediators involved in bone homeostasis in RA patients.

Methods: The effects of anti TNF-α therapy on bone homeostasis was studied in 15 active RA patients (DAS28 5.9 $\pm$ 0.9) and compared with 20 healthy controls (HC); data were collected at baseline, after 6, 12 and 24 weeks. Adalimumab 40 mg (ADA) was administered every other week according to guidelines, all patients experienced a satisfactory clinical response according to EULAR criteria. The serum levels of DKK-1, Sclerostin, Cathepsin-K were measured by enzyme-linked immunoassorbent assay (ELISA), all purchased from Biomedica (Vienna, Austria); LIGHT protein was detected with Quantikine ELISA (R&D System, Europe, UK). Values are presented as the median and interquartile range. Serum levels at different times after treatments were compared with those before therapy and HC. The significance of the results was analysed using the non parametric Mann-Whytney U-test or Wilcoxon, as appropriate, using Prism 5.0 software (GraphPadInc). P values less than 0.05 were considered significant.

Results: Cathepsin-K levels were found to be higher in active RA patients (12.7 IQR 11.3–15.3) compared to HC (9.1 IQR 45-14.3 pmol/mL, p=0.019) and after ADA at W6 (15.5 IQR 12.5–26.8 p=0.001), W12 (16.4 IQR 12.1–20.5 p=0.003), W24 (15.0 IQR 12.9–16, p=0.003). LIGHT levels were also consistently higher in the active RA group (96,6 IQR 65.3–179.2) compared with HC (66.0 IQR 42.6–112.0 pg/L, p=0.03) and after ADA, W6 (101.6 IQR 88.7–203.1 p=0.006), W12 (150.4 IQR 88.8–192.2 p=0.003) and W24 (138.9 IQR 66–228.5 p=0.015). Sclerostin levels were higher in the untreated RA group (31.5 IQR 26.3–48.7 pmol/L) compared to HC (24.5 IQR 18.7–29.6 p=0.007). It is noteworthy that long term adalimumab treatment induced a significant reduction in sclerostin levels at W24 (19.50 IQR 14.6–29.9 p=0.002); conversely, no significant differences in DKK-1 levels were observed in active RA (21.1 IQR 7.9–57pmol/L) compared to HC (19.0 IQR 11–27) and following ADA, W6 (19.5 IQR 6.7–59.5), W12 (20.1 IQR 9.2–57.5), W24 (11.1 IQR 5.2–54.6).

Conclusion: The decreased levels of sclerostin following anti TNF-α treatment may reduce the inhibition of the WNT/β-catenin pathway leading to increased osteoblast activity which may balance the increased osteoclast function in RA patients (as mirrored by the persistent increase in cathepsin-K and LIGHT) and therefore contributing to the inhibition of joint damage seen in patients treated with anti-TNF-α drugs.

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What Is the Right Dose to Start Methotrexate (7.5 or 15mg) in Rheumatoid Arthritis? (A Randomized Controlled Trial). Varun Dhir, Mandeep Singla, Palvi Goyal, Vinay Sagar, Aman Sharma and Shefali K. Sharma. Post Graduate Institute of Medical Education and Research, Chandigarh, India

Background/Purpose: Recent recommendations have suggested higher starting doses of methotrexate, i.e. 15 mg/week (3E initiative) in rheumatoid arthritis. However, studies comparing conventional (7.5mg) and newer (15mg) starting dose are limited. Unclear if any difference in control of disease activity or adverse effects with these starting doses.

Methods: This randomized controlled trial included 100 rheumatoid arthritis patients (fulfilling 1987 ACR), having active disease ('Disease activity score 28 joints 3 variables' DAS28-3v≥5.1) and not on methotrexate[3] 3 months. Using random number tables, patients were allocated (concealed by envelopes) to two groups—starting methotrexate at 7.5mg or 15 mg/week. Methotrexate escalated by 2.5 mg every 2 weeks; similar folic acid dose (10 mg/week). Patients assessed 4 weekly (blinded assessor) for disease activity (DAS28-3v). In addition, minor adverse effects (symptoms like nausea etc) determined using a performa and major adverse effects determined using blood tests (cytopenias- WBC<4000, Platelet<1lac or transaminitis- ALT or AST>80) or CXR (PA) if required. Analysis by intention to treat; difference in disease activity, adverse effects compared using students t and chi-square test respectively (or Fishers exact). (Trial Reg# NCT01404429)

Results: Patients in the two groups—7.5 mg and 15 mg had similar age (44.5±10.3, 42.8±11.2 yrs, p=0.4), gender (F:M=36:11, 42:11, p=0.4),

disease duration (4.8±4.8, 4.7±4.5 yrs, 0.9), disease activity (DAS28-3v=6.2±0.7, 6.2±0.8, p=0.9) and HAQ (1.3,1.3,p=0.9). In the 7.5 and 15 mg groups, 38 and 46 patients completed study, reaching final methotrexate dose of 19.3±1.8 mg and 24.3±2.0 mg per week respectively. Significant reduction in disease activity in both groups at 12 weeks (p<0.001), however, there was no intergroup difference at 4, 8 or 12 weeks (Figure 1), nor in HAQ at 12 weeks (1.1,0.9,p=0.4). No difference in 7.5 and 15mg groups in episodes of cytopenias (1,2, p=0.9) or transaminitis (6,7, p=0.8) or pneumonitis (0,0). However, minor adverse effects lower in 7.5mg compared to 15mg group (Relative Risk=0.58, 95% CI:0.36–0.95). Common were nausea (more in 15mg), loss of appetite, fatigue and uneasiness (Table 1).

Table 1. Frequency of minor adverse effects (symptoms) in the two groups

Minor adverse effect (Symptom)	7.5 mg group	15 mg group	P value	Relative Risk 7.5 versus 15 mg (95% confidence intervals)
Any	31.9	54.7	0.02*	0.58 (0.36–0.95)
Nausea	19.2	39.6	0.02*	0.48(0.25, 0.94)
Fatigue	6.4	13.2	0.43	0.48(0.13, 1.76)
Loss of appetite	12.8	11.3	0.80	1.13(0.39, 3.26)
Diarrhea	0.0	5.7	0.29	0.18 (0.01, 3.62)
Uneasiness or dizziness	17.0	13.2	0.59	1.29 (0.51, 3.28)

*statistically significant

Time →	0 weeks	4weeks	8 weeks	12 weeks
DAS28-3 7.5 mg	6.22	6.00	5.88	5.75
15 mg	6.16	6.05	5.83	5.61
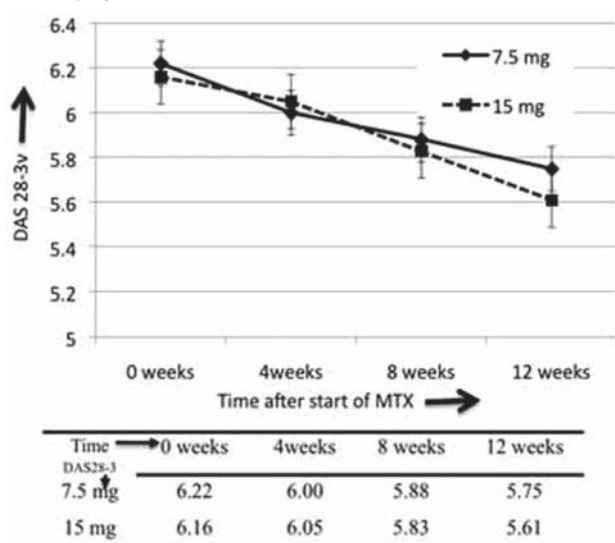
Figure 1. Disease activity in the two groups at 4 weekly visits.

Conclusion: Starting treatment with either 7.5 mg or 15 mg per week of methotrexate followed by similar fast escalation (5mg/month) is equivalent in control of disease activity at 12 weeks. Although, no difference in transaminitis or cytopenia, higher minor adverse effects, especially nausea in 15mg group.

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Comparison of Tolerability Between Tumor Necrosis Factor-Inhibitors and Tocilizumab for the Treatment of Rheumatoid Arthritis. Yoshihiro Hishitani, Yoshihito Shima, Toru Hirano, Keisuke Hagihara, Kosuke Ebina, Yasuo Kunugiza, Kenrin Shi, Masashi Narazaki, Atsushi Ogata, Tetsuya Tomita, Toshio Tanaka and Atsushi Kumanogoh. Osaka University Graduate School of Medicine, Suita, Japan

Background/Purpose: Some patients with rheumatoid arthritis (RA) receiving tumor necrosis factor-inhibitors (TNF-Is) show inadequate response to TNF-Is. But it has not been clarified what is better as the second biological agents by clinical trials, so observational study is necessary. We conducted a retrospective cohort study, especially focused on the difference of the drug retention rates between bio-naïve patients and switching patients.

Methods: We retrospectively reviewed the medical records of patients with RA, who were administered biologics (tocilizumab (TCZ) or TNF-Is

(infliximab, etanercept, adalimumab, and golimumab)) in our institute from September 1999 to April 2012, and analyzed the retention rates and causes of the discontinuation of the biologics. Kaplan-Meier estimate and log-rank test were used to analyze the differences of the drug continuation rates between bio-naïve patients and switching patients.

Results: TCZ was administered to 97 bio-naïve patients and 53 switching patients. TNF-Is were administered to 318 bio-naïve patients and 89 switching patients. Median (range) administration duration of TCZ was 2.54 years (0.08–12.6) for bio-naïve patients and 1.78 years (0.08–3.87) for switching patients, respectively. And that of TNF-Is was 1.87 years (0–11.3) for bio-naïve patients and 0.94 years (0–5.95) for switching patients, respectively. Kaplan-Meier Curves of the time to discontinuation due to unfavorable causes were shown (Figure 1, 2). Regarding TCZ, there was no significant difference of the drug retention rates between bio-naïve patients and switching patients (p = 0.9561), while regarding TNF-Is, there was a significant difference (p = 0.0037). To clarify the reason for this difference between TCZ and TNF-Is, we conducted Kapran-Meier estimate for cause-specific rates of discontinuation. About TCZ, the cumulative occurrence of discontinuation due to lack or loss of efficacy and adverse events were not statistically different between bio-naïve patients and switching patients (p = 0.1376, p = 0.3683, respectively). But about TNF-Is, discontinuation due to lack or loss of efficacy was significantly more in switching patients than in bio-naïve patients (p < 0.0001), while cumulative discontinuation due to adverse events was not statistically different (p=0.8334).
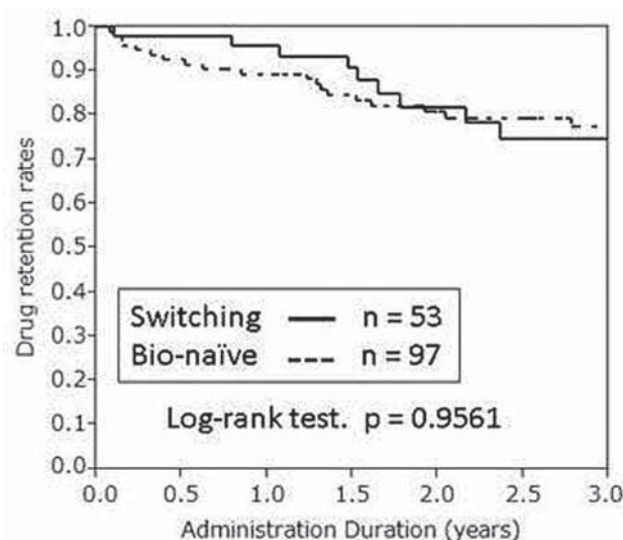
Figure 1. Tocilizumab. Bio-naïve vs Switching.
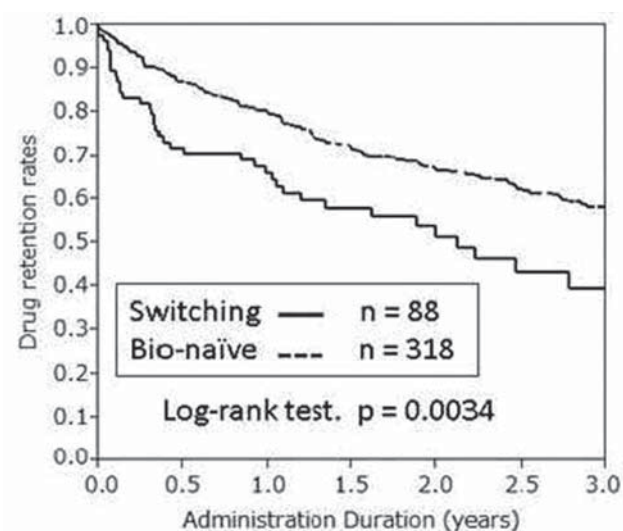
Figure 2. TNF-i. Bio-naïve versus Switching.

Conclusion: TCZ showed high tolerability in both bio-naïve patients and switching patients, while TNF-Is showed significantly lower tolerability in switching patients than in bio-naïve patients. This high retention rate of TCZ for switching patients was considered to be due to durability of its efficacy.

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TNF Inhibitor Treatment in Rheumatoid Arthritis (RA) Patients with Moderate Versus High Disease Activity At Baseline: A Comparison of Utility Gains, Response and Remission Rates. Elisabeth Lie, Siri Lillegraven, Karen M. Fagerli, Till Uhlig and Tore K. Kvien. Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: Randomized clinical trials in RA have until recently focused on patients (pts) with high disease activity, but the majority of pts in the clinic have moderate disease activity. A specified threshold of disease activity for institution of TNF inhibitors (TNFi) has not been mandatory in Norwegian health care, thus pts with low or moderate disease activity have gained access to these therapies. Our objective was to assess what proportion of pts starting TNFi therapy had moderate disease activity at baseline, and to compare the outcomes in these pts to those with high disease activity.

Methods: Data for this study were provided by NOR-DMARD – a Norwegian multicentre, longitudinal observational study of consecutive pts with arthritides starting new DMARD regimens. The current analyses included biologics naïve pts with moderate (DAS28 3.2–5.1) or high (DAS28 >5.1) baseline disease activity who started treatment with TNFi + methotrexate (MTX). Baseline characteristics, utility gains (SF-6D and EQ-5D), ACR responses as well as remission rates at 3 and 6 months were compared by Chi^2 test, two-samples t test and Mann-Whitney U test as appropriate. 2-yr drug survival was compared by Kaplan-Meier analysis with log-rank test.

Results: The study included 296 pts with moderate (DAS28 3.2–5.1) and 347 pts with high (DAS28 >5.1) disease activity. 73 pts with DAS28 ≤3.2 at baseline were excluded. Mean(SD) DAS28 were 4.30(0.49) vs. 6.18(0.76), respectively. Overall, 73% were female, mean/median disease duration was 9.2/5.4 years, 75% were rheumatoid factor positive and 30% current smokers (no significant differences between the groups). The pts with moderate disease activity were significantly younger (mean 52 vs. 54 years, p=0.03) and had better baseline scores for 28-SJC, 28-TJC, patient and physician global, CRP, ESR, pain VAS and fatigue VAS (all p<0.001). Further, mean(SD) MHAQ scores were 0.57(0.41) vs. 0.97(0.52), SF-6D 0.62(0.11) vs. 0.54(0.11), and EQ-5D 0.56(0.28) vs. 0.32(0.31) in the moderate vs. high disease activity group (all p<0.001). Three- and 6-month utility gains were significantly larger in the high disease activity group while there were no statistically significant differences in ACR responses (table). As expected, remission rates were significantly higher in the moderate disease activity group (table). 2-yr drug survival was similar in the 2 groups (estimated 57% vs. 56%, p=0.42) and reasons for discontinuation were also similar.

	3 months			6 months		
	Moderate	High	*P*	Moderate	High	*P*
ΔEQ-5D [mean (SD)]	0.10 (0.29)	0.27 (0.33)	<0.001	0.09 (0.26)	0.31 (0.34)	<0.001
ΔSF-6D [mean (SD)]	0.07 (0.12)	0.10 (0.12)	0.005	0.07 (0.13)	0.11 (0.13)	0.006
ACR20 response	47.9%	54.4%	0.14	56.7%	64.4%	0.10
ACR50 response	26.1%	25.1%	0.80	33.8%	38.0%	0.36
ACR70 response	14.3%	13.8%	0.87	19.4%	23.6%	0.28
ACR/EULAR remission (Boolean)	9.1%	3.9%	0.013	12.0%	6.7%	0.049
SDAI remission (SDAI ≤3.3)	15.8%	5.0%	<0.001	21.0%	10.5%	0.003
DAS28 remission (DAS28 <2.6)	32.3%	12.7%	<0.001	42.6%	18.3%	<0.001

Conclusion: Of biologics naïve pts starting TNFi + MTX, 52% had a baseline DAS28 <5.1. Pts with moderate disease activity when starting their first TNFi achieved higher remission rates but lower utility gains than pts with high disease activity, while ACR responses and drug survival were similar. Such comparisons can provide information for cost-effectiveness analyses which are increasingly important and necessary to guide decision making in this field.

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Safety and Efficacy of Rituximab in Patients with Rheumatoid Arthritis and Lung Involvement. Elena Becerra, Geraldine Cambridge and Maria J. Leandro. University College London, London, United Kingdom

Background/Purpose: Lung involvement is common in patients with Rheumatoid Arthritis (RA), including interstitial lung disease (ILD), pleural disease and small airway disease. There are no full reports in the literature analyzing the influence of Rituximab (RTX) in patients with RA with pre-existing lung disease, although it is a rising question in daily clinical practice. We aim to evaluate the safety and efficacy of RTX in our cohort of RA patients with pre-existing lung involvement.

Methods: Retrospective observational study of the RA cohort treated with RTX at University College Hospital, identifying patients treated with RTX with any lung involvement. Data were collected on type of lung disease, mortality, respiratory infections and stabilization/progression of symptoms.

Results: 264 patients with RA have received RTX in our unit between 1998 and 2012. A total of 38 patients (14%) had lung involvement, 24 of them (63%) were female, mean age was 64 years (range 37–79), mean disease duration was 19 years (range 3–42), mean number of RTX cycles was 4 (range 1–10), total follow up duration was 146.7 patient years (median 2.5 years, range 0.5–13.5). 19 of them (50%) had ILD: 3 usual interstitial pneumonitis (UIP), 5 nonspecific interstitial pneumonitis (NSIP, 2 of those had an overlap antisyntetase syndrome), 4 organizing pneumonia (OP) and 7 undetermined ILD. 15 patients (40%) had bronchiectasis. The remaining 4 patients had diagnosis of chronic obstructive pulmonary disease (COPD), small airway disease, pleural effusion requiring decortication and pleural plaques. 6 of the above patients had concomitant COPD.

Lung disease has remained clinically and radiologically stable in most patients. One patient with severe UIP before RTX showed slow lung progression over 4 years of follow up, and Mycophenolate mofetil is being considered. The 2 patients with antisynthetase syndrome have stable NSIP but on combination therapy (1 azathioprine, 1 mycophenolate mofetil). 25 patients (66%) reported respiratory infections but in only 6 of these patients was an increased frequency of infections after starting rituximab treatment noted. 2 of these 6 patients had low serum immunoglobulins (1 IgG only, 1 IgG and IgM). 2 patients had serious infections requiring hospitalization.

There were 2 deaths, both in patients with bronchiectasis and multiple comorbidities, none directly related to rituximab treatment.

Conclusion: RTX seems to be a relatively safe therapy in the cohort of RA patients with lung involvement. There is no definite evidence for improvement in lung involvement in RA patients treated with rituximab, but nor there is data suggesting that RTX can lead to a progression of lung symptoms. Only one patient with severe UIP before RTX showed lung progression after 4 years of follow up.

Disclosure: **E. Becerra**, None; **G. Cambridge**, None; **M. J. Leandro**, Roche and Chungai, 5.

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Safety Update On Certolizumab Pegol in Patients with Active Rheumatoid Arthritis with Long Term Exposure. Xavier Mariette[1], RF. van Vollenhoven[2], Vivian P. Bykerk[3], Marc de Longueville[4], Catherine Arendt[4], Kristel Luijtens[5] and John J. Cush[6]. [1]Université Paris-Sud, Le Kremlin Bicetre, France, [2]The Karolinska Institute, Stockholm, Sweden, [3]Hospital for Special Surgery, New York, NY, [4]UCB Pharma, Brussels, Belgium, [5]UCB, Brussels, Belgium, [6]Baylor Research Institute, Dallas, TX

Background/Purpose: The safety of certolizumab pegol (CZP) in rheumatoid arthritis (RA) has been reported in previous pooled analyses of clinical trials. An update of long-term safety data of CZP in RA with a cut-off date of 30 Nov 2011 is provided.

Methods: The pooled analysis included 10 completed randomized controlled trials (RCTs) of CZP in RA and their open-label extensions (OLEs). Pooling was done across all doses. Some patients (pts) received CZP 400 mg Q2W (twice the registered dose) as per protocol. Adverse events were defined as those occurring after first dose and within a maximum of 84 days of last dose. Serious adverse events (SAEs) were defined conservatively by the regulatory definition[1] with the addition of opportunistic infections (OIs), malignancies and medical events important to the investigator. Serious infectious events (SIEs) were defined according to the regulatory definition with addition of the need for IV antibiotics. Search terms for OIs were defined by 6 external experts and validated by the steering committee (JC, VB, RVV and XM). All cases of death, SIEs (including OIs) and malignancies were manually reviewed by external experts, classified according to pre-defined standard procedures and validated by the study authors. Deaths were categorized as primarily associated with cardiovascular (CV), infectious, malignant or other causes; malignancies were classified as non-melanoma skin cancer (NMSC), solid tumors or lymphoma. Incidence rates (IR) and event rates (ER) per 100 pt-years (PY) are presented.

Results: By 30 Nov 2011, 4049 RA pts had received CZP in all studies (RCTs and OLEs) for a total of 9277 PY. Mean exposure to CZP in all studies was 2.1 yrs (Y) (min 0.04, max 7.6); median exposure was 0.7 Y. SIEs were the most common SAEs. In total, 43 tuberculosis (TB) infections occurred in 43 pts, of which 39 occurred in Central and Eastern Europe (CEE). 58 deaths occurred in CZP pts (IR: 0.63/100 PY) as a result of 19 CV events, 13 infections, 13 malignancies and 18 other causes. 65 CZP pts in all studies developed malignancies (ER: 0.72/100 PY), with 60 pts developing solid tumors (ER: 0.67/100 PY) and 5 developing lymphoma (0.05/100 PY).

| | RCTs | | | | | | | | All studies (RCTs and OLEs) | | | |
	PBO N=1137				All CZP doses N=2965				All CZP doses N=4049			
Total exposure (PY)	373				1302				9277			
Mean exposure (days)	110				152				782			
Median exposure (days)	111				112				267			
	IR/ 100 PY	ER/ 100 PY	N pts	% pts	IR/ 100 PY	ER/ 100 PY	N pts	% pts	IR/ 100 PY	ER/ 100 PY	N pts	% pts
AEs	362.27	589.10	713	62.7	335.86	568.30	2048	69.1	188.83	328.93	3561	87.9
Leading to death	0.27	–	1	0.1	0.84	–	11	0.4	0.63	–	58	1.4
SAEs	17.01	21.73	61	5.4	20.97	29.49	260	8.8	13.96	21.31	1063	26.3
SIEs	1.35	1.34	5	0.4	5.61	6.07	72	2.4	3.64	4.32	323	8.0
All malignancies excluding NMSC	0.81	1.34	3	0.3	0.69	0.77	9	0.3	0.70	0.72	65	1.5
OIs*	0	0	0	0	1.0	1.08	13	0.4	0.67	0.69	62	1.5

* Treatment-emergent adverse events of oesophageal candidiasis were included as OIs

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Conclusion: No new safety signals associated with CZP have emerged in this updated long-term safety analysis. While SIE rates were higher for CZP than for PBO in the RCTs, they did not increase with continued exposure to CZP. Due to the shorter duration of PBO treatment compared with CZP, comparisons between the CZP and PBO groups should be interpreted cautiously. TB incidence may be explained by high recruitment in CEE prior to 2007. The rates of malignancies and serious infections are in line with CZP data reported in the product label and anti-TNF registry data.[2,3]

References

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ACR Poster Session A
Sjögren's Syndrome - Pathogenesis
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Pathogenic Autoantibodies to the Anti-Muscarinic Type 3 Receptor Act by Competitive Inhibition of Acetylcholine-Mediated Receptor Signalling in Sjögren's Syndrome. Michael W. Jackson[1], Isabell Bastian[2] and Thomas P. Gordon[3]. [1]Flinders University, Adelaide, Australia, [2]Flinders University and Flinders Medical Centre, Adelaide, Australia, [3]Flinders Medical Centre, Bedford Park, Australia

Background/Purpose: Primary Sjögren's syndrome (SS) is a systemic autoimmune disorder characterized by exocrine failure and widespread autonomic dysfunction. Functional autoantibodies (Abs) directed against the muscarinic type 3 receptor (M3R) have been postulated to underpin gastrointestinal, bladder and cardiac dysfunction in SS, and we have recently demonstrated that SS IgG acts specifically at the M3R to disrupt cholinergic neurotransmission and motility in murine gastrointestinal tissues.To date, the mechanism by which anti-M3R Abs exert an effect on receptor signalling has remained difficult to determine, due to a lack of suitable functional assays. In the current study, we use a novel, real-time cell bioassay of M3R signalling to explore the physiological mechanism by which anti-M3R Abs inhibit M3R activity.

Methods: HEK293 cells (2×10^5) were transiently transfected in 96 well culture plates for 24 hours with DNA encoding the human M3R, and with the pGL4.33 vector (Promega) containing a luciferase gene driven by the serum response element promoter. Cells were then incubated for 4 hours in the presence of the cholinergic agonist, carbachol, (0.3 to 300 μM) and patient IgG (4 mg/ml) characterised as positive (M3R+; n = 4) or negative (M3R-; n = 2) for inhibitory anti-M3R activity, as determined by in vitro bladder strip assays. IgG from healthy donors (n = 6) was used as controls. Luciferase gene activity was determined on a DTX 880 MultiMode Detector (Beckman Coulter).

Results: All M3R+ IgGs, but not control or M3R- IgG, significantly inhibited carbachol-induced luciferase activity at carbachol concentrations ranging from 0.3 to 30 μM, with a maximum inhibition of approximately 40%. In contrast, inhibition of luciferase activity by anti-M3R Abs was lost at carbachol concentrations of 100 and 300 μM, consistent with competitive antagonist activity by the Abs at the carbachol-binding site. Anti-M3R Abs had no effect on luciferase activity in M3R-expressing cells in the absence of carbachol.

Conclusion: We have used a real-time cell-based bioassay incorporating a luciferase reporter to characterise inhibitory anti-M3R antibodies in IgG from patients with SS. The bioassay allows a functional measure of receptor signalling activity, thereby facilitating investigation of the mechanism by which patient Abs alter M3R activity. We found that Ab inhibition of carbachol-mediated M3R activity was reversible at high agonist concentrations, consistent with competitive displacement of agonist at the carbachol-binding site. These findings contrast previous studies suggesting non-competitive interactions between anti-M3R Abs and receptor agonists, and confirm the carbachol binding site as the target of the functional anti-M3R Abs in SS. The ability of the assay to detect anti-M3R Abs compare favourably with whole-tissue in vitro assays, thereby combining the sensitivity of ex-vivo tissues with the convenience of a 96-well assay format. The bioassay should facilitate both detailed pharmacological characterization of the mechanism of antibody action at the M3R, and the studies required to establish the role of anti-M3R antibodies in the autonomic dysfunction associated with SS.

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Characterization of an in Vitro Model of Human Salivary Gland for Studying Sjögren Syndrome (SS).

M. Jesus Dominguez-Luis[1], M.Teresa Arce-Franco[1], Estefania Armas-Gonzalez[1], Ada Herrera-Garcia[1], Teresa Giraldez[2], Pablo Miranda[2], Diego Alvarez de la Rosa[3], Jose Garcia-Verdugo[4], Carlos Martinez-Jimeno[5] and Federico Diaz-Gonzalez[1]. [1]Rheumatology Service. Hospital Universitario de Canarias., La Laguna, Spain, [2]Unidad de Investigación of Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain, [3]Department of Physiology. Universidad de La Laguna,, La Laguna, Spain, [4]Cellular Morphology Laboratory, Centro de Investigación Príncipe Felipe., Valencia, Spain, [5]Maxilofacial Department, Hospital Universitario de Canarias,, La Laguna, Spain

Background/Purpose: Sjögren's syndrome (SS) is an autoimmune exocrinopathy of unknown etiology that is characterized by decreased salivary secretion (xerostomy) and lacrimal (xerophthalmy). Histopathological lesions of the glandular tissue in SS are characterized by the presence of mononuclear cell infiltrates and acinar atrophy. Studies on the pattern of inflammatory mediators have shown high amounts of IL-2, IFN-γ, IL-10, IL-1β, IL-6, SDF-1α and TNF-α. However, little is known about the implication of this cytokine profile in de SS pathogenesis.

Objectives: 1) to establish and characterize a model of human salivary gland in vitro, and 2) analyze if this model the functional effect of proinflammatory mediators present in the glandular microenvironment of SS patients.

Methods: human epithelial cells from biopsies of non-cancerous parotid gland, were enzymatically dispersed, cultured and expanded in medium MCDB153 supplemented with insulin, hydrocortisone and epidermal growth factor. Proliferation assays were performed using a cell proliferation kit. The expression of amylase, VAMP-2, SMA1 and epithelial sodium channels (ENaC), were studied by immunofluorescence in confocal microscopy. The gene expression of the mineralocorticoid receptor, sodium channels (α, β, γ) and a number of genes characteristic of ducts or acini were analyzed by real-time RT-PCR. For the functional study of sodium channels in the plasma membrane were determined by patch clamp assays. Amylase activity in cell-free supernatant was assayed by a fibril-degradation assay and was used as a surrogate marker of exocrine gland function.

Results: Cells from human salivary gland had morphology of epithelial cells and were able to proliferate in culture. The pattern of gene expression of these cells was more compatible with an acinar rather than ductal origin. Furthermore, the functionality of epithelial sodium channel in their surface was analyzed by patch clamp experiments. The presence of 10μM isoproterenol and 2 mM Ca^{++} for 24 hours increased three times the basal activity of amylase in the cell-free supernatant of these cells. Moreover, the presence of TNF-α and SDF-1α caused a significant dose-response reduction in the amylase activity in the cell-free supernatant.

Conclusion: It is possible to set up a functional model of human salivary gland in vitro that allows the development of studies which could lead to better understanding of the pathogenesis of SS and may help to develop therapeutic interventions for this disease.

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Ebv-Mir-Bart13 Affects the Expression of AQP5 in Human Salivary Gland Cell Lines Contributing to the Pathogenesis of Sjögren's Syndrome.

Alessia Gallo[1], Mayank Tandon[1], Shyh-Ing Jang[1], Hwei Ling Ong[1], Indu Ambudkar[1], Gabor G. Illei[2] and Ilias Alevizos[3]. [1]NIDCR, Bethesda, MD, [2]NIDCR/ NIH, Bethesda, MD, [3]NIDCR/ NIH #10 1N110, Bethesda, MD

Background/Purpose: Loss of secretory function of salivary glands is one of the most important functional effects of Sjögren's syndrome (SS), a chronic systemic autoimmune disease. We have previously shown that an EBV microRNA (ebv-miR-BART13) is significantly over-expressed in minor salivary gland biopsies of SS patients, when compared to the healthy volunteers. We have also shown that the over-expression of ebv-miR-BART13 in human salivary gland cell line is responsible of the down regulation of STIM1, an ER-Ca2+ sensor protein regulating SOCE and to the consequent decrease in Calcium influx. We demonstrated that the decrease of Calcium influx, due to the presence of ebv-miR-BART13, is responsible of the loss of translocation of NFAT, a transcriptional factor that drives the transcription of several genes, but most interestingly AQP5. The objective of this work is to establish if ebv-miR-BART13 leads to the decreased level of AQP5 not only trough the Calcium-NFAT pathway but also by directly binding the 3'UTR of the AQP5 mRNA.

Methods: We checked the AQP5 messenger lever by Real-time PCR in a primary salivary epithelial cells line. To investigate if the viral microRNA is able to bind the 3'UTR the AQP5 messenger we transfected HSG cells and a primary salivary epithelial cells line derived by human minor salivary gland biopsy with a luciferase plasmid containing the AQP5 3'UTR fused with the luciferase firefly coding sequence and ebv-mir-BART13.

Results: We first checked if the mRNA level of the endogenous AQP5 is affected by the presence of ebv-miR-BART13. For this, we used as system primary salivary epithelial cells because they maintain their acinar phenotype thus expressing AQP5 mRNA level, compared to established salivary cell lines such as HSG cells. After 48 hour of transfection with ebv-miR-BART13, the AQP5 mRNA was decreased (4 fold change) by the presence of this viral miRNA.

In order to examine if ebv-miR-BART13 also exerts its effect by binding directly the AQP5 mRNA, we used a plasmid containing the AQP5 3'UTR sequence fused with the luciferase firefly sequence. The luciferase plasmid was co-transfected with ebv-miR-BART13 analogues and antagonists in both HSG cells (human submandibular salivary gland cells) and primary salivary epithelial cells line derived from human minor salivary gland biopsies. After 48 hour of transfection, the cells were collected, proteins were extracted and the luciferase activity was measured. Luciferase expression decreased by 30 % in HSG cells and by 40 % in the primary cell line, confirming that ebv-miR-BART13 directly targets the 3'UTR of AQP5 mRNA.

Conclusion: We first checked if the mRNA level of the endogenous AQP5 is affected by the presence of ebv-miR-BART13. For this, we used as system primary salivary epithelial cells because they maintain their acinar phenotype thus expressing AQP5 mRNA level, compared to established salivary cell lines such as HSG cells. After 48 hour of transfection with ebv-miR-BART13, the AQP5 mRNA was decreased (4 fold change) by the presence of this viral miRNA.

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Expression of Micrornas (miRNAs) Predicted to Target Ro/SSA and La/SSB Autoantigens in Sjögren's Syndrome (SS).

Vasiliki C. Gourzi[1], Efstathia K. Kapsogeorgou[1], Nikolaos C. Kyriakidis[1], Menelaos N. Manoussakis[1], Haralampos M. Moutsopoulos[2] and Athanasios G. Tzioufas[3]. [1]School of Medicine, National University of Athens, Greece, Athens, Greece, [2]School of Medicine, University of Athens, Athens, Greece, [3]School of Medicine, National University of Athens, Athens, Greece

Background/Purpose: microRNAs (miRNAs) are key post-transcriptional regulators of gene expression and might be implicated in the over-expression of Ro/SSA and La/SSB autoantigens in the salivary gland (SG) tissues and epithelial cells (SGEC) of SS patients. We have previously identified 11 miRNAs (let-7b, miR-16, miR-129-5p, miR-153, miR-181a, miR-200b, miR-200b*, miR-223, miR-483-5p, miR-573, miR-583) that are predicted to target the Ro/SSA (TRIM21 or TROVE2) and La/SSB mRNAs. Herein, we sought to investigate the expression of these miRNAs in SS. Therefore, we studied their expression in SG-tissues, SGECs and peripheral blood mononuclear cells (PBMC) of SS patients and sicca-complaining non-SS controls (CT), as well as their association with the expression of target mRNAs.

Methods: miRNAs and mRNAs expression of Ro52/TRIM21, Ro60/TROVE2 and La/SSB were investigated by real-time PCR in total RNA from SG-tissues, SGECs and PBMCs obtained from 27 SS patients and 22 sicca-CT. Significant differences between SS patients and CT and associations between miRNAs and mRNAs expression were evaluated by non-parametric Mann-Whitney and Spearman's rank correlation tests, respectively.

Results: From the 11 microRNAs studied, miRs 129-5p, 153, 573 and 583 were not expressed in any of the samples studied, whereas miR-200b* was not detected in PBMCs. All others miRNAs were found to be expressed in all samples tested. Differential miRNA expression between SS and controls involved miR-16 and miR-223 in SG tissues, miR-200b in SGECs and miR-223 in PBMCs (mean±SE: 12.71±5.26 vs 2.47±0.67, p=0.05, 8671±2430 vs 3519±777, p=0.008, 2353±367 vs 1116±196.5, p=0.02 and 447200±224400 vs 50470±9577, p=0.01 in SS vs CT, respectively; Mann-

Whitney analysis). miR-16 and miR-200b levels were positively associated with Ro52/TRIM21 mRNA expression (r=−0.5858, p=0.003, r=−0.4930, p=0.02 respectively) and miR-16 negatively associated with Ro60/TROVE2 mRNA expression (r=−0.4270, p=0.04) in SG-tissues. In SGECs, miR-181a expression was negatively associated with Ro52/TRIM21, whereas miR-200b with Ro60/TROVE2 mRNA expression (r=−0.3071, p=0.04, r=−0.3292, p=0.03 respectively; Spearman's test). In addition, miR-200b* levels were positively associated with Ro52/TRIM21, Ro60/TROVE2 and La/SSB mRNA expression (r=0.3366, p=0.03, r=0.3580, p=0.02, r=0.4398, p=0.003 respectively). In PBMCs, miR-16 and miR-483-5p levels were found to positively correlate with Ro52/TRIM21 mRNA expression (r=−0.3202, p=0.05, r=−0.4698, p=0.003 respectively).

Conclusion: Our findings indicate that miR-16, miR-200b and miR-223 are deregulated in SS. Attention should be noted to the role of miR-200b in the regulation of Ro/SSA and La/SSB mRNAs. Further functional studies are now undertaken to enlighten the role of the deregulated miRNAs in disease pathogenesis and autoantigen expression.

Disclosure: V. C. Gourzi, None; E. K. Kapsogeorgou, None; N. C. Kyriakidis, None; M. N. Manoussakis, None; H. M. Moutsopoulos, None; A. G. Tzioufas, None.

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TLR3-Signaling Induces the Expression of Ro/SSA and La/SSB Autoantigens in Salivary Gland Epithelial Cells (SGECs). Nikolaos C. Kyriakidis[1], Efstathia K. Kapsogeorgou[1], Vasiliki C. Gourzi[1], Haralampos M. Moutsopoulos[2] and Athanasios G. Tzioufas[3]. [1]School of Medicine, National University of Athens, Greece, Athens, Greece, [2]School of Medicine, University of Athens, Athens, Greece, [3]School of Medicine, National University of Athens, Athens, Greece

Background/Purpose: Previous studies have shown that the mRNA expression levels of the Ro52/TRIM21, Ro60/TROVE2 and La/SSB intracellular autoantigens are elevated within the immunopathologic lesions of SS. High surface constitutive expression of TLR-3 has been described in long-term cultured SGECs, whereas stimulation of TLR-3 via synthetic analogues or viral RNA has been shown to be potent inducer of several immune-modulatory molecules, interferons and other cytokines, as well as apoptosis, in SGEC. Given that TLR3-mediated inflammatory responses have been shown to be negatively regulated by Ro52/TRIM21 autoantigen we sought to investigate whether TLR3 stimulation has a reciprocal effect in Ro52/TRIM21, as well as Ro60/TROVE2 and La/SSB mRNA, expression by SGECs.

Methods: SGEC lines from SS patients (n=5) and non-SS controls (n=10), were treated with the analogue of the TLR3 ligand polyinosinic:cytidylic acid (polyI:C; 5 μg/ml) and the TLR4-ligand lipopolysaccharide (LPS, 1 μg/ml, control TLR treatment) for various time-points. The expression of Ro52/TRIM21, Ro60/TROVE2 and La/SSB mRNAs was analyzed by real-time PCR at 0, 6, 12, 24, 48 and 72 hrs of treatment. The results were normalized by the expression of the HPRT1 gene and calculated by the ΔΔCT method using HeLa as calibrator. The expression of Ro52, Ro60 and La/SSB proteins was analyzed by immunoblotting, using specific antibodies. Mann-Whitney test was employed to analyze statistical significances.

Results: SGECs obtained from SS patients and controls were found to respond similarly to TLR3 signaling. The basal (constitutive) La/SSB and Ro60/TROVE2 mRNA levels were significantly upregulated following treatment of SGECs with polyI:C for 48-hrs (mean fold induction±SE: 0.86±0.18, p=0.003 and 3.29±1.75, respectively; p<0.0001 each). PolyI:C was found to be a strong inducer of Ro52/TRIM21 mRNA expression by SGECs at 6-hrs of treatment (mean fold induction of basal expression±SE: 13.12±4.5, p<0.0001). The polyI:C-induced Ro52/TRIM21 mRNA expression remained stable until 12-hrs of treatment, whereas a further increment was observed at 48-hrs of treatment (mean fold induction: 34.3±9.1 compared to basal levels, p<0.0001). The effect of polyI:C treatment in Ro52, Ro60 and La/SSB expression by SGECs was further confirmed at the protein level by immunoblotting. Treatment with LPS was not found to affect the mRNA expression of the molecules studied (Ro52/TRIM21, Ro60/TROVE2 and La/SSB). PolyI:C or LPS treatment of HeLa cells did not show any effect on the expression levels of Ro52/TRIM21, Ro60/TROVE2 and La/SSB mRNAs.

Conclusion: Our findings indicate a reciprocal regulation of TLR3 signaling in SS-related intracellular autoantigens, and particularly Ro52 expression, by SGECs. Further investigation is needed to clarify the mechanisms involved in this regulation.

Disclosure: N. C. Kyriakidis, None; E. K. Kapsogeorgou, None; V. C. Gourzi, None; H. M. Moutsopoulos, None; A. G. Tzioufas, None.

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IL-7 and Toll-Like Receptor 7 Synergistically Increase Th1/Th17/Th22 Cytokine Secretion and Activity of B Cells. A. Bikker[1], A.A. Kruize[1], F. Redegeld[2], W. de Jager[3], F.P.J.G. Lafeber[1] and J.A.G. van Roon[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Dept Pharmacology UU, Utrecht, Netherlands, [3]Dept Immunology, UMC Utrecht, Utrecht, Netherlands

Background/Purpose: IL-7 is a potent T cell activating cytokine that has been shown to cause proliferation, survival and differentiation of T cells as well as T cell-dependent activation of myeloid cells in numerous conditions. In inflamed tissues of patients with several autoimmune diseases (RA, pSS, psoriasis) increased IL-7 production by tissue cells and immune cells has been documented. Although reduced serum immunoglobulin levels in IL-7-deficient individuals suggested that IL-7 might play a role in activation of mature human B cells, direct evidence for this is lacking. Previously, it has been demonstrated that EBV, one of the suggested triggers of pSS, induces TLR7-dependent B cell activation and that EBV-transformed B cells express significant levels of the IL-7R as well as IL-7. Furthermore, we have shown that both intracellular IL-7R and IL-7 expression is up regulated in vitro upon TLR7 triggering of B cells. Our purpose was to investigate the potential synergy of IL-7-driven T cell-dependent and TLR7-mediated B cell activation and to assess the additive effects of monocyte/macrophages in this respect.

Methods: Isolated CD19 B cells and CD4 T cells from HC (n=7) were co-cultured (1:1) with and without IL-7, TLR7 agonist (TLR7A, Gardiquimod) or the combination of IL-7/TLR7A with and without CD14 monocytes/macrophages (T/B/mono; 1:1:0,1). Proliferation of T and B cells was measured using 3H-thymidine incorporation and by Ki67 expression (FACS analysis). Activation marker (CD19, HLA-DR, CD25) expression was measured by FACS analysis. In addition, in culture supernatants cytokines (IFNg, IL-17A, IL-22, IL-6 and IL-10) and IgM and IgG were measured by Luminex and ELISA, respectively.

Results: Exogenously added IL-7 did not activate B cells directly, in line with the absence of surface IL-7R. However, in the presence of T cells, IL-7 activated both T and B cells (Ki67+ CD4 cells from 1.1% to 14.4%, p<0.01 and Ki67+ B cells from 1.9% to 4.10.9%, p<0.05). TLR7A induced B cell activation, as measured by increased proliferation (%Ki67 from 1.2% to 9.3%) and up regulation of activation markers on B cells, which was facilitated in the presence of monocytes. TLR7-induced B cell activation in T/B or T/B/monocyte co-cultures was not associated with T cell activation. IL-7 added to TLR7A synergistically increased both B cell (TLR7A *vs*. IL-7/TLR7A; 9.3% *vs*. 33.4%) and T cell proliferation (IL-7 vs. IL-7/TLR7A; 0.8% *vs*. 29.2 %), which for B cells again was further increased by monocytes (TLR7A *vs*. IL-7/TLR7A; 30.2% *vs*. 63.0%)(all p<0.05). Similar results were observed for activation marker expression on B cells (CD19, HLA-DR CD25) and on T cells (HLA-DR, CD25). More important, IL-7 and TLR7, in the presence of monocytes, synergistically induced Th1/Th17/Th22 cytokine secretion and IgG production (all p<0.05)

Conclusion: IL-7 and TLR7 signaling synergistically activates T and B cells, which is markedly enhanced by the presence of monocytes/macrophages. Our results indicate that previously described increased local expression of IL-7 and TLR7 and increased numbers of macrophages in patients with pSS could contribute to enhanced lymphocyte activation and immunopathology in these patients.

Disclosure: A. Bikker, None; A. A. Kruize, None; F. Redegeld, None; W. de Jager, None; F. P. J. G. Lafeber, None; J. A. G. van Roon, None.

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IL-7 and IL-7 Receptor Blockade to Selectively Inhibit TLR7-Induced B Cell Activation in Primary Sjögren's Syndrome. A. Bikker[1], C.R. Willis[2], A.A. Kruize[1], J.W.J. Bijlsma[1], F.P.J.G. Lafeber[1] and J.A.G. van Roon[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Amgen Inc., Seattle, WA

Background/Purpose: Toll-like receptors (TLRs) are involved in the recognition of nucleic acids (viral, bacterial, and possibly self) and have been implicated in several auto-immune diseases. In primary Sjögren's syndrome (pSS) TLR7-induced B cell activation (e.g. by EBV) has been implicated in the immunopathology. An increased expression of TLR7 mRNA has been found in the parotid gland of pSS patients. In addition, TLR7 specifically

recognizes ssRNA from viruses, and possibly self-ssRNA, with which Ro- and/or La-proteins form complexes, facilitating anti-SSA/SSB auto-antibody production, one of the hallmark disease parameters of pSS. Interestingly, EBV-transformed B cells have been shown to express the IL-7R and secrete IL-7. Recently, we found increased levels of IL-7 and its receptor in the minor salivary gland of pSS patients. Our purpose was to investigate the role of IL-7/IL-7 receptor-mediated immune activation in TLR7-induced B cell activation in pSS patients.

Methods: Isolated CD4 T cells and CD19 B cells from HC (n=7) and pSS patients (n=5) were co-cultured with and without a TLR7 agonist (TLR7A, Gardiquimod) in the presence or absence of CD14 monocytes/ macrophages. Additionally, PBMCs (HC n=5, pSS n=8) were cultured with TLR7A with and without soluble human IL-7R (shuIL7R) and fully human anti-human IL-7 mAb. Proliferation of T cells and B cells was measured using ^{3}H-thymidine incorporation and Ki67 expression (FACS analysis). Activation markers (CD19, HLA-DR, CD25) and intracellular IL-7 and IL-7Rα expression by B cells were measured by FACS analysis.

Results: A strongly TLR7A-increased proliferation of T and B cell co-cultures was associated with significant and selective increases in Ki67-proliferating CD19 B-cells (HC from 1.2% to 9.3%, p<0.01 $vs.$ pSS from 1.2% to 7.0%, p<0.05), but not CD4 T-cells. Additionally, markers of activation on CD19 B cells (HC: CD25+ from 42.2% to 80.1%; CD19 MFI from 26.8% to 63.4%; HLA-DR MFI from 214 to 649) were significantly increased as well, equally effective in HC and pSS (all p<0.05). TLR7-induced B cell activation was increased in the presence of monocytes (Ki67+ B cells: HC from 0.9% to 30.2% $vs.$ pSS from 1.0% to 11.6%, both p<0.05). IL-7R blockade markedly inhibited lymphocyte proliferation of TLR7A stimulated PBMCs from HC (from 8880 to 2289 cpm; p<0.05) and pSS patients (from 8580 to 4802 cpm; p<0.01), which was associated by a selective inhibition of Ki67-proliferating B cells (from 47.5% to 9.4%). The specific role of IL-7R-mediated activation was supported by an increase in intracellular IL-7Rα and IL-7 upon TLR7 triggering in B cells. The role of IL-7 was confirmed by blockade of TLR7-induced B cell activation with a fully human anti-IL-7 mAb (mean inhibition 50%, p<0.05).

Conclusion: TLR7A-induced B cell activation is potently and selectively inhibited by IL-7 and IL-7R blockade. Together with the up regulation of IL-7 and IL-7R in B cells upon TLR7 activation, these results suggest that shuIL-7R/anti-IL-7 mAb blocks an autocrine function of IL-7 in B cells. This indicates that IL-7/IL-7R blockade, targeting not only T cells as previously shown, but also B cells, represents an interesting new therapeutic approach in pSS.

Disclosure: A. Bikker, None; **C. R. Willis**, Amgen Inc. Seattle, WA, USA, 3; **A. A. Kruize**, None; **J. W. J. Bijlsma**, None; **F. P. J. G. Lafeber**, None; **J. A. G. van Roon**, None.

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A New Pathogenic Role of Salivary Gland Epithelial Cells in the Costimulation of T Lymphocytes in Primary Sjögren's Syndrome: 0×40 Ligand Expression, T-Cell Induction of OX40 and Promotion of T-Cell Survival, Proliferation and Activation. Yazhuo Gong, Ghada Alsaleh, Jean Sibilia and Jacques-Eric Gottenberg. EA4438 Laboratoire Physiopathologie des Arthrites, Illkirch-Strasbourg, France

Background/Purpose: OX40/OX40L interaction is a pivotal costimulatory pathway involved in multiple autoimmune diseases. It provides a key signal for T-cell proliferation and differentiation in effector and memory subsets. Polymorphisms of OX40L are involved in the genetic predisposition to primary Sjögren's syndrome (pSS). Since SGECs express other costimulatory molecules such as CD80, CD86 or ICOSL, we investigated the expression of OX40L by salivary gland epithelial cells (SGECs) and the expression of OX40 by T cells cocultured with SGECs.

Methods: Primary culture of salivary epithelial cells was derived from minor salivary gland biopsies isolated from patients with SS or control subjects (complaining from dry symptoms without any feature of autoimmunity). Expression of OX40L by SGEC was measured using qPCR and immunohistochemistry. Naïve CD4$^+$ T cells were activated by anti-CD2, anti-CD3 and anti-CD28 and cultured alone or with SGECs. T-cell expression of OX40 was analyzed using flow cytometry. T-cell proliferation and survival were assessed by CFSE dilution and propidium iodide (PI)/DiOC6 staining, respectively. Levels of IFN-γ, IL-2, IL-4 and IL-6 were assessed in culture supernatants using ELISA.

Results: SGECs isolated from pSS patients (n=4) or controls (n=4) expressed OX40L mRNA and protein. Coculture of T cells with SGECs from patients with pSS (n= 7) significantly increased the expression of OX40 by CD4+T cells (67.3% ± 9.2) compared to T cells cultured alone (33.9% ± 6.9, $p= 0,02$). A similar induction of OX40 expression was observed in coculture of T cells with SGECs from controls.

In addition, SGECs isolated from pSS patients promoted T cell survival and proliferation: 82% vs 22% living T cells (PI negative DiOC6 positive) were detected when cultured with SGEC, compared to cultured alone. IFN-γ and IL-2, markers of T-cell proliferation and activation, were detected in the supernatant of cocultures (8.3 ± 0,2ng/ml for IFN-γ and 4.8 ± 0,4 ng/ml for IL-2) but not in the supernatant of SGEC or of T cells cultured alone. IL-6 was also increased in the supernatants of cocultures (2,7 ± 0,6 ng/ml, compared to SGECs isolated from pSS cultured alone (1,2 ± 0,7 ng/ml), or T cells cultured alone (0 ng/ml). The induction of T-cell expression of OX40 was not altered when the coculture of T cells and SGECs was performed using a transwell or not (n=3), which demonstrates that this OX40 induction depends on cytokine(s) and not of cell-cell contacts.

Conclusion: SGECs are capable to induce a dramatic increase of OX40 expression, and promote T-cell survival, proliferation and activation. This crosstalk between epithelial and T cells might also result in subsequent B-cell activation as shown by the increase of IL-6 in coculture supernatants. Further analyses are ongoing to determine the mechanisms involved in the induction of OX40 and consequences on T-cell polarization. These results demonstrate a new mechanism by which salivary gland epithelial cells play a pathogenic role in this autoimmune epithelitis. These results also suggest that OX40/ OX40L might represent relevant therapeutic targets in pSS.

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Memory B Cell Phenotypic and Gene Expression Profiling in Primary Sjögren's Syndrome: Implications for Disease Diagnosis. Mustimbo E. P. Roberts[1], Craig Maguire[1], Alex Rosenberg[2], Andreea Coca[3], Jennifer H. Anolik[2] and Inaki Sanz[4]. [1]University of Rochester School of Medicine and Dentistry, Rochester, NY, [2]University of Rochester, Rochester, NY, [3]Univ of Rochester, Rochester, NY, [4]Rochester, Rochester, NY

Background/Purpose: A paucity of known causative mechanisms in primary Sjögren's Syndrome (pSS) contributes to inadequate classification criteria. However, known memory-phenotype B cell aberrations could enrich diagnostic criteria if such alterations precede clinical disease onset. Therefore, to determine diagnostic potential, we compared the phenotype and gene expression of B cells in pSS patients, $sicca$ patients (individuals with symptoms but without pSS diagnosis), and healthy controls (HCs).

Methods: CD19^{pos} B cells from pSS (n=26), from $sicca$ symptomatic patients (n=27), and from healthy controls (n=22) were analyzed using flow cytometry to identify canonical B cell subsets. Sub-groups of these subjects were further analyzed for expression of CD21, CD23, CD24, CD95 CXCR5 and CD1c. Additionally, purified B cell subsets (n=3–5, per group, per test) were analyzed for gene expression using Affymetrix gene arrays.

Results: pSS patients had lower frequencies and numbers of CD27^{pos}/ IgD^{neg} switched memory (SM) and CD27^{pos}/IgD^{pos} unswitched memory (UM) phenotype B cells compared with HCs. A sub-group of sicca patients shared a B cell profile similar to pSS. Interestingly, lower UM B cell frequencies were evident in $sicca$ patients before disease-associated autoantibodies were detectable. Importantly, patient UM B cell frequency significantly associated with serologic hyperactivity. Extended phenotypic profiling in pSS revealed that the deficient UM cells had marginal zone B cell characteristics, whereas the SM cells were enriched for likely pathogenic effectors. CD27^{pos} memory B cell gene-expression profiling identified 135 differentially expressed genes between pSS patients and HCs. Additionally, clustering analysis identified a subgroup of $sicca$ patients with a gene expression profile similar to pSS. Whereas SM B cells gene expression analysis was similar in pSS and HCs, UM B cell gene expression analysis identified 187 differentially expressed genes between pSS patients and HCs. Interestingly, some of the these genes encoded signaling molecules and transcriptional factors associated with many B cell related biological pathways.

Conclusion: Collectively, these findings suggest that UM B cells contribute to regulating autoimmunity and also that B cell profiling could enhance diagnosis of pSS onset. Thus, B cell profiling in pSS has the potential to identify early disease-onset candidates for earlier therapeutic intervention and for novel therapies under investigation.

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Regulatory B Cells in Primary Sjögren's Syndrome. Gabriela Hernandez-Molina, Janette Furusawa-Carballeda, Guadalupe Lima, Yahaira Rivera and Luis Llorente. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Background/Purpose: B cells have traditionally been considered as positive regulators of humoral immune response, however their negative regulatory role has recently being recognized. **Objective.** To characterize the phenotypes of regulatory B cells in peripheral blood of primary Sjögren syndrome (pSS) patients and compare their presence according to the clinical and/or serologic activity disease status.

Methods: We included 50 pSS patients according to the AECG classification criteria, all of them were evaluated by a rheumatologist. We defined clinical activity as the presence of parotid enlargement or any extraglandular manifestation assessed by the SDAI or the ESSDAI indexes (except fatigue, fever or arthralgias). We defined serologic activity as IgG immunoglobulin >16 g or low C3, C4 or serum viscosity >1.9 cp. Twelve healthy age matched subjects were used as controls. PBMCs were isolated by centrifugation over a Lymphoprep gradient. CD19-mAb-coated microbeads were used to purify B cells by positive selection. We used the following mAbs: anti-CD38-PECy5, anti-CD38-PE, anti-CD24-FITC, anti-IgA-PE, anti-IgD-PE, anti-IgG-PECy5, anti-IgM-APC, anti-CD5-APC, anti-CD10-APC, anti-CD20-APC, anti-CD27-APC, anti-CXCR4-APC and anti-CXCR7-Cy5. Cells immunofluorescent staining was analyzed by a FACScalibur flow cytometer. The relative % of the subtypes of Il-10 cells producers was calculated on basis of the total positive selection of the phenotype $CD19^+$/$CD38^{bright}$/$CD24^{bright}$. We used One way ANOVA analysis (post-hoc analysis Dunn method) with the Sigma Stat 11.2 software.

Results: Patients were predominantly females, mean age 53 ± 12 years and median disease duration of 9.7 years. Seventeen patients (34%) were clinical active (parotid enlargement, vasculitis, arthritis, leucopenia, lymphopenia, pneumonitis or optic neuritis). Patients with or without clinical activity were similar in age, disease duration but received more frequently prednisone and azathioprine. Twenty-seven (54%) patients had serologic activity regardless their clinical status. $IL-10^+$ B cells represented the 0.55% of the total pSS B cell population and was higher in clinical inactive patients(0.63%), whereas controls had a lower prevalence (0.22%, p<0.05). We found a statistically significant increment in the following subtypes of Bregs cells: $CD19^+$/$CD38^{bright}$/IgA^+/$IL10^+$ cells (pSS 79%, clinical inactive 80% vs. control 66%), $CD19^+$/$CD24^{bright}$/$CD38^{bright}$/$CD5^+$/$IL10^+$ (clinical inactive 24% vs. control 14%), $CD10^+$/$IL10^+$ (pSS 23%, clinical inactive 26% vs. control 15%). IgD^+ cells and $CD27^-$/$IL10^+$ cells were increased in all the groups regardless their clinical activity when compared vs. controls. The phenotypes $CD19^+$/$CD24^{bright}$/$CD38^{bright}$$IL10^+$/$CD20^{+,}$ $CD27^{+,}$ $CXCR4^+$ and $CXCR7^+$ were similar among groups. We did not find a difference when we analyzed by serologic activity.

Conclusion: Most of the studied Bregs phenotypes were increased in pSS patients, particularly in those without clinical activity. The presence of these cells emphasizes the importance of the immunobiology of B cells in pSS.

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Frequencies and Numbers of Circulating IL-10 Producing Regulatory B Cells Are Not Disturbed in Pss-Patients but Correlate Negatively with the EULAR Sjögren Syndrome Disease Activity Score (ESSDAI). Wayel H. Abdulahad, Gwenny Verstappen, Arjan Vissink, Minke G. Huitema, Petra M. Meiners, Hendrika Bootsma and Frans Kroese. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: Recently, a specific and functionally important subset of regulatory B cells (B$_{reg}$) that negatively regulate autoimmunity and inflammation has been described. B$_2$ cells exert their suppressive role through the production of interleukin-10 (IL-10), and can be *immunophenotypically identified by high expression of CD38 and CD24. Possible involvement of B$_{reg}$ cells in primary Sjögren's syndrome (pSS) has not been yet elucidated. This study aimed to assess the frequency and number of B$_{reg}$ cells in pSS-patients, the impact of rituximab (RTX) treatment on B$_{reg}$ cell reconstitution, and the association between B$_{reg}$ cells and pSS disease activity score.*

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 12 pSS-patients (at baseline and 48 weeks after RTX-treatment) and from 8 age- and sex-matched healthy controls (HC). Frequency and number

of circulating $CD38^{high}CD24^{high}CD19^+$ B$_{reg}$ cells were assessed by flow cytometry. Next, since IL-10 secretion was recognized as a functional mechanism of suppression in B$_{reg}$ cells, we determined the frequency and number of IL-10 producing B-cells after *in vitro* stimulation of PBMCs with CpG (0.5mg/ml) for 3 days and re-stimulation with PMA (5ng/ml) and Ca-I (0,2mg/ml) in the presence of Brefeldin A (10mg/ml) during the last 16 hours. E*xpression of TNFα was used to discriminate between B$_{reg}$ cells (IL-10$^+$ TNFα$^-$) and TNFα$^+$ effector B cells (IL-10$^-$ TNFα$^+$; B$_{eff}$).* Intracellular production of IL-10 and *TNFα* in B cells were determined by flow cytometry. In addition, EULAR Sjögren Syndrome Disease Activity scores (ESSDAI) were calculated for each patient before and after RTX-treatment, and compared to the B$_{reg}$ results in order to assess the clinical relevance of data.

Results: At baseline, based on the surface phenotype of B$_{reg}$cells ($CD38^{high}CD24^{high}CD19^+$), pSS-patients displayed higher frequencies and numbers of B$_{reg}$ cells in blood compared to HCs. Following RTX-treatment, a significant increase in $CD38^{high}CD24^{high}CD19^+$ B$_{reg}$ cell frequencies and numbers was observed in pSS-patients when compared to baseline and HCs. Since IL-10 production is the hallmark of B$_{reg}$ cells, we also measured IL-10 production by B-cells. Frequencies and numbers of IL-10 producing B$_{reg}$ cells (*IL-10$^+$ TNFα$^-$) did, however, not differ between pSS-patients before and after RTX-treatment and HCs. Ratios of* B$_{reg}$:B$_{eff}$ did not significantly change after RTX-treatment too. Frequencies and numbers *of both IL-10$^+$TNFα$^-$ B$_{reg}$ cells as well as* $CD38^{high}CD24^{high}CD19^+$ B$_{reg}$ cells at baseline correlated negatively with ESSDAI.

Conclusion: Frequencies and numbers of IL-10 producing B$_{reg}$ cells were not impaired in pSS-patients, neither before nor after RTX-treatment. Given that circulating IL-10 producing B$_{reg}$ cells correlate negatively with ESSDAI, these B$_{Reg}$ cells might serve as a monitor to assess disease activity in pSS-patients.

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Stages of Sjogren's Syndrome Defined by Immune Mediators. Lakshmanan Suresh[1], Julian Ambrus Jr.[2] and Long Shen[3]. [1]IMMCO Diagnostics Inc., Amherst, NY, [2]State University of New York at Buffalo, Buffalo, NY, [3]SUNY at Buffalo, Buffalo, NY

Background/Purpose: Sjogren's syndrome (SS) is characterized by destruction of the salivary and lachrymal glands but also systemic manifestations such as lung disease, kidney disease and lymphomas. We have utilized an animal model for SS, the IL-14alpha transgenic mouse (IL14aTG; *J. Immunol.* 177: 5676 – 5686, 2006; *Clin. Immunol.* 130: 304–312, 2009) to understand factors regulating various aspects of the disease. Previous studies had demonstrated that IL14aTG mice lacking lymphotoxin did not develop any features of SS (IL14aTG.LTa−/−; *J. Immunol.* 185: 6355 – 6363, 2010).

Methods: IL-14aTG mice lacking the type 1 interferon receptor (IL14aTG.IFNR−/−) or marginal zone B cells (MZB; IL14aTG.CD19Cre.RBP-J−/−) were compared to IL14aTG mice with regards to autoantibodies (determined by Western blots), salivary gland secretions (determined after Pilocarpine stimulation), and histology of the salivary glands.

Results: Both IL14aTG mice and IL14aTG.IFNR−/− developed IgM autoantibodies at 6 months, but only IL14aTG mice developed IgG antibodies at 12 months of age. IgM antibodies were eliminated in IL14aTG.CD19Cre.RBP-J−/− at 6 months of age. Salivary gland secretions were normal in IL14aTG.LTa−/− and IL14aTG.CD19Cre.RBP-J−/− mice, mildly decreased in IL14aTG.IFNR−/− and severely decreased in IL14aTG mice at 12 months of age. Both IL14aTG and IL14aTG.IFNR−/−mice had lymphocytic infiltration of their submandibular and lachrymal glands at 10 months of age. Only IL14aTG mice had lymphocytic infiltration of the parotid glands at 14 months of age. Neither IL14aTG.LTa−/− nor IL14aTG.CD19Cre.RBP-J−/− had lymphocytic infiltration of any salivary or lachrymal glands.

Conclusion: These studies suggest a model for SS in which early injury to the submandibular and lachrymal glands is regulated by MZB that produce IgM antibodies and lymphotoxin. Later development of IgG autoantibodies and parotid gland injury is dependent upon type 1 interferon. Further studies will be needed to investigate these observations in patients with SS.

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Characterization of Dominant B- and Plasma Cell Clones in Patients with Primary Sjögren's Syndrome and Patients with Sicca Syndrome.

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Background/Purpose: Primary Sjögren's syndrome (pSS) is an auto-immune exocrinopathy characterized by chronic inflammation and destruction of the salivary and lacrimal glands. Infiltration of B and T-cells and sometimes plasma cells in the salivary glands as well as the presence of lympho-epithelial lesions are characteristic for pSS. Recent studies showed clinical improvement upon rituximab therapy up to 9 months, enforcing the notion that B cells and to a lesser extent plasma cells are important in the pathogenesis. To further unravel BCR involvement in the development of pSS we characterize B-cell and plasma cell clones in an early stage of parotid gland inflammation.

Objectives: 1) to compare B cell and plasma cell clonality in patients with pSS and sicca in the absence of an auto-immune disease. 2) To determine isotypes in clones identified and compare these between pSS and sicca.

Methods: Five patients with pSS and 5 patients with complaints of sicca without any auto-immune disease (sicca) were included. All pSS patients fulfilled the AECG criteria for pSS and were antibody (ANA, SSA, SSB, Rf) positive. All sicca patients were antibody negative. Immunohistochemistry stainings were performed on formalin-fixed paraffin embedded sections using antibodies against CD22, CD138, IgA, IgG and IgM and scored semi-quantitatively. mRNA was isolated from all parotid gland biopsies and full-repertoire analysis of the immunoglobulin heavy-chain was performed. All amplified products encode the CDR3, a unique sequence that defines a unique clone. The number of sequences reflects the amount of immunoglobulins produced by that clone and can be used as a measure for 'dominance' of that particular clone. Of each sample >10,000 BCR sequences were obtained. Clones with a frequency of > 0.5% were arbitrarily considered as dominant clones.

Results: In all patients, almost 3000 clones were recovered (mean 2910 and 2946 and SD 704 and 783 in pSS and sicca resp., p=n.s.) Multiple dominant clones were detected in the parotid gland of all pSS patients (mean 6.2 clones, SD 1.5), only a few dominant clones were detected in the sicca patients (mean 2.4 clones, SD 1.1, p=0.02). Immunohistochemical stainings of the pSS parotid gland biopsies showed that the majority of the infiltrate consisted of B-cells, although a few plasma cells were detectable in all 5 pSS patients. In sicca patients, much less B cells and plasma cells were detectable. Further isotyping revealed that the plasma cells in pSS were mainly expressing IgG (55% IgG, 30% IgA, 15% IgM), while plasma cells from sicca patients were only IgA+ (100% IgA). In line, the highly dominant clones in pSS patients were mainly of the IgG isotype (80% IgG, 16% IgA, 4% IgD), or showing a micture of isotypes, often including IgG. In sicca patients, the very few dominant clones all expressed IgA (100%).

Conclusion: Our observations suggest that the inflamed parotid gland in pSS can be distinguished from sicca based on the expression of IgG by the most dominant B-cell and plasma cell clones. This provides the opportunity to further study the IgG+ B-cell and plasma cell clones in particular for their potential auto-reactive properties. This in turn might lead to understanding of the pathogenesis of pSS and might lead to more targeted therapy.

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Overexpression of BMP6 Is Associated with Loss of Salivary Gland Activity in Sjögren's Syndrome Patients and Mice.

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Background/Purpose: A hallmark of Sjögren's syndrome (SS) is the loss of activity in secretory epithelia, specifically the larcrimal and salivary glands. The mechanism(s) driving this disorder are poorly understood and may involve a combination of environmental and genetic factors. To date exten-sive efforts have been focused on understanding the changes in the immune system in these patients, however little is understood regarding the changes in the epithelia associated with the loss of gland activity.

Methods: To identify genes associated with changes in the epithelia, RNA was isolated from patients with both low flow and low lymphocytic infiltrates (focus score) and used to probe customized high density microar-rays. After normalization, the signal from the patient RNA samples was then compared to the signal from RNA isolated from healthy volunteers. The list of differentially expressed genes was then filtered for genes associated with salivary gland specific cell types.

Results: A significant increase in expression of the bone morphogenic protein 6 (BMP6) was observed in RNA isolated from patients compared with healthy volunteers. Overexpression of BMP6 locally in the salivary gland or lacrimal glands of mice resulted in the loss of fluid secretion as well as changes in the connective tissue of the salivary gland. Assessment of the fluid movement in either isolated acinar cells of mice overexpressing BMP6 or HSG cells cultured in the presence of BMP6 identified a loss in volume regulation in these cells. Loss of fluid movement also correlated with a decrease in sodium concentration in the saliva. Lymphocytic infiltration in SMG of BMP6 overexpressing mice was increased. No significant changes were found in proinflammatory cytokines production, neither the auto-antibodies associated with SS, such as anti-Ro/SSA, anti-La SSB and anti-nuclear antibody (ANA) after BMP6 overexpression.

Conclusion: Our study identified BMP6 as a novel gene associated with xerostomia associated with Sjögren's syndrome, which may become a new target for therapeutic intervention. In mice, a loss of salivary and lacrimal gland function can be induced by overexpression of BMP6, which further support our finding in patients. This study suggests the loss of salivary gland function can be separated from the autoantibodies and proinflammatory cytokines associated with this disease.

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Spontaneous Sialadenitis Like Sjögren's Syndrome in Orphan Nu-clear Receptor γt (RORγt) Transgenic Mice.

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Background/Purpose: The nuclear receptors retinoic-acid-receptor-related orphan receptors gt (RORγt) is required for the generation of Th17 cells expressing the proinflammatory cytokine IL-17. Th17 cells expressing IL-17 are involved in various autoimmune diseases including Sjögren's syndrome (SS). Recent studies reported the expression of IL-17 and IL-23 in the salivary glands and serum from patients with SS. However, the patho-logical roles of RORγt in SS remain to be elucidated. We examined the RORγt transgenic (Tg) mice in order to clarify the role of RORγt in the pathogenesis of SS.

Methods: (1) Histological analysis of salivary glands from RORγt Tg mice and C57BL/6 mice were determined and saliva flow was measured. (2) Infiltrating cells were isolated from the salivary glands and then analyzed their character by fluorescent immunostaining and flow cytometer. (3) Cytokine expressions in salivary glands were detected by quantitative PCR. (4) CD4+ T cells from RORγt Tg mice were transferred to Rag2−/− mice (RORγt Tg→Rag2−/− mice).

Results: (1) RORγt Tg mice developed the severe sialadenitis like SS and focus score was significantly increased in RORγt Tg mice ($2.33\pm0.88/4$ mm^2, $p<0.05$, Mann-Whitney U Test), compared with C57BL/6 mice ($0.22\pm0.38/4$ mm^2). Saliva flow collected from RORγt Tg mice (6.11 ± 1.08 μl/g, $p<0.05$, Mann-Whitney U Test) was significantly decreased than that of C57BL/6 mice (8.63 ± 0.76 μl/g). (2) The majority of infiltrating cells were CD4+ T cells at the early phase of sialadenitis, and B220+ cells were gradually increased at the late phase. (3) Expression of IL-17 and IL-21 mRNA was significantly increased in salivary glands of RORγt Tg mice by the side of C57BL/6 mice ($p<0.05$, Mann-Whitney U Test). (4) In RORγt Tg→Rag2−/− mice, cellular infiltrations were observed in salivary glands.

Conclusion: These results suggested that the overexpression of RORγt on CD4+ T cells showed play a crucial role in the development of spontaneous sialadenitis like SS.

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Sex-Specific Regulatory T Cell Dysfunction in a Mouse Model of Sjögren Syndrome. Scott M. Lieberman[1], Portia A. Kreiger[2] and Gary A. Koretzky[3]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Nemours/A.I. DuPont Hospital for Children, Wilmington, DE, [3]University Pennsylvania, Philadelphia, PA

Background/Purpose: CD4+Foxp3+ regulatory T cells (Tregs) are a specialized population of lymphocytes which prevent autoimmunity in normal hosts. Treg dysfunction has been implicated in autoimmunity; however results are conflicting. Sjögren syndrome is an autoimmune disease characterized by destruction of lacrimal and salivary glands resulting in profound ocular and oral dryness. In the nonobese diabetic (NOD) mouse model of Sjögren syndrome, females develop earlier and more severe sialadenitis while males develop primarily dacryoadenitis. We previously reported that female NOD mice harbor a lacrimal gland-protective Treg population (Arthritis Rheum 2011;63 Suppl 10:495). Here, we characterize the role of sex-based Treg dysfunction in the sexually dimorphic disease manifestations in our NOD mouse-based transfer model of Sjögren syndrome.

Methods: Sjögren-like disease was induced by transfer of cervical lymph node cells, either whole or depleted of the Treg-enriched CD4+CD25+ population, to lymphocyte-deficient NOD-SCID mice, which do not develop spontaneous autoimmunity. Five to seven weeks following adoptive transfer, dacryoadenitis and sialadenitis were quantified by an experienced, blinded pathologist using a standard focus score.

Results: Transfer of whole cervical lymph node cells from NOD mice to sex-matched NOD-SCID mice recapitulated sexually dimorphic features (i.e., males develop dacryoadenitis; females develop sialadenitis). Moreover, dacryoadenitis developed in female and male recipients of sex-matched donor cervical lymph node cells depleted of Tregs. Interestingly, in a male environment, female NOD donor cervical lymph node cells (not depleted of Tregs) induce dacryoadenitis; whereas, in a female environment, male NOD donor cervical lymph node cells fail to induce dacryoadenitis unless Tregs are depleted prior to transfer.

Conclusion: These data demonstrate that females harbor a population of lacrimal gland-protective Tregs that become dysfunctional in a male environment and suggest that dacryoadenitis in males is due to an underlying lacrimal gland-specific Treg defect. Studies to identify the sex-specific factors responsible for these findings are underway.

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Genetic Associations to Germinal Centre Formation in Primary Sjögren's Syndrome. Tove Ragna Reksten[1], Malin V. Jonsson[2], Roland Jonsson[1], Gunnel Nordmark[3] and The Swedish-Norwegian Sjögren's syndrome Network[4]. [1]Broegelmann Research Laboratory, the Gade Institute, University of Bergen, Bergen, Norway, [2]University of Bergen, Bergen, Norway, [3]Rheumatology, Uppsala, Sweden, [4]Bergen

Background/Purpose: Primary Sjögren's syndrome (pSS) is an autoimmune rheumatic disease mainly affecting the salivary and lacrimal glands causing xerostomia and keratoconjunctivitis sicca. Focal mononuclear cell inflammation in the form of germinal center-like structures (GC) is found in the minor salivary glands of 20–25 % of patients. We have previously shown that GC+ pSS patients presented with elevated serum levels of IL-1RA, IL-4, IL-17 and MCP compared to GC- patients. In this follow-up study, we aimed to assess the genetic variations in GC+ and GC- pSS patients.

Methods: In a Swedish-Norwegian pSS cohort (n=540), GC+ (n=76) and GC- (n=244) patients were identified. 1536 single-nucleotide polymorphisms (SNPs) were analysed in whole blood DNA by the Illumina GoldenGate assay (Illumina Inc.). Minor allele frequencies in GC+ and GC- patients were compared using Fisher's exact test and associations were considered significant when p<0.001 and suggestive when p<0.01. Statistical analysis were performed using the PLINK software.

Results: In this case-only analysis of 320 pSS patients with known GC status, we identified two SNPs in *Eotaxin* associated with GC+ patients with OR 0.45 and 0.41. Furthermore, we found suggestive associations with *BANK-1, ICA-1, IL-17, PRKCL1, CARD-8, Bcl-2, TANK, IKBKE, AID* and *APRIL*. We also detected weak associations (p<0.05) with SNPs in the BLK, STAT1, STAT4, SSA1, SSB, IL15RA, IL-6 and TNF-a genes. Serum eotaxin (CCL11) has previously been identified as a key discriminator between GC+ and GC- pSS patients. The formation of GCs depends on B cell stimulation by helper T cells via the CD40-CD40L system, which also contribute to the expression of activation induced deaminase (AID). Genetic variations in *CD40L* and *AID* suggest that GC+ patients may be genetically predisposed for ectopic GC formation. B lymphoid kinase (BLK) has a role in the development and activation of marginal zone B cells present in the GC formations, and Bcl-2 is an anti-apoptotic protein which gene is implicated in a number of cancers and autoimmunity. CARD-8, IKBKE and TANK are regulators of the NF-κB pathway, a pathway with a well-established role in secondary lymphoid organ development.

Conclusion: Taken together, our findings suggest that genetic variations may help explain why ectopic GC-like structures are present in some pSS patients but not all

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Differences in Genome-Wide DNA Methylation Profiles Across Multiple Cell and Tissue Types in Sjögren's Syndrome (SS). Lindsey A. Criswell[1], Diana Quach[2], Hong L. Quach[2], Emon Elboudwarej[2] and Lisa F. Barcellos[2]. [1]University of California San Francisco, San Francisco, CA, [2]University of California, Berkeley, Berkeley, CA

Background/Purpose: Increasing evidence supports a role for epigenetic factors, including DNA methylation status, in autoimmune disease risk and severity. Our goal is to characterize DNA methylation profiles in SS, including multiple cell and tissue types relevant to disease.

Methods: We generated genome-wide DNA methylation profiles using Illumina HumanMethylation450 bead chips in minor salivary gland biopsy tissue, parotid saliva, PBMCs, and the following cell subpopulations: CD14+ monocytes, CD19+ B cells, and CD4+ T cells in a subset of participants from the Sjögren's International Collaborative Clinical Alliance (SICCA) repository (http://sicca.ucsf.edu/). All subjects were Caucasian females. SS cases (n=5) had severe disease, meeting all 3 of the ACR classification criteria for SS (Arth Care & Res 2012; 64:475), including focal lymphocytic sialadenitis on minor salivary gland biopsy, keratoconjunctiva sicca based on ocular staining pattern (ocular staining score ≥ 3), and presence of SSA and/or SSB autoantibodies. A single control individual with no evidence of SS based on the aforementioned and other objective tests was also studied. Sorting of freshly collected blood samples was performed using MACS® technology. Labial salivary gland biopsy tissue, parotid saliva and PBMCs were collected at entry to the SICCA repository, and a second blood sample was collected from each subject for isolation of the aforementioned cell subpopulations an average of 4.4 years following the baseline visit. Genome-wide DNA methylation profiles (450k sites) were compared across the 7 cell and tissue types within the 6 study subjects to characterize cell and tissue differences in DNA methylation status.

Results: DNA yields for all cell and tissue types were high, with the exception of parotid saliva, which yielded between 0.75 – 1.07 μg DNA but was still sufficient for whole genome methylation profiling. Assessments of purity for sorted cell subpopulations ranged from a mean of 59% (for CD4+ T cells) to 80% (for CD14+ monocytes). Within-individual comparisons of tissue-specific genome wide DNA methylation profiles revealed striking differences, with r^2 ranging from 0.105 (for saliva vs. B cells) to 0.998 (baseline vs. followup PBMCs).

Conclusion: These preliminary results emphasize the cell and tissue specificity of DNA methylation status, which is an important epigenetic process with potential to influence patterns of gene expression in health and disease. Additional work, including detailed analysis of site-specific DNA methylation differences in larger samples of SS case and control individuals,

followed by studies of gene expression for regions associated with disease risk or severity will be required to fully define the role of DNA methylation in SS.

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Genetic Variation in the *NCR3* Locus Is Associated with Anti-SSA/SSB Positive Primary Sjögren's Syndrome in Scandinavian Samples.
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Background/Purpose: Candidate gene studies in primary Sjögren's syndrome (pSS) have identified polymorphisms in genes involved in the type I interferon (IFN) system and the type I IFN system is activated in pSS. NK cells have been shown to increase the immune complex stimulated IFN-alpha production by plasmacytoid dendritic cells but the role for NK cells in pSS autoimmunity has not been well studied. The natural cytotoxicity triggering receptor 3 (*NCR3*) gene locus (6p21.3) encodes the NKp30 activating receptor on NK cells. A French study identified an association between two rare alleles in the *NCR3* promoter region and pSS, independent of the association to *HLA-DRB1–03* (6p21.3) (1). The aim of this investigation was to analyze if the two *NCR3* single nucleotide polymorphisms (SNPs) were associated with pSS in Scandinavian samples. The potential association with anti-SSA/SSB positivity or clinical phenotypes was investigated. In addition, the association with the *HLA-DRB1–03* SNP proxy was studied.

Methods: A total of 671 Caucasian pSS patients from Sweden (n=478) and Norway (n=193) and 1586 healthy controls (Sweden, n=1369 and Norway, n=217) were included in the study. Two SNPs in the *NCR3* locus, rs11575837 and rs2736191 and the SNP rs2187668 as a marker for *HLA-DRB1–03* were selected. Genotyping was performed by single base extension with Fluorescent Polarization Template Dye Incorporation (FP-TDI). Data on anti-SSA and/or anti-SSB positivity and clinical manifestations were extracted from the patient files. Case-control and case-only allelic association analyses were performed using PLINK.

Results: In our case-control analysis we did not find any association between the *NCR3* SNPs and pSS in Sweden or Norway or in meta-analysis of the two cohorts. In case-only analysis of the combined cohorts, comparing anti-SSA/SSB positive (n=496, 74%) versus negative (n=175, 26%) pSS patients, we found an association between the SNP rs11575837 and anti-SSA/SSB positivity, p=0.006, OR 0.27 (95% CI 0.10–0.73). There were no associations between the *NCR3* SNPs and clinical phenotype. The *HLA-DRB1–03* SNP marker rs2187668 was strongly associated with pSS, $p=1\times10^{-51}$, OR 3.2 (95% CI 2.8–3.8). When analyzing only anti-SSA/SSB positive patients versus controls the association was even stronger, $p=6.9\times10^{-67}$, OR 4.1 (95% CI 3.5–4.9). In case-only analysis rs2187668 was associated with major salivary gland swelling and leucopenia (p<0.05), dermal vasculitis (p<0.01), hypergammaglobulinemia ($p=7.4\times10^{-8}$) and anti-SSA/SSB positivity ($p=1.6\times10^{-12}$, OR 3.0, 95% CI 2.2–4.1).

Conclusion: We found an association between anti-SSA/SSB positivity and genetic variation in the *NCR3* locus and confirmed the strong *HLA-DRB1–03* association with anti-SSA/SSB positive pSS. We conclude that different mechanisms, possibly involving NK cell functions, might contribute to this autoimmune disease in anti-SSA/SSB positive versus negative patients. The potential functional implications for this rare promoter SNP on NKp30 receptor activity has yet to be elucidated.

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Use of Global Gene Expression Profiling to Characterize Sjögren's Patients Who Underexpress Interferon-Inducible Genes.
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Background/Purpose: Sjögren's syndrome (SS) is a progressive autoimmune exocrinopathy characterized by symptoms of dry eyes and mouth. We previously reported overexpression of interferon-inducible (IFI) genes in a subset of SS patients. Using global gene expression profiling (GEP) and autoantibody serologies, we characterized SS patients who underexpress IFI genes in order to better understand a potentially divergent SS subgroup.

Methods: A total of 48803 mRNA transcript levels from whole blood were measured using the Illumina HumanWG-6 v3.0 BeadChip in 201 SS cases and 79 healthy controls. After quality control, Welch's t-tests, q-values, and fold changes (FC) were calculated for 20342 probes (15607 genes). Differentially expressed (DE) transcripts were selected by: q<0.05; and FC >1.25 or <0.87. Hierarchical clustering was performed and cases were divided according to underexpression (UNDER; n=53) or overexpression (OVER; n=128) of 32 IFI genes; both groups were then compared to healthy controls. Pathway analysis for DE genes was carried out in Genomatix. Antibodies to Ro, La, centromere B, chromatin, dsDNA, Jo-1, ribosomal P (riboP), ribonucleoprotein (RNP), Scl-70, Sm and Sm/RNP were determined using Bioplex assays. Antinuclear antibody (ANA) and rheumatoid factor (RF) were determined by immunofluorescence and ELISA, respectively. Autoantibody composition was compared using Fisher's exact test.

Results: Comparing the UNDER group (n=53) vs. controls (n=79) and removing IFI genes yields 1767 DE genes involved in cellular metabolism (725/7548 genes; P<10E-13); RNA processing (89/618 genes; P<10E-7); viral transcription (31/140 genes; P<10E-6); and viral reproduction (41/224 genes; P<10E-6). These genes comprise canonical pathways that include: protein import into the nucleus (6/12 genes; P<10E-3); TCR signaling in naïve CD8+ T cells (13/56 genes; P<10E-3) and CD4+ T cells (14/69 genes; P<10E-3); and BCR signaling (14/69 genes; P<10E-2). Additional genes of interest include ANTXR2 (q=2.6×10E-4; FC=1.35) and CTAGE5 (q=3.2×10E-4; FC=1.45). ANTXR2, an anthrax toxin receptor that binds collagen IV and laminin with potential involvement in extracellular matrix adhesion, has been associated with ankylosing spondylitis, while mutations in this gene cause juvenile hyaline fibromatosis. CTAGE5 encodes an antigen found in T-cell lymphoma and other cancers. Anti-Ro and anti-La are more common in the OVER group compared to the UNDER group (P<10E-12 and P<10E-7, respectively), as is ANA alone (P<10E-5) and in combination with RF (P<10E-3). Interestingly, by excluding subjects positive for anti-Ro, anti-La, RF, and ANA, we find that patients in the UNDER group are more likely to produce any combination of antibodies to centromere B, chromatin, dsDNA, Jo-1, riboP, RNP, Scl-70, Sm, or Sm/RNP autoantibodies than are those in the OVER group (P=0.015).

Conclusion: SS patients who underexpress IFI genes are more likely to produce non-traditional antibodies and are less likely to produce anti-Ro, anti-La, ANA, or ANA/RF than their counterparts. Additionally, GEP within this subphenotype has identified novel candidate genes and molecular pathways for further study that may help elucidate complex SS pathophysiology.

RNA-Sequencing Identifies Novel Differentially Expressed Coding and Non-Coding Transcripts in Sjögren's Syndrome.

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Background/Purpose: Sjögren's syndrome (SS) is a common, clinically heterogeneous autoimmune disease characterized by exocrine gland dysfunction that involves both innate and adaptive immune responses. SS etiology is complex, with both environmental and genetic/genomic factors contributing. Recent genetic studies in complex disease have shown that 80% of associations map to transcriptionally active non-protein coding DNA sequences that comprise 60% of the human genome. Microarray technology, which requires prior knowledge of the transcripts being interrogated, has been extensively used to study gene expression of mRNA. Far more powerful, emerging RNA-sequencing (RNA-seq) technology allows for unbiased transcript identification and quantification across the genome. We used RNA-seq to identify differentially expressed (DE) protein-coding (3% of the genome) and non-coding transcripts in 60 SS cases and 30 healthy controls.

Methods: RNA samples were isolated from whole blood and prepared for sequencing using the NuGEN Encore kit, and sequencing was performed using the Illumina HiSeq 2000. Quality of raw sequence data was assessed using FASTQC. Raw FASTQ files were aligned to the human genome (hg19) using TOPHAT. Probable transcripts were assembled using CUFFLINKS, and DE transcripts were determined using CUFFDIFF using a false discovery rate (FDR) q-value of 0.1. Fold change (FC; positive values = overexpressed and negative values = underexpressed) calculations were obtained using the $\log2(FPKM_{Cases}/FPKM_{Control})$, where FPKM is the fragments per kilobase of exon model per million mapped fragments. Transcripts were verified using the Integrated Genome Viewer (IGV).

Results: The average number of reads per sample was 38.6 million, representing 346,234 transcripts across the genome. Of the protein-coding regions, TGF-beta activated kinase 1/MAP3K7 binding protein 1 (TAB1) was the most statistically DE locus ($p=3.03\times10E-7$, $q=0.049$, FC=1.56). TAB1, regulates MAP kinase kinase kinase MAP3K7/TAK1 and is involved in TGF beta, interleukin 1, WNT-1, NF-□B pathways. Genome-wide association studies of primary biliary cirrhosis and Crohn's disease have reported association to 22q13.1. Two other DE protein-coding transcripts of interest were identified: GRIN2D (glutamate receptor, ionotropic, N-methyl D-aspartate 2D; $p=1.36\times10E-5$, $q=0.088$, FC=2.123) and SH2D4B (SH2 domain containing 4B; $p=3.35\times10E-6$, $q=0.070$, FC=1.78). Biological functions of these genes are unclear. Among non-protein coding transcripts, we observed DE of a long non-coding RNA (lncRNA) at 11p15.2 ($p=3.77\times10E-6$, $q=0.070$, FC=1.69). lncRNAs are important regulators of the human genome with diverse functions. Bioinformatic evaluation in the 11p15.2 region showed transcription of lncRNA sequences and transcription factor binding sites using immunologically-relevant cell lines.

Conclusion: In this first of its kind SS RNA-seq study, we identified four novel candidate loci: TAB1, GRIN2D, SH2D4B and, for the first time, a DE lncRNA in SS. Future studies in SS are warranted to further elucidate the functional consequences of these novel RNA associations.

Gene Expression Profiling in a Large Cohort of Europeans with Sjögren's Syndrome Reveals Candidate Genes in Viral, Immune, and Interferon-Related Pathways.

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Background/Purpose: Sjögren's syndrome (SS), characterized by lymphocytic infiltration of exocrine glands, is a progressive autoimmune exocrinopathy present in 0.7–1% of Europeans. To better understand the molecular pathways involved in SS pathophysiology, we performed global gene expression profiling (GEP) on SS cases and healthy controls.

Methods: GEP was determined on 48803 probes from the Illumina HumanWG-6 v3.0 BeadChip microarray using whole blood from 162 primary SS cases and 58 healthy controls of European ancestry. Analyses were performed in the R Bioconductor suite. After quality control assessments, 20035 probes were quantile normalized, and differentially expressed (DE) genes were determined using q-values and mean expression fold change (FC) (significance thresholds: q<0.05; and FC >1.25 or <0.87). Pathway analysis for DE genes was carried out in Genomatix. Subsequent *cis*-expression quantitative trait loci (*c*-eQTL) analysis was performed in SS cases on selected genes using Matrix eQTL package.

Results: In total, 2410 genes were DE between SS cases and controls. *OTOF* was the most upregulated gene in SS patients (FC=94.87, q<1E-7, expressed in 86/162 cases compared to 2/58 controls), while *LRRN3* was the most downregulated (FC=0.39, q<1E-3). Interestingly, mutations in *OTOF* are responsible for hearing loss, a symptom observed in approximately one third of SS patients. Several DE genes overlap with genetic associations identified through genome-wide association studies in SS, including the MHC genes *TRIM38* (q<10E-12), *TAP1* (q<1E-14), and *TAP2* (q<1E-13), in addition to those identified previously by candidate gene approaches, including *IL1RN* (q<1E-5), *FAS* (q<1E-2), and *EBF1* (q<1E-2). Additionally, *c*-eQTL analysis identified 51 single-nucleotide polymorphisms (SNPs) within and flanking *TAP2* associated with gene expression levels (1E-10<q<0.01). The most significant canonical pathways of DE genes were apoptotic DNA-fragmentation/tissue homeostasis (7/11 genes; p<1E-4) and antigen processing/presentation (5/12 genes; p<1E-2). DE genes were also involved in several biological processes, including immune response (171/906 genes; p<1E-16), translational termination/elongation (42/105 genes; p<1E-15), viral transcription and genome expression (47/140 genes; p<1E-13), and type I interferon (IFN)-mediated signaling (31/70 genes; p<1E-13). Thirteen of the top 50 upregulated genes belong to the IFN pathway, which mirrors the IFN signature observed in lupus patients. Of note, elevated IFN expression levels were found to be correlated with anti-Ro and anti-La in SS. Nearly all DE genes in viral pathways were down-regulated with the notable exception of SP100 (q<1E-12, FC=1.58), an interferon-inducible protein believed to play a role in transcriptional regulation and the innate immune response following viral infection toward which antibodies are made in primary biliary cirrhosis.

Conclusion: These results highlight alterations in immunologically-relevant pathways in SS, reveal several new candidate expression quantitative trait loci, and provide focus for the development of novel hypotheses for further studies of this complex autoimmune disorder.

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Use of a Novel Probe to Demonstrate Granzyme B Activity in Sjogren's Syndrome Salivary Glands. Kimberly Doering Maurer[1], Laura Gutierrez-Alamillo[1], Efstathia K. Kapsogeorgou[2], Athanasios G. Tzioufas[3], Livia Casciola-Rosen[4] and Antony Rosen[5]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]School of Medicine, National University of Athens, Greece, Athens, Greece, [3]School of Medicine, National University of Athens, Athens, Greece, [4]Johns Hopkins University, Baltimore, MD, [5]The Johns Hopkins University, Baltimore, MD

Background/Purpose: Salivary glands are a prominent target organ in Sjögren's syndrome (SS), with patients having abnormal secretory function and inflammatory infiltration of these glands. Little is currently known about the mechanisms whereby the immune system contributes to ongoing tissue damage and dysfunction in this disease. IRF1 is one of the most efficiently cleaved granzyme B substrates ever defined. The purpose of this study was to define whether cytotoxic lymphocytes in the gland actively induce proteolysis in salivary gland epithelial cells in situ by using an antibody highly specific for granzyme B (GrB)-cleaved IRF-1 to probe for activity of the GrB pathway *in vivo* in SS salivary gland biopsies.

Methods: Immunohistochemical staining of salivary gland paraffin sections was used to assess the presence of CD8 infiltrates, and the extent of GrB staining. Lysates generated from frozen salivary gland biopsies were immunoblotted to detect CD8 and IRF1 expression. ^{35}S-methionine labeled IRF1 was generated by *in vitro* transcription and translation, and was used to demonstrate cleavability by GrB, and as a template for site-directed $D^{204}A$ mutagenesis to confirm the GrB cleavage site in IRF1. Using this information, an antibody detecting exclusively the N-terminal GrB cleaved IRF1 fragment (R6017) (and not the intact molecule) was generated. This antibody was carefully validated and used for immuno-histochemistry and immunoblotting on salivary gland tissue and lysates obtained from SS patients.

Results: CD8 infiltrates were prominent in 60% of SS salivary glands by immunoblotting and immunohistochemistry. IRF1 is expressed at high levels in SS salivary glands, but not control salivary glands. IRF1 is efficiently cleaved by GrB at D^{204}. Using the antibody R6017 that is highly specific for the N-terminal fragment generated by GrB cleavage, we demonstrated the presence of GrB-induced fragments by immunoblotting and immunohistochemistry performed on SS patient but not control salivary gland tissue.

Conclusion: These studies provide the first direct in *vivo* evidence that the cytotoxic lymphocyte granule pathway is actively modifying salivary epithelial cells in patients with SS. Defining granzyme-induced effects on salivary epithelial function may provide important understanding of the mechanisms of salivary epithelial function in this disease, with therapeutic implications.

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Multiplexed Nanostring Screening for Salivary Gland Viral Elements in Sjogren's Syndrome. Kristin Haffizulla[1], Glen Barber[1], Juan Chen[2] and Eric L. Greidinger[3]. [1]University of Miami Miller School of Medicine, Miami, FL, [2]The First Afflicted Hospital of Xiamen University, China, Miami, FL, [3]University of Miami, Miami, FL

Background/Purpose: To test the hypothesis that viruses are associated with Sjogren's syndrome, salivary gland RNA extracts from Sjogren's patients and non-Sjogren's controls were screened for virus-associated sequences using a multiplexed NanoString nCounter chip designed to detect sequences from all known human viral and endogenous retroviral families.

Methods: Samples were obtained following IRB approved protocols from study subjects recruited at the rheumatology clinics of The First Afflicted Hospital, Xiamen University, China who had minor salivary gland biopsies performed as part of routine clinical care. Using the classification criteria from the American-European Consensus Group, subjects were classified as having (cases, N = 12) or not having Sjogren's Syndrome. Subjects who did not meet Sjogren's classification criteria, and who did not have any salivary inflammatory process were designated the controls (N = 7). RNA was extracted from a 10 μm whole FFPE tissue section for each sample on a Siemens VERSANT robotic kPCR Molecular System. RNA was then directly assayed by Nanostring nCounter gene expression system for 334 viral, retroviral, and human immune gene sequences at once.

Results: Cases (11 female, 8 primary SS, 4 in RA) were confirmed by serology, histopathology, and parotid sialography. Controls were 7 patients (6 female) with normal histopathology, including 4 with negative ANA, SS-A, and SS-B. RNA extract quality and nCounter internal controls were robust for all tested samples. Gene expression in all samples was normalized to GAPDH expression. Cases and controls were compared for expression levels of the studied sequences. The 45 genes with the highest fold difference between cases and controls were all increased in the Sjogren's cases. Genes represented in this group included primarily HPV and polyoma-derived viral sequences but not endogenous retroviruses. The SS group had two distinct subsets, one of which (N = 6) showed increased expression of multiple viral genes compared to controls, and one of which (N = 6) showed reduced expression of multiple viral genes compared to controls. Subgroup analysis of the cases with high viral expression revealed multiple HPV Type 35 and 56 genes that were at least 2 fold overexpressed compared to controls. CD79a was the only tested gene at least 2 fold upregulated in the patients without high viral gene expression when compared to controls. A trend toward more Primary SS was present in patients with high viral expression (5/6 vs 2/6 for other SS, Fisher's Exact p = 0.2).

Conclusion: Using a new highly sensitive and specific technique, we find evidence of overexpressed viral elements in salivary tissue in a subset of a Chinese Sjögren's Syndrome cohort. This data increases scrutiny of HPV and polyoma subtypes for potential pathogenic roles in SS, but does not support a role for endogenous retroviruses. This work also for the first time identifies two distinct subsets of SS patients with regard to salivary viral expression.

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Mxa As a Biomarker for Systemic Interferon Type I Activation in Primary Sjögren′s Syndrome. Naomi I. Maria[1], Zana Brkic[1], Matti Waris[2], Cornelia G. van Helden-Meeuwsen[1], Kim Heezen[1], Joop P. van de Merwe[1], Paul L. van Daele[1], Virgil A. Dalm[1], Hemmo A. Drexhage[1] and Marjan A. Versnel[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]University of Turku, Turku, Finland

Background/Purpose: To establish an easy and practical assay for detection of systemic Interferon (IFN) type I activation in primary Sjögren's syndrome (pSS). The monocyte IFN type I signature is present in over half of pSS patients and identifies a subgroup of patients with higher clinical disease activity [Z. Brkic *et al.*, 2012]. Currently, detection of the IFN type I signature is performed via laborious mRNA expression profiles of multiple IFN type I inducible genes.

Methods: In a cohort of 35 pSS patients Myxovirus resistance protein A (MxA) was tested as potential biomarker for systemic IFN type bioactivity. An MxA-enzyme immunoassay (EIA) on whole blood was compared with flow cytometric detection of MxA in CD14$^+$ monocytes. In addition CD64 (Fcγ RI), CD169 (Siglec-1) and BAFF (B-cell activating factor), previously described as biomarkers for IFN type I in other systemic autoimmune diseases, were assessed in CD14$^+$ monocytes using flow cytometry. The IFNscore, a measure for total IFN type I activation, was calculated using expression values of the IFN type I signature genes – IFI44, IFI44L, IFIT3, LY6E, MX1 – in CD14$^+$ monocytes, determined by real-time quantitative PCR. pSS patients were stratified in an IFN-positive (IFNscore>10) and IFN-negative pSS subgroup (IFNscore<10).

Results: Twenty-one out of 35 pSS patients were IFN-positive (IFNpos), whereas HC were negative for the IFN type I signature. Significant correlations were found between IFNscores and CD14+ monocyte protein expression of MxA (p<0.001;r=0.733), CD64 (p=0.007;r=0.436), CD169 (p<0.001;r=0.495) and MxA protein expression in whole blood (p<0.001;r=0.717). MxA assessed by the MxA-EIA showed significantly elevated levels in IFNpos patients with a median of 212.5 (10–1295) μg/l, whereas IFNneg patients [1μg/l(1–330)] expressed MxA at levels equal to HC [15μg/l(1–150)] (p<0.001). Similar results were obtained for MxA assessed by flow cytometry (p<0.001). MxA-EIA protein levels correlated with the EULAR Sjögren's syndrome Disease Activity Index score; Immunoglobulin levels; rheumatoid factor; haemoglobin levels and neutrophil counts.

Conclusion: MxA protein analysis is a promising tool for assessment of IFN type I activation in pSS. MxA levels determined by MxA-EIA correlated with features of disease activity. The EIA was shown to be a functional assay and could contribute to future studies on disease pathogenesis and pSS subclassification, possibly leading to more targeted treatment strategies.

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The Axis P2X7 Receptor-Inflammasome: A Role in Modulating Inflammatory Response in Primary Sjögren's Syndrome? Chiara Baldini[1], Chiara Rossi[1], Eleonora Santini[1], Francesco Ferro[1], Alessia Gallo[2], Daniela Martini[1], Francesca Sernissi[1], Valentina Donati[1], Camillo Giacomelli[1], Nicoletta Luciano[1], Anna Solini[1] and Stefano Bombardieri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]NIDCR, Bethesda, MD

Background/Purpose: The exact cause of exocrine gland dysfunction in primary Sjögren's syndrome (pSS) has not been fully delineated, but it is thought that both innate and adaptive immunity may contribute significantly. Recent data have unveiled the structure and function of the P2X7 receptor/NLRP3 inflammasome pathway in stimulating caspase-1 activation and the subsequent release of the inflammatory cytokines IL-1β and IL-18. Thus, the growing evidence for the presence of P2X7R in salivary gland has suggested a fascinating scenario for the initiation and amplification of the innate immune response in pSS exocrinopathy.

Aim of the study: 1) to assess the expression of P2X7 receptor in minor salivary gland biopsies (MSGBs) and in peripheral lymphocytes of pSS patients; 2) to explore any correlation among P2X7 receptor, the other components of the inflammasome (i.e.NLRP3, caspase-1) and salivary levels of the released IL-18; 3) to correlate P2X7 receptor to patients clinico-serological and histopathological features

Methods: Consecutive patients with a diagnosis of pSS (AECG criteria) were enrolled in this proof of concept study. The control group consisted of subjects with suspected SS who did not fulfill the AECG criteria for pSS. Analysis of P2X7R, NLRP3 and caspase-1 gene expression was performed by real-time PCR on an ABI PRISM 7900 sequence detector (Applied Biosystems). Levels of IL-18 were assessed in patients unstimulated whole saliva by Western blot. Patients' clinico-serological and histopathological data were prospectively collected. For statistical comparisons, the t-test, the chi square test and logistic regression analysis were employed. P-values <0.05 were considered significant.

Results: Out of the 36 consecutive patients included in the study, 21/36 met the AECG criteria for pSS while the other 15/36 no-SS represented the control group. The P2X7R-mRNA was represented in MSGBs and in peripheral lymphocytes of both pSS and no-SS but its expression was significantly higher in pSS subjects than in no-SS control group (MSGBs p<0.0001; peripheral lymphocytes p=0.002). Similarly NLRP3 (p=0.0002) and caspase-1 (p=0.0004) gene expression was significantly higher in pSS and this was paralleled by an increased expression of IL-18 in pSS salivary samples. The P2X7R-mRNA was significantly higher in pSS patients with positivity for anti-Ro/SSA (p<0.0001) and correlated with MSGBs focus score (p=0.01).

Conclusion: This study suggests a potential involvement of the P2X7R/inflammasome-caspase-1- IL-18 axis in the pathogenesis of pSS exocrinopathy and opens novel opportunities for studying the complex mechanisms underlying pSS.

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S100A8/A9 Is Upregulated and Triggers the Secretion of Pro-Inflammatory Cytokines in Primary Sjögren's Syndrome. Laura Weichselbaum[1] and Muhammad S. Soyfoo[2]. [1]Department of rheumatology,Hôpital Erasme, Brussels, Belgium, [2]Hôpital Erasme,Université Libre de Bruxelles, Brussels, Belgium

Background/Purpose: To determine the involvement of S100A8/A9 in the pathogenesis of primary Sjögren's syndrome (pSS)

Methods: The serum levels of S100A8/A9, IL-17A and IL-17C were determined by ELISA. The expression of S100A8/A9, TLR4, IL-17A, IL-17C, IL-17RA, IL-17RC and IL-17RE was assessed by immunohisto-chemistry. PBMCs were isolated from 10 pSS patients and 10 healthy controls, stimulated with increasing concentrations of S100A8/A9 and interferon-γ. The cytokine profile was next investigated by flow cytometry and ELISA.

Results: Serum levels of S100A8/A9 were increased in pSS patients compared to controls. The expressions of S100A8/A9, TLR4, IL-17A, IL-17C, IL-17RA, IL-17RC, IL-17RE were enhanced in the salivary glands of pSS patients. No significant serum levels of IL-17A and IL-17C were detected in both groups of patients. S100A8/A9 significantly increased the production of TNF-α and IL-1β in pSS patients. We observed increased production of IL-17A following stimulation with S100A8/A9 but not achieving statistical significance. No secretion of IL-17C was detected upon PBMC's stimulation by S100A8/A9. Moreover, S100A8/A9 with IFN-γ synergistically increased significantly the production of TNF-α and IL-1β.

Conclusion: S100A8/A9 is increased in pSS and contributed to the increased production of TNF-α and IL-1β alone and in synergy with IFN-γ. S100A8/A9 induced the secretion of IL-17A in controls and pSS patients. IL-17A, IL-17C and their respective receptors were upregulated in the salivary glands of pSS patients.

Disclosure: L. Weichselbaum, None; **M. S. Soyfoo**, None.

ACR Poster Session A
Spondylarthropathies and Psoriatic Arthritis:
Clinical Aspects and Treatment
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Developmen and Validation of a New Instrument to Asess Health Related Quality of Life in Psoriasis Arthritis: The Vitacora Questionnaire. Juan Carlos Torre-Alonso[1], J. Santos-Rey[2], JM Ruiz-Martin[3], P. Valdazo-De Diego[4], Mireia Moreno[5] and Juan-Antonio Fernández[6]. [1]Hospital Monte Naranco, Oviedo, Spain, [2]Rheumatology, Toledo, Spain, [3]Rheumatology, Viladecans, Spain, [4]Rheumatology, Zamora, Spain, [5]Corporació Sanitària Parc Taulí, Sabadell, Spain, [6]MP, Oviedo, Spain

Background/Purpose: To develop and validate a specific questionnaire to measure health-related quality of life (HRQoL) in adults with psoriasis arthritis (PA) for use in clinical studies and clinical practice.

Methods: Item selection was generated through an extensive literature review, the experience of patients with PA, and discussion with PA expert rheumatologists. Item reduction was performed using clinimetric and psychometric approaches after administration of the item selection to 66 PA patients. The resulting questionnaire, named VITACORA, consists of 19 items. The factorial analysis explained its unidimensionality and an overall HRQoL score. Internal consistency, test–retest (10 days) reliability, sensitivity analysis, known groups and convergent validity were tested in a prospective, observational, multicenter study conducted in 10 Spanish hospitals with 323 subjects, who also completed the Euro-QoL 5 Dimensional questionnaire (EQ-5D) and a health status transition item. Three study groups were defined: group A (n=209) comprised PA patients; group B (n=71) comprised patients with arthritis no psoriasis; and group C (n=43) comprised healthy people. All subjects attended baseline visit and group A patients also test-retest and final visits (10 days and 6 months later, respectively).

Results: VITACORA questionnaire was considered easy or very easy to answer by 94.7% of PA patients. Missing response rate was less than 3.8% in all questionnaire items. Floor and ceiling effects were less than 2% for the overall score. Cronbach's alpha values and intraclass correlation coefficient values for the overall score exceeded 0.90. Statistically significant differences (p<0.001) were observed on the overall score between groups: subjects from group C (healthy people, mean overall score 93.7, SD 9.1) had a better HRQoL, following from group B (patients with arthritis no psoriasis, mean overall score 69.2, SD 24.8), and finally group A (PA patients, mean overall score 56.2, SD 24.8) had the worse HRQoL. As expected, the VITACORA scores showed significant correlations (p<0.001) to EQ-5D and to perceived health state scores. Likewise, lower correlations to clinical variables were found. At follow-up, the VITACORA scores showed significant correlations to health state change reported by PA patients and investigators. Effect sizes for the global score changes between two study visits (baseline and 6 months later) among PA patients ranged from 0.20 to 0.80, reporting an improvement in health status. The minimum important difference was established as an 8-point change in the global VITACORA score.

Conclusion: This new, developed instrument to measure HRQoL in PA patients has shown good reliability, validity, and sensitivity to change. It has also proved easy to use and administer in daily clinical practice and future research projects.

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The Prevalance of Autoimmune Thyroid Disfunction in Ankylosing Spondylitis. Hakan Emmungil[1], Mehmet Erdogan[2], Melike Kalfa[1], Gonca Karabulut[1], Hayriye Kocanaogullari[1], Vedat Inal[1], Yasemin Kabasakal[3], Fahrettin Oksel[3], Kenan Aksu[4] and Gokhan Keser[1]. [1]Dept. of Internal Medicine, Division of Rheumatology, Ege University, Izmir, Turkey, [2]Dept. of Internal Medicine, Division of Endocrinolgy, Ege University, Izmir, Turkey, [3]Ege University, Izmir, Turkey, [4]Dept. Of Internal Medicine, Division of Rheumatology, Ege University, Izmir, Turkey

Background/Purpose: Although the association of autoimmune thyroid dysfunction and primary Sjögren's syndrome (SjS) is well known, it is less clear whether a similar relationship also exists between autoimmune thyroid dysfunction and ankylosing spondylitis (AS). Therefore, we aimed to define the frequency of autoimmune thyroid dysfunction in patients with AS, to find out whether the frequency was significantly different from the healthy controls.

Methods: Eighty patients with AS (mean age: 40.57 ± 10.13 years; M/F: 50/30) fulfilling the 1984 Modified New York Criteria and 80 healthy subjects, age and sex-matched with AS patients were included. As the positive control group, 62 female patients with primary SjS (mean age: 50.27 ± 10.84 years) fulfilling the diagnostic criteria of the European Consensus Group were also studied. All cases underwent thyroid ultrasonography by a single endocrinologist to evaluate the size, nodularity and homogeneity of the thyroid gland. Besides, serum free triiodothyronine (fT3), thyroxine (fT4), thyroid-stimulating hormone (TSH), and thyroid autoantibodies were measured. The diagnosis of Hashimoto's thyroiditis was made only if the patient had thyroid autoantibody positivity plus at least one of the following criteria, namely diffuse goiter with physical examination, abnormality in thyroid function tests and ultrasonographic thyroid hypoechogenicity. Statistical analysis was performed with SPSS.15 for Windows. The chi-squared test and Fisher's exact test, when appropriate, were used to compare cases and controls. p values < 0.05 were considered statistically significant.

Results: The frequency of Hashimoto's thyroiditis was significantly higher in patients with AS compared with age and sex-matched healthy controls (10% vs 1.3% p: 0.034). Similarly, the frequencies of any thyroid autoantibody positivity (13.8% vs 2.5% p: 0.017) and ultrasonographic thyroid hypoechogenicity (30% vs 11.3% p: 0.045) were also significantly higher in AS group. Other parameters such as thyroid gland volume and nodularity, and thyroid function tests did not differ significantly between AS and healthy control groups. As expected, frequencies of Hashimoto's thyroiditis, thyroid autoantibodies and thyroid hypoechogenicity were highest in primary SjS group, however differences did not reach to statistically significant levels between the SjS and AS groups.

Conclusion: The present study showed that the frequency of autoimmune thyroid dysfunction was significantly higher in AS group, compared with healthy controls. It should be kept in mind that, patients with AS may have concomitant autoimmune thyroid dysfunction, and in case of clinical suspicion, such patients should be further evaluated with clinical and laboratory parameters.

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NT-Probnp and Inflammation in Active Ankylosing Spondylitis Receiving TNF Blockers: Is There a Link? Julio C. B. Moraes[1], Ana C. M. Ribeiro[2], Carla G.S. Saad[3], Alessandro C. Lianza[4], Nadia E. Aikawa[2], Clovis Artur Silva[5] and Eloisa Bonfa[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]University of Sao Paulo, São Paulo, Brazil, [4]Radiology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [5]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Cardiovascular disease plays a central role in morbidity and mortality in rheumatic patients. N-terminal pro-brain natri-uretic peptide (NT-proBNP) is a strong marker of cardiovascular risk with recent evidence that inflammation may also influence its levels. The discrimination of this confounding variable is of particular interest in rheumatic diseases. Therefore, we evaluated NT-proBNP in ankylosing spondylitis (AS) patients pre- and post-TNF blockage therapy to determine the possible association between NT-proBNP levels and inflammatory parameters.

Methods: Forty-five consecutive AS patients without previous/current cardiovascular disease or systolic myocardial dysfunction, who were eligible to anti-TNF therapy, were prospectively enrolled. All patients received TNF blockers (infliximab, adalimumab and etanercept in their regular schedule) and they were evaluated for circulating NT-proBNP levels, clinical and laboratory parameters of disease activity including BASDAI, ASDAS, ESR and CRP, traditional cardiovascular risk factors including blood pressure, body mass index, waist circumference and dyslipidemia; conventional and tissue Doppler imaging echocardiography and treatment data at baseline (BL) and six months after (6M). Statistical analysis included: Spearman rank order correlation, Mann-Whitney test or t-test to observe differences between patients with high or normal NT-proBNP levels at BL; paired-sample t tests or the Wilcoxon signed-rank test to observe differences between measurements at BL and 6M; Fisher exact test to compare categorical variables and multivariable linear regression analysis. All analyses used a two-sided significance level of 0.05.

Results: At BL, all patients had active AS, NT-proBNP levels had a median of 36 (20–72)pg/ml and 11% were high in spite of no systolic alteration. Multiple linear regression analysis revealed that this peptide, at BL, was independently correlated with ESR (p<0.001), age (p=0.01) and pulse pressure (p=0.01). After 6M, all disease parameters improved and NT-proBNP levels were significantly reduced [24 (16–47) pg/mL, p=0.037] compared to BL. Changes in NT-proBNP were positively correlated with ESR changes (r=0.41, p=0.006). Cardiovascular risk factors remained stable during follow-up.

Conclusion: Elevations of NT-proBNP should be interpreted with caution in active AS patients with no evidence of cardiovascular disease. The short-term reduction of NT-proBNP levels in these patients treated with anti-TNF therapy appears to reflect an improvement in inflammatory status. (ClinicalTrials.govnumber:NCT01072058).

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Increased Risk of Acute and Chronic Renal Comorbidity in Ankylosing Spondylitis: Results From a Population-Based Study. Walter P. Maksymowych[1], Shelagh Szabo[2], Sumati Rao[3], M. Cifaldi[3] and AR Levy[4]. [1]University of Alberta, Edmonton, AB, [2]Oxford Outcomes, Vancouver, BC, [3]Abbott Laboratories, Abbott Park, IL, [4]Oxford Outcomes Ltd, Vancouver, BC

Background/Purpose: Clinical evidence points to an increased risk of renal comorbidity in ankylosing spondylitis (AS) compared to the general population. However, there are no population-based estimates available in the literature. An increased risk of renal comorbidity would have substantial implications for the monitoring and treatment of AS because the mainstay of pharmacological treatment is the use of non-steroidal anti-inflammatory agents (NSAIDs). We aimed to estimate the prevalence and age- and sex-standardized increased risk of renal comorbidity, including acute and chronic kidney disease, and amyloidosis in a population-based cohort of persons diagnosed with AS in Québec between 1996 and 2006, compared to the general population.

Methods: A retrospective cohort study was conducted using the administrative physician-billing database of the Régie de l'Assurance Maladie du Québec. The cohort included individuals with at least one International Classification of Diseases, 9th Revision (ICD-9) billing code for AS between 1996 and 2006. A comparison cohort was generated using a 1% random sample of individuals without AS. Renal complications were identified by ICD-9 codes for amyloidosis, hypertensive chronic renal disease, acute and chronic renal disease. Age- and sex-stratified prevalence, and standardized prevalence ratios with 95% confidence intervals (CI), of renal complications in AS compared with the general population were calculated. Sensitivity analysis was conducted using two ICD-9 codes for AS.

Results: There were 8,616 individuals identified with AS; 56% were male and the median age at diagnosis was 42 years. Overall, renal complications were diagnosed among 3.4% and 2.1% of males and females with AS, compared to 2.0% and 1.6% of males and females in the general population cohort, respectively. Prevalence of renal complications increased with age in both the AS and general population cohort. Age- and sex-stratified prevalence ratios, comparing the risk of renal complications among those with AS to the general population, demonstrated a significantly excess risk of renal complications that was highest among younger individuals with AS. Overall, individuals with AS were at a significantly increased risk of renal complications compared to members of the general population (irrespective of a coding for hypertension), with a standardized prevalence ratio of 1.7 (1.5–2.0). Standardized prevalence ratios were 6.0 (2.0–18.0) for amyloidosis, 1.7 (1.4–2.0) for chronic kidney disease, 3.2 (0.8 – 12.4) for hypertensive kidney disease, and 1.9 (1.5 – 2.3) for acute kidney disease. The excess risk was highest among younger individuals with AS, and results were similar when two ICD-9 codes were used to identify AS.

Conclusion: This population-based analysis shows that individuals with AS are at increased risk of many types of renal complications, including acute kidney disease, with the point estimates of excess risk being greatest among younger individuals. These data highlight the importance of careful monitoring for renal complications among those with AS, particularly during long-term continuous use of NSAIDs.

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Reduced Joint Counts Misclassify Psoriatic Arthritis Patients with Oligoarthritis and Miss Significant Active Disease. Laura C. Coates[1], Oliver M. FitzGerald[2], Dafna D. Gladman Gladman[3], Neil J. McHugh[4], Philip Mease[5], Vibeke Strand[6], Philip S. Helliwell[7] and GRAPPA Composite Exercise (GRACE) collaboration[8]. [1]Division of Rheumatic and Musculoskeletal Disease, Leeds, United Kingdom, [2]St. Vincent's Univ Hospital, Dublin, Ireland, [3]Toronto Western Hospital and University of Toronto, Toronto, ON, [4]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [5]Swedish Medical Center, Seattle, WA, [6]Stanford University, Portola Valley, CA, [7]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8]Leeds

Background/Purpose: Despite recommendations to use full joint counts to assess patients with PsA, reduced joint counts designed for RA are often used for reporting outcomes in PsA registry studies and are used in clinical practice to assess patients with PsA. Analysis of RCTs suggested that 28 joint counts were responsive in PsA but this analysis was based on polyarticular patients enrolled into drug trials. The aim of this analysis was to investigate full and reduced joint counts in patients with oligoarticular PsA.

Methods: The study was an analysis of baseline visits for patients in the GRACE study, an international observational cohort recruited to develop new outcome measure in PsA. Oligoarthritis was defined as less than 5 tender and swollen joints. At baseline, full 66/68 tender and swollen joint counts were assessed. Active joint counts were calculated with an active joint defined as either tender and/or swollen. Reduced joint counts used for RA including the 28 and 44 joint count were analysed for comparison. In addition, new proposed shortened joint counts for PsA were tested to investigate their possible future use: PsA-44 (elbows, wrists, MCPs, PIPs, DIPs, knees and MTPs) and PsA-56 (as before plus ankles and PIP toes). ROC analysis was used to see how well different joint counts predicted treatment change for high disease activity. The proportion of patients with active disease missed by reduced joint counts was also analysed.

Results: In the cohort of 503 patients, 270 were classified as oligoarthritis. ROC analysis revealed that tender or active joint counts did not predict treatment change for high disease activity even when using a full 66/68 joint count (tender: AUC 0.56,p=0.18, active: AUC 0.55,p=0.23). A 66 SJC did predict treatment change (AUC 0.60, p=0.018) as did the SJC PsA44 and PsA56 (p<0.04). Neither of the RA reduced joint counts showed a significant relationship with treatment change. Of the 270 patients, 164 patients did not have any tender joints identified on a 28 joint count. However, of these 164, 38 did have 1 or more tender joints that had been missed (23%), leaving 126 patients with no tender joints. The PsA-44 and PsA-56 missed tender joints in 18 and 7 patients respectively. When considering swollen joints, 256 patients did not have any swollen joints identified on a 28 joint count but 48 of these (19%) did have swollen joints elsewhere. The PsA-44 and PsA-56 missed swollen joints in 26 and 7 patients respectively.

Conclusion: Patients with oligoarticular PsA cannot be assessed using joint counts borrowed from RA. Ideally full joint counts should be performed to assess PsA patients with the 66/68 joint count being the preferred measure due to difficulties distinguishing between the PIPs and DIPs of the toes. Reduced joint counts designed specifically for PsA do show correlation with treatment change but can still underestimate disease activity.

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Psoriasis and Psoriatic Arthritis in a Diverse Ethnic Cohort. Gail S. Kerr[1], Seema Qaiyumi[2], John S. Richards[2], Chesahna Kindred[3], Sean A. Whelton[4] and Florina M. Constantinescu[5]. [1]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [2]Washington DC VA and Georgetown University, Washington, DC, [3]Howard University Hospital, Washington, DC, [4]Georgetown University, Washington, DC, [5]Washington Hospital Center, Washington, DC

Background/Purpose: Few clinical studies describe psoriasis (PSO) and psoriatic arthritis (PsA) in ethnic minority groups. Previous patient-reported data show PSO/PsA to be less frequent in African Americans (AA) compared to Caucasians, but of equal severity. We describe the clinical characteristics of a diverse ethnic cohort of patients with PSO and PsA in an urban setting.

Methods: IRB consented patients with PSO diagnosed by a dermatologist and PsA satisfying CASPAR criteria, were enrolled from 4 academic outpatient clinics. Socio-demographic data, disease duration, time to diagnosis, disease phenotype and activity, quality of life measures, comorbidities, use of disease modifying anti-rheumatic drugs (DMARD) and biologic therapies were recorded.

Results: There were 160 PSO/PsA patients enrolled; 41.9% were non-Caucasian, 90% of whom were AA (Table). Mean PSO and PsA disease duration was 18.1 (SD14.3) and 13.3 (SD10.9) years, respectively. Mean BMI was 30.3 (SD5.7) kg/m^2 and PsA patients had a mean DAS28 of 2.7 (SD1.7). Non-Caucasians had worse PASI scores. Compared to Caucasians, AA had a lower frequency of PsA, worse SF-36 mental component and psoriasis related quality of life scores, received less years of education, had lower frequencies of private insurance coverage, DMARD and biologic use, and lower Vitamin D levels. AA also had higher frequencies of tobacco use, hypertension, diabetes, hyperlipidemia and cerebrovascular accidents. There were no differences in alcohol use, uric acid levels or other psoriatic disease-related parameters.

Variable, n (%)	Cohort	Caucasian	Non Caucasian**	African American	p-value
Cohort	160 (100)	93 (60.8)	67 (41.9)	60 (39.2)	—
PSO Only	75 (49.0)	33 (35.5)	44 (65.7)	42 (70.0)	<0.001
PSA	78 (51.0)	60 (64.5)	23 (34.3)	18 (30.0)	<0.001
Age (Mean ± SD)	56.7 ± 13.3	55.6 ± 13.4	56.8 ± 14.7	58.7 ± 13.2	0.18
Male	120 (78.4)	77 (82.8)	48 (71.6)	43 (71.7)	—
Education Years (Mean ± SD)	14.5 ± 3.3	15.1 ± 3.2	13.6 ± 3.2	42.8 ± 12.1*	0.0025*
Private Insurance	71 (46.4)	51 (54.8)	8 (11.9)	20 (33.3)*	0.009*
Tobacco Use	39 (26.4)	19 (20.7)	21 (33.3)	20 (35.7)	0.044
Dactylitis	15 (9.8)	13 (14.0)	2(11.1)	2 (3.3)	0.034
Oligoarthritis	42 (53.8)	32 (53.3)	10 (43.5)	7 (38.9)	—
Symmetric	14 (17.9)	12 (20)	2 (8.7)	2 (11.1)	—
PASI (Mean ± SD)	6.6 ± 8.1	5.5 ± 6.4	8.6± 10.4	8.4± 10.0	0.04
SF36 Physical	40.5 ± 11.9	41.0 ± 12.3	40.1 ± 11.1	39.7 ± 11.4	0.54
SF36 Mental	45.8 ± 12.0	47.7 ± 11.7	43.5 ±12.2	42.8 ± 12.1*	0.02*
PSAQOL	5.5 ± 5.8	5.2 ±5.7	5.81 ± 6.23	6.3 ± 6.4	0.56
PSOQOL	7.5 ± 6.8	6.1 ± 6.6	9.32 ±6.6	9.9 ± 6.7*	0.02*
DMARD	31 20.3)	26 (28.0)	7 (10.5)	4 (8.3)*	0.044*
Biologic	51 (33.3)	43 (46.2)	9 (13.4)	8 (13.3)*	0.014*
Diabetes	28 (18.3)	14 (15.0)	14(25.5)	14 (23.3)	0.05
Hypertension	68 (44.4)	33 (35.5)	36(65.5)	35 (58.3)*	<0.001*
Hyperlipidemia	51 (33.3)	28 (30.1)	25(45.5)	23 (38.3)	0.046
Cerebrovascular Accident	7 (4.6)	2 (2.2)	5(8.8)	5 (8.3)	0.045
Vitamin D (Mean ± SD)	28.3 ± 13.8	31.2 ± 13.9	21.8 ± 10.8	21.6 ± 11.0*	0.02*

* Indicates corresponding p-value
** Includes African American, Hispanic and Asian

Conclusion: Compared to Caucasians, African Americans had less frequent PsA but experienced greater impact on quality of life from psoriatic disease. Improved implementation and evaluation of disease activity and quality of life measures are needed in psoriatic disease, particularly in African American patients. Ours is the first study to use validated clinical measures to describe psoriatic disease in a diverse ethnic cohort.

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The Association of alpha7 Nicotinic Acetylcholine Receptor Polymorphisms with Psoriatic Arthritis and Its Interaction with Smoking. Lihi Eder[1], Vinod Chandran[2], Fawnda Pellett[2], Remy Pollock[2], Fatima Abji[2], Adele Carty[2], Sutharshini Shanmugarajah[2], Cheryl Rosen[2] and D. D. Gladman[2]. [1]Carmel Medical Center, Haifa, Israel, [2]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Alpha7 nicotinic acetylcholine receptor (CHRNA7) is an ion channel that is gated by the binding of nicotinic ligands. Nicotine interacts with CHRNA7 leading to down-regulation of intracellular pro-inflammatory pathways. It has been suggested that smoking may protect against the development of PsA among patients with psoriasis. We aimed to study the association of *CHRNA7* gene polymorphisms with PsA and their interaction with smoking.

Methods: We genotyped three groups of Caucasian individuals: patients with PsA, patients with psoriasis without arthritis (PsC) and healthy controls, for the following Single Nucleotide Polymorphisms (SNPs): rs904952, rs6494223, rs12915265, rs3826029 and rs6494165 within the *CHRNA7* locus. PsA patients satisfied the CASPAR criteria. The psoriasis patients were assessed by a rheumatologist to rule out inflammatory arthritis. The control DNA was from a commercial bio-bank. Smoking status was defined as current smoker for smokers and lifetime non-smoker for non-smokers. SNP genotyping was performed using Taqman SNP Genotyping Assays run on an ABI 7900HT Real-Time PCR system. The differences in allelic and genotype distributions were compared by Chi square test and trend test using PLINK software. The frequencies of rs6494223*TT/C genotypes were then compared across the patient groups within smokers and non-smokers and the interaction term of genotype and smoking was tested using logistic regression analysis.

Results: 238 PsA patients, 219 PsC patients and 210 healthy controls were included in the study. A significant inverse association was found between the rs6494223*T/C genotype and PsA (Table 1) compared to PsC (p=0.01) and to healthy controls (p=0.01), although no significant association was found between the minor allele rs6494223*T and PsA compared to PsC (p=0.14) and to healthy controls (p=0.26). Among smokers, the minor allele rs6494223*T was inversely associated with PsA compared to PsC (Odds Ratio (OR) 0.65, p[-allele]=0.04, p[-genotype]=0.02) and to healthy controls (OR 0.63, p[-allele]=0.02, p[-genotype]=0.004). Among non-smokers, the association between rs6494223*T and PsA compared to PsC and to healthy controls was not significant (p[-allele] =0.79 and 0.54, respectively). A statistically significant interaction between smoking status and rs6494223*TT genotype was found when PsA patients were compared to healthy controls (p=0.02). The remaining SNPs were not found to be associated with PsA compared to either PsC patients or to healthy controls in the entire study population and after stratification by smoking status.

Table 1. The association between rs6494223*T/C genotype and PsA vs. PsC and healthy controls by smoking status

		PsA	PsC	P allele	P genotype	Control	P allele	P genotype
All	TT	24 (10.1%)	43 (19.7%)	0.14	0.01	39 (19.1%)	0.26	0.01
	TC	137 (57.8%)	105 (48.2%)			96 (47.1%)		
	CC	76 (32.1%)	70 (32.1%)			69 (33.8%)		
Smoker	TT	6 (6.5%)	27 (29.6%)	0.04	0.02	26 (23.9%)	0.02	0.004
	TC	53 (57.6%)	45 (49.5%)			49 (45%)		
	CC	33 (35.9%)	19 (20.9%)			34 (31.1%)		
Non-Smoker	TT	18 (12.3%)	24 (18.9%)	0.79	0.14	13 (13.4%)	0.54	0.47
	TC	85 (58.2%)	60 (47.2%)			49 (50.5%)		
	CC	43 (29.5%)	43 (33.9%)			35 (36.1%)		

Conclusion: A *CHRNA7* gene polymorphism is associated with PsA. The rs649223*TT genotype may protect against the development of PsA particularly among smokers. This effect was not significant among non-smokers. This finding may explain why psoriasis patients who smoke are less likely to develop PsA.

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Association Between Biomarkers (Metalloproteinase-3, Dikkopf-1 and Sclerostin) with Disease Activity and Prediction of Anti-TNFα Therapy Response in Patients with Ankylosing Spondylitis. Victoria Navarro-Compán, Rafael Ariza, Rufino Mondéjar-García, Virginia Moreira-Navarrete, Enrique Melguizo-Madrid, Blanca Hernández-Cruz, Concepción González-Rodríguez and Federico Navarro-Sarabia. University Hospital Virgen Macarena, Sevilla, Spain

Background/Purpose: Better objectives measures for evaluating disease activity and anti-TNFα response in patients with ankylosing spondylitis (AS) are needed. MMP-3 seems to be the most promising biomarker but published data are not conclusive. The aim of this study was to investigate the association between serum biomarkers (MMP-3, DKK-1 and sclerostin) levels with disease activity parameters and to evaluate if these biomarkers are useful to predict anti-TNFα response in patients with AS.

Methods: From November 2010 to July 2011, consecutive patients with AS (New York criteria) who initiated anti-TNFα therapy in a University hospital were included. Before and after 3 months of therapy, disease activity was measured using BASDAI, ASDAScrp, CRP, patient's VAS of pain and patient's and physician's VAS of global disease activity (GDA). Blood samples for determination of serum levels of biomarkers by enzyme immunoassay were also collected at both visits. Spearman correlation test was used to evaluate association between biomarkers and disease activity parameters. Biomarkers change was compared in responders versus non-responders, based on BASDAI50 and ASDAS response using Mann-Whitney U test. Accuracy to predict response (ROC analysis) was performed.

Results: Twenty AS patients were included; 80% received adalimumab and 20% received etanercept. Median (IQR) age and disease duration were 42.4 (31–49) years and 6.8 (3–10) years, respectively; 86% were men, and 83% HLA-B27 positive. Inverse correlation between patient's VAS pain and MMP-3 at baseline was the only significant observed correlation between investigated biomarkers and disease activity parameters (table 1). MMP-3 levels decreased only in patients who responded to anti-TNF therapy but increased in patients who did not response (table 2). Baseline biomarkers serum levels (including CRP) for both groups were similar except for MMP-3 (122.9 vs 58.9; p<0.05). The area under the curve for MMP-3 to predict BASDAI50 and ASDAS response was 0.73 and 0.78, respectively. The best cut-off was established for levels higher than 59.5, with sensibility of 79–85% and specificity of 50–57%.

Table 1. Correlation between serum levels of biomarkers with disease activity parameters.

	BASDAI	ASDAScrp	Pt GDA	Pt VAS pain	Phy GDA	CRP
At baseline						
MMP-3	−0.318	−0.086	−0.334	−0.477*	−0.551	0.222
DKK-1	−0.017	−0.045	0.003	0.149	0.234	0.107
SOST	−0.096	−0.039	−0.074	0.066	−0.154	0.002
CRP	−0.288	0.577**	0.122	0.039	0.032	1.000
After 3 months						
MMP-3	−0.135	−0.144	−0.169	−0.154	−0.156	−0.024
DKK-1	−0.007	0.168	0.155	0.179	0.270	0.296
SOST	−0.006	0.114	0.306	0.166	0.427	0.172
CRP	0.003	0.457*	0.177	0.173	0.266	1.000

* p<0.05 ** p<0.01

Table 2. Change in serum levels of MMP-3, DKK-1, sclerostin and CRP after 3 months of anti-TNFα therapy based on the clinical response.

	Responders N=13 (65%)			Non−responders N=7 (35%)		
	Baseline	3 months	p	Baseline	3 months	p
MMP-3 (ng/dl)	122.2	64.1	0.01	58.9	75.5	0.6
DKK-1 (ng/dl)	6.9	8.1	0.6	7.3	6.7	0.6
SOST (pmol/dl)	23.6	23.4	0.9	18.1	21.3	0.2
CRP (mg/l)	16.3	4.0	0.002	8.3	5.3	0.3

Conclusion: No correlation was observed between serum levels of MMP-3, DKK-1 and sclerostin and disease activity parameters in patients with AS. Serum levels of MMP-3 may be useful to predict response to anti-TNFα therapy in patients with AS.

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Efficacy and Safety of Adalimumab for the Treatment of Peripheral Arthritis in Spondyloarthritis Patients without Ankylosing Spondylitis or Psoriatic Arthritis. Jacqueline E. Paramarta, Leen De Rycke, Tanja F. Heijda, Carmen A. Ambarus, Koen Vos, Huib J. Dinant, Paul P. Tak and Dominique L. Baeten. Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: The treatment of spondyloarthritis (SpA) has improved dramatically since the introduction of TNF-blockade. However, this therapy is only approved and reimbursed for the treatment of ankylosing spondylitis (AS) and psoriatic arthritis (PsA), which are the best described and studied phenotypic subtypes of SpA. Approximately one third of the SpA population can not be classified as AS or PsA. Randomized clinical trials (RCTs) in non-radiographic axial SpA have recently been performed and showed good results, but for peripheral non-AS, non-PsA SpA patients RCTs are lacking. This study aimed to assess the efficacy and safety of adalimumab in patients with peripheral SpA not fulfilling the criteria for AS or PsA.

Methods: Forty patients with active peripheral SpA fulfilling the ESSG or Amor criteria but not the criteria for AS or PsA were included in a randomized, double-blind, placebo-controlled clinical trial. Patients were treated 1:1 with adalimumab or placebo for 12 weeks, followed by an open label extension up to week 24. Safety and efficacy measurements were performed every 6 weeks, with as primary endpoint the patient's global assessment of disease activity at week 12.

Results: The baseline demographic and disease characteristics were similar across both treatment arms, except for HLA-B27 positivity which tended to be higher in the adalimumab group (55%) versus the placebo group (25%) (P=0.053), and the physician's global assessment of disease activity which was somewhat higher in the placebo (57.0 $\pm$ 12.6 mm) versus the adalimumab treated patients (47.8 $\pm$ 11.8 mm) (P=0.022). At week 12 the patient's and physician's global assessment of disease activity, swollen joint count, BASDAI, ASDAS and ESR improved significantly in the adalimumab group compared with the baseline values and compared with placebo (Table 1). A similar improvement was seen upon adalimumab treatment from week 12 to 24 in the patients originally randomized to placebo, whereas the clinical response was maintained or even augmented at week 24 in the patients who received adalimumab from the beginning. ASDAS inactive disease and BASDAI50 responses were met in 42% of the adalimumab group versus 0–5% in the placebo group at week 12 (P=0.001 and P=0.008 respectively), and were further increased at week 24. Quality of life and disability scores also improved upon adalimumab treatment. Multiple regression analysis showed that features such as gender, HLA-B27 status and concomitant DMARD treatment did not act as confounders in this trial. The number of adverse events was not different between the adalimumab and placebo group.

Table 1. Mean changes in disease activity from baseline to week 12 by treatment group

| | Baseline to week 12 | | |
	Adalimumab	Placebo	*P*-value
Patient's global assessment, 0–100 mm VAS	−31.0 (23.3)	−5.9 (21.4)	0.001
Physician's global assessment, 0–100 mm VAS	−19.8 (19.5)	−4.1 (16.4)	0.011
Swollen joint count, 0–66 joints	−2.5 (4.0)	−0.4 (1.8)	0.046
Tender joint count, 0–68 joints	−1.8 (9.2)	1.7 (6.5)	0.174
BASDAI	−1.8 (2.6)	−0.3 (1.5)	0.030
ASDAS	−1.0 (1.0)	−0.1 (0.6)	0.003
CRP, mg/l	−5.7 (12.4)	4.0 (22.9)	0.112
ESR, mm/hour	−6.0 (12.5)	1.7 (9.3)	0.039

Values are the mean change (standard deviation) from baseline to week 12.
Significance of the comparisons is determined by an independent sample t-test.

Conclusion: Adalimumab is effective and safe in SpA patients with active peripheral disease, also in those patients not fulfilling the AS or PsA criteria. Therefore, this treatment should be considered and made available for these patients when their peripheral SpA is refractory to conventional treatments.

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The Predictors of Reduced Work Productivity in Patients with Psoriatic Arthritis. Anjali Papneja[1], Matthew Kennedy[2], Arane Thavaneswaran[3], Daniel Pereira[3], Vinod Chandran[3] and Dafna D. Gladman[3]. [1]University of Toronto, Toronto, ON, [2]University of Toronto, TOronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Psoriatic arthritis (PsA) is a unique inflammatory musculoskeletal disorder associated with psoriasis. Related to its detrimental impact on health and quality of life, PsA patients have also been affected with reduced work productivity. Work productivity is an essential determinant of health because it affects a patient's physical and psychological wellbeing. The purpose of this study was to identify the factors that predict reduced work productivity, as measured by the Work Limitations Questionnaire (WLQ), among patients with PsA. These predictors can be divided into demographic factors, clinical factors, and work related factors.

Methods: Patients attending a single centre Psoriatic Arthritis Clinic were recruited for participation. Employed participants (including home makers) first completed a Questionnaire for the Assessment of Work Related Factors (QAWRF), to shed light upon the nature of their work. Eligible participants then completed the WLQ. The WLQ scores were used as the dependent variable in a linear regression analysis. The independent variables assessed in this study included work characteristics, demographic factors, and clinical measures, such as PASI, active joint count, damage joint count, and ESR.

Results: 152 patients participated (53% males) with a mean age of 50.7 years, disease duration of 14.6 years, and 85.6% with a post-secondary school education. The mean actively inflamed joint count was 5.3. The damage joint count was 10.4. The mean PASI was 3.2. All patients completed the WLQ, of whom 137 completed both the WLQ and the QAWRF. 18.8% of patients lost 1 or more full days at work and 28.3% lost 1 or more partial work days, due to their health. On both univariate and multivariate linear regression education status, PASI, active joint count, and ESR were associated with reduced work productivity among working PsA patients. Support in the workplace was negatively correlated with reduced work limitations.

Table 1. Univariate and multivariate linear regression to determine associates of WLQ (N=137)

| | Univariate Model | | Multivariate Models | | | |
| | | | Full Model | | Reduced Model | |
Covariate	Estimate	P-value	Estimate	P-value	Estimate	P-value
Age at visit	0.06	0.1543	0.03	0.56	–	–
Sex	−3.89	<0.0001	−1.28	0.18	–	–
Duration of PsA	−0.04	0.41	−0.08	0.11	–	–
Education status	−2.96	0.026	−2.57	0.03	−3.13	0.0003
PASI	0.25	0.061	0.26	0.03	0.27	0.017
Active joint count	0.36	<0.0001	0.33	<0.001	0.33	<0.0001
Damage joint count	−0.007	0.87	0.06	0.13	–	–
ESR	0.19	<0.0001	0.07	0.09	0.096	0.012
Physical labour work	0.50	0.1521	−0.19	0.61	–	–
Control work schedule	−0.38	0.2440	−0.06	0.87	–	–
Support at work	−1.32	0.0002	−0.35	0.38	–	–

Conclusion: Work productivity is associated with demographic, clinical, and work related factors. This endorses the use of an effective drug to control disease activity and advocates for a more supportive work environment for these patients.

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Prevalence of Sacroiliitis in the General Population: Comparative Analysis with Cutaneous Psoriasis and Psoriatic Arthritis. Jose Luis Fernandez-Sueiro[1], Carlos Fernandez-Lopez[1], S. Pertega-Diaz[1], JA Pinto[1], E. Gonzalez[1], Francisco J. de Toro-Santos[1] and Francisco J. Blanco[2]. [1]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain

Background/Purpose: At least grade 2 unilateral sacroiliitis in the presence of spinal symptoms (defined as a combination of inflammatory back pain plus back stiffness) in our criteria allows to classify axial psoriatic arthritis (axPsA). However it is unknown to what extent this sacroiliac involvement is specific for axPsA. The objecive was to determine the prevalence of at least grade II unilateral radiological sacroiliitis in the general population, cutaneous psoriasis and PsA.

Methods: Descriptive cross sectional study of 3 cohorts: a) general population: consecutive digitalized pelvis x ray films taken to patients that acceded to the emergency room of the Complexo Hospitalario Universitario A Coruña (CHUAC) between January-March 2010 for spinal pain (1174 x-rays out of 928 patients, 621 patients met inclusion criteria for the analysis), b) patients of a follow up cohort of cutaneous psoriasis (Ps) (n=106), c) PsA patients from CHUAC (n=168) and Complexo Hospitalario Universitario de Orense (CHOU) (n=89). X ray films were red independently by two expert's rheumatologist, x ray films were discarded if: absence of vision of both sacroiliac joints, blurred x rays, age <18 years old, prosthesis, dysplasia, Paget's disease and osteitis condensans ilii. If there was a discrepancy consensus was reached between both readers. Prevalence of sacroiliitis, together with its 95% confidence interval (CI), was estimated in each cohort. Odds ratio and prevalence ratio values were estimated from a multivariate logistic regression model, adjusted by age and gender.

Results: 621 sacroiliac x-rays in the general population, 106 in Ps and 257 in PsA were analysed. Medium age was 58,7±20,1, 54,6±13,1 and 54,6±15,9 years, respectively. The percentage of males in each cohort was 43%, 39,6% y 63%, respectively. Prevalence of at least unilateral grade II sacroiliitis or higher was significantly higher in Ps (16,0%; 95% IC: 8,6%–23,5%) and in PsA (34,2%; 95% IC: 28,2%–40,2%) than in the general population (0,6%; 95% IC: 0,2%–1,6%). Logistic regression analysis showed that the prevalence of sacroiliitis was significantly higher in Ps (OR=35,2; p<0,001) and in PsA (OR=78,6; p<0,001) independently of age and sex. Older age (OR=1,02; p=0,016) and male sex y (OR=4,02; p<0,001) were associated to a higher prevalence of sacroiliitis.

Conclusion: The prevalence of at least grade 2 unilateral sacroiliitis or higher was 34,2% in PsA and 16% in Ps, both were higher than in the general population. Prevalence was higher in PsA than in Ps. Prevalence of sacroiliitis increased with age and male gender. These data suggest that the presence of at least grade II unilateral sacroiliitis is specific of PsA and may be used to classify a patient with axial involvement.

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Validation of a Reference Imaging Module for Calibration of Readers Scoring with the Modified Stoke Ankylosing Spondylitis Spine Score. Walter P. Maksymowych[1], Thomas J. Learch[2], Robert GW Lambert[1], Michael M. Ward[3], Nigil Haroon[4], David Salonen[5], Robert D. Inman[6] and Michael H. Weisman[7]. [1]University of Alberta, Edmonton, AB, [2]Cedars-Sinai, Los Angeles, CA, [3]NIAMS/NIH, Bethesda, MD, [4]University Health Network, Toronto Western Research Institute, University of Toronto, Toronto, ON, [5]University Health Network, Toronto, ON, [6]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [7]Cedars-Sinai Medical Center, Los Angeles, CA

Background/Purpose: The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is used to assess progression in AS based on the lateral spinal radiograph but the methodology is not well standardized and the role of the lumbar antero-posterior (AP) radiograph is unclear. In the Spondyloarthritis Research Consortium of Canada (SPARCC) and the SPondyloArthritis Research and Treatment Network (SPARTAN) conjoint imaging group (SPAR) we aimed to develop and validate a reference image module to calibrate readers using the mSASSS.

Methods: The group readers comprised 5 rheumatologists and 3 musculoskeletal radiologists with special expertise in AS. We conducted the following: 1. Systematic review of the literature to identify aspects of the mSASSS requiring methodological clarity. 2. Independent assessment by 6 readers of baseline and 2 year radiographs from 25 patients with AS (exercise 1). 3. Consensus development of an imaging module (SPAR module) which clarifies definitions, scoring methodology, and a set of extensively annotated reference images. In exercise 2 the same 6 readers assessed radiographs from 39 patients with AS, which included 15 from exercise 1 (Subgroup 1), where baseline and 2 year radiographs were scored blinded to time point. Readers first scored only the lateral radiographs of the lumbar (LS) and cervical spine (CS), then only the AP radiograph, and then both radiographs simultaneously. Inter-observer reliability of the mSASSS was assessed by the intraclass correlation method (ICC).

Results: The first exercise demonstrated excellent reliability for status scores (ICC for 6 readers (range) = 0.92; Median (range) ICC for 15 reader pairs = 0.92 (0.84–0.96)) but poor reliability for change scores (ICC for 6 readers = 0.46; Median (range) for 15 reader pairs = 0.52 (0.11–0.66)). In particular, ICC for change score for the radiologist reading pair was only 0.46. In exercise 2, the ICC for change score for the radiologist reading pair improved substantially to 0.62 while improvement from 0.49 to 0.57 was also noted for the overall group in the subgroup of patients scored in both exercises. Reliability was not further enhanced when lateral and A-P radiographs were assessed simultaneously for either status or change mSASSS score. There was substantial variation between readers in the contribution of the AP radiograph to staging (mean (range) 27.2% (21.1–42.1)) and progression (mean (range) 15.4% (5.3–31.6)) and was most consistent for staging.

Exercise	All readers ICC	Radiologist pair ICC
All patients (n = 25) Exercise 1		
Status reliability	0.92	0.94
Change reliability Subgroup (n = 15)	0.46	**0.46**
Status reliability	0.93	0.98
Change reliability	**0.49**	0.64
All patients (n = 39) Exercise 2		
Status reliability	0.91	0.95
Status reliability	0.90	0.96
Change reliability	**0.57**	0.68

Conclusion: Calibration according to the standardized methodology developed for the SPAR module led to improved reliability in the scoring of the mSASSS even for expert readers. The contribution of the AP radiograph affects a substantial proportion of patients and requires further systematic study.

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Wnt Pathway Inhibitors in Patients with Psoriatic and Rheumatoid Arthritis Treated with Anti-TNF Therapy. Agnes Szentpetery[1], Harjit P. Bhattoa[2], Peter Antal-Szalmas[2], Zoltan Szekanecz[3] and Oliver M. FitzGerald[4]. [1]Department of Rheumatology, St. Vincent's University Hospital, Dublin, Ireland, [2]Department of Laboratory Medicine, University of Debrecen, Medical and Health Science Center, Debrecen, Hungary, [3]Department of Rheumatology, University of Debrecen Medical and Health Sciences Center, Debrecen, Hungary, [4]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Both rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are characterised by bone erosion but aberrant bone formation is also a feature in PsA. Wnt proteins have recently been identified as key promoters of osteoblastogenesis hence new bone formation in inflammatory arthritis. Dickkopf-1 (Dkk-1) and sclerostin are natural inhibitors of Wnt signalling. Dkk-1 induces sclerostin expression by osteocytes and promotes osteoclastogenesis through suppression of osteoprotegerin (OPG). It has been shown that TNF-alpha inhibits bone formation by inducing Dkk-1 and sclerostin expression. The effect of anti-TNF on endogenous antagonists of the Wnt pathway in RA and PsA has not been studied previously in a prospective study design.

The aim of this study was to: (1) investigate serum levels of Dkk-1 and sclerostin in patients with RA and PsA; (2) compare both the very early (1 month) and more long-term (12 months) effects of anti-TNF treatment on

inhibitors of Wnt signalling; and (3) explore associations between serum levels of Dkk-1 and sclerostin and acute phase response measures.

Methods: RA and PsA patients with active disease were recruited prior to starting anti-TNF therapy. Serum levels of Dkk-1, sclerostin and OPG were measured by ELISA at baseline, 1 month and 12 months and were related to CRP levels at all time points. OPG/Dkk-1 and OPG/sclerostin ratios were calculated from previously measured OPG levels.

Results: 62 patients (35 RA, 27 PsA) were recruited with a median age of 53 years (28–74) and median disease duration of 7 years. Older age was associated with lower sclerostin levels in the entire group (r=-0.316 p= 0.023).

No significant difference in Dkk-1 and sclerostin levels was observed between RA and PsA at any time point, though Dkk-1 levels were lower in PsA at 12 months approaching significance (p=0.08). Serum Dkk-1 and sclerostin levels did not change significantly with anti-TNF therapy in either RA or PsA during the course of the study. There were significant positive correlations between both DKK-1 and sclerostin levels across the different time points with the exception of DKK-1 between baseline and 1 year in both diseases. High serum sclerostin levels were associated with low Dkk-1 levels in PsA (r=−0.605 p= 0.04) and in the entire group (r=−0.453 p= 0.001) after 12 months of anti-TNF therapy.

OPG/Dkk-1 and OPG/sclerostin ratios reflecting remodeling balance were similar and did not change significantly in either RA or PsA during the study. There was no correlation between Dkk-1 or sclerostin and CRP levels.

Conclusion: This study provides data suggesting differences in the cross-talk between TNF-alpha, Dkk-1 and sclerostin between RA and PsA. After 12 months of anti-TNF treatment Dkk-1 levels were lower in PsA compared to RA. This may contribute to an imbalance in bone remodeling in favour of bone formation in PsA. High serum sclerostin levels were associated with low Dkk-1 levels in PsA and in the entire group after 12 months only suggesting that DKK-1 but not sclerostin might be altered with anti-TNF therapy. Neither Dkk-1 nor sclerostin correlated with CRP at any time point indicating that these Wnt inhibitors may not linked to inflammation.

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Anterior Chest Wall Pain in Recent Inflammatory Back Pain. Data From the DESIR Cohort. Daniel Wendling[1], Clément Prati[2], Christophe Demattei[3], Damien Loeuille[4], P. Richette[5] and Maxime Dougados[6]. [1]Minjoz University Hospital, Besancon, France, [2]CHU J Minjoz, Besancon, France, [3]CHU, Nimes, France, [4]CHU Brabois, Vandoeuvre les Nancy, France, [5]Hôpital Lariboisière, Paris, France, [6]Paris-Descartes University, APHP, Cochin Hospital, Paris, France

Background/Purpose: Anterior chest wall pain (ACW) may be suggestive of spondyloarthritis (SpA), but little is known about this clinical feature in recent inflammatory back pain (IBP).

Objective: To determine the prevalence of ACW in patients with recent IBP suggestive of SpA, and to investigate the influence of ACW on the overall features of patients presenting with recent IBP.

Methods: The DESIR cohort is a prospective, multicenter French cohort of patients with early IBP (Calin or Berlin criteria) (>3 months and <3 years of duration) suggestive of SpA according to the investigator, including 708 patients (mean age 33.8 years, 53.8% female, 57.3% HLA B27 positive). ACW was defined by at least one episode of chest wall pain attributed to SpA by the rheumatologist, after ruling out other causes of chest pain. Data on the baseline demographic characteristics, functional status and quality of life, imaging features (standard X-Rays, MRI, Ultrasounds), BMD, and blood tests were compared in patients with and without ACW. Both the date of the first symptom of IBP and the symptoms of ACW were recorded, as well as the date of the visit. Factors associated with ACW were identified both by uni and multivariate analysis (logistic regression).

Results: The prevalence of ACW in the DESIR cohort was 44.6 % [95%CI 40.9–48.3] (n=316/708 patients). ACW occurred after the first symptoms of IBP in 62 %, before in 14 %, and simultaneously (±1month) in 24 % of the cases. Localization was diffuse in 41% of the positive cases, sterno costal (35%), manubrio sternal (29%) or sterno clavicular (26%). Presence of ACW was significantly associated in univariate analysis with pain in cervical and thoracic spine, buttock, peripheral arthritis and

enthesitis, fulfilment of ASAS and ESSG criteria, associated reactive arthritis and SAPHO, increased BASDAI, ASDAS, BASFI, BASG, SF-36, BASMI, articular index, increased CRP, radiographic sacro iliac involvement and reduced BMD. ACW was not associated with HLA-B27, uveitis, psoriasis, smoking, age and MRI findings. A stepwise multivariate analysis found an association between ACW and (Table): the enthesitis score, involvement of the thoracic spine, diagnosis of ankylosing spondylitis and radiographic abnormality of the sacro iliac joints.

	ACW (n=316)	No ACW (n=392)	Adjusted OR	p-value
Global enthesitis score (0–13)	3,65 ± 3,57	1,91 ± 2,53	1.213 [1.148–1.282] For an increase of 1 unit	<0.0001
Involvement of the thoracic spine (pain) Yes versus no	212 (67%)	192 (49%)	2.201 [1.582–3.062]	<0.0001
Diagnosis before inclusion: Ankylosing Spondylitis Yes versus No	150 (47%)	148 (38%)	1.642 [1.176–2.293]	0.0036
Radiographic sacro iliac score	142(46%)	209 (55%)	1.692 [1.128–2.538]	0.0109
0: normal	81 (26%)	75 (20%)	1.295 [0.863–1.943]	0.2121
1: doubtful	76 (24%)	96 (25%)	7.299 [1.938–27.48]	0.0033
2: established	12 (3.90%)	3 (0.78%)		
3: fusion				

Conclusion: In recent IBP suggestive of SpA, presence of ACW is associated with enthesitis, thoracic spine involvement, radiographic sacro iliitis and the diagnosis of ankylosing spondylitis. Since there are no differences in symptoms duration between ACW positive and ACW negative patients, ACW could be interpreted as an independent diagnosis feature for ankylosing spondylitis.

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Correlates of Inflammatory Back Pain in a Nationally Representative Sample of the US Population. Shervin Assassi[1], Michael H. Weisman[2], Zhongxue Chen[1], Mohammad Rahbar[1], Daniel O. Clegg[3], Robert A. Colbert[4], Atul A. Deodhar[5], Laurie M. Savage[6], Tiffany Graham[1], James P. Witter[7] and John D. Reveille[1]. [1]Univ of Texas Health Science Center at Houston, Houston, TX, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]George E. Wahlen VA Medical Center, Salt Lake City, UT, [4]NIAMS NIH, Bethesda, MD, [5]Oregon Health & Science University, Portland, OR, [6]Spondylitis Association of America, Van Nuys, CA, [7]NIH, Bethesda, MD

Background/Purpose: There are no published studies on correlates of inflammatory back pain (IBP) based on a large-scale nationally representative sample. In the present study, we examine the demographic and clinical features that are associated with IBP among adults with chronic back pain who participated in the US National Health and Nutrition Examination Survey (NHANES) 2009–2010.

Methods: NHANES 2009–2010 surveyed 5106 adults (ages: 20 to 69), representative of the US population. The study participants were interviewed and examined by trained personnel to obtain demographic and clinical data. A detailed questionnaire focused on back pain and associated features was administered. Chronic back pain was defined as back discomfort present on most days for more than 3 months. Based on this definition, 980 (19.2%) had chronic back pain. Two published sets of criteria for IBP were utilized to identify participants with IBP in the chronic back pain group. Specifically, the outcome variable was IBP as defined by presence of four (out of five) European Spondyloarthritis Study Group (ESSG) or two (out of four) 2006 Berlin Criteria. The investigated independent variables included a comprehensive list of demographic features including age, gender, ethnicity, education, income, exercise habits, body mass index (BMI), alcohol use, and smoking status. In addition, laboratory and clinical features including C-reactive protein, presence of diabetes, hepatitis C, arthritis, uveitis, inflammatory bowel disease, psoriasis, rapid response to NSAIDs, and heel pain were also investigated. Specifically, presence of arthritis was determined by affirmative response to the question "has a doctor ever told you that you had arthritis". Obesity was defined as BMI >30. Among patients with chronic back pain, the association of demographic and clinical features with IBP was assessed with weighted logistical regression analysis in univariable and multivariable models in order to identify the independent correlates of IBP.

Results: First, correlates of IBP according to the ESSG criteria were examined. Among participants with chronic back pain, absence of morbid obesity (OR: 1.86, p<0.001), presence of arthritis diagnosed by a physician (OR: 1.6, p=0.021), rapid response to NSAIDs (OR: 1.6, p=0.032), younger age (20–49 versus 50–65 age group, OR: 3.68, p<0.001) were independent correlates of IBP in the multivariable model. Next, correlates of IBP according to Berlin Criteria were investigated. For this purpose, participants over 50 year of age were excluded because the Berlin Criteria are not applicable to this age group. The presence of arthritis diagnosed by a physician (OR=1.7, p=0.039), psoriatic skin disease (OR=3.2, p=0.04), current smoking (OR: 1.8, p=0.017), and lower education level (high school diploma or less versus the rest, OR=1.6, p=0.04) were independently associated with IBP in the multivariable model.

Conclusion: Certain demographic features including younger age, lower BMI, lower educational level, and current smoking, as well as several clinical characteristics, specifically arthritis, psoriasis, and rapid response to NSAIDs are associated with IBP in adults with chronic back pain in the US population.

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The Immunogenicity to the First Anti-TNF Therapy Determines the Outcome of Switching to a Second Anti-TNF in Spondyloarthritis Patients. Chamaida Plasencia[1], Dora Pascual-Salcedo[2], Sara Garcia-Carazo[1], Gema Bonilla[3], Leticia Lojo[1], Laura Nuño[3], Alejandro Villalba[1], Diana Peiteado[1], Concepcion Castillo-Gallego Jr.[4], Florencia Arribas[2], Daniel Nagore[5], E. Martin-Mola[4] and Alejandro Balsa[6]. [1]RHEUMATOLOGY UNIT, Spain, Spain, [2]Hospital La Paz. IdiPaz, Madrid, Spain, [3]Hospital La Paz-IdiPaz, Madrid, Spain, [4]Hospital Universitario La Paz, Madrid, Spain, [5]Proteomika S.L., [6]Hospital La Paz, Madrid, Spain

Background/Purpose: Spondyloarthropathies (SpAs) encompass a heterogeneous group of diseases that primarily affect the axial skeleton and entheses. Although anti-TNF drugs have proven to be effective against SpA, approximately 30% of patients fail to respond or experience adverse events leading to treatment discontinuation. In rheumatoid arthritis, it has been shown that the development of antibodies (Abs) against the first anti-TNF treatment determines the response to the second anti-TNF treatment. Our aim was to assess whether the response to a second anti-TNF treatment after failing to respond to a first TNF antagonist is related to the previous development of Abs to the first TNF inhibitor.

Methods: We studied 33 patients diagnosed with SpA who began treatment with a second anti-TNF after failing to respond to the first anti-TNF: 23 (69.7%) patients with ankylosing spondylitis (AS), 6 (18.3%) with undifferentiated SpA, 3 (9%) with psoriatic SpA and 1 (3%) with SpA secondary to reactive arthritis. Clinical activity was assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) at baseline (at the beginning of the 1° and 2° anti-TNF treatments) and at 6 months after switching. Clinical improvement was evaluated using the delta-ASDAS. The drug and anti-drug Ab (ADA) levels were measured by ELISA before each administration.

Results: Of the 33 patients examined, 18 (54.5%) were male. The mean age was 50.1±10.2 years, and 75% (21/28) were positive for HLA B27. All patients were initially treated with anti-TNF drugs; 14/33 (42.4%) were treated with infliximab (Ifx), 3/33 (9.1%) with adalimumab (Ada) and 16/33 (48.5%) with etanercept (Eta). Nine of 33 (27.3%) developed ADAs during the first biologic treatment [8 Abs to Ifx (ATI) and 1 Abs to Ada (ATA)]. Mainly due to inefficacy, the first anti-TNF was exchanged for a second anti-TNF: 7 (21.2%) switched to Ifx, 16 (48.5%) to Ada, 5 (15.2%) to Eta and 5 (15.1%) to golimumab (Gol). No differences in ASDAS were not observed at baseline in patients with or without ADAs to the first (3.35±0.87 with ADAs vs 3.51±1.04 without ADAs, p=0.953) and second (2.99±0.96 with ADAs vs 3.31±0.97 without ADAs, p=0.392) anti-TNF treatments. At six months after switching, patients who had previously developed ADAs had lower disease activity (1.76±0.98 with ADAs vs 2.79±1.11 without ADAs, p=0.020), and a trend was observed towards greater clinical improvement (delta-ASDAS 1.23±1.22 with ADAs vs 0.52±1.08 without ADAs, p=0.065). At six months after switching, most patients without ADAs were classified as having high or very high disease activity state by the ASDAS (18 out of 24 (75%) without ADAs vs 3 out of 9 (33.3%) with ADAs, p=0.022), and more patients with ADAs had inactive disease (2 out of 9 (22.2%) with ADAs vs 1 out of 24 (4.2%) without ADAs, p=0.022).

Conclusion: In SpA, the failure to respond to the first anti-TNF treatment due to the development of ADAs predicts a better clinical response to a second anti-TNF treatment. The study of immunogenicity in biological treatment failure may help predict the response to a second biological treatment for SpA.

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Comparison and Validation of Screening Questionnaires for Psoriatic Arthritis in Patients with Psoriasis. Devy Zisman[1], Lihi Eder[1], Bosmat Zamir[2], Arie Laor[1] and Joy Feld[1]. [1]Carmel Medical Center, Haifa, Israel, [2]Clalit Health Services, Haifa and Western Galilee District, Haifa, Israel

Background/Purpose: Several self-administered screening questionnaires are available to identify patients suspected as suffering from psoriatic arthritis (PsA) among patients with psoriasis, thus facilitating their referral to a rheumatologist. Two questionnaires, the Toronto Psoriatic Arthritis Screen (ToPAS) and the Psoriatic Arthritis Screening and Evaluation tool (PASE), were found to have high sensitivity and specificity among Canadian and American psoriasis patients. The aim of our study was to validate and compare the Hebrew versions of PASE and ToPAS questionnaires among Israeli psoriasis patients.

Methods: A cross-sectional study included 99 patients with psoriasis attending dermatology clinics and 15 patients from a combined rheumatology-dermatology clinic who completed the PASE and ToPAS questionnaires. Psoriasis patients who had PASE scores of ≥44 and ToPAS scores of >8 were considered to be suspected PsA cases. Specialized rheumatologists, blind to the questionnaires' results, evaluated all participants for symptoms and signs of PsA. Patients with inflammatory arthritis underwent laboratory and radiology work-ups. A definitive diagnosis of PsA was made by a rheumatologist applying the CASPAR criteria. The questionnaires' performance was assessed using the receiver operating curve (ROC) analysis and the magnitudes of sensitivity and specificity.

Results: The questionnaires were completed by 114 patients with psoriasis, of which 38 (33.3%) met the CASPAR criteria for PsA (group A) and 76 (66.7%) did not (group B). The two groups were comparable with regard to age, gender, duration of psoriasis, family history of psoriasis, ethnicity and education. A statistically significant difference was noted between the average scores of patients with PsA and those with psoriasis but without arthritis (Mean (95% Confidence Interval)): PASE symptoms (24.2 (21.67–26.76), 12.3 (11.01–13.52) P<0.0001, respectively), PASE functional (26.02 (23.28–28.77), 11.75 (10.42–13.08) P<0.0001, respectively), PASE total (50.24 (43.32–55.15), 24.04 (21.63–26.45) P<0.0001, respectively) and ToPAS (8.26 (7.58–8.95), 4.4 (3.92–4.9) P<0.0001, respectively). The sensitivity and specificity of the PASE questionnaire were 71.1% and 89.5%, respectively, and those of the ToPAS questionnaire were 52.6% and 93.4%, respectively. The area under the ROC curve (AUC) was 0.9093 and 0.8901 for the PASE and ToPAS questionnaires, respectively. The difference between the AUC's (0.0192) was not significant (P=0.59).

Conclusion: The ToPAS and PASE questionnaires identified PsA patients with moderate to high sensitivity and specificity among Israeli patients with psoriasis. No statistically significant difference in the performance of the two questionnaires appeared, although the PASE questionnaire had higher sensitivity. Administering the questionnaires may facilitate early detection, referral and treatment of psoriatic arthritis patients.

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Assessment of the T1-Weighted Sequence Is Essential in Defining a Positive MRI Scan of the Sacroiliac Joints in Spondyloarthritis. Ulrich Weber[1], Veronika Zubler[1], Susanne Juhl Pedersen[2], Kaspar Rufibach[3], Robert GW Lambert[4], Stanley Chan[4], Mikkel Ostergaard[5] and Walter P. Maksymowych[4]. [1]Balgrist University Hospital, Zurich, Switzerland, [2]Glostrup Hospital, Copenhagen, Denmark, [3]University of Zurich, Zurich, Switzerland, [4]University of Alberta, Edmonton, AB, [5]Copenhagen University Hospital at Glostrup, Glostrup, Denmark

Background/Purpose: Inflammation on MRI of the sacroiliac joints (SIJ) in patients with spondyloarthritis (SpA) is a major criterion in the Assessment of SpondyloArthritis (ASAS) classification criteria for axial SpA, which are

based on expert clinical opinion as gold standard. The definition of a positive SIJ MRI in the ASAS criteria was generated by consensus among experts. Studies using a data-driven approach are scarce. We aimed to assess candidate definitions for a positive SIJ MRI using both clinical gold standard and confidence in the diagnosis of SpA according to global assessment of MRI (T1-weighted and STIR sequences) by expert readers.

Methods: The study population comprised 2 independent cohorts (cohort A/B) of 157 consecutive patients with back pain ≤50 years newly referred to 2 university clinics, and 20 healthy controls. Patients were classified according to clinical examination and pelvic radiography as having non-radiographic SpA (n=51), ankylosing spondylitis (n=34), or mechanical back pain (n=72). SIJ MRI were assessed by 4 blinded readers according to a standardized module. Readers recorded their level of confidence in the diagnosis of SpA by global evaluation of the MRI scan on a 0–10 scale (0 = definitely not SpA; 10 = definite SpA). An MRI-based gold-standard criterion for SpA was pre-specified as the majority of readers (≥3/4) recording a confidence of 8–10. We estimated the type and extent of involvement according to number of affected SIJ quadrants attaining specificity of '90% for SpA using ROC analysis according to both clinical and MRI-based gold-standard criteria.

Results: The agreement between 4 readers regarding confidence for MRI-based global assessment of SpA was substantial with kappa of 0.76/0.80 for cohort A/B. BME was recorded in up to 30.0%/24.2% of controls in cohort A/B, whereas erosion was seen in only 0%/12.1% of controls. The combination of erosion and/or BME increased sensitivity compared to either lesion alone without reducing specificity irrespective of which gold standard criterion was used.

Sensitivity and cut-off for number of affected SIJ quadrants for a pre-defined specificity ≥0.90, and AUC, for the 2 gold standards and for cohort A/B

Gold standard	Lesion	Sensitivity	Number of SIJ quadrants	AUC
MRI criterion	BME	0.91/0.83	3/2	0.97/0.91
Clinical evaluation	BME	0.73/0.48	4/4	0.91/0.75
MRI criterion	ER	1.00/1.00	1/1	1.00/1.00
Clinical evaluation	ER	0.83/0.58	1/2	0.94/0.79
MRI criterion	BME+ER	1.00/1.00	3/2	1.00/1.00
Clinical evaluation	BME+ER	0.83/0.58	4/6	0.96/0.83

AUC: Area under the curve. BME: Bone marrow edema. ER: Erosion. Number of SIJ quadrants: Cut-off for the number of affected SIJ quadrants

Conclusion: This data driven study shows that assessment of the T1-weighted sequence enhances diagnostic certainty when viewed simultaneously with the STIR and supports the case for revision of the ASAS definition of a positive MRI in SpA.

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A Randomized, Open-Label Study of Maintenance of Partial Remission with Naproxen Vs No Treatment: Results of the Infliximab As First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial, Part II. Joachim Sieper[1], Jan Lenaerts[2], Jürgen Wollenhaupt[3], Vadim Mazurov[4], L. Myasoutova[5], Sung-Hwan Park[6], Yeong W. Song[7], Ruji Yao[8], Denesh Chitkara[8] and Nathan Vastesaeger[9]. [1]Charité, University Medicine Berlin, Berlin, Germany, [2]Reuma-instituut, Hasselt, Belgium, [3]Schön-Klinik, Hamburg, Germany, [4]St. Petersburg Medical Academy, St. Petersburg, Russia, [5]Kazan State Medical University, Kazan, Russia, [6]Catholic University of Korea, Seoul, South Korea, [7]Seoul National University, Seoul, South Korea, [8]Merck Sharp and Dohme, Kenilworth, NJ, [9]Merck Sharp and Dohme, Brussels, Belgium

Background/Purpose: In patients with axial SpA who have achieved partial remission, it is unclear whether continuous treatment with NSAIDs is superior to stopping treatment.

Objectives: To investigate whether continued treatment with naproxen (NPX) was superior to discontinuing all treatment in order to maintain disease control for 6 months in early, active axial SpA patients who were in partial remission after 28 weeks of therapy with either infliximab (IFX)+NPX or placebo (PBO)+NPX.

Methods: Part I of the INFAST study was a double-blind, randomized controlled trial of IFX in biologic-naïve patients 18–48 years of age with early, active axial SpA. Patients were randomized (2:1) to receive 28 weeks of treatment with either IV IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24)+NPX 1000 mg/d or IV PBO+NPX 1000 mg/d. In Part II of INFAST, patients who had achieved ASAS partial remission at week 28 continued in Part II of the study with no IFX treatment. These patients were randomized in a 1:1 ratio to continue on NPX or to stop NPX until week 52. Patients from the 2 treatment arms in Part I were equally balanced over the 2 groups in Part II. The main outcome was the proportion of subjects who maintained ASAS partial remission at week 52. Treatment group differences were analyzed using Fisher exact tests or ANCOVA. Predictors of remission were explored using Cox regression models. A flare was defined as BASDAI ≥30 mm (on a 100 mm VAS) during 2 consecutive visits within 1–3 weeks.

Results: 41 patients were randomized to NPX and 41 to no treatment in Part II of INFAST. 78% of patients in Part II had been in the IFX+NPX arm in Part I. At week 52, similar numbers of patients in the NPX group (19/40, 47.5%) and the no-treatment group (16/40, 40.0%) met the ASAS partial remission criteria, P=0.6525. In regression analyses, patients who received NPX in Part II stayed in remission longer than those who stopped all treatment (HR=0.21, 95% CI: 0.08, 0.52). Initial therapy with IFX+NPX was a significant predictor of the duration of partial remission and sustained remission to week 52. Overall, the group data reflected low disease activity status through week 52 (BASDAI and ASDAS results in Table 1) with a slight, nonsignificant advantage for the NPX group over the no treatment group. The overall low disease activity status was consistent with the low flare rates in both groups (NPX, 1/40, 2.5% vs no treatment, 3/40, 7.5%; P=0.6153).

Table 1. Efficacy Outcomes by Treatment Group

	NPX (N=40)			No Treatment (N=40)			
Outcome	Week 28, mean	Week 52, mean	Change, mean (SD)	Week 28, mean	Week 52, mean	Change, mean (SD)	P Value
BASDAI (100 mm VAS)	7.1	12.2	5.8 (10.64)	5.4	16.9	10.9 (13.74)	0.1079
ASDAS	0.9	1.5	0.6 (0.71)	1.0	1.6	0.6 (0.63)	0.8374
ESR (mm/hr)	7.1	14.7	7.6 (11.63)	9.4	13.6	5.1(10.10)	0.4637
CRP (mg/dL)	0.37	0.69	0.29 (0.924)	0.53	0.72	0.26(0.707)	0.9930

During the follow-up period, 1 serious adverse event was reported in the no-treatment group. No deaths occurred.

Conclusion: In patients with axial SpA who reached partial remission after treatment with either IFX+NPX or NPX alone, disease activity remained low during 6 months in which NPX was maintained or all treatment was discontinued. About half of patients remained in clinical remission for 6 months. A slight advantage may occur for patients continuing NPX treatment vs no treatment at all.

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Differences in the Prevalence of Inflammatory Articular Disease in Psoriatic Patients, Applying Clinical, Ultrasound and/or Radiological Data. Implications in the Classification of Psoriatic Arthritis according to Caspar Criteria. Jose Luis Fernandez-Sueiro, S. Pertega-Diaz, JA Pinto and E. Gonzalez. Complejo Hospitalario Universitario La Coruña, La Coruña, Spain

Background/Purpose: a) To determine differences in the prevalence of inflammatory articular disease (IAD) in patients with cutaneous psoriasis when applying clinical, ultrasound (PDUS) or radiological diagnostic criteria.

b) To determine the prevalence of PsA in these patients, applying different definitions for the initial stem of the CASPAR criteria, and to compare this prevalence with that based on clinical judgment.

Methods: Descriptive, observational, cross-sectional study of 122 patients referred from the primary care with a confirmed diagnosis of cutaneous psoriasis, without arthritis.

For the diagnosis of IAD, the following criteria were used:

Peripheral arthritis: a) Clinical (TJC>0 or SJC>0 (78/76)), b) PDUS (carpal, MCP, PIP, MTsP, carpal tendons, hands, feet tendons), c) Radiological (hands and/or feet erosions).

Spine: a) Clinical (inflammatory back pain (IBP) (4/5) and/or nocturnal and VAS overall spinal pain past week >5), b) Radiological (sacroiliitis grade II unilateral or higher).

Entheseal: a) Clinical (MASES plus lateral and medial epycondile, quadriceps tendon, proximal and distal patella, plantar aponeuroses). b) PDUS (lateral and medial epycondile, quadriceps tendon, proximal and distal patella, aquilles tendon plantar aponeuroses)

Prevalence of IAD was obtained, according to different definitions. PsA prevalence was also determined according to CASPAR criteria and clinical judgement. Agreement was evaluated by the Kappa's index.

Results: Criteria for peripheral arthritis: clinical criteria 12 (9.8%), PDUS 16 (15%) and erosions 20 (19%). Of 122 patients, 41 (41.4%) met at least one of the criteria for peripheral arthritis. None of them met all three criteria.

Criteria for spinal disease: IBP 8 (12.3%), VAS overall spinal pain in the past week>5 22 (18%), unilateral sacroiliitis grade II or higher 17 (15.5%). Of the patients studied, 5 (4.4%) met the radiological criteria plus one of the clinical criteria. None of them met the 3 criteria altogether.

Criteria for enthesal disease: clinical 13 (10.7%), PDUS 40 (32.8%). Of the 122 patients, 45 (36.9%) met one of this two criteria, 8 patients met both of them.

Prevalence of inflammatory articular disease, based on clinical criteria, was 44.2% (95% CI: 33.1%–52.3%). By combining clinical, ultrasound and radiological results, the prevalence was 61.8% (95% CI: 51.8%–71.7%).

Using only clinical criteria for the diagnosis of inflammatory articular disease, PsA prevalence according to CASPAR criteria was 27.2% (95% CI: 16.9%–37.5%). Combining clinical, ultrasound and radiological criteria, the prevalence was 34.7% (95% CI: 24.6%–44.8%). Only 12 (9.8%) of the patients had PsA according to clinical judgment. Agreement between clinical judgment and CASPAR criteria was low, both when clinical criteria (Kappa=0.247) or clinical+ultrasound+radiologic criteria (Kappa=0.140) were used to define IAD.

Conclusion: The prevalence of PsA in patients with psoriasis varies from 27.2% to 34.7%, according to the definition of the initial stem in CASPAR criteria. On the other hand, only 9.8% were diagnosed of PsA based on clinical judgment. These data suggest the need for clarifying the stem definition of CASPAR criteria.

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Prevalence of Enthesitis in Psoriatic Patients: Agreement Between Clinical and Power Doppler Ultrasonography Exploration and Its Implications for the Classification of Psoriatic Arthritis. Jose Luis Fernandez-Sueiro[1], JA Pinto[1], S. Pertega-Diaz[1] and Carlos Fernandez-Lopez[2]. [1]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [2]INIBIC- Complejo Hospitalario Universitario La Coruña(CHUAC). Rheumatology Division., La Coruña, Spain

Background/Purpose: Enthesitis constitutes one of the CASPAR stem criteria for the classification of psoriasis arthritis, however as enthesitis may be clinically silent many psoriatic patients may have unnoticed enthesitis and may in fact have silent psoriatic arthritis. Objective: To determine the prevalence of enthesitis by PDUS examination in a cohort of psoriatic patients without a diagnosis of PsA. To determine the agreement between clinical exploration and ultrasound results, and the prevalence of "silent" disease according to CASPAR criteria.

Methods: Descriptive and observational cross-sectional study of 122 patients referred from the primary care with cutaneous psoriasis without arthritis, 20 healthy subjects were used as controls. The entheseal examination was performed by the MASES plus lateral and medial epycondile, quadriceps tendon, proximal and distal patella and plantar aponeuroses. PDUS was performed in longitudinal and transverse multiplanar examination (Logiq 5 PRO; General Electric Healthcare, Kyunnggi-do, Korea), using multifrequency linear array transducers (7–12 MHz) in the following enthesis: lateral and medial epycondile, quadriceps tendon, proximal and distal patella, aquilles tendon plantar aponeuroses. Active enthesitis was defined by the presence of thickness or altered echogenecity as well as the presence of vascularisation. Intraobserver realiability was verified by blindly assessed the stored baseline images 3 months after the real time examination. Prevalence of enthesitis between psoriatic patients and controls was compared with the chi-squared test. Considering PDUS results as the gold standard, sensitivity, specificity and predictive values of clinical exploration were estimated. Agreement was evaluated with the Kappa index.

Results: 107 psoriatic patients had both clinical and PDUS examination performed. 10.3% (n=11) of the patients had clinical enthesitis, whereas 70.1% (n=75) of psoriatic patients and 45% (n=9) (p=0.030; OR=2.86) of controls had PDUS findings of present or past enthesitis. 37.4% (n=40) of psoriatic

patients and 5% (n=1) of controls had active enthesitis by PDUS criteria (p=0.003; OR=11.34). Agreement between clinical exploration and PDUS to identify present enthesitis was low (Kappa index=0.182). Only 8 of the 40 patients with active enthesitis in PDUS had clinical enthesitis. Considering PDUS results as the gold standard, clinical findings showed a sensitivity of 20% (95% CI: 6.3–33.6%), specificity 95.5% (95% CI: 89.8%–100%), positive predictive value 72.7% (95% CI: 41.9%–100%), negative predictive value 66.7% (95% CI: 56.7%–76.6%). By applying CASPAR criteria, 8 (8.7%) patients would have a diagnosis of PsA based on clinical enthesitis, whereas 22 (23.9%) would have, by PDUS, a diagnosis of silent enthesal PsA.

Conclusion: The prevalence of PDUS enthesopathy in psoriatic patients without psoriatic arthritis is high, 70.1%. There is not a good agreement between clinical and PDUS findings. If active enthesitis, although clinically silent, is considered only by PDUS definitions, 23.9% of patients would meet CASPAR criteria in this study

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Simple Questions in the Dermatology Office May Reasonably Exclude, but Do Not Reliably Identify Psoriatic Arthritis Patients: Results From the Center of Excellence for Psoriasis and Psoriatic Arthritis. Neha Garg, Atul A. Deodhar, Benjamin Ehst, Andrew Blauvelt, Jennifer Ku and Brian Truong. Oregon Health and Sciences University, Portland, OR

Background/Purpose: Psoriatic arthritis (PsA) affects between 10–30% of patients with psoriasis (PsO), but is often missed when assessed in a dermatology clinic. The Center of Excellence for Psoriasis and Psoriatic Arthritis (CEPPA) is a specialized multidisciplinary clinic consisting of expert dermatologists and rheumatologists experienced in diagnosing PsO as well as PsA. We wanted to identify simple clinical questions and findings on physical examination for dermatologists to screen PsO patients for PsA so as to refer appropriate patients to rheumatology.

Methods: This is a cross-sectional study of all PsO patients seen by dermatologists in the CEPPA clinic since its inception in 2006 through 2010. Possibility of PsA was assessed by four screening questions: "Do you have a history of joint pain or swelling," "Do you have morning stiffness," "Have you ever had x-rays taken"," and "Do you have PsA". Since nail involvement is known to predict development of PsA, assessment of nail changes was included as a physical finding for screening. Quality of life (QoL) measures were assessed with validated instruments (SF12, PQOL12 and RAPID3).

Results: Of 524 patients assessed in dermatology, 237 were referred to rheumatology, 34 were lost to follow up, 203 were evaluated and 128 (24.4%) were found to have PsA. Of those who answered 'no' to all the four screening questions 95.3 % did not have PsA. However, of those fulfilling all five parameters, including the four screening questions plus nail changes, 88.9 % had PsA. Table shows the sensitivity, specificity, PPV and NPV for screening questions and nail changes individually and in combination. The median age (48 years) and smoking history (in 20%) was not significantly different in patients with and without PsA. The median body mass index (BMI) and PsO body surface area (BSA) were significantly higher in patients with PsA than those without [31.5(IQR 11) vs 28.6 (IQR 8) and 10% (IQR 15) vs 7% (IQR 12), respectively, p <0.01]. PsA patients were more likely to have nail changes (OR 12.4, 95% CI: 5.9 – 26.5, P < 0.01). Onset of PsO occurred 10 years earlier in patients with a family history of PsO than those without (median age 25 vs 38, p <0.01). Six percent of patients developed PsA before, 8% with and 86% after the onset of PsO. Ninety percent were diagnosed with PsA within 25 years of PsO onset. Mean delay in PsA diagnosis from onset of joint pain was 1 year. Compared to PsO patients, patients with PsA had significantly worse QoL scores (P < 0.01). Percent of BSA involvement with PsO did not correlate with any clinical variables.

Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of four screening questions and examination for psoriatic nail changes

	Sensitivity	Specificity	PPV	NPV
Do you have joint pain or swelling	88.7	54.7	41.8	93
Do you have morning stiffness	88.5	51	39.3	92.6
Do you have psoriatic arthritis	68.1	86.6	64.8	88.2
Have you ever had x-rays taken	56.6	73.2	43.2	82.4
Have you ever had x-rays taken	85.4	68.1	70.7	83.8
All five of the above	22.4	95.9	88.9	46.1

Conclusion: In this large cohort of PsO patients, the prevalence of PsA was 24.4%. PsA patients had significantly worse QoL than those with PsO alone. A negative response to all four screening questions correctly ruled out the diagnosis of PsA in 95.3% of patients. Positive response to all four screening questions with PsO nail changes led to a correct diagnosis of PsA in 89% of patients.

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Identification of Axial Spondyloarthritis Among Patients with Chronic Back Pain in Primary Care – How Does Determination of HLA B27 Influence the Performance of Clinical Assessments of Inflammatory Back Pain? Annalina Braun[1], Holger Gnann[2], Ertan Saracbasi[1], Joachim Grifka[3], Uta Kiltz[1], J. Schnittker[4], Katrin Letschert[5] and Juergen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Abteilung Biostatistik, GKM Gesellschaft für Therapieforschung mbH, München, Germany, [3]University of Regensburg, Bad Abbach, Germany, [4]Institut für angewandte Statistik Dr. Jörg Schnitker GmbH, Bielefeld, Germany, [5]Abbott Inc., Wiesbaden, Germany

Background/Purpose: The value of a combination of items defining inflammatory back pain (IBP) to screen for axial spondyloarthritis (axSpA) in primary care has recently been studied. However, whether and how measurement of HLA B27 may contribute to that is unclear. To study the value of HLA B27 determination for early identification of patients with axSpA in primary care.

Methods: Consecutive patients <45 years (n=950) with back pain >2 months who presented to orthopaedists (n=143) were randomized based on 4 key questions related to inflammatory back pain (IBP) for referral to rheumatologists (n=36) who made the diagnosis. HLA B27 was either assessed in primary or in secondary care in 298 patients. The predictive value of HLA B27 alone and in combination with other items for a diagnosis of axSpA was calculated. For variable selection logistic regression was applied, optimizing sensitivity, specifity and likelihood ratios using different strategies to predict axSpA.

Results: Rheumatologists saw 325 randomly selected patients. Due to missing HLA B27 values the main analysis is based on 298 patients, mean age 36 years (y), 52% female, median duration of back pain 32 months: 107 patients were diagnosed as axSpA (36%), 46 ankylosing spondylitis and 61 axial non-radiographic axSpA. A simple model with only HLA B27 as independent variable, indicates that HLA B27+ patients have an odds ratio (OR) of 12.24 to have axSpA in comparison with HLA B27- patients (sensitivity 62.6%, specifity 88.0%). The positive likelihood ratio (LR+) was 5.2 and the negative LR- 0.43. Thus, HLA B27 alone performed better than our recent 3/5 items proposal, which had a LR+ of 1.47 and LR- 0.53. Simply adding HLA B27 to those 5 criteria did not improve the LR+ substantially: for 3/6 items it was 1.64 (LR-: 0.33) and for 4/6 LR + 3.26 (LR-: 0.51). However, the simple combination of HLA B27 and/or buttock pain was 89.7% sensitive and 40.3% specific.A model based on determination of HLA B27 in primary care enabled us to analyse the performance of a two-phase strategy by dividing the patients into two groups according to their B27 status. Including additional variables to HLA B27+ patients did not improve the overall performance. However, in the HLA B27- group the following items were most relevant: improvement by movement, buttock pain and psoriasis. Moreover, a combination of this information revealed that a young patient with chronic back pain is likely to have axSpA if HLA B27 is positive and/or if 2 or 3 of the following symptoms are present: improvement by movement, buttock pain (both sided) and history of psoriasis. This combination was 80.4% sensitive and 75.4% specific (LR+: 3.27 and LR-: 0.26).

Conclusion: This study shows that patients with axSpA can be identified with or without knowledge of HLA B27 based on questions specific for IBP in primary care. However, since models including HLA B27 had better predictive results in this study, it seems to be more useful to generally determine HLA B27 in all patients with chronic back pain of young age in primary care to further reduce the delay in diagnosing axSpA.

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A Reduction in Ultrasound Synovitis Score Discriminates Between Clinical Responders and Non-Responders and Is Predictive for a Favourable Clinical Outcome in Early Psoriartic Arthritis. Axel P. Nigg[1], Anna M. Malchus[1], Joerg C. Prinz[2], Mathias Gruenke[1] and Hendrik Schulze-Koops[1]. [1]Medizinische Klinik IV, University of Munich, Munich, Germany, [2]Department of Dermatology, University of Munich, Munich, Germany

Background/Purpose: Accurate monitoring of disease activity in early PsA is limited by the potential underestimation of inflammation by clinical examination, the absence of disease-specific biochemical markers and heterogeneity of clinical manifestations. Sensitive and reliable diagnostic modalities enabling visualization of early inflammatory changes are considered as useful tools for monitoring the response to therapy. The aims of this prospective study were to assess the utility of musculosceletal ultrasound (US) in detection of inflammatory changes in early PsA and to analyze the association of changes in a semiquantitative ultrasound score on the overall clinical response, defined by EULAR response criteria and MDA (minimal disease activity).

Methods: 51 patients with early PsA (onset of symptoms <5 years) naive to immunosuppressive treatment were eligible for study inclusion (disease duration 18.6 months). Patients were evaluated by US and clinically (baseline, 3/6/12 months). In each patient, 56 joints were examined by Grey-Scale-US (GSUS) and power doppler (PDUS). US findings were scored separately on a 0–3 semi-quantitative scale. US synovitis score was calculated by adding the GSUS and PDUS scores for all joints examined. Clinical assessment included TJC68, SJC66, VAS for disease activity (patient/physician), DAS28-CRP, LDI, HAQ and CRP. Treatment was initiated and modified at the discretion of the primary rheumatologist following international recommendations. Criteria for EULAR response and minimal disease activity (MDA) (Coates L. et al.) were defined for each follow-up period.

Results: Clinical responders were more likely to have higher US scores and PDUS scores at baseline and showed a significantly higher relative reduction of the mean US synovitis and the mean PDUS score during follow-up intervals compared to non-responders. A reduction of the ultrasound score after 3 months of systemic treatment was predictive for achieving or maintaining a good/moderate EULAR response (OR 3.64, p=0.21) or MDA respectively (OR 6.01, p=0.05) after 6 and 12 months. Reduction of ultrasound inflammatory activity during systemic treatment was not only detected in symptomatic joints but also in those joints with subclinical inflammation, however clinical responders showed a tendentially larger relative reduction of subclinical synovitis than non-responders.

Conclusion: Reduction of inflammatory changes detected by US during systemic treatment allows discrimination between clinical responders and non-responders (defined by EULAR response criteria and MDA) in early PsA. A reduced US synovitis score 3 months after initiation of treatment is predictive for a favourable clinical outcome after 6 and 12 months. Longitudinal analysis of subclinical synovitis in responders and non-responders reveal evidence that subclinical US findings have to be regarded as a pathophysiologically relevant pre-stage of clinical synovitis.

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Performances of the ASAS Axial Spondyloarthritis Criteria for Diagnosis and Classification Purposes in Patients Visiting a Rheumatologist Because of Chronic Back Pain: The Declic Study. Anna Moltó[1], Simon Paternotte[1], Denis Comet[2], Cécile Hacquard-Bouder[3], Martin Rudwaleit[4], Pascal Claudepierre[5], Désirée van der Heijde[6] and Maxime Dougados[1]. [1]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [2]Axonal, Nanterre, France, [3]Abbott France, Rungis, France, [4]Endokrinologikum Berlin, Berlin, Germany, [5]Université Paris Est, Laboratoire d'Investigation Clinique (LIC) EA 4393, AP-HP, Hôpital Henri-Mondor, Rheumatology department, Creteil, France, [6]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: To evaluate the performances at diagnosis (sensitivity [Se], specificity [Spe], positive and negative predictive values) and study visit (classification purpose) of the ASAS criteria in axial spondyloarthritis (SpA) in patients visiting their rheumatologist for chronic back pain (CBP). Secondary objectives: identifying the most contributive item to diagnosis/classification of SpA, evaluating the performances of each arm of the ASAS criteria and other SpA criteria's performances.

Methods: Multi-centric, cross-sectional. *Patients:* history of CBP before the age of 40 visiting a rheumatologist in France. *Data:* a) items of the different sets of criteria, checking if present at diagnosis or at study visit; b) diagnosis of the rheumatologist at study visit. *Statistical analysis:* description of the population. Rheumatologist's diagnosis was considered as the "gold standard" for the estimation of all psychometric properties.

Results: 1210 patients were included for our analysis. At diagnosis, Se was 0.76 and Spe 0.94 for ASAS axial criteria and Se 0.87 and Spe 0.92 for classification. LR+ of the ASAS axial criteria was 13.6 for diagnosis and 10.30 for classification. The most contributive item to diagnosis and classification was X-ray sacroiliitis, followed by MRI sacroiliitis for diagnosis and history of uveitis for classification. MRI+ imaging ASAS criteria were more sensitive for diagnosis and classification, but as specific as ASAS clinical criteria.

Conclusion: we confirm the validity of the ASAS criteria in diagnosis and classification, in a clinical rheumatological setting of patients with CBP, with good performances compared to the other axial SpA criteria, and for any of their arms.

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Eos Imaging Could Replace Conventional Computed Radiography for Ankylosis Assessment in Axial Spondyloarthritis. Anna Moltó[1], Veronique Freire[2], Antoine Feydy[2], Simon Paternotte[1], Walter P. Maksymowych[3], Mathilde Benhamou[4], François Rannou[4], Maxime Dougados[1] and Laure Gossec[1]. [1]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [2]Radiology B Department, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France, [3]University of Alberta, Edmonton, AB, [4]Physical Medicine and Rehabilitation Service, Paris-Descartes University, Cochin Hospital, Paris, France

Background/Purpose: EOS® is a new osteoarticular imaging modality with significantly lower radiation than conventional computed radiography (CR). However, the diagnostic performance of this 2D biplanar imaging technique has yet to be evaluated and compared to CR. Diagnosis and follow-up of spondyloarthritis (SpA) by assessment of sacroiliitis and spinal ankylosis with the mSASSS is usually assessed by CR. We aimed to establish whether EOS could replace CR for SpA diagnosis and follow-up by: 1) validating the diagnosis of sacroiliitis by EOS versus by pelvic CR. 2) validating the analysis of spine involvement in SpA by EOS vs spine CR.

Methods: Study design: Observational, single center, prospective. Patients: 108 patients were included. 56 had a definite diagnosis of axial SpA (according to the rheumatologist). In order to assess the specificity of the imaging, 52 control patients with chronic mechanical back pain were enrolled. Data collected: demographic and disease data. All patients underwent CR and 2D EOS imaging of the pelvis and entire spine. Radiologic analysis: a) The diagnostic capacity of 2D EOS and CR for detection of sacroiliitis between SpA patients and controls was compared by calculation of sensitivity (Se) and specificity (Spe). b) Agreement between modalities was compared for spinal involvement scored with the mSASSS, and for sacroiliitis scored according to the modified New York (mNY) score. c) Subjective global visibility of anatomical structures and lesions on both modalities was assessed by the readers and compared by visual numeral scale (in a 0–10 scale). Two independent readers performed a blinded reading of both imaging modalities. Statistical analysis: Weighted kappa and ICC were used with a defined non-inferiority limit of 0.7.

Results: Demographics: Among SpA patients: Mean (SD) age was 48.4 (±15.1) years, sex ratio was 42 males/14 women. Disease duration was 16.6 (±11.2) years. Fifty-two (92.9%) patients fulfilled the ASAS criteria. Thirty-seven (74.0%, n=50) patients presented with sacroiliitis according to mNY criteria according to medical files. Radiologic analysis: a) *sacroiliitis diagnostic capacity:* Sen was 0.62 and 0.63 for EOS and CR, respectively, and Spec was 0.84 for both modalities; b) *agreement between the 2 imaging modalities:* Spine: ICC (95%CI) agreement between EOS and CR by mSASSS scoring was 0.82 (0.71–0.89). Sacroiliac joints: Kappa (95% CI) agreement for the scoring of sacroiliac joint abnormalities according to the mNY criteria between EOS and CR was 0.5 (0.26–0.74); c) *Subjective global visibility of EOS in SpA:* was evaluated at 7.2 (±0.8), vs. 8.2 (±0.9) for CR (p<0.0001).

Conclusion: This study suggests that EOS 2D imaging could replace CR for the diagnosis and follow-up of ankylosis of the spine in SpA, since radiation exposure is much lower However its place in the diagnosis of sacroiliitis remains unclear. Forward studies using MRI as a discriminative modality are ongoing.

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Effect of Certolizumab Pegol On the Multiple Facets of Psoriatic Arthritis As Reported by Patients: 24 Week Patient Reported Outcome Results of a Phase 3 Double Blind Randomized Placebo-Controlled Study. Dafna D. Gladman[1], Roy M. Fleischmann[2], Geoffroy Coteur[3], Franz Woltering[4] and Philip Mease[5]. [1]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [2]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [3]UCB Pharma, Brussels, Belgium, [4]UCB Pharma, Monheim, Germany, [5]Seattle Rheumatology Associates, Seattle, WA

Background/Purpose: RAPID-PsA (NCT01087788) reports efficacy and safety of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, in psoriatic arthritis (PsA).[1] The effect of different imputation methodologies on radiographic progression outcomes is reported.

Methods: The ongoing 158 week (Wk) RAPID-PsA trial is double-blind and placebo (PBO) controlled to Wk24, dose-blind to Wk48 and then open label to Wk158. Recruited patients (pts) had active PsA and had failed ≥1 DMARD. Pts could have been secondary failures to 1 previous anti-TNF. Pts were randomized 1:1:1 to PBO or 400mg CZP at Wk0, 2 and 4 (loading dose, LD) followed by either 200mg CZP every 2 wks (Q2W) or 400mg CZP every 4 wks (Q4W).[1] Pre-specified analyses included change from baseline (CFB) in modified Total Sharp Score (mTSS) (average scores of 2 independent readers), the primary endpoint, and % non-progressors (mTSS CFB ≤0). In the pre-specified imputation methodology performed in all randomized pts minimum observed baseline (BL) score for missing BL values (0) and maximum observed Wk24 score for missing Wk24 values (356.5) in pts with <2 available x-rays were imputed. Post hoc analyses used alternative methods of imputation for change from BL in mTSS for pts with <2 available x-rays, including no imputation, imputation with the median, mean or maximum CFB in mTSS scores.

Results: 409 pts were randomized. BL demographics were similar between groups. 19.1% and 19.8% of PBO and CZP (combined dose) pts received prior anti-TNF. The pre-specified imputation analysis inappropriately overestimated radiographic progression in all arms including PBO (LS mean 28.9 and 18.3 for PBO and CZP (combined dose) respectively p≥0.05) (Table) as pts with missing Wk24 values were assigned to a change from BL in mTSS of up to 356.5, which is an implausible progression with respect to clinical practice. Significantly more pts were non-progressors in both CZP groups (200mg Q2W and 400mg Q4W) compared with PBO (83.3% and 76.3% vs 34.6%, respectively, p<0.001). Multiple post-hoc analyses showed that CZP effectively inhibited radiographic progression compared to PBO (Table). ACR20 response at Wk12 was significantly higher in both CZP arms (200mg Q2W and 400mg Q4W) vs PBO (58.0% and 51.9% vs 24.3%, respectively, p<0.001). The safety profile was similar to that observed with CZP in RA.

Table. LS mean CFB in mTSS at Wk24, evaluated using an analysis of covariance model

		LS mean mTSS CFB at Wk24 (SE)			
	Imputation in pts with <2 x-rays available~	PBO (n = 136)	CZP 200mg Q2W (n = 138)	CZP 400mg Q4W (n = 135)	CZP 200mg Q2W + CZP 400mg Q4W (n = 273)
Pre-specified†	Minimum observed score (0) if missing BL Maximum observed score (365.5) if missing Wk24	28.92 (7.73)	11.52 (7.59)	25.05 (7.92)	18.28 (6.07)
Post-hoc 1*	No imputation	0.29 (0.08)	0.01 (0.08)**	0.12 (0.08)	0.06 (0.06)**
Post-hoc 2*	Median mTSS change from BL of all pts observed	0.28 (0.07)	0.01 (0.07)**	0.11 (0.08)	0.06 (0.06)**
Post-hoc 3*	Mean mTSS change from BL of all pts observed	0.28 (0.07)	0.01 (0.07)**	0.11 (0.08)	0.06 (0.06)**
Post-hoc 4*	Maximum mTSS change from BL of all pts observed	0.66 (0.13)	0.18 (0.13)**	0.52 (0.13)	0.35 (0.10)**
Post-hoc 5*	Maximum mTSS change from BL by treatment group	0.39 (0.11)	0.14 (0.11)	0.49 (0.12)	0.31 (0.09)

For PBO pts who escaped early to CZP, the Wk 24 values, if available, were ignored and linearly extrapolated
†21 pts had <2 x-rays, number of pts was equally distributed between treatment groups
*26 pts had <2 x-rays, as in post-hoc analyses the x-rays had to be at least 8 weeks apart;
~ for pts with 2 x-rays but missing Wk24 or BL film, linear extrapolation was performed in all approaches
**p < 0.05 vs PBO

Conclusion: Conventional radiographic imputation methods showed that CZP effectively inhibited radiographic progression in pts with PsA. Significantly fewer patients had progression with either CZP dose compared to placebo. The highly conservative pre-specified imputation method resulted in an unrealistic assessment of progression in all arms including PBO Differences in methodologies for imputing missing radiographic data can greatly impact assessment and reporting of mean changes from BL in mTSS.

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Rapid Improvements in Patient Reported Outcomes with Certolizumab Pegol in Patients with Axial Spondyloarthritis, Including Ankylosing Spondyltitis and Non-Radiographic Axial Spondyloarthritis: 24 Week Results of a Phase 3 Double Blind Randomized Placebo-Controlled Study. Joachim Sieper[1], Alan J. Kivitz[2], A.M. Van Tubergen[3], Atul A. Deodhar[4], Geoffroy Coteur[5], Franz Woltering[6] and Robert B. M. Landewé[7]. [1]Charité University Medicine, Berlin, Germany, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Maastricht University Medical Center, Maastricht, Netherlands, [4]Oregon Health & Science University, Portland, OR, [5]UCB Pharma, Brussels, Belgium, [6]UCB Pharma, Monheim, Germany, [7]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Heerlen, Netherlands

Background/Purpose: Axial spondyloarthritis (axSpA) is a form of spondyloarthritis (SpA) that includes both ankylosing spondylitis (AS) and non-radiographic axial SpA (nr-axSpA), as defined by the ASAS criteria. Both subgroups of patients (pts) have been shown to have a similar burden on Quality of Life (QoL).[1] A recent survey estimated that SpA may affect up to 1.4% of the US population.[2] Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF that improved patients reported outcomes (PRO) in rheumatoid arthritis (RA).[3] RAPID-axSpA (NCT01087762) is the first report of the effect of CZP on PRO in axSpA.

Methods: The ongoing 158-Wk RAPID-axSpA trial is double-blind and placebo controlled to Wk24, dose-blind to Wk48 and then open label to Wk158. Recruited pts had adult-onset active axSpA as defined by the ASAS criteria,[1] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, spinal pain ≥4 on a 10 point NRS, and CRP > upper limit of normal or sacroiilitis on MRI. Pts must have failed ≥1 NSAID. Pts could have been secondary failures to 1 previous TNF inhibitor. The pt population reflected the broad axSpA population, including AS pts also meeting the modified New York criteria and nr-axSpA pts who met the ASAS MRI or clinical criteria. Pts were randomized 1:1:1 to placebo (PBO), or 400mg CZP at week (Wk) 0, 2 and 4 (loading dose, LD) followed by either 200mg CZP every 2 weeks (Q2W) or 400mg CZP every 4 weeks (Q4W). Pts receiving PBO who failed to achieve an ASAS20 response at both Wks14 and 16 were rescued and randomized at Wk16 to receive CZP 200mg Q2W or CZP 400mg Q4W following LD. The primary endpoint was ASAS20 response at Wk12. PRO endpoints included SF-36 physical component summary (PCS), physical function (BASFI), total spinal pain (NRS), fatigue (NRS from BAS-DAI), Ankylosing Spondylitis Quality of Life (AsQoL), Sleep Problems Index II domains of the MOS Sleep scale (MOS-SPI), and SF-36 mental component summary (MCS) and domains. All PRO were analyzed on the full analysis set using analysis of covariance on change from baseline (CFB) with last observation carried forward imputation.

Results: 325 pts were randomized. Baseline characteristics were similar between groups. Improvements in the CZP-treated groups were observed in pain NRS, fatigue NRS, BASFI and AsQoL from the first measurement at Wk1 through to Wk24 compared to PBO. Pts in both CZP-treated dosage arms had greater improvements in SF-36 PCS. compared to PBO (Table). Improvements were also seen in MOS-SPI, SF-36 MCS and domains.

Table 1. Mean BL scores (SD) and mean change from baseline (CFB) at Wk12 and Wk24 in PRO

Mean (SD)			PBO (n = 106)	CZP 200mg Q2W (n = 111)	CZP 400mg Q4W (n = 107)
SF-36#	PCS	BL	32.63 (7.79)	32.05 (7.20)	32.79 (7.62)
		Wk12	+2.36 (6.53)	+9.07 (8.41)*	+8.13 (8.22)*
		Wk24	+2.71 (6.63)	+9.86 (8.55)*	+8.86 (9.66)*
	MCS~	BL	39.47 (12.67)	41.9 (11.78)	40.65 (11.89)
		Wk12	+1.22 (10.56)	+3.32 (9.36)	+4.08 (10.81)
		Wk24	+0.62 (10.96)	+4.69 (10.16)	+5.42 (10.85)
BASFI		BL	5.49 (2.13)	5.26 (2.28)	5.40 (2.34)
		Wk12	−0.56 (1.71)	−1.92 (2.33)*	−2.01 (2.20)*
		Wk24	−0.52 (2.10)	−2.39 (2.35)*	−2.30 (2.32)*
Total Spine Pain NRS		BL	7.08 (1.85)	7.06 (2.04)	6.92 (1.78)
		Wk12	−1.40 (2.04)	−3.03 (3.00)*	−2.91 (2.47)*
		Wk24	−1.33 (2.16)	−3.25 (3.00)*	−3.21 (2.71)*
Fatigue NRS		BL	6.48 (2.03)	6.77 (1.78)	6.74 (1.91)
		Wk12	−0.85 (2.21)	−2.25 (2.41)*	−2.21* (2.43)*
		Wk24	−0.85 (2.49)	−2.62 (2.54)*	−2.75 (2.58)*
AsQoL		BL	12.06 (4.24)	11.83 (4.18)	11.34 (4.58)
		Wk12	−1.31 (3.70)	−4.59 (4.98)*	−4.17 (4.77)*
		Wk24	−1.70 (4.32)	−5.13 (5.36)*	−5.10 (4.99)*
MOS sleep scale~	Sleep Problems Index II	BL	49.48 (19.00)	49.71 (20.47)	48.22 (17.80)
		Wk12	−4.78 (14.49)	−10.43 (17.36)	−10.77 (15.97)
		Wk24	−4.02 (16.14)	−12.65 (18.49)	−12.94 (17.19)

*p-value ≤0.001; ~No statistical testing was performed on these variables. All statistical analysis was performed on the Least Squares (LS) mean (not shown).
#For SF-36 component summaries, positive CFB indicates improvement.

Conclusion: Both dosing regimens of CZP rapidly improved all PRO including pain, fatigue, physical function and QoL of axSpA pts. CZP effectively improved patient-relevant outcomes in the broad population of axSpA pts classified using the ASAS criteria.

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Utility of Dual-Energy X-Ray absorptiometry Scanning and Risk of Osteoporosis in Ankylosing Spondylitis; A Prospective Study. Marina N. Magrey[1] and Muhammad Asim Khan[2]. [1]Case Western Reserve University School of Medicine at MetroHealth Medical Center, Cleveland, OH, [2]CASE at MetroHealth Med Center, Cleveland, OH

Background/Purpose: Conventional DXA imaging of spine and hip to measure bone mineral density (BMD) has limitations in patients with ankylosying spondylitis (AS) as their spinal DXA measurements may be falsely elevated due to syndesmophyte formation and ligament ossification. Therefore, we investigated the correlation of hip and spine BMD measurements in patients with AS to determine if hip DXA will prove clinically useful while avoiding the confounding effect of spinal disease. We also studied risk factors for osteoporosis (OP) in AS.

Methods: We identified patients from our AS registry ≥ 18 years of age who met the ASAS (Assessment of Spondyloarthritis International Society) classification criteria for AS. Patients with thyroid and parathyroid disease, chronic liver or kidney disease, on anti-convulsant medications, surgical spinal fusions and hip arthroplasties were excluded. Demographic and clinical data were recorded and included HLA- B27 status, disease duration >5 years, presence of syndesmophytes on lumbar X-ray. Disease activity was measured using Bath AS Disease Activity Index (BASDI). BMD was measured using a Hologic machine and interpreted using ISCD 2005 guidelines and WHO criteria for definition of OP. Patients were divided into 3 groups- osteoporosis (T-score< −2.5), osteopenia (T-score of − 1.0 and −2.5) and normal (T-score of >−1.0). In addition, ESR and blood levels of CRP, and 25-hydroxy vitamin D were measured.

Correlation between the lowest T-scores of hip (total hip or femoral neck) and lumbar spine was measured using Spearman's correlation coefficient (rho). Chi-square and odds ratio using logistic regression were used to assess the association of the purported risk factors for OP in these patients.

Results: We identified 101 patients with AS; 26.2 % females, and 25.2 % African-Americans (AA). The mean age was 43.0 years (±13.7) in patients with normal BMD versus 47.8 years (±14.4) with OP and osteopenia (p= 0.0867), and 40.5 % of patients had syndesmophytes on lumbar Xray. Prevalence of OP = 16.8%, osteopenia = 36.6% and 46.5% had normal BMD. There was moderate correlation between the lowest T-values of hip and lumbar spine (AP view), rho= 0.59 (figure 1). The AA with AS had higher odds of having osteoporosis compared to Whites; Odds ratio (OR) = 5.3 (1.03–26.84) (95% CI), p = 0.045 and also AS patients with high CRP levels had higher odds of having OP, OR= 4.1(1.22–13.97) (95% CI), p=0.0226. There was no association between OP and age, sex, BASDI, vitamin D levels, HLAB27 positivity, and ESR.
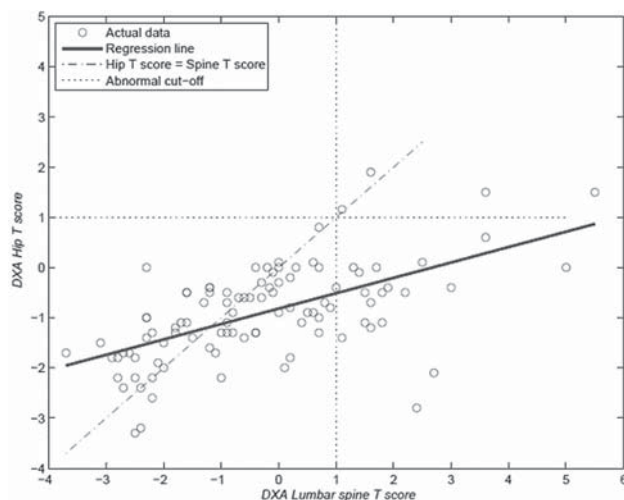
Conclusion: Our results demonstrated a correlation between T-scores of hip and lumbar spine in patients with AS with disease duration of > five years, suggesting that DXA of the hip and the lumbar spine are useful in diagnosing OP in patients with AS. Elevated CRP level increases the risk of OP in patients with AS. African-Americans with AS are at higher risk of developing OP compared to whites.

Disclosure: **M. N. Magrey**, None; **M. A. Khan**, None.

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Proteomic Profiling of Synovial Fluid Reveals Candidate Psoriatic Arthritis Biomarkers. Daniela Cretu[1], Ihor Batruch[2], Punit Saraon[1], Dafna Gladman[3], Fawnda Pellett[3], Eleftherios Diamandis[2] and Vinod Chandran[4]. [1]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON, [4]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Psoriatic arthritis (PsA) is a unique form of arthritis occurring in 30% of psoriasis patients. There is a high prevalence of undiagnosed PsA in patients seen in dermatology clinics and identifying soluble biomarkers for PsA will help in screening psoriasis patients for appropriate referral to a rheumatologist, as well as provide further insight into disease pathogenesis. However, identification of novel biomarkers in peripheral blood is difficult and unreliable. Potential PsA biomarkers are likely to originate in sites of inflammation such as inflamed joints and subsequently enter systemic circulation. Our purpose was to identify candidate PsA biomarkers by conducting high-throughput quantitative proteomic analysis of synovial fluid from inflammatory and non-inflammatory arthritides.

Methods: Using strong cation exchange chromatography, followed by LC-MS/MS on an LTQ-Orbitrap mass spectrometer in conjunction with database searching for protein identification and quantification, we extensively characterized the proteomes of SF from 3 individual PsA patients, as well as 2 Rheumatoid Arthritis (RA), 2 Gout, 3 Late Osteoarthritis (LOA), and 3 pooled non-inflammatory (NI) controls. All samples were analysed in triplicates, and extracted ion current (XIC) intensities were used to calculate protein abundance ratios. Two strategies were then employed for identification of candidate biomarkers: (1) examination of differential protein expression between the PsA, RA, Gout, LOA, and Non-Inflammatory controls, and (2) tissue specificity analysis through mining of publicly available databases

Results: A total of 594 non-redundant proteins were identified with one peptide (384 with two-peptides or more) in SF from all arthritis subsets, with a false discovery rate <1.5%. Of the 521 high-confidence proteins that were quantified from all patient groups, there were significant quantitative differences in 89 PsA SF-derived proteins compared to other arthritides. Following additional manual filtering, we obtained a preliminary list of 35 proteins as increased in PsA compared to all arthritic and non-inflammatory controls. Gene ontology (GO) analysis classified these proteins into categories pertaining to five main biological processes: complement activation, defense response, immunoglobulin mediated response, response to wounding, and extracellular matrix remodelling, all of which are attributes of PsA. The candidate proteins include also COMP, CD14, and MMP2, all of which have been previously investigated as PsA biomarkers.

Conclusion: Quantitative proteomic profiling of synovial fluid has the potential to identify candidate PsA screening biomarkers. Verification and validation of these markers in SF and serum, respectively, is essential and is currently under way.

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Performance of Magnetic Resonance Imaging in Detection of Chronic Structural Changes in Sacroiliac Joints As Compared to Conventional X-Rays in Axial Spondyloarthritis. Denis Poddubnyy[1], Inna Gaydukova[2], Hildrun Haibel[1], In-Ho Song[1] and Joachim Sieper[1]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Saratov State Medical University, Saratov, Russia

Background/Purpose: Conventional x-rays of the sacroiliac joints (SIJ) remains the first imaging method in case of suspicion of axial spondyloarthritis (SpA). Moreover, a diagnosis of definite ankylosing spondylitis (AS) according to the modified New York criteria relies on the presence of definite radiographic sacroiliitis (SI). Magnetic resonance imaging (MRI) is a reliable method of detection of active inflammatory changes in the SIJ (active SI) and is potentially able to detect also chronic structural changes (such as sclerosis, erosions, and ankylosis) visible on conventional X-rays. Furthermore, chronic changes might be better visible in MRI because of tomography and MRI is not associated with radiation exposure. However, reliability of MRI in detection of chronic structural changes in SIJ remains unclear.

This study was aimed at comparing the performance of MRI in comparison to conventional X-rays in detection of chronic structural changes in patients with axial SpA.

Methods: We included 112 patients with definite axial SpA (68 with AS and 44 with non-radiographic axial SpA – nr-axSpA), for whom sets consisting of an X-rays of the SIJ and an MRI of the SIJ (at least in a T1-weighted sequence) performed at the same time point were available. X-rays of the SIJ were scored according to the modified New York criteria (grade 0 to grade IV) and according to the recently proposed new scoring system [1], which contains separate scores for subchondral sclerosis (score 0–2), erosions (score 0–3), and joint space changes (score 0–5) in each SIJ. MRIs of the SIJ (T1) were scored in the similar way for the same structural changes. In addition, readers were asked to provide an overall impression of the damage extent on MRI according to the scoring system of the modified New York criteria. X-rays and MRIs were scored separately by two trained readers, which were blinded for all clinical data and for the diagnosis of AS or nr-axSpA.

Results: 224 SIJ from 112 patients were available for the analysis. There was a moderate agreement between MRI and X-ray regarding definite subchondral sclerosis scored by both readers (Kappa=0.46, p<0.001), rather low agreement concerning definite erosions (Kappa=0.11, p=0.07), moderate agreement regarding definite joint space abnormalities (Kappa=0.41, p<0.001) and very good agreement regarding joint ankylosis (Kappa=0.85, p<0.001). Importantly, there was a good overall agreement regarding the presence of definite SI: in 84% of the SIJ (128 out of 153) with definite X-rays SI it was also seen in MRI. Interestingly, in 16% of the cases definite SI was seen in X-rays only in 18% of the cases – in MRI only. Furthermore, on the patients' level, SI fulfilling the modified New York criteria was confirmed on MRI in 81% of the cases (55 out of 68).

Conclusion: MRI demonstrated good overall performance regarding detection of chronic structural changes in the SIJ and was able to confirm the presence of definite sacroiliitis in more than 80% of the cases.

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Prevalence and Predictors of Significant Liver Fibrosis in Methotrexate Treated Rheumatoid and Psoriatic Arthritis Patients Using Transient Elastography (fibroscan). WC Chan, ML Yip and CK Loo. Kwong Wah Hospital, Kowloon, Hong Kong

Background/Purpose: Methotrexate (MTX) is an anchor drug in the treatment of Rheumatoid (RA) and Psoriatic arthritis (PSA)and is the first line therapy in RA according to international guidelines and recommendations. However, there is constant concern on drug related hepatoxicity in long term use, particularly in patients with psoriasis. Guidelines had laid out the need for liver biopsy depending on the cumulative methotrexate dose but were controversial as liver biopsy itself carries considerable risk. Fibroscan (transient elastography TE) is a newly developed non-invasive technique to examine liver stiffness and hence liver fibrosis. Validation and correlations have been made in various liver diseases for fibrosis and cirrhosis detection and screening.

Methods: RA and PsA patients in a local rheumatology clinic were recruited. Patients with known pre-existing liver diseases were excluded. Demographic variables including age, sex, alcohol use, disease characteristics, concurrent co-morbidities, cumulative and duration of MTX use were recorded. TE were performed on these patients and liver stiffness were measured. A stiffness level of 7.9 kPa was used as cut off value as probable significant liver fibrosis and liver biopsy was offered.

Results: A total of 50 PsA and 215 RA patients were contacted and 128 (33 PsA,95 RA) of them were eligible for TE. Average disease duration was 8 years (SD 6.2). Mean cumulative MTX dose was 2427.3 mg (SD 2330.6). 55 % of patients had cumulative dose of MTX > 1500 mg and 21 % had cumulative dose of MTX > 3500 mg. Mean duration of MTX use was 4.2 years (SD 3.59). PsA patients had higher body mass index (25.2 vs 23.2, p=0.02), higher percentage of insulin resistance (45.5 vs 21.1 %, p=0.07) and abnormal HDL cholesterol level (63.3 vs 37.9 %, p=0.01) at baseline but lower cumulative MTX dose use (1775 mg vs 2654 mg, p=0.06) than RA patients. Mean liver stiffness was significantly lower in RA- 4.67kPa (SD 1.42) than in PsA patients- 5.67 kPa (SD 3.34). In univariate analysis, liver stiffness determined by TE was found to be positively associated with the presence of psoriasis, age, insulin resistance, hypertension, metabolic syndrome and duration of MTX use. However, only presence of psoriasis (β=0.947; p=0.022), insulin resistance (β=0.815; p=0.043) and age (β=0.058; p<0.001) was found to be significant associative factors on multivariate analysis. At a cutoff point of 7.9 kPa, only 4.9 % of patients (3 RA and 3 PsA) had probable significant fibrosis. All 6 patients had cumulative MTX dose > 1500 mg. However, logistic regression analysis only found that hypertension (OR= 11.02, 95% CI: 1.13–107.5, p= 0.039) to be an independent risk factor for development of significant fibrosis. There is no correlation of MTX dose, duration of MTX use, and disease entity with significant fibrosis. 2 of these 6 patients had liver biopsies performed showing mild peri-portal fibrosis and steatosis.

Conclusion: PsA patient on MTX had higher liver stiffness than RA patients on TE. However, significant liver fibrosis was not common in these patients on methotrexate. Cumulative dose of MTX was probably not related to the development of significant liver fibrosis.

Disclosure: W. Chan, None; **M. Yip**, None; **C. Loo**, None.

In Ankylosing Spondylitis, a Decrease in MRI Spinal Inflammation Predicts Improvement in Spinal Mobility Independently of Patient Reported Symptomatic Improvement. Pedro Machado[1], Robert Landewé[2], Jürgen Braun[3], Xenofon Baraliakos[3], Kay-Geert A. Hermann[4], Benjamin Hsu[5], Daniel Baker[5] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Academic Medical Center, University of Amsterdam and Atrium Medical Center, Heerlen, Netherlands, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Charité Medical School, Berlin, Germany, [5]Centocor Inc., Malvern/Philadelphia, PA

Background/Purpose: It has been previously shown that spinal mobility in ankylosing spondylitis (AS) is associated with the level of inflammation of the spine. However an association does not necessarily imply causation and only longitudinal studies can evaluate if a change in an outcome measure translates into a subsequent change in the associated measure. Our aim was to study the relationship between change in MRI spinal inflammation and change in spinal mobility in patients with AS, taking potential confounders into account.

Methods: Baseline, 24- and 102-week data of a random 80% sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort were used. Spinal mobility was expressed by the linear version of the Bath AS Metrology Index (BASMI), spinal inflammation by the AS spinal MRI activity (ASspiMRI-a) score and clinical disease activity by the Bath AS disease activity index or by the AS disease activity score (ASDAS). BASMI, ASspiMRI-a, BASDAI and ASDAS change scores were calculated (from baseline to 24 weeks and from 24 weeks to 102 weeks). The longitudinal association between change in BASMI (dependent variable) and change in ASspiMRI-a (independent variable) was investigated using generalised estimating equations (GEE). Potential confounders (change in BASDAI, change in ASDAS, change in C-reactive protein, gender, age, disease duration, body mass index, HLA-B27 status and baseline modified Stoke AS Spine Score (mSASSS)) and interactions were tested.

Results: In total 199 patients and 367 visits were analysed (31 patients did not have complete 102-week data). After taking potential confounders into account, multivariable GEE analysis showed that change in ASspiMRI-a, change in BASDAI and baseline mSASSS are longitudinally associated with change in BASMI (table 1, model A). When change in BASDAI was replaced by change in ASDAS in the multivariable model, only change in ASDAS and baseline mSASSS were significantly associated with change in BASMI, but not change in ASspiMRI-a (table 1, model B).

Table 1. GEE models for change in BASMI

Independent variable	Model A (with change in BASDAI) B (95% CI), p-value	Model B (with change in ASDAS) B (95% CI), p-value
Change in ASspiMRI-a	0.016 (0.001, 0.031), p=0.034	0.011 (−0.004, 0.026), p=0.152
Change in BASDAI/ASDAS	0.099 (0.065, 0.132), p<0.001	0.183 (0.122, 0.244), p<0.001
Baseline mSASSS	0.006 (0.003, 0.009), p<0.001	0.006 (0.003, 0.009), p<0.001

Conclusion: A decrease in MRI spinal inflammation predicts improvement in spinal mobility. This relationship is confounded by change in ASDAS but not by change in BASDAI. Spinal inflammation plays an important role in spinal mobility and therefore ASDAS (semi-objective) is a better means to follow (changes in) disease activity in AS than BASDAI (subjective). Therapeutic strategies specifically targeting MRI inflammation may contribute to improving spinal mobility of AS patients, independently of patient reported symptomatic improvement.

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Almost 40% of Patients with Chronic Back Pain Starting Before the Age of 45 Fulfill the ASAS Axial Spondyloarthritis Criteria. Manouk de Hooge, Rosaline van den Berg, Floris van Gaalen, Monique Reijnierse, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Chronic back pain is a very prevalent complaint in the general population but only a small proportion of these patients suffer from spondyloarthritis (SpA). Unfortunately, it is not clear when primary care or other physicians should refer a patient with chronic back pain to a rheumatologist. Many rheumatologists fear their practices will be overloaded with patients not having SpA if they have to see all patients with chronic back pain. Some have recommended inflammatory back pain (IBP) as the referral symptom but this is not an ideal criterion since many patients with SpA do not have IBP[1].

The purpose of this study is to describe how many patients with chronic back pain referred to the rheumatology outpatient clinic fulfill at least one of the classification criteria sets for spondyloarthritis (SpA).

Methods: We started the SpondyloArthritis Caught Early (SPACE)-project and included all (n=157) patients with chronic back pain (almost daily ≥3 months), starting before the age of 45 years of short duration (≤2 years). Patients were classified according to the modified New York (mNY), European SpA Study Group (ESSG), Amor and ASAS axial SpA classification criteria sets.

Results: In total, 93 (59.2%) patients fulfilled any of the criteria sets. Twelve (7.6%) patients fulfilled the mNY criteria; 68 (43.3%) patients fulfilled the ESSG criteria, 44 (28.0%) the Amor criteria and 60 (38.2%) the ASAS criteria for axial SpA. The overlap of the criteria is presented

in the table and the figure. Eight of the 12 patients who fulfill the mNY criteria also fulfilled all the other criteria sets. The one patient only fulfilling the mNY criteria and no other criteria sets has 'night pain' as only SpA feature.

Classification criteria sets	Patients (n)
No criteria set	64
Any criteria set	93
All criteria sets	8
All ASAS	60
All ESSG	68
All Amor	44
All mNY	12
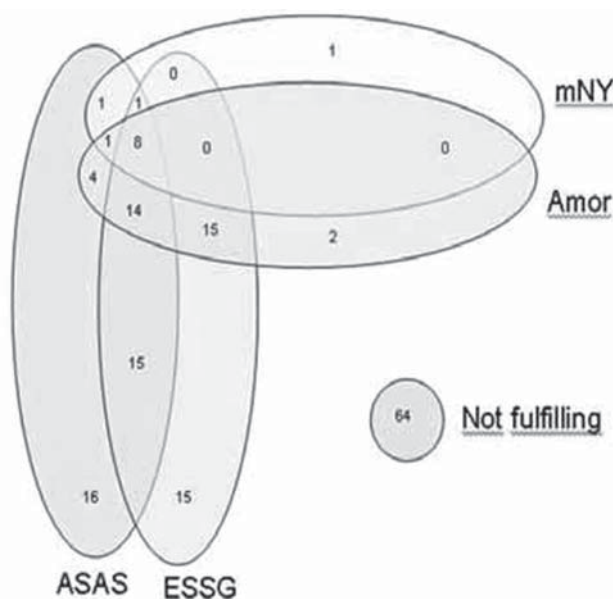
Conclusion: Approximately 60% of the patients included in the SPACE-cohort fulfill at least one of the SpA criteria sets; 38% fulfill the ASAS axial SpA criteria. The selection criteria as used in the SPACE-project are easily applicable and work very well. Almost daily chronic back pain of short duration starting before the age of 45 years (in accordance with the entry criterion of the ASAS axial SpA criteria) appears to be a very good and simple referral strategy at a rheumatology department, with a high yield of patients with SpA.

References:
[1]van den Berg R. Ann Rheum Dis 2012;71(Suppl3):566

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Fetuin A: A New Biomarker Related with Syndesmophytes in Patients with Ankylosing Spondylitis. Tugba Tuylu[1], Dilek Solmaz[1], Ismail Sari[1], Didem L. Kozaci[2], Servet Akar[3], Necati Gunay[2] and Nurullah Akkoc[4]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Adnan Menderes University School of Medicine, Aydin, Turkey, [3]Dokuz Eylul University School of Medicine Department of Internal Medicine Division of Rheumatology, Izmir, Turkey, [4]Dokuz Eylul University School Of Medicine, Department Of Internal Medicine, Division Of Rheumatology, Izmir, Turkey

Background/Purpose: In recent years, there is considerable interest regarding prediction and pathogenesis of syndesmophyte formation. Thus, several studies were conducted in order to identify the factors affecting this process. Today, biomarkers have become a very important field of research in spondyloarthropathy. In this regard, various biomarkers have been used to understand the underlying factors responsible from syndesmophyte forma-

tion. However, available data on this subject is still limited and additional information is required. In this study, we aimed to determine the levels of different biomarkers and analyze their relationships with syndesmophytes in ankylosing spondylitis (AS).

Methods: Lateral plain radiographs of the cervical and lumbar spine were used for scoring syndesmophytes. The anterior sites of the lower and upper portion of each vertebra were randomly and blindly scored by 2 experienced rheumatologists. Any presence of syndesmophytes or bridging syndesmophytes was categorized as positive. The following ELISA kits were studied: hsCRP, IL-6, dickkopf-1 (DKK-1), receptor activator of nuclear factor-κB ligand (RANKL), osteoprotegerin (OPG), bone morphogenetic protein-7 (BMP-7), and fetuin A.

Results: There were 86 patients (31 non-syndesmophyte, 65% male [M], 41.5±8.2 years; 55 with syndesmophyte, 71% M, 43.9±9.7 years) in the study group. Disease duration, age and sex distributions, BASFI and BAS-DAI were similar between the non-syndesmophyte and syndesmophyte groups (P > 0.05). However, BASMI values and current or past smoking history percentages were significantly different between the syndesmophyte negative and positive patients (P < 0.05, 3.18±1.5 vs. 4.53±1.9, and 86% vs. 58% respectively). Evaluation of soluble biomarkers revealed that the levels of OPG, sRANKL, DKK-1, sclerostin, and BMP-7 were comparable between AS patients with and without syndesmophytes (P > 0.05, table 2). However, fetuin A was significantly higher in the in the patients with syndesmophytes compared to non-syndesmophyte group (P < 0.05, Table 1). Correlation analysis showed that the presence of syndesmophytes were significantly and positively correlated with BASMI, current or past smoking history, and fetuin-A (P < 0.05, r= 0.3, 0.3 and 0.2 respectively). Regression analysis showed that fetuin A was the most important predictor of syndesmophytes (odds ratio, and 95% confidence interval = 31.2, and 0.94–1039).

Table 1. Laboratory characteristics of the study group

	AS patients		
	Syndesmophyte (+), n= 55	Syndesmophyte (−), n= 31	P value
DKK-1 (pg/ml)	1967±1318	1718±1054	0.37
Sclerostin (pg/ml)	143±117	130±116	0.64
sRANKL (pmol/l)	110±95	130±74	0.32
OPG (pg/ml)	1916±593	1905±493	0.93
BMP-7 (pg/ml)	7.8±14	8.4±17	0.87
Fetuin-A (mg/ml)	1.15±0.17	1.08±0.12	0.04
hsCRP (mg/ml)	9.9±6.4	9.2±7.1	0.62
IL-6 (ng/ml)	0.003±0.001	0.003±0.001	0.86

Conclusion: We suggest that fetuin A may be used as a novel biomarker to predict new bone formation in patients with AS.

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Effect of TNF Antagonists On Radiographic Progression in Psoriatic Arthritis: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Radjiv Goulabchand[1], Gael Mouterde[1], Cédric Lukas[1], Thomas Barnetche[2], Jacques Morel[1] and Bernard Combe[1]. [1]Montpellier 1 University, Lapeyronie Hospital, Montpellier, France, [2]CHU Bordeaux Pellegrin, Bordeaux, France

Background/Purpose: Psoriatic arthritis (PsA) can cause important structural damages which can lead to disability. TNF antagonists have shown their clinical efficacy in PsA, but only limited data are available regarding their structural effect.

To determine whether TNF antagonists have an effect on radiographic progression in patients with PsA by performing a systematic review and meta-analysis based on data from randomized controlled trials (RCTs) versus placebo. To evaluate whether the combination with methotrexate (MTX) has an additional efficacy over monotherapy.

Methods: A systematic review of literature was performed until March 2011. Bibliographic references were selected from Embase and Medline databases, and from the two last EULAR and ACR annual meetings. Radiographic progression was scored by Sharp method modified for PsA (mTSS). Primary endpoint was the proportion of patients showing no radiographic progression at week 24 (defined by a mTSS variation score ≤ 0.5). Secondary end point included the proportion of non progressors at week 48 and mean variation of mTSS at week 24. The

Mantel-Haenszel method was used to provide a common odds-ratio (OR) estimate and 95% confidence interval (CI) in TNF antagonists (+/− DMARDs) versus placebo (+/− DMARDs) treated patients for inflix- imab, etanercept, adalimumab and golimumab RCTs. Statistical hetero- geneity was assessed by the Q test (χ^2), using a significance level of 0.05. OR and 95% CI were shown on forest plots.

Results: Search found out 206 articles and 3 abstracts. Retrieved data allowed meta-analysis on 4 articles and 1 abstract for the proportion of non progressors at week 24. Data from 1110 patients were pooled, 484/584 (82,9%) were considered as non-progressors at week 24 in the TNF antagonists group versus 362/526 (68,8%) in the placebo group (OR=2.68 [1.99; 3.60] p<0.0001), without significant heterogeneity (I^2=3%;p=0.39) (*figure 1*). Based on 3 studies, similar results were found at week 48 in favor of TNF antagonists group (OR=2.42 [1.57;3.71] I^2=0%;p=0.91). Among 533 patients receiving TNF antagonists versus 454 receiving placebo in 3 studies (4 comparisons), the mean change of the mTSS at week 24 was lower in the TNF antagonist group versus placebo (mean difference= −0,69 [−1.12; −0.27], with substantial heterogeneity (I^2=76%;p=0.006). Only two RCTs provided data on the combination with MTX: the mean or median change of the mTSS was similar in adalimumab or infliximab subgroups, irrespective of the MTX use.

Conclusion: This meta-analysis of RCTs showed that all TNF antagonists lead to a better control of structural damage due to PsA than a placebo after 24 and 48 weeks of treatment. The respective role of the additional DMARDS could not be determined due to a lack of data.

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Prevalence of Psoriasis and Psoriatic Arthritis in a Northern Population of Spain. Jose Luis Fernandez-Sueiro[1], JA Pinto[1], S. Pertega-Diaz[1], Manuel Acasuso[2] and Ignacio Herrero de Padura[2]. [1]Complejo Hospitalario Univer- sitario La Coruña, La Coruña, Spain, [2]Centro de Salud, San José, La Coruña, Spain

Background/Purpose: There are few data in Spain evaluating the prevalence of psoriasis in the general population, accordingly there are not data evaluating the prevalence of psoriatic arthritis in Spain.

Objectives: to estimate the prevalence of psoriasis and PsA in the general population. To estimate the prevalence of PsA in patients with cutaneous psoriasis, referred from the primary care and the prevalence in of PsA in the general population.

Methods: All patients identified with a diagnose code of cutaneous psoriasis or PsA, from the database of a primary care centre (San José from La Coruña, northwest of Spain) were invited to participate in the study by a telephonic call. Patients were evaluated in the following way: personal and family history, criteria for inflammatory back pain (IBP), spinal and peripheral pain (VAS), peripheral joint count: tender and swollen (78/76), metrology (cervical rotation (CR), occiput to wall distance (OW), lateral lumbar flexion (LLF), modified Schober (mS)), MASES, SF12, DLQI, PASI, BSA, 'peripheral and axial x-rays, ESR, CRP, anti CCP and HLA-B27. Case definition was made according to clinical judgement. A descriptive analysis of the variables was performed. Prevalence estimates were obtained, together with their 95% confidence intervals. Adjustment to the prevalence figures was made based on detected erroneous psoriasis coding.

Results: From a referral population of 36610 persons, 458 patients were identified with a code diagnosis of psoriasis or PsA. From those, 21 had already a diagnosis of PsA, 161 agreed to participate, 126 came to the hospital. From those, 4 patients were excluded because they do not have a diagnosis of psoriasis, at the end 122 psoriatic patients without arthritis were evaluated.

From a total of 122 patients studied, 12 patients were judged to have a clinical diagnosis of PsA. This leads to an estimated prevalence of PsA in psoriatic patients of 9.8% (95% IC: 4.1%–15.5%). From these figures, the estimated prevalence of cutaneous psoriasis in the general population was 1,2% (95% CI=1,1%–1,3%), whereas the prevalence of PsA in the general population taken into account all cases was 0,17% (95% CI=0,13%–0,21%). The prevalence of undiagnosed cases was 0,06% (95% CI=0,03%–0,08%). The clinical features of the patients 12 patients diagnosed as PsA were as follows: nail involvement: 25%, dactylitis

8.3%. Nocturnal and overall spinal pain past week 3.25±3.57 and 4.17±3.35, peripheral VAS 6.33±3.31, TJC 4.50±9.04, SJC 0.00, mS 4.48±1.03, OW 0.00, LLF 14.92±4.42. CR <70°: 8.3%, enthesitis 41,7%, PASI 0,33±1,15, BSA <10%: 100%, DLQI 1.42±1.56 SF12 physical 43.09±11.39, SF12 mental 39.28±12.11, ESR≤20 70%, CRP <0.8 80%, anti-CCP ≤25 100%, Negative FR 91.7%. Negative HLA-B27 91.7%. Peripheral erosions 18.2%, sacroiliitis grade II unilateral or higher 45.5%

Conclusion: In this study, the estimated prevalence of cutaneous psoriasis in a northern general population of Spain was 1.2%. The estimate (clinically judged) prevalence of psoriatic arthritis in patients with psoriasis was 9.8%, and the estimate prevalence of psoriatic arthritis in the general population was 0,17%, of these 0,06% of the cases may be undiagnosed.

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14-3-3 Eta Is a Modifiable Serum Biomarker That Marks Adalimumab Response in Psoriatic Arthritis. Anthony Marotta[1], A. W van Kuijk[2], Walter P. Maksymowych[3] and Paul Peter Tak[4]. [1]Augurex Life Sciences Corp, North Vancouver, BC, [2]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [3]University of Alberta, Edmonton, AB, [4]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: 14-3-3 eta is a synovial-derived biomarker whose serum expression is independently associated with joint damage in RA and PsA. We previously reported that 14-3-3 eta pre-treatment levels predict a Good EULAR response in RA patients on anti-TNF therapy and that the change in 14-3-3 eta titres correlates with measures of clinical improvement. We therefore examined whether a change in 14-3-3 eta expression may also serve as a useful marker of adalimumab therapy response monitoring in PsA.

Methods: Serum 14-3-3 eta levels of 24 patients (15 males and 9 females) with active PsA fulfilling the CASPAR classification criteria were measured before receiving adalimumab therapy and 8- or 12-weeks post-treatment. Clinical assessment at those time points included SJC68, PASI, CRP, ESR, DAS28 and ACR50 response. Pearson correlations (r) were performed to examine relationships between the changes in clinical variables and the change in 14-3-3 eta (Δ14-3-3 eta). Contingency analysis was used to determine if absolute decrease, increase or no change in 14-3-3 eta post-treatment levels corresponded with an ACR50 response. Regression analyses were performed to determine the predictive power of changes in CRP (ΔCRP) and Δ14-3-3 eta for that response, represented by the significance of chi-square likelihood ratios (LR). Areas under the receiver operating characteristic curves (AUC) were used to determine the accuracy of the regression model.

Results: Of the 24 PsA patients, 10 patients achieved an ACR50 response while 14 did not. Baseline 14-3-3 eta titres were predictive of an ACR50 response delivering a significant LR=5.53, p=0.02, AUC=0.75 which increased to a LR=8.35, p=0.02, AUC=0.83 when Δ14-3-3 eta was added to the model. Contingency analysis reveals that a post- treatment decrease as compared to no change or an increase in 14-3-3 eta titres in PsA patients reflected a 10.2 times greater likelihood of achieving an ACR50 response to adalimumab therapy (p=0.001) with a relative risk of 3.6 (95%CI 1.71 to 7.58). Δ14-3-3 eta correlated moderately with the following clinical response variables; ΔCRP r=0.58, p=0.004, ΔESR r=0.47, p=0.02 and ΔPASI r=0.49, p=0.02. Consistent with published data, the ΔCRP reflected ACR50 response LR=5.98, AUC=0.74, p=0.01 with the model strengthened when 14-3-3 eta baseline positivity was added LR=10.1, p=0.006, AUC= 0.87.

Conclusion: In PsA, 14-3-3 eta titres together with a decrease in the levels of 14-3-3 eta following treatment is independently associated with ACR50 response to adalimumab therapy. 14-3-3 eta enhances the predic- tive capacity of CRP and serves as a biomarker of treatment response for both RA and PsA.

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Ustekinumab Improves Arthritis-Related and Skin-Related Quality of Life in Patients with Active Psoriatic Arthritis: Patient Reported Outcomes From Randomized and Double Blinded Phase III Psummit I Trial.

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Background/Purpose: To examine the impact of ustekinumab treatment on general and disease specific patient reported outcomes (PROs) of patients with active psoriatic arthritis (PsA) using data from PSUMMIT 1, a Phase 3 clinical study.

Methods: In PSUMMIT I, adult PsA patients (n=615) with active disease despite DMARD and/or NSAID therapy were randomized to receive ustekinumab 45mg, 90mg, or placebo (PBO) at wks 0, 4, and q12wks, thereafter. Patients treated with prior anti-TNF agents were excluded. At wk16, patient with <5% improvement in swollen and tender joint counts entered blinded early escape (PBO→ ustekinumab 45mg; ustekinumab 45mg→90mg; 90mg→90mg). Patient reported outcomes were measured with Health Assessment Questionnaire (HAQ), Dermatology Quality Life Index (DLQI), SF-36 health survey questionnaire (SF-36), Visual Analogue Scales (VAS) for impact of PsA on work productivity (0–10), patient assessment of pain (0–10) and disease activity (0–10). An ANOVA on van der Waerden normal scores was used for continuous variables and chi-square or the Cochran-Mantel-Haenszel (CMH) test for binary variables between groups.

Results: At baseline, PRO measures indicated that the study population had severe physical disability and impaired health related quality of life with a mean HAQ score of 1.25 and mean DLQI score of ≥10. At wk 24, greater improvements in HAQ, DLQI, and SF-36 PCS were observed in ustekinumab groups compared to the PBO group. Proportions of patient who achieved clinical meaningful improvements in HAQ (≥0.3), DLQI (≥5), and SF-36 PCS (≥5) were greater in the ustekinumab 45mg or 90 mg group than in the PBO group. Additionally, ustekinumab-treated patients also achieved greater improvements in patient assessment of pain, patient assessment of disease activity and greater reduction in impact of disease on work productivity than PBO-treated patients (Table).

Table. Baseline Characteristics and Change in Patient Reported Outcomes at Week 24 by Treatment Group: Results from PSUMMIT I

PROs at Week 24	PBO (N=206)	Ustekinumab 45mg (N=205)	Ustekinumab 90mg (N=204)
Age (years)	47.4	47.1	46.8
Male Gender (%)	52.4	51.7	56.9
Baseline HAQ (0–3)	1.2	1.2	1.2
Baseline DLQI (0–30)[a]	11.7	11.0	10.5
Baseline SF-36 PCS (0–100)	36.2	35.7	36.5
Baseline SF-36 MCS (0–100)	41.9	43.1	42.1
Mean improvement in DLQI	1.4	6.6++	7.5++
Achieving DLQI score of 0 or 1 (%)	8.3	37.2++	53++
Mean improvement in HAQ	0.1	0.31++	0.4++
Improvement in HAQ≥0.3 (%)	28.2	47.8++	47.5++
Mean Change in SF36 PCS	0.3	3.0++	3.3++
Improvement in SF-36 PCS ≥5 (%)	17.9	30.5+	38.1++
Mean Change in SF-36 MCS	1.2	0.5	2.5*
Improvement in SF-36 MCS ≥5 (%)	30.1	23	36.5
Percent improvement in pain	4.5	25.9++	29.6++
Percent improvement in disease activity	7.6	25.4++	27.6++
Mean improvement in productivity	0.78	1.82++	2.64++

*Data presented were mean or percent; Compared with PBO, * p<0.05, +, p<0.01; +, p<0.001;*
[a]: *Footnote DLQI only for Patients with baseline BSA>=3%.*

Conclusion: Ustekinumab improves general as well as arthritis and skin-related quality of life, and reduces the impact of disease on work productivity in patients with active PsA.

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Randomized Controlled Trial of Adalimumab in Patients with Peripheral Spondyloarthritis.

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Background/Purpose: Adalimumab (ADA) is indicated for the treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Patients (pts) with peripheral spondyloarthritis (SpA) not previously diagnosed with psoriasis or PsA (non-PsA), presenting primarily with arthritis, enthesitis and/or dactylitis, may also benefit from anti-TNF therapy. ABILITY-2, the first randomized controlled trial to use the ASAS peripheral SpA criteria[1] to classify pts for study entry, evaluated the efficacy and safety of ADA in pts with active non-PsA peripheral SpA.

Methods: ABILITY-2 is an ongoing, multicenter phase 3 study. Eligible pts were age ≥18 yrs, fulfilled ASAS peripheral SpA criteria, did not have a diagnosis of psoriasis, PsA, or AS, and had inadequate response or intolerance to NSAIDs. Pts were randomized 1:1 to ADA 40 mg every other wk or placebo (PBO) for 12 wks followed by a 144-wk open-label extension. Primary endpoint was the proportion of pts achieving peripheral SpA response criteria (PSpARC 40) at wk 12: ≥40% improvement (≥20 mm absolute improvement in VAS) from baseline (BL) in Pt's Global Assessment of Disease Activity (PGA) and of pain (PGA-pain) and ≥40% improvement in ≥1 of the following: swollen joint count (SJC) and tender joint count (TJC); Enthesitis Count, or Dactylitis Count. Other outcomes analyzed included Physician's Global Assessment (PhGA), BASDAI, enthesitis indices, PSpARC 20/50/70 responses, HAQ-S, and SF-36v2. Adverse events (AE) were collected throughout the study.

Results: 165 pts (ADA 84/PBO 81) were randomized. BL demographics/ disease characteristics were similar between groups, except for mean age and % pts with dactylitis count>0. BL characteristics include (ADA/PBO): 57/52% female, 67/56% HLA-B27+, mean TJC 13.0/13.6, mean SJC 6.1/7.3, mean enthesitis count 6.7/7.3, and dactylitis count 0.4/0.7. At Wk 12, the % of ADA pts achieving PSpARC 40 was higher vs. PBO (P=0.006) (table), primarily due to the proportion of patients meeting the PGA, PGA-pain, and TJC/SJC components. Overall, improvement based on other outcomes was greater with ADA vs. PBO. AE incidence rates were similar [ADA/PBO (%)]: any AEs (54.8/54.3), serious AEs (1.2/1.2), and infectious AEs (21.4/28.4); there were no serious infections, TB, or malignancies during the double-blind period.

Table. Week 12 Efficacy Outcomes

	ADA N=84	PBO N=81	P value[a]
Primary endpoint[b]			
PSpARC 40, %	39.3	19.8	0.006
Proportion of patients achieving improvement in each PSpARC 40 component [c] (≥40% improvement, plus ≥20 mm improvement in PGA and PGA-pain VAS)			
PGA, %	54.3	28.8	<0.001
PGA pain, %	53.7	31.3	0.004
TJC/SJC, %	57.3	29.6	<0.001
Enthesitis, %	51.2	42.0	0.237
Dactylitis, %	13.6	18.5	0.392
Other efficacy endpoints			
PSpARC 20[b], %	56.0	37.0	0.015
PSpARC 50[b], %	34.5	11.1	<0.001
PSpARC 70[b], %	22.6	3.7	<0.001
PGA[d] (VAS 0–100), mm	−27.5	−16.4	0.003
PGA-pain[d] (VAS 0–100), mm	−28.9	−17.1	0.001
PhGA[d] (VAS 0–100), mm	−32.2	−18.2	<0.001
BASDAI[d]	−2.1	−1.0	0.003
TJC[d] (0–78)	−5.9	−1.8	<0.001
SJC[d] (0–76)	−3.6	−3.1	0.045
Leeds enthesitis index[d] (0–6)	−0.8	−0.1	<0.001
SPARCC enthesitis index[d] (0–16)	−1.7	−0.7	<0.001
Dactylitis count[d] (0–20)	−0.2	−0.3	0.808
SF-36v2 PCS[e]	6.7	2.4	<0.001
HAQ-S score[d]	−0.3	−0.2	0.051

Values are mean change unless otherwise indicated; Ns may vary by outcome. [a]ADA vs. PBO; [b]NRI; [c]Observed analysis; [d]LOCF; [e]Observed data (N=83/79, ADA/PBO). ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HAQ-S, Health Assessment Questionnaire modified for spondyloarthropathies; PBO, placebo; PGA, patient's global assessment of disease activity; PGA-pain, patient's global assessment of pain; PhGA, physician's global assessment; PSpARC, peripheral spondyloarthritis response criteria; PSpARC 20, ≥20% (≥10 mm in VAS) improvement; PSpARC 50, ≥ 50% (≥20 mm in VAS) improvement; PSpARC 70, ≥70% (≥30 mm in VAS) improvement; SF-36v2 PCS, short form-36 health status survey version 2 physical component summary; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC, tender joint count.

Conclusion: Adalimumab significantly improved signs, symptoms, and physical function of pts with active non-PsA peripheral SpA and was well-tolerated. ABILITY-2 results suggest that ADA may be an effective treatment option for non-PsA peripheral SpA pts with inadequate response or intolerance to NSAIDs. Further, these results suggest that the PSpARC assessment instrument, pioneered in this study to evaluate this patient population, is a responsive and discriminative outcome measure.

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Description of Distribution of Active Inflammatory Lesions On Magnetic Resonance Imaging of the Sacroiliac Joints and the Spine in Patients with Early Axial Spondyloarthritis – Analysis of the Esther Trial baseline Data.
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Background/Purpose: To address the question whether active inflammation starts at specific sites of the sacroiliac joints (SI-joints) and/ or the spine.

Methods: Wb-MRIs of 75 patients with early axial spondyloarthritis (SpA) with a disease duration of < 5 years [1] were scored for active inflammatory lesions on STIR sequences and T1 weighted images in the 23 vertebral units (VUs) of the spine and in the 8 sacroiliac (SI)-joint quadrants. Scoring was performed by two blinded radiologists.

Results: In the total group of patients, 52% (39/75) showed active inflammation only at the SI-joints (active sacroiliitis), 41.3% (31/75) in the SI-joints and the spine and 5.3 (4/75) only in the spine (isolated spinal inflammation).

Mean scores for active inflammatory changes were 6.7 (SD 5.8) out of possible 24 points for the SI-joints and 1.9 (SD 3.3) out of possible 69 for the spine.

Active inflammation in the SI-joint quadrants were found as the following (in decreasing order): quadrant I (sacral bone, upper quadrant; 66% of patients, n= 50); quadrant II (sacral bone, lower quadrant; 60%, n= 45), quadrant IV (iliac bone, upper quadrant, 53%, n= 40) and quadrant III (iliac bone, lower quadrant, 69%, n=52).

The most frequently affected sites of active inflammation in the spine were the lower thoracic spine and the lumbar spine: in decreasing order the most frequently affected VUs were T6/T7 (n= 11), T10/T11 (n= 11), T7/T8 (n= 10), L1/L2 (n= 10) and L4/L5 (n= 9) and L5/S1 (n= 9). The cervical spine was less often affected.

Table. Distribution of active inflammation in the Sacroiliac Joint Quadrants and the Spinal vertebral units

Anatomie site	Percentage of affected patients
SI-joint quadrant I (sacral bone, upper quadrant)	66%
SI-joint quadrant II (sacral bone, lower quadrant)	60%
SI-joint quadrant IV (iliac bone, upper quadrant)	53%
SI-joint quadrant III (iliac bone, lower quadrant)	69%
C2/C3	3%
C3/C4	1%
C4/C5	1%
C5/C6	4%
C6/C7	7%
C7/T1	3%
T1/T2	4%
T2/T3	7%
T3/T4	7%
T4/T5	9%
T5/T6	8%
T6/T7	15%
T7/T8	13%
T8/T9	11%
T9/T10	8%
T10/T11	15%
T11/T12	5%
T12/L1	8%
L1/L2	13%
L2/L3	9%
L3/L4	11%
L4/L5	12%
L5/S1	12%

[1] Song I.-H. et al. 2011. Ann Rheum Dis. 2011 Apr;70(4):590–6.

Conclusion: In this cohort of early axial SpA patients there was no significant predilection of SI-joint quadrants affected by active inflammtion. In the spine the thoracic and lumbar parts were mostly affected.

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Radiographic Damage in Ankylosing Spondylitis Over 12 Years of Follow-up: A Longitudinal Analysis.
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Background/Purpose: Radiographic damage is one of the core outcomes recommended by the Assessment in Spondyloarthritis international Society (ASAS) for follow-up of patients with axial SpA. So far, the evolution of radiographic damage over a long period has not been described in detail. We aimed to describe the evolution of radiographic abnormalities over time in a prevalence cohort of patients with ankylosing spondylitis (AS).

Methods: The modified Stoke AS Spine Score (mSASSS) was calculated using 2-yearly radiographs of patients followed for 12 years in the Outcome in AS International Study (OASIS). Two readers independently scored the x-rays and scores were averaged. Status and progression scores (2- and 12-year-progression) were computed for patients with at least one 2-year interval available (n=186) and for those with an mSASSS at 12-years (n=68). New syndesmophytes at vertebral corners (VCs) "at risk" (i.e. without a previous syndesmophyte or bridge) were computed. Radiographic progression over time was investigated using generalized estimating equations. Relevant interactions with time were explored. Time was modeled in different forms (linear and non-linear) and the best model fit was assessed using the quasi-likelihood information criterion.

Results: 809 radiographs of 186 patients (70% males, mean (SD) age 43(12) years, mean disease duration 11.0(8.8) years and 83% HLA-B27 positive) were included. The mean (SD) mSASSS at baseline was 11.6 (16.2) [11.2 (15.7) in patients with mSASSS at 12-years]. The mean (SD) 2-year interval progression score (in 520 2-year intervals) was 2.0 (3.5) [2.2 (3.9) for the subset of 12-year-completers]. Over the 12 years, the mean (SD) progression was 11.7 (11.5). A new syndesmophyte was assessed in 38% by one reader (R1) and 39% by reader 2 of all 2-year intervals and, throughout follow-up, in 55% (R1) and 63% (R2) of the patients with at least one VC "at risk". In 24% of the patients (39% of the 2-year intervals) there was no progression in mSASSS. A progression ≥1 mSASSS occurred in 72% of the patients (54% of the intervals) and a progression ≥5 mSASSS in 22% of the patients (12% of the intervals). At the group level, a linear time course model fitted the observed data the best. Time was positively associated with radiographic progression, with an increase of 0.98 mSASSS/year (≈1.96 mSASSS in 2 years) (Table).

Table. Progression of radiographic damage over time

	Univariable regression analysis β (95% CI)	P-value
Time (years)	0.98 (0.84;1.12)	<0.001
Time × HLAB27		0.052
– Time in HLAB27 negative	0.70 (0.48;0.90)	<0.001
– Time in HLAB27 positive	1.03 (0.88;1.19)	<0.001
Time × gender		0.005
– Time in women	0.69 (0.57;0.80)	<0.001
– Time in men	1.11 (0.93;1.29)	<0.001
Time × HLAB27 in women		0.958
Time × HLAB27 in men		0.044
– Time in female HLAB27 positive	0.69 (0.34;1.03)	<0.001
– Time in male HLAB27 positive	1.18 (0.98;1.38)	<0.001
Time × disease duration		0.701
Time × symptom duration		0.214

Radiographic progression occurred significantly faster in males (vs females) and in HLA-B27 positive patients (vs HLA-B27 negative). HLA-B27 positive male (but not female) patients had a significantly higher progression than HLA-B27 negative males. Progression was independent of disease- and symptom duration.

Conclusion: Long-term radiographic progression in AS is more severe in HLA-B27-positive males. About 60% of all patients have at least one new syndesmophyte. Radiographic progression is dependent on time and, at the group level, linear.

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Differential Association Between Human Leukocyte Antigen (HLA) Alleles and Joint Subluxation and Ankylosis in Patients with Psoriatic Arthritis. Vinod Chandran, Arane Thavaneswaran, Amir Haddad, Fawnda Pellett and Dafna Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: We have previously reported the association between HLA and KIR gene variants with the development of Arthritis Mutilans (AM) in psoriatic arthritis (PsA). However, severe joint damage in PsA may be further classified into disorganization, subluxation, pencil-in-cup change and ankylosis. We therefore sought to determine whether previously identified *HLA* and *KIR* variants associated with AM also associate with sub-phenotypes of AM.

Methods: Data on the presence of severe joint were obtained form a large cohort. Radiographs of the hands, feet and spine are obtained at baseline and 2-yearly intervals and scored according to the modified Steinbrocker method by at least 2 rheumatologists by consensus. Grade 4 is considered severe joint destruction Radiographs previously rated as 4 were reviewed and reclassified as disorganization (4.0), subluxation (4.1), pencil-in-cup change (4.2) and ankylosis (4.3). Data on the time when severe joint destruction was first observed was obtained on 555 Caucasian subjects with PsA satisfying CASPAR criteria who were seen in the clinic within 5 years of diagnosis. HLA typing was performed by PCR-SSO, and KIR typing by PCR-SSP. The principal outcome measure was the time to development of severe joint destruction after diagnosis of PsA. Parametric survival analyses with interval censoring using a Weibull model adjusted for age at diagnosis of PsA and sex were conducted. Gene variants previously reported to be associated with arthritis mutilans- HLA-A*11, -A*29, -B*27, -C*02, -C*03, -C*04, -DQB1*02 and KIR3DS1 were predictor variables.

Results: The 555 subjects 312 (56.2%) males, mean age at diagnosis of 40 (13.5) years, mean age at first visit 42 (13.3) years, mean duration of PsA 2.0 (1.7) years, mean tender joint count 7.9 (7.9), mean swollen joint count 4.9 (5.4)] had a median number of 3.4 (3.1) radiographic assessments during a median follow up of 6.9 (8.4) years. 102 (19%) subjects were observed to develop severe joint damage. No association between 4.0 and gene variants could be demonstrated. Univariate analyses adjusted for age and sex showed that HLA- C*02 (p=0.06) and -B*27 (p=0.004) were associated with an increased hazard of developing 4.1. Multivariate analysis with alleles significant at p<0.1 showed that only HLA-B*27 (HR 2.76, 95% CI (1.39, 5.49), p=0.004) was associated with increased hazard of developing 4.1.

When analyzing 4.2, no association with HLA alleles and only a trend for association with KIR3DS1 (HR 1.72, p=0.08) was demonstrated. Association between 4.3 and HLA-DQB1*02 (p=0.03) was found on univariate analysis adjusted for age and sex. Multivariate analysis revealed that HLA- DQB1*02 (HR 1.86, 95% CI (1.09, 3.18)), p=0.02) was associated with increased hazard of developing 4.3, and there was a trend for association with KIR3DS1 (HR = 1.61, 95% CI (0.98, 2.64), p=0.06).

Conclusion: Differential HLA association with sub-phenotypes of severe damage was demonstrated. HLA-B*27 was associated with increased risk of subluxation, whereas - DQB1*02 was associated with increased risk of ankylosis.

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Long Term Inhibition of Interleukin (IL)-17A with Secukinumab Improves Clinical Symptoms and Reduces Spinal Inflammation As Assessed by Magnetic Resonance Imaging in Patients with Ankylosing Spondylitis. Xenofon Baraliakos[1], Jurgen Braun[1], D. D. Laurent[2], D. Baeten[3], D. van der Heijde[4], J. Sieper[5], Paul Emery[6], Iain B. McInnes[7], J. van Laar[8], R. Landewe[9], Paul Wordsworth[10], Jurgen Wollenhaupt[11], Herbert Kellner[12], Andrew Wright[2], Francois Vandenhende[13], Kath Radford[14], Babul Borah[14] and Hueber Wolfgang[14]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Novartis Pharma AG, Basel, Switzerland, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Charitè Berlin, Campus Benjamin Franklin, Berlin, Germany, [6]University of Leeds, Leeds, United Kingdom, [7]University of Glasgow, Glasgow, United Kingdom, [8]Newcastle University, Newcastle upon Tyne, United Kingdom, [9]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [10]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [11]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [12]Centre for Inflammatory Joint Diseases, Munich, Germany, Munich, Germany, [13]Clinbay, Genappe, Belgium, Genappe, Belgium, [14]Novartis Institutes for BioMedical Research, Basel, Switzerland

Background/Purpose: In a recent proof-of-concept (PoC) trial it was shown that secukinumab, a fully human IgG1k anti-IL17A monoclonal antibody, significantly improved clinical signs and symptoms of patients with active ankylosing spondylitis (AS). Magnetic resonance images (MRI) of these patients showed reduction of spinal inflammation at week (wk) 6 and wk 28 after initiation of treatment. Here we report on a subgroup of patients (N=13) who entered the open label extension study, received and completed treatment and had MRI assessments at wk 28 and up to 24 months.

Methods: In the 28-wk PoC study, 27/30 patients had sequential MRI studies, 22 had received secukinumab 2×10 mg/kg administered intravenously 3 wks apart, and 5 patients had been randomized to placebo. Of those 27 patients, 20 entered the extension study. 13 of these 20 patients had MRI data at wk 94. Of these 13, ten had been treated with secukinumab and 3 with placebo in the core study. In the extension study, all received secukinumab 14×3 mg/kg administered 4 wks apart. MRIs (T1 and STIR) were rescored for this study by analyzing the images from baseline (BL), wk 28 and wk 94. All MRIs were analyzed together by an independent blinded reader using the ASspiMRI-a scoring system, and also recording the amount of vertebral edges (VEs) which showed inflammation or fatty degeneration at the different time points.

Results: All 13 patients completed the study. For patients receiving 2×10 mg/kg secukinumab followed by 14×3 mg/kg (n=10, group 1), or receiving placebo followed by secukinumab 14×3 mg/kg (n=3, group 2), the ASAS20 and ASAS40 responses are shown in Table 1. In group 1, ASspiMRI-a scores were reduced in comparison to BL at wk 28 – similar to the results of the core study – and these reduced scores were sustained at a similar level at wk 94 (Table 1). Of the 920 VEs evaluated, the proportion of inflammatory lesions was reduced from 9.9% (N=91) at BL to 3.7% (N=34) at wk 28 and 3.6% (N=33) at wk 94. There was no increase in the number of VEs with fatty lesions between BL and wk 28 and 94 (Table 1). In the 3 patients who had initially received placebo and who were then switched to secukinumab at wk 28 (group 2), MRI inflammatory scores at wk 94 also improved (Table 1).

Table 1. Clinical and MRI parameters in patients receiving secukinumab 2 × 10 mg/kg followed by 14 × 3 mg/kg monthly (group 1), or placebo followed by secukinumab 14 × 3 mg/kg monthly (group 2)

| | Secukinumab alone (group 1) | | | Placebo/Secukinumab (group 2) | | |
	BL	Secukinumab 2 × 10 mg/kg Week 28	Secukinumab 14 × 3 mg/kg Week 94	BL	Placebo Week 28	Secukinumab 14 × 3 mg/kg Week 94
Number of Patients	10	10	10	3	3	3
ASAS20/ASAS40 Responders	-	4/2	6/5	-	1/0	2/1
ASspiMRPa Mean ± SD	8.8+/−12.2	3.4 ± 7.3	3.3 ± 4.4	20.0+/−23.3	19.7+/−23.0	12.7+/−20.2
p value (vs BL)		0.036	0.107		0.667	0.148
Number of VEs evaluated	920	920	920	276	276	276
Number (%) of VEs with inflammation	91 (9.9)	34 (3.7)	33 (3.6)	64 (23.2)	64 (23.2)	35 (12.7)
Number (%) of VEs with Fatty lesions	124 (13.5)	132 (14.3)	126 (13.7)	18 (6.5)	21 (7.6)	16 (5.8)

BL = Baseline; VE = Vertebral Edge

Conclusion: This exploratory MRI analysis shows that the IL-17 inhibitor secukinumab may reduce spinal inflammation and this effect may be sustained for up to 24 months using a lower dose in the maintenance compared to induction phase. Interestingly, there was no change in the amount of fatty lesions in the patients treated with secukinumab–this differs from what was recently reported for the treatment with TNF-blockers. Whether this has an impact on radiographic progression needs to be studied in future trials.

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Profiling of Response to Anti-TNFα Therapy by Serum Markers of Tissue Degradation End Products in Ankylosing Spondylitis Patients.
Anne Sofie Siebuhr[1], Anne C. Bay-Jensen[2], Morten Asser Karsdal[2], Efstathios Vassiliadis[1], Stephanie Wichuk[3], Claus Christiansen[4] and Walter P. Maksymowych[3]. [1]Nordic Bioscience, Herlev, Denmark, [2]Nordic Bioscience A/S, Herlev, Denmark, [3]University of Alberta, Edmonton, AB, [4]CCBR, Ballerup, Denmark

Background/Purpose: Chronic inflammatory diseases such as Ankylosing Spondylitis (AS) are diverse and therefore hard to clearly diagnose and treat. Conventional biomarkers for AS, as CRP and ESR, often reflect systemic inflammation rather than local joint inflammation. We therefore investigated the effect of anti-TNFa treatment on the level biomarkers of tissue degradation end products reflecting cartilage and synovial turnover in AS patients and whether specific biomarker profiles could be identified for anti-TNFa response.

Methods: Serum samples from AS patients (n=114, age 19–78 yrs, 80% males) were collected at baseline and 3 months following standard anti-TNF-a treatment; Infliximab (n=46), Etanercept (n=28), Adalimumab (n=25) and Golimumab (n=15). Biomarkers of tissue turnover were measured: i) MMP-degraded and citrullinated vimentin (VICM), i) MMP-degraded CRP (CRPM), iii) MMP-degraded type II and III collagen (C2M. C3M), iv) conventional CRP, v) MMP-3, and vi) ESR. All values are presented as geometric mean ± 95% CI. Data was log transformed prior to statistical analysis. Differences between before and after treatment were determined using paired Student's t-test. Pearson's correlation was used to determine correlations between the biomarkers.

Results: Serum C3M (p<0.0002), CRPM (p<0.0001), and VICM (P=0.0011) all decreased significantly after three months of anti-TNF-alpha therapy. There was no significant difference in serum C2M (p>0.05) and MMP-3 (p>0.05) before and after anti-TNF-alpha therapy, although 1/3 of the patients did decrease in response to treatment. CRP (p<0.0001) and ESR (p<0.0001) decreased significantly with treatment. There was a significant correlation between CRPM and the conventional biomarkers before treatment. However, this correlation was lost after 3 months of treatment (table). VICM was strongly correlated to C3M at both time points and to CRPM after treatment, but not at baseline. There was a significant correlation between C2M and VICM at baseline, which was lost after treatment. Before treatment CRP was correlated to C3M, but not after treatment.

		C3M	CRPM	C2M	VICM	CRP	ESR	MMP-3	Disease duration
					baseline				
C3M	r		−0.1	0.01	0.3	0.3	0.1	−0.1	−0.2
	p		ns	ns	**0.0002**	**0.006**	ns	ns	**0.05**
CRPM	r	−0.02		0.04	−0.03	0.4	0.4	0.4	−0.06
	p	ns		ns	ns	**<0.0001**	**<0.0001**	**0.004**	ns
C2M	r	0.11	0.1		0.2	0.01	0.03	0.02	−0.1
	p	ns	ns		**0.05**	ns	ns	ns	ns
VICM	r	0.3	0.5	0.01		0.2	0.1	−0.03	−0.2
	p	**0.0005**	**<0.0001**	ns		ns	ns	ns	**0.04**
CRP	r	−0.04	0.2	−0.08	−0.03		0.7	0.3	0.3
	p	ns	ns	ns	ns		**<0.0001**	**0.04**	ns
ESR	r	0.1	−0.07	−0.04	−0.02	0.6		0.3	0.06
	p	ns	ns	ns	ns	**<0.0001**		ns	ns
MMP-3	r	0.1	−0.2	−0.06	0.06	−0.1	0.09		−0.2
	p	ns	ns	ns	ns	ns	ns		ns
					post treatment				

Conclusion: Biomarkers of cartilage degradation (C2M), synovial inflammation (C3M, CRPM. VICM and MMP3) and systemic biomarkers (CRP and ESR) were decreased in response to anti-TNF-alpha treatment in these AS patients. Whereas the level of CRP and ESR was completely blocked by treatment in a majority of the patients, the suppression in the level of the other markers was patient-dependent. It was clear that each marker reflects different molecular processes in the tissue and responded differentially to the treatment. Thus specific profiles for treatment efficacy may be generated by measuring a biomarker panel of tissue degradation end products.

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MRI of the Spine for Detection of Bone Spurs and Ankylosis in Patients with Ankylosing Spondylitis: Does MRI Offer Any Advantages Over Radiography? Susanne Juhl Pedersen[1], Mikkel Østergaard[1], Robert GW Lambert[2] and Walter P. Maksymowych[2]. [1]Glostrup Hospital, Copenhagen, Denmark, [2]University of Alberta, Edmonton, AB

Background/Purpose: The current gold standard for detection of disease progression in ankylosing spondylitis (AS) is conventional radiography. The most reliable method mSASSS includes the anterior parts of the cervical and lumbar spine. However, sensitivity to change is limited (1). MRI, that visualizes the total spine tomographically, may therefore improve detection of new bone formation. The aim of this study was to develop standardized definitions for new bone formation on MRI, to test the reliability of their detection in patients with AS, to compare this reliability with radiography, and to determine whether availability of radiographs enhances the reliability of detection on MRI.

Methods: The Canada-Denmark MRI working group developed standardized consensus based definitions for bone spurs and ankylosis

observed on sagittal images of T1-weighted MRI scans. The definitions included lesions at anterior and posterior vertebral corners as well as non-corner lesions in the disc space and lesions in the lateral segments. A reference image set was generated that included examples of all these lesions as well as variations in normal anatomy. In the MRI-based score, bone spurs and ankylosis were assigned a score of 2 and 3, respectively. In exercise 1, reliability for status and change scores for lesions were assessed on baseline and 2 year scans in 55 patients with AS by 3 readers scoring in known time sequence. Discrepant scans were reviewed extensively using radiography as a reference. In exercise 2, baseline/2 year pairs of radiographs and MRIs of 25 patients with AS (numbered independently) were assessed in 3 reads. Read 1: Radiographs were assessed for syndesmophytes and ankylosis; Read 2: MRI scans were assessed for new bone; Read 3: Simultaneous assessment of radiographs and MRI scans. Reliability was assessed by intra-class correlation coefficient (ICC).

Results: ICC for 3 readers reading MRI scans in the first exercise were 0.79 and 0.23 for baseline status and 2 year change scores, respectively. In exercise 2, radiography was superior to MRI in reliably detecting new bone (Table). Simultaneous availability of radiographs enhanced the reliability of detecting new bone in the C spine by MRI but this was still inferior to radiography. ICC for detection of new bone in the thoracic spine by MRI was 0.48 and 0.36 for baseline status and 2-year change scores, respectively.

Table. Intra-class correlation coefficient (ICC) for detection of bone spurs and ankylosis in exercise 2

	X-ray*	X-ray vs. MRI**	MRI 1st read *	MRI 2nd read*
C spine ICC	0.95	0.67	0.50	0.77
T spine ICC	NA	NA	0.48	0.51
L spine ICC	0.91	0.75	0.75	0.77

*ICC (status) for 3 readers
**Mean ICC for comparison of radiography and MRI

Conclusion: Standardization of MRI features, scoring methodology, and calibration of expert readers with radiography failed to show any major advantage of MRI over radiography in the reliable detection of new bone in the cervical and lumbar spine of patients with AS. Future efforts should focus on the methodology for assessment of the thoracic spine.

Reference
Wanders AJ et al. AR 2004

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Assessment of the Link Between Inflammation and Fat Metaplasia in Patients with Spondyloarthritis On Non-Biological Therapy: A Long Term Magnetic Resonance Imaging Study. Zheng Zhao[1], Susanne Juhl Pedersen[2], Robert GW Lambert[3], Stephanie Wichuk[3], Mikkel Ostergaard[4] and Walter P. Maksymowych[3]. [1]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China, [2]Glostrup Hospital, Copenhagen, Denmark, [3]University of Alberta, Edmonton, AB, [4]Copenhagen University Hospital at Glostrup, Glostrup, Denmark

Background/Purpose: There is growing awareness of the importance of fat metaplasia in the pathogenesis of SpA and its potential link with inflammation and new bone formation. recent data has demonstrated fat metaplasia at vertebral corners after resolution of inflammation in patients receiving anti-TNF therapies. There is no data that assesses this link in patients receiving non-biological (non-B) therapies. These processes can be reliably measured using STIR and T1-weighted (T1W) MRI sequences, respectively, and we aimed to compare these findings in patients with SpA according to treatment.

Methods: Two readers assessed MRI scans from 103 patients with SpA, males n = 81, mean age = 39.3 years, mean disease duration = 16.2 years, in a prospective cohort. MRI was conducted at intervals up to 4 years (mean 18.1 months) and 56 patients received anti-TNF while 47 received non-B therapies. Fat metaplasia was scored on T1W scans using a new scoring method, the CanDen FAt SpA Spine Score (FASSS) which scores six different types of fat lesions defined according to anatomical location. Lesions are recorded dichotomously (present/absent) at each vertebral endplate from

C2 lower to S1 upper (scoring range per disco-vertebral unit (DVU) in C spine: 0–8, and in T and L spine: 0–18). Inflammation was scored on STIR scans using the SPARCC MRI Spine 23DVU method with lesions being scored at each DVU (scoring range per DVU 0–18). We calculated SPARCC 23DVU and FASSS change scores, responsiveness by standardized response mean (SRM), and associations by Pearson c^2 and regression.

Results: Change (a decrease) in SPARCC 23-DVU score from baseline was significant in anti-TNF treated patients (p = 0.01) but not non-B patients while a significant increase in FASSS was evident in both anti-TNF (p = 0.005, SRM = 0.38) and non-B (p = 0.003, SRM = 0.45) treated patients indicating new fat lesions irrespective of treatment. For patients with at least 2 year follow up, 14(56%) and 16 (61.5%) of anti-TNF and non-B treated patients, respectively, had an increase in FASSS score while 7 (28%) and 6 (23.1%), respectively, had a decrease in FASSS score indicating resolution of fat lesions in a minority of patients. However, change in FASSS and SPARCC 23-DVU were highly correlated in anti-TNF treated patients (c^2 = −0.58, p = 3×10^{-6}) but not in non-B treated patients. Change in SPARCC 23-DVU was also independently associated with change in FASSS only in anti-TNF treated patients (β = −0.61, p <0.0001) (adjusted for age, sex, disease duration, BASDAI, CRP).
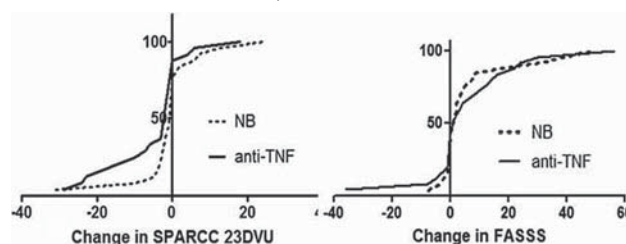
Conclusion: Long-term follow up reveals a strong link between inflammation and fat metaplasia in patients on anti-TNF while a disconnect is evident in patients receiving non-B therapies. This may have implications for pathways leading to new bone formation.

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Prevalence of Psoriatic Arthritis in Psoriasis Patients According to Newer Classification Criteria. Hernan Maldonado-Ficco[1], Gustavo Citera[1], Ana Alba Porrini[2] and Jose A. Maldonado-Cocco[1]. [1]Instituto de Rehabilitacion Psicofisica - Fundacion Reumatologica Argentina Dr. Osvaldo Garcia-Morteo, Buenos Aires, Argentina, [2]Hospital Argerich, Buenos Aires, Argentina

Background/Purpose: To determine the prevalence of Psoriatic Arthritis (PsA) in a cohort of psoriasis patients according to CASPAR criteria, and compare it with that resulting from the use of ASAS peripheral and axial criteria for SpA and New York criteria for AS.

Methods: The first 100 patients that consecutively attended the Psoriasis clinic of a Dermatology Service were assessed. Demographic and clinical data were collected, and all patients were questioned and examined by a rheumatologist for joint manifestations. In all cases, rheumatoid factor and radiographies of hands, feet, cervical spine and pelvis for sacroiliac joints were obtained. All X-rays were read independently by two observers in blind fashion. Patients with objective joint manifestations, both axial and peripheral, were evaluated for their fulfillment of CASPAR, ASAS peripheral and axial, and New York criteria. Correlations were calculated by Spearman's test. Categorical variables were compared by x^2, and continuous variables were compared by Student's test.

Results: Of the 100 patients included (62 males) median age was 48 years and median duration of psoriasis 11 years. 93% of patients presented psoriasis vulgaris, and 56% nail involvement. Seventeen patients had peripheral arthritis, mono/ oligoarticular in 9 and polyarticular in 8. Median time of arthritis duration was of 8 years. Seven patients had chronic neck pain while 6 patients had chronic low back pain.13 patients had cervical spine and 6 patients lumbar spine limitation. Among all psoriatic patients, radiographic sacroiliitis grade 2 and 3 was detected in 12, and grade 4 in 2, being symmetric in 7 of the patients. At cervical level, 10 patients presented syndesmophytes and 3 had interapophyseal ankylosis. Of all patients, 17% fulfilled CASPAR and ASAS peripheral criteria, 6% New York and 5% ASAS axial criteria. Patients who met CASPAR criteria showed a signifi-

cantly higher time of psoriasis duration compared to those without arthritis (m16 vs 10 years p=0.02), and a higher frequency of nail involvement (88.2% vs 49.4% p=0.003). Five patients (29.4%) fulfilled the ASAS axial criteria; all of them presented peripheral involvement: mono/olygoarticular in 3 and polyarticular in 2 patients. Patients with peripheral and axial involvement presented a significantly higher frequency of erythrodermic psoriasis compared to the other patients (35.3% vs 1.2% p=0.0006 and 80% vs 16.7% p=0.02). Among the 95 patients without the ASAS axial criteria, 9 showed sacroiliitis grade 2 or higher. Among the 83 patients without arthritis, only 1 presented peripheral radiological changes, whereas 5 presented sacroiliitis grade 2 or 3.

Conclusion: Prevalence of PsA, for both CASPAR and ASAS peripheral criteria was of 17%. According to the ASAS criteria, 5% of patients presented axial involvement, while 6% presented axial involvement regarding the New York criteria. All cases with articular involvement presented a higher frequency of psoriasis nail involvement and skin severity. It is worth to note that few patients without signs or symptoms of arthritis had radiolcgical changes, both axial and peripheral, precluding a proper classification.

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ACR Poster Session A
Spondyloarthritis and Psoriatic Arthritis - Pathogenesis, Etiology
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Changes in Sclerostin, Dickkopf-1 and Serum Markers of Inflammation, Cartilage and Bone Turnover in Patients with Axial Spondyloarthritis Treated with Adalimumab. Susanne Juhl Pedersen[1], Inge Juul Sørensen[2], Julia S. Johansen[3], Patrick Garnero[4], Anne Gitte Loft[5], Jens Skoedt[6], Gorm Thamsborg[1], Karsten Asmussen[7], Elka Kluger[8], Jesper Nørregaard[9], Torben Grube Christensen[10] and Mikkel Østergaard[1]. [1]Glostrup Hospital, Copenhagen, Denmark, [2]Hvidovre Hospital, Copenhagen, Denmark, [3]Herlev Hospital, Herlev, Denmark, [4]INSERM, Lyon, France, [5]Sygehus Lillebaelt, Vejle, Copenhagen, Denmark, [6]Gentofte Hospital, Copenhagen, Denmark, [7]Bispebjerg Hospital, Copenhagen, Denmark, [8]King Christian 10th Rheumatism Hospital at Gråsten, Denmark, [9]Hørsholm Hospital, Denmark, [10]Slagelse Hospital, Slagelse, Denmark

Background/Purpose: Few studies have investigated changes in plasma sclerostin and Dickkopf1 (DKK-1) in relation to other biomarkers of inflammation, cartilage and bone turnover during treatment with tumor-nckrosis-factor-alpha (TNFα) inhibitors. The aim of this study was to investigate plasma concentrations of sclerostin, DKK-1 and serum markers of inflammation, cartilage and bone turnover in patients with axial spondyloarthritis (SpA) before and during treatment with adalimumab.

Methods: In a randomized double-blind placebo-controlled trial, 52 patients with axial SpA (77% male, disease duration median 10,range 1–35 years) were allocated to adalimumab 40 mg (n=27) or placebo (n=25) s.c. e.o.w. for 12 weeks, followed by an open label extension, where all received adalimumab. Patients were included if they had: 1) SpA according to ESSG criteria; 2) sacroiliitis on MRI and/or X-rays; and 3) BASDAI ≥40 mm despite treatment with two NSAIDs. Six patients were excluded before week 12 (adalimumab n=2; placebo n=4). At week 24, 43 (83%) patients were BASDAI responders (i.e. reduction of 50% or 20 mm). P<0.005 was regarded as statistical significant. Plasma sclerostin, plasma DKK-1, serum C-reactive protein (CRP), interleukin-6 (IL-6), YKL-40, plasma vascular endothelial growth factor (VEGF), urinary CTX-II, matrix metalloproteinase 3 (MMP-3), total aggrecan (TA), cartilage oligomeric matrix protein (COMP), CTX-I and total osteocalcin (OC) were measured by ELISAs.

Results: Patients with SpA had higher (compared to healthy subjects) baseline levels of IL-6, YKL-40 and CTX-II (p<0.001) and lower levels of aggrecan (p<0.0001). Levels of VEGF, MMP-3, COMP, CTX-I, OC, sclerostin and DKK-1 were within the normal levels. The treatment groups did not differ in baseline biomarker levels. At baseline, IL-6 correlated with CRP (0.73, p<0.0001) and CTX-II (0.48, p=0.0004); VEGF with YKL-40 (0.46, p=0.001); CTX-II with CTX-I (0.40, p=0.004) and OC (0.45, p=0.0008), and OC with CTX-I (0.55,

p<0.0001). From baseline to week 12 significant correlations between the percentage changes in IL-6 and CRP (0.76 and 0.67, p<0.0002) and OC (−0.67 and −0.54, p≤0.005) were found in both treatment groups. In the placebo group only CRP and OC (−0.62, p=0.002) correlated and in the adalimumab group only CRP and MMP-3 (0.65, p=0.0004) and TA and YKL-40 (−0.55, p=0.004). From baseline to week 12, patients treated with adalimumab had larger percentage decreases in CRP (p=0.009), IL-6 (p<0.0001) and YKL-40 (p=0.04) compared to placebo treated patients. After 12 weeks of adalimumab treatment significant percentage decreases were seen in CRP (p=0.003), IL-6 (p=0.001), VEGF (p=0.006), YKL-40 (p=0.02) and MMP-3 (0.01). In the placebo group TA (p=0.01) increased. No significant changes were seen for VEGF, CTX-I, MMP-3, TA (adalimumab), DKK-1, sclerostin, CTX-I and OC after the first 12 weeks of treatment.

Conclusion: In patients with SpA treatment with adalimumab significantly reduced biomarkers of inflammation. No significant early changes were seen in sclerostin, DKK-1 and biomarkers of cartilage and bone turnover.

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Examining a Role for Th17 Regulation and Toll-Like Receptor Signaling in Psoriatic Arthritis. Fatima Abji, Remy Pollock, Fawnda Pellett, Vinod Chandran and Dafna D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Psoriatic arthritis (PsA) is a seronegative inflammatory arthritis that develops in 30% of patients with cutaneous psoriasis (PsC). Joint inflammation in PsA is mediated in part by natural killer (NK) cells which are an important arm of the innate immune system. We have previously shown that PsA is associated with activating ligands of NK cell receptors, including the killer cell immunoglobulin-like receptors (KIRs) and NKGD2. Toll-like receptors (TLRs) and Th17 cells are components of the innate immune response which have been implicated in other inflammatory arthridities such as rheumatoid arthritis and ankylosing spondylitis. We sought to determine whether a dysregulation in these pathways is also found in PsA.

Methods: Total RNA was isolated from peripheral blood of 20 PsA, 17 PsC, and 19 control subjects. Quantitative RT-PCR arrays (SABiosciences) were used to profile expression of 155 genes related to the Th17 regulatory network and toll-like receptor signaling. Expression was quantified using the ΔΔCt method and fold change differences between groups was determined by Student's t-test (p<0.05 cutoff).

Results: Out of 30 genes significantly dysregulated in psoriatic disease patients (PsA & PsC), two (TLR9 and IL13) were dysregulated greater than 1.5-fold (a 50% increase). 6 genes were significantly dysregulated less than 1.5-fold in PsC patients compared to controls, and one gene (IL23R) was increased 1.6-fold (p=0.049). In PsA patients compared to controls, 9 out of 45 significant genes were dysregulated greater than 1.5-fold: CLEC7A, CLEC4E, CXCL10, CXCL6, IL2, IL15, LY96, TBK1 and TLR9. Comparing PsA to PsC patients, 4 out of 50 significant genes were dysregulated greater than 1.4-fold (LY96, TBK1, CXCL10 and TLR4) and 13 of 50 significant genes were dysregulated less than 1.5-fold, including CD4, CD8A, CXCL5, NFATC2, SYK, TBX21, IRAK2 and RELA.

Conclusion: A majority of the changes observed in PsA were related to TLR signaling. LY96 dysregulation was previously identified in microarray analyses of PsA compared to PsC patients and controls. Over-expression of TLR3 and TLR4 in synovial tissue from patients with early RA has also been reported. Future studies will validate these results, examine the role of TLR signaling pathways in PsA, and determine whether they can serve as biomarkers of PsA susceptibility in patients with PsC.

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Proteomic Analysis of Synovial Tissue: A Unique Tool to Predict Response to Anti-TNF Alpha Therapy in Patients with Inflammatory Arthritis. Opeyemi S. Ademowo[1], Emily S. Collins[1], Cathy Rooney[1], A. W. van Kuijk[2], Danielle M. Gerlag[2], Paul P. Tak[2], Oliver M. FitzGerald[3] and Stephen R. Pennington[1]. [1]UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin 4, Ireland, [2]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [3]St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Inflammatory arthritis, which includes rheumatoid arthritis (RA) and psoriatic arthritis (PsA), is a leading cause of joint deformity, disability and reduced quality of life with a high economic cost [1]. A common target for therapeutic intervention is TNF-α, a key cytokine that drives the inflammatory and destructive processes of these diseases. However, due to common drug failure, diverse degree of response to therapy, cost of treatment as well as adverse drug events [2, 3] there is an urgent need for personalised medicine [4]. We hypothesized that there are distinct proteins or peptides within the synovial tissue that may predict the degree of response to anti TNF-α therapy in patients with inflammatory arthritis. Hence we aim to discover, develop and validate potential predictive biomarkers of treatment outcomes and map the protein changes to potential pathways.

Methods: Baseline protein expressions were investigated and compared in the synovium of 20 PsA patients with diverse responses to adalimumab (a monoclonal antibody against TNF-α) [5]. The EULAR response criteria were used to classify patients' treatment response categories at 3 months follow-up. Synovial proteins were extracted, subjected to digestion with trypsin and the resulting peptides were analysed by label free liquid chromatography-mass spectrometry (LC-MS) on an Agilent 6520 QTOF with HPLC chip cube source attached. Progenesis LC-MS software (version 2.6) was used for the differential protein expression analysis. The potential biomarkers discovered were targeted by multiple reaction monitoring (MRM) technique in a triple quadrupole mass spectrometer for quantitative measurement with the aid of skyline software for instrument method optimization.

Results: The protein profile of the different response categories varied. 313 proteins were differentially expressed between responders and non-responders; a cut off p-value<0.05 and fold change>2 were used to select the biomarker panel. The majority of these proteins have been found to be associated with inflammation. 54 proteins were successfully targeted with the MRM and quantified in synovial tissue. Of the 54 proteins, 25 were significantly over expressed in good responders and 30 were over expressed in non responders.

Conclusion: Label-free LC-MS of synovial tissue is a robust approach to the discovery of differentially expressed proteins that might predict response to anti-TNF-α therapy in PsA patients. These proteins are potential candidate synovial biomarkers of response to anti-TNF-α therapy and will be validated on a larger cohort of patients. The possibility of detecting and measuring these candidate markers in the serum will be explored.

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Familial Aggregation and Heritability of Ankylosing Spondylitis in Taiwan: A Nationwide Population Study. Chang-Fu Kuo[1], Matthew J. Grainge[1], Lai-Chu See[2], Kuang-Hui Yu[3], Shue-Fen Luo[3], Ana M. Valdes[4], I-Jun Chou[3], Weiya Zhang[1] and Michael Doherty[1]. [1]University of Nottingham, Nottingham, United Kingdom, [2]Chang Gung University, Taoyuan, Taiwan, [3]Chang Gung Memorial Hospital, Taoyuan, Taiwan, [4]St. Thomas' Hospital, King's College London, London, United Kingdom

Background/Purpose: To estimate the risk of ankylosing spondylitis (AS) among individuals with affected first-degree relatives and to assess the magnitude of genetic contribution to the susceptibility of AS in the general population of Taiwan.

Methods: Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study in 11,770,921 men and 11,697,080 women in 2004. The case definition of AS was based on physician diagnosis. The relative risk (RR) was calculated as the prevalence of AS among individuals with affected first-degree relatives, divided by the prevalence of AS among individuals with no affected first-degree relatives. The identification of first-degree relatives of each individual was determined using the NIHRD registry for beneficiaries. The marginal Cox proportional hazard model with an equal follow-up time for all subjects was used to estimate RR and the 95% confidence interval (CI). This model was used to account for shared environment and case clustering within families with robust variance, and to adjust for age, sex, place of residence, income levels and occupation. Heritability was calculated based on multifactorial polygenic model.

Results: There were 82,618 men (0.70%) and 58,445 women (0.50%) who had AS diagnosis in 2004. The prevalence of AS was higher in individuals with affected first-degree relatives (3.28%) than those without (0.58%). The overall familial relative risk (RR) was 7.95 (95% CI, 7.68–8.24). The RRs (95% CIs) for an individual with an affected twin, sibling, parent and offspring were 21.70 (18.75–25.11), 15.07 (14.78–16.13), 6.98 (6.66–7.32) and 6.77 (6.50–7.06) respectively. The RR (95% CI) increased with the number of affected first-degree relatives, from 7.35 (7.10–7.62), 43.00 (38.77–47.70) and 141.85 (103.50–194.41) for one, two or three, or more affected relatives, respectively. The heritability of AS was 0.95 (95% CI, 0.92–0.98). Among individuals with AS, only 4.16% had a family history. The population attributable risk associated with familial aggregation in Taiwan was 3.73% (95% CI, 4.24%–4.59%).

Conclusion: The risk of AS is higher among individuals with affected first-degree relatives. In addition, the heritability of AS is very high in the general population in Taiwan, confirming that genetic predisposition plays a major role in AS susceptibility.

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Association of Platelet Endothelial Cell Adhesion Molecule-1 and α1 Integrin Gene Polymorphisms with Uveitis Development in Ankylosing Spondylitis. Seung Cheol Shim, Donghyuk Sheen, Mi Kyoung Lim and Hyo Park. Eulji University Hospital, Daejeon, South Korea

Background/Purpose: Genetic factors provide over 90% of the susceptibility to ankylosing spondylitis (AS) and recent studies have focused on non-major histocompatibility complex genes. The etiology of uveitis in AS has been suggested to involve two adhesion molecules including intercellular adhesion molecule and leukocyte functional antigen.

Platelet-endothelial cell adhesion molecule 1 (PECAM1), a member of the immunoglobulin superfamily, may be an important regulator of antigen induced cell activation of lymphocytes. The β1 integrin (ITGB1) can associate with different membrane proteins and cause signal transduction by interactions in the extracellular and trans-membrane domain. Therefore, we examined the association of PECAM1 and ITGB1 gene polymorphisms with development of uveitis in patients with AS.

Methods: We conducted a case–control study where 223 AS patients who met the Modified New York criteria and 239 ethnically matched controls were genotyped for 9 single nucleotide polymorphisms (SNPs) in the PECAM-1 promoter and gene. Genomic DNA was isolated from peripheral blood leukocytes by a standard phenol–chloroform method and a GoldenGate assay (Illumina, http://www.illumina.com) was used for genotyping.

Results: Conditional logistic regression was used to evaluate the association between the PECAM1 or ITGB1 SNPs with susceptibility to AS, and no significant association was found on both genes. However, in the subgroup analyses between AS patients with uveitis and those without, seven SNPs in PECAM1 gene were associated with the presence of uveitis, including rs1050382 (dominant model (DM), p=0.022), rs2812 (recessive model (RM), p=0.013), rs4968721 (DM, p=0.016), rs6808

(DM, p=0.011), rs6809 (DM, p=0.013), rs9899806 (DM, p=0.013) and rs9913080 (DM, p=0.019) (Table 1). In addition, seven polymorphisms in ITGB1 gene including rs11009147 (DM, p=0.012; co-dominant model (CDM), p=0.034), rs17468 (DM, p=0.012; CDM, p= 0.019), rs2153875 (CDM, p= 0.030), rs2230396 (DM, p=0.012; CDM, p=0.034), rs2488330 (DM, p=0.004; CDM, p=0.017), rs3780871 (DM, p=0.031) and rs7079624 (RM, p=0.004; CDM, p=0.017) were associated with uveitis development (Table 2).

Table 1. Logistic analysis of PECAM1 polymorphisms and the risk of uveitis among AS patients

rs No.	Dominant Model		Recessive Model		Co-dominant Model	
	Odds (95% CI)	P. Value (adj. P.)	Odds (95% CI)	P. Value (adj. P.)	Odds (95% CI)	P. Value (adj. P.)
rs1050382	2.170 (1.116–4.219)	0.022 (0.027)	0.456 (0.129–1.611)	0.223 (0.262)	1.314 (0.824–2.095)	0.250 (0.294)
rs11079538	1.623 (0.745–3.537)	0.222 (0.261)	1.289 (0.568–2.924)	0.543 (0.571)	1.345 (0.821–2.202)	0.238 (0.297)
rs2812	2.190 (0.620–7.736)	0.223 (0.247)	0.424 (0.215–0.837)	0.013 (0.024)	0.732 (0.457–1.173)	0.195 (0.300)
rs4968721	2.302 (1.167–4.541)	0.016 (0.022)	0.412 (0.117–1.446)	0.166 (0.237)	1.304 (0.820–2.075)	0.261 (0.290)
rs6808	2.406 (1.220–4.743)	0.011 (0.020)	0.456 (0.129–1.611)	0.223 (0.278)	1.379 (0.862–2.205)	0.178 (0.298)
rs6809	2.354 (1.193–4.641)	0.013 (0.020)	0.456 (0.129–1.611)	0.223 (0.297)	1.364 (0.852–2.184)	0.195 (0.279)
rs8065316	1.124 (0.490–2.578)	0.781 (0.822)	1.774 (0.908–3.468)	0.093 (0.155)	1.360 (0.848–2.180)	0.201 (0.268)
rs9899806	2.354 (1.193–4.641)	0.013 (0.022)	0.509 (0.143–1.813)	0.297 (0.330)	1.414 (0.876–2.283)	0.155 (0.282)
rs9913080	2.252 (1.141–4.443)	0.019 (0.025)	0.392 (0.112–1.373)	0.143 (0.220)	1.270 (0.800–2.016)	0.310 (0.326)

Table 2. Logistic analysis of ITGB1 polymorphisms and the risk of uveitis among AS patients

rs number	Dominant Model		Recessive Model		Co-dominant Model	
	Odds (95% CI)	P. Value (adj.P.)	Odds (95% CI)	P. Value (adj.P.)	Odds (95% CI)	P. Value (adj.P.)
rs11009147	0.436 (0.226–0.839)	0.012 (0.021)	0.712 (0.273–1.858)	0.488 (0.596)	0.582 (0.353–0.960)	0.034 (0.046)
rs1187078	0.873 (0.261–2.921)	0.826 (0.865)	0.919 (0.486–1.737)	0.796 (0.834)	0.926 (0.560–1.532)	0.767 (0.804)
rs17468	0.436 (0.226–0.839)	0.012 (0.019)	0.563 (0.249–1.272)	0.167 (0.245)	0.589 (0.377–0.918)	0.019 (0.030)
rs2153875	0.527 (0.249–1.117)	0.094 (0.122)	0.465 (0.202–1.071)	0.072 (0.113)	0.582 (0.356–0.949)	0.030 (0.044)
rs2230396	0.436 (0.226–0.839)	0.012 (0.020)	0.712 (0.273–1.858)	0.488 (0.565)	0.582 (0.353–0.960)	0.034 (0.044)
rs2298141	1.340 (0.702–2.559)	0.374 (0.457)	3.718 (1.126–12.28)	0.031 (0.052)	1.508 (0.906–2.511)	0.113 (0.131)
rs2488330	0.390 (0.203–0.748)	0.004 (0.008)	0.712 (0.273–1.858)	0.488 (0.631)	0.546 (0.330–0.901)	0.017 (0.032)
rs2503997	1.278 (0.659–2.477)	0.466 (0.540)	1.308 (0.586–2.920)	0.511 (0.562)	1.205 (0.778–1.865)	0.401 (0.441)
rs3780871	0.268 (0.081–0.888)	0.031 (0.042)	0.745 (0.390–1.424)	0.374 (0.514)	0.662 (0.398–1.103)	0.113 (0.139)
rs7079624	1.403 (0.538–3.662)	0.488 (0.536)	2.560 (1.335–4.909)	0.004 (0.008)	1.830 (1.109–3.021)	0.017 (0.030)

Conclusion: This is the first analysis of the PECAM1 and ITGB1 gene polymorphisms in AS, demonstrating a clear association with uveitis in AS. Given the functional role of PECAM-1 and ITGB1 variants in the immune system, larger studies are now warranted to elucidate the association of PECAM-1 and ITGB1 in the pathogenesis of uveitis in AS.

Disclosure: S. C. Shim, None; **D. Sheen**, None; **M. K. Lim**, None; **H. Park**, None.

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Relative Overexpression of Membrane-Bound Versus Soluble TNF in Human and Experimental Spondyloarthritis. Carmen Ambarus[1], Leonie M. van Duivenvoorde[1], Huriatul Masdar[1], Melissa N. van Tok[1], Paul P. Tak[1], Nataliya Yeremenko[1] and Dominique L. Baeten[2]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Macrophages and their pro-inflammatory cytokines, including TNF, are pivotal mediators of chronic synovitis in rheumatoid arthritis (RA) as well as spondyloarthritis (SpA). Despite similar levels of synovial macrophage infiltration and similar clinical responses to TNF blockade in both diseases, SpA is characterized by a more pronounced infiltration with alternatively activated CD163+ macrophages and ongoing osteoproliferation. This study aimed to investigate whether these differences were related to a differential expression and/or function of TNF between both diseases.

Methods: Healthy donor peripheral blood-derived monocytes were polarized in vitro by IFN-γ, IL-4 or IL-10 for 4 days. The expression of membrane-bound TNF (mTNF) and soluble TNF (sTNF) was measured by FACS and ELISA, respectively. Expression of TNF and its receptors was also measured by qPCR and ELISA in synovial fluid (SF) and synovial tissue biopsies (ST) of actively inflamed knee joints of SpA and RA patients. Mice transgenically overexpressing mTNF (TgA86) were evaluated clinically and histologically for spondylitis and peripheral arthritis.

Results: The expression of mTNF was increased in IL-10 and IL-4 polarized macrophages (alternatively activated macrophages) in comparison with IFN-γ polarized cells (classical activated macrophages). Moreover, the production of sTNF was clearly impaired in the IL-10 polarized CD163+ macrophages and IL-4 polarized macrophages (p<0.01 versus IFN-γ polarized macrophages), indicating a relative shift from sTNF to mTNF by alternative macrophage activation. In line with these in vitro data, the sTNF SF levels were significantly lower in SpA compared to RA (p=0.01) despite similar TNF mRNA levels in ST. This was not related to altered expression of TNF receptors as both TNF-R1 and TNF-R2 were similarly expressed in ST, both at protein and mRNA levels. The mRNA levels of TACE, the enzyme responsible for the cleavage of TNF, TNF receptors and other molecules from the cell membrane were also similar between SpA and RA ST. To investigate whether relative overexpression of mTNF could be relevant in SpA pathophysiology, we characterized mTNF transgenic mice. As previously described, these mice developed a moderate peripheral arthritis with 100% incidence, resulting in deformation of the paws and loss of grip strength. Histologically, the joints were characterized by moderate synovitis and appearance of lymphoid aggregates in the bone marrow, mostly in the absence of osteoclastic infiltration or extensive destruction. Besides arthritis, all transgenic animals spontaneously developed spondylitis as evidenced by a crinkled tail, a hunchback and histological inflammation in the connective tissue next to the intervertebral disc. Interestingly, also bone remodeling was observed both in axial and peripheral joints. None of the non-transgenic littermates developed signs of arthritis and/or spondylitis.

Conclusion: mTNF is relatively overexpressed by CD163+ alternatively polarized macrophages in SpA synovitis and leads to an axial and peripheral SpA phenotype in transgenic mice, including osteoproliferation.

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High Prevalence of Anti-CD-74 Antibodies with Specificity for the Class II-Associated Invariant Chain Peptide in Patients with Axial Spondyloarthritis but Not in Controls. Xenofon Baraliakos[1], Niklas T. Baerlecken[2], Frank Heldmann[3], Torsten Witte[4] and Jügen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]MD, Hannover, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Ghana, [4]Hannover Medical School, Hanover, Germany

Background/Purpose: The pathogenesis of axial spondyloarthritis (axSpA) is still unclear. Based on the strong association with HLA-B27 and ERAP-1, T cells are believed to play a major role but a role of B cells seems also possible. Autoantibodies have not been frequently found in axSpA but recently anti-CD74 antibodies with specificity to a class II-associated invariant chain peptide (CLIP) have been detected. We studied the prevalence of antibodies against CLIP (anti-CLIP-ABs) in patients with axSpA in comparison to controls and determine their sensitivity and specificity.

Methods: Sera of patients with axSpA and non-SpA were analyzed for IgG-antibodies against CD74 using an ELISA with specificity for CLIP, developed in cooperation with AESKU Diagnostics (Germany). A cut-off of ≥4 standard deviations of arbitrary units (AU) from the mean serum level was used to differentiate results. The laboratory workers were completely blinded for the clinical data.

Results: A total of 145 sera from 94 patients with axSpA and 51 with other diseases were analyzed. The patient demographics differed: axSpA patients were more often male and younger. The HLA-B27 status was available in 72 patients. Anti-CLIP-ABs were detected in 85.1% in axSpA but in only 7.8% in non-SpA patients (p£0.0001). Higher levels of anti-CLIP-ABs were found in axSpA vs. non-SpA: mean 14.5 vs. 0.8 AU (p£0.0001). The sensitivity of anti-CLIP-ABs for a diagnosis of axSpA was 85.1% and the specificity 92.2%, with a positive likelihood ratio (LR) of 10.8 and a negative LR of 0.08. The relative contribution of anti-CLIP-ABs and HLA-B27 was largely similar: 87.5% of the patients with axSpA were positive for both, but only 14.9% were anti-CLIP-negative while 23.6% were HLA-B27-negative.

Conclusion: Anti-CLIP antibodies were strongly associated with axSpA including AS. The LR for diagnosing AS was even higher than for HLA-B27. More studies using this promising new method in patients with non-radiographic axial SpA or peripheral SpA are needed to establish its usefulness in clinical practice.

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Brain MRI and Psychophysics Analysis Demonstrate Neuropathic Pain to Be a Component of Back Pain in Ankylosing Spondylitis. Q. Wu[1], R. D. Inman[2] and Karen Davis[1]. [1]Toronto Western Research Institute, Toronto, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: The mechanisms underlying pain in ankylosing spondylitis (AS) are unclear. The aim of this study was to investigate whether there is a neuropathic component in AS pain and to delineate gray matter brain abnormalities associated with AS.

Methods: Seventeen patients with back pain secondary to AS (12M/5F; 34.4 +/− 12.4yo) and age/sex-matched controls consented to the approved study. Mean BASDAI scores in the AS patients were 6.6 +/− 2.1, and none were on biologic agents at the time of the study. Patients were assessed with the PainDETECT (scores <12 indicate low probability of neuropathic pain) and McGill Pain Questionnaires. Mechanical and thermal pain thresholds were determined, 3T MRI scans obtained for all subjects. Brain gray matter was measured with cortical thickness analysis (Freesurfer) and voxel based morphology (FSL-VBM) for subcortical structures with age included as a covariate.

Results: The mean painDETECT score in AS patients was 15.1 ± 7.08 (eleven scored >12). Compared to controls, AS patients had significantly decreased mechanical and cold sensitivity on their dorsal feet but pain thresholds were not abnormal. The gray matter analysis identified that AS patients had significant cortical thinning in left primary sensory (S1), insular, and anterior mid-cingulate cortices (MCC), and right supplemental motor area and ACC. Furthermore, painDETECT scores correlated with cortical thinning in the left S1 and thickening in the left motor cortex, right anterior cingulate and prefrontal cortex. All cortical findings were significant at p< 0.05 image-wise, corrected for multiple comparisons.

Conclusion: Our psychophysical testing and self-reports identified signs of neuropathy. The imaging results of abnormal brain gray matter linked to neuropathic pain are concordant with the clinical picture of AS having sensorimotor and mood deficits as well as neuropathic pain. These data suggest that back pain in AS is a mixed pain condition that includes a neuropathic pain component.

Disclosure: Q. Wu, None; **R. D. Inman**, None; **K. Davis**, None.

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Discovery of Two Public T Cell Receptor Clonotypes in B27+ Ankylosing Spondylitis by Deep Repertoire Sequence Analysis. Malek Faham[1], Victoria Carlton[1] and R. D. Inman[2]. [1]Sequenta, Inc., South San Francisco, CA, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: The strong association of AS with HLA-B27 implicates a T cell response restricted by this Class I MHC molecule, predicting that specific T Cell Receptor (TCR) sequences would be shared among AS patients.

Methods: We have developed a technology for large scale sequencing of TCR to assess the repertoire profile. All TCR sequences are amplified from peripheral blood and 1 million TCR sequences are obtained to generate a comprehensive profile of TCR repertoire. We applied this technology to profile B27+ AS (n=128), B27- AS (n=24), B27- mechanical back pain (n=24), healthy controls (n=25) and SLE patients (n=176).

Results: We used a TCR repertoire data from the controls (HC and SLE) to filter out clonotypes present in an appreciable number of these samples. After rigorous control of multiple testing using train and test data sets, two clonotypes were discovered to have significantly different frequencies in B27+ AS population and controls (41% vs 5% and 54% vs19%, p <0.0001). These clones were further tested in 24 patients with mechanical back pain and 24 B27- AS patients. The frequency of both clonotypes in the MBP population was similar to that in controls (4% vs 5% and 25% vs 19%). In B27- AS one clonotype had frequency similar to controls (8% vs 5%), and one had a higher frequency than controls (42% vs. 25% p =0.016). The table below shows the frequency of both clonotypes in the different populations.

Diagnosis	n	Clone 1: no. positive (%)	Clone 2: no. positive(%)
B27+ AS	128	54 (41%)	69 (54%)
B27− AS	24	2 (8%)	10 (42%)
MBP	24	1 (4%)	6 (25%)
Controls	201	11 (5%)	38 (19%)

Conclusion: We provide evidence that there is a distinctive set of shared clonotypes in the T cell repertoire in AS patients. This sheds light on the immunological role of HLA B27 in AS and demonstrates promising specificity for potential diagnostic utility.

Disclosure: M. Faham, Sequenta, Inc, 3; **V. Carlton**, Sequenta, Inc, 3; **R. D. Inman**, None.

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NGF and Trka: A Novel Therapeutic Target in Chronic Inflammation. Siba P. Raychaudhuri[1], Ananya Datta Mitra[2] and Smriti K. Raychaudhuri[2]. [1]VA Sacramento Medical Center/UC Davis School of Medicine, Mather, CA, [2]VA Sacramento Medical Center, Mather, CA

Background/Purpose: Outside the nervous system, several studies have established the regulatory role of nerve growth factor (NGF) and its high affinity receptor, TrkA. A clinical trial showed that NGF monoclonal antibody reduced osteoarthritic pain. We have reported regulatory role of NGF/TrkA in chronic inflammatory diseases, e.g., psoriasis, psoriatic arthritis (PsA) and rheumatoid arthritis (RA). These observations suggest the functional significance of NGF and its high affinity receptor, TrkA in pain and inflammation. We are reporting the role of NGF and TrkA on two key pathological events of inflammatory cascade: angiogenesis and T cell proliferation.

Methods: Human dermal microvascular endothelial cells (HDMEC) tubule formation (angiogenesis) was assessed using bovine type I collagen. HDMECs (40000 cells/ml) were incubated in presence or absence of NGF, K252a for 6 hours at 37°C. Tubule formation was checked under microscope (20x). Magnetically sorted CD3^{+} T cells from psoriasis, PsA and RA were stimulated with CD3/CD28 cocktail and cultured in presence or absence of NGF, TrkA inhibitor K252a. Cell proliferation was measured by MTT and CFSE dilution assay.

Results: Angiogenesis was markedly increased with NGF (68.39±2.10%) compared to media (15.57±0.80%, p<0.001). K252a (20.42±0.98%) significantly inhibited NGF induced angiogenesis (68.39±2.10%, p<0.001) (Figure 1). CD3^{+}T cells proliferation was significantly increased by NGF (OD: 1.2±0.09) compared to media (OD: 0.73±0.07, p<0.05). In presence of physiological stimulus (CD3/CD28), NGF induced more proliferation (OD: 2.17±0.23) of CD3^{+}T cells compared to only physiological stimulus (1.62±0.23, p<0.01). Potent TrkA inhibitor, K252a significantly blocked the NGF induced CD3^{+}T cells proliferation (1.33±0.16 vs. 2.17±0.23, p<0.01). Similar results were observed in CFSE assay too (Figure 2).
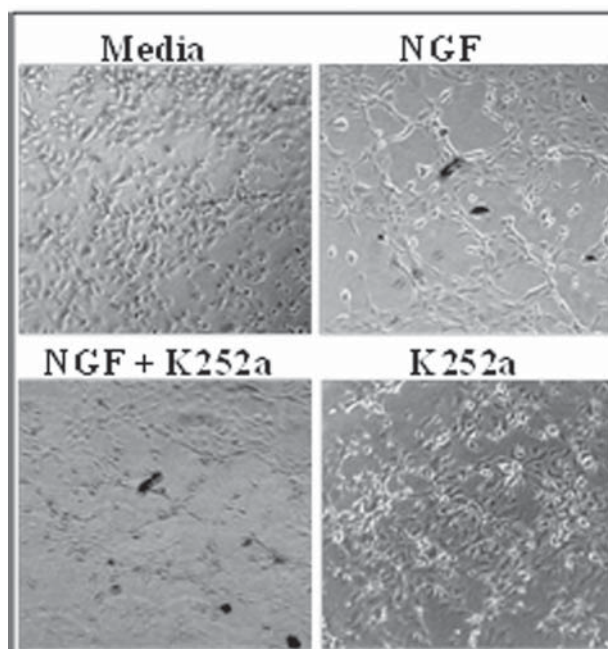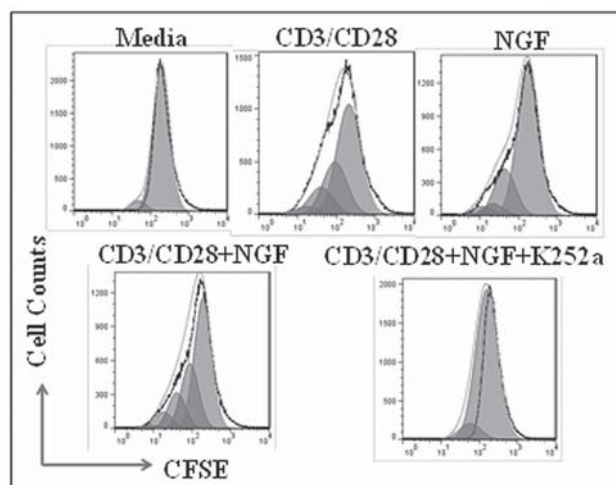
Conclusion: This study suggests the regulatory role of NGF/TrkA interaction on two major events of inflammatory cascade: angiogenesis and T cell proliferation. Thus inhibition of NGF/TrkA interaction either by NGF monoclonal antibody or TrkA inhibitor could be a new therapeutic approach for chronic inflammatory diseases.

Disclosure: S. P. Raychaudhuri, None; **A. Datta Mitra**, None; **S. K. Raychaudhuri**, None.

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The Association Between KIR3DL1 Alleles and Psoriatic Arthritis.
Remy Pollock, Jeffrey Berinstein, Arane Thavaneswaran, Fawnda Pellett, Dafna Gladman and Vinod Chandran. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Killer-cell immunoglobulin-like receptors (KIRs) are activating and inhibitory receptors that regulate NK and NK-T cells, which have been found in psoriatic plaques and synovial fluid of patients with psoriatic disease (PsD). The inhibitory KIR3DL1 receptor binds to HLA-B alleles with the Bw4 motif. Binding of KIR3DL1 to HLA-Bw4 alleles with isoleucine at codon 80 (Bw4–80I) results in stronger inhibition than Bw4 alleles with threonine at codon 80 (Bw4–80T). KIR3DL1 alleles can be classified according to their expression levels on NK cells as High, Low, Null or KIR3DS1 (an activating allele of 3DL1). We examined the association of KIR3DL1 alleles and the Bw4 dimorphism with PsD.

Methods: Genomic DNA was available on 656 Caucasian patients with PsD (395 PsA patients: mean age 42 years, males 58%, age at psoriasis 28 years, age at PsA 36 years, PASI 5.6, active joint count 11, axial disease 33% who satisfied CASPAR criteria and 261 PsC patients: mean age 48 years, males 56%, age at psoriasis 30 years, PASI 5.4) and 377 Caucasian controls (mean age 41 years, males 48%). A nested quantitative PCR assay was designed to selectively amplify the KIR3DL1 locus and High, Low, Null, and KIR3DS1 alleles using custom Taqman SNP genotyping assays. DNA from the UCLA International KIR Exchange program was used for assay validation and optimization. Chi-squared test and tests for interaction were conducted and KIR3DL1 low and null allele categories were grouped together.

Results: The genotype frequencies across the 3 groups are given in Table 1. We observed statistically significant differences in the frequency of KIR3DL1 low/null alleles, and between Bw4–80I and –80T alleles. The frequencies of KIR3DL1 low/null alleles were lower in psoriatic disease and PsA compared to controls (Table 2). No significant differences between PsA and PsC could be demonstrated. We also investigated the interaction between KIR3DL1/3DS1 alleles and Bw4–80I and –80T and observed a trend towards significant interaction between KIR3DL1 low/null and Bw4–80T when comparing PsA to controls (p=0.1). The association between KIR3DL1 low/null was present only in the absence of Bw4–80T alleles (OR=0.86, 95% CI 0.78, 0.94, p=0.002).

Table 1. Differences in allele frequencies between the three groups.

Allele	Controls (n=377)	PsC (n=261)	PsA (n=395)	P value
KIR3DL1 low/null	225 (60%)	140 (54%)	199 (50%)	0.03
KIR3DLI High	194 (52%)	126 (48%)	199 (50%)	0.73
KIR3DS1	126 (33%)	98 (38%)	150 (38%)	0.37
HLA-B Bw4	233 (62%)	177 (68%)	292 (74%)	0.002
HLA-B Bw4- 80I	101 (27%)	93 (36%)	140 (35%)	0.02
HLA-B Bw4- 80T	151 (40%)	102 (39%)	191 (48%)	0.02

Table 2. Association between KIR3DL1 low/null alleles and disease groups.

Comparison	OR (95% CI)	P value
Psoriatic disease vs. controls	0.72 (0.56,0.93)	0.01
PsA vs. controls	0.69 (0.52,0.91)	0.01
PsC vs. controls	0.78 (0.57,1.08)	0.13
PsA vs. PsC	0.88 (0.64,1.20)	0.41

Conclusion: In PsA patients, there was a significantly decreased expression of the KIR3DL1 Low/Null alleles particularly in the absence of HLA-B Bw4–80T. The results support the role of KIR genes and their interaction with HLA-B alleles in susceptibility to PsA.

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Structural Progression of Ankylosing Spondylitis Associated with Elevation in Two NOVEL, Inflammatory Biomarkers; Matrix Metalloproteinase and Cathepsin-Derived.
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Background/Purpose: Current inflammatory biomarkers, such as CRP, have insufficient sensitivity and specificity to be broadly accepted for diagnosis and prognosis of AS. We hypothesized, that quantification of inflammation markers derived from the affected tissue might have improved clinical utility compared to the systemic markers. We developed two novel biomarker assays detecting MMP and cathepsin-derived CRP (MMP-CAT and CAT-CRP) and aimed to determine their diagnostic utility and association with radiological progression.

Methods: Serum samples (n=124) from AS patients, mean disease duration (SD) 18.0 (11.4) years were assessed. Within this cohort, samples from 16 AS patients with structural progression over two years and 29 without were selected for prognostic evaluation (sub-cohort 1A). A progressor was defined as having a baseline mSASSS of ' 10 units and progression of ≥5 units plus ≥ 1 new syndesmophyte over two years. Non-progressors were defined as disease duration at baseline of > 10 years, baseline mSASSS < 5 units, and no change in mSASSS over 2 years Sub-cohort 1B comprised samples from 53 AS patients pre- and post- anti-TNF treatment. We also included samples (n=39) from healthy controls.

Results: CRP-MMP and CRP-CAT were both elevated in AS compared to controls; mean (SD) 9.84 (4.40) ng/ml vs. 4.82 (1.49) ng/ml (p<0.05), respectively, for CRP-MMP, and 299.6 (137.6) ng/ml vs 178.6 (54.03) ng/ml (p<0.05), for CRP-CAT. AUC according to ROC analysis was 0.94 (p<0.0001) and 0.85 (p<0.0001) for CRP-MMP and CRP-CAT, respectively. In AS patients with progression CRP-MMP and CRP-CAT were significantly elevated compared to non-progressors. Both CRP-related markers decreased significantly after short term (2–3 months) anti-TNF treatment.

Conclusion: Both MMP and Cathepsin-derived fragments of CRP are significantly elevated in AS patients. These markers, but not CRP, were significantly elevated at baseline in patients having structural progression defined by a composite index including mSASSS and syndesmophyte quantification.

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Two Novel Diagnostic Biomarkers of Cartilage Degradation and Connective Tissue Inflammation Are Predictive of Disease Progression in Ankylosing Spondylitis. Anne C. Bay-Jensen[1], Stephanie Wichuk[2], Inger Byrjalsen[3], Zheng Zhao[4], Robert GW Lambert[2], Morten Asser Karsdal[1] and Walter P. Maksymowych[2]. [1]Nordic Bioscience A/S, Herlev, Denmark, [2]University of Alberta, Edmonton, AB, [3]Nordic Bioscience, Herlev, Denmark, [4]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China

Background/Purpose: Cartilage degradation and inflammation of synovial and connective tissue are key events in inflammatory arthropathies such as SpA. Presently there are no prognostic tools available for measuring these tissue related processes. Inflammation induces an increase in collagenases which lead to increased degradation of cartilage and synovial tissue. Type II collagen is the primary protein component of cartilage and type III collagen is one of the major proteins of synovial membrane. We aimed to investigate the diagnostic and prognostic utility of cartilage and synovial turnover biomarkers in AS.

Methods: Serum samples from patients with AS (n=124), RA (n = 47), and controls (n = 56) were assessed for type II and III collagen degradation using the C2M competitive ELISA and the C3M ELISA, respectively. Standard AS clinical outcome scores were collected: BASDAI (health questionnaire), hsCRP, and mSASSS. Progressors were defined as having new vertebral syndesmophytes over a two year period. Logistic regression and CART were used to analyze the prognostic value of the markers individually or in combination.

Results: Both cartilage and connective tissue degradation fragments, C2M and C3M, were significantly elevated in serum samples from AS patients compared to healthy controls (P<0.0001). The area under the curves of C2M and C3M, respectively, were 70% and 81% for AS. C2M and C3M were also significantly elevated in RA patients compared to controls (P<0.0001). Diagnostic utility analyzed by ROC and AUCs were 72% and 89% for C2M and C3M, respectively. C3M correlated significantly with AS score BASDAI and mSASSS (p<0.01). C2M did not show the same correlations. A combination of the two markers could identify 80% of those who were defined as progressors and 61% of the non-progressors.

Conclusion: This study is the first to show that the two novel biomarkers of cartilage and synovial tissue degradation add additional information to the understanding of the diagnosis and progression of SpA.

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DKK1 Serum Level Is Increased in Recent Spondyloarthritis and Is Associated with Higher Prevalence of Syndesmophytes. Sclerostin Is Highly Correlated with Age. Data From the DESIR Cohort. Gaetane Nocturne[1], Stephan Pavy[2], Désirée van der Heijde[3], Philipe M. Goupille[4], Maxime Dougados[5], Christian Roux[6], Xavier Mariette[7] and Corinne Miceli-Richard[2]. [1]Université Paris Descartes, Paris, France, [2]Université Paris Sud, Le Kremlin Bicêtre, France, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Hopital Trousseau, Tours, France, [5]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [6]Paris Descartes University, Paris, France, [7]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Dickkopf-1 (DKK-1) and sclerostin (SOST) are 2 inhibitory proteins of the Wnt signalling pathway that could rationally be involved either in AS osteoporosis or in the osteoblastogenesis associated with syndesmophyte construction. We aimed to investigate serum levels of DKK-1 among patients with recent inflammatory back pain fulfilling ASAS criteria for spondyloarthritis (SpA) and to investigate the parameters associated or correlated with DKK-1and SOST serum levels.

Methods: The DESIR cohort is a prospective, multicenter French cohort of patients with early IBP (Calin or Berlin criteria) (>3 months and <3 years of duration) suggestive of SpA, including 708 patients. DKK-1 and SOST serum levels were assessed at baseline on the whole cohort by sandwich ELISA (Biomedica, Vienna). DDK-1 and SOST serum levels were further analyzed in the subgroup of patients fulfilling ASAS criteria for SpA (N=479; 68.9%) and compared with serum levels from 71 controls (without autoimmune or chronic inflammatory disease). 461 SpA patients (94.8%) were treated with NSAIDs, 62

with corticosteroids (less than 10 mg per day) and 67 with DMARDs (35 SSZ and 32 MTX) at inclusion in the study. All SpA patients were naive of any TNF blocker at inclusion in the study. Univariate and multivariate analyses were performed in order to identify the main predictors of DKK-1 and SOST serum levels in SpA patients.

Results: Serum DKK-1 levels were available for 695 patients with IBP (472 of them fulfilling ASAS criteria for axial SpA) and were significantly increased in SpA patients (mean $\pm$ SEM 30.7 $\pm$ 0.7 pmol/L) compared with controls (10.8 $\pm$ 1.1 pmol/L) ($p<0.0001$). DKK-1 serum levels were significantly correlated with ESR (P=0.04; r=0.10), CRP (P=0.015; r=0.11), ASDAS-ESR (P=0.03; r=0.10), ASDAS-CRP (P=0.016; r=0.11). A significant positive correlation between DKK-1 serum levels and lumbar spine BMD was observed (P=0.04; r=0.13). DKK-1 serum levels were significantly higher among SpA patients with syndesmophytes (mSASSS>0; N=131) (mean $\pm$ SEM 35.4 $\pm$ 1.6 pmol/L) compared with patients with normal X-Rays (N=334) (mean $\pm$ SEM 28.6 $\pm$ 1.1 pmol/L) (P<0.0001). Multivariate analysis led to a significant association of DKK-1 serum levels with the presence of syndesmophytes at baseline. SOST was not significantly increased among SpA patients compared with controls. SOST serum levels were significantly correlated with US CRP (r=−0.20; P<0.0001), DKK-1(r=0.13; P<0.006), and age (r=0.31; P<0.0001). Neither axial structural lesions nor BMD measurements were associated or correlated with SOST serum levels. Multivariate analysis led to a significant association of SOST serum levels with age, DKK-1 and us-CRP.

Conclusion: This study conducted in a large cohort of patients presenting with early axial SpA clearly showed an increase in DKK-1 serum levels, such increase being even more important in the sub group of patients with axial structural lesions. SOST was mainly correlated with age and to a lesser extend with DKK-1 serum levels and us-CRP. Their respective role in SpA pathogenesis needs further investigation.

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Evidence of Human Leucocyte Antigen-B27 in Healthy Individuals and Patients with Uveitis Is a Risk Factor for Alterations in Bone Metabolism. Sarah Schmidt[1], Stephanie Finzel[1], Jürgen Rech[1], Matthias Englbrecht[1], Silke Winkler[1], Isabel Schmidt[1], Roula Said-Nahal[2], Maxime A. Breban[2] and Georg A. Schett[3]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Ambroise Paré Hospital (AP-HP), and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: To test whether positivity for HLA-B27 *per se* is associated with changes of biomarkers of the Wnt pathway.

HLA-B27 is strongly associated with the development of spondyloarthritis (SPA), a disease characterized by new bone formation and ankylosis of joints and intervertebral spaces. We have recently shown the role of the two Wnt antagonists, dickkopf 1 (DKK1) and sclerostin in new bone formation in SPA. We therefore hypothesized that HLA-B27 itself may be associated with alterations in expression of DKK1 and sclerostin.

Methods: 31 patients with HLA-B27 positive SPA, 30 patients with HLA-B27 positive uveitis as well as 30 healthy carriers of HLA-B27 were included. Furthermore, we assessed 32 HLA-B27 negative healthy controls comparable for age and gender. We evaluated total DKK1 and sclerostin levels in sera of all individuals by enzyme-linked immunosorbent assays (ELISA). Statistical analysis was done by t-tests using SPSS version 18.0.

Results: Healthy HLA-B27 positive individuals showed significant lower levels of DKK1 compared to negative controls (T (60)= −4.615, p< 0.001). Moreover, DKK1 levels were significant reduced in HLA-B27 positive SPA-patients (T (61)= −3.670, p=0.001) and in HLA-B27 positive uveitis patients (T(60)= −2.445, p=0.017). Lowest levels of DKK1 were found in HLA-B27 positive healthy carriers. Serum levels of sclerostin were significantly lower in HLA-B27 positive SPA-patients compared to HLA-B27 negative individuals (T (61)= −3.130, p=0.003). Additionally, serum levels of sclerostin were distinctly reduced in HLA-B27 positive uveitis patients and in HLA-B27 positive healthy carriers.

Conclusion: HLA-B27 positivity is associated with low levels of DKK1 and sclerostin independent from the presence of clinical symptoms of SPA. Both HLA-B27 healthy carriers as well as HLA-B27 associated uveitis without SPA

show lower levels of these two Wnt antagonists than normal HLA-B27 negative controls. These data suggest that alterations in bone metabolism even occur in the absence of clinical SPA and are associated with HLA-B27 carriage.

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A Genomewide Association Study of Anterior Uveiti. Dorith Claushuis[1], Adrian Cortes[2], Linda A. Bradbury[1], Tammy M. Martin[3], James T. Rosenbaum[4], John D. Reveille[5], Paul Wordsworth[6], Jennifer Pointon[6], Australo-Anglo-American Spondyloarthritis Consortium[7], David Evans[8], Paul Leo[2], Pamela Mukhopadhyay[2] and Matthew A. Brown[2]. [1]The University of Queensland Diamantina Institute, Brisbane, Australia, [2]The University of Queensland Diamantina Insititue, Brisbane, Australia, [3]Oregon Health & Science Univ, Portland, OR, [4]Oregon Health & Science University, Portland, OR, [5]Univ of Texas Health Science Center at Houston, Houston, TX, [6]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [7]Houston, TX, [8]Bristol University, Bristol, United Kingdom

Background/Purpose: Anterior uveitis (AU) is the most common extra-articular manifestation of ankylosing spondylitis (AS), occurring in up to 30–40% of AS cases. The aim of the current study was to investigate clinical associations of AS, and to identify genes associated with the risk of developing AU.

Methods: 972 AS cases with AU (AS+AU+) and 1404 AS cases without AU (AS+AU-) were available for study. All cases were of white European descent. A genomewide association study was performed using SNP data from the TASC and TASC-WTCCC2 AS studies, 291,537 SNPs being available in the merged dataset. Case-control analysis comparing the AS+AU+ and AS+AU- cohorts was performed using Eigenstrat to control for population stratification effects.

Results: Male and female AS cases were equally likely to develop AU. As expected, AU complicating AS was strongly associated with AS disease duration (beta=0.027, $P<10^{-6}$). No association was seen with age, independent of AS disease duration. Considering AS+AU+ cases in comparison with AS+AU- cases, no SNP achieved genomewide significance. Three loci showed suggestive association with AU. At chromosome 6q26, two SNPs in the *PARK2* gene achieved $P<10^{-5}$ (rs2849576, $p=7.6\times10^{-6}$; rs13205287, $p=2.0\times10^{-6}$). Five SNPs (rs379796, rs419519, rs445890, rs452186, rs45218) in an intergenic region on chromosome 4q33 achieved $P=9.0\times10^{-6}-9.5\times10^{-6}$. Association was noted with HLA-B27 (antigen carriage, odds ratio 2.58, $P=5.6\times10^{-8}$). There was a marginal association of B27-homozygosity in this analysis (odds ratio 2.1, $P=0.06$). No known AS locus was differentially associated in AS+AU+ cases in comparison with AS+AU- cases.

Conclusion: This analysis found that with the exception of HLA-B27, no differences were identified between AS+AU+ and AS+AU- cases. The study was adequately powered to identify moderately large genetic effects, but not small-moderate genetic effects for which larger studies will be required. Further, as all patients studied have AS, whether genetic associations of AS-AU+ cases are different to those of AS+AU+ remains unclear. Nonetheless, these findings suggest that AU has very similar genetic risk factors to AS, and therefore that they likely share similar aetiopathogenisis.

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Evolution of Atherosclerosis in Psoriatic Arthritis: Is the Former an Independent Inflammatory Process? Roberta Ramonda[1], Massimo Puato[2], Valentina Modesti[1], Mariagrazia Lorenzin[1], Paola Frallonardo[1], Augusta Ortolan[1], Carla Campana[1], Alessandro Lo Nigro[1] and Leonardo Punzi[3]. [1]Unit of Rheumatology, University of Padova, Padova, Italy, [2]Department of Internal Medicine, University of Padova, Padova, Italy, [3]Rheumatology Unit - University of Padova, Padova, Italy

Background/Purpose: A non-invasive study focusing on the structural and functional properties of the carotid arteries was carried out in psoriatic arthritis (PsA) patients. Increased cardiovascular morbidity and mortality and accelerated atherosclerosis were observed in patients with several rheumatic diseases, including PsA. The impact of two years of Tumor Necrosis factor alpha (TNF-a) blockade treatment on vascular structure and function was assessed.

The aim of this study was to evaluate the presence of subclinical atherosclerosis in PsA patients before and after 24 months of TNF blockade therapy and to investigate the efficacy of treatment not only with regard to disease activity but also in improving atherosclerotic indexes.

Methods: Thirty-two PsA patients were studied before and after 24 months of TNF blockade therapy. Subclinical atherosclerosis was investigated on the basis of B-mode ultrasound measurements of the carotid intima-media thickness (IMT) expressed as the mean IMT value (the mean IMT measured bilaterally at 3 levels: the common carotid artery, the carotid artery bulb and the internal carotid artery,) and as the MMax (the mean maximum IMT). Post-occlusion flow mediated dilation (FMD) of the brachial artery was evaluated by high-sensitivity brachial ultrasonography and endothelial independent dilatation (GTN) using carotid duplex scanning. Response to therapy was studied by evaluating the tender and swollen joints (Tj and Sj), DAS 28, ESR and CRP. Patients' lipid profiles before and after the 24 month treatment period were also evaluated. Differences in parameters over the observation period were assessed using the Wilcoxon test.

Results: After a 24 month treatment period there was no improvement in ultrasonographic parameters with respect to baseline values. Indeed, there was a significant deterioration in both mean IMT and MMAX (respectively 0.75 ± 0.20 vs 0.96 ± 0.40 and 0.91 ± 0.25 vs 1.09 ± 0.44, $p<0.01$), while no alterations were observed in the FMD (5.81 ± 2.07 vs 5.29 ± 2.64, ns) or the GTN (7.76 ± 2.96 vs 7.84 ± 3.08, ns). There was instead a good response to therapy with significant reduction in the Tj (8.10 ± 5.56 vs 2.09 ± 2.32, $p<0.01$), the Sj (3.85 ± 3.84 vs 0.25 ± 0.72, $p<0.01$), the DAS 28 (4.16 ± 0.66 vs2.30 ± 0.82, $p<0.01$), the ESR (26.3 ± 16.4 vs 14.88 ± 13.99, $p<0.01$) and the CRP (11.25 ± 9.16 vs 2.91 ± 1.72, $p<0.01$). There were no significant alteration with regard to lipid profile after the two year treatment period.

Conclusion: PsA per se implies a pro-atherogenic remodelling of carotid arteries that did not seem to be affected by the 2 year anti-TNF blockade therapy despite clinical improvement. There was in fact a slight progression in subclinical atherosclerosis as assessed by ultrasonography. Both the mean IMT and the MMAX showed a slight worsening over the two year period, while FMD, which we expected to be improved, was instead stable. Other inflammatory mechanisms not related to TNF may be responsible for the progression in atherosclerotic disease and the possible role of a genetic predisposition should not be underestimated. PsA patients seem, in fact, to have a higher risk of atherosclerosis compared to subjects with other inflammatory rheumatic diseases.

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Investigating the Genetic Association Between *ERAP1* and Spondyloarthritis. Amir Kadi[1], Brigitte Izac[1], Roula Said-Nahal[2], Ariane Leboime[2], Kurt L. de Vlam[3], Dirk Elewaut[4], Gilles Chiocchia[1] and Maxime A. Breban[2]. [1]Institut Cochin - INSERM U1016 - CNRS (UMR 8104), Paris, France, [2]Ambroise Paré Hospital (AP-HP), and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [3]University Hospitals Leuven, Leuven, Belgium, [4]Ghent University Hospital, Ghent, Belgium

Background/Purpose: A robust association was recently identified between polymorphisms in the non-major histocompatibility complex gene ERAP1 and ankylosing spondylitis (AS) in several populations. The aim of the current study was to determine the level of association of ERAP1 polymorphisms with spondyloarthritis (SpA) in French/Belgian population with a particular attention to genotype-phenotype correlations.

Methods: We studied 734 independent SpA cases and 632 controls from 2 European cohorts. Five single nucleotide polymorphisms (SNPs), rs27044, rs17482078, rs10050860, rs30187 and rs2287987 were genotyped and case-control association analyses were carried using PLINK. Linkage disequilibrium and haplotypes were estimated with Haploview. Analysis was first carried in SpA as a whole group, and then separately in AS and non-radiographic SpA (non-AS) patients.

Results: Consistent with previous studies conducted in AS, rs30187 was the most significantly associated SNP with SpA ($P=0.008$ in the French and $P=6.46\times10^{-4}$ in the Belgian cohorts). In the combined cohort, this SNP was associated with both AS and non-AS ($P_{Combined}=3.9\times10^{-5}$ and $P_{Combined}=0.005$, respectively). A similar trend was observed with other SNPs. The rs17482078/rs10050860/rs30187-CCT haplotype was significantly associated with increased risk of SpA in both cohorts

($P_{combined}=9.08\times10^{-4}$), including AS and non-AS ($P_{combined}=6.16\times10^{-4}$ and $P_{combined}=0.049$, respectively), whereas the -TTC haplotype was associated with reduced risk of SpA, including AS and non-AS ($P_{combined}=2.36\times10^{-7}$, $P_{combined}=5.69\times10^{-6}$ and $P_{combined}=2.13\times10^{-4}$, respectively).

Conclusion: This is the first study to show an association between several polymorphisms located in ERAP1 and SpA as a whole. Our findings demonstrate consistent association of the same SNPs and haplotypes with both AS and non-AS subtypes of SpA.

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The Non-Synonymous Polymorphism *IL23R* Arg381Gln Is Associated with Ankylosis in Spondyloarthritis.
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Background/Purpose: Spondyloarthritis (SpA) is a group of articular disorders sharing genetic background. Single-nucleotide polymorphisms (SNP) of the interleukin 23 receptor (IL23R) gene have been reproducibly reported as associated with ankylosing spondylitis (AS) a subset of SpA, defined by advanced radiographic sacroiliitis. Here, we examined the association between several SNPs in the IL23R gene and SpA as a whole. A particular attention was devoted to genotype-phenotype correlations.

Methods: Eight single-nucleotide polymorphisms (SNPs) located in the IL23R gene were genotyped in a collection of 414 independent French SpA patients and 264 healthy controls. In addition, the most significantly associated polymorphism rs11209026 (Arg381Gln) was genotyped in 156 multiplex families of SpA and in 136 independent trios. Association analyses were carried using UNPHASED, in SpA as a whole group, and then separately in AS and non-radiographic SpA (non-AS) patients.

Results: Strong association with AS was observed in the 3 datasets (case/control, familial and trios) with the non-synonymous polymorphism rs11209026 Arg381Gln ($P=2.86 \times 10^{-3}$ $P=4.59 \times 10^{-3}$ and p=0.02, respectively). In contrast, such association was not detected with the non-AS group (P=0.878, p=0.65 and p=1). Furthermore, association with this polymorphism was significantly different between the AS and non-AS patients in both studies ($P=2.5 \times 10^{-3}$).

Conclusion: Our results confirm that IL23R polymorphisms are associated with SpA, either in sporadic or in familial cases. However, phenotypic analysis revealed that association with Arg381Gln polymorphism is restricted to the AS subtype, suggesting that IL23R could influence the phenotypic expression of SpA by promoting ankylosis.

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LIGHT (TNFSF14), Cathepsin K, DKK-1 and Sclerostin in Ankylosing Spondylitis: Osteoclast/OSTEOBLAST Imbalance Unrelated to Disease Activity and Effect of ANTI-TNFα Treatment On the WNT/β Catenin Pathway.
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Background/Purpose: Ankylosing Spondylitis (AS) is an inflammatory arthritis characterized by erosions and new bone formation. These processes appear to be related by the fine balance of mediators involved in osteoclast activation, such as LIGHT (TNFSF14) protein and cathepsin K, and inhibition of osteoblast influenced by DKK-1 and sclerostin, although data available is still controversial. The aim of this study was to investigate in AS the main mediators involved in bone methabolism, and their relation to disease activity and anti-TNF-α treatment.

Methods: 63 patients with AS have been consecutively recruited as well as 19 healthy controls (HC). 15 patients underwent anti-TNF-α treament (Adalimumab), and were evaluated at baseline (w0) and 12 weeks after treatment (w12). Serum levels of DKK-1, Sclerostin, Cathepsin K and LIGHT were measured by ELISA assay (Biomedica, R&D System) and correlated with clinical scores (BASMI, BASFI e BASDAI) and inflammatory markers (ESR and CRP). Data were expressed as mean $+/-$SD.

Differences among groups and statistical correlation have been analyzed according to data distribution by means of paired t-test, unpaired t-test with Welch's correction and Spearman's test.

Results: Mediators of osteoclast activation were increased in AS patients compared to HC: LIGHT (115.1 pg/mL±74.8 vs 75.8 pg/mL ± 49.2; p= 0.009), cathepsin-k (21 pmol/L ± 35.9 vs 9.6 pmol/L ± 5.8; p= 0.03), as well as mediators involved in osteoblast function: DKK-1 (36.4 pmol/L ± 18.8 vs 23.5 pmol/L; ± 17.6; p=0.009), sclerostin (36.4 pmol/L ± 21.8 vs 25.1 pmol/L ± 9.1; p=0.001). The increase of these mediators resulted unrelated to disease activity, as evidenced by the lack of correlation of DKK-1, sclerostin, LIGHT and cathepsin-K with clinical scores; only LIGHT showed to correlate with ESR (p=0,01; r=0,4). It is also noteworthy the little modulation induced on these mediators by TNF-α antagonists, regardless the good clinical response according to EULAR criteria: DKK-1, LIGHT and cathepsin-k, w0 vs w12 p= ns, while increased sclerostin levels were observed at w12 compared with baseline (p=0.03).

Conclusion: AS patients showed an increased bone metabolism, characterised by an increase of both mediators responsible of osteoclast activation and erosions, and mediators of osteoblast activation and new bone formation. This increased bone turn-over appear not linked to the inflammatory process and to disease activity, as perceived by the patient. Furthermore it appear to be independent to TNF-α related mechanisms, as recently suggested by radiological progression in patients with disease in clinical remission following anti-TNF-α treatment.

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Regulatory T Cells in Spondyloarthritis (SpA) Animal Model and Modulatory Role of Inducible Costimulator (ICOS).
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Background/Purpose: HLA-B27/human β2m transgenic rats (B27-rats), a model of SpA develop spontaneous colitis and arthritis. It was recently shown in this model that IL-17 producing T cells are expanded both in mesenteric and popliteal lymph nodes (LN). Moreover, after *in vitro* stimulation, Th17 cells were preferentially induced and expanded by DCs from B27-rats (A&R 2012;64:110–20). Given that regulatory T cells (Treg) and Th17 cells have been described as two distinct subsets with opposing effects on inflammatory disorders, we hypothesized that the Th17 bias observed in B27-transgenic rats could be explained by a decreased frequency and/or a functional defect of Treg cells.

Methods: We examined the phenotype and function of Treg in the LN of B27- and control nontransgenic (NTG) rats, using the following methods: cell surface expression of Treg-associated markers; *in vitro* suppression assay; intra-cellular IL-17 and IL-10 production by flow cytometry and RT-PCR assay of *ex vivo*-sorted Treg cells; differentiation of naives T cells into Treg in Treg-polarizing conditions and transcription factor expression by RT-PCR.

Results: Based on the combination of Foxp3 and CD25 expression, two suitable markers for Treg in the rat, we distinguished two populations of CD4+ LN T cells, namely regulatory CD25+Foxp3+ T cells (Treg) and activated CD25+Foxp3- T cells (Teff). We observed that Teff cells were specifically enriched in the B27-rats. However, accumulation of Teff cells was not correlated with a defect in Treg differentiation, since we observed similar differentiation of naives Tcells to Treg in Treg-polarizing conditions, in both NTG and B27-rats. Despite a decreased proportion of Treg their suppressive activity was not compromised in the B27-rats. Indeed, Treg from NTG and B27-rats inhibited T cell proliferation to a similar extent. Cell surface expression of several Treg markers, i.e. GITR, CTLA-4 and LAG-3 was equivalent between NTG and B27-rats. In contrast, we observed an up-expression of ICOS marker in Treg cells from B27-rats, as compared to NTG-rats. High levels of ICOS expression usually define a population of Treg that present superior suppressive activity and expression of IL-10. Paradoxically, we observed that Treg from B27-rats down-expressed IL-10, as compared to those from NTG rats. Furthermore, Treg from B27-rats expressed higher levels of IL-17 than those from control rats. Interestingly, anti-ICOS mAb blocking assay resulted in a decrease of IL-17 expression and increase of IL-10 expression by naive or effector CD4+ T cells cocultured with DCs from B27-rats.

Conclusion: Our data suggest that an IL-10/IL-17 imbalance observed in Treg from B27-rats may contribute to disease development and reveal a critical role for ICOS signaling in the generation and maintenance of IL-17 producing T cells in this animal model of SpA.

Disclosure: **L. Krause**, None; **I. Fert**, None; **K. Labroquère**, None; **M. Andrieu**, None; **G. Chiocchia**, None; **M. A. Breban**, None.

ACR Poster Session A
Biology and Pathology of Bone and Joint
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Bath Ankylosing Spondylitis Functional Index (BASFI) Is a Better Indicator of Poor Quality of Life Than Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in Ankylosing Spondylitis: Results From SIRAS – the Scotland and Ireland Registry for Ankylosing Spondylitis. Gareth T. Jones[1], Linda E. Morton[1], Gary J. Macfarlane[1] and Scotland and Ireland Registry for Ankylosing Spondylitis[2]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Aberdeen

Background/Purpose: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Functional Index (BASFI) are validated instruments used to determine disease activity and function amongst ankylosing spondylitis patients. BASDAI is more commonly collected in clinic due, in part, to its use as a clinical criterion for commencing biologic therapy, however the relationship between both BASDAI and BASFI, and quality of life (QoL), is not well established. The aim of this study was to investigate this relationship in the context of other QoL markers.

Methods: The Scotland and Ireland Registry for Ankylosing Spondylitis (SIRAS) collects data on clinically diagnosed ankylosing spondylitis patients in Scotland. Various clinical measures including BASDAI, BASFI are obtained from medical records, and postal questionnaires provide various demographic and patient-reported data, including pain, fatigue, extra spinal manifestations and QoL as determined by the Ankylosing Spondylitis Quality of Life (ASQoL) instrument. In addition, patient postcodes were used to determine a deprivation score from 1 (most affluent) to 20 (most deprived) using the Scottish Index of Multiple Deprivation scale. Factors associated with poor QoL (characterised by an ASQoL score ≥11) were examined using Poisson regression, and results are given as risk ratios with 95% confidence intervals.

Results: As of the 26th March 2012, 311 patients had been recruited and provided complete data on BASDAI, BASFI and QoL (75% male; median age 51yrs inter-quartile range: 42–61yrs; median ASQoL: 6.0,: 1–11). Poor QoL was associated with both high disease activity (BASDAI ≥4: risk ratio: 3.7, 95%CI 2.3–6.0) and poor function (BASFI ≥4: 6.1; 3.4–10.9). However, these were not independent of each other. After mutual adjustment only poor function (BASFI) remained an independent predictor of QoL (4.8; 2.4–9.6). The relationship with disease activity (BASDAI) was greatly reduced and no longer statistically significant (1.4; 0.8–2.4).

Other factors independently associated with poor QoL were: female gender (1.6; 1.1–2.4), reporting either chronic widespread body pain (2.7; 1.5–4.8) or moderate/severe fatigue (1.8; 1.2–2.8), ever receiving anti-TNF therapy (1.5; 1.0–2.2), and social deprivation (RR most versus least deprived): 2.0; 1.1–3.5). No other clinical measures, including markers of inflammation (CRP or ESR), any peripheral joint involvement, or co-morbid disease of the eyes, skin or gut, were associated with poor QoL.

Conclusion: As it is integral to anti-TNF prescribing guidelines, disease activity (BASDAI) is considered as the important clinical indicator in AS. However, clinicians should be aware that function (BASFI) is a stronger predictor of poor QoL. Patients with a high BASFI were almost five times more likely to report poor QoL than other patients. In addition, after adjusting for BASFI, few other clinical variables were independently associated with QoL.

Disclosure: **G. T. Jones**, Abbott Laboratories, 2, Pfizer Inc, 2; **L. E. Morton**, None; **G. J. Macfarlane**, Abbott Laboratories, 2, Pfizer Inc, 2.

ACR Poster Session A
Systemic Lupus Erythematosus: Clinical Aspects
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Sexual and Reproductive Health Counseling Among Adolescents with Systemic Lupus Erythematosus. Xue Tian, Murray H. Passo, Janice D. Key, Thomas C. Hulsey and Natasha M. Ruth. The Medical University of South Carolina, Charleston, SC

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that is known to target young adults, especially women of child-bearing age. Although it is well-accepted that teratogenic SLE medications can cause negative pregnancy outcomes, there has been little research conducted to examine sexual health and contraceptive counseling among young adults with SLE, specifically teens and adolescents. The purpose of this study is: 1) to determine how much female adolescents with SLE know about their disease, SLE medications, how SLE relates to their sexual health, and how SLE symptoms can be impacted by pregnancy, STDs and contraceptives containing estrogen. 2) to educate the same group of patients about sexual and reproductive health using a face-to-face counseling session. 3) to reassess their knowledge after the intervention.

Methods: Female adolescents with SLE were recruited from the MUSC Pediatric Rheumatology clinic. Information on age, race, gender, medications, previous pregnancies, and length of diagnosis with SLE was obtained. The questionnaire (31 items regarding SLE medications, contraceptives, and STD's) was completed by all subjects before and after the intervention, which was a face to face educational session. The resulting data was analyzed by using a paired t-test.

Results: 13 female SLE patients, ages 12–21, were studied (11 African Americans, 1 Caucasian, 1 other). The average percent correct on the pretest questions was 30.8% on questions regarding the effects of SLE medications on pregnancy, 38.8% on questions regarding contraceptives, and 78.8% on questions regarding sexual health and STD's. The average percent correct on post-tests for those 3 categories of questions were 88%, 77%, and 99% respectively. The average improvement between pre- and post-tests for the 3 categories were 57.7% with a p-value of 0.0001, 46.2% with p-value of 0.0001, and 20.2% with p-value of 0.0006 respectively.

Conclusion: The low scores on the initial baseline assessment show that SLE adolescents are under-educated about contraceptives and the effects of SLE medications on pregnancy. After the counseling session, the average percent correct scores on the post-test significantly improved in all 3 categories. The issues surrounding contraceptives and pregnancy are important for this population, and it is imperative to advise SLE adolescents and teens on effective contraceptives in order to avoid unplanned pregnancies with unfavorable outcomes. This study demonstrates the need to establish routine counseling on contraceptives and reproductive health for women with SLE.

Disclosure: **X. Tian**, None; **M. H. Passo**, None; **J. D. Key**, None; **T. C. Hulsey**, None; **N. M. Ruth**, None.

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Cell Bound Complement Activation Products Are Associated with Disease Activity in Systemic Lupus Erythematosus. Kenneth C. Kalunian[1], W. Winn Chatham[2], Elena M. Massarotti[3], Joyce Reyes-Thomas[4], Richard Furie[5], Jill Buyon[6], Emily C. Somers[7], Chaim Putterman[8], Rachel L. Gross[9], Kyriakos A. Kirou[10], Rosalind Ramsey-Goldman[11], Christine Hsieh[12], Thierry Dervieux[13] and A. Weinstein[14]. [1]UCSD School of Medicine, La Jolla, CA, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Albert Einstein College of Med, Bronx, NY, [5]North Shore-LIJ Health System, Lake Success, NY, [6]New York University School of Medicine, New York, NY, [7]University of Michigan, Ann Arbor, MI, [8]Albert Einstein College of Medicine, Bronx, NY, [9]Albert Einstein College of Medicine, New York, NY, [10]Hospital for Special Surgery, New York, NY, [11]Northwestern University Feinberg School of Medicine, Chicago, IL, [12]University of Chicago, Chicago, IL, [13]Exagen Diagnostics, Albuquerque, NM, [14]Washington Hospital Center, Washington, DC

Background/Purpose: Elevated cell-bound complement activation products (CBCAPs) and decreased erythrocyte complement receptor 1 (ECR1) expression may correlate with disease activity in systemic lupus erythema-

tosus (SLE). We evaluated the relationship between CBCAPs, ECR1 and SLE disease activity as part the multicenter study of complement activation products in the assessment of lupus (CAPITAL).

Methods: The CAPITAL study was cross-sectional and enrolled SLE patients who met the ACR classification criteria. ECR1 as well as complement C4d levels on erythrocytes (EC4d), platelets (PC4d), and B cells (BC4d) were determined using flow cytometry. Disease activity was measured at the time of the study visit using the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLE Disease Activity Index (SLEDAI). Disease activity was dichotomously stratified by SELENA-SLEDAI scores <6 (low disease activity) or ≥6 (high disease activity). Statistical analyses utilized Wilcoxon rank-sum tests, area under receiver operating characteristic (ROC) curves, Fisher Exact tests and multivariate logistic regression.

Results: Among 209 SLE evaluable patients (90% females, mean age 41years), a total of 41 (19.6%) had high disease activity at the time of sample acquisition. As presented in Table I, high disease activity was associated with elevated levels of EC4d, BC4d, PC4d and reduced levels of ECR1 ($p<0.004$). ROC analyses indicated that EC4d above 14.8 units (ROC AUC=0.646) was associated with a 3.4-fold (95% CI: 1.6–7.4) higher likelihood of high disease activity. Similarly, BC4d above 71.5 units (ROC AUC=0.643) and PC4d above 6.3 units (ROC AUC=0.718) were associated with a 4.3-fold (95% CI:1.9–10.8) and 5.3-fold (95% CI:2.3–13.5) greater likelihood of high disease activity, respectively. Conversely, ECR1 levels below 10 net MFI (AUC=0.694) were associated with a 4.2-fold (95% CI:1.9–9.3) higher likelihood of high disease activity. By multivariate logistic regression analysis only elevated PC4d and low ECR1 were associated with high disease activity. Among patients presenting with both elevated PC4d (>6.3 net MFI) and reduced ECR1 (<10.2 net MFI), 45% had high disease activity compared to 5% of those having PC4d and ECR1 below 6.3 and above 10.2 net MFI respectively ($p<0.01$).

Table. CB-CAPS and ECR1 levels in SLE patients with low or high disease activity (MFI: mean fluorescence intensity)

	Low disease activity N=168	High disease activity N=41	P value
EC4d Net MFI	11.4 (7.4–19.5)	16.6 (11.3–26.0)	<0.004
Net MFI>14.8	33.9%	63.4%	<0.001
BC4d Net MFI	66.7 (35.1–130.0)	117.0 (75.2–188.6)	<0.005
Net MFI>71.5	45.2%	78.0%	<0.001
PC4d Net MFI	5.2 (2.4–10.8)	13.9 (7.3–43.4)	<0.001
Net MFI >6.3	39.9%	78.0%	<0.001
ECR1 Net MFI	13.5 (9.2–17.9)	9.3 (6.7–12.4)	<0.001
Net MFI>10.2	67.9%	34.1%	<0.001

Conclusions: These hypothesis generating data suggest that elevated EC4d, BC4d, PC4d and reduced ECR1 levels are associated with high disease activity. Prospective longitudinal studies will be essential to establish the predictive value of CBCAPs and ECR1 measurements for determining SLE disease flares.

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Comparing the ACR and the SLICC Criteria for the Classification of SLE Patients Using Data from an Existing Multi-Ethnic Cohort. Graciela S. Alarcon[1], Gerald McGwin Jr.[1], Larry Madger[2] and Michelle Petri[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: The SLICC group has proposed a modification of the revised/updated SLE ACR classification criteria; it has comparable metric properties but is felt to be clinically more relevant (Arthritis Rheum 2012, May 2, ePub ahead of print). We have now compared both sets of criteria in a well-characterized SLE cohort.

Methods: At cohort entry (V0), all patients had met 4 updated/revised ACR criteria. Using the data up to V0, we determined the dates at which the ACR and SLICC criteria were first met. Some SLICC criteria could not be applied (some acute and chronic forms of cutaneous lupus, non-scarring alopecia, mononeuritis multiplex and complement values). We compared

groups of patients based on whether the SLICC criteria were met before, at the same time or after the ACR were met.

Results: Of 640, using the SLICC criteria 319 (49.8%) were classified at the same time using either criteria set, 78 earlier (12.2%, mean 0.7 years) and 225 (35%) later (mean 4.4 years) compared to the ACR criteria; 18 patients (2.8%) did not meet the SLICC criteria despite a mean of 1.2 years from the time the ACR criteria were met and V0. Five of the 78 earlier patients (6.4%) met the SLICC rule of lupus nephritis (LN) plus 1 immunologic criterion. Of the patients diagnosed later, the majority did so because of the combination of malar rash and photosensitivity into the Acute Cutaneous Lupus criterion. There were no differences in terms of age, gender and disease activity between the groups, but African Americans and Texan-Hispanics were more likely to be in the no difference group and Caucasians and Puerto Rican-Hispanics in the later or in the no diagnosis groups. Tables 1 and 2 show the distribution of the ACR and SLICC criteria among all 4 groups; only those criteria which differ between the 2 sets are shown in Table 2.

Table 1. Patients who met ACR Criteria at V0

ACR criteria	N (positive)	SLICC criteria met earlier, % n=78	SLICC criteria met later, %, n=225	SLICC criteria not met, % n=18	SLICC criteria met at the same time, % n=319	p-value
Malar rash	316	30.8	57.3	88.9	46.1	<0.001
Discoid rash	76	9.0	11.1	11.1	13.2	0.757
Photosensitivity	332	48.7	64.9	100.0	40.8	<0.001
Oral ulcers	263	38.5	39.6	44.4	42.6	0.785
Synovitis	484	74.4	76.0	61.1	76.5	0.506
Serositis	265	28.2	35.1	5.6	51.1	<0.001
Neurologic	59	5.1	4.4	5.6	13.8	<0.001
Renal	202	29.5	24.4	5.6	38.6	<0.001
Hematologic	437	70.5	60.0	27.8	75.9	<0.001
Immunologic	451	65.4	59.1	5.6	83.4	<0.001
ANA	621	100.0	99.1	55.6	97.2	<0.001

Table 2. SLICC Criteria in SLE Patients at V0

Clinical	N (positive)	SLICC criteria met earlier, % n=78	SLICC Criteria met later, %, n=225	SLICC criteria not met, % n=18	SLICC criteria met at the same time, % n=319	p-value
Acute cutaneous lupus or SCLE	419	57.7	72.4	100.0	60.5	<0.001
Neurologic	76	11.5	4.9	11.1	16.9	<0.001
Hemolytic anemia	59	10.3	5.3	5.6	11.9	0.067
Leukopenia	464	85.9	62.2	27.8	79.0	<0.001
Thrombocytopenia	104	12.8	7.1	0	24.5	<0.001
Immunologic						
Anti-DNA	427	83.3	52.9	5.6	75.9	<0.001
Anti-Sm	290	73.1	24.0	0	56.1	<0.001
Anti-phospholipid	186	47.4	14.2	0	36.7	<0.001

Conclusion: Despite the lack of data for some of the items on the SLICC criteria, we have shown that some patients could be classified earlier with them than with the ACR criteria (major organ involvement or LN plus 1 immunologic criterion); however, a relatively high proportion of patients could not be classified until later (malar rash/photosensitivity combination in 1 criterion, main reason) or not at all. Longitudinally complete data collection is needed to better define the role of the SLICC criteria in the clinical and research settings.

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Increased Incidence of Herpes Zoster Among Patients with Systemic Lupus Erythematosus. Eliza F. Chakravarty[1], Kaleb Michaud[2], Robert S. Katz[3] and Frederick Wolfe[4]. [1]Oklahoma Medical Research Foundation, Oklahoma City, CA, [2]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [3]Rush University Medical Center, Chicago, IL, [4]National Data Bank for Rheumatic Diseases, Wichita, KS

Background/Purpose: Herpes zoster (HZ) is the painful reactivation of latent varicella zoster virus infection. The incidence of HZ may be increased in some autoimmune diseases including systemic lupus erythematosus (SLE). We examined the incidence and risk factors for HZ in a prospective cohort of patients with physician-diagnosed SLE compared to those diagnosed with non-inflammatory musculoskeletal conditions (MSK).

Methods: Study subjects were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of rheumatic disease outcomes. Participants are followed prospectively with semi-annual detailed questionnaires collecting data on medication use, comorbid conditions, infections (including specific questions on HZ), hospitalizations, and standard patient reported outcomes. After excluding 808 participants with a history of prior HZ at enrollment, we followed 1,485 SLE patients and 2,775 MSK for incident HZ between 2001 and 2010. Reports of HZ were validated by confirmation of a physician diagnosis. Age adjusted incidence rates were calculated for each group. Cox proportional hazard regression models were used to identify predictors of HZ for the entire cohort as well as for specific predictors for SLE patients. Zostavax vaccination rates for individuals ≥ 60 years old were compared between groups.

Results: SLE patients were younger than MSK (48.3 vs. 64.9 years), but had a similar disease duration of 13–14 years at enrollment. Health Assessment questionnaire at baseline was similar between groups (0.90 SLE vs. 0.87 MSK), although 25% of SLE patients were disabled from work compared to 9% of MSK. SLE patients had increased incidence of HZ at all ages, with an age-adjusted incidence of 12.0/1000 person-years compared to MSK (8.7/1000 person-years) and a hazard ratio of 1.7 (95% CI 1.08–2.71) for SLE (Figure). Increasing age (HR 1.01, 95%CI 1.00–1.02 per year) and increased HAQ (HR 1.26, 95% CI 1.10–1.44) were independent predictors of HZ. Among SLE patients, prednisone (HR 2.29, 95% CI 1.24–4.23) and mycophenolate mofetil (HR 5.00, 95% CI 1.40–17.6) conferred additional risk. SLE had the lowest HZ vaccination rates among age-eligible subjects; 7.1% SLE vs. 13% MSK, p<0.001.
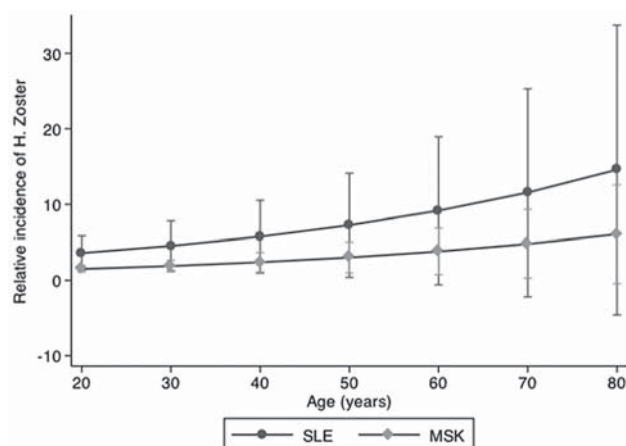
Figure. Sex-adjusted relative incidence of incident herpes zoster by age for each diagnosis.

Conclusion: The incidence of HZ is increased in SLE at all ages when compared to MSK, while vaccination rates remain low. Prednisone and mycophenolate mofetil are associated with increased risk.

Disclosure: E. F. Chakravarty, None; **K. Michaud**, None; **R. S. Katz**, None; **F. Wolfe**, None.

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Risk Factors Associated with Cervical Human Papillomavirus Infection in Women with Systemic Lupus Erythematosus: The Role of Rituximab. Mario Garcia-Carrasco[1], Claudia Mendoza Pinto[1], Alejandro Taboada-Cole[1]. Verónica Vallejo-Ruiz[2], Julio Reyes-Leyva[2] and Aurelio Lopez-Colombo[3]. [1]HGR 36 CMN Manuel Ávila Camacho, Instituto Mexicano del Seguro Social, Puebla, Mexico, [2]Centro de Investigación Biomédica de Oriente, Instituto Mexicano del Seguro Social, Hospital General de Zona No. 5, Puebla, Mexico, [3]Delegación Estatal, Instituto Mexicano del Seguro Social, Puebla, Mexico

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystemic disease that affects women of reproductive age. Women with SLE have an increased risk of cervical abnormalities and cervical human papillomavirus (HPV) infection. Studies have investigated risk factors for cervical infection with HPV, with contradictory results. The role of biological therapy on the risk of HPV infection in women with SLE has not been explored. The objective of our

study was to identify the prevalence and factors associated with cervical infection by HPV in women with SLE.

Methods: In this cross-sectional study, we investigated 148 women with SLE. A structured questionnaire was administered to identify traditional and SLE-related disease risk factors. A gynecological evaluation and cervical cytology was made. Polymerase chain reaction for viral DNA was performed for HPV determination.

Results: The mean (± SD) age and disease duration of SLE patients were 42.5 ± 11.8 years and 9.7 ± 5.3 years, respectively. The prevalence of squamous intraepithelial lesions was 6.8%. The prevalence of HPV infection was 29%, with HVP 18 being the most frequent type (found in 25.5% of patients without multiple infections). HPV (+) patients were younger than HPV (−) patients (38.2 ± 11.2 vs. 44.2 ± 11.5; p = 0.05) and were receiving a higher daily dose of prednisone (12.8 ± 6.8 mg vs. 9.7 ± 6.7 mg; p = 0.01). In the multivariate logistic analysis, only age at the time of the study was associated negatively with HPV infection (B= 0.04, OR 0.95, 95% CI: 0.95–0.98). There was a non-significant trend to more-frequent administration of immunosuppressive and biologic therapy with rituximab in HPV (+) patients.

Table. Sociodemographic, clinical and treatment characteristics of systemic lupus erythematosus patients with and without cervical human papillomavirus infection

Variable	VPH + (n=43)	VPH − (n=105)	P
Age, mean ± SD DE years	38.2 ± 11.2	44.2 ± 11.5	0.05
Current smoker, n (%)	4 (9.3)	12 (11.4)	0.4
Age at first intercourse, mean ± SD	20.4 ± 3.4	20.5 ± 3.8	0.8
Number of sexual partners, mean ± SD	1.65 ± 1.0	1.42 ±0.8	0.16
Oral contraceptive use, n (%)	1 (2.3)	0 (0)	0.29
Disease duration, mean ± SD years	9.5 ± 6.2	9.8 ± 6.1	0.77
Current medication	36 (83.7)	81 (77.1)	0.5
Antimalarials, n (%)	12.8 ±6.8	9.7 ± 6.7	0.01
Prednisone (mg/d), mean ± SD	25 (58.1)	57 (54.1)	0.7
Immunosuppressive therapy, n (%)	16 (37.2)	30 (28.5)	0.33
Azathioprine, n (%)	5 (11.6)	25 (23.8)	0.17
Methotrexate, n (%)	5 (11.6)	6 (4.7)	0.28
Leflunomide, n (%)	4 (9.3)	1 (0.9)	0.02
Mycophenolic acid, n (%)	7 (16.2)	9 (8.5)	0.24
Rituximab			

Conclusion: Women with SLE, and especially younger patients, had an increased prevalence of cervical HPV infection. Conventional and biologic therapy with rituximab may not influence HPV infections. Screening for HPV infection is recommended in patients with SLE.

Disclosure: M. Garcia-Carrasco, None; **C. Mendoza Pinto**, None; **A. Taboada-Cole**, None; **V. Vallejo-Ruiz**, None; **J. Reyes-Leyva**, None; **A. Lopez-Colombo**, None.

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Activity Index After Renal Failure in a Cohort of 32 Patients with Lupus Nephritis. Cristina Gonzalez-Pulido[1], Sara Croca[2] and D.A. Isenberg[3]. [1]University Hospital Virgen del Rocio, Seville, Spain, [2]University College London, London, United Kingdom, [3]University College of London, London, United Kingdom

Background/Purpose: Most published studies that have measured activity in patients with lupus nephritis suggest the disease is relatively quiescent after renal failure.

Purpose: To analyze retrospectively the activity index of 32 patients in end-renal stage disease (ESRD) from a cohort of 182 patients with lupus nephritis during dialysis and/or post renal transplant.

Methods: We used the BILAG index, levels of complement C3 (n = 0.9–1.8 g/L) and anti-DNA antibodies (n = 0–50 IU/ml) to measure the lupus activity every 6 months after the beginning of dialysis and after renal transplant. Inactive disease was defined as no BILAG A/B both C3 and DNA level within the normal range. Mild-moderate disease was defined as at least 1 B in BILAG and/or mild serological involvement (C3 levels= 0.89–0.73 g/L and/or DNA levels= 51–149 IU/ml). We considered patients to be severely activity when at least 1 A or 2 B were present in BILAG and/or major serological abnormality (C3 levels< 0.73 g/L and/or DNA levels >149 IU/L).

Results: We followed up a cohort of 182 patients with lupus nephritis from January 1978 to February 2012. 32 patients went into ESRD defined as the need of haemodialysis (HD) or peritoneal dialysis (CAPD). Ethnically, 37,5% were

Afrocaribbean, 25% from the Indian subcontinent, 28% Caucasian and 9,4% others. The duration of follow up during ESRD dialysis ranged from 1 to 144 months (median 24, IQR 12–54). 14 of them had a renal transplant. We divided our cohort in two groups: 1) all patients in ESRD (n=32). 2) Transplant patient (n=14). **Group 1:** 15.1% of the measurements showed completely inactive disease and 84.9% had at least mild-moderate activity at some time (58.5% had both BILAG index and serological activity, 26.3% only serological involvement, 16.95% only activity by BILAG. Severely active disease only was present in 54.7% of them (34.2% BILAG and serological, 50% serological, 15.8% only BILAG activity). The BILAG involvement was haematological (29.6%), musculoskeletal (19.7%), mucocutaneous (15.5%), constitutional (11.3%), neurological (8.4%) and gastrointestinal (1.4%). 12 patients died. **Group 2:** 42.3% of the measurements showed inactive disease and 57.7% had at least one flare in this period (43.3% BILAG and serological, 23.3% serologically, 33,3% by BILAG). Severe activity markers were present in only 26.92% (50% BILAG and serological, 32,14% BILAG, 17.9% serologically). The BILAG involvement in this group was due to renal alteration (34%), haematological (30%), constitutional (10%), neurological and cardiovascular (8% each), mucocutaneous (6%), musculoskeletal and gastrointestinal (2%) each. 2 patients died.

Conclusion: We report a 34 years follow-up of a cohort of 32 patients with SLE nephritis in renal failure. The activity after ESRD was much lower in the group of transplant patients. Serological activity was the main finding in both groups.

Disclosure: **C. Gonzalez-Pulido**, None; **S. Croca**, None; **D. A. Isenberg**, None.

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Association of Discoid Lupus with Other Clinical Manifestations Among Patients with Systemic Lupus Erythematosus. Joseph F. Merola, Christina Iversen, Jose A. Gomez-Puerta, Tabatha Norton, Hsun Tsao, Peter H. Schur, Elena M. Massarotti, Bonnie L. Bermas and Karen H. Costenbader. Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Prior studies suggest that cutaneous discoid lupus (DLE) is a marker for less severe disease with a low frequency of nephritis and end-stage renal disease among SLE patients. These past studies have not included diagnostic confirmation of DLE by expert dermatologists and did not adjust for medication use. We investigated associations of validated cases of DLE with other specific SLE manifestations in a large validated SLE Cohort.

Methods: Our academic hospital SLE registry contains data on 5,030 patients seen for potential SLE, 1970–2011. Inclusion criteria for this study were: definite SLE per treating rheumatologist and an SLE expert, 4/11 of 1997 ACR classification criteria for SLE, >2 visits and >3 months of follow-up, and a documented year of SLE diagnosis. The presence of DLE was validated by an expert dermatologist with review of multispecialty notes, pathology and digital images, when available. We collected SLE manifestations, medication and serologic data from review of electronic medical records. We tested for associations between DLE and each of the ACR SLE criteria, as well as end-stage renal disease (ESRD), using multivariable-adjusted logistic regression analyses.

Results: Of 1,043 SLE patients included, 92% were female and 51% White, 100% were ANA positive, 66% were anti-dsDNA positive. Mean age at diagnosis was 32 years ($\pm$ 13) and mean duration of follow-up was 10 years ($\pm$ 6.5). DLE (n=117) was significantly associated with the presence of photosensitivity, leukopenia and anti-Smith antibodies (**Table**). DLE was inversely associated with both arthritis and pleuritis. We found no significant associations between DLE and nephritis or ESRD.

Table. Associations between Discoid Lupus (n=117) and other ACR Criteria for SLE and End-Stage Renal Disease

SLE Manifestation	Number with DLE	Number without DLE	OR* (95% CI)	p-value
Anti-Smith (n=246)	45	201	2.41 (1.58–3.69)	<0.01
Photosensitivity (n=434)	60	374	1.63 (1.09–2.44)	0.02
Leukopenia (n=351)	50	301	1.55 (1.03–2.32)	0.04
Pleuritis (n=380)	31	349	0.56 (0.36–0.87)	0.01
Arthritis n=817)	79	738	0.49 (0.31–0.76)	<0.01

No significant associations between discoid lupus and the following were found: malar rash, oral ulcers, pericarditis, proteinuria, casts, lupus nephritis, seizure, psychosis, anemia, lymphopenia, thrombocytopenia, anti-dsDNA, antiphospholipid antibodies, end-stage renal disease
* OR= odds ratio, adjusted: Multivariable logistic regression analyses modeling the odds ratio of DLE associated with each SLE manifestation or laboratory finding separately, adjusted for age at diagnosis, sex, race/ethnicity, disease duration, ever medication use (azathioprine, cyclophosphamide, hydroxychloroquine, methotrexate, mycophenolate mofetil, systemic corticosteroids)

Conclusion: In this large cohort of SLE patients, we have found an increased frequency of photosensitivity, leukopenia and anti-Smith antibodies among SLE patients with DLE and an inverse association of DLE with both pleuritis and arthritis. We did not observe the inverse associations of DLE with anti-dsDNA antibodies, lupus nephritis, or ESRD that have been noted in other studies. These findings have important implications for prognosis among patients with DLE and possibly for different underlying pathophysiologies of SLE subtypes.

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Peripheral Neuropathy in Systemic Lupus Erythematosus. Amin Oomatia[1], Hong Fang[2], Michelle Petri[2] and Julius Birnbaum[3]. [1]University of Cambridge, Cambridge, United Kingdom, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD

Background/Purpose: Whilst Neurological disorders are a common manifestation of systemic lupus erythematosus (SLE), peripheral neuropathies have received little attention. The literature consists mostly of small case series with very few studies investigating larger samples. Consequently, various features of SLE-associated peripheral neuropathies such as prevalence, symptoms, severity, chronicity, clinical and serological associations, and electrophysiological and biopsy findings, are poorly described. Small fibre neuropathies are almost entirely un-reported. The aim of this study is to determine the prevalence, clinical features, electrophysiological and biopsy findings of peripheral neuropathies in systemic lupus erythematosus and to identify clinical and laboratory correlations.

Methods: We performed a retrospective study of 2,097 SLE patients seen at a single Center since 1987, and ascertained for the presence of neuropathy according to diagnostic criteria laid down by the American Academy of Neurology. We categorized subtypes of peripheral neuropathies on the basis of symptoms, examination, electrophysiological studies, and punch skin biopsy features. We excluded patients with co-morbid features associated with neuropathies. We evaluated for an association of demographic, SLE-related clinical features, antibodies, and other immunological data in SLE patients with neuropathies versus without neuropathies by student's t-test or chi-squared test, with p-values <0.05 considered statistically significant.

Results: The prevalence of neuropathies was 4.4%, present in 82 of 2097 patients. Of these 82 patients, the most common neuropathy was a large fiber neuropathy (68.3%): including neurophysiological assessment demonstrating 36 (44%) symmetric axonal neuropathies and 42 (51%) patients with a pure axonal loss, 18 patients had small-fiber neuropathies, characterized by decreased intra-epidermal nerve fiber density and/or morphological changes of unmyelinated fibers on skin biopsy. Altogether, patients with neuropathies were older at time of SLE diagnosis (39.16 versus 32.05, p<0.0001), had an increased risk of Zoster infection, but otherwise had similar profile of SLE-related clinical and laboratory features).

Conclusion: Our characterization of small-fiber neuropathy in patients, has never been systematically evaluated and reported in unselected SLE cohorts, and suggests that this neuropathy may be an unrecognized cause of morbidity in SLE patients. SLE patients with neuropathies versus without neuropathies shared similar clinical and immunological features. Given the tropism of VZV for peripheral neuronal structures, prospective studies are warranted to evaluate whether re-activation of VZV is a risk factor for SLE neuropathies.

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B Lymphocyte Stimulator Levels Are Higher in Caucasian SLE patients Earlier in Disease Course and Predict Damage Accumulation. Eoghan M. McCarthy[1], Ruth Lee[1], Joan Ni Gabhann[2], Siobhan Smith[2], Michele Doran[3], Gaye Cunnane[3], Donough G. Howard[1], Paul G. O'Connell[1], Grainne M. Kearns[1] and Caroline Jefferies[2]. [1]Beaumont Hospital, Dublin 9, Ireland, [2]Royal College of Surgeons in Ireland, Dublin, Ireland, [3]St. James Hospital, Dublin, Ireland

Background/Purpose: B Lymphocyte Stimulator(BLyS) plays an important role in the pathogenesis of Systemic Lupus Erythematosus(SLE). Whilst trials of anti BLyS-targeted therapy have shown promise, the optimal timing and benefits of anti BLyS therapy remain undetermined. We sought to assess the relationship

between BLyS levels, disease activity, damage scores and clinical profiles in Caucasian SLE patients.

Methods: BLyS levels were determined by ELISA. Elevated BLyS levels were defined as values above the 95% percentile in a cohort of healthy controls. Patients were enrolled only if they could confirm three generations of their family were of Irish descent. Patients with SLE were divided into two groups: those with elevated BLyS levels(Group 1) or normal BLyS levels(Group 2).Demographic data, disease activity as per SLEDAI and damage scores(SLICC) at 5 year follow-up were recorded. Categorical variables were analyzed using Fisher's exact test and continuous variables by unpaired *t*-tests. The Mann-Whitney test was used in instances of non-normality.

Results: 45 patients were recruited.In this homogenous Caucasian population BLyS levels were higher in those with malar rash (920pg/ml v 594pg/ml, p<.05), musculoskeletal involvement (930pg/ml v 591pg/ml, p<.04), immunologic activity(1041pg/ml v 646pg/ml, p <.005) and renal disease (1127 pg/ml v 748pg/ml, p<.009).

In keeping with previous reports BLyS levels showed significant correlation with disease activity as measured by SLEDAI (r =.682, p<0.001). Twenty three SLE patients (51%) fell above the defined cutoff in healthy controls and were therefore classified as having "elevated" BLyS levels with the remaining twenty two patients having "normal" BLyS levels, the difference between groups being significant(1173 pg/ml v 558pg/ml, p<.001).

Patients with elevated BLyS levels at time of enrolment were found to be significantly younger at time of study visit (32.97 v 44.32 years, p<0.0019) with a shorter disease duration (4.96 v 9.23 years, p <0.0125). They also accrued significantly more damage over the subsequent five year period with a mean increase in damage score of 0.53 compared to 0.13 for patients with normal BLyS levels (p< 0.012). The odds ratio (OR) was 5.8 (p=0.023 by Fishers exact test). The change in SDI correlated significantly with plasma BLyS levels (r =.399,p<0.007). There was no difference in BLyS levels between those requiring steroid therapy to control their disease versus those steroid free. However, BLyS levels were higher in those patients requiring additional immunosuppression (Azathioprine or greater) to control their disease (926pg/ml v 642 pg/ml, p<0.005).

Sm antibody (OR 13.4, p=0.049), low C4 (OR 8, p=.016) and dsDNA positivity (OR 6.1, p=0.007) predicted BLyS elevation.

Conclusion: BLyS levels are higher in younger patients and those with a shorter disease duration. Although further validation of these clinical and immunological associations are warranted in larger cohorts of genetically homogenous populations our study suggests BLyS blockade may be most beneficial if introduced early in disease in young patients in an effort to prevent damage. BLyS levels remain elevated despite the use of additional conventional immunosuppressive agents.

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Impaired Diffusion Tensor Imaging Findings in the Corpus Callosum and Cingulum May Underlie Impaired Learning and Memory Abilities in Systemic Lupus Erythematosus. Daphna Paran[1], Elissa Ash[1], Ira Litinsky[1], Valerie Aloush[1], Marina Anouk[1], Dan Caspi[2], Talma Hendler[3] and Irit Shapira-Lichter[3]. [1]Tel Aviv Sourasky Medical Ctr, Tel-Aviv University, Tel Aviv, Israel, [2]Tel Aviv, Israel, [3]Tel-Aviv Sourasky Medical Ctr, Tel-Aviv University, Tel Aviv, Israel

Background/Purpose: Memory impairment is prevalent in systemic lupus erythematosus (SLE), however the pathogenesis is unknown. In a previous functional Magnetic Resonance Imaging (MRI) study we demonstrated altered brain activity dynamics and less brain deactivation in patients with SLE without overt neuropsychiatric manifestations as compared to healthy controls, when performing a learning and memory task. Our findings localized this impairment to the anterior medial prefrontal cortex of the default mode network (DMN). In addition altered networking of the hippocampal subsystem of the DMN was seen in patients with SLE when performing this task. These findings may reflect compensatory mechanisms to overcome memory impairment. The purpose of the present study is to search for a structural substrate for the abnormal recruitment pattern observed in the functional MRI studies using Diffusion Tensor Imaging (DTI).

Methods: Using a DTI sequence in a 3.0T MRI scan, we characterized brain diffusivity in ten SLE patients and nine healthy controls. We examined two tracts associated with the DMN: the corpus callosum and the cingulum.

Results: In the left cingulum fibers higher apparent diffusion coefficient

(ADC, $F_{(1,16)}$ = 4.9, p<0.05) and radial diffusivity (Dr, $F_{(1,16)}$=4.6, p<0.05) values were seen in SLE patients as compared to controls. Similarly, in the corpus callosum, higher ADC values ($F_{(1,16)}$=13, p<0.005), radial diffusivity (Dr)($F_{(1,16)}$=7.4, p<0.05) and longitudinal diffusivity (Da) ($F_{(1,16)}$=14.4, p<0.005) were evident in SLE patients.

Conclusion: Higher diffusion coefficients in the corpus callosum and the left cingulum may indicate impaired organization/reduced integrity of these tracts which may underlie the abnormal pattern of brain activity recruitment of the DMN observed during a verbal learning and memory task. The abnormal findings in the left cingulum are in line with the central role of the left hippocampus in verbal memory and suggests that these findings may contribute to the impairment seen in patients with SLE on performance of a verbal memory task.

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Thrombosis Recurrence in Systemic Lupus Erythematosus Patients with and without Antiphospholipid Antibodies. Ibrahim AlHomood, D. D. Gladman, Dominique Ibanez and Murray B. Urowitz. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: To determine the outcome of thrombotic events in the presence and absence of antiphospholipid antibodies (aPL) in patients with systemic lupus erythematosus (SLE).

Methods: Patients with SLE and thrombotic events followed prospectively at the Lupus clinic were divided into two groups: 1) those with one event (no recurrence) and 2) those with recurrent events.

Demographic and clinical data collected at time of thrombosis included age, race, gender, aPL status (anticardiolipin antibodies &/or lupus anticoagulant), disease duration, disease activity (SLEDAI-2K), hypertension, diabetes mellitus (DM), hypercholesterolemia, smoking and use of aspirin (ASA). Thrombotic events (TE) were divided into arterial TE(ATE) and venous TE (VTE).ATE was defined as angina, myocardial infarction, stroke, or peripheral arterial thrombosis, and VTE was defined as deep vein thrombosis or pulmonary emboli. Comparison between patients with and without recurrence was done using descriptive statistics. Time to recurrence was compared using Kaplan-Meier curves and stepwise Proportional hazard models.

Results: 613 TE were identified in 400 patients. 213 recurrences were observed in 132 patients. The aPL status is known in 367 patients of whom118 (32.2%) have had a recurrence. The mean time to recurrence in these 118 patients is 5.0 ± 5.1 years.

Kaplan-Meier curve for the prediction of Recurrence by aPL +ve ever at time of 1st TE

	Patients with Recurrence	Patients with no Recurrence	p value
No.	118	249	
Sex(F)	94 (79.7%)	219 (88.0%)	0.04
Age at SLE Dx	35.9 ± 14.1	33.2 ± 15.3	0.11
Age at 1st TE	46.7 ± 14.4	42.9 ± 14.7	0.02
SLE Disease Duration at 1st TE	10.8 ± 10.0	9.7 ± 8.8	0.28
Race Caucasian	96 81.4%)	187 75.1%)	0.18*
Black	13 11.0%)	25 10.0%)	
Asian	1 0.8%)	16 6.4%)	
Other	8 6.8%)	21 8.4%)	
aPL +ve (ever at 1st TE)	82 69.5%)	143 57.4%)	0.03
Hypertension			
Ever to 1st TE	78 66.7%)	157 63.1%)	0.50
At 1st TE	52 45.2%)	124 50.0%)	0.40
Cholesterolemia†			
Ever to 1st TE	84 77.1%)	170 70.5%)	0.21
At 1st TE	63/101 62.4%)	116/235 49.4%)	0.03
Diabetes Mellitus			
Ever to 1st TE	14 12.0%)	17 6.9%)	0.10
At 1st TE	12 10.3%)	14 5.7%)	0.11
SLEDAI-2K at 1st TE	9.3 ± 9.1	8.8 ± 8.4	0.64
Smoker			
Ever to 1st TE	40 34.8%)	62 25.3%)	0.06
At 1st TE	29 25.2%)	42 17.1%)	0.07
ASA ever in the 5 years following 1st TE (or until recurrence if within 5 years)	39/110 35.5%)	60/231 26.0%)	0.07
Venous TE	43 36.4%)	117 47.0%)	0.06
Arterial TE	80 67.8%)	141 56.6%)	0.04

HR = 1.53; 95% CI (1.03,2.27); p=0.036
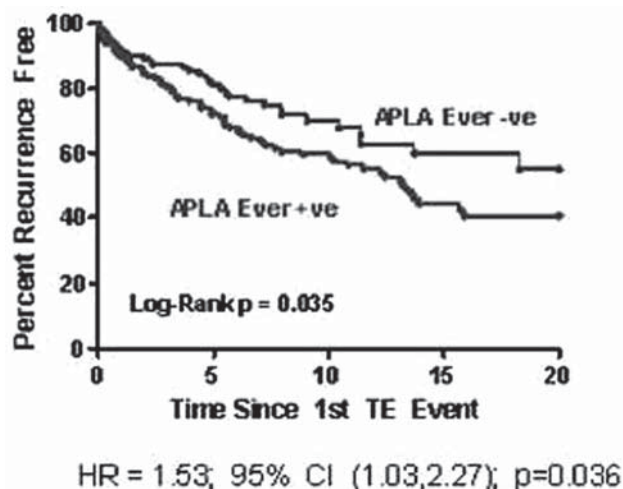
Conclusion: Recurrent TE occurs in 32.2% of lupus patients with TE. ATE recurred more often than VTE. Patients with high cholesterol level at time of thrombosis or antiphospholipid antibodies have an increased the risk of recurrence.

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Serum Level of Syndecan-1 Is Associated with Disease Activity in Patients with Systemic Lupus Erythematosus. In-Woon Baek[1], Ki-Jo Kim[2], Ji-Young Kim[3], Su-Jung Park[3], Chong-Hyeun Yoon[4], Wan-Uk Kim[5] and Chul Soo Cho[6]. [1]Internal medicine, Catholic University of Korea, Callege of Medicine, Seoul, South Korea, [2]College of Medicine, Catholic University of Korea, Seoul, South Korea, [3]Research Institute of Bone & Joint Diseases, Catholic University of Korea, Seoul, South Korea, [4]College of Medicine, The Catholic University of Korea, Seoul, South Korea, [5]College of Medicine, The Catholic University of Korea, Suwon, South Korea, [6]St Marys Hospital, Seoul, South Korea

Background/Purpose: Syndecan-1(SDC1), a transmemebrane heparansulfate glycoprotein, is predominantly expressed by plasma cells and is a receptor for a proliferation-inducing ligand (APRIL). SDC-1 is readily shed and release into plasma under certain pathologic conditions and remains biologically active to affect cellular behaviour of plasma cells. Plasma cells are effector cells producing pathogenic autoantibodies in systemic lupus erythematosus (SLE). The purpose of this study are to evaluate serum SDC1 concentration and to determine association between its levels and certain clinical manifestation in patients with SLE.

Methods: Serum samples from 127 patients with SLE and 24 normal healthy controls were assayed for SDC1 and APRIL by enzyme linked immunosorbent assay. Medical records were thoroughly reviewed for clinical features and serologic values. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Results: Serum SDC1 levels were significantly elevated in patients with SLE compared to controls (61.2 ± 6.5 versus 31.4 ± 4.5 ng/ml, $P<0.001$). The level was correlated positively with anti-double stranded DNA (dsDNA) antibody titer and SLEDAI score ($r=0.263$, $P=0.004$, and $g=0.231$, $P=0.012$, respectively), but negatively with C3 and CH50 levels associated with the presence of active proteinuria (>0.5 gm/day) in SLE patients with lupus nephritis. Moreover, serum SDC1 levels had significant correlation with level of APRIL, which was known as surrogate marker of disease activity ($r=0.507$, $P=0.001$).

Conclusion: Serum SDC1 levels are elevated and correlated with markers of disease activity in patients with SLE, suggesting that serum SDC1 could be used as a potential marker of disease activity in patients with SLE.

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Predictors of Systemic Lupus Erythematosus Flares: Baseline Disease Activity and Demographic Characteristics From the Combined Placebo Groups in the Phase 3 Belimumab Trials. Ronald F. van Vollenhoven[1], Michelle A. Petri[2], Roger A. Levy[3], Sandra V. Navarra[4], Jill P. Buyon[5], Z. John Zhong[6], William W. Freimuth[6] and Ricard Cervera[7]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Univ Estado Do Rio De Janeiro, Rio de Janeiro, Brazil, [4]University of Santo Tomas Hospital, Manila, Philippines, [5]New York University School of Medicine, New York, NY, [6]Human Genome Sciences, Inc., Rockville, MD, [7]Hospital Clínic of Barcelona, Barcelona, Spain

Background/Purpose: Predicting which SLE patients are at increased risk for clinically meaningful flares may be useful in making management decisions. The purpose of this analysis was to identify demographic and disease-related predictors of flares.

Methods: Baseline demographic and SLE-related disease activity characteristics were evaluated for their ability to predict new SLE flares by treatment wk 52 in the combined dataset of 562 patients receiving placebo + standard SLE therapy from the phase 3 belimumab BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) trials. Flare was defined as the development of 1 new British Isles Lupus Assessment Group (BILAG) A or 2 new B organ domain scores; any BILAG A score; or according to the modified severe SLE Flare Index (SFI). Baseline variables included race, age, gender, BMI, SELENA-SLEDAI (mean score, range, and 24 items with ≥30/group), PGA, BILAG A–E scores, ACR diagnostic criteria, Systemic Lupus International Collaborating Clinics Damage Index, SLE duration, and concurrent medications. Baseline disease characteristics associated with a $\geq10\%$ absolute difference (% flare - % no flare) or $\geq50\%$ increase ([% flare - % no flare]/% no flare) in flare rate were considered predictors of flare.

Results: By wk 52, 180 patients (32%) receiving placebo had 1 new BILAG A or 2 new B scores; 130 (23%) had a BILAG A score; and 133 (24%) had a severe SFI flare. By all 3 flare indices, SELENA-SLEDAI ≥12, and moderate–severe disease activity involving renal and hematologic domains were predictors of flare (see table). Serologic markers were predictors of severe SFI flare and 1 BILAG A or 2 B scores. Use of corticosteroids, immunosuppressives, antimalarials, and other concomitant medications did not predict flare.

Predictors of Flare

Characteristic	% 1 New BILAG A or 2 New B Scores		% Any BILAG A Score		% Severe SFI Flare	
	With (n = 180)	Without (n = 382)	With (n = 130)	Without (n = 432)	With (n = 133)	Without (n = 429)
SS ≥12	38.9#	24.1	39.2+	25.7	41.4#	24.9
SS proteinuria	20.0+	11.3	20.8*	12.0	21.1+	11.9
SS vasculitis	10.0*	5.0	10.0	5.6	9.0	5.8
SS low complement	70.0+	56.8	67.7	59.0	72.2+	57.6
SS DNA binding	75.0+	64.1	73.1	66.0	77.4+	64.6
BILAG renal (A8722'2dC)	53.3#	31.7	56.9#	33.1	54.9#	33.6
BILAG vasculitis (A/B)	14.4*	6.8	14.6*	7.6	15.0*	7.5
BILAG hematologic (A/B)	22.8+	12.3	27.7#	12.0	25.6+	12.6

Nominal p values for pairwise comparison (likelihood ratio test). SS, SELENA-SLEDAI. #$p<0.001$; +$p<0.01$; *$p<0.05$.

Conclusion: SLE patients on standard therapy alone with moderate–severe renal, vasculitic, hematologic, or serologic disease activity, or SELENA-SLEDAI ≥12 were at increased risk of having a clinically meaningful flare over 52 wk.

Disclosure: **R. F. van Vollenhoven**, Abbott, BMS, GSK, HGS, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, GSK, HGS, MSD, Pfizer, Roche, UCB, 5; **M. A. Petri**, HGS, GSK, 5; **R. A. Levy**, HGS, GSK, 8; **S. V. Navarra**, HGS, GSK, 8; **J. P. Buyon**, HGS, 2, HGS, GSK, 5; **Z. J. Zhong**, HGS, 1, HGS, 3; **W. W. Freimuth**, HGS, 1, HGS, 3; **R. Cervera**, HGS, GSK, 2, HGS, GSK, 5.

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Baseline Laboratory Characteristics From the Combined Placebo Groups in the Phase 3 Belimumab Trials Are Predictive of Severe Flare At 52 Weeks. Michelle A. Petri[1], Ronald F. van Vollenhoven[2], Roger A. Levy Sr.[3], Sandra V. Navarra[4], Ricard Cervera[5], Z. John Zhong[6], William W. Freimuth[6] and Jill P. Buyon[7]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [4]University of Santo Tomas Hospital, Manila, Philippines, [5]Hospital Clinic, Barcelona, Spain, [6]Human Genome Sciences, Inc., Rockville, MD, [7]New York University School of Medicine, New York, NY

Background/Purpose: Identification and validation of potential serologic biomarkers of clinically meaningful SLE flare are major unmet medical needs

in clinical practice and trials. The purpose of this analysis was to examine biomarker predictors of SLE flares at baseline in the combined placebo groups from the phase 3 belimumab BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) trials.

Methods: The BLISS trials enrolled patients with active SLE (SELENA-SLEDAI ≥6) who were autoantibody positive (antinuclear antibody or anti-double-stranded DNA [anti-dsDNA]), on stable standard SLE therapy for 30 d, and without severe active lupus nephritis or CNS SLE. Patients were randomized to placebo, or belimumab 1 or 10 mg/kg, plus standard therapy. Changes in prednisone were allowed early in the trials, but had to be within 25% or 5 mg of baseline dose. Flare was defined as the development of 1 new British Isles Lupus Assessment Group (BILAG) A or 2 new B organ domain scores; any new BILAG A score; or according to the modified severe SLE Flare Index (SFI). Laboratory biomarkers evaluated included antinuclear antibody, anti-dsDNA, anti-Smith, complement (C) 3 and 4, C-reactive protein (CRP), proteinuria >0.5 g/24 h, immunoglobulin, B- and T-cell subsets, and B-lymphocyte stimulator (BLyS) quartile levels. The proportion of placebo patients with abnormal laboratory values who developed a new flare was compared with the proportion without a flare. Meaningful difference was defined as: a ≥10% absolute difference (% flare - % no flare) or nominal p value for pairwise comparison (likelihood ratio test); or a ≥50% increase ([% flare - % no flare]/% no flare). Study limitations: laboratory tests were defined as categorical variables (present/absent at baseline), and the time-varying nature of the characteristics over the 52 wk was not examined.

Results: By wk 52 in the placebo group (n = 562), 32% of patients (n = 180) had 1 new BILAG A or 2 new B scores; 23% (n = 130) had a BILAG A score; and 24% (n = 133) had a severe SFI flare. Predictors of wk-52 flare (% with vs without flare) are shown in the table.

Univariate Analysis of Predictors of 52-Wk Flare

Baseline Laboratory Value	% 1 New BILAG A or 2 New B Scores		% Any BILAG A Score		% Severe SFI Flare	
	With (n = 180)	Without (n = 382)	With (n = 130)	Without (n = 432)	With (n = 133)	Without (n = 429)
Low C3 <90mg/dL	52.8#	40.1	51.5	41.9	59.4#	39.4
Low C4 <16mg/dL	61.1+	50.5	60.8	51.9	63.2*	51.0
CRP >3mg/L	43.4+	34.9	46.0*	35.2	44.6*	35.5
Proteinuria ≥0.5g/24 h	29.5+	17.3	32.3#	17.8	32.3#	17.7
Positive anti-dsDNA (>200 IU/mL)	44.4#	28.0	46.2#	29.4	49.6#	28.2
Serum BLyS ≥2 ng/mL	35.8#	20.1	37.8#	21.3	41.7#	19.9

# p <0.001; + p <0.01; * p <0.05.

Conclusion: SLE patients on standard therapy with low C3 or C4, elevated CRP, proteinuria >0.5 g/24 h, positive anti-dsDNA, or serum BLyS ≥2 ng/mL were at increased risk for SLE flare over 52 wk. The 3 flare definitions had high concordance regarding predictors; univariate risk factors, with the exception of C3/C4, were the same for all flare definitions at 52 wk. The data suggest serologic tests predict clinically meaningful flare over 52 wk of standard SLE therapy, and may be useful in the identification of patients at greater risk for flares in clinical practice and trials.

Disclosure: M. A. Petri, HGS, GSK, 5; **R. F. van Vollenhoven**, Abbott, BMS, GSK, HGS, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, GSK, HGS, MSD, Pfizer, Roche, UCB, 5; **R. A. Levy Sr.**, HGS, GSK, 8; **S. V. Navarra**, HGS, GSK, 8; **R. Cervera**, HGS, GSK, 2, HGS, GSK, 5; **Z. J. Zhong**, HGS, 1, HGS, 3; **W. W. Freimuth**, HGS, 1, HGS, 3; **J. P. Buyon**, HGS, 2, HGS, GSK, 5.

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Bioavailability, Pharmacokinetics, and Safety of Belimumab Administered Subcutaneously in Healthy Subjects. Wendy Cai[1], Cecil Chen[1], Z. John Zhong[1], William W. Freimuth[1], William Lewis[2] and David Subich[3]. [1]Human Genome Sciences, Inc., Rockville, MD, [2]Covance Clinical Research Unit, Inc., Dallas, TX, [3]Covance Clinical Research Unit, Inc., Daytona Beach, FL

Background/Purpose: Belimumab is a recombinant, human Ig-G1λ monoclonal antibody that binds and antagonizes the biological activity of soluble B-lymphocyte stimulator protein, a member of the tumor necrosis factor ligand superfamily that promotes the survival of B lymphocytes. This study (NCT#01583530) evaluated the absolute bioavailability, PK, tolerability, and safety of belimumab (200 mg/mL) administered SC to healthy subjects as a single dose and as multiple doses up to 240 mg.

Methods: In all, 118 healthy subjects (aged 18−55 y; body weight 51−115 kg) were enrolled. Seventy-eight subjects received a single dose of belimumab 240 mg IV, or 2 × 120, 1 × 240, or 1 × 200 mg SC. Forty subjects received 4 weekly injections of belimumab 2 × 120 or 1 × 200 mg

SC. Randomization was stratified by weight (< vs ≥ 75 kg) and, for SC administration, by injection site (abdomen vs thigh), with a target enrollment of 50% women/treatment group. Serial blood samples were collected and the serum belimumab concentrations measured by a validated electrochemiluminescence-based assay. Belimumab PK parameters were derived by noncompartmental or compartmental analysis.

Results: The bioavailability and PK parameters of belimumab following single IV and SC administration are summarized in the table. Following 4 weekly SC belimumab doses, bioavailability values (90% CI) were 75% (63%−89%) and 78% (67%–91%) for the 2 × 120- and 1 × 200-mg SC groups, respectively. Four subjects had persistent positive immune responses; neutralizing antibodies in these subjects were not detected and there was no apparent impact on PK. Single and multiple dosing of belimumab was generally safe and well tolerated, with no severe/serious injection-site reactions, eg, rash, edema, erythema, and pruritus.

PK and Bioavailability of Belimumab

Parameter	Belimumab			
	240 mg IV	2 × 120 mg SC	1 × 240 mg SC	1 × 200 mg SC
No. of subjects	19	19	18	18
t_{max}, d[a]	0.09 (0.05–0.30)	3.9 (0.9–9.8)	4.9 (2.9–13.9)	5.9 (1.9–13.9)
C_{max}, μg/mL[b]	86.2 (20.2)	32.7 (29.0)	31.6 (27.9)	24.3 (40.3)
$AUC_{0-\infty}$, μ·d/mL[b]	1030 (32.1)	788 (36.1)	812 (36.2)	612 (37.9)
$t_{1/2\cdot term}$, d[c]	18.2 ± 6.3	15.9 ± 5.3	18.2 ± 6.0	16.0 ± 5.1
F, %[d]	–	76 (64–90)	82 (70–95)	74 (60–91)

[a] Median (range); [b]geometric mean (coefficient of variance); [c]mean ± SD; [d]absolute bioavailability (F) and 90% CI.
$AUC_{0-\infty}$, area under plasma concentration-time curve from time 0 to ∞; C_{max}, maximum plasma drug concentration; t_{max}, time to reach maximum plasma concentration; $t_{1/2\cdot term}$, terminal half-life.

Conclusion: Following single belimumab SC doses, bioavailability was 74%−82%, indicating that belimumab SC was well absorbed, and bioavailability was similar among the 3 SC groups. Bioavailability after 4 weekly SC doses was similar to that following single SC administration. Belimumab was generally safe and well tolerated after single and multiple SC dosing.

Disclosure: W. Cai, HGS, 1, HGS, 3; **C. Chen**, HGS, 1, HGS, 3; **Z. J. Zhong**, HGS, 1, HGS, 3; **W. W. Freimuth**, HGS, 1, HGS, 3; **W. Lewis**, None; **D. Subich**, None.

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Soluble Urokinase Plasminogen Activator Receptor (suPAR) Levels Reflect Organ Damage in Systemic Lupus Erythematosus. Helena Enocsson[1], Jonas Wetterö[2], Thomas Skogh[2] and Christopher Sjöwall[1]. [1]Linkoping University, Linkoping, Sweden, [2]Linköping University, Linköping, Sweden

Background/Purpose: Disease activity assessment in systemic lupus erythematosus (SLE) remains a challenge due to lack of reliable biomarkers and disease heterogeneity. Ongoing tissue inflammation can be difficult to distinguish from irreversible damage caused by previous flares or side-effects of medication. Soluble urokinase plasminogen activator receptor (suPAR) is a part of the plasminogen activation system and is involved in inflammation, tissue remodelling and cancer metastasis. Cell-surface expression of uPAR on endothelial cells, megakaryocytes, monocytes, neutrophils and activated T cells is up-regulated upon stimulation with growth factors and cytokines, such as IL-1β and TNF. suPAR is released by protease-mediated shedding of cell-bound uPAR, and has emerged as a useful biomarker in disparate conditions (*e.g.* sepsis, malignancies, and focal segmental glomerulosclerosis). Herein, we evaluated suPAR as a marker of disease activity and organ damage in lupus.

Methods: Cross-sectional sera from 100 healthy blood donors and 198 SLE patients fulfilling the 1982 American College of Rheumatology (ACR) classification criteria (81%) and/or the 'Fries criteria' (a clinical SLE diagnosis based upon a history of abnormal ANA titre and ≥2 typical organ manifestations) were analyzed for suPAR by enzyme immunoassay. Patients were recruited consecutively; most were prevalent cases (91%), but a few (9%) had recent-onset disease at the time of sampling. Disease activity was assessed by SLE disease activity index-2K (SLEDAI) and the physician's global assessment (PGA). Organ damage was evaluated by SLE international collaborating clinics (SLICC)/ACR damage index (DI). Routine analyses included blood cell counts, erythrocyte sedimentation rate, C-reactive protein (CRP), C3, C4, creatinine, creatine kinase, urinalysis and anti-dsDNA (*Crithidia luciliae* IF test, CLIFT). Informed consent was obtained from all subjects and the research protocol was approved by the Regional Ethics Committee in Linköping (M75-08).

Results: No significant difference was found comparing suPAR in healthy controls and patients. In SLE, suPAR levels were highly associated with leukocyte count; and thus, this was adjusted for, as well as for age, sex and glucocorticoid dose in further analyses. Yet, no associations were recorded between suPAR levels and disease activity reflected by SLEDAI or PGA. However, a highly significant association was observed between suPAR and global SLICC/ACR DI (p<0.0005), and a borderline significant association was found between CRP and SLICC/ACR DI (p=0.05). Dissecting SLICC/ACR DI into organ systems in a multiple regression analysis, we found renal, ocular, neuropsychiatric, skin and peripheral vascular damage to have a significant positive impact on suPAR levels, whereas no separate organ system had significant impact on CRP.

Conclusion: This study demonstrates a strong association between suPAR and organ damage, but not with disease activity, in lupus. The high association between suPAR and leukocyte count could possibly explain why no difference in suPAR was found between patients and healthy blood donors. Analysis of suPAR may be a valuable clinical tool to assess disease outcome in SLE.

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BAFF/BLyS Gene Expression Predicts Disease Activity in Systemic Lupus Erythematosis Over One Year. Eric Zollars[1], Hong Fang[1], Jadwiga Bienkowska[2], Norm Allaire[2], Susan Kalled[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA

Background/Purpose: The search for a marker of SLE disease activity has included inflammatory markers, chemokines and gene signatures. We explored the ability of the BAFF gene expression to predict SLE disease activity in the subsequent year after measurement.

Methods: 292 patients (59% Caucasian, 34% African-American, 92% female, mean age 46 ± 12 years) were enrolled in a prospective observational study. At baseline, BAFF gene expression level was determined in peripheral blood RNA using Affymetrix chips. Clinical associations, based on the same-day visit disease activity (using the Physician Global Assessment and SELENA SLEDAI) as well as activity over the ensuing year were then determined. **Results** were determined with a generalized estimating equation to account for the repeated observations among the same patients.

Results: The number of visits within a year after the measurement of BAFF gene expression varied from 1–9. Six patients had 1 visit, 46 patients had 2–3 visits, 159 patients had 4 visits, and 81 patients had more than 4 visits.

Table 1. Percentage of visits with disease activity by BAFF gene expression

Variable	Low BAFF (<10.7) (%, N=387)	Med BAFF (10.7–11.4) (%, N=476)	High BAFF (>11.4) (%, N=347)	P-value	Adjusted P-value for Race
Physician global assessment >1	8%	21%	24%	.0003	.0041
SLEDAI ≥2	36%	57%	71%	<.0001	<.0001
Urine Protein/ Creatinine Ratio (≥0.5)	3%	13%	13%	.0004	.0096
Anti-dsDNA ≥ 10	9%	21%	35%	<.0001	<.0001
C3 <79 mg/dL	4%	11%	21%	.0002	.0004
C4 <12 mg/dL	4%	11%	19%	.0004	.0005
ESR >20	35%	55%	63%	<.0001	.0005

We controlled for race, sex, baseline low complement and baseline anti-dsDNA.

Table 2. Average disease activity over a year of follow-up.

Variable	BAFF gene expression	Unadjusted Activity	Adjusted Mean Differences	P-values
PGA	Low (<10.7)	0.48	0 (Ref.Group)	
	Med (10.7–11.4)	0.70	0.14	.044
	High (>11.4)	0.74	0.15	.045
SLEDAI	Low (<10.7)	1.08	0 (Ref.Group)	
	Med (10.7–11.4)	2.10	0.39	.031
	High (>11.4)	2.98	0.72	.0029

Conclusion: We have previously shown that the BAFF gene expression correlates with same-day disease activity. We now can prove that BAFF gene expression predicts disease activity over the ensuing year. This supports BAFF/BLyS as a target for clinical intervention.

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Elevated Plasma Levels of CXCL2 and CXCL10 Have Distinct Predictive Value in Systemic Lupus Erythematosus. Felipe Andrade[1], Ehtisham Akhter[2], Hong Fang[2] and Michelle Petri[2]. [1]The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Serum levels of chemokines have been previously used as downstream markers of the interferon (IFN) pathway in SLE. CXCL2 (GROB) and CXCL10 (IP-10) have been found to be elevated in SLE (over controls) and in SLE with high type I IFN gene signature over controls (Bauer et al, 2006). CXCL2, however, may be an IFN-independent marker, in contrast to previous reports. We compared CXCL2 with CXCL10 (which is IFN-induced) over time in SLE, and determined the relationship with disease activity.

Methods: 25 SLE patients (84% female, 72% Caucasian, 28% African-American, mean age at baseline 48 + 10 yrs) had CXCL10 and CXCL2 levels measured in plasma by ELISA at baseline and at follow-up visit 0.72 years (mean) later. Chemokine levels were defined as low (<150 ng/ml for CXCL10 and <100 ng/ml for CXCL2) or high (>150 ng/ml for CXCL10 and >100 ng/ml for CXCL2).

Results: Baseline high CXCL2 levels were associated with a history of proteinuria. High CXCL10 was associated with low C3 (p=0.007), low C4 (p<0.0001) and anti-dsDNA (p=0.0094). The high CXCL10 group had a significant increase in SLEDAI at the second visit (2.4 to 4.5, p=0.021). The high CXCL2 group had an increase in activity by both PGA (p=0.02) and SLEDAI (p=0.011), as well as lower C3 (p=0.023) and lower C4 (p=0.096) at the second visit. Urine pr/cr went up (0.3 to 0.7), but was not statistically significant.

Changes in Measures of Disease Activity by Chemokine High/Low

CXCL10	Mean at baseline	p–value for baseline between groups	Mean at followup	Mean Change between baseline and followup	p–value for change within group	p–value for change between groups
PGA						
Low CXCL10(n=12)	0.6	0.47	0.7	0.1	0.57	0.73
High CXCL10(n=13)	0.8		0.8	0.0	0.98	
SLEDAI						
Low CXCL10(n=12)	0.8	0.061	1.3	0.5	0.54	0.16
High CXCL10(n=13)	2.4		4.5	2.2	0.021	
C3						
Low CXCL10(n=12)	118.5	0.0007	119.8	1.3	0.85	0.97
High CXCL10(n=13)	79.0		80.5	1.5	0.74	
C4						
Low CXCL10(n=12)	25.7	<0.0001	25.9	0.3	0.88	0.63
High CXCL10(n=13)	12.2		13.4	1.2	0.31	

CXCL2	Mean at baseline	p–value for baseline between groups	Mean at followup	Mean Change between baseline and followup	p–value for change within group	p–value for change between groups
PGA						
Low CXCL2(n=18)	0.8	0.48	0.6	−0.2	0.49	0.052
High CXCL2(n=7)	0.5		1.1	0.6	0.022	
SLEDAI						
Low CXCL2(n=18)	1.8	0.47	2.5	0.7	0.33	0.058
High CXCL2(n=7)	1.1		4.3	3.1	0.011	
C3						
Low CXCL2(n=18)	96.9	0.81	103.4	6.4	0.19	0.033
High CXCL2(n=7)	100.6		89.0	−11.6	0.023	
C4						
Low CXCL2(n=18)	18.1	0.66	20.2	2.1	0.080	0.026
High CXCL2(n=7)	20.0		17.3	−2.7	0.096	

Conclusion: The lack of correlation between levels of CXCL2 and CXCL10 strongly supports that these chemokines are driven by distinct mechanistic pathways in SLE. Although the IFN pathway is likely to be responsible of changes in CXCL10 levels in SLE, the mechanism(s) that regulate CXCL2 in SLE is unclear. High CXCL2 is predictive of increasing disease activity over a mean of 0.7 marks, by both PGA and SLEDAI, and reduction in C3 and C4. Neither chemokine, however, significantly changed from baseline to second visit.

Disclosure: F. Andrade, None; **E. Akhter**, None; **H. Fang**, None; **M. Petri**, None.

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Development of A Quantitative PCR Method to Determine Interferon Signature Metric Status in SLE Patients: Distribution and Clinical & Serological Associations in Two Lupus Clinical Trials. Bruce C. Richardson[1], William P. Kennedy[2], John C. Davis Jr.[2], R. Maciuca[2], A. Morimoto[2], J. M. McBride[2], Alexander R. Abbas[2], Timothy W. Behrens[2] and Michael J. Townsend[2]. [1]University of Michigan, Ann Arbor, MI, [2]Genentech, Inc, South San Francisco, CA

Background/Purpose: Elevated and coordinated expression of multiple Interferon-regulated genes (IRGs) in peripheral blood cells is present in most systemic lupus erythematosus (SLE) patients. Here we describe the development of a validated quantitative PCR (qPCR) test to accurately measure relative levels of IRGs in SLE blood at baseline and over the course of clinical trials.

Methods: A cross sectional SLE cohort (n=150) and a healthy cohort (n=70) were used for qPCR development. Subject samples from two clinical trials with rontalizumab (anti-IFN alpha), Phase 1 with mild to moderate lupus (n=60) and Phase 2 with moderate to severe lupus (ROSE, n=238) were used for validation. Expression of type I IRGs was determined by expression microarray and qPCR analysis of peripheral blood RNA. Relationships between IRGs were assessed using Spearman's rank correlation. Exploratory hypothesis testing between patient subsets was performed using Wilcoxon rank sum or Fisher's exact tests.

Results: Unsupervised hierarchical clustering revealed a region comprised of a high density of IRGs and a representative 3-gene combination (r >0.98) was chosen for measurement by qPCR. An Interferon Signature Metric (ISM) score was derived from the average normalized expression of these 3 genes. ISM scores in the Rontalizumab trials followed a bimodal distribution compared with controls. Determination of threshold cutoff for ISM high vs. low designation was based upon the 95th percentile of the ISM scores of healthy controls, allowing discrimination of the two modes of distribution in SLE. In the ROSE trial there were no differences in disease activity as measured by BILAG and SELENA-SLEDAI between identified ISM high and ISM low subjects. Further, longitudinal assessment of subjects in the placebo arm of the ROSE trial followed over 36 weeks showed that the probability of maintaining either ISM low or high status was 94% (95% CI 91%–97%).

IFN signature metric (ISM) distribution in normal and SLE populations
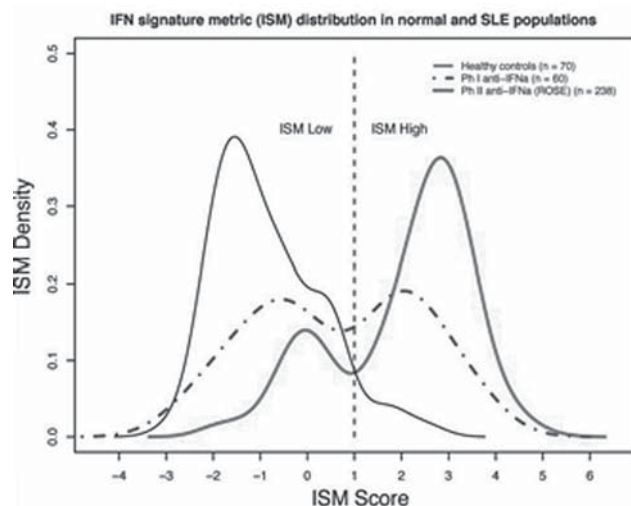
Conclusion: The ISM test accurately quantifies the bimodal blood Interferon Signature in SLE subjects. ISM high status was not associated with increased BILAG and SELENA-SLEDAI-defined disease activity. ISM status was observed to be stable over 36 weeks of longitudinal assessment. The ISM test may provide useful information in clinical trials of targeted therapies and in the understanding of disease heterogeneity in SLE.

Disclosure: B. C. Richardson, None; **W. P. Kennedy**, Genentech, Inc, 3, Roche Pharmaceuticals, 1, Merck co, 1; **J. C. Davis Jr.**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **R. Maciuca**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **A. Morimoto**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **J. M. McBride**, Roche Pharmaceuticals, 1, Genentech, Inc, 3; **A. R. Abbas**, Genentech, Inc, 3, Roche Pharmaceuticals, 1; **T. W. Behrens**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **M. J. Townsend**, Roche Pharmaceuticals, 1, Genentech, Inc., 3.

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Prolonged Improvement of Systemic Lupus Erythematosus Following Systematic Administration of Rituximab and Cyclophosphamide. Thomas J. A. Lehman[1], Emily Baird[2], Anusha Ramanathan[3], Risa Alperin[3], Emma J. MacDermott[3], Alexa B. Adams[3], Laura V. Barinstein[4] and Lakshmi N. Moorthy[5]. [1]Hosp for Special Surgery, New York, NY, [2]Hospital for Special Surgery, NY, [3]Hospital for Special Surgery, New York, NY, [4]Maimonides Medical Center, Brooklyn, NY, [5]Robert Wood Johnson-UMDNJ, New Brunswick, NJ

Background/Purpose: We report sustained improvement in 15 patients with corticosteroid dependent SLE who received a systematic regimen of rituximab and cyclophosphamide administered at months 0, 6, and 18. All patients had active SLE despite prior therapy. Five patients were male and 10 were female. Seven patients had biopsy proven DPGN. Three patients were Hispanic, 5 were Asian, 1 African American, and 6 Caucasian. All experienced a marked and sustained reduction in their corticosteroid dose with improvement in C3, C4, Hb, ESR, Cr, serum albumin and SLEDAI which persisted at 60 months following initiation of therapy (42 months following the last dose of these medications).

Methods: All patients received rituximab 750 mg/m^2 (max 1 gram) on day 1 and cyclophosphamide 750 mg/m^2 on day 2. This regimen was repeated on days 15 and 16. All patients received a further two doses of rituximab and cyclophosphamide at month 6 and two doses at month 18. Patients with active DPGN received additional doses of cyclophosphamide (750 mg/m^2) at 6, 10, 14, and 18 weeks. The prednisone dosage was gradually decreased at the discretion of the treating physician. Because the data were nonparametric Wilcoxon signed rank tests were used for all statistical comparisons.

Results: Significant improvement occurred in prednisone dose, C3, C4, Hb, ESR, Cr, serum albumin and SLEDAI which persisted (see chart). No patient experienced a disease flare requiring hospitalization. The mean SLEDAI score decreased from 8.929 to 1.917 after the first six months of therapy and remained low thereafter. Four patients are known to be ANA negative at month 36 following the initiation of treatment.

	N = 15 Month 0	N = 15 Month 12	N = 15 Month 24	N = 13 Month 36	N = 9 Month 60
Prednisone dose (mg daily)	29.10 ± 21.88	14.74*** ± 7.35	10.43*** ± 3.518	8.409** ± 2.567	8.5** ± 4.802
C3(mg/dl)	60.78 ± 26.55	105.8*** ± 32.74	108.3*** ± 30.50	117.2** ± 23.50	105.6** ± 16.56
C4(mg/dl)	10.61 ± 5.807	21.57*** ± 9.832	22.85*** ± 9.584	24.86*** ± 10.80	24.40* ± 8.876
HGB(g/dl)	11.43 ± 1.958	12.44*** ± 1.588	12.76*** ± 1.372	12.68** ± 1.696	13.24** ± 1.459
ESR(mm/hr)	39.40 ± 25.87	19.60*** ± 21.73	16.67*** ± 18.00	11.08** ± 13.10	15* ± 16.07
Cr(mg/dl)	0.8067 ± 0.2120	0.8143*** ± 0.1994	0.7933*** ± 0.1672	0.7683** ± 0.1938	0.7100** ± 0.1115
Alb(mg/dl)	3.336 ± 0.8545	4.107*** ± 0.4148	4.080*** ± 0.5784	4.254** ± 0.4294	4.289** ± 0.4197
WBC(/nl)	9.049 ± 7.149	7.558*** ± 3.237	8.101*** ± 2.801	7.402*** ± 1.877	6.550** ± 1.907

Conclusion: A specific 18 month regimen of systematically administered cyclophosphamide and rituximab led to sustained improvement in prednisone dosage, C3, C4, Hb, ESR, Cr, serum albumin and SLEDAI which persisted at 60 months following initiation of therapy which was maintained 42 months following the completion of therapy.

Disclosure: T. J. A. Lehman, Genentech and Biogen IDEC Inc., 5; **E. Baird**, None; **A. Ramanathan**, None; **R. Alperin**, None; **E. J. MacDermott**, None; **A. B. Adams**, None; **L. V. Barinstein**, None; **L. N. Moorthy**, None.

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Headache in Systemic Lupus Erythematosus (SLE): Results From a Prospective, International, Inception Cohort Study. John G. Hanly[1] and Systemic Lupus International Collaborating Clincs[2]. [1]Dalhousie University and Capital Health, Halifax, NS, [2](SLICC)

Background/Purpose: Headache is common in SLE patients and in the general population. We examined the frequency, characteristics and attribution of headaches in a large, prospective, inception cohort of SLE patients and determined the association with global disease activity and health related quality of life.

Methods: An international network of 31 academic medical centers enrolled patients within 15 months of SLE diagnosis. Assessments occurred annually for up to 10 years for headache (5 types) and other neuropsychiatric (NP) events as per the ACR case definitions for 19 NP syndromes. Additional data were demographic and clinical variables, SLE global disease activity (SLEDAI-2K), SLICC/ACR damage index (SDI) and self-report mental (MCS) and physical (PCS) component summary scores of the SF-36. Statistical analyses of time to first headache (all headaches and migraine only) were based on Cox's proportional hazards model. SF-36 scores were examined by linear regression models with generalized estimating equations to account for within patient correlation.

Results: Of the 1732 enrolled patients 89% were female with the following racial/ethnic distribution: Caucasian (48%), African (16%), Asian (16%), Hispanic (16%) and other (4%). At enrollment the mean ($\pm$ SD) age was 34.6 ± 13.4 years, disease duration was 5.6 ± 4.8 months and followup was 3.8 ± 3.1 years. Mean SLEDAI-2K at enrollment was 4.0 ± 5.3 and SDI was 0.32 ± 0.78. Within the enrollment window (6 months pre-diagnosis up to the enrollment visit) the proportion of patients with headache was 17.8% subdivided into: migraine (55.2%), tension (35.1%), intractable non-specific (6.5%), cluster (2.4%) and intracranial hypertension (0.9%). The estimated proportion of patients ever reporting a headache increased to 57% after 10 years (Kaplan-Meier estimate) with similar subset distribution. Only 2% of patients in 0.6% of assessments had "lupus headache" in SLEDAI-2K scores over the study. Headache was associated with other NP events as indicated by Hazard Ratio (HR) estimates (95% CI) for: aseptic meningitis 3.8 (1.2, 12.0), autonomic disorder 13.3 (3.3, 53.6), cerebrovascular disease 2.3 (1.5, 3.6), anxiety disorder 2.2 (1.5, 3.2) and mood disorder 2.1 (1.6, 2.7). Headache increased with rising SLEDAI-2K (excluding "lupus headache" variable). The estimated risk for any 5 unit increase in SLEDAI-2K corresponded to an HR (CI) of 1.13 (1.03, 1.23). The mean (SD) SF-36 MCS scores were lower in patients with headache compared to patients without headache (mean $\pm$ SD: 42.5 ± 12.2 vs 47.8 ± 11.3; $p < 0.001$) as were PCS scores (38.0 ± 11.0 vs 42.6 ± 11.4; $p < 0.001$). Comparable results were found in all analyses when migraine was examined separately. All associations with headache and migraine alone remained significant after adjustment for gender, race/ethnicity, geographic location and age at diagnosis.

Conclusion: Headaches, particularly migraine and tension types, occur frequently among SLE patients and are associated with other types of NP events. Although the majority of headaches are not attributable to active lupus, they are associated with higher global SLE disease activity and lower self-reported health-related quality of life.

Disclosure: J. G. Hanly, None;

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Endothelial Microparticles As a Biomarker for Endothelial Dysfunction in Active Systemic Lupus Erythematosus. Ben Parker[1], Awal Zaki[2], M. Yvonne Alexander[3] and Ian N. Bruce[4]. [1]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [3]The University of Manchester, Manchester, United Kingdom, [4]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom

Background/Purpose: Systemic Lupus Erythematosus (SLE) is associated with an increased risk of clinical and subclinical cardiovascular disease (CVD) including endothelial dysfunction, in part due to systemic inflammatory disease activity. Endothelial microparticles (EMPs) are membrane-bound subcellular particles produced by endothelial cells in response to a variety of activation triggers, including inflammatory cytokines and classic CVD risk factors. EMPs reflect endothelial damage and may correlate with measures of endothelial function, such as flow-mediated dilatation (FMD) of the brachial artery. EMPs may therefore serve as a biomarker for endothelial dysfunction in SLE. We aimed to: 1) compare EMP levels and FMD in patients with active SLE compared to controls; 2) assess change over time in EMP and FMD following improved disease control and 3) assess the correlation between EMPs and FMD.

Methods: Patients with active SLE ($\geq$4 ACR criteria) were recruited and assessed at baseline and 4 months after a change in therapy. Disease activity (BILAG 2004 and SLEDAI 2K) and clinical features were recorded at each visit. Healthy age-matched controls were assessed once. FMD (%) of the brachial artery was measured using 2D ultrasound and automated edge-tracking software. EMPs were quantified (number/ml) using flow cytometry after incubating platelet-poor-plasma with the cell surface markers CD31, CD42b and Annexin-V. Events positive for annexin-V and CD31, and negative for CD42b, were classified as EMPs. Continuous data were compared using Mann-Whitney test, and Spearman's Rank was used to correlate EMP levels with %FMD.

Results: 27 patients with SLE (mean (SD) age 41.5 (14.1) yrs) and 22 controls (mean age (SD) 38.5 (9.3) yrs) underwent assessment of endothelial function. In SLE patients the mean (SD) SLEDAI-2K and total BILAG scores were 8.2 (5.5) and 16.9 (10.6) respectively. Endothelial-dependent FMD was significantly reduced in the SLE group compared to controls at baseline (median (IQR) FMD 1.63% (-1.22, 5.32) vs. 5.40% (3.02, 8.57); p = 0.05). EMPs (n/ml) were significantly elevated in the SLE cohort compared to controls at baseline (median (IQR) 157,548/ml (59,906, 272,643) vs. 41,025 (30,179, 98,082); p = 0.003). In patients with paired results, disease activity significantly improved 4 months after a change in therapy (SLEDAI-2K 3.8 (3.4); BILAG 2004 score 6.9 (5.4) (p= 0.001 and 0.001 vs. baseline respectively). The median (IQR) FMD improved over time (0.33% (-2.31, 4.1) vs. 3.19% (0.98, 5.09); p = 0.1), as did median (IQR) EMP levels (166,982/ml (59906, 278,775 vs. 55655 (29475, 188,659; p = 0.02). In the whole cohort, EMPs demonstrated a significant negative correlation with %FMD (correlation coefficient -0.42; p =0.008). In SLE patients with paired data the correlation coefficient was -0.51 (p = 0.005).

Conclusion: Endothelial function is significantly impaired and EMPs are significantly elevated in young patients with active SLE compared to healthy controls. Both EMPs and FMD improve over time, following a reduction in disease activity. EMPs also correlate with FMD, and may serve as a useful biomarker of endothelial damage/dysfunction and CVD risk in SLE.

Disclosure: B. Parker, None; **A. Zaki**, None; **M. Y. Alexander**, None; **I. N. Bruce**, None.

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Excess Health Care Utilization Prior to Diagnosis of Systemic Lupus Erythematosus in England. Amy Steffey[1], Trung N. Tran[1], Jie Li[1] and Herve Caspard[2]. [1]MedImmune, Gaithersburg, MD, [2]MedImmune LLC, Gaithersburg, MD

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic auto-immune disease resulting in significant excess morbidity and health care utilization. Since time of disease onset is often unknown, we hypothesized that there is an excess of health care utilization prior to diagnosis of SLE cases (but after disease onset).

Methods: We identified a cohort of incident cases of SLE among individuals documented in the Clinical Practice Research Datalink (CPRD) and linked with Hospital Episode Statistics (HES). CPRD is a database of anonymized longitudinal medical records from primary care from over 600 practices in the United Kingdom. HES is a database documenting all admissions to the National Health System hospitals in England that can be linked with CPRD since 1997. All individuals documented in GPRD and HES prior to October 1st, 2010 and aged 18 years or older were retained in the analysis.

Patients with SLE were identified as individuals with at least one relevant diagnosis code in CPRD or HES (list of codes available upon request).

Incident cases were defined as patients with at least 12 months of registration in CPRD prior to the date of first diagnosis. All incident SLE cases were matched with up to 5 controls registered in CPRD and linked with HES at the time of and during the one year prior to first diagnosis of the SLE case, and matched by age, gender, and practice. The index date for the controls is the index date (or date of first diagnosis) of the matched case.

Results: The proportions of individuals in the controls group who were hospitalized at least once, had an encounter with a health care practitioner (HCP) or were treated with corticosteroids during each 6 month period over the 3 years prior to the index date remained relatively stable (Table 1).

Table 1. Health care utilization three years prior to diagnosis of SLE or prior to index date of the matched controls

Matched Controls	M.–36/M.–31 n=3,954	M.–30/M.–25 n=4,344	M.–24/M.–19 n=4,752	M.–18/M.–13 n=5,139	M.–12/M.–7 n=5,557	M.6–to D.0 n=5,687
Hospitalization	7%	8%	9%	8%	9%	9%
Treatment with cortico steroids	10%	10%	11%	10%	10%	11%
Encounter with HCP	75%	74%	75%	75%	75%	74%

SLE Cases	M.–36/M.–31 n=973	M.–30/M.–25 n=1,024	M.–24/M.–19 n=1,096	M.–18/M.–13 n=1,126	M.–12/M.–7 n=1,159	M.6–to D.0 n=1,159
Hospitalization	14%	16%	16%	17%	20%	26%
Treatment with cortico steroids	20%	20%	21%	23%	27%	33%
Encounter with HCP	73%	73%	73%	75%	76%	81%

The proportions of SLE cases who were hospitalized at least once or were treated with corticosteroids per 6 month period grew from 14% to 26% and from 20% to 33%, respectively, over the 3 years prior to the date of incident diagnosis. The proportion of patients who had at least one encounter with a HCP grew also from 73% to 81%.

There is a significant excess of health care utilization in SLE cases versus matched controls during the 3 years prior to the date of incident diagnosis. The excess was still significant between M.-36 and M.-31, when the proportions of individuals hospitalized at least once and treated with corticosteroids were twice as high among SLE cases than in matched controls: 14% versus 7% and 20% versus 10%, respectively.

Conclusion: Excess health care utilization prior to incident diagnosis of SLE should be taken into account to assess the total burden of disease. This analysis suggests that there is an excess health care utilization for at least 3 years prior to diagnosis.

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Control of Hypertension and Hypercholesterolemia Is Not Associated with a Decreased Rate of Atherosclerotic Vascular Events in Patients with Systemic Lupus Erythematosus. Joanna Ueng, D. D. Gladman, Dominique Ibanez and Murray B. Urowitz. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology. It has been shown that patients with SLE are at a higher risk for premature atherosclerosis because of their disease and its treatment. Hypertension and hypercholesterolemia are treatable risk factors for the prevention of coronary artery disease in these patients. The purpose of this study was to determine if controlling hypertension and hypercholesterolemia is associated with a decreased rate of atherosclerotic vascular disease in patients with SLE who have been followed prospectively in a long term study.

Methods: SLE patients registered in the Lupus Clinic within 1 year of diagnosis between 1985 and 2002 were studied. Thirty-one patients with atherosclerotic vascular events (AVEs), defined as myocardial infarction, angina, pacemaker insertion, coronary artery bypass surgery, transient ischemic attack, stroke, or peripheral vascular disease, were identified from the computerized database. AVEs were subsequently confirmed by a detailed chart review. Controls, defined as having no history of AVEs, were matched to cases based on age at SLE diagnosis, gender, decade of clinic entry, disease duration at clinic entry, Adjusted Mean SLE Disease Activity Index-2K (AMS) at time of AVE and SLE Disease Activity Index-2K (SLEDAI-2K). Successful control of blood pressure and cholesterol (total and LDL) was determined for patients with AVEs and for those without AVEs. Successful control was defined as normal levels in 90% of follow-up visits (ie. systolic BP ≤140 mmHg, diastolic BP ≤90 mmHg, serum total cholesterol ≤5.2 mmol/L, serum LDL ≤3.2 mmol/L). P-values were calculated based on the chi-square test.

Results: 30 patients with AVEs and 60 matched controls without a history of AVEs were included. Average disease duration at time of AVE for cases was 6.9 ± 4.8 years, and matched disease duration for controls was 6.1 ± 4.2 years (p=0.45). Successful control of hypertension and hypercholesterolemia are shown in Table 1, according to risk factor profile.

Table 1. Number of patients with successful control of hypertension and hypercholesterolemia

Risk factor profile	Cases (n=30)	Controls (n=60)	p–value
Hypertension and hypercholesterolemia	17	23	
Both success	2 (12%)	2 (9%)	
BP only success	6 (35%)	3 (13%)	0.08*
Cholesterol only success	3 (18%)	2 (9%)	
Neither success	6 (35%)	16 (69%)	
Hypertension only	8	12	
BP success	2 (25%)	1 (8%)	0.54
Unsuccessful	6 (75%)	11 (92%)	
Hypercholesterolemia only	2	12	
Cholesterol success	1 (50%)	3 (25%)	0.51
Unsuccessful	1 (50%)	9 (75%)	
Neither hypertension nor hypercholesterolemia	3 (10%)	13 (22%)	

*Mantel-Haenszel chi-square test where "BP only success" was combined with "Cholesterol only success"

Conclusion: Hypertension and hypercholesterolemia are infrequently controlled in patients with SLE. Inadequate control of these risk factors is seen in both patients who have had an AVE and those who have not, suggesting that other risk factors or protective factors must play a role in the development of AVEs.

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The Interferon Alpha Gene Signature Is Not Associated with Nor Does It Predict Progression of Coronary Artery Calcium (CAC) or Carotid Intima-Media Thickness (IMT) in Systemic Lupus Erythematosus (SLE). Adnan Kiani, Hong Fang, Jie Xu, Ehtisham Akhter and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Accelerated atherosclerosis is the major cause of late mortality in SLE. Interferon alpha plays a role in atherosclerosis by deleting endothelial progenitor cells and causing endothelial dysfunction. NZM and Apo E −/− mice exposed to IFN-alpha develop platelet activation and thrombosis. Loss of Type I interferon receptor signaling improves endothelium dependent vasorelaxation, endogenous progenitor cell numbers and function and neoangiogenesis. We investigated whether the interferon alpha gene signature would predict changes in subclinical measures of atherosclerosis in human SLE over 2 years.

Methods: 70 SLE patients, 91% female, 60% Caucasian, 34% African-American, 6% others, mean age 43±10 yrs had coronary artery calcium (CAC) measured by helical CT and carotid intima-media thickness by carotid duplex. The IFN gene signature was determined in peripheral blood RNA using Affymetrix chips.

Results: At baseline, there was no difference in coronary calcium or IMT progression with low vs. high interferon gene signature. Patients with high interferon signature had lower CAC scores at baseline and 2 years but the difference between the 2 groups was not statistically different.

Table 1. Changes in coronary artery calcium (CAC) and carotid intima-media thickness (IMT)

Measure	Mean at baseline	Mean after 2 years	Mean Change	p-value for baseline between groups*	p-value for change within group	p-value for change between groups*
Log_e(CAC score+1)						
Low IFN	1.48	1.69	0.21	0.38	0.22	0.24
High IFN	0.90	0.81	–0.09		0.68	
Carotid IMT						
Low IFN	0.58	0.67	0.10	0.52	0.0008	0.54
High IFN	0.56	0.63	0.07		<0.0001	

* P-value when age, gender, and ethnicity are controlled

Conclusion: In contrast to in vitro and murine studies which clearly show a role of interferon alpha in atherosclerosis, our study failed to find any difference in coronary calcium progression or carotid IMT progression over 2 years, comparing low vs. high signature patients. In fact, the high interferon gene signature group had no progression in coronary calcium over 2 years. Although interferon could still be acting locally at the level of the coronary artery, our study suggests that we must look elsewhere to identify a genetic biomarker of atherosclerosis in SLE.

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Zostavax Vaccine Is Safe in Lupus Patients with Low Disease Activity.
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Background/Purpose: The Zostavax vaccine was FDA approved in 2006 for the prevention of herpes zoster in healthy adults over age 50. Because it is a live-attenuated vaccine, concerns exist regarding the safety of vaccination in individuals with autoimmune diseases and those on immunosuppressive therapies. We sought to evaluate the safety and immunogenicity of Zostavax vaccination in a group of SLE patients compared to healthy control subjects.

Methods: Ten SLE patients and ten healthy control subjects, all older than 50 years, were recruited to receive Zostavax vaccination followed by 12 weeks of follow-up for safety and immunogenicity. All study subjects had serologic confirmation of primary varicella infection before vaccination. SLE patients had mild, stable disease, with SLEDAI ≤ 4 at enrollment. SLE medications were restricted to azathioprine, methotrexate, anti-malarials, and ≤ 10 mg prednisone daily. Exclusion criteria included history of any varicella vaccination, herpes zoster within 5 years, and use of mycophenolate mofetil, cyclophosphamide or biologic therapies within 6 months of enrollment.

Each subject received Zostavax subcutaneously in the deltoid region during the baseline visit. Follow-up visits were scheduled at 2, 6, and 12 weeks following vaccination for safety and efficacy assessments. The primary safety endpoint was development of herpetiform or bullous lesions at the injection site at any time. Secondary safety endpoints were SLE flare by SLEDAI flare index, any injection site reaction, and any treatment-related adverse events. Primary immunogenicity endpoint was change in VZV-specific cell mediated immunity at 6 weeks compared to baseline between groups. Secondary endpoints included changes in WBC subsets by FACs analysis at each time point.

Results: All study participants were women. Baseline demographics are outlined in Table 1. Among SLE patients, mean baseline SLEDAI was 1.1 (range 0–2). Four patients were receiving prednisone (range 2.5–10 mg daily), two, methotrexate, and seven hydroxychloroquine. All subjects received Zostavax vaccination and have completed at least 6 weeks of follow-up, and 13 have completed the 12 week study. No episodes of herpes zoster, bulliform lesions at the injection site, serious AEs, or SLE flares occurred during the study. Three subjects in each group experienced injection site reactions of erythema or tenderness. All were mild and transient. Mean change in SLEDAI score at six weeks was 0.2. Proportions of leukocyte subsets or plasmacytoid dendritic cells were not significantly changed following vaccination in either group. Functional varicella response cellular assays will be performed on batched samples once all 12-week visits have been completed.

Table 1. Demographic and Safety Outcomes

	SLE	Healthy
n	10	10
Age, mean (SD)	60.5 (5.4)	55.3 (4.2)
European American	7	7
African American	3	3
h/o shingles	4	2
Taking prednisone	4	–
mean daily dose	6.9 mg	–
Taking HCQ	7	–
Taking MTX	2	–
Baseline SLEDAI	1.1 (0.99)	–
ISR (any), n	3	3
Erythema, tenderness	3	3
Vesicular	0	0
6 week SLEDAI	1.3 (1.2)	–
mean Δ SLEDAI	0.2 (1.5)	–
SLE flare	0	–

Conclusion: Zostavax vaccination appears to be well tolerated in this cohort of patients with mild SLE on mild to moderate immunosuppressive therapy.

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Urinary Heparanase Activity Is Elevated in Patients with Lupus Nephritis and Correlate with Protein Excretion.
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Background/Purpose: The heparin sulphate proteoglycans (HSPGs) in the glomerular basement membrane (GBM) play an important role in the charge-selective permeability of the glomerular filter. The b-D-endoglycosidase heparanase has been proposed to be important in the pathogenesis of proteinuria by selectively degrading the negatively charged side chains of HSPGs within the GBM in various forms of glomerulonephritis. We evaluated plasma and urinary activity of heparanase and determined association between its levels and proteinuria in patients with lupus nephritis.

Methods: Plasma from 86 patients with systemic lupus erythematosus (SLE) and 24 normal healthy subjects were collected. The clinical and laboratory data of the patients were obtained at the time of sampling. Forty six patients had a history of lupus nephritis and their urine was also collected. Proteinuria was defined as more than 500 mg/24h or spot urine protein/creatinine ratio > 0.5. Heparanase activity of plasma and urine was determined by a commercially available kit.

Results: Plasma heparanase activity was significantly elevated in SLE patients compared to healthy controls (734.9 ± 91.1 vs. 203.6 ± 87.1 mIU/ml, $p = 0.038$), but its activity was not different between patients with lupus nephritis and those without (743.3 ± 105.5 vs. 722.3 ± 166.1 mIU/ml, $p = 0.915$). However, urinary heparanase activity was significantly elevated in SLE patients with lupus nephritis compared to those without lupus nephritis and healthy controls (1299.7 ± 200.5 vs. 337.5 ± 35.2 and 203.6 ± 87.1 mIU/ml, $p = 0.046$ and 0.026, respectively). Thirty six of patients with lupus nephritis showed significant proteinuria and urinary heparanase activity of them was significantly elevated compared with those of patients without proteinuria (997.0 ± 245.3 vs. 194.6 ± 122.0 mIU/ml, $p = 0.006$). Importantly, urinary heparanase activity was positively correlated with protein excretion (r = 0.381, $p = 0.003$). Moreover, urinary heparanase activity showed an inverse correlation with C3 complement level and complement haemolytic activity (CH50) (r = −0.495, $p = 0.002$ and r = −0.565, $p < 0.001$) and had a tendency to associate negatively with C4 complement levels (r = −0.299, $p = 0.072$).

Conclusion: Urinary heparanase activity was elevated in patients with lupus nephritis and reflect the urinary protein excretion, suggesting a potential role in the pathogenesis of proteinuria in lupus nephritis.

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Inflammatory Biomarkers of Atherosclerosis and Oxidative Stress Are Associated with Disease Flare in SLE.
Maureen A. McMahon[1], Jennifer M. Grossman[1], Brian Skaggs[1], Elaine Lourenco[1], Cheryl Lee[1], Lori Sahakian[1], John D. FitzGerald[1], Christina Charles-Schoeman[1], Alan H. Gorn[1], George A. Karpouzas[2], Michael H. Weisman[3], Daniel J. Wallace[3], Weiling Chen[1] and Bevra H. Hahn[1]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]Harbor-UCLA Medical Center, Torrance, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA

Background/Purpose: Although our current serologic measures of disease activity are useful for predicting flare in some patients, other patients experience disease flare in the absence of fluctuations in complement or antibody titers. We previously reported that novel inflammatory biomarkers of oxidative stress and endothelial activation, including pro-inflammatory HDL (piHDL), elevated leptin, and soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), independently confer increased risk for carotid artery plaque (ATH). We hypothesized that biomarkers of ATH are reflective of alternate pathways driving inflammation and disease activity in SLE, and will also be associated with increased non-ATH disease flares.

Methods: We retrospectively calculated longitudinal disease activity and flare measurements for 204 SLE women from our "Biomarkers of Atherosclerosis in SLE" cohort. SELENA-SLEDAI disease activity measures were calculated for each patient visit in the 12 month period following their baseline ATH biomarker assessment. Mild/moderate and severe flares were categorized at each visit using the SELENA flare tool.

Antioxidant function of HDL was measured as the change in fluorescence intensity caused by oxidation of DCFH by LDL in the presence or absence of test HDL. Plasma leptin, sTWEAK, and Lp(a) were measured in the baseline blood samples using ELISA (R&D Biosystems). Homocysteine was measured in the UCLA clinical labs by Fluorescence Polarization Immunoassay.

Results: 57.4% of SLE subjects experienced a mild to moderate flare and 22.5% experienced a severe flare in the 12 months following study entry. In univariate analysis, high sTWEAK and Lp(a) were positively associated and C3 levels were inversely associated with mild to moderate SLE flares. High leptin and high homocysteine were positively associated with severe SLE flares. In multivariate analysis controlling for lupus medications and other potential confounders, high levels of sTWEAK were associated with 2.3 fold increased odds ratio (OR) for mild to moderate disease flare (p=0.02), and high leptin (OR 5.4, p=0.04), homocysteine (OR 5.8, p=0.02), and baseline prednisone dose (OR 1.1, p<0.001) were associated with severe flare (TWEAK trended towards association, OR 2.3, p=0.08). When we substituted our *combined ATH biomarker* variable for individual biomarkers, patients with baseline High risk scores had 6.7 fold increased odds for experiencing a severe flare in the subsequent year, and a shorter time to severe flare (Hazard ratio for high PREDICTS score 3.1, p=0.01).

Conclusion: In conclusion, many of our biomarkers of interest for the progression of ATH in SLE may also have implications for overall progression of disease flares. A panel of atherosclerosis biomarkers may help identify SLE patients at risk for both cardiovascular and lupus disease related flares.

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Risk Factors Associated with Early Central Nervous System Damage Detected Through Diffusion Tensor Imaging (DTI) in Patients with Systemic Lupus Erythematosus. Paola Tomietto[1], Federica Casagrande[2], Maja Ukmar[3], Luca Weis[2], Pia Morassi[4], Rita Moretti[2], Gianni Biolo[2], Carlo Giansante[2] and Maria Assunta Cova[2]. [1]AOU Ospedali Riuniti, Trieste, Italy, [2]University of Trieste, Trieste, Italy, [3]University of Trieste, Trieste, [4]AOU Ospedali Riuniti di Trieste, Trieste, Italy

Background/Purpose: Antiphosholipid antibodies, SLICC-DI and some cardiovascular risk factors have been identified as risk factors for neuropsychiatric lupus (NPSLE). Diffusion tensor imaging (DTI) is an advanced MRI technique with an increased accuracy compared to conventional MRI (cMRI) in evaluating white matter microstructure. Our purpose was to assess the main factors affecting early SNC damage detected through DTI in SLE.

Methods: 20 consecutive SLE patients underwent a clinical evaluation to characterize CNS involvement (NPSLE) including: clinical hystory, a neuropsychological battery and pychiatric tests (HADS). All the patients and 14 healthy controls underwent MRI examination on a 1.5T magnet with a standard protocol for cMRI and DTI sequences. Region of interest (ROI) were placed symmetrically on normal appearing white matter (NAWM) in 12 areas (frontal and parietal WM, amygdala, corpus callosum, middle cerebellar peduncles). Mean diffusivity (MD) and fractional anisotropy (FA) were calculated bilaterally. ROI relevant to distinguish patients with NPSLE vs patients without and controls were selected on the basis of the receiver operating characteristic (ROC) curve analysis. SLEDAI, SLICC-DI, generic cardiovascular risk factors, positivity for Raynaud's phenomenon, livaedo reticularis, cutaneous vasculitis, aPL, anti-RNP and anti-DNA were determined for all the patients and included as independent variables in several stepwise regression analysis to determine which of them affected changes in FA/MD in NAWM in an independent way.

Results: Measures of MD at the level of frontal right WM, corpus callosum and right middle cerebellar peduncle and of FA in left middle cerebellar peduncle showed moderate accuracy (AUC>0,71) in distinguishing SLE patients and healthy controls, while MD and FA of right corpus callosum and FA in right amygdala in differentiating patients with and without NPSLE, according to the clinical classification (AUC>0.73). Among cardiovascular risk factors, diabetes, smoking and hypertension resulted as independent factors affecting MD and FA in corpo callosum bilaterally; hypertension was associated also to changes in FA and MD of amygdala. Among SLE-related factors, aPL, anti-DNA and SLEDAI were independent factors affecting FA of corpus callosum; aPL were associated also to changing in FA of fronto-parietal WM while SLICC-DI to modifications of FA in amygdala. Finally cutaneous vasculitis resulted as an independent factor affecting MD in corpus callosum.

Conclusion: This preliminary analysis showed as some cardiovascular risk factors (smoking, hypertension, diabetes), and some SLE-related factors (aPL, anti-DNA, SLEDAI, SLICC-DI, cutaneous vasculitis), previously reported as related to NPSLE, are associated to changes of FA and MD in normal appearing white matter of fronto-parietal lobes, corpus callosum and amygdala. These data, if confirmed, suggest a probable multifactorial pathogenesis of white matter abnormalities in SLE and underlie the possible role of DTI in detecting early SNC damage

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Peripheral Neuropathy Due to Systemic Lupus Erythematosus (SLE) Itself: Incidence, Disease Risk Factors and Outcome. Simone Fargetti[1], Samuel K. Shinjo[2], Sandra G. Pasoto[1], Ana L. Calich[1], Eloisa Bonfa[3] and Eduardo F. Borba[1]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]University of São Paulo, São Paulo, Brazil

Background/Purpose: Peripheral neuropathy (PN) solely attributable to SLE itself is difficult to define since most of these patients are exposed to several other conditions that may cause this manifestation. The aim is to determine characteristics and outcome of PN attributed exclusively to SLE and its possible association with clinical/laboratorial features in a large cohort.

Methods: SLE patients (ACR 1997) with PN were identified from our Lupus Outpatient Clinic computerized database of 1038 patients. Only patients with definitive PN proved by electroneuromyography were included. Exclusion criteria were conditions related to PN: diabetes mellitus, alcohol consumption, use of any drug related to neuropathy (thalidomide, statins, etc.), thyroid disease, infection, cancer, vitamin B12 deficiency, renal or hepatic failure, and other autoimmune disease (antiphospholipid syndrome, Sjogren's syndrome, etc.). Medical records were extensively reviewed and included clinical/laboratorial data, treatment, and evolution. Each SLE patient with PN [n=22] was compared with 2 SLE patients without PN (controls) [n=44] that were age- and sex-matched and had similar disease duration.

Results: PN exclusively attributed to SLE was identified in 22 patients (2.1%). The mean age (34.4±11.6 vs. 33.9±9.6 years, p=0.85) and disease duration (9.2±7.7 vs. 9.9±6.8 years, p=0.73) of PN were similar to controls. The interval between SLE onset and PN diagnosis was 4.9±5.7 years and the mean SLEDAI scores was higher in PN patients (5.4±7.6 vs. 1.8±2.9,p=0.001). The most common pattern on electroneuromyography was sensorimotor polyneuropathy of lower limbs (50%), followed by mononeuropathy (26.9%), and polyradiculoneuropathy (15.3%). PN was associated to hematological involvement (72.7% vs. 43.2%,p=0.036), leukopenia (50% vs. 20.5%,p=0.022), lymphopenia (68.2% vs. 29.5%,p=0.004), cutaneous vasculitis (54.5% vs. 22.7%,p=0.014), and anti-Sm (50% vs. 15.9%,p=0.007). Multivariate analysis revealed that PN was related to anti-Sm (OR=5.36; 95%CI 1.37–20.99) and cutaneous vasculitis (OR=4.97; 95%CI 1.23–20.08). All SLE patients received corticosteroids, most of them associated with immunosuppressive drug (59% cyclophosphamide; 31.8% azathioprine). After immunosuppressive therapy, 63.6% improved of neurological symptoms and 31.8% remained stable.

Conclusion: Our study suggested that PN attributed to SLE itself is rare in the absence of other conditions and seems to be strongly associated to anti-Sm antibodies and cutaneous vasculitis. A favorable outcome with immunosuppressive therapy is observed in most of SLE patients with this neurological manifestation.

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The Effects of Co-Existing Proliferative Histopathology On Membranous Lupus Nephritis. Jennifer L. Graybill, Catarina Vila-Inda, Chaim Putterman and Irene Blanco. Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Lupus nephritis (LN) affects up to 60% of SLE patients and is worse in minority communities. Traditionally membranous LN confers a better prognosis than proliferative, but a significant number of patients do develop renal failure. Moreover, mixed membranous and proliferative histology is not uncommon. To determine if co-existing proliferative lesions worsen the prognosis of membranous disease, we studied SLE patients who underwent renal biopsy at a large tertiary center.

Methods: We analyzed all biopsies with classes: III±V, IV±V and V from January 1997-December 2011, and confirmed that all patients met ≥4/11 ACR SLE criteria. We collected baseline demographic and laboratory information at the time of biopsy as well as medications given. Our composite endpoint was the development of end stage renal disease (ESRD) requiring dialysis and/or death.

Results: Of the 202 patients included, 81.3% were female and the median age was 30.5y. The predominant race was black (54.5%), followed by Hispanic (37.1%) and 8.4% were another race/ethnicity. There was no significant difference between the groups in age, gender or disease duration.

123 patients had proliferative LN (Class III or IV, P), 55 had membranous LN (Class V, M), and 24 had mixed disease (P+M). Black patients were more likely to have class V (p=0.02). Creatinine was higher in P (p<0.01) but there was no difference between M or P+M (p=0.12). There was no difference in median protein to creatinine ratios, serum albumin, and BP between groups.

62/202 (31%) patients reached the composite end point: 41.5% P, 14.6% M, and 12.5% P+M (p<0.01). Survival was significantly worse for P compared to M (p<0.01) and P+M (p=0.05), but no difference was seen between M and P+M (p=0.74). As previously reported, on univariate analyses, urine protein to creatinine ratio (p<0.01), creatinine (p<0.01), systolic BP (p=0.02), and age (p=0.05) were associated with the end point. There was no association with cyclophosphamide (p=0.07) or mycophenolate induction (p=0.2), ACEI/ARB use (p=0.85), or treatment with antimalarials (p=0.2).

Unadjusted Kaplan-Meier Survival Curves For Composite Score By Class

Log-Rank P v M : p<0.01
Log-Rank P v P+M: p=0.05
Log-Rank M v P+M: p=0.74
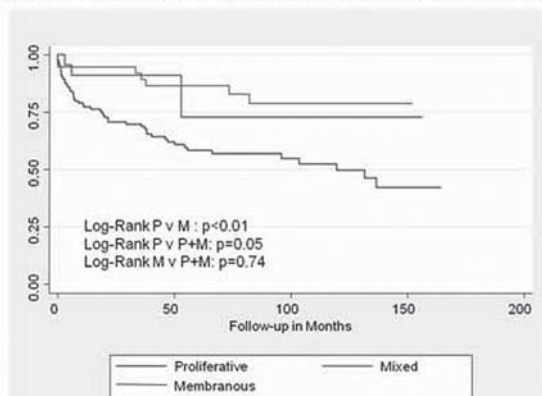
In multivariate models, M as compared to P had improved survival (HR=0.31, p=0.02) but there was no longer a significant difference between P and P+M (p=0.18) As in the univariate analysis, age (p=0.03), protein to creatinine ratio (p=0.03), and creatinine at biopsy (p<0.01) were all associated with a decreased risk of survival.

Conclusion: At first glance membranous with or without proliferative lesions on histology have a similar prognosis. However, in multivariate models the difference between proliferative and mixed disease was no longer seen when adjusted for age, protein to creatinine ratio and creatinine at biopsy. Therefore proliferative lesions alone on biopsy do not confer a worse prognosis for membranous disease rather it is likely disease severity itself that drives prognosis.

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Missed Work Days in Systemic Lupus Erythematosus. Jie Xu, Hong Fang and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Indirect costs are part of the medical and financial burden of SLE. These costs are easy to undervalue because a significant portion of this economic loss results from lost productivity in the workforce (Clarke A, et al. Am J Manag Care, 2001; 7(16):S496-S501.). This effect is magnified by the population typically affected by SLE, young women, who may suffer disabilities that affect the most productive years of life (Panopalis P, et al. Arthritis & Rheumatism, 2008; 59(12):1788–1795.). We attempted to identify both demographic and disease variables that may serve as predictors of this loss in work-related activities.

Methods: The medical resource use questionnaire was distributed to SLE patients in the Hopkins Lupus Cohort that covered the last 3 months before the baseline visit and then at the following two quarterly clinic visits. 199 SLE patients (89% female, 58% Caucasian, 31% African-American, 11% other ethnicities, mean age at baseline 44±11 years) were included in the analysis. Exclusion criteria were diagnosis with lupus less than 6 months ago, age younger than 18 or older than 75, pregnant at baseline, and active HIV patients. Those who were unemployed were also excluded.

Results: The mean number of missed work days over 6 months was 2.6 days (range 0 to 39). Predictors of missed work days are shown in Table 1. The two significant predictors were low family income (p=0.019) and a history of missed work days in the 3 months before the study year (p<0.0001). A multivariate linear regression model for number of missed work days was then constructed (Table 2). In the multivariate model, disease activity (mean SLEDAI) was not associated with the number of missed work days. Renal activity (urine protein/cr ratio) had a borderline association. Family income was not predictive.

Table 1. Predictors of missed work days (any vs none) - univariate analysis.

		Number (%) missed work days during followup	P–value
Age at baseline (years)	≤ 40 (n=86)	36 (41.9)	0.68
	> 40 (n=113)	44 (38.9)	
Gender	Female (n=177)	71 (40.1)	0.94
	Male (n=22)	9 (40.9)	
Ethnicity	African–American (n=61)	29 (47.5)	0.16
	Caucasian (n=115)	42 (36.5)	
Family income ($)	≤ 50K (n=75)	38 (50.7)	0.019
	> 50K (n=124)	42 (33.9)	
Education (years)	< 12 (n=7)	4 (57.1)	0.44
	≥ 12 (n=192)	76 (39.6)	
Use of prednisone at baseline	No (n=126)	46 (36.5)	0.16
	Yes (n=73)	34 (46.6)	
PGA[1] at baseline	≤1 (n=176)	67 (38.1)	0.090
	>1 (n=23)	13 (56.5)	
Mean PGA over year	≤1 (n=170)	65 (38.2)	0.17
	>1 (n=29)	15 (51.7)	
SLEDAI at baseline	≤2 (n=154)	59 (38.3)	0.31
	>2 (n=45)	21 (46.7)	
Mean SLEDAI over year	≤2 (n=140)	54 (38.6)	0.47
	>2 (n=59)	26 (44.1)	
Anti–dsDNA at baseline	Negative (n=148)	58 (39.2)	0.65
	Positive (n=49)	21 (42.9)	
C3 or C4 at baseline	Low (n=40)	15 (37.5)	0.74
	Normal (n=156)	63 (40.4)	
Increased ESR at baseline	No (n=117)	46 (39.3)	0.72
	Yes (n=74)	31 (41.9)	
Urine Pr:Cr ratio at baseline	≤0.5 (n=178)	70 (39.3)	0.23
	>0.5 (n=12)	7 (58.3)	
Diabetes	No (n=187)	72 (38.5)	0.070
	Yes (n=12)	8 (66.7)	
BMI at baseline	≤30 (n=143)	52 (36.4)	0.10
	>30 (n=55)	27 (49.1)	
Vitamin D	<32 (n=57)	26 (45.6)	0.32
	≥32 (n=137)	52 (38.0)	
Baseline history of missed work days	No (n=108)	22 (20.4)	<0.0001
	Yes (n=75)	52 (69.3)	

[1]PGA: Physician's global assessment (0–3 scale)

Table 2. Multivariate Linear Regression Model

	Effect on number of missed work days	P–value
Age at baseline (per 10 years)	0.03 ± 0.04	0.39
Ethnicity (African–American)	0.19 ± 0.91	0.83
Family income (>50K)	0.29 ± 0.85	0.73
Mean SLEDAI (per unit)	0.05 ± 0.20	0.79
Urine Pr:Cr ratio at baseline (per unit)	1.23 ± 0.66	0.063
Diabetes	2.81 ± 1.88	0.13
Vitamin D at baseline	–0.04 ± 0.03	0.19
Number of missed work days at baseline	0.67 ± 0.11	<0.0001

Conclusion: This study found that disease activity (either by physician's global assessment or SLEDAI) is not predictive of missed work days. However, renal lupus had a borderline association. Demographic factors (sex, ethnicity, income) were not significant in the multivariate model. The most important factor remains a pattern of past history of missed work days.

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Adherence to Adult Treatment Panel III Guidelines for Systemic Lupus Patients. Matthew Basiaga and Lisabeth Scalzi. Penn State Univ/Hershey, Hershey, PA

Background/Purpose: The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) has provided education and guidance for decades on the management of hypercholesterolemia. Systemic lupus erythematosus (SLE) patients are in an intermediate risk category for cardiovascular disease. We examined a SLE cohort to examine whether patients were being treated according to ATP III guidelines.

Methods: Data from 133 patients with SLE was examined to see whether ATP III guidelines were being adhered to. All patients were free of any known clinical heart disease. Available information that was used included traditional CVD risk factors (a history (or present use) of cigarettes, hypertension (HTN) (BP ≥ 140/90 mmHg or on an antihypertensive agent for the purpose of lowering blood pressure), HDL cholesterol < 40 mg/dL, family history of premature CVD, diabetes (self reported history or a fasting blood glucose of >126 mg/dL), fasting cholesterol profiles, and age (men ≥ 45 years; women ≥ 55 years). We then compared the proportion of SLE patients who met ATP III criteria for initiation of lipid therapy and who reported ever having been/or were presently on therapy to those who had never been on a lipid lowering medication. We evaluated group differences between those patients who have been treated versus those who have not using t-tests and chi-square analyses.

Results: The mean age of the cohort was 50.7 ± 8.8 years, 96% were female, and 78% were Caucasian. Thirty-four of the 133 (26%) participants met ATP III criteria for the initiation of lipid lowering therapy. Only 9 (26%) in this group had ever been on any lipid lowering medication and only 4 (12%) were currently being treated. Significant variables associated with lipid lowering therapy versus no therapy included, the mean number of ATP III risk factors (4.8 versus 4.0; p=0.03), body mass index (35.4 versus 27.8; p=0.001), age (50.2 vs. 57.3 years; p=0.02), cholesterol level (249 versus 187 mg/dL; p<0.0001), LDL (163 vs. 109 mg/dL; p<0.0001), and HTN (78% vs. 40%; p=0.03). Race, SLICC scores, diabetes, HDL, family history, and smoking were not significant variables as to whether a patient was treated.

Conclusion: ATP III guidelines are standard guidelines for assessing whether patients should have interventions, including drug therapy, to treat hyperlipidemia and decrease CVD risk. More than a quarter of our SLE participants met ATP III guidelines for lipid lowering therapy and only 12% of those who fulfilled ATP III criteria were being treated. Younger patients who met criteria were not treated, while older, obese, and those with a higher number of ATP III risk factors were treated. Given that SLE patients are already at an intermediate CVD risk, similar to diabetes, more awareness is needed in addressing the needs of this at-risk population. This is an excellent area for quality improvement for rheumatologists and highlights the need for communication between rheumatologists and primary physicians regarding treatment and/or referral to cardiology for primary preventative care. Future studies addressing obstacles in initiation and maintenance of therapy are needed in SLE patients.

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Elevated Transglutaminase Levels On Microparticles From Systemic Lupus Erythematosus Patients. Leslie Harris, Ratnesh Chopra, Ann K. Rosenthal and Mary E. Cronin. Medical College of Wisconsin, Milwaukee, WI

Background/Purpose: Systemic Lupus Erythematosus (SLE) is characterized by the formation of autoantibodies, and over-exuberant antigen presentation may account for some of this pathology. Circulating microparticles (MP) are membrane-bound 100–1000 nM sized vesicles derived from platelets, leukocytes, endothelial cells and red cells. They are immunomodulatory and participate in antigen presentation. The protein crosslinking enzymes, transglutaminases (Tgases), are involved in antigen presentation. Evidence from mouse studies supports a potential role for excess Tgase activity in SLE and TGase inhibitors have been shows to ameliorate murine lupus. Interestingly, we also noted a single report of Tgase inhibition with hydroxychloroquine (HCQ), a commonly used drug for SLE. Previous studies have shown increased numbers of circulating MPs in SLE patients. We sought to characterize the cell sources of MPs and determine protein levels of the Tgase enzymes (type II Tgase and factor XIIIA) on MPs from SLE patients and controls. We also measured Tgase activity on MPs from several normal donors and investigated the effect of HCQ on MP-associated Tgase activity.

Methods: We obtained 12 ml of blood from 25 SLE patients and 25 age and sex-matched normal controls after IRB approval. SLE patients satisfied ACR criteria for SLE and were excluded if they had anti-phospholipid antibody syndrome. MPs were isolated from platelet rich plasma according to published protocols. Flow cytometry was used to enumerate MPs and determine the percent of MPs from each cell source. Cell markers included CD45 for leukocytes, CD41 (GPIIb) + CD42 (GPIX+GPIb) for platelets, CD144 (VEcadherin) for endothelial cells, CD235a (glycophorin A) for red cells, as well as the Tgase enzymes, type II Tgase and factor XIIIA. Tgase activity was measured with a standard radiometric assay detecting crosslinking activity in the presence and absence of 10 mM HCQ. The Mann-Whitney test was used to determine statistically significant differences between groups.

Results: Numbers of MPs were similar in SLE patients and controls. SLE patients had higher numbers of MPs derived from red cells 1448 (CI 908–2640) positive particles (PP)/μl compared to 2570 (CI 1069–9035) PP/μl in SLE patients (p=0.027). Type II Tgase enzyme levels were significantly higher in the SLE cohort, which had 1531 (CI 854–4097) PP/μl, compared to the control group with 895 (CI 402–1526) PP/μl (p=0.007). Factor XIIIA levels were slightly higher in the SLE group, but did not reach statistical significance (p=0.068). Tgase activity on a random sample of MPs from controls demonstrated an average Tgase activity level of 163 ± 75 mU/mg protein (n=3). Activity levels fell to 112.8± 14.9 mU/mg protein with HCQ (p<0.05).

Conclusion: Type II Tgase enzyme levels are significantly higher on MPs from SLE patients than controls, and activity is inhibited with HCQ. Because Tgase enzymes may have active roles in antigen presentation as well as platelet aggregation, the ability of HCQ to suppress Tgase activity may be an additional mechanism of action for this effective SLE drug. Further studies of the role of Tgase in SLE and on MPs are warranted.

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Retrospective Study of Allogenic Mesenchymal Stem Cells Transplantation in Active and Refractory Lupus Nephritis for Induction Therapy. Lingyun Sun, Dandan Wang, Xia Li and Huayong Zhang. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Allogenic mesenchymal stem cells (MSCs) transplantation demonstrated significant clinical efficacy on various autoimmune diseases. Here we retrospectively analyzed the role of allogenic MSCs transplantation in renal remission in patients with active and refractory lupus nephritis (LN).

Methods: Eighty-one patients with active and refractory lupus nephritis in China from 2007 to 2010 were enrolled in the study. Allogenic bone marrow or umbilical cord derived MSCs were administered intravenously at the dose of one million cells per kilogram of bodyweight. Then all the patients were followed up for 12 months to evaluate renal remission as well as possible adverse events. The primary outcomes were renal complete remis-

sion (CR) and partial remission (PR) at each visit times, as well as renal flares. The secondary outcomes included renal activity score, total disease activity score, renal function and serologic index. Rates of overall survival, renal remission, as well as relapse at different visit times were calculated by using the Kaplan-Meier method and were statistically tested with the log-rank test. We calculated the HR and their 95% CIs using the univariate *Cox* proportional hazards model.

Results: The overall survival rate during 12 months follow-up was 95% (77/81). The probability of renal remission was 41% (18% CR and 23% PR) at 3 months, 45% (18% CR and 27% PR) at 6 months and 44% (23% CR and 21% PR) at 12 months after allogenic MSCs transplantation. Renal remission was not correlated with age, disease duration, MSCs source and baseline SLEDAI score, but was significantly correlated with baseline proteinuria (P=0.003, 95%CI 0.336–0.794) and serum creatinine levels (P=0.047, 95%CI 0.224–0.990) by *COX* regression analysis. Eleven in 81 (14%) patients underwent renal flare in 12 months follow up after a prior complete or partial remission. Renal activity evaluated by BILAG score significantly declined after MSCT, in parallel with the obvious amelioration of renal function. Total disease activity evaluation by SLEDAI score also decreased after treatment. Additionally, the doses of concomitant prednisone and immunosuppressive drugs were tapered. Four of 81 patients died of uncontrolled lupus nephritis unrelated to MSCT.

Conclusion: Allogenic MSCs transplantation resulted in renal remission within 12 months visit, which could be used early as a potential induction therapy for active and refractory lupus nephritis.

Disclosure: **L. Sun**, None; **D. Wang**, None; **X. Li**, None; **H. Zhang**, None.

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Anti-Mullerian Hormone and Ovarian Reserve in Systemic Lupus Erythematosus. Chi Chiu Mok[1], Pak To Chan[2] and Chi Hung To[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Hong Kong, Hong Kong

Background/Purpose: To study the level of anti-mullerian hormone (AMH) and its relationship with age and previous cyclophosphamide (CYC) exposure in patients with systemic lupus erythematosus (SLE).

Methods: Consecutive female patients aged 18–52 years who had menstruation in the preceding 12 months and fulfilled [3]4 ACR criteria for SLE were recruited. AMH was assayed by an ELISA kit (Beckman Coulter, Inc., USA). Serum AMH level was compared between patients with and without previous use of immunosuppressive agents. The relationship of AMH level to age and CYC exposure was studied by linear regression.

Results: 216 female SLE patients were studied. The mean age of patients at the time of venepuncture was 35.1 ± 10.1 years and the mean SLE duration was 7.6 ± 5.9 years. Immunosuppressive drugs ever received by these patients were: prednisolone (90%), AZA (69%), MMF (30%), tacrolimus (21%), cyclosporin A (17%), CYC (22%) and HCQ (67%). Prednisolone was exclusively used in combination with one or more of the other immunosuppressive drugs. Of the 48 CYC users, 29 (40%) received daily oral treatment and 19 (40%) received monthly intravenous pulse therapy. The median total duration of CYC exposure was 20 weeks (inter-quartile range [IQR] 12.3–32.8). Fifty-four (25%) patients had undetectable AMH level (78% aged >40 years). These patients were significantly older than those with measurable AMH level (median age 47 [IQR 42–51] vs 31 [IQR 25–38.3] years; p<0.001). Significantly lower levels of AMH were observed for past users of CYC than non-users, after adjustment for age (1.58 ± 2.92 vs 1.73 ± 2.11 ng/mL; p=0.04 by ANCOVA). The mean time interval between AMH assay and last dose of CYC administered was 6.28 ± 3.8 years. AMH levels were not statistically different between users and non-users of other immunosuppressive agents that included prednisolone, mycophenolate mofetil, azathioprine and the calcineurin inhibitors. Linear regression revealed age (Beta -0.32; p=0.02) and each 5g of CYC exposure (Beta -0.28; p=0.047) were independently associated with lower AMH level. The route of CYC administration, duration of CYC treatment, disease activity score and duration of SLE was not significantly associated with AMH level on univariate regression analyses.

Conclusion: AMH is a sensitive marker for ovarian damage due to previous CYC treatment in SLE patients.

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The Progression of Brain MRI Biomarker of Cognitive Impairment (White Matter Hyperintensity) in Systemic Lupus: A Clinical and Imaging Longitudinal Study. Jamal Mikdashi and Umran Ashruf. University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: SLE patients are at high risk for accumulation of white matter hyperintensity (WMH) on brain MRI which has been correlated with cognitive impairment. Our goal is to determine whether the progression of WMH in newly diagnosed SLE patients predicts increased risk of cognitive impairment.

Methods: Brain MR T2 weighted images were compared at baseline and annually for 5 years among newly diagnosed SLE patients, presenting with neuropsychiatric SLE (NPSLE), {(n= 30), [mean age 37.6 years, 73 % African American, and 90 % women]}, and age- and gender- matched non NPSLE patients (n= 25), and healthy controls (n=20) to assess WMH burden (mild, moderate or severe). Standard cognitive tests were examined at enrollment and at end of study. Demographic and clinical manifestations were compared among the groups. Significant variables in the analyses, depression, cardiovascular risk factors and worsening of WMH grade using dichotomous measures were entered into multivariable and Cox proportional hazard analyses to determine their contribution to cognitive impairment.

Results: At baseline, 59 MRI were normal and16 had WMH lesions (NPSLE = 9, non NPSLE= 4 and controls = 3). The WMH burden was higher among NPSLE patients compared to non NPSLE patients (OR= 3.1, 95 % CI: 0.7– 13.2, p value =0.09). At baseline, frontal and parieto -occipital lesions were more frequent among NPSLE patients, whereas periventricular lesions were more frequent among non NPSLE patients or controls. At end of study, 24 patients had normal MRI findings and 21 had new and increased WMH lesions (NPSLE =13, non NPSLE =6, control= 2). The rate of WMH burden progression was variable across the groups. NP SLE patients had a faster rate of accumulation of WMH lesions, as compared to non NPSLE (OR =3.5, 95 % CI: 1.1–10.7; p value= 0.03). The median number of impaired cognitive domains increased, regardless of the presence of baseline WMH lesions particularly among NPSLE compared to non NPSLE or controls.

Ischemic strokes and MRI -defined incident infarcts (OR = 5.8; 95% CI = 1.2–29.4; p value = 0.04), and worsened WMH grade (OR = 4.3; 95% CI = 2.1–16.3; p value = 0.03), were associated with increased risk of cognitive impairment in the areas of attention, processing speed and executive function. Hydroxychloroquine use was associated with reduced risk for WMH progression (OR= 0.3, 95 % CI: 0.1– 0.7; p value= 0.02), but not cognitive impairment.

Conclusion: The progression of WMH has prognostic relevance for long-term cognitive outcome in newly diagnosed SLE. Strategic preventive measures are needed to optimally target individuals at highest risk of cognitive decline.

Disclosure: **J. Mikdashi**, None; **U. Ashruf**, None.

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Safety and Efficacy of Epratuzumab in an Open-Label Extension Study (SL0006). K. Hobbs[1], D.J. Wallace[2], V. Strand[3], K. Kalunian[4], B. Kilgallen[5], S. Bongardt[6], W.A. Wegener[7] and D.M. Goldenberg[7]. [1]Denver Arthritis Clinic, Denver, CO, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Stanford University, Palo Alto, CA, [4]UCSD School of Medicine, La Jolla, CA, [5]UCB Pharma, Smyrna, GA, [6]UCB Pharma, Brussels, Belgium, [7]Immunomedics Inc, Morris Plains, NJ

Background/Purpose: Epratuzumab, a monoclonal antibody targeting CD22, is in development for the treatment of systemic lupus erythematosus (SLE). Two randomized, double-blind trials (ALLEVIATE 1 and 2) were prematurely terminated due to interruption of drug supply. SL0006 was an open-label extension study in which patients previously enrolled in the ALLEVIATE trials received epratuzumab. This abstract reports final long-term safety and efficacy data from SL0006 in patients with moderately-to-severely active SLE.

Methods: Patients (*n*=29) in SL0006 received 12-week cycles of epratuzumab 360 mg/m² (2 infusions, at days 1 and 8 of each cycle). Ten were from ALLEVIATE-1 and had severe (BILAG A) SLE activity in ≥ 1 body/organ system, while 19 were from ALLEVIATE-2 with moderate (BILAG B) activity in ≥ 2 body/organ systems. All patients were eligible for enrollment in SL0006, subject to investigator's judgment of treatment benefit. There was a median delay in epratuzumab dosing of 165 days (range 1–400)

between premature termination of the ALLEVIATE studies and entry into SL0006. Assessments were every 4 weeks from screening (Visit 1; V1).

Results: Patients were aged 22–61 years; almost 90% were women, and 72% were of European descent (79% Caucasian). Median study duration was 4.0 years (0.3–5.3). Median corticosteroid dose (range) at the start of ALLEVIATE (baseline) was 21 mg/day (10–80), and by the start of SL0006 (V1) dose reduced to 7.5 mg/day (0–30). Lower levels of corticosteroid were maintained to the last visit (0–105). Median (range) total BILAG scores decreased throughout the study from baseline of 17 (12–30) (last visit 12 [1–34]). BILAG improvement from baseline was maintained from SL0006 V1 to end of study, with most V1 BILAG A/B grades improving to C/D at least once during the study (Table). Median (range) total SLEDAI scores also decreased throughout the study from baseline of 10 (4–26) (last visit 8 [0–16]). SLEDAI improvement from baseline was also maintained from V1 to end of study. Median patient and physician global assessments of disease activity each improved from 3.0 and 2.8, respectively, at baseline by a median of 1.0 categories. Median reductions in absolute B-cell (CD19+) counts were observed throughout the study, from screening (34.0% reduction) until the last visit (45.0% reduction). All patients reported at least 1 AE, with 14 patients (48.3%) experiencing at least one SAE. Four patients (13.8%) discontinued because of AEs. The most frequent AEs, occurring in at least 5% of subjects, were infections and infestations (upper respiratory tract infections 58.6%, and sinusitis, nasopharyngitis, urinary tract infections [all 37.9%], anxiety, and nausea [both 34.5%]).

Table.

BILAG organ system (Total n = 29)	Baseline* A/B grades n	Baseline* A/B grades New C/D grade during study	Visit 1† A/B grades n	Visit 1† A/B grades New C/D grade during study	Baseline* C/D/E grades n	Baseline* C/D/E grades New A/B grade during study	Visit 1† C/D/E grades n	Visit 1† C/D/E grades New A/B grade during study
General	14	14 (100%)	8	8 (100%)	15	6 (40%)	21	7 (33.4%)
Mucocutaneous	24	22 (91.7%)	17	15 (88.2%)	5	2 (40%)	12	9 (75%)
Neurological	4	4 (100%)	2	2 (100%)	25	7 (28%)	27	8 (29.6%)
Musculoskeletal	25	25 (100%)	14	14 (100%)	4	3 (75%)	15	10 (66.7%)
CV and Respiratory	4	4 (100%)	2	2 (100%)	25	8 (32%)	27	9 (33.3%)
Vasculitis	4	4 (100%)	1	1 (100%)	25	2 (8%)	28	4 (14.3%)
Renal	1	1 (100%)	0	0	28	9 (32.1%)	29	10 (34.5%)
Hematology	1	1 (100%)	2	1 (50%)	28	8 (28.6%)	27	7 (25.9%)

*Baseline of ALLEVIATE study.
†Visit 1 = Baseline of SL0006 study.

Conclusion: With continued administration, epratuzumab maintained improvements in SLE disease activity over approximately 4 years, with a tolerable safety profile. No new safety concerns were identified.

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Association of Body Weight with Cardiovascular Events in Systemic Lupus Erythematosus. George Stojan[1], Homa Timlin[2], Hong Fang[1], Laurence S. Magder[3] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]West Drayton, United Kingdom, [3]University of Maryland, Baltimore, MD

Background/Purpose: Excessive body mass among healthy subjects carries an increased risk of subsequent cardiovascular (CV) events. In healthy subjects, the relationship between body mass index (BMI) and total and CV mortality follows a U-shaped curve, with the lowest mortality in overweight (BMI $25.0-29.9$ kg/m²) and mildly obese (BMI $30.0-34.9$ kg/m²) individuals. Despite a high burden of CV disease in systemic lupus erythematosus (SLE), the relationship between BMI and CV outcomes in SLE has not been studied.

Methods: We estimated the effect of BMI on CV events in a cohort of 2000 patients with SLE. We analyzed the rate of CV events during cohort participation, for five predetermined body weight groups: low (BMI<20 kg/m²), normal weight (reference, BMI 20–24.9 kg/m²), overweight (25–29.9 kg/m²), obese (BMI 30–34.9 kg/m²), and severely obese (BMI>35 kg/m²). CV events were defined as either stroke, myocardial infarction, incident angina, a coronary procedure (CABG or PCI), or claudication. Those with a CV event prior to cohort entry were excluded. We adjusted for various confounding factors (age, sex, race, complement, hematocrit, anti-dsDNA, immunosuppressant use), including related CV risk factors: hypertension, hypercholesterolemia, diabetes and smoking.

Results: There were 140 CV events observed over 11,374 person-years of follow-up. The rate of CV events per 1000 patient years of follow up was 6.0 for low weight, 9.3 for normal weight, 14.5 for overweight, 17 for obese, and 13.2 for severely obese. The rate of CV events in obese patients was statistically significantly higher compared to patients with normal weight (p=0.015) in a non adjusted model. After adjusting for confounding factors the p-value approached statistical significance (p=0.062).

BMI (kg/m²)	Person–years	CV events	Rate[1]	Unadjusted model RR (95% CI)	Unadjusted model P–value	Adjusted model RR (95% CI)	Adjusted model P–value
<20	1006	6	6.0	0.6 (0.3, 1.5)	0.31	0.5 (0.2,1.3)	0.14
20–24.9	3644	34	9.3	1.0 (REF.GP)		1.0 (Ref.Gp)	
25–29.9	3095	45	14.5	1.6 (1.0, 2.4)	0.051	1.2 (0.7,1.9)	0.52
30–34.9	1884	32	17.0	1.8 (1.1, 3.0)	0.015	1.6 (0.9,2.7)	0.078
>35	1744	23	13.2	1.4 (0.8, 2.4)	0.20	1.1 (0.6,2.0)	0.73

[1]Per 1000 person years

Conclusion: Obesity (BMI 30–34.9 kg/m²) is associated with the highest rate of adverse cardiovascular events in SLE. Interestingly, the CV event rate in severe obesity (BMI>35 kg/m²) was lower than in overweight and obese patients, suggesting the presence of a unique obesity paradox in SLE that differs from the one described in the general population.

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Study of Anti-Müllerian Hormone and Probability of Pregnancy in 112 Systemic Lupus Erythematosus Patients Exposed or Not to Cyclophosphamide. Nathalie Morel[1], Anne Bachelot[1], Zeina Chakhtoura[1], Zahir Amoura[1], Olivier Aumaitre[2], Jean-Emmanuel Kahn[3], Du Boutin[1], Pierre Duhaut[4], Dominique Farge[5], Camille Francès[1], Lionel Galicier[6], Gaëlle Guettrot-Imbert[2], Jean-Robert Harlé[7], Olivier Lambotte[8], Véronique Le Guern[9], Jean-Charles Piette[1], Jacques Pourrat[7], Karim Sacre[10], Damien Sene[11], Salim Trad[12], Elisabeth Vidal[13], Lamiae Grimaldi[14], Christiane Coussieu[1], Nathalie Costedoat-Chalumeau[1] and PLUS[15]. [1]Groupe Hospitalier Pitié-Salpétrière, Paris, France, [2]Centre Hospitalier de Clermont-Ferrand, Clermont-Ferrand, France, [3]Internal Medicine, Foch Hospital, Suresnes, France, [4]CHU Nord, Amiens, France, [5]EBMT, Paris, France, [6]Hopital Saint Louis, Paris, France, [7]CHU Toulouse, Toulouse, France, [8]Hopital Kremlin Bicêtre, Kremlin Bicêtre, France, [9]Cochin Hospital, Paris, France, [10]Bichat Hospital, University Paris-7, APHP, Paris, France, [11]Hopital Lariboisière, Paris, France, [12]Hopital Ambroise Paré, Paris, France, [13]Hopital de Limoges, Limoges, France, [14]Société Laser, Paris, France, [15]Paris, France

Background/Purpose: Cyclophosphamide (CYC), a drug commonly used in systemic lupus erythematosus (SLE), is associated with a risk of ovarian failure resulting in infertility. In the general population, anti-Müllerian hormone (AMH) level is correlated with ovarian reserve in adult women. We compared AMH serum levels in SLE patients with and without previous cyclophosphamide treatment (exposed and unexposed group). For the first time, we analyzed their subsequent probability of pregnancy.

Methods: This ancillary study was done on serum bank collected during the PLUS study between 07/2007 and 11/2009 (ClinicalTrials.gov: NCT00413361). SLE women included in the PLUS study, below 40 years and who had been exposed to CYC were compared to SLE patients unexposed to CYC and matched for age at 6 months. AMH concentration was determined by Elisa using Immunotech kit (Beckman-Coulter). All patients were contacted by phone in May 2012, and provided information regarding their pregnancies following the date of sample.

Results: 112 patients (56 exposed and 56 not exposed patients) were included. Mean age was 31.6 ± 5.8 years.

The mean AMH serum level was 1.21 ± 1.01 ng/ml. 82% of the patients had AMH < 2 ng/ml and 50 % had AMH ≤1 ng/ml. The mean AMH serum level was significantly lower in patients exposed to CYC than in unexposed (1.02 ± 0.97 vs 1.41 ± 1.01 ng/ml, p = 0.03) and in patients older than 30 years-old (1.02 ± 0.97 versus 1.43 ± 1.02 ng/ml, p = 0.02).

Mean follow-up (interval between sample and phone interview) was 3.9 ± 0.6 years. During this follow-up, 36 of the 112 patients willed to become pregnant, and 30 succeed (83.3%). In univariate analysis, the risk of failure was associated with exposure to CYC (5 failure in 15 versus 1 failure in 21, p=0.023), older age (35.5 ± 4.8 years old at sample in failure versus 30 ± 4.3 years old in success, p = 0.024) and lower AMH serum level (0.64 ± 0.68 ng/ml in failure versus 1.6 ± 1.15 ng/ml in success, p=0.052).

Interestingly, pregnancy occurred in 6 out of 10 women who had very low AMH serum level (≤ 0.05 ng/ml), and in 10 out of 14 who had AMH serum level ≤ 1 ng/ml.

Conclusion: As previously reported, we confirm that the AMH level is low in many SLE patients, and that this level decreases significantly with age and with exposition to CYC. However, and despite this, we show for the first time that the risk of failure to become pregnant was low with pregnancy obtained in 83.3% of the patients who were willing to become pregnant. Successes were observed even in the patients with the lowest level of AMH. Preliminary results show that failure was associated with older age and CYC exposition. Additional analyses (multivariate analyses) are ongoing.

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Effects of Treatment On the Expression of CCL2 and CXCL10 in Systemic Lupus Erythematosus Patients. Paul R. Dominguez-Gutierrez, Angela Ceribelli, Minoru Satoh, Eric S. Sobel, Westley H. Reeves and Edward K.L. Chan. University of Florida, Gainesville, FL

Background/Purpose: Several candidate biomarkers for Systemic Lupus Erythematosus (SLE) have been reported including STAT1, ADAR, CCL2, CXCL10, and miR-146a. This study examines the effects of treatment on their levels.

Methods: Leukocytes were collected from 103 SLE patients (59 had 2 or more visits) fulfilling ACR criteria and 65 healthy donors (HD). Gene expression of type I- interferon (I-IFN) signature genes (ISGs) and chemokines was analyzed by Taqman qPCR and determined by $\Delta\Delta C_T$ method. IFN score was calculated from Mx1, OAS1, and Ly6e. Biomarkers expression, multiple comparisons of therapies, linear correlations, and slope comparisons were analysed by Wilcoxon/Kruskal-Wallis Test, Steel method with control, Spearman Rho constant (ρ), and ANCOVA respectively.

Results: STAT1, ADAR, CCL2, and CXCL10, but not miR-146a, were significantly elevated (p< 0.0001) in SLE patients. STAT1, ADAR, CCL2, and CXCL10 showed significant correlations (p<0.003) to IFN score in both HD and SLE. Next, therapies were analyzed for significant effects on the biomarkers. The effects of interest would be those that reduce the biomarkers levels below untreated (UTX) SLE and that are not significantly elevated above HD. As a further measurement, the slopes of biomarkers that significantly correlated to IFN score were compared to determine if the therapy was capable of reducing (directly or indirectly) the biomarkers response to I-IFN. A lack of correlation and/or decreased slope may indicate disruption of the relationship between biomarkers and I-IFN by the therapy. Alone or in combination, prednisone (PD), hydroxychloroquine (HCQ), and mycophenolate mofetil (MMF) did not have significant effects on IFN score, STAT1, or miR-146a. Both CCL2 and CXCL10 were affected by the therapy (see figure). CCL2 was significantly higher (p<0.0009) in UTX SLE and in HCQ- and HCQ+MMF-treated SLE and CXCL10 was significantly higher (p<0.009) in UTX SLE, SLE treated with HCQ, HCQ+MMF, PD, and PD+MMF compared to HD. CCL2 and CXCL10 maintained a significant correlation (p<0.009; ρ> 0.35) with IFN score in UTX SLE, HCQ, and HCQ+MMF SLE. Furthermore, comparing CCL2 and CXCL10 vs IFN score, UTX SLE patients display a significantly higher slope (p<0.009) than HD, HCQ, and HCQ+MMF. CCL2 in HCQ, PD-, and PD+HCQ- treated SLE was significantly lower (p<0.038) than UTX SLE, nor significantly correlated with IFN score, except for HCQ. But only PD and PD+HCQ had significantly lower CXCL10 than UTX SLE. When comparing CXCL10 vs IFN score, UTX SLE display a significantly higher (p<0.02) slope than PD-, PD+MMF-, and PD+HCQ-treated SLE patients.
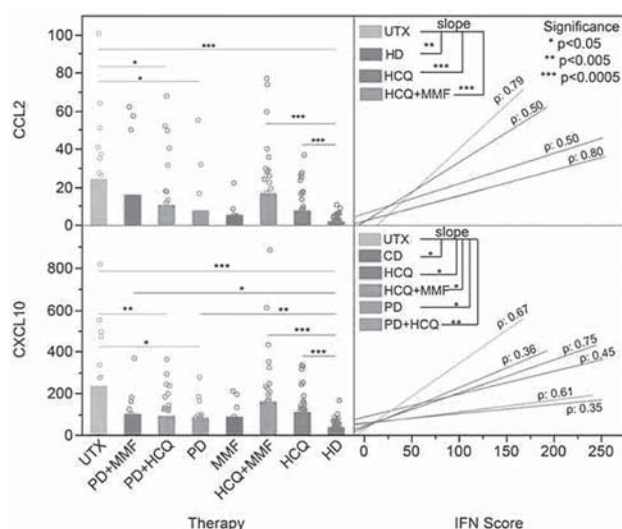
Conclusion: CCL2 and CXCL10 levels were significantly lower for several treatments compared to UTX. Therapies appear to attenuate the response of CCL2 and CXCL10 to I-IFN. Overall, CCL2 and CXCL10 are candidate markers of response to treatment for SLE.

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Clinical Characteristics for Future Development of Systemic Lupus Erythematosus in Korean Patients with Idiopathic Thrombocytopenic Purpura. Yeon-Ah Lee[1], Somi Kim[1], Ran Song[2] and Sang-Hoon Lee[2]. [1]Kyung Hee University, Seoul, South Korea, [2]Hospital at GANGDONG, Kyung Hee University, Seoul, South Korea

Background/Purpose: Systemic lupus erythematosus (SLE), a chronic inflammatory autoimmune disease capable of exhibiting virtually any clinical symptoms, occasionally presents itself with thrombocytopenic purpura as an initial manifestation. Some patients with initial diagnosis of idiopathic thrombocytopenic purpura (ITP) develop symptoms of SLE as time goes by. Our aim was to investigate the prevalence of SLE in patients with the initial diagnosis of ITP and recognize the salient characteristics of these patients, thereby identifying early diagnostic clues.

Methods: We retrospectively analyzed the clinical and laboratory features of 337 (203 females, 134 males) patients initially diagnosed with ITP between January 1993 and April 2012 at a single center, Kyung Hee University Hospital. At the time of diagnosis of ITP, patients with autoimmune diseases were excluded and ITP was classified into chronic, acute, and recurrent acute types. The following data were obtained for every patient: age at diagnosis, sex, presence of ANA and anti-platelet antibody, bone marrow findings, and bleeding manifestations. The patients were followed-up for development of symptoms indicative of SLE and clinical events including immune hemolytic anemia, splenectomy, infections and thrombosis.

Results: Fifteen of the 337 patients (4.5%) developed SLE; 14 were females while all 15 showed ANA positivity. The patients who eventually developed SLE were more likely to have chronic type ITP, higher ESR, and speckled type ANA, irrespective of its titer (p< 0.05, respectively). The mean incubation period turned out to have SLE was 33.3 months (range: 2–159). For these patients, the mean age at initial diagnosis of ITP was 26.6 years (range: 13–65), and the mean age at diagnosis of SLE was 29.4 years (range: 15–66). Splenectomy was performed in 4 patients, and 3 of them suffered from at least one event of infection. Six of the 15 ITP patients with later development of SLE had been diagnosed as having Evan's syndrome (ITP with immune hemolytic anemia). The most notable SLE manifestations were thrombotic complications such as deep vein thrombosis or cerebral infarction (40%), and accordingly, high positivity of anti-phospholipid antibody (6/13, 46.2%). Contrary to previous reports, renal involvement appeared to be quite frequent (7/15, 46.6%).

Conclusion: SLE was developed in 4.5% of patients with initial diagnosis of ITP during follow-up. ITP patients with later development of SLE are associated with adverse clinical course, therefore early recognition and accurate interventions are imperative. The presence of speckled type ANA,

elevated ESR or immune hemolytic anemia in ITP patients warrant careful monitoring, as they are prone to develop other manifestations of SLE or thrombotic complications. With increased clinical attention, unnecessary invasive procedures, such as splenectomy, can be avoided and timely initiation of disease-specific treatment possible.

Disclosure: **Y. A. Lee**, None; **S. Kim**, None; **R. Song**, None; **S. H. Lee**, None.

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Pulmonary Hypertension in Systemic Lupus Erythematosus: A 6-Year Follow-up Study Cohort. Claudia Hübbe-Tena, Selma Gallegos-Nava, Rafael Bojalil and Luis M. Amezcua-Guerra. Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico

Background/Purpose: Systemic lupus erythematosus (SLE) may present hemodynamic alterations including pulmonary hypertension (PH). Echocardiography (ECHO) is a noninvasive imaging technique useful to classify pulmonary hypertension (PH) as improbable (sPAP ≤36 mmHg), possible (37–50 mmHg), or probable (>50 mmHg).

Methods: Study cohort with 6-year follow-up including 139 SLE patients. At baseline, demographics, organ involvement, disease activity (SLEDAI-2K), cumulated organ damage (SLICC/ACR), and laboratory analyses including antibody profile were obtained. Serum samples were stored in standard conditions. Clinical follow-up was performed 3 months. SLE patients who had an ECHO for any reason by the time of recruitment (±6 months) were included. From stored sera, levels of endothelin 1 (ET1), monocyte chemotactic protein 1 (MCP1), and interferon gamma (IFNg) were measured by ELISA. Discrete variables are described as percentages and continuous variables as medians (interquartile range). Analyses were performed by either chi-square test for trends or Kruskal-Wallis with Dunn's post-test. Spearman's rank correlation coefficient (r) was used to assess associations. Survival was assessed by the Kaplan-Meier method with log-rank test for trends.

Results: 55 SLE patients were included. Patients were classified in 3 groups by ECHO: improbable PH (n=26, 96% female, age 34.5, 24–46 years); possible (n=16, 81% female, age 49, 38–53 years); probable (n=13, 100% female, age 41, 38–56 years). No differences in demographic or serologic features between groups, whereas organ damage was higher in patients with PH (SLICC/ACR index of 1 (1–2), 3 (1.7–4), and 3 (2–6), respectively; P=0.0009). Active arthritis was present in 12%, 13%, and 38% (P=0.05); history of pulmonary thromboembolism in 8%, 13%, and 46% (P=0.005). Serum levels of ET1, MCP1 and IFNg were similar between groups. The sPAP showed a positive correlation with age (ρ 0.29), disease duration (ρ 0.32), serum creatinine (ρ 0.26), SLEDAI-2K (ρ 0.26), SLICC/ACR (ρ 0.55), left atrium diameter (ρ 0.45), interventricular septum thickness (ρ 0.33), and right ventricular diastolic diameter (ρ 0.71). An inverse correlation with C3 (ρ −0.25) and CH50% (ρ −0.25) was found. Main causes of PH (sPAP >37) were: connective tissue disease (32%), intrinsic cardiac disease (26%), pulmonary thromboembolism (26%), and pulmonary disease (16%). Rates of survival in the first year were: improbable PH 92%, possible PH 94% and probable PH 90%. After three years, these were 92%, 89% and 77%, respectively. After six years 88%, 87% and 68%, respectively.

Conclusion: In SLE, PH (sPAP >50 mmHg) is associated with decreased survival in the medium term. Also, it is related to cumulated organ damage and history of pulmonary thromboembolism. Validated biomarkers in idiopathic PH such as ET1, MCP1 and INFg as well as SLE- and scleroderma-related autoantibodies are not useful to distinguish PH in patients with SLE.

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Altered Soluble Inflammatory Mediators Mark Impending Systemic Lupus Erythematosus Disease Flare in European-American Lupus Patients Who Receive Influenza Vaccination. Melissa E. Munroe[1], Jourdan R. Anderson[1], Joan T. Merrill[1], Joel M. Guthridge[1], Virginia C. Roberts[1], Gillian M. Air[1], Linda F. Thompson[1] and Judith A. James[2]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation; University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background/Purpose: SLE is a multifaceted autoimmune disease denoted by immune dysregulation that contributes to increased morbidity and mortality in part due to infectious complications. Vaccination against common infections, such as influenza, is recommended for SLE patients to decrease infection risk. Using a unique resource of SLE patients participating in an influenza vaccination protocol with samples available before and at the time of clinically-defined disease flare, this study seeks to identify biomarkers of disease flare.

Methods: Over 6 flu seasons, 101 unique SLE patients and 101 healthy controls (HC) were enrolled in the SLE Influenza Vaccination Cohort. Plasma samples were obtained on the day of vaccination (BL) and at 6 and 12 weeks post-vaccination (FU). Demographics, detailed clinical information (disease activity, medication use), serum autoantibody profiles, and antibody response to influenza were collected at each visit. BL and FU samples from 29 European American (EA) SLE patients who exhibited SELENA-SLEDAI defined disease flare at 6 (n=14) or 12 (n=15) weeks post-vaccination were tested. Each SLE patient was matched by race/gender/age (+/− 5 years)/time of sample procurement/ANA status at BL to a unique SLE patient who did not exhibit disease flare (NF), as well as to a HC. Samples from 14 (n=7 each at 6 and 12 weeks at FU) of 29 SLE patients with flare were compared to samples from the same SLE patients from another year where disease flare did not occur (self nonflare, SNF). Plasma samples were tested for 52 soluble inflammatory mediators, including cytokines, chemokines, and soluble receptors using xMAP multiplex bead-based assay or sandwich ELISA (BLyS and APRIL).

Results: SLE patients who exhibited disease flare had significant ($p \le 0.01$) alterations in 23 soluble mediators at BL compared to unique NF/SNF patients and HC. Altered BL mediators were also seen at time of disease flare, usually with no significant change in analyte levels compared to BL. SLE patients who exhibited disease flare had significantly ($p \le 0.01$) higher levels of BL pro-inflammatory adaptive cytokines, including IL-12, IL-12, IFN-γ, IL-6, and IL-17 compared to NF/SNF SLE patients and HC. Of particular interest were increased TNFR family members at BL in flare SLE patients, including TNFRI, TNFRII, Fas, FasL, and CD40L. Regulatory cytokines, including IL-10 and TGF-β were significantly increased ($p \le 0.01$) at BL in SLE patients not exhibiting disease flare (NF/SNF) compared to flare SLE patients and HC. A number of analytes, including MIP-1α and BLyS, were significantly higher in SLE patients compared to HC, but no difference was seen between flare and NF/SNF in this cohort.

Conclusion: Shed TNF receptors and proinflammatory adaptive cytokines representing Th1, Th2 and Th17 pathways are elevated in lupus patients who flare within the next 6–12 weeks. These remain unaffected by influenza vaccine, suggesting their utility as resilient, predictive biomarkers of flare and that influenza vaccination itself does not further promote risk for flare.

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Comparison of the Lupusqol and SF-36 Scores As Valid Measures of Change in Health Related Quality of Life. Zahi Touma, Murray B. Urowitz, Dominique Ibanez, Shahrzad Taghavi-Zadeh and D. D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: The LupusQoL questionnaire is a disease-specific instrument for adults with lupus while the short form-36 (SF-36) is a generic questionnaire.

We aimed to compare the LupusQoL and the SF-36 questionnaires to determine if they are comparable measures of change in patients with SLE on standard of care therapy.

Methods: We analyzed the results of SF-36 and LupusQoL questionnaires available from a group of lupus patients who were followed at the Lupus Clinic. Patients were studied if they had at least one follow-up visit within 6 month period while receiving standard of care therapy.

Each of the questionnaires, SF-36 and LupusQoL, includes 8 domains and its scores ranges from 0 (worst possible) to 100 (best possible) quality of life. The SF-36 subscales can be further summarized into 2 component scores: the physical component summary (PCS) and the mental component summary (MCS).

The mean change in the domains scores for both questionnaires was determined by subtracting the scores of the follow-up visits from the score of the baseline visit.

We determined the correlation (Pearson) of the change in scores of LupusQoL and the change in scores of SF-36. The correlation of the comparable domains of LupusQoL was determined with the corresponding domains of SF-36. For each of the non-comparable domains of the LupusQoL questionnaire the correlation was determined with PCS and MCS individually.

Results: 99 patients (91% F) had baseline and at least one follow-up visit available. 44% were Caucasian, 33% Black, 10% Asian and 12% others. For the 99 patients 251 observations were identified for which both SF-36 and LupusQoL questionnaires were available. Age at lupus diagnosis and lupus duration at first

visit were 27.2 ± 12.4 and 11.9 ± 7.7 years. The mean SLEDAI-2K on all visits was 7.49 ± 5.21.

The correlation of the change in scores of the comparable LupusQoL and SF-36 domains ranged from 0.38–0.65. The correlation between LupusQoL Pain and SF-36 Bodily Pain was 0.65, LupusQoL Physical Health and SF-36 Physical Functioning was 0.38, LupusQoL Emotional Health and SF-36 Mental Health was 0.56 and LupusQoL Fatigue and SF-36 Vitality was 0.48 (all p were significant). For the non-comparable domains the correlation of the LupusQoL domains with SF-36 MCS and PCS ranged from 0.02–0.33 (Table 1).

Table 1. Correlation of change in SF-36 and LupusQoL for comparable and non-comparable domains

	Lupus QoL domains	SF–36 domains	
Comparable domains	Pain	Bodily Pain	0.65 (<0.0001)
	Physical Health	Physical Functioning	0.38 (<0.0001)
	Emotional Health	Mental Health	0.56 (<0.0001)
	Fatigue	Vitality	0.48 (<0.0001)
Non–comparable domains	Body Image	PCS	0.09 (0,28)
		MCS	0.28 (0.0007)
	Planning	PCS	0.33 (<0.0001)
		MCS	0.29 (0.0004)
	Intimate Relationships	PCS	0.27 (0.01)
		MCS	0.02 (0.89)
	Burden to others	PCS	0.25 (0.002)
		MCS	0.29 (0.0004)

Conclusion: The correlation of the change in the scores of comparable domains of Lupus QoL and SF-36 ranged from moderate to large. The correlation of the change in the scores of non-comparable domains of Lupus QoL and SF-36 was insubstantial to small. Thus these questionnaires measure different aspects of quality of life and both questionnaires might be used together.

Disclosure: Z. Touma, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **S. Taghavi-Zadeh**, None; **D. D. Gladman**, None.

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Adjusted Framingham Risk Factor Scoring for Systemic Lupus Erythematosus: Results from an Inception Cohort Followed for Eight Years. Murray B. Urowitz[1], Dominique Ibanez[1], D. D. Gladman[1], SLICC[2] and Systemic Lupus International Collaborating Clinics (SLICC)[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto, ON

Background/Purpose: There is a high prevalence of premature atherosclerosis among patients with SLE, with a risk 7–9 times that of the general population. The traditional Framingham risk factor underestimates the risk for coronary artery disease (CAD) in patients with SLE. It has been suggested that a modified Framingham risk score (FRS) where each item is multiplied by 2 more accurately identifies patient at Moderate/High risk of CAD, and more accurately predicted subsequent CAD. The aim of this study was to determine whether the modified FRS (mFRS) more accurately reflected the prevalence of CAD(MI, angina, pacemaker) among patients in an inception cohort.

Methods: An inception cohort of SLE patients from 31 centres from 12 countries has been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. Only patients with all variables necessary to calculate the FRS at enrolment and who did not have diabetes mellitus were included in this analysis. Patients are followed at yearly intervals according to a standard protocol which included demographics, disease characteristics and classic risk factors for CAD as well as CAD events. Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate Sensitivity and Specificity (95% CI) of FRS and MFRS were evaluated in their prediction of future CAD.

Results: At enrolment 853 patients had sufficient data to calculate FRS. Of these, 140 patients had 8 years of follow-up available. 85% female, 50% Caucasian, 11.4% Black, 20.7% Asian 16.4% Hispanic and 1.4% other. 13.6% were current smokers, 22.2% past smokers. Age at diagnosis was 34.2 yrs and disease duration at enrolment was 5.0 mos. BMI was 24.4, and 25.7% were obese. 35%, were hypertensive and 42% had hypercholesterolemia. The 140 patients did not differ from those not followed for 8 years in either demographic features, disease characteristic, atherosclerotic risk factors. Table shows the calculated classic FRS and mFRS for the 140 patients.

	Classic FRS		Modified FRS	
Risk Category	**Number**	**%**	**Number**	**%**
Very low risk	133	95	112	80
Low risk	2	1.4	6	4.3
Moderate risk	2	1.4	6	4.3
High risk	3	2.1	16	11.4
Moderate + High	**5**	**3.5**	**22**	**15.7**

Of the 140 patients 14 subsequently developed CAD, 8 of which are attributed to AS. The sensitivity of the FRS for CAD due to AS was 25.0 (3.2, 65.1) and specificity 97.7 (93.5, 99.5), whereas for the mFRS the sensitivity rose to 50.0 (15.7, 84.3) while the specificity decrease slightly to 86.4 (79.3, 91.7).

Conclusion: The mFRS, where each item is multiplied by 2, more accurately identifies patients at Moderate/High Risk of CAD. It provides higher sensitivity with little loss in specificity. Therefore the mFRS could be used to identify SLE patients for more intensive risk factor modification.

Disclosure: M. B. Urowitz, None; **D. Ibanez**, None; **D. D. Gladman**, None;

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Atherosclerotic Vascular Events in a Multinational Inception Cohort of Systemic Lupus Erythematosus: Incidence Over a Ten Year Period. D. D. Gladman[1], Dominique Ibanez[1], Murray B. Urowitz[1] and SLICC[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto, ON

Background/Purpose: A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. The purpose of this study was to determine the incidence of vascular events during a 10 year follow-up and their attribution to AS.

Methods: An inception cohort of SLE patients from 31 centres from 12 countries has been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. Patients enter the cohort within 15 months of SLE diagnosis ($\geq$4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Vascular events (VE) are described and attributed to SLE and AS on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), stroke, transient ischemic attack (TIA). Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate. Attribution to AS was made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. The incidence of VE was calculated over the 10 years for all VE occurring after diagnosis, and then for atherosclerotic VE (AVE). Kaplan-Meier curves were used to estimate the cumulative incidence rates since SLE diagnosis

Results: Since 2000 1844 patients have been entered into the cohort (88.9%F, age at SLE 34.7y). Caucasian 49.2%, Black 16.5%, Asian 14.9%, Hispanic 15.3%, other 4.1%. Thus far there have been 157 VE in 115 patients after the diagnosis of SLE. These include: MI (14), angina (26), CHF (36), PVD (11), TIA (27), stroke (38), pacemaker insertion (5). 64 of the events were attributed to active lupus and 44 to other causes or missing. 49 events in 37 patients were attributed to AS including: MI (8), angina (19), CHF (6), PVD (6), TIA (5), pacemaker (3), stroke (2).

Table. Cumulative incidence of 1st vascular events since diagnosis of SLE

Years since SLE Dx	Number	VE N=115	AVE N=37
0	1844	0.2%	0.1%
1	1479	3.0%	0.7%
2	1305	4.0%	0.9%
3	1097	5.4%	1.4%
4	948	6.2%	1.9%
5	768	7.3%	2.4%
6	600	7.7%	2.5%
7	459	8.9%	2.9%
8	342	9.4%	3.2%
9	233	10.1%	3.9%
10	138	11.2%	4.4%

Conclusion: Over the follow-up of an inception cohort with SLE there were 157 vascular events of which 49 were attributable to AS. The incidence of AVE increased by 0.5% per year reaching a total of 4.4% at 10 years.

Disclosure: D. D. Gladman, None; **D. Ibanez**, None; **M. B. Urowitz**, None;

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Increased Male-to-Female Ratio in Children Born to Women with Systemic Lupus Erythematosus. Evelyne Vinet[1], Sasha Bernatsky[2], Mohammed Kaouache[2], Emil P. Nashi[1], Christian A. Pineau[1], Ann E. Clarke[3], Robert W. Platt[4], Meggan C. Mackay[5] and Cynthia Aranow[6]. [1]McGill University Health Centre, Montreal, QC, [2]Research Institute of the McGill University Health Ctre, Montreal, QC, [3]MUHC, Montreal, QC, [4]McGill University, Montreal, QC, [5]The Feinstein Institute, Manhasset, NY, [6]Feinstein Institute for Medical Research, Manhasset, NY

Background/Purpose: Recent experimental evidence suggests that anti-DNA antibodies, cross-reacting with brainstem neuronal receptors, induce apoptosis and cause a marked preferential loss of female foetuses in SLE murine models. Observational studies assessing the sex of offspring born to women with SLE are scant and limited by their sample size. In a large population-based study, we aimed to determine the sex ratio of children born to women with SLE and to compare with children born to women without SLE.

Methods: We identified all women who had at least one hospitalization for a delivery (either for a stillbirth or live birth) after SLE diagnosis using Quebec's physician billing and hospitalization databases (from 01/01/1989 to 31/12/2009). Women were defined as SLE cases if they had any of the following: 1) at least one hospitalization with a diagnosis of SLE prior to the delivery, 2) a diagnosis of SLE recorded at the time of their hospitalization for delivery, or 3) at least 2 physician visits with a diagnosis of SLE, occurring 2 months to 2 years apart, prior to the delivery. We randomly selected a general population control group, composed of women matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We obtained information on sex for all births occurring in both groups of women, and calculated the respective male-to-female ratio. We performed a multivariate logistic regression, with the offspring's sex as the dependent variable, adjusting for the potential effect of preeclampsia (previously shown to increase the male-to-female ratio in the general population).

Results: 507 women with SLE had a total of 731 births after diagnosis, while 5862 matched control women had 8631 births. The prevalence of preeclampsia was 5.5% (95% CI 4.0, 7.6) in children born to women with SLE and 2.2% (95% CI 1.9, 2.5) in children born to control women. The unadjusted male-to-female ratio was increased in children born to women with SLE (1.26, 95% CI 1.09,1.46) compared with controls (1.06, 95% CI 1.02,1.11). In multivariate analysis adjusting for the effect of preeclampsia, mothers with SLE had substantially increased odds of having male offspring than mothers without SLE (OR 1.19, 95% CI 1.02, 1.38).

Conclusion: Compared to children from the general population, there is a substantial increase in the male-to-female ratio in children born to women with SLE. These results should prompt further research on the male predominance in children born to women with SLE.

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Clinical Variables Associated with Thrombosis At Systemic Lupus Erythematosus Diagnosis. Differences Between Patients with Positive/Negative Lupus Anticoagulant. Andrea Hinojosa-Azaola[1], Alba Cicero-Casarrubias[1], Mario César Ocampo-Torres[1], Juanita Romero-Díaz[1] and Jorge Sánchez-Guerrero[2]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Mount Sinai Hospital and University Health Network, Toronto Canada

Background/Purpose: Thrombosis in patients with Systemic Lupus Erythematosus (SLE) is a major cause of morbidity, it occurs in 9–37%, at younger age, and it represents 27% of mortality. Lupus anticoagulant (LA) is strongly associated with thrombosis; however, most events occur in patients who are negative for LA. The aim of our study was to determine the baseline characteristics associated with thrombosis in an inception cohort of SLE patients and in the subset of patients without LA.

Methods: A longitudinal inception cohort of 223 SLE patients (less than 12 months of accrual ≥4 criteria), predominantly female (90%), mean age 27.2 years at diagnosis, was studied. Baseline evaluation included medical history, physical exam, clinical variables, SLE characteristics, SLE activity (SLEDAI-2K), modified damage index (SLICC/DI), autoantibodies, laboratory tests, homocystein and high-sensitivity C-reactive protein (hs-CRP). Thrombotic events were diagnosed on clinical manifestations and confirmed by appropriate studies. Statistical analyses: Descriptive statistics, Student T-test, Mann-Whitney U-test, Chi-square, Fisher exact test, Logistic Regression. P <0.05.

Results: During 1269 patient-years of follow-up, thrombosis occurred in 35 patients (16%), incidence rate 25.6 per 1000 patient-years. Most of the events (57%) occurred at onset or during the first year of diagnosis of SLE. At baseline, patients with thrombosis had lower body mass index (BMI) (p=0.03), smoking (p=0.02), vascular insufficiency (p=0.05), immobilization (p<0.0001), recent surgery (p=0.004), anti-RNP (p=0.04), lupus anticoagulant (LA) (p=0.006), and higher modified SLICC/DI (p=0.03). Since only 8/35 thromboses were associated to LA, we identified those variables associated with thromboses in patients with LA negative: smoking (p=0.004), vascular insufficiency (p=0.03), immobilization (p<0.0001), serositis (p=0.04), and hs-CRP (p=0.02). In the multivariate analysis, BMI (OR 0.79 95% CI 0.65–0.95, p=0.016), anti-RNP (OR 1.02 95%CI 1.00–1.03, p=0.003) and LA+ (OR 8.05 95% CI 1.75–36.88, p=0.007) were independent risk factors for thrombosis in the general cohort. After excluding patients with LA, smoking (OR 6.1, 95% CI 1.7–21.8 p=0.006), vascular insufficiency (OR 28.7 95% CI 2.4–342.9, p=0.008), and immobilization (OR 31.3 95%CI 2.6–381.4, p=0.007) were independent risk factors for thrombosis.

Conclusion: Patients with SLE are at an increased risk of thrombosis, particularly during the first year of diagnosis. Although LA is a strong risk factor, most thrombotic events occur in patients without LA; in this subset, smoking, immobilization and vascular insufficiency are the most important. All of them are potentially modifiable.

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Suicidal Ideation in Patients with Systemic Lupus Erythematosus: Incidence and Relationship with Anxiety/Depression Score, Disease Activity and Organ Damage. Chi Chiu Mok[1], Kelly Chan[1] and Paul Yip[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]University of Hong Kong, Hong Kong, Hong Kong

Background/Purpose: To study the incidence of suicidal ideation in patients with SLE and its relationship with anxiety/depression score, disease activity and organ damage

Methods: Consecutive patients who fulfilled the ACR criteria for SLE were recruited for a questionnaire study on suicidal ideation, which was assessed by (1) 3 standard questions on suicidal thoughts and suicidal plans in the past 1 month; and (2) the validated Chinese version of the Beck Scale for Suicidal Ideation (BSSI) for suicidal intention: 19 questions (each scores 0–2, final score is the summation of the scores of the 19 questions (0–38 points; higher score more suicidal intention). History of suicidal attempts and self assessment of suicidal tendency was also included in this tool. Anxiety and depressive symptoms were assessed simultaneously by the Hospital Anxiety and Depression (HAD) scale (0–21 points for each of depression and anxiety). Disease activity of SLE was assessed by SLEDAI and physicians' global assessment (PGA), whereas organ damage since SLE diagnosis was assessed by the ACR SLICC damage index (SDI). The BSSI score was correlated with the demographic and clinical features of the participants, HAD, SLEDAI and SDI score. Linear regression models were established to study the independent factors associated with suicidal intention.

Results: 319 SLE patients were studied (300 women; mean age at SLE onset was 30.2±12.2 years; disease duration 9.0±7.0 years). 43 (13%) patients had clinically active SLE (SLEDAI >=5). 106 (33%) patients had organ damage (SDI >=1). 29 (9%) patients had suicidal thoughts and 4 (1%) patients had suicidal thoughts together with solid plans within 1 month of study. 39 (12%) patients had previous suicidal thoughts/attempts whereas 18 (6%) had documented suicidal attempts. The mean BSSI score was 1.37±3.62 points (0–24). Compared to those without suicidal thoughts within 1 month of study, patients with suicidal thoughts had significantly higher BSSI scores (6.0±6.1 vs 0.89±2.9 points; p<0.001), HAD-anxiety (13.1±5.2 vs 5.70±4.2; p<0.001) and HAD-depression (12.4±4.3 vs 4.50±3.9; p<0.001) scores. Linear regression analysis

revealed that the total BSSI scores (suicidal intention) correlated significantly with HAD-depression (Beta 0.52; p<0.001), HAD-anxiety (Beta 0.47; p<0.001), age (Beta 0.15; p=0.009), male sex (Beta −0.13; p=0.02), previous suicidal attempts (Beta 0.17; p=0.003) and SDI score (Beta 0.21; p<0.001) but not with SLEDAI (Beta 0.05; p=0.44). In a multivariate regression model, only HAD-depression score (Beta 0.30; p<0.001), HAD-anxiety score (Beta 0.28; p<0.001), age (Beta 0.12; p=0.02) and SDI damage score (Beta 0.11; p=0.03) correlated positively and significantly with the total BSSI score.

Conclusion: In this cross-sectional study, suicidal ideation in the preceding month occurred in 9% of patients with SLE, whereas previous suicidal thoughts/attempts were present in 12% of participants. The suicidal intention was stronger in older patients, men, and those with more organ damage, anxiety or depressive symptoms. Suicidal intention did not correlate with disease activity. Further study on the contribution of socioeconomic factors to suicidal ideation in SLE patients is in progress.

Disclosure: C. C. Mok, None; **K. Chan**, None; **P. Yip**, None.

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Serum Rituximab Levels and Efficiency of B-Cell Depletion: Differences Between Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis. Venkat Reddy[1], Sara Croca[1], Delia Gerona[2], Inmaculada De La Torre Ortega[2], David A. Isenberg[1], Maria Leandro[1] and Geraldine Cambridge[1]. [1]University College London, London, United Kingdom, [2]Gregorio Marañón Hospital, Madrid, Spain

Background/Purpose: Variability in rituximab-induced B-cell depletion (BCD) occurs in a significant number of patients with Systemic Lupus Erythematosus (SLE) and to a lesser extent in patients with Rheumatoid Arthritis (RA). A failure to adequately deplete (CD19+ B cells <5/μl) probably underlies poor clinical response in many patients with SLE. In this prospective study, we investigated whether the levels of rituximab influence the degree of peripheral BCD.

To determine the serum levels of rituximab at 1 and 3 months post-rituximab in SLE and RA in conjunction with the measurement of absolute number of peripheral CD19+ B cells.

Methods: A total of 16 patients with SLE were included and 23 with RA. All were treated with rituximab (2 × 1g doses given 2 week apart). Rituximab levels at 1 and 3 months post treatment was measured with a capture ELISA using sera diluted at a concentration of 1/40,000. CD19 counts were determined by flow cytometry. Adequate depletion was defined as CD19+ count below 5cells/μl. Data were compared using the Mann Whitney U test for non-parametric data and the Spearman Rank for correlation.

Results: At 1 month, 6 of 15 (40%) patients with SLE and 6 of 23 (26%) patients with RA had CD19 counts >5 cells/μl. The median CD19 count in these patients was 0.02cells/μl and 0.008cells/μl for SLE and RA, respectively. The levels of rituximab were significantly lower in SLE when compared with RA, at both 1 and 3 months after rituximab treatment. The median rituximab level at 1 month for SLE was 43.07μg/ml (range 0–777) and for RA, 391.9μg/ml (range 1.3–2500) (p=0.0008). The median rituximab level at 3 months were <10μg/ml (range 0–54) for SLE and 2.6μg/ml (range 0–1153) for RA (p=0.008). Amongst patients who had depleted well, rituximab levels were significantly lower in patients with SLE when compared with patients with RA at 1 month (p=0.003) and also at 3 months (p=0.008). No such difference was found in patients who did not deplete well. Six patients with SLE had lupus nephritis (LN) and the presence of LN did not influence the levels of rituximab or the degree of BCD, in this small group of patients. The levels of rituximab correlated inversely with the absolute numbers of CD19+ B cells in patients with RA at 1 month (r^2 =0.69) and in patients with SLE at 3 months (r^2=0.51).

Conclusion: Our data indicated that patients with SLE had markedly (>9 fold at 1 month) lower serum levels than RA patients at both 1 and 3 months. A higher proportion of patients with SLE depleted less well with significantly higher residual CD19+ B cells due to factors involved in clearance of rituximab such as impaired recycling through FcRn, internalisation and destruction by target B cells.

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Longitudinal Analysis of Plasma Factors and Disease Activity Identifies Von Willebrand Factor As A Biomarker of LUPUS FLARE. Mikhail Olferiev[1], Kyriakos A. Kirou[2], Elena Gkrouzman[3], Dorthe Lundsgaard[4], Klaus S. Frederiksen[5], Jan Fleckner[5] and Mary K. Crow[2]. [1]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, New York, NY, [4]Novo Nordisk A/S, Måløv, Denmark, [5]NovoNordisk, Copenhagen, Denmark

Background/Purpose: Lupus, a chronic autoimmune disease, is characterized by a variable clinical course, with periods of active disease termed flares. The severity of flares can be measured using clinical scores [SELENA-SLEDAI (SS); BILAG], but those scores do not define or suggest underlying pathophysiologic mechanisms of flare. Identification of a biomarker associated with clinical lupus flare would be useful for disease management, for assessment of response to therapeutic intervention in practice or clinical trials, and might suggest cellular or molecular targets for future therapies. To identify biomarkers that reflect lupus flare, we assessed longitudinal clinical and proteomic data from SLE patients.

Methods: One hundred sixty-nine plasma samples were collected longitudinally (up to 3 years) from 23 SLE patients and 5 healthy donors (HD), and SS and BILAG scores recorded. All SLE patients fulfilled ACR criteria for the disease. A panel of pro-inflammatory cytokines was evaluated using Multi-Analyte Profiling (MAP) technology (Rules-Based Medicine, Austin, TX). Longitudinal data analysis was performed using R (R Development Core Team) and the R packages lme4 and languageR. Data were analyzed using Linear Mixed Effects models (LME). A second validation set of 15 patients (175 visits) was used to confirm changes in the level of selected mediators in relation to clinical flare.

Results: Thirteen plasma factors were identified as significantly increased in SLE patients compared with HD, and 14 plasma factors were significantly deregulated during flaring compared with non-flaring visits, based on LME. However, in paired t-test analysis only von Willebrand factor (vWF) was significantly increased during severe flares compared to both first non-flaring visit before (p<0.02) and first non-flaring visit after (p<0.01) the identified flare. The association of changes in vWF with lupus flare was confirmed in the validation cohort.

Conclusion: vWF is produced by endothelial cells and is required for normal hemostasis and vascular function. Levels of circulating vWF are increased following endothelial cell damage and during acute phase responses. The significantly increased level of vWF during lupus flare in the majority of SLE patients highlights the role of endothelial injury as a major pathogenic mechanism in SLE and identifies vWF as an informative biomarker for patient management and clinical studies.

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Incidence Studies of Systemic Lupus Erythematosus in Southern Sweden. Have the Tides Turned? Ragnar Ingvarsson[1], Andreas Jönsen[2], Ola Nived[3], Gunnar Sturfelt[1] and Anders Bengtsson[4]. [1]Department of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [2]Section of Rheumatology, Lund, Sweden, [3]University Hospital - Lund, Lund, Sweden, [4]University Hospital Lund, Lund, Sweden

Background/Purpose: The main objective was to study the incidence of Systemic Lupus Erythematosus (SLE) within a defined area in Southern Sweden over a period of more than 25 years. By prospectively identifying all new cases within this region using validated retrieval methods. A secondary objective was to investigate whether the phenotypic expression of SLE has changed during the study period.

Methods: The health care district of Lund-Orup had a mean population during 1981–2006 of 176.460 persons (>15 yrs of age). SLE cases were identified from multiple sources including diagnosis registries and from central laboratory databases using a previously validated "capture-recapture" methodology (Jonsson et al). The patients were observed prospectively within a structured follow-up program. Diagnosis of SLE was based on the presence of two clinical manifestations typical for SLE together with immunological

abnormalities. Other causes for these manifestations were excluded and the diagnosis was continuously re-evaluated during the follow-up.

Results: One-hundred seventy-five new cases were diagnosed with SLE from 1981–2006. There were 148 women and 27 male patients that received the diagnosis of SLE, with a mean age of diagnosis at 44.3 years. In the first half of the study, from 1981–1993, the incidence of SLE was 5.0/100.000 inhabitants compared to the second half of the study, 1994–2006, where it had decreased to an annual incidence of 2.8/100.000 inhabitants (p≤0.001). During the first half of the study period the highest incidence was among females between the ages 45–54 were it was 15.1/100.000 inhabitants whereas in the second half of the study the incidence was reduced to 3.8/100.000 in this age group (p≤0.001). Between the years 1994–2006 the highest age and sex specific incidence was amongst women between 25–34 years of age (6.6/100.000 inhabitants), unchanged from the prior period. During the whole period the age and sex specific was highest among women between the ages 45–54 (8.9/100.000 inhabitants). The point prevalence of SLE on 31st of December 1993 was 55/100.000 inhabitants compared to the 31th of December 2006 where it was 66/100.000 inhabitants. 163 of the 175 patients fulfilled 4 or more ACR classification criteria SLE giving the criteria a sensitivity of 93 % for diagnosing SLE in our cohort. The disease phenotype did not vary over time.

Conclusion: The incidence rate of SLE in Southern Sweden remains stable in younger females over a 26 year period from 1981–2006. However, the incidence was reduced significantly in the older patients groups in the later period of the study.

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Non-White Race, Younger Age, and Use of Primary and Gynecologic Care Are Associated with Higher Rates of Cervical Cancer Screening in Systemic Lupus Erythematosus Patients At a Public Hospital. Jennifer Stichman[1], Angela Keniston[1], Joann Zell[2], Jinoos Yazdany[3], Itziar Quinzanos[1] and Joel M. Hirsh[1]. [1]Denver Health Med Ctr, Denver, CO, [2]National Jewish Health, Denver, CO, [3]University of California San Francisco, San Francisco, CA

Background/Purpose: Patients with Systemic Lupus Erythematosus (SLE) are at increased risk of cervical dysplasia and persistent Human Papilloma Virus (HPV) infection. There are few prior studies looking at cervical cancer screening in SLE, and these have relied upon self-report to document if screening was done appropriately. These studies have also not included uninsured and non-English speaking subjects. We examined performance of cervical cancer screening in patients with SLE at Denver Health (DH) as well as sociodemographic and other predictors of screening.

Methods: Using data from the DH electronic health record (EHR), we identified rheumatology clinic patients with initial encounters between July 2006 and August 2011 who had SLE, were female, and were between the ages of 21–50 years. We queried data from the EHR including age, race/ethnicity, primary language, use of interpreter services and primary payer. We also queried the EHR regarding the rates of cervical cancer screening in this cohort and at DH overall. Manual record review was conducted to review medication use and possible history of hysterectomy. A chi-square test was used to test differences in the proportion of SLE patients with cervical cancer screening documented within one year pre or post index encounter and within three years pre or post index encounter by patient demographics. We looked at screening rates at both 1 and 3 year intervals depending on age, as 2003 American College of Obstetrics and Gynecology guidelines had recommended annual screening in women younger than 30.

Results: One hundred twenty eight patients with SLE were identified. Six of these patients were status post hysterectomy unrelated to cervical cancer. Data was analyzed for the remaining 122 patients. Eighty percent were non-White and half did not have health insurance. Overall, rates of cervical cancer screening within 3 years were 75% in DH primary care clinics and 66% in SLE patients. In our SLE cohort, only 60% of women age 30–50 underwent cervical cancer screening in 3 years, in contrast to 81% of patients age 21–29 (p = 0.0235). In unadjusted analyses, White women were less likely to have screening in 3 years compared to non-White women in the 21–29 age group (p=0.0147). Women in the 21–29 age group with a history of gynecologic care were had a higher likelihood of screening at 3 years (p=0.0378). In the 30–50 age group, having seen a primary care physician was associated with a higher likelihood of screening at 1 and 3 years (p=0.0013 and 0.0040 respectively) and history of gynecology care was associated with increased likelihood of having a screening test at 1 and 3 years

(p=0.0013 and 0.0003 respectively). Patients receiving immunosuppressive medications were no more likely to receive cervical cancer screening than other SLE patients.

Conclusion: We identified a gap in care in large subsets of the SLE patients at DH. White women age 21–29 and patients age 30–50 were less likely than the general primary care DH population to have appropriate cervical cancer screening. Rheumatologists need to help connect female SLE patients of all races and ethnicities with primary or gynecology care services as patients who limit physician visits to rheumatology are at risk of not being screened for cervical cancer.

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Effects of Nelfinavir On Anti-dsDNA Antibody Binding and Pro-Inflammatory Cytokine Gene Expression. Maria Espinosa[1], Julisa Patel[2], Meggan Mackay[3], Cynthia Aranow[4] and Betty Diamond[5]. [1]Cohen Children's Hospital-North Shore LIJ, New Hyde Park, NY, [2]Cohen Children's Hospital, New Hyde Park, NY, [3]The Feinstein Institute for Medical Research, Manhasset, NY, [4]Feinstein Institute for Medical Research, Manhasset, NY, [5]Feinstein Institute Med Rsch, Manhasset, NY

Background/Purpose: The hallmark of SLE is pathogenic autoantibody (aab) production that is closely associated with organ damage. Anti-dsDNA aab are specific to SLE; their deleterious effects are mediated by direct binding of aab or anti-dsDNA containing immune complexes to tissue antigen and TLRs leading to stimulation of inflammatory pathways. Current therapies include immunosuppressive/cytotoxic drugs with significant potential toxicities. Protease inhibitors (PIs) such as nelfinavir, in addition to direct anti-viral properties, are safe and well-tolerated and have been shown to have immunomodulatory effects. Previous studies have shown that nelfinavir inhibits murine anti-dsDNA aab binding by ELISA. We hypothesized that nelfinavir would similarly inhibit binding of human anti-dsDNA antibodies from SLE subjects, decrease pro-inflammatory cytokine gene expression in stimulated peripheral blood mononuclear cells (PBMC) and inhibit anti-DNA aab binding to mouse glomeruli *ex-vivo*.

Methods: Sera from 4 SLE subjects with elevated serum anti-DNA aab and increased disease activity (SLEDAI of ≥4) were incubated with increasing concentrations of nelfinavir (1 μM, 10 μM, and 100 μM) and added to the ELISA plate followed by spectrophotometric analysis. Healthy PBMC were stimulated with lipopolysaccharide (LPS)(5μg/mL) or high-mobility group box 1 protein (HMGB1)(10μg/mL) and incubated with nelfinavir (1 μM, 10 μM, and 100 μM). Cytokine gene expression (IL-6, IL-12α, TNFα, INFα, IL-1β) and IFN inducible gene expression (IFIT1, MX1, IFI44, and OAS1) were measured in the PBMCs by PCR. The glomerular binding assay was used to measure inhibitory effects of nelfinavir on murine anti-DNA aab binding to glomerular antigen(s) with and without DNase treatment.

Results: Nelfinavir at 1, 10 and 100 μM concentrations resulted in 59%, 60% and 56% inhibition of DNA binding by ELISA respectively (p=0.01, p=0.02, p=0.01). Increasing concentrations of nelfinavir incubated with LPS-stimulated PBMC resulted in decreased gene expression of IL-12α (99%, 99%, and 99%), TNFα (90%, 90%, and 90%), IFNα (99%, 99%, and 99%) and IL1β (64%, 51%, and 24%). IL6 gene expression was decreased with 1 and 10μM concentrations but increased with 100 μM concentration. HMGB1 stimulated PBMC demonstrated increased expression of TNFα, IL12α, IFNα, IL1β and the IFN inducible genes IFIT 1, MX1, IFI44 and OAS1 that was inhibited by nelfinavir with no clear dose response. IL6 gene expression was not increased by HMGB1 although addition of nelfinavir inhibited the expressed levels. The 100 μM concentration of nelfinavir abrogated glomerular binding of murine anti-DNA aab to glomerular antigens.

Conclusion: Nelfinavir inhibits human anti-dsDNA binding to dsDNA and murine anti-DNA aab binding to glomerular antigen. Additionally, nelfinavir reduces expression of pro-inflammatory cytokines and IFN inducible genes in LPS and HMGB-1 stimulated PBMC suggesting that the mechanism for inhibition may be interference with the antigen binding site of the anti-dsDNA aab. We plan to use these measures as biologic outcome measures for a phase IIa clinical trial exploring the *in-vivo* inhibitory effects of nelfinavir in SLE patients.

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Serial Screening Shows That 28% of Systemic Lupus Erythematosus Adult Patients Carry an Underlying Primary Immunodeficiency. Sandro F. Perazzio[1], Reinaldo Salomao[1], Neusa P. Silva[2], Magda Carneiro-Sampaio[3] and Luis Eduardo C. Andrade[4]. [1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil, [4]Universidade Federal de São Paulo, Sao Paulo, Brazil

Background/Purpose: Systemic Lupus Erythematosus (SLE) is known to be associated with deficiency of C1q, C4, and C2. There is high frequency of discoid lesions (2.7%) and SLE (0.5%) in Chronic Granulomatous Disease (CGD). Selective IgA Deficiency (SIgAD) has been associated with juvenile (5.2%) and adult (2.6%) SLE. About 25% of patients with Common Variable Immunodeficiency (CVID) develop autoimmune manifestation, including SLE. Although there are reports of individual primary immunodeficiency (PID) in SLE, there is no systematic study estimating the fraction of SLE adult patients presenting any form of PID. This study aimed to estimate the prevalence of overall PID in a cohort of SLE patients and healthy controls, and to compare the clinical characteristics of the SLE patients with and without PID.

Methods: 300 SLE patients (ACR criteria) and 301 controls (blood donors) underwent clinical examination and were evaluated for total hemolytic complement (CH50), C2, C3, C4A and C4B gene copy number, immunoglobulin isotypes and IgG subclasses, as well as quantification of the oxidative burst in neutrophils. Patients who presented any laboratory indication of PID underwent a novel examination after 60 days for confirmation. Patients with active disease and abnormal results were followed and underwent novel tests after the end of the flare or excluded if no remission was attained up to the end of the study. Cases with low C2 serum levels underwent C2 gene analysis by PCR for confirmation. Those who presented altered unexplained CH50 underwent C1q analysis. Those with C4A and/or C4B low copy number had C4 serum levels determined. Diagnosis of PID was established according to "*2009 International Union of Immunological Societies Expert Committee on PID*".

Results: There were 84 SLE patients (28%) and 10 controls (3.33%) with established diagnosis of PID (p<0.001). SLE patients had a significantly (p<0.01) higher frequency of IgG_2 deficiency (n=37; 12.3%), IgG_3 deficiency (n=24; 8%), IgG_4 deficiency (n=11; 3.6%), and IgM Deficiency (n=24; 8%) as compared to HC (0.3%, 0%, 0%, and 1.6%, respectively). One female patient presented neutrophil oxidative burst profile compatible with CGD gene carrier status (0.33%). There were no cases of C2, C3, C4 or C1q deficiency, CVID, CGD, Hyper-IgM and Hyper-IgE syndromes. Patients with IgG_3 or IgG_4 deficiency presented higher frequency of lupus nephropathy and those with IgM deficiency presented higher prevalence of oral ulcers. Overall PID was not associated with most SLE clinical manifestations, infection rate, immunosuppressant use, age at disease onset, disease duration, comorbidity, SLEDAI and SLICC-DI.

Conclusion: Over one quarter of SLE patients presented some form of PID, largely represented by immunoglobulin deficiency. Due to the important role of immunoglobulins in the clearance of immunocomplex, apoptotic bodies and pathogens, low levels of these components might induce a state of frequent and persistent immunological stimulation, which may foster autoimmunity development in genetically predisposed individuals. Our results suggest that an underlying immunodeficiency state may be involved in the disease pathophysiology in a substantial fraction of SLE patients.

ACR Poster Session A
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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Up-Regulation of A Disintegrin and Metalloprotease with Thrombospondin Type I Repeats-13 Correlates with Ischemic Cerebrovascular Disease in Systemic Lupus Erythematosus Patients Consuelo Lopez de Padilla[1], Molly Hein[1], Cynthia S. Crowson[1], Christopher Choo[2], Abigail B. Green[1], Michelle Petri[3], Hatice Bilgic[4], Emily Baechler Gillespie[4] and Ann M. Reed[1]. [1]Mayo Clinic, Rochester, MN, [2]Rochester, MN, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]University of Minnesota Medical School, Minneapolis, MN

Background/Purpose: ADAMTS13 (A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 motif) belongs to a recently described group of metalloproteinase enzymes which possess proteoglycanase and anti-angiogenic activities. ADAMTS13 limits platelet thrombogenesis through the cleavage of von Willebrand factor (vWF) and has been implicated in the pathogenesis of thrombotic thrombocytopenic purpura (TTP), a potentially fatal complication of systemic lupus erythematosus (SLE) and other rheumatic diseases. The pathogenic role of ADAMTS13 in TTP associated to SLE has been investigated; however, although TTP and SLE may have overlapping clinical features, they are distinct entities. We investigated ADAMTS13 messenger RNA (mRNA) levels as a biomarker of disease features in SLE.

Methods: Here, we measured and compared mRNA levels of ADAMTS13 in peripheral blood cells in 309 SLE and 23 healthy subjects by whole-genome microarray using the Illumina Bead Array Platform. We examined correlations of ADAMTS13 mRNA expression levels with clinical features, laboratory parameters and disease activity (systemic lupus erythematosus disease activity index; SLEDAI). Comparisons of mRNA levels and their association with distinct clinical characteristics were assessed using the rank sum test and Spearman rank correlation analysis.

Results: The results showed that the median of ADAMTS13 mRNA expression levels were significantly increased in blood cells of SLE patients (median, 121.3 [25th, 75th quartile, 116.8, 126.4] compared to healthy controls (median, 119.1 [25th, 75th quartile, 114.8, 121.3] (*p=0.028*). No significant differences were found between ADAMTS13 mRNA levels and symptoms associated with the ACR criteria for classification of SLE. Notably, mRNA copy number levels of ADAMTS13 were significantly increased in SLE patients with a history of stroke (n= 11) (median, 126.5, [25th, 75th quartile, 121.3, 129.2]) or Transient Ischemic Attack (TIA) (n= 5) (median, 126.6, [25th, 75th quartile, 126.3, 137.8]) compared to those without stroke or TIA (median, 121.0, [25th, 75th quartile, 116.6, 126.3]; (median, 121.6, [25th, 75th quartile, 116.6, 127.4], respectively) (*p=0.015*; *p=0.024*; respectively). We next sought to compare the mRNA ADAMTS13 levels in the 26 of 309 SLE patients with coronary artery disease (CAD). No significant differences were observed between ADAMTS13 mRNA levels in SLE patients with CAD compared to patients without CAD (*p*=0.35). Similarly, ADAMTS13 expression was not found to be correlated with SLE disease activity.

Conclusion: These results indicate that increased expression of ADAMTS13 mRNA in blood cells is associated with presence of ischemic cerebrovascular disease (stroke and TIA) in SLE patients and suggests a potential role for ADAMTS13 in the pathogenesis of ischemic cerebrovascular disease in SLE patients.

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The Small Molecule Activator to ACE2 Prevents the Inhibition of ACE2 Activity by Autoantibodies. Shiori Haga[1], Yuko Takahashi[2], Yukihito Ishizaka[1] and Akio Mimori[2]. [1]National Center for Global Health and Medicine, Research Institute, Tokyo, Japan, [2]National Center for Global Health and Medicine, Tokyo, Japan

Background/Purpose: Angiotensin-converting enzyme 2 (ACE2) is a member of renin-angiotensin system that plays a critical role in regulating blood pressure and cardiovascular function. It is a homologue of ACE and converts angiotensin (Ang) II into Ang-(1–7), which has the vasoprotective effects. Recent studies have demonstrated the therapeutic effects of ACE2 activation by a synthetic molecule or by forced expression of *ace2* cDNA in experimental pulmonary hypertension models. We recently reported that inhibitory anti-ACE2 antibodies were detected in patients with autoimmune diseases (AID) with constrictive vasculopathy, pulmonary arterial hypertension, or persistent digital ischemia. We investigate whether 1-[(2-dimethylamino) ethylamino]-4 (hydroxymethyl)-7- [(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one (XNT), ACE2 activator identified by Ferreria *et. al.*[1]) overcomes on the inhibitory effect of anti-ACE2 antibodies in AID patients.

Methods: Immunoglobulin G was purified from sera of 13 vasculopathy and 11 non-vasculopathy patients with protein G sepharose beads. To evaluate the inhibitory effect against ACE2 by anti-ACE2 antibodies, we performed the measurement of ACE2 activity. ACE2 activity was monitored with fluorescent substrate following pre-treatment of ACE2 and purified IgG.

Moreover, the interacting alternation of between ACE2 and IgG by XNT was examined by ELISA and western blot analysis.

Results: ACE2 activity was reduced by IgG purified from sera of 12 of 13 AID patients (92.3 %) with vasculopathy, but not that of 10 of 11 non-vasculopathy patients (90.9 %) and healthy subjects. Furthermore, in 2 of 12 samples retained ACE2 inhibitory effects, XNT overcame the inhibitory effects when added to IgG-ACE2 complex mixture. Moreover, XNT cancelled the binding of anti-ACE2 to ACE2.

Conclusion: The ACE2 activator, XNT increased ACE2 activity suppressed by IgG of AID patients. Our results suggested that XNT cancelled antigen-antibody reaction inducing a dynamic conformation change of ACE2. We propose that it is important to identify the activator which has the inducible capability of structural change against ACE2 and such compound is sufficiently expectable as candidate of therapeutic agent.

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Abnormal Neutrophil Development in Human Systemic Lupus Erythematosus. Namrata Singh[1], Mariana J. Kaplan[2], Philip L. Cohen[1] and Michael F. Denny[1]. [1]Temple University, Philadelphia, PA, [2]University of Michigan, Ann Arbor, MI

Background/Purpose: Recent research has increased the appreciation of the contributions of neutrophils to systemic lupus erythematosus (SLE). An abnormal circulating pool of granulocytes has been associated with certain disease manifestations, and we previously developed techniques to isolate these low-density granulocytes (LDGs) from the blood of SLE patients. While LDGs express surface markers consistent with mature neutrophils, their nuclear morphology suggests an immature phenotype. This pattern of mature neutrophils possessing an abnormal nuclear morphology is frequently observed in patients with alterations in granulocyte development, suggesting that neutrophil differentiaton may be disrupted in SLE patients.

Methods: Because disrupted neutrophil development is frequently associated with genomic alterations, we compared genomic alterations in autologous pairs of LDGs and normal-density neutrophils. Somatic alterations were detected by cytogenetic microarray analysis of genomic DNA extracted from LDGs and neutrophils from 13 female SLE patients, as well as neutrophil samples from 9 age-matched healthy female donors. The Affymetrix 2.7M Cytogenetics Microarray chip was used to assess both copy number state and heterozygosity across the genome. For each SLE patient we compared genomic DNA from LDGs to DNA from autologous neutrophils. Variations present in both samples are inherited, while alterations found exclusively in the LDG sample represent the acquisition of additional somatic alterations.

Results: The SLE normal density neutrophils and healthy donor neutrophils had similar levels of copy number variations, most of which corresponded to known variants. In contrast, the LDG samples from SLE patietns had a two-fold increase in copy number alterations relative to either autologous normal-density neutrophils or healthy controls. The elevation in genomic copy number variations in the LDG samples included an increased incidence of both duplications and deletions. These LDG somatic alterations were found in 6 of the 13 patients. Thus, the LDGs isolated from a subset of SLE patients displayed evidence of genomic instability as determined by alterations in copy number. Moreover, these genomic alterations occurred preferentially on certain chromosomes, as opposed to random distribution across the genome. No correlation between genomic instability and the use of immunosuppressive drugs, disease activity or manifestations was observed.

Conclusion: In a subset of SLE patients, the LDGs show an elevated level of genomic alterations that is consistent with genetic damage or instability. These alterations occur in discrete chromosomal intervals, suggesting these regions reflect an increased propensity for damage or that the alteration confers a selective advantage to the affected cell. Whether the inflammatory environment present in SLE patients promotes these genetic alterations, or whether it is an intrinsic property of the SLE genome, remains to be determined.

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Co-Localization of C-Reactive Protein, Immunoglobulin G and Complement in Renal Subendothelial Immune Deposits of Proliferative Lupus Nephritis Detected Using Immunogold Electron Microscopy. Christopher Sjöwall[1], Anders I. Olin[2], Thomas Skogh[3], Jonas Wetterö[3], Mattias Mörgelin[2], Ola Nived[4], Gunnar Sturfelt[5] and Anders A. Bengtsson[5]. [1]Linkoping University, Linkoping, Sweden, [2]Infection Medicine, Department of Clinical Sciences, Lund University, Lund, Sweden, Lund, Sweden, [3]Linköping University, Linköping, Sweden, [4]University Hospital Lund, Lund, Sweden, [5]Department of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden

Background/Purpose: The pattern recognition molecules C-reactive protein (CRP) and complement protein 1q (C1q) are pivotal parts of the innate immune system and display relevant biological functions in the pathogenesis of systemic lupus erythematosus (SLE). Circulating autoantibodies directed against CRP and C1q are frequently found in SLE patients with active disease, especially those with lupus nephritis, and raised serum autoantibody levels reportedly relate to both disease activity and prognosis. This study was performed to assess glomerular localization of IgG, CRP and C1q as a reflection of nephritogenic immune complexes (ICs) in patients with active diffuse proliferative lupus nephritis.

Methods: Renal specimens from five well-characterized patients with active diffuse proliferative lupus nephritis were examined by immunogold electron microscopy to pinpoint glomerular localization of CRP, C1q, C3c and double-stranded (ds) DNA in relation to IgG. Renal biopsies from patients with Henoch-Schönleins purpura, pauci-immune nephritis and renal cancer served as controls. In addition, serum IgG class antibodies against CRP, C1q, and nucleosomes were analyzed by ELISA in the lupus nephritis patients before, during and after renal flares. Informed consent was obtained from all subjects and the research protocol was approved by the Regional Ethics Committee in Lund (H4 207/2005).

Results: Tissue CRP, C1q, C3c and dsDNA were found to co-localize with IgG in renal subendothelial electron dense deposits. Disease controls only showed negligible staining for the tissue markers as compared with lupus nephritis and none had detectable anti-C1q, anti-CRP or anti-nucleosome antibodies. All SLE patients had circulating anti-nucleosome antibodies, and four of five were anti-CRP, anti-dsDNA, and anti-C1q antibody positive at the time of biopsy/flare. Using accumulated data (pre–post nephritis), one could observe that anti-nucleosome and anti-C1q antibody levels were more interrelated ($r=0.42$, $p=0.046$) than were the levels of anti-CRP versus anti-C1q or anti-nucleosome antibodies, respectively.

Conclusion: The results support the notion of a pathogenic role not only for antibodies directed against dsDNA, but also for anti-CRP and anti-C1q in lupus nephritis. The glomerular ICs may have been generated by deposition of circulating ICs or by *in situ* IC formation. The demonstrated correlation between anti-C1q and anti-nucleosome antibodies, but not between these autoantibodies and anti-CRP, indicate that the latter may reflect an independent role in the pathogenesis of lupus nephritis.

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Increased C1q, C4 and C3 Deposition On Platelets in Patients with Systemic Lupus Erythematosus – A Possible Link to Venous Thrombosis? Christian Lood[1], Sam Eriksson[1], Birgitta Gullstrand[2], Andreas Jönsen[1], Gunnar Sturfelt[1], Lennart Truedsson[2] and Anders A. Bengtsson[1]. [1]Department of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [2]Department of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund, Sweden

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased risk of developing vascular diseases (VD) such as myocardial infarction, stroke and venous thrombosis, which can only partly be explained by traditional risk factors. The role of platelets in this process has not been extensively studied. Platelet activation support complement binding to the platelet surface, and increased C4d has been seen on platelets in SLE patients as well as in non-rheumatic patients with stroke. In this study we investigated *in vivo* platelet deposition of the classical complement pathway components C1q, C4d and C3d in relation to VD in SLE patients. Furthermore, the ability of serum to support *in vitro* complement deposition on fixed heterologous platelets was analyzed.

Methods: Blood from 69 SLE patients and age- and sex-matched healthy individuals was collected in sodium-citrate tubes and platelets isolated by centrifugation. Complement deposition on platelets was detected by flow cytometry.

Results: We could demonstrate that SLE patients had increased C1q, C3d and C4d deposition on platelets as compared to healthy controls (p<0.0001). SLE patients with a history of venous thrombosis had increased complement deposition on platelets as compared to SLE patients without this manifestation (p<0.05). *In vitro* studies demonstrated that serum from patients with lupus anticoagulant, venous thrombosis or the antiphospholipid antibody syndrome supported increased platelet C4d deposition *in vitro* as compared to SLE patients without these manifestations (p<0.05). Our data support the hypothesis that platelet activation and the subsequent complement deposition on platelets are central in development of venous thrombosis in SLE.

Conclusion: Altogether we suggest that complement deposition on platelets could reflect important pathogenetic events related to the development of venous thrombosis in SLE and might be used as a marker for venous thrombosis in SLE.

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The Clinical Significance and Expression of P2X7 Purinergic Receptor in Peripheral Blood from Patients with New-Oneset Systemic Lupus Erythematosus. Xiangpei Li, Meiyun Wang, Jinhui Tao, Xiaomei Li and Ning Yu. Anhui Medical University Affiliated Provincial Hospital, Hefei, Anhui, China

Background/Purpose: P2X7 purinergic receptor (P2X7R) is encoded by a gene within the human SLE locus SLEB4. Extracellular adenosine triphosphate (ATP) regulates inflammatory cells by activation this pro-inflammation receptor. Our aim was to describe the expression of the P2X7R on peripheral blood lymphocytes in patients with SLE and explore its significance in the pathogenesis and clinical features of SLE.

Methods: Surface expression of P2X7R on total lymphocytes, CD4+T cells, and CD19+B cell in peripheral blood from 29 SLE patients were determined by flow cytometry. As controls, 28 age and sex-matched healthy subjects (HC) were used. ELISA was performed to detect P2X7R-related serum cytokines IL-1β, IL-6, TNF-α level.

Results: Compared to HC, SLE patients had higher expression of P2X7R on CD4+ T cells (2.21(3.55) *vs* 0.89(1.15) *p*=0.015) and CD19+B cells (11.53(20.01) *vs* 6.66(6.27), *p*=0.037). The same result was also observed in total lymphocytes (1.85(5.75) *vs* 1.19(0.74), *p*=0.082), though it was not statistically significant. As reported before, increase of IL-1β, IL-6 and TNF-α were observed in patients with SLE. Meanwhile, the percentage of P2X7R+ cells in lymphocytes was positively correlated with the serum IL-6 level in SLE patients(*r*=0.449,*p*=0.015). Regarding the clinical manifestations, patients with arthritis showed higher expression of P2X7R on total lymphocytes compared to patients without arthritis(*p*=0.006); Neuropsychiatric lupus (NPSLE) patients had increased P2X7R expression on CD19+B cells. In addition, the percentage of P2X7R+ cells in total lymphocytes and CD19+B cell were both positively correlated with the SLEDAI score (r=0.374, p=0.00 5; r=0.274,p=0.041) and so was that in total lymphocytes with anti-β2GP1.

Conclusion: These preliminary results suggest that an increased expression of P2X7R may contribute to the flare and organ damage of SLE by inducing the secretion of IL-6, which suggests that therapeutic targeting of P2X7Rmight be beneficial for treatment of human SLE.

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Estrogen Upregulates Interleukin-21 Production of Clusters of Differentiation 4 Positive T Lymphocytes in Patients with Systemic Lupus Erythematosus. Jennifer Lee[1], Daejun Kim[1], Jae Ho Lee[1], Seung Min Jung[1], Mi-La Cho[2], Seung-Ki Kwok[1], Ji Hyeon Ju[1], Kyung-Su Park[1], Sung-Hwan Park[1] and Ho-Youn Kim[1]. [1]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]Rheumatic research center, Catholic University of Korea, Seoul, South Korea

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease in which various organs and tissues are damaged through abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition. As the majority of SLE patients are women of child-bearing age, estrogen has been suggested to play an important role in the pathogenesis of SLE. One of the proposed roles of estrogen is to induce B cell activation culminating in increased autoantibody production. IL-21, a common-γ chain cytokine, has been shown to be crucial in the differentiation of activated B cells into plasma cells. Based on these concepts, we hypothesized that estrogen contributes to pathogenesis of SLE via IL-21 dependent pathway and investigated the effect of estrogen on the production of IL-21 by T cells and subsequent B cell activation in SLE patients.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from peripheral blood of 23 SLE patients and 16 healthy controls. CD4+ T cells, non CD4+ T cells and B cells were isolated using microbeads. Isolated cells were treated with 17-β estradiol at various concentrations for 48hrs (up to 72hrs in some experiments). The expression of IL-21 and its receptor was assessed by measuring the level of protein and mRNA using ELISA and RT-PCR, respectively. The level of immunoglobulin G secreted by activated B cells were measured with specific ELISA.

Results: The expression of IL-21 and its receptor in serum, PBMCs, and CD4+ T cells were higher in the patients with SLE compared to healthy controls. Exposure of CD4+ T cells from SLE patients to 17-β estradiol leads to a dose-and time-dependent increase in the IL-21 expression. The increase was abolished in the presence of MAP kinase (MEK, p38, JNK) inhibitors. B cells of healthy controls showed an increased antibody production when they were co-cultured with estrogen treated CD4+ T cells of patients with SLE. Treatment with anti-IL-21 antibody abrogated the increased antibody production of the co-culture systems, suggesting the increase was mediated by IL-21 dependent manner.

Conclusion: This study revealed the association of estrogen and IL-21 in the pathogenesis of SLE. Estrogen upregulates IL-21 expression of CD4+ T cells via MAPK dependent pathways in SLE patients, which in turn induces increased antibody production by B cells.

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Cytokines and Their Relation to Autoantibodies Before Disease Onset in Systemic Lupus Erythematosus. Catharina Eriksson[1] and Solbritt Rantapää Dahlqvist[2]. [1]Department of Clinical Immunology/clinical microbiology, Umeå, Sweden, [2]Umeå University Hospital, Umeå, Sweden

Background/Purpose: Cytokines and autoantibodies are involved in the pathogenesis of systemic lupus erythematosus (SLE). The presence of autoantibodies preceding disease onset by years has been reported both in patients with SLE and in other rheumatic diseases, and changes in cytokine levels have been shown before disease onset in rheumatoid arthritis. The cytokine group interferons and interferon-related molecules are considered to be of importance in SLE pathogenesis. Therefore, we intended to measure cytokine levels, and relate them to autoantibodies, in a northern European population before the onset of symptoms of SLE.

Methods: The register of patients fulfilling the American College of Rheumatology criteria for SLE and with a given date of the onset of symptoms was coanalysed with the register of the Medical Biobank, Umeå, Sweden. Thirty-six patients were identified as having donated blood samples prior to symptom onset. A nested case-control study (1:4) was performed with 144 age- and sex-matched controls identified from the Medical Biobank register (Umeå, Sweden). The cytokines interferon alpha (IFN)-α, interleukin (IL)-4, IL-9, IL-10, interferon inducible protein 10 (CXCL10/IP-10) and monocyte chemotactic protein-1 (CCL2/MCP-1), were analysed before and after onset of symptoms of SLE using a multiplex kit from Millipore on a Bio-Plex Array Reader (Luminex[200]). The associations of these cytokines to autoantibodies (ANA, ENA, anti-dsDNA och anti-histone antibodies), from the same blood samples, before disease onset was estimated.

Results: The IP-10 levels were significantly higher in the individuals who later developed SLE ("prepatients") than in the controls (median value ±IQR) 372pg/mL±293 versus 253pg/mL±192. IFN-α and IP-10 were strongly correlated (p<0.01) and IP-10 had the most obvious association to autoantibodies, being significantly higher in ANA, SSA and Jo-1 positive individuals (p=0.03, 0.01 and 0.03, respectively) and also to autoantibody

positivity over all (p<0.001). MCP-1 was related to SSA and SSB positivity (p=0.009 and 0.047) and with antibody positivity over all (p=0.015), IFN-α with anti-SSB and antibody positivity over all (p=0.027 and 0.025), IL-4 to anti-dsDNA (p=0.019) and IL-10 to anti-RNP positivity (p=0.041). IL-10, IP-10 and MCP-1 increased significantly between the pre-patient sample, 7.44 pg/mL ±8.93, 372 pg/mL± 293 and 278pg/mL ± 475 respectively, and after SLE was diagnosed, 12.3 pg/mL±20.1, 666 pg/mL± 602 and 1098 pg/mL± 765, respectively (p=0.029, <0.0001 and <0.0001 respectively). The cytokines showed no significant changes in relation to time before disease onset or to the debut SLE-symptom.

Conclusion: IP-10, MCP-1 and IFN-α had the clearest relationships with autoantibody formation before disease onset of SLE. Since IFNs and IP-10 were strongly correlated with each other these findings support previous theories that the IFN-system is important in the early SLE pathogenesis and autoantibody formation.

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Leukadherin 1, a CR3 Mimetic, Negatively Regulates Toll Like Receptor (TLR) Dependent Inflammatory Responses via Degradation of an Adaptor Protein. Kristen Lee[1], Joanne H. Reed[1], Vineet Gupta[2], Tejaskumar Patel[1], Jill P. Buyon[3] and Robert M. Clancy[1]. [1]New York University School of Medicine, New York, NY, [2]Division of Nephrology and Hypertension, Department of Medicine, University of Miami, Miami, FL 33136, U.S.A., Miami, FL, [3]NYU School of Medicine, New York, NY

Background/Purpose: Systemic Lupus Erythematosus is characterized by continuous and cyclic stimulation of the innate immune system by endogenous nucleic acids. Immune complexes of Ro60, ssRNA and anti-Ro60 have been shown to engage TLR7 and promote secretion of inflammatory mediators. Recent evidence demonstrates that activation of the integrin, CR3, negatively regulates TLR signaling in dendritic cells. Leukoadhedrin (LA1), a novel small molecule, allosterically activates CR3 and suppresses inflammation. This study was initiated to molecularly address whether, and by what mechanism, LA1 downregulates ssRNA-induced TLR7 signaling in macrophages.

Methods: THP-1 cells and PBMC derived CD14+ macrophages from healthy human donors were incubated with TLR7/8 agonists (hY3 (2.5 ug) or R848 (1 uM)) with and without LA1 (7.5μM) added 30 minutes pre or post stimulation. Quantification of TNFα secretion, the readout of TLR7/8 activation, was assessed by ELISA and MyD88 was evaluated by immunoblot.

Results: Exposure of healthy human macrophages to hY3 resulted in a significant release of TNFα compared to unstimulated cells (348±45 vs 4±2 pg/ml, respectively P=0.0001, N=9). Stimulated TNFα release was markedly decreased by pre-treatment with LA1 but not post-treatment (53±47 and 1275±467 pg/ml, respectively, P=0.035, N=6). In parallel with the results for isolated macrophages, TNFα was induced after exposure of THP-1 macrophages to hY3 (315±59 vs 15±13 pg/ml, stimulated vs. unstimulated respectively P=0.0015, N=7). Pre-treatment with LA1 profoundly decreased hY3-induced secretion (18±9 pg/ml, P=0.0013 vs hY3) and exceeded the inhibition observed with a TLR7 inhibitor (117±16 pg/ml, P=0.004 vs hY3). Moreover, R848 stimulated TNFα release was also significantly decreased by pre-treatment with LA1 (1113±218 vs 55±47 pg/ml, respectively P=0.0006, N=11). To identify the potential mechanism for downregulation of TLR7 signaling, adaptor protein degradation was studied. LA1-mediated inhibition of both hY3 and R848 stimulated TNFα release was accompanied by degradation of MyD88 (immunoblot, N=3 for each stimuli), an effect not seen with a TLR7 antagonist, oligonucleotide IRS661 (inhibits at level of TLR ligation, not downstream). Reprobe of blot demonstrated that the expression of actin did not vary with treatment condition. Evidence against cytotoxcity of LA1 was provided by the absence of LDH in culture supernatants. The *ITGAM*assignment of THP-1 cells and all the donor macrophages was homozygous common at rs1143679 supporting that the inhibitory effect of LA1 was applicable to the dominant genotype.

Conclusion: The data suggest that activation of CR3 downregulates macrophage TLR7 signalling via degradation of MyD88. These findings may be particularly relevant in disease states such as SLE and neonatal lupus in which inflammatory cells are triggered by ssRNA containing immune complexes.

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Interferon-Alpha Impairs the Survival and Function of Circulating Angiogenic Cells *in Vitro*: A Model of Failed Endothelial Repair in SLE. John A. Reynolds[1], David W. Ray[2], Terence O'Neill[2], M. Yvonne Alexander[1] and Ian N. Bruce[3]. [1]The University of Manchester, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom

Background/Purpose: Patients with Systemic Lupus Erythematosus have an increased risk of cardiovascular disease (CVD). No specific targeted therapies for CVD in lupus exist and there are no *in vitro* models to study potential novel agents. Endothelial dysfunction, the earliest stage of vascular damage, is associated with interferon-alpha (IFNα) expression. It has been proposed that IFNα may act by impairing endothelial repair mechanisms. When compared to healthy controls, lupus patients have fewer circulating angiogenic cells (CAC) and endothelial progenitor cells (EPCs). Mixed EPC/CAC populations have been shown to be sensitive to IFNα, resulting in apoptosis and change in phenotype. We aimed to investigate the effects of IFNα2b on an *in vitro* model of angiogenesis/vascular repair.

Methods: Peripheral blood mononuclear cells were obtained from healthy subjects and cultured on human fibronectin in endothelial growth media. Myeloid phenotype was confirmed by LDL uptake/lectin binding and expression of cell surface markers by RT-PCR. Cell survival in response to IFNα2b (0.01–10ng/ml) was determined by the number of LDL-uptake-positive cells at 7 days. An angiogenesis assay was used to study CAC function. Supernatant from CACs cultured for 7 days ± 10ng/ml IFNα2b was added to human aortic endothelial cells cultured on growth factor reduced Matrigel. Tubule formation was assessed at 14 hours using an automated computer algorithm. Mean values of the calculated network parameters were compared using 2-tailed t tests.

Results: CACs expressed markers of both endothelial (CD31) and myeloid lineage (CD14, CD45). In addition, CACs strongly expressed the macrophage markers CD68, CD163 and CD206 suggesting an alternatively-activated (M2) macrophage phenotype. IFNα2b significantly reduced the number of CACs at day 7 in a dose-dependent manner (r^2= −0.769, p<0.0001).

In co-culture with endothelial cells on Matrigel, CACs co-localised to the endothelial tubules but did not form tubule networks alone. CAC supernatant significantly increased the density of the tubule network when in terms of: total pixel area (27781 vs 36283, p=0.0065), number of branches (340.2 vs 510.6, p=0.0434), number of junctions (162.4 vs 241.1, p=0.0104) and number of closed loops within the network (21.8 vs 38.3, p=0.005). IFNα2b significantly reduced the number of closed loops (38.2 vs 24.1, p=0.0094). All other network parameters were reduced by IFNα2b but did not reach statistical significance.

Conclusion: CACs are of myeloid lineage and have angiogenic capacity *in vitro*. CAC supernatant contains potent angiogenic factors which augment endothelial tubule networks. IFNα2b dramatically reduces the survival of CACs *in vitro*, resulting in reduced tubule network formation and may be a mechanism by which IFNα promotes vascular damage in SLE. Quantification of the angiogenic nature of CACs and the effects of IFNα2b, using a tubule formation assay, offers a potential *in vitro* model in which to study the effects of novel vasculoprotective agents in this patient population.

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Markers of Nitric Oxide and Hydroxyl Radical Formation Are Increased in Proliferative Lupus Nephritis and May Emanate From Increased Nitric Oxide Synthase and NADPH Oxidase Production and Reduced Endothelial Nitric Oxide Synthase-Derived NO Scavenging. Jim Oates, Ahmad Mashmoushi, Thomas Fleury, Ann Hofbauer and Gary S. Gilkeson. Medical University of South Carolina, Charleston, SC

Background/Purpose: The role of redox regulation of cell function in the different International Society of Nephrology/Renal Pathology Society (ISN/RPS) classes of lupus nephritis (LN) is not known. Different reactive intermediate (RI) species lead to differential changes in proteins that are important in transcriptional regulation and signaling. RIs are unstable species that can be measured indirectly by their ability to modify protein tyrosines (Tyr) and phenylalanines to form nitroTyr (NTyr, via peroxynitrite), metaTyr (mTyr, via hydroxyl radicals (OH·), usually

metabolized from SO and H_2O_2), and chloroTyr (ClTyr, via HOCl). This study was designed to address the hypothesis that different classes of LN have distinct profiles of RI production.

Methods: 62 patients with active LN had a renal biopsy with ISN/RPS classification at screening. Serum and urine samples were collected before induction therapy for active LN. Serum (n=62) was analyzed for nitrate and nitrite (NO_X, a marker of nitric oxide (NO) production) by chemiluminescence analyzer. In a random subset of patients (n=34), serum proteins were analyzed for NTyr, mTyr, and ClTyr by HPLC with electrochemical detection and reported as the ratio of modified to unmodified Tyr * 1000. Snap frozen murine renal cortical tissue lysates from MRL/lpr and MRL/lpr NOS3 −/− (endothelial NO synthase or eNOS) mice with active proliferative LN were analyzed for superoxide (SO) production by lucigenen assay with and without inhibitors of NOS and NADPH oxidase. **Results** were normalized to untreated MRL/lpr wildtype control tissue. Groups were compared by Wilcoxen rank sum or Student t test, and $p < 0.05$ was significant.

Results: Those with class IV LN had significantly higher levels of serum NO_X. mTyr was elevated in those with class III and IV LN. In class V LN, NTyr and ClTyr were increased (differences not significant). SO production was increased (to 160%) in MRL/lpr NOS3−/− kidney cortex. This increase was reduced by both L-NMMA (a nonspecific NO synthase inhibitor, 70% of control) and DPI (a nonspecific NADPH oxidase inhibitor, 40% of control).

Table. Levels of markers of RI production in patients with LN by ISN/RPS class

ISN/RPS Class	nitrate + nitrite	mTyr/Tyr*1000	ClTyr/Tyr*1000	Ntyr/Tyr*1000
Pure I	39 (n = 1)	0.6 (n = 1)	0.1 (n = 1)	0.2 (n = 1)
Pure II	30.2 ± 7.2 (n = 9)	0.2 ± 0.1 (n = 4)	0.1 ± 0 (n = 4)	0.3 ± 0.1 (n = 4)
Pure and mixed III	30.4 ± 5.3 (n = 29)	**9 ± 5.5 (n = 17)**	0.1 ± 0 (n = 18)	0.7 ± 0.3 (n = 18)
Pure and mixed IV	**59.6 ± 17.8 (n = 12)**	**7.8 ± 4.2 (n = 8)**	0.6 ± 0.3 (n = 9)	1.1 ± 0.3 (n = 9)
Pure V	24.9 ± 6.3 (n = 10)	0.7 ± 0.4 (n = 4)	13.9 ± 13.7 (n = 5)	21.2 ± 21 (n = 5)

Values reported as means ± standard error. Bolded values are significantly different from other classes.

Conclusion: These results suggest increased NOS activity in class IV LN. In those with proliferative LN, increased OH· production or reduced antioxidant scavenging appears to be occurring. OH· can indirectly come from NADPH oxidase and NO synthase. Higher levels of SO in MRL/lpr cortical tissue from NOS3 −/− mice suggests that eNOS-derived NO can scavenge SO. Reduction of SO with both a NOS inhibitor and an NADPH oxidase inhibitor suggests that both enzymes produce SO, perhaps in a synergistic fashion, in proliferative LN. Therefore, effective therapy for SO-mediated redox signaling in proliferative LN may need to induce increases in the scavenging effect of eNOS-derived NO or target SO directly with scavengers. Myeloperoxidase (forms NTyr and ClTyr) may be an important enzyme target in class V disease.

Disclosure: **J. Oates**, None; **A. Mashmoushi**, None; **T. Fleury**, None; **A. Hofbauer**, None; **G. S. Gilkeson**, None.

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Serum Anti *N*-Methyl-D-Aspartate Receptor Subunit 1 Antibodies Are Elevated in SLE. Ogawa Eisuke, Nagai Tatsuo, Arinuma Yoshiyuki and Hirohata Shunsei. Kitasato University School of Medicine, Kanagawa, Japan

Background/Purpose: Previous studies have demonstrated that the presence of autoantibodies against *N*-methyl-D-aspartate (NMDA) receptor subunit 2 (NR2) is closely associated with brain damages leading to the development of diffuse neuropsychiatric SLE (NP-SLE). NR1 is another subunit forming functional NMDA receptor with NR2. However, it is not clear whether anti-NR1 antibodies (anti-NR1) might be expressed in SLE. Nor has their role in the pathogenesis in NP-SLE been clarified. The present study therefore explored the serum levels of anti-NR1 in SLE.

Methods: Sera were obtained from 108 patients with SLE, 36 various rheumatic diseases other than SLE (7 patients with RA, 8 with Behcet's disease, 3 with vasculitis syndromes, 6 with SSc, 6 with PM/DM and 6 with MCTD) and 91 healthy individuals. Among the 108 SLE patients, 67 showed neuropsychiatric manifestations. IgG anti-NR1 antibodies were measured by ELISA, using the N-terminal 100-amino acid of murine NR1, which is more than 90% homologous to human NR1. The results were reported as arbitrary units determined using a positive serum. Some sera positive for anti-NR1 were further analyzed for the fine epitopes they recognize, using 4 different preparations of synthetic 25

amino-acid sequences within the N-terminal 100 amino-acid sequence of human NR1.

Results: The mean ± SEM values for serum anti-NR1 in 91 healthy individuals were 4.48 ± 2.19 units/ml. Serum anti-NR1 levels were significantly elevated in SLE (52.18 ± 15.22 units/ml) compared with healthy individuals or with non-SLE rheumatic diseases (4.50 ± 2.23 units/ml). There was no significant difference in serum anti-NR1 between non-SLE rheumatic diseases and healthy individuals. Of note, serum anti-NR1 were significantly higher in NP-SLE (74.60 ± 23.96 units/ml) than those in SLE without neuropsychiatric manifestations ((15.54 ± 5.62 units/ml) (p=0.044)). Finally, anti-NR1 bound most efficiently to the sequence of amino acids between position 57 and position 81 from the N-terminus of human NR1.
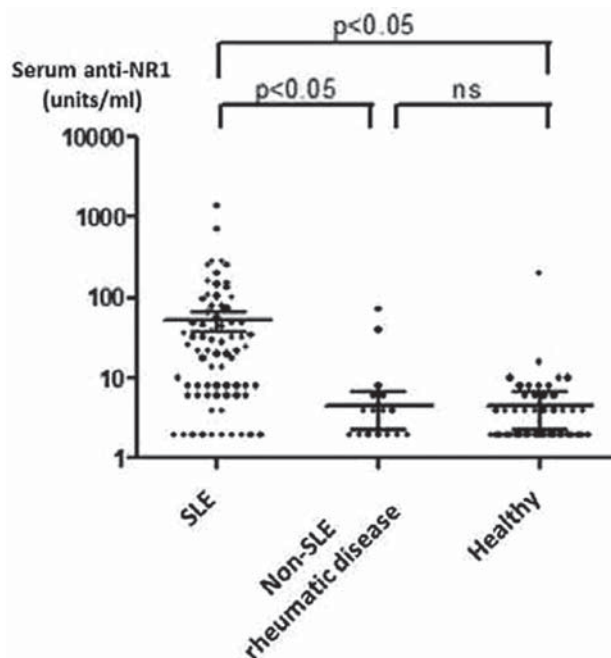
Conclusion: The results indicate that anti-NR1 were specifically elevated in SLE patients. Moreover, the data also suggest that anti-NR1 might be involved in the pathogenesis of NP-SLE, presumably through transudation through blood-brain barrier into CNS.

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Prolidase Deficiency Induces Antibodies to Sm, Ro60 and Double Stranded DNA. Biji T. Kurien[1], Anil D'souza[2], Skyler P. Dillon[1], Benjamin F. Bruner[3], Timothy Gross[4], Judith A. James[5], Ira N. Targoff[6], Jacen S. Maier-Moore[1], Isaac T.W. Harley[7], Heng Wang[8] and Robert H. Scofield[1]. [1]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Harding University, Searcy, AR, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [6]Oklahoma Medical Research Foun, Oklahoma City, OK, [7]Cincinnati Children's Hospital Research Foundation, Cincinnati, OH, [8]Das Deutsch Center Clinic for Special Needs Children, Middlefield, OH

Background/Purpose: Prolidase is a ubiquitous enzyme found in the cytoplasm. The enzyme specifically cleaves dipeptides containing C-terminal proline or hydroxyproline, in one of the last steps of collagen metabolism. Prolidase deficiency is a rare inborn error of metabolism characterized by the secretion of dipeptides in the urine and a variety of clinical manifestations. Only about 50 patients have been reported with the deficiency, of which approximately 10% have systemic lupus erythematosus.

Methods: A large extended Amish pedigree, having four patients deficient for prolidase, three individuals with heterozygous prolidase activity and eight unaffected individuals, was studied for lupus-associated autoimmunity. Prolidase genetics and enzyme activity were confirmed. Antinuclear antibody was measured using indirect immunofluorescence. Antibodies against extractable nuclear antigens were determined by double immunodiffusion, immunoprecipitation, and BioRad 2200 multiplex bead assay. Serum C1q levels were determined by ELISA.

Results: Two of the four homozygous prolidase deficient patients had a positive ANA. One had anti-dsDNA antibodies, while another had precipitating anti-Ro60 antibodies. Three of the four patients had anti-Sm and anti-chromatin by the BioRad 2200 multiplex bead assay. One of the three heterozygous subjects had a positive ANA and immunoprecipitation of a 75,000 MW protein. Serum C1q levels were not changed in the prolidase deficient patients. The unaffected controls had normal prolidase activity and were negative for autoantibodies.

Conclusion: Prolidase deficiency leads to a loss of immune tolerance to lupus-associated autoantigens even without clinical systemic lupus erythematosus.

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Differences in the SLE Clinical Phenotype by Age of Diagnosis. T. Clark Powell[1], Elizabeth E. Brown on behalf of PROFILE[1], Gerald McGwin Jr.[1], Luis M. Vila[2], Yesenia C. Santiago-Casas[3], Michelle Petri[4], Rosalind Ramsey-Goldman[5], John D. Reveille[6], Sergio Duran[7], Sergio M.A. Toloza[8], Robin L. Brey[9], Agustin Escalante[10], Randy Q. Cron[11], Robert P. Kimberly on behalf of PROFILE investigators[12] and Graciela S. Alarcon[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of PuertoRico Medical Sciences Campus, San Juan, PR, [3]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Univ of Texas Health Science Center at Houston, Houston, TX, [7]UIECD, Guadalajara, Mexico, Guadalajara, Mexico, [8]Hospital San Juan Bautista, Catamarca, Argentina, [9]UTHSCSA, San Antonio, TX, [10]University of Texas Health Science Center at San Antonio, San Antonio, TX, [11]Univ of Alabama-Birmingham, Birmingham, AL, [12]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease that is characterized by the presence of antinuclear autoantibodies, complement activation and the formation and deposition of immune complexes resulting in multisystem organ damage. Trends in SLE vary by age, with pediatric SLE (pedSLE) patients presenting with more active, severe and rapidly progressive disease than adult SLE patients. However, the basis for this variation is unknown. In this investigation, we sought to characterize the clinical phenotype associated with the age of diagnosis including pedSLE, adult SLE and late onset SLE in a large multiethnic cohort.

Methods: We evaluated clinical manifestations, disease course and severity (per the Systemic Lupus International Collaborating Clinics/ACR Damage Index) and autoantibody profiles using a total of 2,564 SLE patients with a cumulative presence of at least 4 of 11 revised and updated ACR classification criteria for SLE, self-defined race/ethnicity (African American, European American, Hispanic), disease duration £10 years at enrollment and with at least 2 years follow up included in the PROFILE longitudinal cohort. Patients were stratified by age of onset including pedSLE ($\leq$16 years), adult SLE (17–49 years) and late onset SLE ($\geq$ 50 years). Risk estimates were calculated using multivariable logistic regression, although frequencies are provided herein.

Results: A total of 2,564 SLE patients were evaluated. The mean ($\pm$standard deviation, SD) age at diagnosis in each of three age strata was 14$\pm$3 years, 32$\pm$9 years and 58$\pm$7 years for pedSLE, adult SLE and late onset SLE, respectively and the mean ($\pm$SD) disease duration was 10.9$\pm$8.7 years, 5.7$\pm$5.8 years and 3.8$\pm$3.4 years for each of the respective groups. Across each age of onset group, the majority were female ($\geq$86%) and slightly more pedSLE patients were of African American (38%) or Hispanic (13%) ancestry. We confirm that compared to SLE patients with adult onset, pedSLE patients are more likely to present with acute and severe disease features including discoid rash (27% vs. 18%), serositis (48% vs. 44%), renal involvement (62% vs.

41%), neurologic involvement (18% vs. 10%), hematologic involvement (73% vs. 68%) and immunological involvement (89% vs. 79%). In contrast, SLE patients with late onset were significantly less likely to present with serositis (34%), renal involvement (20%), neurological involvement (8%) and immunological involvement (67%) compared to each of the pedSLE and adult onset SLE groups. Consistent with increasing age, the late onset SLE group demonstrated more damage associated with ocular, neuropsychiatric, pulmonary, cardiovascular, musculoskeletal, diabetes and malignancy domains than did the pedSLE or adult SLE groups, whereas the pedSLE group had significantly more renal damage.

Conclusion: These findings confirm more aggressive disease, particularly renal involvement, in SLE patients presenting in childhood. They further suggest SLE disease manifestations decrease with age of onset throughout adulthood. These results will inform future studies aimed at delineating the etiology and natural history of the more aggressive clinical phenotype observed in children.

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Immune Complexes and Autoantibodies to Oxidized Lipids in Systemic Lupus Erythematosus. Yujin Ye, Tianfu Wu and Chandra Mohan. University of Texas, Southwestern Medical Center at Dallas, Dallas, TX

Background/Purpose: SLE is a chronic autoimmune inflammatory disease. Increasing evidence suggest that excess production of reactive oxygen species (ROS) may cause oxidative stress and favor the development of immune-cell dysfunction, autoantigen production and autoantibody development. Oxidized-lipids have chemotactic, immune-stimulatory, and toxic properties and play an important role in the pathogenesis of atherosclerosis and kidney injury in SLE. In the current study, we evaluated the serum levels of oxidized-lipids and their autoantibodies in SLE patients and identified the relationships between oxidized-lipids, auto-antibodies and disease.

Methods: Serum MDA was measured by a colorimetric method and HODE was assayed by mass spectrometry. Serum levels of specific oxidized-LDL immune complex (ox-LDL-IC), autoantibodies to ds-DNA, ox-LDL, MDA-LDL, 9-HODE (9-hydroxy-10,12-octadecadienoic acid), 13-HODE (13-hydroxy-9,11-octadecadienoic acid), POVPC (1-palmitoyl-2-oxovaleroyl-sn-glycero-3-phosphorylcholine) were detected by ELISA in 64 SLE patients (37 with active SLE, SLEDAI > 6) and 9 healthy controls.

Results: (1) Active SLE patients exhibited increased serum levels of anti-ds-DNA-IgG (0.349$\pm$0.039 vs 0.115$\pm$0.018; p=0.0001), anti-MDA-LDL-IgG (1049.0$\pm$116.2 ku/L vs 468.7$\pm$103.6 ku/L; p=0.003), anti-LDL-IgG (1368.0$\pm$183.6 EU/ml vs 654.0$\pm$87.17 EU/ml; p=0.004), anti-9-HODE-IgG (0.632$\pm$0.044 vs 0.298$\pm$0.058; p=0.001), anti-13-HODE-IgG (0.542$\pm$0.047 vs 0.251$\pm$0.048; p=0.0003), anti-POVPC-IgG (0.429$\pm$0.030 vs 0.297$\pm$0.030; p=0.001) and ox-LDL-IC (0.375$\pm$0.018 vs 0.270$\pm$0.022; p=0.003) compared to healthy controls, but decreased serum levels of anti-9-HODE-IgM (0.257$\pm$0.016 vs 0.335$\pm$0.032; p=0.019) and anti-13-HODE-IgM (0.336$\pm$0.025 vs 0.441$\pm$0.042; p=0.029). (2) Serum HODE levels were positively correlated with proteinuria (r=0.68/p=0.002), CRP (r=0.51/p=0.03) and ox-LDL-IC (r=0.45/p=0.04). Serum anti-ox-LDL-IgG was positively correlated with SLEDAI (r=0.34/p=0.02), and negatively with C3 (r= $-$0.39/p=0.01). Anti-9-HODE-IgG was positively correlated with SLEDAI (r=0.27/p=0.02), and negatively with C4 (r= $-$0.3/p=0.01). Anti-POVPC-IgG was positively correlated with SLEDAI (r=0.23/p=0.04), and negatively with C4 (r= $-$0.27/p=0.03).

Conclusion: Active SLE patients exhibit significantly increased serum levels of IgG anti-oxidized-lipid autoantibodies. Taken together with our recent metabolomic screen indicating that oxidized lipids are also elevated in SLE sera (PLOS ONE, June 2012), the current findings suggest that coordinate elevation of oxidized lipids, autoantibodies to these lipids, and immune complexes of these antigen-antibody components could serve as potential serum markers of disease activity in SLE.

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Altered Soluble Mediators in Individuals with Incomplete Lupus (ILE) in the Lupus Autoimmunity in Relatives (LAUREL) Study. Melissa E. Munroe[1], Jill M. Norris[2], Joel M. Guthridge[1], Diane L. Kamen[3], Kathy Moser Sivils[1], Timothy B. Niewold[4], Gary S. Gilkeson[5], Michael H. Weisman[6], Mariko L. Ishimori[6], Daniel J. Wallace[6], David R. Karp[7], John B. Harley[8] and Judith A. James[9]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Colorado School of Public Health, Aurora, CO, [3]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC, [4]University of Chicago, Chicago, IL, [5]Medical University of South Carolina, Charleston, SC, [6]Cedars-Sinai Medical Center, Los Angeles, CA, [7]UT Southwestern Medical Center, Dallas, TX, [8]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [9]Oklahoma Medical Research Foundation; University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background/Purpose: SLE is a complex autoimmune disease marked by autoantibody production and immune dysregulation. Identification of at-risk populations is essential to minimize morbidity and mortality from early inflammatory reactions and to identify appropriate individuals for prevention trials. A number of patients have autoantibodies and some clinical features of SLE, but do not meet the required ≥ 4 ACR criteria (or incomplete lupus, ILE). Healthy blood relatives of lupus patients are known to have significantly increased risk of SLE development. Using a unique resource of family members with samples available before and after transition to SLE, we initially found that blood relatives (FDRs) who transition to SLE have altered inflammatory mediators compared to those who remain unaffected. This study seeks to determine potentially pathogenic inflammatory mediators in blood relatives classified with ILE, compared to those who have transitioned to SLE, and matched blood relatives who remain unaffected.

Methods: This study has initially re-enrolled 375 FDRs of known SLE patients with samples available from previous genetic studies for follow-up evaluation; 22 previously unaffected FDRs have transitioned to SLE (≥ 4 ACR criteria) and 17 are classified as ILE (cumulative ACR criteria = 3). Individuals provided detailed clinical and demographic information, and completed the Connective Tissue Disease Screening Questionnaire (CSQ) at baseline (BL) and follow-up (FU). Medical records were obtained and reviewed for ACR classification criteria. BL and FU serum samples were tested for autoantibody production, including ANA, anti-dsDNA, aCLs and precipitating levels of Ro, La, Sm, nRNP, and ribosomal P autoantibodies. We assessed 52 soluble inflammatory mediators, using either xMAP multiplex technology or sandwich ELISA (BLyS and APRIL). Samples from ILE participants were compared to FDRs who transitioned to SLE, as well as race/gender/age ($+/- 5$ years)/ANA status matched FDRs who remain unaffected.

Results: ILE FDRs had BL and FU CSQ scores similar to those who transitioned to SLE classification (*n.s.*), yet > 2 fold higher than matched, unaffected FDRs ($p < 0.001$). Both ILE and SLE had similar BL and FU levels of a number of chemokines, including MIG, MIP-1α, MIP-1β, MCP-3, and eotaxin. Of particular interest were shed TNFR family members (TNFRI, TNFRII, TRAIL, and CD40L) that were 50% higher in ILE FDRs and those who transitioned to SLE than matched, unaffected FDRs ($p \leq 0.01$). Compared with FDRs who transitioned to SLE or remained unaffected, ILE FDRs had significant ($p < 0.05$) BL and FU alterations in 22 (of 52) soluble mediators, most notably innate and adaptive cytokines, including a >2-fold increase in Th2-type cytokines IL-4, IL-5, and IL-13 and regulatory cytokines IL-10 and TGF-β.

Conclusion: FDRs of known SLE patients classified with ILE or transition to SLE demonstrate significantly altered levels of soluble inflammatory mediators. These alterations suggest that multiple perturbations in immune-mediated inflammatory processes occur with accumulation of ACR criteria and potentially allow for identification of individuals at high risk for development of SLE.

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Altered Response to B Cell Receptor (BCR) Crosslinking in SLE: Correlation with Genetic Risk Variants Predicted to Impact BCR Signaling. Nan-Hua Chang[1], Timothy Li[1], Paul R. Fortin[2], Dafna D. Gladman[3], Carolina Landolt-Marticorena[4], Jorge Sanchez-Guerrero[5], Murray B. Urowitz[4] and Joan E. Wither[3]. [1]Toronto Western Research Institute, University Health Network, Toronto, ON, [2]University of Laval, Quebec, [3]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [4]University Health Network, University of Toronto, Toronto, ON, [5]Mount Sinai Hospital, University Health Network, Toronto, ON

Background/Purpose: Altered B cell signaling has been proposed to play an important role in susceptibility to SLE. In mice, genetic manipulations or polymorphisms that attenuate BCR signaling have been shown to lead to altered selection or survival of self-reactive lymphocytes whereas those that lead to enhanced BCR signaling can breach B cell anergy, with both types of defects reported in various murine models of SLE. Most previous reports indicate that SLE B cells are hyper-responsive to BCR crosslinking. However, these findings contrast with preliminary evidence suggesting that some of the genetic risk variants associated with SLE may lead to attenuated BCR signaling. In this study we have examined the association between these risk variants and the altered B cell function observed in SLE.

Methods: Patients (N=44) satisfying at least 4 ACR criteria and (N=30) healthy age-matched controls without a family history of systemic autoimmune disease were recruited. PBMC were isolated over a Ficoll gradient, rested for 1 hr at 37°C, and then stimulated for 2' with media alone, or 2' and 10' with media containing 20 μg/ml of F(ab')$_2$ goat anti-human IgM. Cells were stained with anti-CD19, -CD27, -IgD, -IgM, and -CD38, to permit gating on naïve mature B cells (CD19$^+$CD27$^-$IgD$^+$CD38$^+$) stratified based on their IgM cell surface expression and transitional B cells (CD19$^+$CD27$^-$IgD$^+$CD38^{++}IgM^{hi}). B cell signaling was examined by Phosflow using anti-pSyk (pY348), -pPLCγ2 (pY759) or -pERK1/2 (pT202/Y204) Ab following fixation and permeabilization. SNP genotyping of subject DNA was performed using TaqMan assays specific for rs2618476 (*BLK*), rs10516487 (*BANK-1*), rs7829816 (*LYN*), and rs2476601 (*PTPN22*).

Results: There was an increased proportion of naïve B cells in SLE patients that had elevated basal levels of pSYK and pERK, suggesting prior activation in-vivo. Following IgM crosslinking, the naïve B cells of SLE patients demonstrated significantly increased levels of p-SYK and trends to increased levels of p-PLCγ2 and p-ERK above basal levels as compared to controls. This increased signaling was most marked in the IgM^{hi} mature naïve and transitional B cell compartments of SLE patients. There was no correlation between the basal levels of phosphorylated signaling molecules and any of the SNPs examined. No association was seen between *BLK* or *LYN* SNPs and any of the phosphorylated signaling molecules following IgM crosslinking. Consistent with attenuated BCR function there was a trend to decreased pPLCγ2 and significantly decreased pERK with the lupus-associated *PTPN22* variant at 10' following IgM crosslinking. The lupus associated *BANK-1* variant was associated with decreased pPLCγ2 at 2'. To further explore the role of non-genetic factors in the B cell hyper-responsive phenotype, serial measurements of pSYK were performed. Significant variations between individual visits were seen in a subset of patients.

Conclusion: No correlation was observed between increased B cell signaling and several of the genetic risk variants predicted to alter B cell receptor function in SLE. It is likely that this phenotype arises from other genetic or non-genetic factors.

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Differential Impairment of Serum Cholesterol Efflux Capacity in Patients with Rheumatoid Arthritis and Systemic Lupus Erythematosus. Pier Luigi Meroni[1], Nicoletta Ronda[2], Elda Favari[3], Orietta Borghi[4], Francesca Zimetti[3], Mariapia Adorni[5], Francesca Ingegnoli[6], Maria Gerosa[7], Claudia Grossi[8] and Franco Bernini[5]. [1]Istituto G. Pini, University of Milan, Milano, Italy, [2]Parma, Italy, [3]University of Parma, Parma, Italy, [4]University of Milan, Milan, Italy, [5]39-02-58318176, Parma, Italy, [6]Rheumatology, Istituto G. Pini, University of Milan, Milano, Italy, [7]Division of Rheumatology, Istituto Ortopedico Gaetano Pini, Milan, Italy, [8]Lab of immunology, IRCCS Istituto Auxologico Italiano, Milano, Italy

Background/Purpose: Accelerated atherosclerosis associated with autoimmune diseases is partly due to immune system dysregulation aggravating cardiovascular damage, but little is known on lipid metabolism derangement in this condition. Serum capacity to promote cholesterol efflux from macrophages (CEC) is the first limiting step of the atheroprotective reverse cholesterol transfer process, mainly reflects HDL function and inversely correlates to subclinical atherosclerosis *in vivo*. Moreover, the relevance of

CEC is strengthened by recent evidence of an impact of cholesterol efflux on inflammatory and immune functions of macrophages and endothelial cells. We measured the four main CEC pathways in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients.

Methods: aqueous diffusion (AD)-, SR-BI-, ABCG1- and ABCA1-mediated CEC was measured by validated radioisotopic *ex vivo* systems in 30 AR and 30 SLE patients, and in 30 age and sex-matched healthy subjects.

Results: SR-BI-mediated CEC (mean±SEM % efflux) was increased in SLE patients (3.84 ± 0.19) as compared to controls (3.20 ± 0.20) and RA patients (2.78 ± 0.17). ABCG1-mediated CEC was reduced in RA and more markedly in SLE (6.04 ± 0.25 and 4.36 ± 0.34, respectively) as compared to controls ($7.13 \pm 0.2\%$). ABCA1-mediated CEC was impaired in SLE (2.55 ± 0.16) as compared to controls and RA patients (3.14 ± 0.19 and 3.54 ± 0.30, respectively). AD-mediated CEC did not differ between the three populations studied. ABCG1-mediated CEC inversely correlated with the disease activity score DAS28 in RA patients. SLE patients as a group showed the lowest ABCG1-mediated CEC in spite of the highest HDL serum level. The correlation between ABCG1-mediated CEC and serum HDL, detected in controls and in SLE patients, was absent in RA. The correlation between ABCG1-mediated and SR-BI-mediated CEC detected in controls and RA patients was absent in SLE.

Conclusion: We report here for the first time a marked and differential CEC impairment in patients with RA and SLE, independent of HDL serum levels, that not only demonstrates a dysfunction and loss of atheroprotective activity of HDL with respect to cholesterol metabolism, but also points to the existence of specific underlying mechanisms in each disease, possibly beyond inflammation. Moreover, the impairment of ABCG1-mediated cholesterol efflux in autoimmune patients, that correlated with disease activity in the RA group, might also have an impact in inflammatory and immune reaction involving macrophages and endothelial cells.

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A Novel Biomarker: Nucleotide-Binding Oligomerization Domain 27 in Systemic Lupus Erythematosus. Annika Cutinha[1], Yangsheng Yu[2], Kaihong Su[2], James R. O'Dell[1], Lynell W. Klassen[1], Amy C. Cannella[1], Ted R. Mikuls[1], Alan R. Erickson[3], Gerald F. Moore[1] and Michelene Hearth-Holmes[1]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Department of Pathology and Microbiology, Omaha, NE, [3]University of Nebraska Medical Center, LaVista, NE

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease in which a variety of autoantibodies contribute to the diversified disease phenotypes. In our previous studies, we generated more than 300 recombinant antibodies from B cells of SLE patients using the single-cell RT-PCR approach. We found that over 20% of SLE-derived antibodies bind to and activate neutrophils. One of the antibodies recognizes a novel pattern recognition receptor Nucleotide-binding Oligomerization Domain 27 (NOD27), which is recently shown to be involved in anti-viral interferon responses. Administration of this antibody in lupus-prone mice accelerated lupus progression, suggesting a role of anti-NOD27 in lupus pathogenesis. The purpose of this study is to determine if anti-NOD27 autoantibodies are detectable in sera from SLE patients and if the serum levels of anti-NOD27 are elevated in SLE patients with active disease.

Methods: 59 SLE patients who met at least four of the 1982 ACR criteria and 92 healthy volunteers with no known rheumatic diseases were enrolled into the prospective study. The SLEDAI disease activity index was obtained in all patients. Patients with a SLEDAI score of 6 or higher were considered to have active disease. Enzyme-linked immunosorbent assay (ELISA) was performed to determine the serum levels of anti-NOD27 antibodies. Serum titers of complements C3 and C4 and anti-dsDNA antibodies were obtained in each patient. The control group, SLE group and the SLE inactive and active groups were compared with each other for the serum titers of anti-NOD27 using the Mann Whitney test (two-tailed). A $p$value of <0.05 was considered significant. The respective correlation of anti-NOD27 titers with anti-dsDNA, C3, C4, or SLEDAI in SLE patients was calculated using Pearson's correlation test.

Results: The mean anti-NOD27 level in the SLE group was 0.518 (in optical density units; SD 0.26, 95% CI 0.45–0.587), which is significantly higher than that in the control group (mean: 0.398; SD 0.15, 95% CI 0.36–0.45; $p=0.0019$). The mean anti-NOD27 level of the active SLE cohort was found to be higher than that of the inactive SLE cohort (mean: 0.617

versus 0.496) although the difference was not statistically significant, likely related to the limited number of active patients in our cohort (11 of 59). The anti-NOD27 titers were significantly correlated with anti-dsDNA titers ($p=0.0014$, Pearson r $=0.38$) and demonstrated a marginal inverse correlation with the C3 levels ($p=0.047$, Pearson r $= -0.22$). No significant correlation of anti-NOD27 with C4 levels ($p=0.118$, Pearson r $=-0.16$) nor SLEDAI scores ($p=0.074$, Pearson r $=0.19$) was seen.

Conclusion: The novel biomarker anti-NOD27 was found to be significantly elevated in patients with SLE compared to controls in this study and concentrations of anti-NOD27 were significantly correlated with anti-dsDNA titers in our cohort of SLE patients suggesting that anti-NOD27 may be an informative biomarker in SLE. Further studies with larger sample sizes and different cohorts of patients including those with active disease and end organ damage will be needed to evaluate the predictive capacity of NOD27 antibody responses in the future.

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Antibodies to Oxidized Low Density Lipoprotein or Anti-Lipoprotein Lipase May Lead to More Atherosclerotic Plaque in a Sub-Set of SLE Patients. Biji T. Kurien[1], James Fesmire[2], Skyler P. Dillon[3], Marianne Reichlin[4], Morris Reichlin[5] and Robert H. Scofield[6]. [1]University of Oklahoma Health Sciences Center, Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Oklahoma Medical Res Fndn, Oklahoma City, OK, [5]Oklahoma Medical Research Foun, Oklahoma City, OK, [6]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK

Background/Purpose: Premature atherosclerosis is associated with systemic lupus erythematosus (SLE). Oxidized low density lipoproteins (ox-LDL) are important in atherosclerosis and have been reported in SLE in association with anti-phospholipid antibodies. Our earlier work showed increased susceptibility of SLE Patients with anti-Ro 60, La and Ro 52 to develop anti-oxidized LDL. In this study we tested the hypothesis that atherosclerotic plaque may be associated with anti-oxLDL and anti-lipoprotein lipase in a specific autoantibody sub-set of SLE.

Methods: We studied 114 SLE patients and 117 age and sex matched normal controls. Antibodies directed against lipoprotein lipase (ALPL), oxidized low density lipoprotein (anti-oxLDL), and low density lipoprotein (ALDL) were measured by enzme-linked immunosorbent assay. Total cholesterol, LDL, HDL, triglycerides and HDL-Trig were also measured. Plaque was measured by bilateral carotid ultrasound. The study was approved by the Institutional Review Board of the Oklahoma Medical Research Foundation and all subjects signed informed consent forms. The patient population (age range of 16– 87 years; average age 43) was 104 females and 10 males.

Results: Double immunodiffusion studies showed that sixty three SLE subjects did not have autoantibodies against extractable nuclear antigen (ENA), 14 had antibodies against ribonucleoprotein (RNP), 16 had anti-Ro60, 7 had anti-Ro60/La, 6 had anti-SmRNP, 4 had unidentified precipitin lines and 4 had miscellaneous antibodies. The ENA negative group had a significantly higher plaque measured as carotid intimal thickening (0.9 ± 1.71; p$<$ 0.05) compared to normal controls (0.54 ± 1.26), but did not have significant levels of anti-oxLDL (OD = 0.41 ± 1.62), ALPL (OD = 0.35 ± 0.18) and ALDL (OD = 0.1 ± 0.09) compared to anti-oxLDL (0.165 ± 0.13), ALPL (0.39 ± 0.2), ALDL (0.09 ± 0.1) in normal controls. The group with anti-RNP antibodies had significant levels of anti-oxLDL (0.29 ± 0.27; p$<$0.005) compared to control group. However, the anti-RNP group did not have significant levels of ALPL (0.39 ± 0.19), ALDL (0.14 ± 0.139) or plaque (0.79 ± 1.43) compared to control group. The 16 subjects with anti-Ro60 had significant anti-oxLDL level (0.26 ± 0.15; p$<$0.003) and plaque (1.29 ± 0.25; p$<$0.02) compared to controls, but no differences in ALPL (0.36 ± 0.16) or ALDL (0.11 ± 0.11). The 7 SLE subjects with anti-Ro60/La had signficantly higher levels of ALPL antibodies (0.56 ± 0.246; p=0.05) compared to control group. This group had the highest levels of ALPL antibodies compared to all other SLE groups. The anti-SmRNP group did not behave significantly different from normal controls with respect to plaque (0.5 ± 0.55), anti-oxLDL (0.265 ± 0.15), anti-LDL (0.14 ± 0.12) or ALPL (0.471 ± 0.27). There was no significant difference in plaque when

anti-oxLDL+/ALPL+ or anti-oxLDL-/ALPL- SLE subjects were compared to either anti-oxLDL+/ALPL+ or anti-oxLDL-/ALPL- normal controls.

Conclusion: Plaque appears to segregate in anti-Ro/La, anti-Ro and ENA negative groups either with or without anti-oxLDL or ALPL.

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Estrogen Modulation of ZAS3 Is Mediated Through Estrogen Receptor α: An Underlying Mechanism of Gender-Bias in Systemic Lupus Erythematosus? Nicholas Young[1], Alexandra Friedman[1], Lai-Chu Wu[1] and Wael N. Jarjour[2]. [1]The Ohio State University Medical Center, Columbus, OH, [2]Ohio State University, Columbus, OH

Background/Purpose: Global population data has indicated that post-pubertal females have decreased rates of infectious diseases when compared to male counterparts and preadolescent or postmenopausal females. In contrast, many autoimmune diseases like Systemic Lupus Erythematosus (SLE) have a significant bias towards post-pubertal women. ZAS3 is an important immuno-regulatory transcription factor involved in both B and T cell maturation and function. We hypothesized that post-pubertal females have more robust immune responses in part through estrogen's regulation of ZAS3. In this study, we examine the influence of estrogen over ZAS3 expression and the functional implication of ZAS3 deficiency on the immune response.

Methods: Wild type (WT) mice were injected subcutaneously with estrogen (E2) daily for 5 days and lymphoid tissues were harvested. Transgenic mice with a luciferase reporter under the control of kB binding sites were bred into ZAS3 knockouts and luciferase activity in males and females was measured by IVIS. Peripheral blood mononuclear cells (PBMCs) isolated from healthy subjects and SLE patients were subjected to experimental analyses of gene expression and assayed for proliferation or cytokine production in the presence of either anti-CD3 or tetanus toxoid with or without estrogen. Nuclear extracts were isolated for EMSA analysis from E2-treated lymphocyte cell lines.

Results: Estrogen treated mice had elevated ZAS3 expression in the spleen, thymus, bone marrow, and lymph nodes when compared to PBS-injected controls. NFkB-mediated luciferase reporter activity in female ZAS3 knockout mice was significantly lower than WT controls, whereas males exhibited no significant differences. Further, ZAS3 knockout mice expressed significantly lower peroxisome-proliferator activated receptor gamma (PPARγ) expression. ZAS3 was also found to be significantly elevated at baseline in SLE patients when compared to age and sex-matched healthy controls. PBMCs from healthy females incubated *in vitro* with estrogen or estrogen receptor alpha (ERα) agonist showed significant upregulation of ZAS3. Similarly, ZAS3 expression was upregulated in response to estrogen both on the protein and RNA level in T Cells, B Cells, monocyte, and NK cell lines. EMSA analysis with intronic estrogen receptor response element probes within the ZAS3 region revealed that ERα binds directly and that E2 stimulation enhanced complex formation. Furthermore, estrogen significantly enhanced the cellular proliferation responses in primary PBMCs cultured with anti-CD3 or Tetanus toxoid. When these cells were stimulated with E2, we also demonstrated significant production of MIP-1β.

Conclusion: Primary human PBMCs display a heightened ZAS3 response to E2 and this effect is mediated at least in part through NFkB and leads to PPARγ upregulation. Furthermore, The E2/ERα-mediated stimulation of ZAS3 expression occurs through direct, genomic interactions with intragenic enhancing elements. Taken together, this data suggests that E2 lowers the threshold of activation by priming the immune system of females. While this may be beneficial in the defense against foreign antigens, it can be detrimental in the development of autoimmunity.

Disclosure: **N. Young**, None; **A. Friedman**, None; **L. C. Wu**, None; **W. N. Jarjour**, None.

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ZAP70+ B Cells and Plasmablasts As Markers of Disease Activity and Remission in Systemic LUPUS Erythematosus Nephritis. Elisa Gremese, Barbara Tolusso, Laura Messuti, Marcin Nowik, Silvia Canestri, Luca Petricca, Maria Rita Gigante and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: To analyze differences in B cells subsets distribution in patients with renal systemic lupus erythematosus (SLE). To define possible cellular biomarkers of active nephritis and of remission in renal disease in SLE patients.

Methods: 60 SLE patients with renal involvement 49 females (82%); mean age 36.9 ± 11.0 years; 37 with active disease and 23 with disease in remission) were analyzed for the distribution of circulating peripheral blood B cell subpopulations by staining for surface markers CD45, CD19, CD38, IgD, CD27 (CD27/IgD classification (Sanz et al. SeminImmunol 2008) and intracellular marker ZAP-70 (Tolusso et al. ClinImmunol 2009) by flow cytometry. All patients had a WHO class III or IV nephritis diagnosed by renal biopsy. Patients with active nephritis were recruited at the renal disease onset, while patients in remission were recruited if the nephritis was in stable remission for at least 12 months. Fourteen patients with active disease at the study entry were reassessed for PB B cell subpopulations at the time of renal remission (nephritis remission criteria in at least two consecutive observations and on an oral steroid dosage<7.5 mg/day).

Results: The 37 subjects with active renal involvement showed higher percentages of CD19/ZAP70+ cells compared to 23 patients with nephritis remission ($13.1\pm10.5\%$ vs$5.4\pm4.5\%$, respectively; p=0.002), as well as of plasmablasts (CD27/CD38+: $10.6\pm7.4\%$ vs $6.3\pm5.8\%$, respectively; p=0.03).There was no differences in other B cells subpopulations between active and inactive lupus nephritis.

In the 60 SLE renal patients, the percentage of CD19+/ZAP-70+ cells directly correlated with disease activity index (SLEDAI) (r=0.44, p=0.002), inversely with complement fractions C3 and C4 (C3: r=−0.44, p=0.001, C4: −0.45, p=0.001), with the number of lymphocytes (r=−0.55, p<0.001) and of the CD19+ B cells (r=−0.61, p<0.001). Moreover, the pool of ZAP70+ B cells directly correlated with the memory cells subsets (CD27+IgD-: r=0.41, p=0.002, CD27-IgD-: r=0.34, p=0.01) and with plasmablasts (r=0.39, p=0.004) and inversely with naive B cells (CD27-IgD+: r=−0.48, p<0.001). The 14 patients evaluated in the follow-up showed a significant reduction of the percentage of ZAP70+ B cells at remission ($4.3\pm2.8\%$) with respect to nephritis onset ($14.4\pm11.6\%$, p=0.002), as well as of the plasmablasts (CD19+/CD27+CD38+: $10.7\pm8.0\%$ at baseline *vs* $5.7\pm2.9\%$ at remission; p=0.05).

Conclusion: The pool of CD19+/ZAP70+ cells is associated with SLE activity parameters (SLEDAI, low complement, low lymphocytes and CD19+ count) and with the B cell memory compartment in SLE patients with renal involvement. The expansion of ZAP70+ B cells and plasmablasts characterizes active renal disease and their reduction is associated with the remission state, suggesting their possible role as biomarker in SLE nephritis.

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Plasma Level of Galectin-3 Binding Protein Reflects Type I Interferon Activity and Is Highly Increased in Patients with Systemic Lupus Erythematosus Christoffer T. Nielsen[1], Ole Østergaard[2], Line V. Iversen[1], Christian Lood[3], Anders A. Bengtsson[4], Anne Voss[5], Søren Jacobsen[6] and Niels H. H. Heegaard[1]. [1]Statens Serum Institut, Copenhagen S, Denmark, [2]Statens Serum Institute, Copenhagen S, Denmark, [3]Department of Clinical Sciences Lund, Lund, Sweden, [4]Department of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [5]Odense University Hospital, Odense C, Denmark, [6]Copenhagen University Hospital, Copenhagen, Denmark

Background/Purpose: Ongoing production of type I interferons (IFN) is a key element in the pathogenesis of systemic lupus erythematosus (SLE). Type I IFNs trigger the over-expression of IFN-regulated genes, including galectin-3-binding protein (G3BP). G3BP serves as a scavenger receptor and is a potent immune stimulator. It mediates cellular adhesion and binding to the extracellular matrix of the basement membrane. Thus G3BP may serve as a measure of type I IFNs and has potentially important pathogenic roles in cell-cell interaction and immune complex trafficking in SLE. We here explore the relationship between type I IFN activity and plasma G3BP, compare plasma concentrations of G3BP in two cohorts of SLE patients to patients with systemic sclerosis (SSc) and healthy controls (HCs), and correlate G3BP concentrations with clinical and serological parameters.

Methods: Plasma and serum concentrations of G3BP were quantified using a commercially available ELISA. Type I IFN activity was assessed by

an Mx1-driven luciferase reporter gene assay. Gene expression scores from 12 genes in peripheral blood mononuclear cells from 26 SLE patients and 10 HCs were compared to plasma concentrations of G3BP. Plasma and serum concentrations were compared in 4 SLE and 4 SSc patient samples. G3BP concentrations in 70 SLE patients were compared to HCs (n =51) and patients with systemic sclerosis (SSc, n =111). Additionally, G3BP levels were validated in an independent cohort of SLE patients (n =67) and HCs (n =50). Non-parametric correlation analyses were used to explore associations between G3BP concentrations and clinical and serological parameters in the two SLE cohorts. In 14 SLE patients consecutive serum samples (3 or 4 per patient, >6 months apart) were analysed and correlated to disease activity (SLEDAI).

Results: G3BP plasma concentrations correlated significantly with the Mx-1 driven luciferase reporter gene assay (r =0.56, p =0.0005) and INF-α gene expression scores (r =0.54, p =0.0002). No significant difference between serum and plasma levels of G3BP was observed (p =0.17). Plasma concentrations were similar in the two SLE cohorts (p =0.42) and highly significantly increased compared to HCs and SSc patients (p <0.0001 and 0.0009, both those with diffuse and limited cutaneous disease). Significant associations (p<0.05) with SLEDAI, cell counts, anti-dsDNA, and active nephritis could not be confirmed in the validation cohort. Temporal variations in serum concentrations were observed in the consecutive SLE-samples but were not associated with disease activity (SLEDAI).

Conclusion: The level of circulating G3BP is elevated in SLE patients compared with HCs and SSc patients. The SLE-specific elevated levels of G3BP correlated with type I IFN activity. G3BP could thus serve as an easy accessible measure of type I IFN gene activation. Additionally, this study highlights G3BP as an IFN-inducible effector molecule that may have a central role in SLE pathogenesis and thus putatively is a possible new target for therapeutic intervention.

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Interferon Alpha Decreases Endothelial Nitric Oxide Synthase Function and Expression in Human Umbilical Vein Endothelial Cells. Joy Buie and Jim Oates. Medical University of South Carolina, Charleston, SC

Background/Purpose: Premenopausal SLE patients have a devastating increase in cardiovascular disease (CVD) and major associated cardiovascular events (MACE) that are not fully explained by Framingham risk factors. Recent in vitro studies suggest that Type I interferons promote endothelial progenitor cell dysfunction and apoptosis while others have shown that Type I interferon gene signature correlates with increased endothelial dysfunction (ED) in SLE. Although causes of ED are likely multifactorial, all pathways converge on the diminished activity of endothelial nitric oxide synthase (eNOS). The low levels of nitric oxide (NO) produced by eNOS has anti-inflammatory, anti-thrombotic, and anti-vasoconstrictive properties all important in preventing atherosclerosis. We examined the effects of IFN-alpha on eNOS gene expression and phosphorylation.

Methods: Human umbilical vein endothelial cells (HUVECs) were cultured and treated as described below. Changes in eNOS expression in response to IFN-α (100, 1000 IU) were quantified by real-time PCR. Functional changes in response to vascular endothelial growth factor (VEGF 50ng/ml, 30 minutes) were assessed by immunoblot. We also evaluated the effect of serum from patients that induce a type I IFN signature (induction of two inducible genes (MX1 and IFIT1); IFIGs) from 5 patients and 2 controls on eNOS expression and VEGF mediated function. Gene expression was assessed using RT[2]PCR and phosphorylated serine 1177 eNOS expression using immunoblot. Type I IFN neutralization studies (IFN-α antibody(Ab), IFNα receptor (IFNAR) Ab) were also performed and eNOS expression was assessed.

Results: HUVECs treated with IFN-α at 100IU and 1000IU exhibited a significant reduction in eNOS gene expression at 24 hours (33% and 42%, respectively) and a reduction in VEGF-induced phosphorylation at the serine 1177 site (64% and 50%, respectively) after 24 hours. SLE serum also caused a 40% reduction in eNOS gene expression in human aortic endothelial cells (HAECs) compared to normal serum. However, addition of IFN neutralizing antibodies to serum did not reverse observed effects on eNOS gene changes.
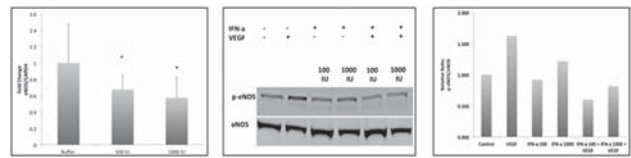
Conclusion: SLE patients are at an increased risk for vascular disease, and 40% of patients present with IFN signature gene expression. Recent studies suggest that Type I IFNs are important for prediction of vascular endothelial function in SLE patients. Endothelial nitric oxide synthase (eNOS) protects the endothelium from damage and our preliminary data suggest that IFNα may have detrimental effects on eNOS expression and function. Thus, a rational target for the effect of IFNα on endothelial function may be the downstream effects of IFNα on eNOS gene expression and protein activation.

Disclosure: **J. Buie**, None; **J. Oates**, None.

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IL-12p70 Levels Play a Role in Damage Accrual in SLE Patients. Eoghan M. McCarthy[1], Ruth Lee[1], Joan Ni Gabhann[2], Siobhan Smith[2], Michele Doran[3], Gaye Cunnane[3], Donough G. Howard[1], Paul G. O'Connell[1], Caroline Jefferies[2] and Grainne M. Kearns[1]. [1]Beaumont Hospital, Dublin 9, Ireland, [2]Royal College of Surgeons in Ireland, Dublin, Ireland, [3]St. James's Hospital, Dublin, Ireland

Background/Purpose: Whilst the role of cytokines in promoting disease activity in SLE is well established, the relationship between cytokines in those who sustain irreversible damage and those who remain damage free over long term follow up is less well studied. An IL-12 driven Th1 polarisation has been proposed as a promoter of irreversible renal damage in patients with lupus nephritis but studies have not extrapolated these findings to composite all organ damage scores.The primary objective of this is to explore the role of IL-12p70 in the aetiology and pathogenesis of SLE in a homogenous Irish Caucasian population.

Methods: Patients who met at least 4 of the American College of Rheumatology (ACR) criteria for SLE were included. To gain entry all patients had to confirm they were of Irish descent for three generations. Serum levels of the following cytokines - IL-1β, IL-10, IL-12p70 and TNF-α - were quantitatively determined by electrochemiluminescence. Demographic data, disease activity as per SLEDAI and damage scores (SLICC) at 5 year follow-up were calculated.

Results: 45 patients were included in the study.

The levels of TNF-α(44.6pg/ml v 5.23pg/ml, p<.001), IL-1(2.8pg/ml v.62pg/ml, p<.001) and IL-10(7.143pg/ml v 2.76pg/ml, p<.001) were significantly higher in patients when compared to controls. IL-12p70 responses were lower in patients than controls, with an IL-12p70 level of 4.6pg/ml recorded in patients and 6.195pg/ml in controls (p=.39).

The ratio of all Th1 cytokines assayed to IL-12 was significantly higher in SLE patients when compared to controls. The levels of IL-1β/IL-12 and TNF-α/IL-12 were 5 times and 4.4 times higher respectively in patients than controls (p<.001). A similar result was seen for Th2 cytokines with the IL-10/IL-12 ratio 3.7 times higher in patients when compared to controls(p<.001).

The IL-1/IL-12 ratio was significantly higher in those patients who suffered new damage compared to those who remained damage free(1.02 v.44, p<.005) at five year follow up. A similar difference was seen in the IL-10/IL-12 ratio (3.07 v 1.88, p<.027) and the TNF/IL-12 ratio (8.14 v 5.04, p<.038).

When the Spearman correlation was computed for SLEDAI and the above cytokine ratios no significant correlation was observed with respect to disease activity. Despite this lack of association with disease activity, when a similar analysis was performed for the cytokines ratios and damage accumulation over the follow-up period a significant correlation was seen between damage accrual and the IL-1/IL-12 ratio (r = 0.431,p=0.003), IL-10/IL-12 ratio (r =0.351,p =.018) and TNF/IL-12 ratio (r = 0.28,p=.028), indicating IL-12 plays a key role in damage accrual in concert with both Th1 and Th2 cytokines.

When the respective ratios were analysed as per ACR diagnostic criteria significant differences were observed for the IL-1/IL-12 ratio(1.86 v.78,p<.0362), IL-10/IL-12 ratio(3.58 v 2.2, p<.0084) and TNF/IL-12 ratio(30.6 v 6,p<.0097) with respect to renal involvement only.

Conclusion: Our results highlight that increased Th1 and Th2 cytokine levels relative to IL-12p70 in this homogenous Caucasian SLE patient population are seen in patients with renal involvement and are associated with increased accrual of damage at five year follow-up.

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Prevalence of Inhibitory or Non-Inhibitory Autoantibodies to Angiotensin Converting Enzyme 2 (ACE2) in Patients with Systemic Lupus Erythematosus. Yuko Takahashi[1], Shiori Haga[2], Yukihito Ishizaka[2] and Akio Mimori[1]. [1]National Center for Global Health and Medicine, Tokyo, Japan, [2]Research Institute, National Center for Global Health and Medicine, Tokyo, Japan

Background/Purpose: We previously reported that inhibitory autoantibodies to angiotensin converting enzyme 2 (ACE2) predisposed individuals to connective tissue diseases (i.e., scleroderma or systemic lupus erythematosus [SLE]) and constrictive vasculopathies. That study included SLE patients with digital ulcer, scleroderma patients with pulmonary arterial hypertension (PAH), and control patients with remitted SLE without vasculopathy. Preliminary data in our further experiment suggested that patients with active SLE without vasculopathy also had high titers of serum anti-ACE2 antibodies. This study investigated the presence of anti-ACE 2 antibodies in patients with SLE and evaluated the effects of these antibodies on ACE2 activity.

Methods: Serum samples were obtained for this study from 35 non-vasculopathy patients with active SLE, three vasculopathy patients with both SLE and PAH, and 44 control patients with rheumatoid arthritis (RA). The sera were assessed for anti-ACE2 antibodies by enzyme-linked immunosorbent assay (ELISA) using purified recombinant human ACE2. Twenty-six non-vasculopathy patients with remitted SLE, 21 of whom were described in our previous study, were also (re)examined by ACE2 ELISA as a control. ELISA score above the baseline level, which was determined using sera from 28 healthy subjects, were classified as positive for anti-ACE2 antibodies. IgG fractions were prepared, using protein G sepharose beads, from the sera of subjects with high ACE2 ELISA scores and were used to evaluate inhibition of ACE2 activity *in vitro*.

Results: All three PAH patients with SLE were positive for anti-ACE2 antibodies (mean optical density [OD], 0.63 ± 0.32). Of the 35 non-vasculopathy patients, 32 (91%) with active SLE were positive for anti-ACE2 antibodies (mean OD, 0.78 ± 0.42), and the mean ELISA score was significantly higher than that of remitted SLE patients (mean OD, 0.18 ± 0.15; $p < 0.00000001$) or RA patients (mean OD, 0.06 ± 0.05; $p < 0.0000000001$). Using serum IgG fractions from SLE patients with high ACE2 ELISA titers, statistically significant suppression of ACE2 activity *in vitro* was found for 1/15 non-vasculopathy patients, 3/3 PAH patients ($p = 0.0049$), and 7/7 vasculopathy (PAH or digital ulcer) patients ($p = 0.000047$), including four who were described in our previous study.

Conclusion: Most patients with active SLE or vasculopathy were positive for serum anti-ACE2 antibodies, and inhibitory antibodies were associated with vasculopathy, but not with active SLE.

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Correlation of Signal Transducers and Activators of Transcription-1 and Microrna-146a with Anaemia and Other Clinical Features in Systemic Lupus Erythematosus Patients. Paul R. Dominguez-Gutierrez, Angela Ceribelli, Minoru Satoh, Eric S. Sobel, Yi Li, Westley H. Reeves and Edward K.L. Chan. University of Florida, Gainesville, FL

Background/Purpose: Anaemia is one of the most common haematological manifestations in SLE patients, occurring in about 50% of active cases. STAT1 is a critical signalling molecule required for the activation of type-1 interferon (I-IFN), CCL2, and CXCL10, all of which are upregulated in SLE. Overexpression of STAT1 has been described as responsible for anaemia in mouse models. CCL2 and CXCL10 are considered as biomarkers for flares. miR-146 has been reported to be downregulated in peripheral monocytes of SLE patients. The aim of this study is to analyze how these components are involved in anaemia in SLE, and what factors can influence their abnormal expression.

Methods: Blood samples were collected from 30 healthy donors and 100 SLE patients (European Americans (EA) 49; African Americans (AA) 34; Latin Americans (LA) 12; others 5)) fulfilling ACR criteria; 58 patients had samples collected from 2 or more visits. Total RNA, isolated from leukocytes, was analysed by Taqman qPCR. miRNA copy number was determined by a standard curve. Expression of I-IFN signature genes and chemokines were determined by the $\Delta\Delta C_T$ method. **Results** were correlated with clinical data and analysed by Wilcoxon/Kruskal-Wallis Test and Fisher's exact test.

Results: Comparing biomarker expression in anaemic vs. non-anaemic SLE, we detected a significant increase of IFN score ($p < 0.0001$), STAT1 ($p < 0.0001$), miR-146a ($p < 0.0004$), CCL2 ($p < 0.0004$), and CXCL10 ($p < 0.015$) in the anaemic SLE patients. Lupus Nephritis (LN), one of the most common serious complications in SLE, can be responsible for anaemia. As expected, LN patients are more likely to be anaemic than patients without nephritis (likelihood ratio (LR) =3.7; $p < 0.024$). Anaemic SLE patients displayed significantly higher STAT1, miR-146a, CCL2, and CXCL10 than SLE without anaemia, whether or not nephritis was present. The use of prednisone (PDN) but not mycophenolate and hydroxychloroquine is consistent with more active SLE in our cohort and thus may explain the association of anaemia with PDN. PDN users were more likely to be anaemic (LR= 10.7; $p < 0.0010$). However, STAT1, miR-146a, CCL2, and CXCL10 were significantly higher in anaemic SLE patients regardless of PDN therapy when compared to those who were not anaemic, whether or not they were on PDN. According to the clinical literature, lupus in AA tends to be more aggressive than in EA. Similarly, AA were more likely to be anaemic than EA (LR= 8.41; $p < 0.0032$). Both miR-146a and STAT1 were significantly higher in anaemic AA ($p < 0.019$ and $p < 0.020$ respectively) compared to non-anaemic AA. These markers in anaemic EA ($p < 0.025$ and $p < 0.0065$ respectively) were significantly higher than non-anaemic EA. CCL2 was significantly higher in anaemic EA compared to non-anaemic EA, but this was not observed in AA. No significant trend was observed for CXCL10.

Conclusion: Anaemic SLE patients demonstrated a significant increase of STAT1, miR-146a, CCL2, and CXCL10 vs non-anaemic patients. Furthermore LN and PDN did not alter STAT1, miR-146a, CCL2, and CXCL10 in anaemic SLE patients. For ethnic analysis, anaemic AA and EA SLE patients were associated with significantly higher levels of miR-146a and STAT1 that could play a prominent role in anaemia.

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Using a Library of Synthetic Autoantigen Mimics to Discover Biomarkers of Systemic Lupus Erythematosus. Akshai Lakhanpal[1], Jiexia Quan[1], Sayed Zaman[1], Nancy J. Olsen[2] and David R. Karp[1]. [1]UT Southwestern Medical Center, Dallas, TX, [2]Penn State MS Hershey Medical Center, Hershey, PA

Background/Purpose: The natural history of systemic lupus erythematosus (SLE) is felt to evolve from a state of normal immunity to serologic autoimmunity and then to pathologic autoimmunity. This process may take several years, and can include a time when only one or two clinical features are present. We have used the term incomplete lupus erythematosus (ILE) to describe such individuals. This study was undertaken to search for biomarkers that characterize ILE, specifically autoantibodies that differentiate these subjects from healthy controls (HC) with moderate to high levels of antinuclear antibodies.

Methods: A library of 7-mer peptoids (polymers of *N*-substituted glycine) was synthesized on Tentagel beads using 10 different monomer amines, leading to a theoretical complexity of 10^7 different species. This bead-coupled library was then depleted of compounds that bound to pooled IgG from HC as well as HC with ANA but no evidence of SLE. The bead library was probed with pooled IgG from individuals with ILE. Peptoids from the positively selected beads were purified, identified by tandem MS, re-synthesized and coupled to ELISA plates. Individual serum samples from subjects with ILE, SLE, RA and controls were then tested for peptoid reactivity.

Results: Screening 375,000 compounds yielded 100 beads that bound ILE IgG. 12 of these were chosen for further analysis and 8 had appropriate full-length peptoid structures. The peptoids with the greatest discrimination a pool of HC sera, designated ILE-2, and ILE-7, were chosen for ELISA analyses. Using individual samples from the training serum pool, the mean ELISA reactivity for 38 SLE patients was significantly different than all 40 HC sera (2.98 vs. 0.638, $p < 0.0001$). The area under the ROC curve was 0.96 with a sensitivity of 89% and specificity of 97%. The mean values for individual ILE patients using the

ILE-2 ELISA were also significantly different from HC (1.81 vs. 0.492, p = 0.0025). A validation set of 40 HC, 18 ILE, and 64 SLE subjects was characterized using the mean + 2SD value for HC. Even with a more stringent cut-off, ILE patients were still significantly different than controls (p = 0.0007), although a proportion of ILE patients fell into the ILE negative range. ILE-2 and ILE-7 reactivity was found at a low level in the subset of ANA+ RA patients, but not in ANA- RA patients or other disease controls.

Conclusion: A novel, un-biased chemical library can serve as practical mimics for unknown autoantigens. The ligands can be used immediately in analytic assays. The peptoids identified in this screen have excellent ability to identify subjects with lupus-related autoimmunity and discriminate them from ANA-positive control subjects.

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Cell-Type Specific Type I Interferon Signatures in Autologous Stem Cell Transplanted Lupus Patients: Different Molecular Behavior Between CD4+ T Cells and Monocytes. Chieko Kyogoku[1], Joachim R. Grün[1], Tobias Alexander[2], Robert Biesen[2], Falk Hiepe[2], Thomas Häupl[2], Andreas Radbruch[1] and Andreas Grützkau[1]. [1]German Rheumatism Research Centre Berlin (DRFZ), an institute of the Leibniz Association, Berlin, Germany, [2]Charité University Hospital Berlin, Berlin, Germany

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that affects multiple organs, whose pathology is mainly caused by the augmented interferon (IFN) signaling pathway. The aim of this study was to analyze the particular contribution of CD4+ T cells and monocytes with respect to cell type-specific IFN signatures detectable in patients with SLE by global gene expression profiling. The major focus was set on the comparison of disease-active and -inactive patients either by standard drug treatment or by autologous stem cell transplantation (ASCT) that is assumed to completely reset the autoreactive immunologic memory.

Methods: Affymetrix Human Genome U133 Plus 2.0 Array were made from purified peripheral CD4+ T cells from 6 active SLE (SLEDAI>6), 2 inactive SLE (SLEDAI<2) by standard drug treatment and 3 inactive SLE who underwent ASCT as well as 3 healthy donors (ND). In addition, using the same donors, arrays were made from purified peripheral monocytes from 1 active SLE, 1 inactive SLE, 3 ASCT-treated SLE and 3 ND. ASCT-treated patients in this study have achieved long-term remission with SLEDAI 02, whose blood were taken at the time point of 611 years after ASCT. A reference list of 2220 IFN pathway-related genes was obtained from a recent publication on PBMCs and used to estimate IFN imprints in SLE patients.

Results: In CD4+ T cells, inactive SLE showed a marginal IFN-imprint characterized by 233 only weakly expressed probe sets compared to active SLE characterized by 573 probe sets. Unexpectedly, 562 differentially expressed probe sets were also identified in ASCT-treated patients who are under long-term remission. However, considering the absolute magnitude of expression of IFN-regulated transcripts, the imprint in ASCT-treated patients was much weaker than in active SLE. For example, significantly up-regulated expression levels of IFI27/IFIT1/IFI44L was greater in active SLE (fold change; FC 41.4/15.8/11.3, respectively) than in ASCT-treated patients (FC 11.8/5.8/4.8), and no significant regulation was observed in inactive SLE. It was obvious that monocytes showed a more complex IFN response characterized by 918 differentially expressed probe sets in active SLE. Marginal IFN-imprint characterized by 652 and 592 probe sets were observed in monocytes respectively from inactive SLE and ASCT-treated patients. Different fromCD4+ T cells, monocytes from ASCT-treated patients showed no apparent IFN signatures. For example, significantly up-regulated expression of IFI27/IFIT1/IFI44L were observed in active SLE (FC 125.1/9.8/8.4), but not in ASCT-treated patients and inactive SLE.

Conclusion: We could show for the first time detailed cell type-specific IFN signatures for CD4+ T cells and monocytes isolated from active and inactive SLE patients. Most interestingly, the intriguing question comes up, why only CD4+ T cells, but not monocytes of ASCT-treated patients, are characterized by an apparent IFN imprint although patients are under long-term remission. Our results indicate for a cell type-specific pro-inflammatory cytokine memory in CD4+ T helper lymphocytes even after ASCT-therapy in patients with SLE.

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Gammadelta T Cells and Their Intracellular Cytokine Profile in Peripheral Blood of Patients with Systemic Lupus Erythematosus. Lingyun Sun, Xia Li and Zhimin Lu. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Gammadelta T cells represent a minor population of human peripheral blood T lymphocytes. As very rapid cytokine-producing cells, gammadelta T cells can regulate other ƒnlymphocytes activation and assist their local inflammatory function. Systemic lupus erythematosus (SLE) is a multi-organ damage autoimmune disease characterized by lymphocyte dysfunction and aberrant cytokine production. The aim was to detect gammadelta T cells numbers in the peripheral blood mononuclear cells (PBMCs) and analyze their intracellular cytokines profile (IFN-γ, IL-4, IL-10, IL-17, TGF-b).

Methods: Gammadelta T cells were detected in peripheral blood from 42 SLE patients and 20 normal controls by flow cytometry (FACS). Lupus disease activity was evaluated with a SLEDAI (SLE Disease Activity Index) score. Active SLE was defined as SLEDAI≥8. Annexin-V/PI double-staining FACS analysis was employed to observe the proportion of the apoptotic gammadelta T cells in 6 active SLE patients and 6 normal controls, respectively. The percentages of cytoplasmic cytokines including IFN-γ, IL-4, IL-10, IL-17 and TGF-b were examined in 20 SLE patients and 10 normal controls by FACS analysis.

Results: The percentages of gammadelta T cells were remarkably down-regulated in active SLE patients (2.96±1.84%, n=30) compared with that of inactive (5.31±3.05%, n=12) and normal controls (6.83±2.85 %, n=10, both p<0.01). The absolute number of gammadelta T cells decreased significantly in active SLE patients ($1.72±1.58×10^7$/L, n=30) than that in inactive SLE ($5.27±3.60×10^7$/L, n=12, p<0.01), both lower than in normal controls ($10.07±4.99 ×10^7$/L, n=10, both p<0.01). There was increased gammadelta T cells apoptosis (17.03±8.71%, n=6) in SLE patients than in normal controls (6.67±1.18%, n=6, p<0.05). The positive rate of gammadelta T intracellular IFN-γ, IL-4, IL-10 and TGF-bƒn production in 20 SLE patients were 33.19±20.20 %, 1.04±0.93 %, 1.91±0.98 % and 2.20±1.97 %, significantly higher than that of 10 normal controls (IFN-γ: ƒn5.87±4.63%, IL-4: 0.30±0.34%, IL-10: 0.18±0.31%, TGF-bƒ[a]0.21±0.22%, all p < 0.01). While there were no differences in the percentages of IL-17-positive gammadelta T cells betweenƒn SLE patients (0.14±0.24%, n=20) and normal controls (0.18±0.31%, n=10).

Conclusion: Gammadelta T cells are down-regulated in SLE partly due to excessive apoptosis. Gammadelta T cells secret both pro- and anti-inflammatory cytokines in SLE microenvironment, suggesting these cells participate in both the regulation and the propagation of lupus.

Disclosure: **L. Sun**, None; **X. Li**, None; **Z. Lu**, None.

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Expression of the Mer Receptor Tyrosine Kinase On Peripheral Blood Mononuclear Cells From Systemic Lupus Erythematosus Patients. Brendan A. Hilliard[1], Gaetano Zizzo[1], Margaret K. Linan[1] and Philip L. Cohen[2]. [1]Temple University School of Medicine, Philadelphia, PA, [2]Temple University, Philadelphia, PA

Background/Purpose: The Mer tyrosine kinase (Mertk) is necessary for optimal removal of apoptotic cells in animal models. Its ligation by apoptotic cell-bound protein S and GAS 6 also leads to an associated suppression of innate immunity. Thus, Mertk may have a role in controlling immune responses to antigens exposed on apoptotic cells. Immunoreactivity to such antigens is a defining characteristic of systemic lupus erythematosus. We therefore compared the level of expression of Mertk in leukocytes from the blood of normal human subjects and patients with lupus erythematosus (SLE).

Methods: Tumor cell lines known to express Mertk at the mRNA level or by western blot were used to identify antibodies that could reliably detect the Mertk and the related Tyro3 kinase by immunofluorescence. Flow cytometry of isolated peripheral blood mononuclear cells was subsequently used to compare the levels of Mertk and Tyro3 on leukocytes from the blood of SLE patients (n=23) and normal control individuals (n=14). Monocytes were identified by their high expression of CD14 together with their forward and side scatter characteristics and in some experiments by their lack of CD15 expression. Myeloid dendritic cells were identified by their lack of lineage specific markers CD3, CD14, CD19, CD56, high expression of CD11c and

low expression of CD123. Plasmacytoid dendritic cells were identified by their lack of lineage specific markers, their high expression of CD123, and low expression of CD11c.

Results: Mertk was detected on dendritic cells (DC) and monocytes from both normal individuals and from SLE patients. There was reduced Mertk expression on myeloid dendritic cells from SLE patients compared to controls (p<.03), whereas on plasmacytoid dendritic cells there was very low expression in both groups. For monocytes, high levels of Mertk expression were observed on the small CD16+ population, whereas the much larger CD16- population of monocytes expressed low levels of Mertk. There was no difference in monocyte Mertk expression on cells from SLE patients compared to controls. Tyro3 was barely detectable on any peripheral blood leukocytes, and there were no statistical differences on its expression in any of the cell types examined.

Conclusion: Myeloid DC from lupus patients express lower levels of Mertk than cells from normal individuals. Mertk expression on monocytes and plasmacytoid DC from SLE patients is not different from expression on cells from normal controls. Because Mertk is an important receptor for clearance of apoptotic cells and because DC Mertk expression regulates cytokine production, the observed lower expression of MertK on myeloid DC may lead to a lack of control of their activation and contribute to the hyper activation of immunity in lupus.

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Activation of the Interferon Pathway Is Dependent Upon Autoantibodies in African-American SLE Patients, but Not in European-American SLE Patients. Kichul Ko, Yelena Koldobskaya, Elizabeth Rosenzweig and Timothy B. Niewold. University of Chicago, Chicago, IL

Background/Purpose: Gene expression studies have been instrumental in defining important aspects of the complex immunological pathogenesis in systemic lupus erythematosus (SLE) which is a heterogeneous disease that manifests differently by ancestry, and by the presence of autoantibodies directed at RNA binding proteins (anti-RBP). Moreover, anti-RBP antibodies are associated with high serum interferon (IFN)-α, which plays an important role in pathogenesis of SLE. Our overall hypothesis was that the molecular pathogenesis of SLE differs between African-American (AA) and European-American (EA) SLE patients, and between those with anti-RBP antibodies and those who lack these antibodies. We aimed to explore this hypothesis using peripheral blood gene expression profiling.

Methods: Whole blood RNA from 33 female SLE patients and 16 matched female controls from AA and EA ancestral backgrounds was analyzed on Affymetrix Gene 1.0 ST gene expression arrays. Two-tailed t-tests were performed to compare the expression values between cases and controls in each ancestry. Differentially expressed genes with a cutoff P of 0.05 were further explored using Ingenuity Pathway Analysis (IPA) to compare the top canonical pathways amongst the sample groups. An independent replication cohort of more than 100 SLE patient samples and 30 controls was used to test the hypotheses generated by the microarray data, using qPCR to quantify gene expression.

Results: Both AA and EA female (AAF and EAF respectively) patients with positive anti-RBP antibodies (RBP+) showed similar IFN-related canonical pathways such as IFN Signaling ($P = 1.3 \times 10^{-7}$ and 6.3×10^{-11} in AAF vs. EAF patients respectively), Antigen Presenting Pathway ($P = 1.8 \times 10^{-5}$ and 2.5×10^{-6}) and a number of pattern recognition receptor pathways. The key pathway difference was shown between AAF and EAF patients with negative anti-RBP antibodies (RBP-) as EAF patients also showed IFN Signaling ($P = 1.0 \times 10^{-5}$) and Antigen Presenting Pathway ($P = 1.3 \times 10^{-11}$) whereas AAF patients with RBP- did not reveal any IFN-related pathways. A replication study was performed through qPCR on 3 IFN-inducible genes, IFIT1, MX1 and PKR, and showed similar results. All three genes were strongly up-regulated in RBP+ patients in both ancestries, and PKR was up-regulated in EAF patients with RBP- but these findings were completely absent in AAF patients with RBP-.

Conclusion: Our data show that IFN-induced gene expression is completely dependent on the presence of autoantibodies in AA SLE patients but not in EA patients. Further studies are needed to explore other novel pathways that may define the heterogeneity in SLE, especially in the RBP- AA group.

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Molecular Analysis of 9G4+ Antibodies in Systemic Lupus Erythematosus. Christopher Richardson[1], Asiya Seema Chida[2], Erin Fox[1], Lin Silver[1], Diana G. Adlowitz[1], Scott Jenks[2], Elise Palmer[1], Christopher Tipton[2] and Ignacio Sanz[2]. [1]University of Rochester, Rochester, NY, [2]Emory University, Atlanta, GA

Background/Purpose: Elevated titers of serum autoantibodies expressing the 9G4 idiotype are highly specific for SLE and correlate with disease activity and clinical manifestations. 9G4+ antibodies have been shown to be reactive to a wide variety of autoantigens, including B cells, dsDNA, and cardiolipin. In this study we analyze the molecular characteristics that contribute to this autoreactivity.

Methods: A panel of 9G4+ monoclonal antibodies was generated from single FACS-sorted naïve (CD19+IgD+CD27-CD24+CD38+) and isotype-switched memory (CD19+IgD-CD27+) B cells from SLE patients and healthy controls. Site-directed mutagenesis of the hydrophobic patch and light chain exchange were performed. Monoclonal antibodies were tested by ANA, dsDNA, and cardiolipin ELISA. Reactivity to B cells and apoptotic cells was determined by flow cytometry. The contribution of the hydrophobic patch, the HCDR3, and light chains to binding of the various self-antigens was analyzed.

Results: A significant percentage of 9G4+ monoclonal antibodies were reactive to autoantigen, including Hep-2 nuclear antigens (65%), B cells (48%), apoptotic cells (22%), dsDNA (9%), and cardiolipin (7%). Strong binding to apoptotic cells, dsDNA, and cardiolipin was more common among antibodies derived from SLE memory cells. Site-directed mutagenesis showed that B cell binding is mediated by the VH4–34-encoded FR1 hydrophobic patch (which also determines the expression of the 9G4 idiotype). By contrast, autoreactivity to the other SLE-related antigens is patch-independent and is actually enhanced by elimination of the 9G4 idiotype. In addition, apoptotic cell and ANA-dsDNA reactivity correlate with the charge of the HCDR3, while B cell binding does not. Finally, light chains can substantially change VH4–34-associated autoreactivity.

Conclusion: Our findings show that 9G4+ antibodies are reactive to several antigens important in SLE pathogenesis, and bind antigen in two fundamentally different ways. We also show that the intrinsic autoreactivity imprinted by the expression of 9G4+ VH4–34 heavy chains can be substantially modulated by somatic hypermutation and light chain replacement.

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Characterization of Pro-Inflammatory Cytokines and Vitamin D Levels in a Lupus Cohort and Correlation with Disease Activity. Rohan Willis[1], Praveen Jajoria[1], Brock E. Harper[1], Emilio B. Gonzalez[1], Michelle Petri[2], Ehtisham Akhter[2], Hong Fang[2] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Multiple cytokines play a role in the immune dysregulation seen in systemic lupus erythematosus (SLE) and the local inflammatory responses that ultimately lead to tissue injury. IL6, TNFα, sCD40L, IFNα and IFN inducible cytokines such as MCP1 and IP10 are correlated with disease activity as measured by the SLEDAI, SLAM-R, ESR and anti-dsDNA antibody titres. Elevated VEGF and IL1β levels have been demonstrated in patients with antiphospholipid syndrome (APS). Low serum 25-hydroxy vitamin D (25OH-VD) levels are found in sera of pts with SLE and have been associated with higher fatigue and pain scores. Studies assessing lupus disease activity and Vit D levels have shown contradictory results. As such we sought to determine the proinflammatory biomarkers elevated in a cohort of SLE patients compared to controls, the correlation with disease activity levels and the prevalence of abnormally low vitamin D levels.

Methods: 388 patients with samples from baseline visit were selected from a longitudinal cohort of SLE subjects. IFNα2, IL1β, IL6, IL8, IP10, TNFα, VEGF and sCD40L levels were determined by a multiplexed immunoassay [Millipore]. Disease activity was assessed using SELENA-SLEDAI scores. 25OH-VD levels were measured using either a chemiluminescence or ELISA assay, and pts classified into 3 groups: normal (25OH-VD >30 ng/mL), insufficient (20–30) and deficient (<20). The

non-parametric two-sample median test was used to compare medians of cytokines in SLE pts vs controls. Pearson correlation was used to identify association of disease activity and physician global assessment (PGA) with cytokine levels.

Results: Most cytokines were significantly elevated in SLE patients vs controls, with the exception of IL8 that was significantly elevated in controls (Table). Of 379 subjects with 25OH-VD results, 36.1% (137/379) had deficiency, 29.3% (111/379) had insufficiency and 34.6% (131/379) had normal 25OH-VD levels. IP10 correlated with PGA and SLEDAI (PGA:0.15, p=0.0034 and SLEDAI:0.26, p<0.0001). All other correlations of cytokines and 25OH-VD with PGA and SLEDAI were not significant.

Table 1. Levels of cytokines in SLE patients vs control group

Cytokines	Controls/Median (N=30)	SLE/Median (N=388)	P–value
INFα2	0	10.37	0.012
IL–6	0	0.63	0.0025
IL–8	27.40	7.07	<0.0001
IL–1β	0	0.02	0.0004
TNFα	0	7.52	<0.0001
VEGF	88.30	158.65	0.0025
IP–10	96.22	413.48	<0.0001
sCD40L	16.39	2163.51	<0.0001

Conclusion: This study confirms numerous reports of elevated proinflammatory cytokines in SLE patients. Interestingly, over 2/3 of this population of SLE patients had below normal vitamin D levels but no correlation with SLEDAI or PGA was seen. The IFN-inducible cytokine IP10 correlated with increased disease activity as determined by both objective and subjective measures.

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ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics
Sunday, November 11, 2012, 9:00 AM–6:00 PM

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A Phase 1 Multicenter, Open-Label Study of MEDI-546, a Human Anti-Type I Interferon Receptor Monoclonal Antibody, in Adults with Scleroderma.

Avram Z. Goldberg[1], Thomas D. Geppert[2], Elena Schiopu[3], Tracy M. Frech[4], Vivien M. Hsu[5], Robert W. Simms[6], Stanford L. Peng[7], Yihong Yao[8], Nairouz Elgeioushi[8], Bing Wang[9], Linda Chang[9] and Stephen Yoo[8]. [1]North Shore-LIJ Health System, Lake Success, NY, [2]Metroplex Clinical Research Center, LLC, Dallas, TX, [3]University of Michigan, Ann Arbor, MI, [4]University of Utah School of Medicine, SLC, UT, [5]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [6]Boston University School of Medicine, Boston, MA, [7]Benaroya Research Institute at Virginia Mason Medical Center, Seattle, WA, [8]MedImmune, Gaithersburg, MD, [9]MedImmune, Hayward, CA

Background/Purpose: Type I interferons (IFNs) have been implicated in the pathogenesis of scleroderma. This phase 1 study evaluated safety, pharmacokinetics (PK), pharmacodynamics, and immunogenicity of single and multiple intravenous doses of MEDI-546, a human monoclonal antibody directed against the type I IFN receptor, in adults with scleroderma.

Methods: Subjects ($\geq$18 years) who met the American College of Rheumatology criteria for scleroderma and had a modified Rodnan Total Skin Score $\geq$2 in an area suitable for repeat biopsy were enrolled in this multicenter open-label, dose-escalation study. Six cohorts received single doses (0.1, 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg) and 3 received multiple doses (0.3, 1.0, or 5.0 mg/kg weekly $\times$ 4) of MEDI-546. Subjects were evaluated through day 84 for single-dose groups and day 105 for multiple-dose groups. Safety assessments included adverse events (AEs) and laboratory tests. Serial blood samples were collected from all subjects for the determination of serum concentration of MEDI-546, the expression of type I IFN-inducible genes, and the presence of antidrug antibodies (ADAs).

Results: Of the 34 subjects, 33 completed the study. No trends in the type, frequency, or severity of AEs reported or laboratory abnormalities assessed were observed with increasing doses of MEDI-546. No deaths occurred during the study. Of the 4 treatment-emergent serious AEs (SAEs) reported, 1 (chronic myelogenous leukemia) was considered to be possibly treatment-related. The other 3 SAEs not considered to be treatment-related occurred in 2 subjects; 1 had vertigo and the other had osteomyelitis and skin ulcer. The most common treatment-emergent AEs were upper respiratory tract infection, headache, diarrhea, nausea, arthralgia, fatigue, and pruritus. Two subjects discontinued MEDI-546 after the first dose: 1 was due to an SAE of vertigo and an AE of head injury and discontinued the study 3 months later; the other was due to a non-SAE of normocytic anemia. MEDI-546 exhibited nonlinear PK at lower dose levels presumably due to the IFN receptor-mediated clearance. ADAs were detected in 2/21 subjects in the single-dose cohorts and 3/11 in the multiple-dose cohorts; 1 subject had persistent titers. The presence of ADAs had no effect on serum drug levels. At baseline, 22 subjects had positive type I IFN gene signature scores in whole blood. Subjects with positive baseline type I IFN gene signature score in whole blood reached or approached maximum inhibition of this signature within 1 day after dosing. The suppression persisted through day 84 in subjects receiving MEDI-546 at single-dose 20.0 mg/kg and multiple-dose $\geq$1 mg/kg. MEDI-546 at single-dose $\geq$0.3 mg/kg and multiple-dose $\geq$1 mg/kg suppressed the type I IFN gene signature in skin 7 and 28 days, respectively, after dosing.

Conclusion: The PK of MEDI-546 was subject to IFN receptor-mediated clearance at low-dose levels. The presence of ADAs had no apparent impact on PK. Decreased type I IFN gene expression in whole blood was seen at doses of $\geq$3 mg/kg after 1 day of dosing; expression decreased in skin after 7 days. These results and the safety profile observed in this study warrant further clinical development of MEDI-546.

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A Placebo-Controlled Phase II Study of Hyperimmune Caprine Serum in Diffuse Cutaneous Systemic Sclerosis: Safety and Potential Efficacy.

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Background/Purpose: We have performed a study to explore safety and tolerability of hyperimmune caprine serum (AIMSPRO®) prepared under GMP conditions in established diffuse cutaneous systemic sclerosis (dcSSc). Potential measures of efficacy and biological activity were also examined.

Methods: A double-blind parallel group placebo controlled clinical trial was performed under clinical trial authorisation with regulatory authorisation and institutional ethical approval. After informed consent, 20 patients with established dcSSc of greater than 3 years duration not receiving immunosuppressive therapy were randomised to receive either active (n=10) or placebo formulation (n=10) by subcutaneous twice weekly injection over 26 weeks. Clinical assessments evaluated over 26 weeks included modified Rodnan skin score (MRSS), pulmonary function indices and HAQ-DI.

Results: There were no safety concerns during this study. Frequency of adverse events was not different between active and placebo groups; 154 AE occurred in those receiving placebo and 139 AE in the AIMSPRO® treated subjects. The commonest adverse event was minor injection site reaction occurring in 12 subjects. There were 6 SAE in 3 subjects in the placebo group and 4 SAE in 3 subjects receiving active treatment. No SAE was judged treatment related.

Mean ($\pm$SD) baseline MRSS for the study cohort was 15.1 $\pm$7.1, with no significant difference between active or placebo groups. Mean skin score fell by 1.4$\pm$4.7 units with active treatment but worsened by 2.1$\pm$6.4 units on placebo. This difference did not reach statistical significance (p=0.18, unpaired t-test) but more cases on active treatment showed significant improvement of more than 4 units and over 20% of baseline MRSS (5/10) compared with placebo (1/10; p=0.01, Fisher exact test). HAQ-DI (Mean$\pm$SD) at baseline was 1.15$\pm$0.07 for active and 1.59$\pm$0.63 for placebo group and at 26 weeks was 1.24$\pm$0.98 for active and 1.56$\pm$0.55 for placebo. These changes were not statistically different (p=0.34, unpaired t-test).

Lung function indices (Table 1) showed a trend of benefit for active treatment compared to the placebo group for those variables that reflect respiratory effort (FVC and FEV1). DLco and TLC did not change during the study.

Table 1.

		Baseline	26 weeks	Units	p-value (unpaired t-test)
FVC	active	2.68±0.76	2.76±0.69	Litres	p=0.06
	placebo	3.12±2.96	2.96±0.92		
FEV1	active	1.99±0.45	2.02±0.44	Litres	p=0.10
	placebo	2.31±0.66	2.21±0.66		
DLco	active	5.73±1.80	5.61±1.87	mmol/min/kPA	p=0.36
	placebo	5.99±2.19	5.67±2.28		

Conclusion: These results demonstrate tolerability and safety of this novel biological agent in established diffuse cutaneous SSc. The value of a placebo treated control group in small clinical trials evaluating skin disease in SSc is confirmed. Potential improvement in MRSS in cases receiving active therapy and trends of improvement for pulmonary function indices suggest that this intervention may be of clinical benefit and warrants further evaluation.

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Nilotinib (Tasigna™) in the Treatment of Early Diffuse Systemic Sclerosis: A Single Group, Open Label Pilot Clinical Trial. Jessica K. Gordon[1], Morgana L. Davids[1], Kamini Doobay[1], Cynthia Magro[2], Horatio F. Wildman[2], Stephen L. Lyman[1], Mary K. Crow[1] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill-Cornell Medical Center, New York

Background/Purpose: Tyrosine kinase inhibitors (TKI) which selectively antagonize c-abl and PDGFR have been shown in preclinical models to decrease fibrosis. TKIs are therapies of interest for Systemic Sclerosis (SSc) with potential efficacy observed in several, but not all, open label studies of imatinib. Side effects relating to fluid retention were common and led to intolerance in some patients. Nilotinib is a second-generation TKI with increased potency and a different side effect profile compared to imatinib, specifically with less associated fluid retention.

Methods: In this single group, open label, pilot trial, we recruited 10 adult patients with diffuse cutaneous (dc) SSc of less than 3 yrs duration since the initial SSc symptom apart from the Raynaud's Phenomenon. Patients were treated with nilotinib 400 mg po twice daily. Patients were excluded if they had a QTc>450 msec. Concurrent immunosuppressive treatment was not allowed. The primary endpoint was safety as assessed by the number of adverse effects (AEs) and serious (S)AEs, and the primary efficacy endpoint was change in the Modified Rodnan Skin Score (MRSS) after 6 mo. Secondary endpoints include forced vital capacity (FVC), diffusion lung capacity (DLCO) and other measures. After 6 mo patients are offered continued treatment for an additional 24 mo. Skin biopsies are performed at baseline and after 6 and 12 mos.

Results: Nineteen patients were initially screened; 5 were excluded due to baseline QTc>450 msec. At baseline the median age was 46 (IQR 33, 52), 80% were female, 50% were Caucasian, and disease duration was 0.7 yrs (0.5, 1.7). 30% were SCL70 and 50% were PolIII positive. 30% had ILD. 70% demonstrated an increase in the MRSS in the 1 mo btwn screen and baseline, and 40% had tendon friction rubs. The baseline MRSS was 27.5 (IQR 22, 35).

Seven patients completed 6 mo; 3 patients stopped early − 2 due to Grade 1–2 QTc prolongation and 1 due to progression of preexisting coronary artery disease. 42 AEs and 2 SAEs were observed during the treatment period; 83% were considered to be at least possibly related to nilotinib. 97% of AEs were grade 1 or 2. No fluid retention was observed.

In the 7 patients who completed 6 mo of treatment, the MRSS improved from a baseline of 27 (IQR 22, 30) to 22 (16, 28) at 6 mo, p=0.047. The FVC was 81% predicted (73, 86) at baseline and 74% (69, 83) at 6 mo, p=0.25, and the DLCO was 73.5% (67, 81) at baseline and 68% (66, 84) at 6 mo, p=0.5. The physician global assessment improved from 61.3 (56.7, 81.3) to 32 (42.3, 55.3), p<0.01. There were no significant differences noted in the following: oral aperture, hand extension, finger to palm distance, ESR, SHAQ-DI, SF-36 mental or physical components, or the Medsger Severity Scale.

Conclusion: Nilotinib was tolerated by the majority of patients in this study. The MRSS improved significantly with 6 mo of treatment in this very early and active group of patients. The FVC and DLCO remained stable as did the additional outcome measures. Tolerability was limited primarily by mildly prolonged QTc, which is a known side effect of nilotinib and an exclusion criterion for continuation in this study. Baseline QTc prolongation also limited patient eligibility. Further study of nilotinib is warranted in a randomized controlled manner.

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Comparison of Intense Pulsed Light and Laser Treatment of Telangiectases in Systemic Sclerosis. Graham Dinsdale[1], Andrea Murray[1], Tonia Moore[1], Janice E. Ferguson[2], Holly Ennis[1], Christopher E.M Griffiths[3] and Ariane Herrick[1]. [1]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom, [2]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom, [3]Dermatology Centre, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom

Background/Purpose: Cutaneous telangiectases commonly occur in systemic sclerosis (SSc) and are distressing for the patient due to their perceived unsightly appearance. The current standard treatment is pulsed dye laser (PDL) therapy which is effective but often painful and does not prevent re-occurrence. Side effects include transient bruising and hypopigmentation. Intense pulsed light (IPL) is a potential alternative treatment using short, high-energy pulses of white light to destroy telangiectases via photothermal effects. IPL causes minimal bruising and no additional side effects compared to PDL. Our aim was to carry out an intra-patient comparison of PDL and IPL treatment of SSc-related telangiectases to determine relative efficacy and tolerability.

Methods: 20 patients (median 58 (range 49–72) years; 1 male) with SSc and approximately bilaterally-symmetric areas (face or upper limb) of telangiectases were recruited (1 withdrew after baseline). Patients were randomised to PDL treatment on the left/right side, with IPL treatment on the other. Following patch test of treatments (week −2; no adverse reactions reported), patients attended 3 treatment sessions at weeks 0 (baseline), 4 and 8. Photographs, dermoscopy and laser Doppler (LD) images of the treatment area were recorded prior to each treatment. Post-treatment, patients returned at 16 weeks and 9 months for repeat imaging and assessment. Photographs were assessed by comparison with baseline/previous image on a standardised scoring scale (−2 "much worse" to +2 "much better"). Dermoscopy images were assessed in the same way as the photographs. Average perfusion for 3 cardinal lesions on each side was extracted from the LD imaging data. Statistical analysis was carried out in SPSS.

Results: Both PDL and IPL treatment resulted in clinical improvement at most time points (Table 1, mean score values positive), as assessed by photographs and dermoscopy. The exception was dermoscopy at the week 16/month 9comparison, which showed slight negative (PDL) or zero (IPL) mean scores suggestive of worsening or neutral appearance of telangiectases. The differences between scores for PDL and IPL suggest that PDL was associated with greater treatment response. Analysis of LD images (ANOVA) showed no significant difference between PDL and IPL treatment response at any time point; however, when comparing baseline perfusion to that at Week 16 (paired-t test) significant differences were found for PDL (median [interquartile range]: baseline 3.3 [2.7–4.7], week 16 2.4 (1.5–3.2), p=0.009) but not IPL (baseline 3.4 [2.5–4.1], week 16 2.8 (1.9–3.1), p=0.053). There were no reported side effects with IPL; PDL caused transient bruising.

Table 1.

	Comparison	IPL	PDL	p–value (IPL–PDL difference)
Photographs‡	**Week 4 vs baseline (n=17)**	1.2 (1.0, 1.4)	1.3 (1.0, 1.5)	0.56
	Week 8 vs baseline (n=16)	1.4 (1.1, 1.8)	1.5 (1.2, 1.8)	0.62
	Week 16 vs baseline (n=15)	1.4 (0.9, 1.8)	1.7 (1.4, 2.0)	*0.01
	Month 9 vs Week 16 (n=8)	0.3 (−0.2,0.7)	0.3 (−0.1,0.7)	0.80
Dermoscopy‡	**Week 4 vs baseline (n=17)**	0.6 (0.3, 0.8)	0.8 (0.6, 1.0)	*0.02
	Week 8 vs baseline (n=16)	0.7 (0.4, 0.9)	1.0 (0.8, 1.3)	*0.04
	Week 16 vs baseline (n=13)	0.8 (0.6, 1.1)	1.3 (1.0, 1.5)	*0.02
	Month 9 vs Week 16 (n=6)	−0.0 (−0.5,0.5)	−0.3 (−0.6,0.0)	0.22

‡ – mean score (95% C.I.), *p<0.05

Conclusion:

1) IPL and PDL are both effective treatments of SSc-related telangiectases, as assessed in this intra-patient study by photographs and dermoscopy.

2) PDL therapy produces a greater treatment response than IPL; however IPL has fewer side effects.

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Risk Factors for EARLY Mortality in Scleroderma Patients: A Report From the EULAR Scleroderma Trials and Research Group (EUSTAR) Database. Patricia E. Carreira[1], Loreto Carmona[2], Beatriz E. Joven[3], Christopher P. Denton[4], Yannick Allanore[5], Ulrich A. Walker[6], Marco Matucci-Cerinic[7], Ulf Müller-Ladner[8] and Eustar[9]. [1]Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Universidad Camilo José Cela, Villanueva de la Cañada, Spain, [3]HOSPITAL UNIVERSITARIO 12 DE OCTUBRE, Madrid, Spain, [4]UCL, London, United Kingdom, [5]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [6]Universitäts-Poliklinik, Felix-Platter Spital, Basel, Switzerland, [7]University of Florence, Florence, Italy, [8]Kerckhoff-Klinik GmbH, Bad Nauheim, Germany, [9]Florence

Background/Purpose: To identify risk factors for early mortality in a large group of recently diagnosed systemic sclerosis (SSc) patients

Methods: EUSTAR collects prospectively the Minimal Essential Data Set (MEDS), on all sequential patients fulfilling the American College of Rheumatology diagnostic criteria in participating centres, in an annual basis. Patients with disease duration of less than 3 years at the first EUSTAR entry, and with at least one follow-up visit, were selected. Baseline data from the first visit were compared between SSc cases registered as dead up to December 2011, and living patients. Kaplan-Meier analysis was used to estimate survival, and Cox proportional hazards regression analysis, corrected by age at the end of follow-up, was used to identify factors associated with early mortality.

Results: From 1188 patients, 671 (19% men) had at least one follow-up visit. From those, 276 had diffuse and 348 had limited disease. Mean age at entry was 53 ± 15 years, and at first non Raynaud symptom 50 ± 15 years. Mean disease duration was 19 ± 6 months and time between the onset of Raynaud and first non Raynaud symptom was 4 ± 7 months. After 43 ± 24 months of follow-up from the first visit and 57 ± 26 months from the first non Raynaud symptom, 111 patients (17%) were dead. Death occurred after 43 ± 27 months from the first non Raynaud symptom. Mean survival for the whole group was 116 (95%CI 110–122) months. By Cox proportional hazards regression multivariate analysis, main risk factors for mortality were: higher skin score (HR 1–03, 95%CI 1.003–1.05, p=0.02), acute phase reactants elevation (HR 1.8, 95%CI 1.1–2.8; p=0.02), joint contractures (HR 1.8; 95%CI 1.1–2.8; p=0.002), CK elevation (HR 1.9, 95%CI 1.1–3.3, p=0.04), cardiac blocks (HR 2.1, 95%CI 1.3–3.3, p=0.004), diastolic dysfunction (HR 2.1, 95%CI 1.3–3.3, p=0.002) and ischemic ulcers (HR 1.9, 95%CI 1.2–2.9, p=0.007). When only diffuse patients were analyzed, CK elevation, FVC below 80% and pulmonary hypertension were the risk factors for mortality. In the other hand, bad prognostic factors in limited patients were joint contractures, CK elevation, cardiac blocks, proteinuria and renal crisis.

Conclusion: In this large group of SSc patients, risk factors for early mortality are higher skin involvement with more severe vascular disease and cardiac involvement, especially if associated to elevated acute phase response. Muscular and cardiac involvement appear as a risk factor for mortality both in limited and diffuse disease, whereas lung and renal involvement have a mayor impact in diffuse and limited cases respectively.

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Demographic, Clinical, Serologic and Socioeconomic Measures Each Predict Mortality in Scleroderma. Allan C. Gelber, Rebecca L. Manno, Adrianne Woods, Ami A. Shah, Francesco Boin, Laura K. Hummers and Fredrick M. Wigley. Johns Hopkins University, Baltimore, MD

Background/Purpose: The epidemiologic literature has identified several demographic, clinical and serologic predictors of mortality in systemic sclerosis (scleroderma). Yet, relatively few cohorts are of sufficient size and racial composition to examine the independent contribution of these parameters to survival. We sought to determine the adjusted risk of mortality in scleroderma associated with gender, race, disease subset, and serologic and socioeconomic status in a large observational cohort study.

Methods: Between January 1, 1990 and December 31, 2009, a total of 2217 patients with scleroderma, either African American (n=409, 18%) or Caucasian (n=1808, 82%), were evaluated at a single university medical center. The vital status of the cohort was ascertained using the Social Security Death Index; cumulative incidence of mortality was estimated using Kaplan-Meier analysis. Next, the independent risk of mortality was estimated using Cox proportional hazards analysis, with adjustment for age at disease onset and disease duration, in addition to each variable depicted in the table below.

Results: This cohort of 2217 patients was 1838 (83%) female; mean age (+SD) at disease onset was 46 (+14) years. Among these patients, 1387 (63%) manifested the limited and 830 (37%) the diffuse cutaneous subtype of disease. Overall, 1846 (83%) fulfilled ACR criteria for scleroderma, whereas 361 (16%) satisfied at least 3 of 5 CREST criteria. Among the 1511 patients whose sera was tested for anti-centromere, and 1393 assayed for anti-topoisomerase antibodies, 452 (30%) and 294 (21%) were seropositive, respectively. In addition, 11% of the cohort had medical assistance or no health insurance, whereas 89% had Medicare or private insurance. During a median follow-up period of 4 years, 700 patients died. Overall, cumulative mortality at 1 and 5 years of follow-up was 8% and 32%, respectively. The relative risk of mortality, in two multivariate models, was as follows:

Multivariate Model 1	Adjusted RR	95%CI	Multivariate Model 2	Adjusted RR	95%CI
Male vs Female	1.4	1.1–1.9	Male vs Female	1.4	1.1–1.9
African American vs Caucasian	1.5	1.1–2.1	African American vs Caucasian	1.3	1.0–1.8
Diffuse vs Limited	1.4	1.0–1.8	Diffuse vs Limited	1.2	0.9–1.5
Topoisomerase antibody, pos vs neg	1.0	0.7–1.3	Anti–centromere antibody, pos vs neg	0.8	0.6–1.0
Health Insurance, MA/no vs Mdcr/yes	1.2	0.8–1.7	Health Insurance, MA/no vs Mdcr/yes	1.4	1.0–1.8

Conclusion: Persons with scleroderma who are male, African American, with diffuse cutaneous disease, and those without private or Medicare health insurance, experienced a heightened risk of mortality. Anti-centromere, but not topoisomerase, antibody was protective against mortality. These findings imply that demographic, clinical features, serologic and socioeconomic status, each impact upon and contribute to the risk of survival in scleroderma.

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External Validation of a Two-Year Mortality Risk Prediction Rule in Early Diffuse Systemic Sclerosis Patients. Robyn T. Domsic[1], Svetlana Nihtyanova[2], Stephen R. Wisniewski[3], Michael J. Fine[4], C. Kent Kwoh[5], Christopher P. Denton[6] and Thomas A. Medsger Jr.[7]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Royal Free Hospital, Medical School, London, England, [3]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [4]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, [5]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [6]UCL, London, United Kingdom, [7]Univ of Pittsburgh, Pittsburgh, PA

Background/Purpose: The ability to risk stratify patients for short term mortality is important in SSc patient care and clinical trial design; but there is no externally validated short term mortality model in early diffuse cutaneous systemic sclerosis (dcSSc). We have previously used a prospectively enrolled large American single center SSc databank to develop and internally validate a 4-factor risk stratification model for two year mortality. Our objective was to externally validate this two year mortality model in a European population of early dcSSc Caucasian patients.

Methods: A large European single-center prospectively enrolled SSc databank was used to identify an inception cohort of adult early dcSSc seen for an initial visit between 2000 and 2006 to serve as the external validation cohort. Patients were considered to have early dcSSc if their first visit occurred< 2 years after the first symptom attributable to SSc with skin thickening proximal to the elbows or knees. Vital status was determined using the UK National Care Records Service.

We used a 4-factor model (age at first visit, gastrointestinal severity, skin thickness progression rate and presence of anemia) to calculate a total sum score (range of −1 to 8) and risk stratify patients into low, moderate and high risk for two year mortality in the original derivation and external validation cohort. Multiple data imputations were used for missing data in the validation

cohort. Stratum-specific chi-squares were compared for the low, moderate and high risk groups.

Results: Of 160 European early dcSSc patients, 110 were Caucasian, and formed the external validation cohort. The validation cohort had a mean age of 51.2 ± 12.4 years, was 74% female and a mean modified Rodnan skin score (mRss) of 26.6 ± 8.1. Median disease duration from first SSc symptom was1.02 years (IQR 0.78, 1.49), or 0.78 years (0.52, 1.17) from first non-Raynaud symptom. There was no significant difference in age, gender, disease duration or mRss between the validation and derivation cohort. At two years, 7.3% had died in the validation cohort, compared to 22.6% in the original derivation cohort (p=0.0005). The stratum-specific comparison of mortality rates using this risk model are shown in Table 1. There was no difference in prediction of low or moderate risk groups between the models.

Table 1. Comparison of risk class specific two-year mortality rates in the derivation and validation cohorts

Risk Class (sum of points)	Derivation cohort (n=252)		Validation cohort (n=110)		p-value
	total n	% who died	total n	% who died	
Low (≤ 0)	63	1.6	33	3.0	0.64
Moderate (1–2)	108	14.8	61	8.2	0.21
High (3 ≤)	81	49.4	16	12.5	0.006

Conclusion: We have now validated a two year mortality risk stratification model for early dcSSc patients in American and European cohorts. In this external validation, the model accurately predicted those at low and moderate risk of death at two years from the first visit. There was a significantly lower rate of death in the validation cohort, possibly related to the inclusion of only recent patients or differences in the underlying populations, which may have affected performance in the high risk group. This model may be used to risk stratify patients for short-term mortality.

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Endothelial Dysfunction and Vascular Stiffness in Early Diffuse Systemic Sclerosis. Robyn T. Domsic[1], Dana Ivanco[1], Hunter C. Champion[1], Ali Shoushtari[1] and Thomas A. Medsger Jr.[2]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh, Pittsburgh, PA

Background/Purpose: Vascular dysfunction is a hallmark of systemic sclerosis (SSc). Current theories postulate endothelial injury and dysfunction as an early event in SSc pathogenesis. Prior cross-sectional studies suggest endothelial dysfunction and increased vascular stiffness in SSc, but generally use longstanding patients. Our aim was to measure and describe endothelial function and vascular stiffness in an inception cohort of early diffuse SSc patients.

Methods: Early diffuse SSc was defined as < 2 years from the first symptom attributable to SSc and skin thickening proximal to the elbows or knees. SSc patients were matched 1:1 with age (± 2 years), gender and race matched healthy controls. Vasodilators were held for 24 hours. Aortic pulse wave velocity (PWV) was used to assess vascular stiffness by averaging two measures recorded simultaneously at the carotid and femoral arteries. In a quiet and temperature controlled exam room, all underwent assessment of endothelial function with three validated methods: 1) assessment of endothelial-dependent flow-mediated dilation (FMD) by ultrasound before and after reactive hyperemia (RH) of the medium-sized brachial artery induced by pneumatic cuff for 5 minutes; 2) endothelial-independent vasodilation of the brachial artery before and after nitroglycerin (NTG); 3) assessment by Endo-PAT™, which measures the pulse wave amplitude before and after RH using a pneumatic probe on the index finger. FMD was expressed as % change in diameter after RH and NTG. EndoPAT calculates a reactive hyperemia index (RHI), with a RHI of < 1.67 previously validated as the cut-off for endothelial dysfunction. Differences in PWV, FMD, NTG and RHI were assessed by paired t-tests.

Results: 16 early diffuse SSc patients were compared to 16 age, gender and race-matched controls. The mean age in cases was 48.9 years (controls 48.2), 56% were female, 94% Caucasian and 6% Asian. The median disease duration at time of vascular study was 1.2 years (0.9, 1.8), and the mean modified Rodnan skin score 20.8 ± 8.3. 86% of patients experienced Raynaud phenomenon, 37% had digital pitting scars and none had renal crisis. 69% were on immunosuppressive agents. There was no difference in PWV between patients (6.58 ± 1.40) compared to controls (6.28 ± 1.04; p=0.67).

The median FMD % change after RH was not significantly different in cases and controls (4.6% ±5.1 vs 5.0%±5.3; p=0.10), or after NTG administration (p=0.90). However, there was a significant difference in EndoPAT RHI of 1.20 (±0.56) for patients and 2.06 (±0.52) for controls (p=0.002). Overall, 80% of patients had abnormal RHI suggesting ED, compared to 20% of controls.

Conclusion: There is no difference in large vessel vascular stiffness between early diffuse SSc patients and age, gender and race matched controls. Similarly, there is no difference in brachial-artery FMD to RH or NTG, suggesting no difference in endothelial function of the medium-sized arteries. However, there was significantly increased endothelial dysfunction of the small arterioles as measured by EndoPAT. These results suggest that endothelial changes occur in smaller arterioles and microvascular beds in early SSc, but not in macrovascular beds.

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Clinical Correlation of Flow-Mediated Endothelium-Dependent Vasodilatation in Systemic Sclerosis. Takehiro Takahashi[1], Yoshihide Asano[1], Eisuke Amiya[2], Masaru Hatano[2], Atsuko Ozeki[2], Aya Watanabe[2], Shuichi Kawarasaki[2], Tomoko Nakao[2], Zenshiro Tamaki[1], Takashi Taniguchi[1], Yohei Ichimura[1], Tetsuo Toyama[1], Masafumi Watanabe[2], Yasunobu Hirata[2], Ryozo Nagai[2] and Shinichi Sato[1]. [1]Department of Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Tokyo, Japan

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by initial vascular injuries and resultant fibrosis of skin and certain internal organs. Evidence has shown that vascular impairment in SSc may be a sign of endothelial dysfunction involving both microvascular and macrovascular systems. Ultrasound assessment of brachial artery endothelial-dependent flow-mediated dilation (FMD) is a noninvasive instrumental evaluation that is routinely performed as an index of macrovascular function. We evaluated the association of FMD with clinical features of SSc to assess the possible contribution of endothelial dysfunction to the developmental process of clinical features associated with this disease.

Methods: Twelve healthy controls and thirty-five consecutive patients with SSc (mean age 53 ± 17 years and 57 ± 11 years, respectively) were studied. In patients, clinical symptoms, such as swollen fingers, nailfold bleeding (NFB), pitting scars, digital ulcers, and Raynaud's phenomenon, were meticulously recorded. Eighteen patients had limited cutaneous SSc (lcSSc) and 17 had diffuse cutaneous SSc (dcSSc). Ultrasound assessment of FMD was performed on all patients. Correlation between FMD value (%FMD) and various typical symptoms, disease duration, and subtype of SSc was studied.

Results: There was significant decrease in %FMD in patients compared to healthy controls (5.72% versus 7.71%, respectively; p = 0.041). Especially, lcSSc patients had significantly lower %FMD values than healthy controls (5.25% versus 7.6%, p = 0.016), while the levels in dcSSc patients (6.8%) were comparable to those of healthy controls. Furthermore, in lcSSc patient group, patients with decreased %FMD had much longer disease duration than those with normal %FMD (p = 0.0088), while the age of these two patient groups was comparable. As for clinical symptoms, lcSSc patients with decreased %FMD showed much higher prevalence of digital ulcers and elevated RVSP than those with normal %FMD (for each; 75% versus 10%, p = 0.040). In addition, there was a trend towards the increase in the prevalence of decreased %DLco, but not decreased %VC, in lcSSc patients with decreased %FMD as compared to those with normal %FMD.

Conclusion: Endothelial function evaluated by %FMD is markedly impaired in SSc patients. lcSSc patients with decreased %FMD exhibited a significantly higher prevalence of clinical symptoms associated with vasculopathy. Furthermore, the values of %FMD greatly and inversely correlated with disease duration in lcSSc patients. Collectively, %FMD is potentially a powerful tool to evaluate the damage of vascular system in SSc, especially in limited cutaneous subtype of this disease.

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Vascular Differences Associated to Genetic Polymorphisms of Endothelial Nitric Oxide Synthase in Mexican Patients with Systemic Sclerosis. A Preliminary Report. Maria Pilar Cruz-Dominguez[1], Maria Angeles Martinez-Godinez[2], Angel Miliar-Garcia[2], Daniel Hector Montes-Cortes[3], Olga Vera-Lastra[4], Luis J. Jara-Quezada[5] and Anabel Reyes-Salazar[6]. [1]Hospital de Especialidades Centro Medico Nacional La Raza., Mexico, DF, Mexico, [2]Escuela Superior de Medicina. IPN, Mexico, D.F., Mexico, [3]Hospital General CMN La Raza, IMSS, Mexico DF, Mexico, [4]MD, Mexico City, Mexico, [5]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico, [6]Hospital de especialidades Centro Medico National "La Raza", IMSS, Mexico, D.F., Mexico

Background/Purpose: Vascular dysfunction usually is observed before clinically detectable fibrosis of systemic sclerosis (SSc). The eNOS catalyses the synthesis of **nitric oxide** (NO), which maintains basal vascular tone **and endothelial** function. **Abnormal production of** e-NOS and/or iNOS impairs NO availability causing vascular disease. Genetic polymorphism may participate in these alterations.

Objective: To investigate vascular differences associated to polymorphisms T-786C and G894T of the *eNOS* gene on differential expression of eNOS/iNOS in the skin and vascular Duplex Sonography parameters of SSc patients.

Methods: We included 139 consecutive SSc patients. The genotyping of T-786C and G894T polymorphisms of *eNOS* gene was performed by **Polymerase Chain Reaction Real-Time Assay**. The control group included 180 age-matched healthy volunteers. For the eNOS/iNOS skin expression we included 31 patients (14 lcSSc and 17 dcSSc).

Results: In lcSSc: T-786C prevalence was TT65.5%, TC30.2% and CC4.3% (OR 1.8, IC 0.4–7.9 associated to SSc); and the G894T prevalence was GT74.3%, GT20.3% and TT5.4% (OR 1.94, IC 0.54–7.04 associated to SSc). In dcSSc: the T-786C prevalence was TT76.6%, TC20%, and CC3.3%, and G894T polymorphism was GT 82%, GT 18% and TT 0% without association with SSc. In control group: the prevalence of T-786C polymorphism was TT68.45%, TC29.4%, and CC2.22%; for G894T polymorphism was GG74.1%, GT23.02%, TT2.87%. The mean relative expression of eNOS was $10.17 +/- 15.5$ and iNOS of $7.6 +/- 13.05$ in lcSSc. For dcSSc the mean relative expression of eNOS was $1.74 +/- 1.16$ and iNOS of $2.1 +/- 2.5$. $1.08 +/- 0.3$ and $1.36 +/- 0.7$ in skin of volunteers of control group. Left brachial intima-media thickness was statistically significantly greater in allelic variants of eNOS in SSc (p=0.025).

Conclusion: In the skin of both subtypes of systemic sclerosis, the relative expression of eNOS and iNOS is increased. Genetic polymorphisms of eNOS is associated with anormal intima-media thicknes in SSc patients.

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Arterial Stiffness Is Increased in Systemic Sclerosis: A Cross-Sectional Comparison with Matched Controls. Gene-Siew Ngian[1], Joanne Sahhar[2], Ian Wicks[3] and Sharon Van Doornum[4]. [1]The University of Melbourne, Parkville, Australia, [2]Monash Medical Centre, Clayton, Australia, [3]Royal Melbourne Hospital, Parkville, Australia, [4]The University of Melbourne, The Royal Melbourne Hospital, Melbourne, Australia

Background/Purpose: Atherosclerosis may be increased in systemic sclerosis (SSc)[1]. Increased arterial stiffness is a predictor of cardiovascular and all-cause mortality across a wide range of patient populations. Our aim was to determine if arterial stiffness is elevated in SSc and to evaluate correlates of arterial stiffness in SSc patients.

Methods: We performed two studies: 1) a comparison of arterial stiffness in 40 SSc patients free from cardiovascular disease or significant vascular manifestations of SSc (i.e. pulmonary arterial hypertension or scleroderma renal crisis) and 40 age- and sex-matched healthy controls, and 2) an analysis of determinants of arterial stiffness in a larger, unselected cohort of 80 SSc patients (which included the 40 patients from study 1). Arterial stiffness was measured using the augmentation index (AIx) and carotid-femoral pulse wave velocity (PWV), both of which increase with increasing arterial stiffness.

Results: In study 1 the SSc and control groups were well matched for age (52.2 vs 50 years respectively), sex (80% female in both groups) and cardiovascular risk factors. SSc patients had significantly higher AIx than controls ($31.2 +8.4$ vs $20.9 + 12.6\%$ respectively, $p<0.001$), with a non-significant increase in PWV ($7.3 +1.8$ vs $6.8 +1.1$m/s respectively, p=0.101).

In study 2, univariate analysis of the entire SSc cohort revealed that higher AIx was significantly associated with age ($p<0.001$), disease duration (p=0.001), anti-centromere antibody positivity (p=0.016), calcium channel blocker (CCB) therapy (p=0.004), systolic blood pressure (BP) (p=0.001) and diastolic BP (p=0.029). Higher PWV was significantly associated with age ($p<0.001$), disease duration (p=0.001), anti-centromere antibody positivity (p=0.022), lack of anti-Scl-70 antibody positivity (p=0.001), lower modified Rodnan skin score (p=0.016), angiotensin converting enzyme inhibitor therapy (p=0.035), systolic BP ($p<0.001$) and diastolic BP ($p<0.001$). After adjusting for age, CCB therapy remained predictive of higher AIx (p=0.014) and systolic ($p<0.001$) and diastolic (p=0.005) BP remained predictive of higher PWV.

Conclusion: Compared with healthy controls, SSc patients had increased arterial stiffness, with significantly higher AIx and non-significantly higher PWV. This suggests that patients with SSc may have an increased prevalence of subclinical atherosclerosis. After adjusting for age, CCB therapy was associated with higher AIx, which is paradoxical given that CCB therapy in hypertensive individuals decreases arterial stiffness, if anything[2]. Given that CCBs are first-line therapy for Raynaud's phenomenon in SSc, this association could reflect generalized vasculopathy rather than atherosclerotic disease. Prospective studies in large cohorts of patients are warranted to clarify this point and elucidate other determinants of arterial stiffness in SSc.

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2. Effects of Antihypertensive Drugs on Arterial Stiffness. Cardiol Rev 2012; doi: 10.1097/CRD.0b013e31825d0a44.

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Vascular Ischemic Events in Systemic Sclerosis - a Cross-Sectional Comparision with population-Based Controls. Annica Nordin[1], Kerstin Jensen-Urstad[2], Lena Björnådal[1] and Elisabet Svenungsson[1]. [1]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Department of Clinical Physiology, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: To investigate the occurrence of ischemic vascular events and subclinical atherosclerosis in patients with systemic sclerosis (SSc) and matched population controls.

Methods: 111 SSc patients (74% of the patients in Stockholm County) and 105 controls were investigated in this population-based study. Previous ischemic vascular events were defined as:

1. Ischemic heart disease (IHD): myocardial infarction (confirmed by electrocardiography and a rise in plasma creatine kinase, muscle and brain fraction (CK-MB) or troponin T) or angina pectoris (confirmed by exercise stress test)

2. Ischemic cerebral vascular disease (ICVD): cerebral infarction (confirmed by computer tomography) or transitory ischemic attacks (TIA, defined as transient focal symptoms from the brain or retina with a maximum duration of 24 hours),

3. Ischemic peripheral vascular disease (IPVD): intermittent claudicatio + ankle-brachial index (ABI) < 0.9 or peripheral arterial thrombosis/embolus (confirmed by angiogram or Doppler flow studies).

As measures of subclinical atherosclerosis intima media thickness (IMT) and plaque occurrence was determined with carotid ultrasound and the ABI was calculated.

Results: Mean age was 62 ± 12 years for patients and controls. In the patient group disease duration was 9.4 (5.6 – 17.4) years, 78% had limited cutaneous systemic sclerosis (lsSSc) and 32% had anti-centromere antibodies (ACA). Ischemic vascular events were more common in the patients (18% vs 7%, p=0.01) due to an increased occurrence of both ischemic heart disease (IHD) and ischemic peripheral vascular disease (IPVD) (12% vs. 4% p=0.03 and 8% vs. 1% p=0.02 respectively). Ischemic cerebral vascular disease was uncommon in both the patient and control group. On a group level frequency of plaques, IMT or ABI did not differ between SSc patients and controls, but the subgroup of patients with ACA had more plaques in comparison both to other SSc patients (67% vs. 39%, p=0.006) and to controls (67% vs. 41%,

p=0.02). Patients with ACA also had more ischemic events than other patients (32% vs 11% p=0.01) and controls (32% vs 7% p=0.0003).

	Patients (n = 111)	Controls (n = 105)	Odd Ratio (95% CI)	P-value
Event % (n)	18 (20)	7 (7)	3.1 (1.2–7.6)	0.01
IHD % (n)	12 (13)	4 (4)	3.3 (1.1–10.6)	0.03
ICVD % (n)	3 (4)	3 (3)	0.9 (0.2–4.7)	ns
IPVD % (n)	8 (9)	1 (1)	9.2 (1.1–73.7)	0.02
Plaque % (n)	48 (52)	41 (43)	1.3 (0.7–2.3)	ns
			b-coefficient	
IMT mm	0.68 ± 0.13	0.68 ± 0.13	−0.02	ns
ABI	1.13 (1.1–1.2)	1.12 (1.1–1.2)	−0.08	ns

Conclusion: Patients with SSc have more ischemic heart disease and ischemic peripheral vascular disease than controls. The subgroup of SSc patients with ACA seems to be at particularly high risk to develop both ischemic event and premature atherosclerosis. This group should thus be followed closely and vascular prevention considered at an early stage when indicated. The importance to investigate subgroups of well-characterized patients is underscored by this study.

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Decreased Number of Endothelial Progenitor Cells in Systemic Sclerosis Patients with Early Disease. Fernando V. Andrigueti, Maria I. Arismendi, Pâmela C.C. Ebbing and Cristiane Kayser. Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Microangiopathy and endothelial dysfunction are present in early phases of Systemic sclerosis (SSc), resulting in decreased blood flow and tissue ischemia. Several mechanisms including insufficient angiogenesis, and defective vasculogenesis mediated by endothelial progenitor cells (EPCs), might be involved in the vascular abnormalities in SSc patients. However, different data have been reported regarding the number and function of EPCs in different clinical subsets of SSc patients. This study aimed to evaluate the circulating number and the in vitro culture of EPCs in SSc patients with early disease compared to healthy controls.

Methods: Thirty-one consecutive SSc female patients (mean age 42.7 years) with less than four years of Raynaud's phenomenon (RP) and 20 age-matched healthy women (mean age 39.9 years) were included. All patients fulfilled the ACR classification criteria for SSc (1980) or the LeRoy and Medsger criteria (2001). Peripheral blood samples (30mL) were collected from each subject at rest. Flow cytometry was performed to quantify the absolute number of EPCs. EPCs were identified by the co-expression of CD34, CD133 and vascular endothelial growth factor receptor type 2 (VEGFR2) and were expressed as the number of EPCs per 10^6 lymphomononuclear (LMN) cells. Besides, in vitro culture of EPCs was performed, and the number of EPC colony-forming units (CFU) per well was quantified in each sample. All procedures were performed according the EULAR recommendations and executed immediately after blood collection. Plasma VEGF levels were assessed by ELISA. p<0.05 were considered statistically significant.

Results: Among SSc patients, the mean duration of RP was 3.75±1.96 years and the mean duration of the first SSc symptom other than RP was 3.24±1.85 years. Digital ulcers were present in ten patients. SSc patients showed decreased number of EPCs (108.6±87.2 vs 246.8±241.4 /10^6LMN, respectively, p=0.04), and decreased number of EPC CFUs compared to controls (14.6±9.1 vs 20.9±11.5 CFUs, respectively, p=0.034). There was no significant difference in the number of EPCs between SSc patients with digital ulcers and those without digital ulcers at the time of the evaluation (90.5±73.2 vs 121.4±96.5 /10^6LMN, respectively, p=0.4). There was a positive correlation between the number of circulating EPCs and the number of EPC CFUs. There was no difference in VEGF levels between patients and controls (88.3±57.9 vs 83.8±74.6 ng/mL, p=0.34).

Conclusion: The present study showed originally decreased EPCs in SSc patients with early disease onset, suggesting presence of defective vasculogenesis in early stages of the disease. Therefore, EPCs could be an important therapeutic target for preventing vascular complications in patients with early stages of SSc.

Disclosure: **F. V. Andrigueti**, None; **M. I. Arismendi**, None; **P. C. C. Ebbing**, None; **C. Kayser**, None.

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Adipose Derived Stem Cells As an Alternative Source of Cellular Repair for Vascular Dysfunction in Systemic Sclerosis. Nevin Hammam[1] and Hazem Orabi[2]. [1]Assiut University, Assiut, Egypt, [2]Knuppe Molecular Laboratory, San Francisco, CA

Background/Purpose: Systemic sclerosis (SSc) is autoimmune disease characterized by autoimmunity, diffuse fibrosis in the skin and internal organs, and vasculopathy in moderate size arteries and arterioles. The vasculopathy associated with SSc is one of the major contributors to the clinical manifestations of the disease and can result in non healing ulcers, gangrene and digit loss, hypertension and cardiovascular disease and it has a profound impact on the quality of life. Endothelial injury, smooth muscle cells proliferation and fibrosis of the vessel wall result in lumen occlusion and tissue hypoxia that is treated currently with pharmacologic agents. New therapies including stem cells are needed to reconstitute the diseased vascular tissue. Adipose derived stem cells (ADSCs) represent an ideal stem cell source for SSc vasculopathy therapy.

The aim of this study is to investigate if human ADSCs can be differentiated into smooth muscle cells (SMC) and endothelial cells (EC) and if these differentiated cells can be constructed into cell sheets and vascular tissue.

Methods: Human ADSCs were isolated expanded, induced into EC and SMC using endothelial growth medium-2 (EGM-2) and Transforming growth factor (TGF-β1) respectively. The growth and morphology of the cells were followed up for 4 weeks. The phenotype of induced cells were checked for SMC markers; actin, calponin and heavy chain myosin and for endothelial cell markers; CD31 and Von Willebrand factor (vWF) through immunocytochemistry and western blot. The induced SMC and EC cells were used to construct either SMC and EC cell sheets or bilayered vascular structures by culturing them in special culture dishes. Confluent cultured cells were harvested as a contiguous cell sheet only by lowering temperature. The cell sheets and vascular structures were stained with H&E and Masson Trichrome and verified for smooth muscle markers and for endothelial cell markers. The formation of extracellular matrix of the both cell sheets was tested using Picrosirius Red staining and collagen IV.

Results: The induced cells showed positive staining for endothelial cell markers after 2 weeks and smooth muscle markers after 3 weeks for SMC cells. The western blot confirmed their phenotype conversion. The cell sheets and vascular structures were detached easily in a consistent manner by lowering the temperature in intact and viable condition. The monolayer cell sheets were formed of 2–5 cell layers that showed positive staining for either SMC or EC markers. They also showed positive staining for Picrosirius Red and collagen IV indicating the formation of extracellular matrix. Vascular structures exhibited upper layer of EC and multiple layers of SMC with collagen layer in between.

Conclusion: The results showed the ability of human ADSCS to form SMC and EC and constitute renewable source for cellular therapy. The cell sheets and vascular structures made of ADSCs form new technology for improvement of vascular dysfunction in SSc.

Disclosure: **N. Hammam**, None; **H. Orabi**, None.

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Excess Mortality From Atherosclerotic Cardiovascular Disease in Systemic Sclerosis Compared to Lupus and Rheumatoid Arthritis. Amish J. Dave[1], Bharathi Lingala[2], David Fiorentino[3], Eswar Krishnan[1] and Lorinda Chung[4]. [1]Stanford University, Stanford, CA, [2]Stanford University, Redwood City, CA, [3]Stanford University School of Medicine, Redwood City, CA, [4]Stanford Univ Medical Center, Palo Alto, CA

Background/Purpose: Patients with autoimmune connective tissue diseases (CTD), including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are at increased risk for atherosclerotic cardiovascular disease (ASCVD) compared with the general population. Recent reports indicate an increased prevalence of ASCVD in patients with systemic sclerosis (SSc), thought to be mediated through inflammatory mechanisms affecting vascular integrity, including endothelial cell damage and increased collagen deposition. Our aim was to utilize the Nationwide Inpatient Sample (NIS) to assess the prevalence of and mortality risk associated with ASCVD among hospitalized patients with SSc.

Methods: The NIS is a national, annual, representative survey of hospitalized patients in the US. We examined the in-hospital frequency and mortality rates of specific diagnoses and procedures associated with ASCVD

among hospitalized adult patients with SSc using data from the NIS from 1993 to 2007. The following diagnoses and procedures were identified by ICD-9 codes: coronary artery disease, myocardial infarction, cerebrovascular accidents, coronary artery bypass grafts, and percutaneous transluminal coronary angioplasty. Analyses were weighted so results are standardized to the US population as a whole. Using logistic regression, we compared the odds of death among hospitalized SSc patients with each ASCVD diagnosis or procedure to patients with SLE or RA, and to a control group that excluded patients with any CTD diagnosis and were matched to cases by age, gender, and race. Multivariate analyses controlled for demographics, comorbid diseases using the Charlson comorbidity index, elective vs. emergent hospitalizations, and the number of diagnoses.

Results: A total of 308,452 hospitalizations of SSc patients occurred in the US between 1993 and 2007. The mean age was 61.5 years, 84% were female, and 59% were white. 12% of all SSc hospitalizations were associated with an ASCVD diagnosis or procedure, compared with 11% of SLE and 15% of RA hospitalizations. SSc hospitalizations associated with ASCVD were 1.5 times more likely to result in death compared with SSc hospitalizations not associated with ASCVD (OR 1.5, 95% CI 1.4–1.6, p<.001). Highest odds of in-hospital death were associated with CAD/MI (OR 1.7, 95% CI 1.6–2.0, p<.001) and CVA (OR 1.4, 95% CI 1.2–1.6, p<.001). Multivariate analyses showed that SSc hospitalizations associated with ASCVD were more likely to result in death than hospitalizations of SLE (OR 1.6, 95% CI 1.4–1.9, p<.001), RA (OR 2.6, 95% CI 2.3–3.0, p<.001), and control patients (OR 1.6, 95% CI 1.4–1.8, p<.001) with ASCVD.

Conclusion: Although the frequency of hospitalizations associated with ASCVD in SSc patients is similar to that in SLE and RA patients in the US, there is an increased risk of in-hospital death associated with SSc. Further studies are necessary to determine whether the underlying vasculopathy, which affects the micro- and macrovasculature in SSc patients, contributes to increased mortality associated with ASCVD.

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Risk of Cancer in Systemic Sclerosis: Meta-Analysis of Population-Based Cohort Studies. Akira Onishi[1], Daisuke Sugiyama[2], Akio Morinobu[1] and Shunichi Kumagai[3]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]School of Medicine, Keio University, Tokyo, Japan, [3]Shinko Hospital, Kobe, Japan

Background/Purpose: The risk of cancer compared with general population has been elevated in several connective tissue diseases. However, the standardized incidence ratios (SIRs) for overall cancer in patients with systemic sclerosis (SSc) were inconsistent. Moreover, most of existing studies were limited in size and based on hospital case series, with attendant selection and referral biases. We therefore aimed to examine, using meta-analysis, cancer risk in patients with SSc deriving from population-based cohort studies, as compared with the expected risks in age- matched background populations.

Methods: We searched five different databases (MEDLINE, Scopus, CINAHL, Web of Science and Cochrane Collaboration databases), reference lists of retrieved studies and review articles from January 1966 until May 2012. Population-based cohort studies relevant for determining cancer risk in patients with SSc were included. All papers fulfilling the strict inclusion criteria were scrutinized for data on population size, time of follow-up and observed to expected cancer rates (standardized incidence ratio (SIR)). Two investigators independently evaluated the quality of the studies by using a scoring system that was created on the basis of a recently used system designed with reference to MOOSE, QUAST and STROBE. Data syntheses were based on random effects model.

Results: Seven articles were included. The pooled SIR for overall cancer was 1.50 (95% CI: 1.23–1.83). The pooled SIR of 1.85 (95% CI: 1.49–2.31) for men was significantly higher than that of 1.33 (95% CI: 1.18–1.49) for women (p =0.009) and stratification on sex eliminated heterogeneity. Stratification based on type of SSc did not produce statistically significant differences in the pooled SIR between limited SSc and diffuse SSc (p = 0.98). The significant increased risk of cancer of the lung (SIR: 3.18; 95% CI: 2.09–4.85), the liver (SIR: 4.36; 95% CI: 2.00–9.51), the hematological system (SIR: 3.55; 95% CI: 1.70–7.43), non-Hodgkin lymphoma (SIR: 2.71; 95% CI: 1.43–5.14), leukemia (SIR: 2.75; 95% CI: 1.32–5.73) and the bladder (SIR: 2.00; 95% CI: 1.06–3.77) was observed. The pooled SIR for non-melanoma skin cancer was significantly increased only in men, while the pooled SIR for bladder cancer was significantly increased only in women.

The appearance of funnel plots was symmetrical and Egger's test results were not significant ($p = 0.60$).
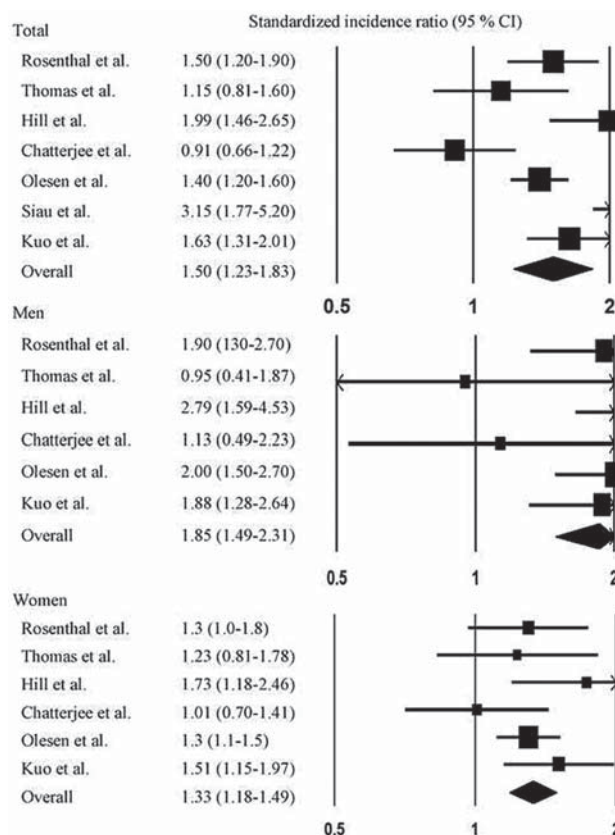
Conclusion: In conclusion, SSc are associated with an increased risk of cancer, particularly lung, liver, hematological and bladder cancer. Men with SSc are at higher cancer risk than women.

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Histological Features of Localized Scleroderma*'en Coup De Sabre'*: A Study of 16 Cases. Takashi Taniguchi, Yoshihide Asano, Zenshiro Tamaki, Kaname Akamata, Naohiko Aozasa, Shinji Noda, Takehiro Takahashi, Yohei Ichimura, Tetsuo Toyama, Miki Sugita, Hayakazu Sumida, Yoshihiro Kuwano, Miki Miyazaki, Koichi Yanaba and Shinichi Sato. University of Tokyo Graduate School of Medicine, Tokyo, Japan

Background/Purpose: Scleroderma is a chronic disease of unknown etiology characterized by skin fibrosis and is divided into two clinical entities: localized scleroderma and systemic sclerosis. Localized scleroderma differs from systemic sclerosis in that it is not accompanied by Raynaud's phenomenon, acrosclerosis, and internal organ involvement. Early lesions of localized scleroderma are histologically characterized by lymphocytic perivascular infiltration in the reticular dermis and swollen endothelial cells. However, there have been few information regarding histological features other than these findings in localized scleorderma. Since en coup de sabre (ECDS) is a certain subset of localized scleroderma with a relatively uniform clinical image, we focused on this disease subset and evaluated its histopathological features.

Methods: We retrospectively evaluated 16 patients with ECDS on the basis of clinical and histological findings. For each patient, age, disease duration, and clinicopathologic data were obtained. Skin biopsies were evaluated for the following features: epidermal atrophy, spongiosis, vacuolar degeneration of the basal cell layer, necrotic keratinocytes, thickening of dermal collagen bundles, perivascular or periappendiceal inflammatory infiltrate, vacuolar changes of follicular epithelium, and melanin incontinence.

Results: Regardless of clinical manifestations, vacuolar degeneration at the dermoepidermal junction was found in all ECDS patients. Furthermore, melanin incontinence was seen in 11 (69%) patients. Importantly, keratinocyte necroses, which are frequently accompanied with severe vacuolar degeneration, were restricted to 2 patients with early and active lesions. Vacuolar changes in hair follicular epithelium were seen in 8 (50%) patients. Regarding the histological features in the dermis, dermal fibrosis was found in all patients, but the degree of fibrosis did not correlate with disease duration. In early ECDS patients (disease duration of < 3 years), moderate to severe perivascular and/or periappendiceal lymphocytic infiltration and vacuolar changes in follicular epithelium were prominent, while epidermal atrophy was less frequently observed, compared with late ECDS patients (disease duration of ≥ 6 years).

Conclusion: Vacuolar degeneration at the dermoepidermal junction is a common histological feature in ECDS and perivascular and/or periappendiceal lymphocytic infiltration and vacuolar degeneration of follicular epithelium are characteristic especially in early ECDS, further supporting a canonical idea that the elimination of mutated epidermal cells by immune surveillance contributes to tissue damage and resultant fibrosis in localized scleroderma.

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Fingertip Skin Hardness in Limited Scleroderma: Durometry versus Manual Assessment.

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Background/Purpose: Skin manifestations of scleroderma involve the digits in nearly all patients. Assessment of change at the level of digital skin involvement is difficult. The Modified Rodnan Skin Score (MRSS) is the most commonly used assessment for quantifying skin involvement. Its use is limited to measuring thickness at only two locations: the dorsum of the third digit of each hand. Recently, the use of a durometer to measure finger hardness at these two sites provided the possibility of improved quantitative assessment of skin involvement. The purpose of this study was to compare manual palpation and durometry as alternate methods of measuring finger involvement in scleroderma.

Methods: Fingertip pads of 30 patients with limited scleroderma (Scl cases), were compared with 30 age- and gender-matched controls without scleroderma. Skin hardness was assessed by manual palpation of the distal phalangeal palmar pad areas digits 1–5 bilaterally, using a scale of 0–3, with 0 indicating no involvement and 3 indicating extreme hardness. After calibration, durometry was performed in the same areas using a Rex 1600 Type 00 durometer rated on a scale of 0 (softest) to 100 (hardest). Two independent investigators recorded their findings on each patient in all digits using both methods. After 1 hour, Scl cases were remeasured by the same two investigators. Manual and durometry-based skin scores were obtained by averaging all digits for each assessment. Intra-class correlation (ICC) coefficients were used to assess differences in skin scores between investigators and repeatability.

Results: Mean age of cases and controls was 56 years (min: 30, max: 80) and 80% were female. There was a significant difference between the mean rating of all digits of Scl-cases and controls using either the manual (mean 1.5 vs 0.1; p<0.001) or the durometer method (mean 38 vs. 15; p<0.001). Between right and left hands, measurements for each finger were compared separately. Only manual ratings of the fifth digits were found be significantly different with right having a higher rating than left. Comparing each hand overall, both the manual durometer measurements showed that the left hand had significantly higher ratings than the right (manual: mean difference=0.19, p=0.008; durometer: mean difference=3.26, p=0.002). Intra-rater variability was low, as demonstrated by a high correlation in initial values recorded by individual raters and values recorded after one hour (ICC>0.90). Inter-rater variability was assessed comparing one main rater's measurements of Scl-cases to other raters. All raters seemed to agree with the main rater (ICCs ≥0.69) for any finger.

Coefficients did not change significantly from baseline to 1 hour assessment. Minimal detectable difference was smaller for durometry (11%) than for manual palpation (29%) indicating durometry may be able to detect smaller changes than manual rating.

Conclusion: Manual palpation and/or durometry performed on distal phalangeal palmar pads provided reproducible tools to assess skin hardness in fingers of Scl patients. Both have minimal inter- and intra-observer variability. Durometry may be able to detect smaller changes than manual palpation. It may have greater utility clinically and in clinical trials.

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Optical Density Measure of the Papillary Dermis Discriminates As Abnormal Clinically Uninvolved Skin in Systemic Sclerosis and Correlates with Severity of Skin Thickness.

Giuseppina Abignano[1], Sibel Z. Aydin[2], Concepcion Castillo-Gallego Jr.[3], Daniel Woods[4], Adam Meekings[4], Dennis McGonagle[1], Paul Emery[1] and Francesco Del Galdo[1]. [1]University of Leeds, Leeds Institute of Molecular Medicine and LM-BRU, Leeds, United Kingdom, [2]Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey, [3]Hospital Universitario La Paz, Madrid, Spain, [4]Michelson Diagnostics Ltd, Kent, United Kingdom, Kent, United Kingdom

Background/Purpose: Skin involvement in systemic sclerosis (SSc) is often primary outcome in clinical trials and its severity inversely correlates with prognosis. Nevertheless, an objective quantitative imaging biomarker to assess skin fibrosis is still lacking in SSc. Optical Coherence Tomography (OCT) is a imaging technology that measures optical density (OD) of a substrate and can provide high contrast 2 mm deep skin images with a 5–10 micron resolution. Concurrent validity and reliability of such technique to assess skin involvement in SSc have been previously reported.[1] The aim of this study was to determine whether OD of the dermis as assessed by OCT could be used to quantitatively discriminate healthy skin from clinically uninvolved SSc skin and to correlate with clinical assessment of skin thickness in SSc patients (construct validity).

Methods: A total of 393 OCT scans of hands and forearms on 20 SSc patients and 15 healthy controls (HC) were performed employing topical probe "VivoSight" (Michelson Diagnostics). Matlab software was employed to calculate mean OD of the scans. Signal changes within epidermis (ED), Dermal-Epidermal Junction (DEJ) and dermis of SSc patients and HC were analysed and collated to a unique graph. Construct validity was determined by correlation with the current gold standard, the modified Rodnan Skin Score (mRss). The minimum (Min) value of OD before the dermis and the maximum (Max) value of OD in the dermis were considered to compare the forearm skin OCT mean A-scans of SSc patients and HC. ROC analysis of HC and mRSS=0 mean A-scans suggested that the OD value at 300 (± 16) micron was the one with best sensitivity/specificity ratio in discriminating HC vs clinically unaffected skin. We therefore included the mean value of OD at 300±16 micron for further analysis. Statistical analysis was performed employing Pearson correlation, one-way Anova and Bonferroni correction tests as appropriate.

Results: OCT mean A-Scans showed a different pattern in HC and four mRSS groups. SSc affected skin showed a consistent decrease of OD in the papillary dermis (PD), which caused a loss of definition of the DEJ. Max OD values of the PD in HC and the four mRSS subgroups was significantly different across the five groups (P<0.0001) and showed a significant correlation with mRSS (r=−0.69, P<0.0001). Similarly, Min OD values were significantly different across the five groups (P<0.0001) and showed a strong correlation with mRSS (r=−0.6, P=0.0002). In both cases after Bonferroni correction for multiple variables, the difference in Min and Max OD remained significant between HC or mRSS=0 and patients with mRSS=2 or 3, suggesting that these measures correlated with skin involvement but could not discriminate between HC and patients with mRSS=0 or 1. On the contrary, OD300 was significantly different between HC and patients with mRSS=0 or 1 (P<0.001).

Conclusion: The decrease of OD in the PD in skin fibrosis as assessed by OCT is a valid quantitative outcome measure of skin fibrosis.

Sensitivity to change ability of OCT is under evaluation to determine whether the technique could be used as outcome measure of skin involvement in SSc in clinical intervention trials and clinical management.

References
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Myopathy Is a Poor Prognostic Feature in Systemic Sclerosis: Results From the Canadian Scleroderma Research Group. Michelle Jung[1], Murray Baron[2], Marie Hudson[3], Ashley Bonner[4], Janet E. Pope[5] and Canadian Scleroderma Research Group[6]. [1]Western University, London, ON, [2]Jewish General Hospital, Montreal, QC, [3]McGill University, Montreal, QC, [4]McMaster University, Hamilton, ON, [5]St. Joseph's Health Care London, London, ON, [6]Montreal, QC

Background/Purpose: Myopathy/myositis is associated with more severe systemic scleroderma (SSc). The aim of this study was to determine such clinical information from the Canadian Scleroderma Research Group database (CSRG).

Methods: Data from the CSRG are collected annually on SSc patients. Two surrogate markers for myopathy used in this study were elevated creatine kinase (CK) and physician-reported history of myopathy/myositis of the patients. Comparisons were made between those with and without myopathy/myositis to determine the strongest associations with this complication; overall, in lcSSc and dcSSc and in early dcSSc subset. Survival with and without myopathy/myositis was determined.

Results: The study included 1143 patients with mean of 8 years of duration. Elevated CK occurred in 5.6%; 9.7 % had a history of inflammatory myositis or myopathy according to physician; 5.7% had proximal muscle weakness. Those with elevated CK compared to remainder were more likely to be male (24.5 % in elevated CK vs. 12.6 % in normal CK; p<0.013), younger (51.93 vs. 56.07 years, p<0.045); have dcSSc, (40.4 % vs. 37.9 %; p<0.002), physician-reported history of myositis/myopathy (45.3 % vs. 8.5 %, p< 0.000), tendon friction rubs (30.0 % vs. 13.4 %; p<0.001), FVC < 70 % (23.9 % vs. 13.1 %; p<0.039), RNP antibody (12.0 % vs. 5.0 %, p < 0.032), Topo1 antibody (26.0 % vs. 14.4 %, p < 0.026), higher skin scores (MRSS 16.14 vs. 9.81; p<0.000), and higher HAQ score (0.98 vs. 0.79; p<0.011). When using logistic regression younger age male, dcSSc, early dcSSc, tendon friction rubs, higher MRSS, Topo1, RNP, PMScl, and FVC<70% were associated with elevated CK. Survival was less in those with myopathy/myositis or elevated CK (p=0.003 and p=0.025 respectively). Those with elevated CK had less survival (p=0.025). Results were similar when the other definition of myopathy/myositis.
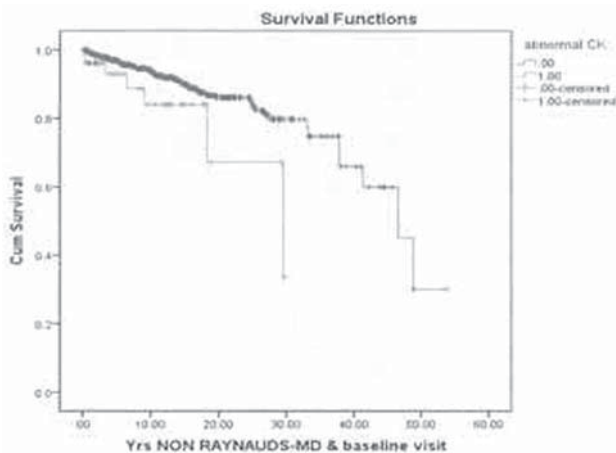
Figure 1. Survival in those with elevated CI vs. without (p=0.025). Disease duration is recorded as time (years) since first Raynaud's symptoms at entry into CSBG registry.
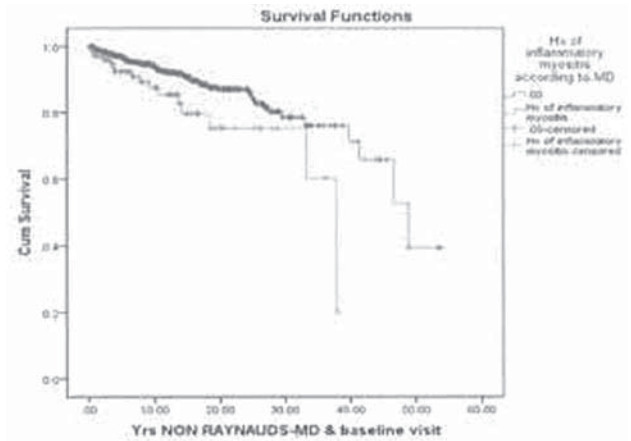
Figure 2. Survival in those with history of myositis/myopathy vs. those without (p<0.001). Disease duration is recorded as time (years) since first non-Raynaud's symptoms at entry into CSBG registry.

Conclusion: Myopathy/myositis has a worse prognosis with respect to function and other organ involvement (ILD) and survival.

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Autoantibodies to Survival of Motor Neuron (SMN) Complex Are Common in Patients with Anti-U1RNP/Sm and Are Associated with Features of Scleroderma and Myopathy. Jason YF Chan, Yi Li, Angela Ceribelli, Eric S. Sobel, Westley H. Reeves, Edward K.L. Chan and Minoru Satoh. University of Florida, Gainesville, FL

Background/Purpose: Survival of motor neuron (SMN) complex that plays a key role in small nuclear ribonucleoproteins (snRNPs) assembly and interacts with snRNPs has recently been identified as a novel target of autoantibodies in patients with polymyositis/dermatomyositis (PM/DM). Although isolated anti-SMN complex antibodies are uncommon autoantibody specificity associated with PM/DM, their frequent coexistence with anti-snRNPs (U1RNP, Sm) autoantibodies was noticed. Clinical significance of autoantibodies to SMN complex coexisting with anti-snRNPs was examined in unselected cohort of rheumatology clinic.

Methods: Sera from patients enrolled to Center for Autoimmune Disease (n = 1966, including 453 SLE, 132 scleroderma, 125 PM/DM, 130 RA, 61 Sjšgren's syndrome) were screened for their autoantibody specificities by immunoprecipitation (IP) using ^{35}S-labeled K562 cells extract. Anti-SMN complex antibodies were determined based on IP of the stable SMN complex (38kD SMN and 120–130kD gemin3 and 4). Antibodies directed to SMN protein were measured by ELISA using SMN recombinant protein. Antibodies to SMN complex were also tested by anti-SMN antigen-capture ELISA using monoclonal antibodies. Clinical information was from the database and chart review.

Results: Anti-snRNPs antibodies were identified in 266 sera (174 anti-U1RNP, 13 anti-U1/U2, and 79 anti-Sm+U1RNP). Although isolated anti-SMN complex antibodies were found previously only in 2 patients with PM, anti-SMN complex antibodies coexisting with anti-snRNPs (11% in anti-U1 or -U1/U2RNP, 6% in anti-Sm+U1RNP) were clearly detected in 28 cases. Prevalence of anti-SMN among anti-snRNPs(+) sera was 14% in Caucasian (P = 0.069 vs African American (AA)), 7% in AA, and 15% in Latin. Levels of anti-SMN antibodies (recombinant protein) were also low in AA (P < 0.005 vs Caucasian, P < 0.05 vs Latin). Clinical features of anti-SMN+snRNPs(+) were compared with anti-snRNPs(+) alone patients (table). Although the diagnosis of SLE and anti-Sm antibodies appears to be less in the anti-SMN+snRNPs(+) group, clinical features of SLE in this group of patients were similar to those of anti-snRNPs(+) patients. Anti-SMN group has more muscle weakness (P = 0.026) and diagnosis of PM/DM (P = 0.051). Diagnosis of SSc (P = 0.022) and features associated with SSc, Raynaud's phenomenon (P = 0.0008) sclerodactyly (P = 0.016), pitting scars (P = 0.03), and interstitial lung disease are more common in anti-SMN+snRNPs(+) group vs anti-snRNPs(+) alone.

Conclusion: Anti-SMN complex antibodies produced in a tight association with anti-snRNPs are relatively common. Anti-SMN complex antibody positive patients have higher prevalence of clinical features associated with SSc and PM/DM.

Clinical features of anti-SMN+snRNPs vs anti-snRNPs antibody positive patients

	Anti-SMN + snRNPs (n = 28)	Anti-snRNPs (n = 239)	
Caucasian	54% (14/26)	36% (87/239)	P = 0.09
Diagnosis of SLE	54% (14/26)	69% (161/235)	ns
Anti-Sm	18% (5/28)	31% (74/238)	ns
Diagnosis of PM/DM	8% (2/26)	3% (6/234)	ns
Elevated CPK	21% (4/19)	30% (55/184)	ns
Muscle weakness	26% (6/23)	9% (19/206)	P = 0.026
Diagnosis of SSc	15% (4/26)	3% (8/235)	P = 0.022
Raynaud's	79% (19/24)	41% (82/198)	P = 0.0008
Sclerodactyly	26% (6/23)	8% (16/199)	P = 0.016
Pitting scars	26% (6/23)	10% (19/199)	P = 0.03
Interstitial lung disease	23% (5/22)	13% (25/198)	ns

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Rpp25 Is a Major Target of Autoantibodies to the Th/to Complex As Measured by ELISA and a New Chemilumiscence Assay. Michael Mahler[1], Cristina Gascon[1], Sima Patel[1], Angela Ceribelli[2], Edward K.L. Chan[2] and Minoru Satoh[2]. [1]INOVA Diagnostics, Inc., San Diego, CA, [2]University of Florida, Gainesville, FL

Background/Purpose: Anti-nuclear antibodies (ANA) play an important role in the diagnosis of systemic autoimmune diseases including systemic sclerosis (SSc). A significant portion of ANA in SSc are directed against nucleolar antigens including the Th/To antigen. Several proteins of the Th/To complex have been reported to react with anti-Th/To antibodies. Although known for over 20 years, anti-Th/To antibodies are rarely used in routine testing algorithms to aid in the diagnosis of SSc. Furthermore, little is known about the clinical association of autoantibodies targeting the individual components of the Th/To antigen. The objective of the present study is to evaluate the newly developed ELISA and chemiluminescence immunoassay (CIA, QUANTA Flash, INOVA) to measure autoantibodies to Rpp25 using immunoprecipitation (IP) as reference method.

Methods: A component of Th/To antigen (Rpp-25) was expressed as histidine-tagged recombinant protein in *E.coli* and purified by a standard method. Anti-Rpp25 antibodies in human sera were tested by ELISA and QUANTA Flash (fully automated on the BIO-FLASH System), and compared with results by immunoprecipitation as a standard. Anti-Th/To by IP was based on detection of 7–2 and 8–2 RNA by immunoprecipitation and silver staining of RNAs. The first cohort consisted of 121 SSc patients including 8 anti-Th/To positive samples confirmed by IP, enrolled in the University of Florida Center for Autoimmune Diseases (UFCAD) registry from 2000–2012. Previously described eight anti-Th/To positive Italian SSc sera from Spedali Civili di Brescia (Brescia, Italy) were also included in some analysis. For evaluation of the QUANTA Flash Rpp25 assay, 10 anti-Th/To positive sera were randomly selected based on the available amount of sera. As controls, sera were collected from ANA positive asymptomatic healthy individuals (n=42), from rheumatoid arthritis patients (n=20) and from random healthy individuals (n=10).

Results: The reactivity to Rpp25 by ELISA was significantly higher in anti-Th/To IP positive than in negative samples ($p<0.0001$). A sensitivity of 64.7% (95% CI 38.3–85.8%) and a specificity of 99.1% (95% CI 95.3–100.0%) was determined. To verify the results using a second method, anti-Th/To IP positive sera and negative controls were tested using the Rpp25 assay on the BIO-FLASH. At cut-off selected by receiver operating characteristic analysis 9/10 (90.0%) of the anti-Th/To positive sera but none of the controls were positive for anti-Rpp25 antibodies by BIO-FLASH ($p<0.0001$). Thus a sensitivity of 90.0% (95% CI 55.5–99.7%) and a specificity of 100.0% (95% CI 95.0–100.0%) were found. Ten samples were tested by ELISA and BIO-FLASH for anti-Rpp25 reactivity and the results were highly correlated (rho=0. 96, 95% CI 0.85–0.99; $p<0.0001$).

Conclusion: Rpp25 is a major target of autoantibodies to the Th/To autoantigen complex. Autoantibodies to Rpp25 detected by ELISA and especially CIA show excellent agreement with IP for anti-Th/To antibodies. The new assays may help to make this long-known antibody specificity widely available to clinicians. Further studies are needed to evaluate the clinical utility of the new assays.

Disclosure: M. Mahler, Inova Diagnostics, Inc., 3; **C. Gascon**, Inova Diagnostics, Inc., 3; **S. Patel**, Inova Diagnostics, Inc., 3; **A. Ceribelli**, None; **E. K. L. Chan**, None; **M. Satoh**, None.

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Line Blot Assay, a Screening Test for Autoantibodies in Systemic Sclerosis (SSc). Kae Takagi[1], Yasushi Kawaguchi[1], Sayuri Kataoka[2], Yuko Ota[3], Yuko Okamoto[2], Masanori Hanaoka[1], Hisae Ichida[1], Takahisa Gono[1], Yasuhiro Katsumata[2] and Hisashi Yamanaka[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan, [3]Institute of Rheumatology,Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Detection of auto-antibody is informative for diagnosis of SSc. Line blot assay (LBA) provides a quantitative in vitro assay for detecting human IgG class auto-antibodies against 13 different antigens simultaneously. The aim of our study is to evaluate availability of LBA for SSc in clinical setting, and assessing the sensitivity comparing with other conventional assay.

Methods: LBA strips coated with thin parallel lines of 13 synthesized antigen (CENPA, CENPB, U1RNP, fibrillarin, RNAPIII(RP11 ARP155), NOR90, Th/To, PM-Scl100, PM-Scl75, Ku, Ro-52, PDGFR) captures serum auto antibody. Captured autoantibody is detected by Alkaline Phosphatase conjugated second antibody combined with automated scan system. Serum samples from SSc patients in our hospital were investigated. Anti-Scl70 antibody and anti-centromere antibody was also measured using conventional DID assay.

Results: Serum from 80 SSc patients, 75 female and 5 male patients between 51.7 ± 15.2 years old, were investigated. Eighty SSc patients consisted with 47 diffuse cutaneous SSc (dcSSc) type and 33 limited cutaneous SSc (lcSSc) type patients. Anti nuclear antibody positivity detected by indirect immunofluorescence methods was 92.5%. Higher total skin score (MRSS), complications of lung fibrosis, Raynaud's phenomena, and arthritis were more frequently observed in dcSSc patients. Sensitivity and specificity of anti-Scl70 antibody using LBA was 90% and 92% respectively. Sensitivity and specificity of anti-centromere antibody using line assay was 87.5 % and 95.5% respectively. Sensitivity against both auto antibodies was much higher in LBA than DID method. Anti U3 RNP antibody, Anti NOR90 antibody and anti Ku antibody was also detected by LBA. Previous reports describe anti Th/To antibody were detected in 5–10 % of SSc patients by immunoprecipitation (IP) method. However, anti Th/To antibody was not detected in this screening using LBA.

We also investigated the relationship between appearance of auto antibody and clinical phenotypes. It is known anti RNA polymerase III antibody positivity correlates with rapid skin sclerosis and higher MRSS points. This correlation was also identical with our cohort study. Anti Ku antibody positivity is known to correlate with myositis and pulmonary hypertension. However, our analysis indicated anti Ku antibody positivity was only correlated with myositis not with pulmonary hypertension.

Conclusion: Although the specificity of LBA was not better than conventional DID method, sensitivity was much higher than conventional DID assay. In case of anti Th/To antibody, none of sera showed positivity. Even though we have not evaluated anti Th/To antibody positivity by IP method, the frequency of anti Th/To antibody by LBA is much lower than previous report. Affinity to anti Th/To antibody by in this LBA may be affected by peptide design interfere conformation. Anti U3 RNP antibody, anti NOR90 and anti Ku antibody are usually detected by IP and western blot assay. These methods are complicated and not widely manipulated by commercial base laboratory. The LBA method provides more easy detection of auto antibody, and gives more beneficial information by measuring multiple parameters at once for characterization of SSc.

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surement Information System 29-item Health Profile (PROMIS-29) and the Functional Assessment of Chronic Illness Therapy-Dyspnea short form (FACIT-Dyspnea) in assessing general health and dyspnea in patients with SSc. No studies to date have assessed the utility of PROMIS-29 and FACIT-Dyspnea in predicting cardiac involvement in SSc as assessed by comprehensive echocardiography. We hypothesized that PROMIS-29 and FACIT-Dyspnea would be comparable to legacy patient-reported outcome instruments such as the Medical Research Council Dyspnea Index (MRC), the Short-Form-36 (SF-36), the Scleroderma Health Assessment Questionnaire (s-HAQ), and the St. George's Respiratory Questionnaire (SGRQ) in predicting cardiac involvement in patients with SSc.

Methods: Comprehensive 2D/Doppler echocardiography + tissue Doppler imaging was performed to screen for cardiac involvement and pulmonary hypertension at the initial clinic visit to a tertiary referral program. All patients fulfilled ACR criteria for SSc. A battery of legacy patient-reported outcome instruments including the MRC, SF-36, s-HAQ, and SGRQ as well as two novel instruments including the PROMIS-29 and FACIT-Dyspnea were administered.

Results: 185 patients underwent echocardiography and completed patient-reported outcome questionnaires at the baseline visit. The mean age of subjects was $53 \pm 12y$, 88% were women, and 60% had limited cutaneous SSc; median modified Rodnan skin score was 6 (interquartile range 4–17). There was echocardiographic evidence for pericardial effusion in 17%, pulmonary artery systolic pressure >40 mmHg in 16%, right ventricular dysfunction in 8%, left ventricular (LV) systolic dysfunction in in 5%, LV diastolic dysfunction in 26% and any of the above in 43% of subjects. FACIT-Dyspnea and FACIT-Functional Limitation scores were highly associated with PASP on echo and overall cardiac involvement (Figure). Area under the ROC curve for FACIT-Dyspnea (c-statistic > 0.8 for PASP) were comparable to legacy instruments (MRC, s-HAQ, and SGRQ) and superior to SF-36 (P<0.01). For overall cardiac involvement, FACIT-Dyspnea and PROMIS-29 were equivalent to legacy instruments (P=NS).
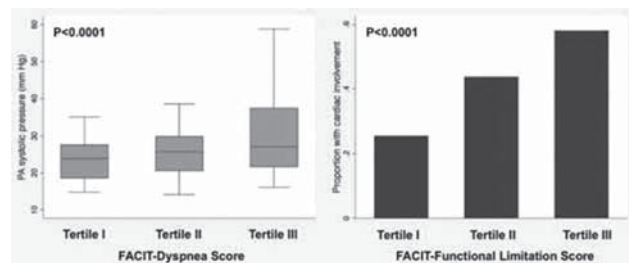
Conclusion: PROMIS-29 and FACIT-Dyspnea are comparable to legacy patient-reported outcome instruments in predicting cardiac involvement and pulmonary hypertension in SSc and may be preferable to legacy instruments because they are freely available in many languages, are readily administered electronically, and are simple to score and interpret.

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Results From a Multi-Tiered Item Collection On Linking Systemic Sclerosis to the International Classification of Functioning, Disability and Health: A EULAR Scleroderma Trials and Research Initiative. Lesley Ann Saketkoo[1], Reuben Escorpizo[2], Kevin J. Keen[3], Kim Fligelstone[4] and Oliver Distler[5]. [1]Louisiana State University Health Science Center, New Orleans, LA, [2]ICF Research Branch in cooperation with the WHO Collaborating Centre for the Family of International Classifications Department of Health Sciences; and Health Policy, University of Lucerne, Switzerland, [3]University of Northern British Columbia, Prince George, BC, [4]Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom, [5]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Systemic Sclerosis (SSc) affects multiple organs with complex combinations of disability. Skin fibrosis, ischemic pain, ulceration, arthritis, joint contractures, myopathy and cardiopulmonary, renal as well as gastrointestinal involvement affect emotional, social and physical functioning.

International Classification of Functioning, Disability, and Health (ICF), introduced by the World Health Organization (WHO), is a universal frame-

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Utility of Novel Patient-Reported Outcome Instruments in Predicting Cardiac Involvement and Pulmonary Hypertension in Patients with Systemic Sclerosis. Monique E. Hinchcliff, Mary A. Carns, Sofia Podlusky, John Varga and Sanjiv J. Shah. Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: Heart involvement in systemic sclerosis (SSc) includes left ventricular systolic and diastolic dysfunction, right ventricular dysfunction, pericardial disease, and pulmonary hypertension. We recently demonstrated the construct validity for discriminative purposes of 2 new patient-reported outcome instruments: the Patient-Reported Outcomes Mea-

work that describes the disabilities associate with a health condition in terms of the bio-psycho-social model with consideration of environmental and personal factors.

Methods: Comprehensive literature review identified all validated outcome measures in SSc. Five instruments were selected to represent the broadest range of SSc manifestations (OD, LAS), deconstructed to concepts and linked separately by 2 health professionals familiar with updated ICF linkage rules (RE, LAS). Inter-reviewer agreement was analyzed (KK). Remaining instruments were deconstructed and linked. Five formal meetings with 27 patients (4 males) and 24 SSc specialists (physicians, therapists and nurses) from 16 countries provided data which were deconstructed, confirmed by participants and then linked to the ICF.

Results: 27 validated instruments were identified. 5 validated SSc instruments were linked to ICF codes and tested inter-linker agreement. The proportion of agreement ranged from 0.8611 (95% CI: 0.7500, 0.9444) to 0.9647 (0.9175, 1.000) (Table 1) with the overall proportion of agreement 0.9359 (0.9172, 0.9506). 228 and 618 categories were linked in instrument and group data respectively. All instrument linkages were captured within the expert group data collection (Table 2).

Table 1. Point and interval estimates of proportion of agreement with and without correction for chance.

Questionnaire	No. of Concepts	No. of ICF Codes	Proportion of Agreement			Proportion of Agreement Corrected for Chance		
			Estimate	Lower Limit	Upper Limit	Estimate	Lower Limit	Upper Limit
HAMIS	9	4	0.8611	0.7500	0.9444	0.7097	0.5291	0.8835
mRSS	17	5	0.9647	0.9176	1.0000	0.8964	0.7631	1.0000
RCS	7	10	0.9082	0.8367	0.9388	0.6736	0.3879	0.7726
SHAQ	7	11	0.9048	0.8477	0.9524	0.6650	0.4848	0.8279
SSc GIT	25	16	0.9506	0.9318	0.9718	0.6599	0.5306	0.7912
Overall	65		0.9359	0.9172	0.9506	0.7230	0.6453	0.7797

HAMIS: Hand Mobility in Scleroderma Test, **mRSS**: Modified Rodnan Skin Score, **RCS**: Raynaud Condition Score, **SHAQ**: Scleroderma Health Assessment Questionnaire, **SSc GIT**: SSc Gastrointestinal Tract Instrument

Table 2. ICF Linkage of Validated SSc Instruments and Expert Data

ICF Domain	Patient & Medical Experts	Validated Instruments	Common to Both	Total Identified
Body Structure	126	16	16	126
Body Function	149	108	107	150
Activities and Participation	265	96	96	265
Environmental Factors	78	9	9	78
Total	**618**	**229**	**228**	**619**

Conclusion: SSc is the most complex disease linked to the ICF. Important challenges exist in ICF Core Set development for SSc. Occurrences in the data suggest ICF level of specificity was insufficient to describe the SSc experience, e.g. Raynaud's and specific aspects of pain. 618 linkages are unusually high for ICF item collection, SSc is likely to require the development of an advanced ICF Core Set model to accommodate its complexity and ensure utility.

Further face, content and construct validation strategies with item reduction are now underway. Very importantly, the weight of these results implies that the global, regional and personal impact of SSc across cultures, age and socioeconomic status is likely to be severely under-estimated. Efforts to establish fair assessment for use in policy making and provision of services and funding are essential towards optimal health and functioning in SSc.

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Worsening Carbon Monoxide Diffusing Capacity Predicts Mortality in Patient with Systemic Sclerosis and Pulmonary Arterial Hypertension Enrolled in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry.
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Background/Purpose: Isolated decreases in carbon monoxide diffusing capacity (DLco) has been a well described risk factor for the development of pulmonary arterial hypertension (PAH) in Systemic Sclerosis (SSc). We used the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) prospective registry to determine whether the changes in the DLco were associated with mortality in patients with SSc-PAH.

Methods: Patients with Group 1 PAH as diagnosed by right heart catheterization with a mean pulmonary pressure (mPAP) $\geq$ 25mmHg, and a wedge pressure $\leq$ 15 who have been entered into PHAROS were eligible for this analysis. Patients had to have repeat pulmonary function tests, including a DLco during the course of follow up. We defined patients who had a decrease in the DLco of 5% or more as "worsening", and those who had less than 5% or who had an improvement in their DLco as "stable" DLco. We compared the patients who had "worsening" DLco to those with "stable" DLco by survival analyses using Kaplan Meyer curves.

Results: 160 patients with Group 1 PAH have been entered into PHAROS. 89 of these patients have had at least 2 DLco measurements after entry. 58 (65%) had limited SSc, 81 (90%) were females, mean/SD age at study entry was 60.2/9.7 years, and mean/SD duration of Raynaud's was 13.4/11.6 years. The mean/SD baseline of the percent predicted DLco (%DLco), last %DLco, mPAP and pulmonary vascular resistance (PVR) were 44.9/16.2, 41.5/16, 35.3/9.1 mmHg and 434/320 dyn·s/cm[5], respectively. 35 patients had a decreasing DLco (>5%, mean 6.7%), 36 had no change in DLco (mean 2.3%) and 18 had an improved DLco (mean 13.2%). Patients with a worsening DLco had a 3 year survival of 75% compared to 90% in those with stable or improved DLco. The Kaplan Meyer curves revealed a statistically different survival rate based on the worsening %DLco (P=.03).

Conclusion: In this multicenter prospective cohort of patients with SSc with PAH, worsening of the diffusion capacity in the course of the disease was associated with increased mortality. Rate of worsening of the DLco should be considered when evaluating the prognosis of patients with SSc-PAH.

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Biomarkers of Pulmonary Hypertension in Patients with Scleroderma: A Case-Control Study.
Zsuzsanna H. McMahan[1], Florian Schoenhoff[2], Jennifer van Eyk[1], Fredrick M. Wigley[1] and Laura K. Hummers[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Berne, Switzerland

Background/Purpose: The objective of this study was to evaluate for an association between various biomarkers and the presence or absence of pulmonary hypertension (PH) in scleroderma

Methods: Proteomic analysis was used to retrospectively compare growth factor and cytokine levels in 48 patients with scleroderma and PH and 48 patients with scleroderma without clinical or ECHO evidence of PH. PH was defined as either an mPAP $\geq$ 25mmHg by right heart catheterization (n = 44) or an RVSP of > 45 mmHg by Echo with strong clinical evidence supporting a diagnosis (n= 4). An additional proteomic analysis was performed on a subset of 24 patients from each group using samples that had been drawn at least 6 months prior to the first sample to determine if changes in candidate biomarker levels were associated with PH. A multiplex proteomic assay was subsequently performed to look at growth factors (bFGF, PIGF, VEGF, HGF, sFLT-1) and cytokine levels (IL 1B, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12 p70, IL-13, TNF-alpha, and INF-gamma) (MesoScale Discovery, Gaithersburg, MD). Univariate and multivariable logistic regression were used to examine the association of growth factor and cytokine levels with the presence of pulmonary hypertension.

Results: The mean age in the PH group was 66 yrs (range 34–89) compared to 56 (range 27–83) in the non-PH group. Seventy-three percent (n=35) in the PH group had limited scleroderma compared to 65% (n=31) in the control group. Average disease duration was 17.3 years in the PH group and 12.2 years in the non-PH group. Differences in gender and scleroderma subtype were not significant between the two groups. We

found levels of IL-12 p70 (9.0 vs. 4.0; p=0.04), PlGF (26.7 vs. 21.3, p = 0.01), and sFLT-1(122.1 vs. 99.1, p=0.02) were significantly higher in the48 patients with PH compared with the 48 without PH at the latest blood sampling time point. When comparing biomarker levels at the earlier time point (17/24 with sample prior to PH diagnosis in the PH group) in the 24 patients with and 24 patients without pulmonary hypertension, sFLT-1 (122.2 vs. 100.5; p= 0.0062; CI −36.87, −6.52), HGF (451.6 vs. 202.1; p =0.003; CI −403.79, −95.28), and IL-10 (12.6 vs. 4.4; p= 0.03; CI −15.67, −.85), were significantly higher in the PH group. In a multivariable model adjusted for age, race, disease duration, and ILD, PlGF remained higher among those with PH (OR 1.06, p=0.16) although this was no longer statistically significant. In examining the stability of markers over time, all biomarkers were stable between the two samples except for VEGF (260.8 vs. 546.1; p=0.001) and bFGF (19.8 vs. 11.1; p= 0.01) which showed wide variability in levels between patients and at the 2 time points. IL-12p70 (−0.24, p = 0.05, CI −0.48, −0.00) and IL-5 (−0.51, p= 0.03, CI −0.952, −0.059) were negatively associated with severity of pulmonary hypertension as measured by mean pulmonary artery pressures (mPAP) among those with PH.

Conclusion: We found that PlGF (and possibly sFLT-1 and IL-12) may be associated with PH in scleroderma. This study confirms prior associations of PlGF with scleroderma vascular disease and suggests that this factor should be further explored as possible biomarkers of development of PH.

Disclosure: Z. H. McMahan, None; F. Schoenhoff, None; J. van Eyk, None; F. M. Wigley, None; L. K. Hummers, None.

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Left-Heart Disease Is a Frequent Cause of Pulmonary Hypertension in Systemic Sclerosis, Is Associated with Increased Levels of MR-ProANP and MR-ProADM but Is Unrelated to Elevated NT-ProBNP Levels: A Retrospective Cohort Analysis. Lada Miller[1], Sandra Chartrand[1], Martial Koenig[2], Jean-Richard Goulet[2], Eric Rich[1], Michal Abrahamowicz[3], Jean-Luc Senécal[1] and Tamara Grodzicky[1]. [1]Hôpital Notre-Dame du CHUM, Montreal, QC, [2]Hôpital Notre-Dame du CHUM, Montréal, QC, [3]Centre Universitaire de Santé McGill (CUSM), Montreal, QC

Background/Purpose: Pulmonary hypertension (PH) is a significant cause of morbidity and mortality in systemic sclerosis (SSc). Pulmonary arterial hypertension (PAH) is reportedly the most frequent cause of PH in SSc, affecting 8–12% of patients. We observed that a significant proportion of our SSc patients with PH as diagnosed by right heart catheterization (RHC) had PH due to causes other than PAH. The frequency of other causes of PH in SSc has not been accurately determined to date. The aim of the present study was therefore to determine the frequency of different causes of PH in our SSc cohort and to identify associated clinical, serological and radiologic variables.

Methods: A retrospective analysis of 432 SSc patients was done. All patients routinely underwent screening for PH. Clinical, serological and radiographic data from patients with PH confirmed by RHC (n=26) were analyzed. Living SSc PH patients (n=21) and 19 control SSc patients without clinical PH were prospectively re-evaluated with serial measurements of NT-proBNP and the hemodynamic biomarkers MR-proANP and MR-proADM.

Results: The most frequent cause of PH was left heart disease (LHD) (15/26, 58%). PAH was seen in 9/26 patients (34%). Other causes of PH were veno-occlusive disease and multifactorial PH. No association was found between the type of PH and the autoantibody profile. LHD-related PH was associated with significantly lower NT-proBNP levels than PAH at the time of established PH (137 ± 137 pg/ml vs 484 ± 248 pg/ml, p=0.024), and all SSc patients without PH had normal levels of NT-proBNP. MR-proANP and MR-proADM levels were significantly higher in SSc patients with PH than those without PH (105 [81–151] pmol/L vs 78 [32–91] pmol/L, respectively, p = 0.004, and 0.7 [0.42–0.87] nmol/L vs 0.5 [0.4–0.6] nmol/L, p = 0.018,). Similarly, MR-proANP and MR-proADM levels were significantly higher in SSc patients with LHD-PH as compared to those without PH (105 [87–137] pmol/L vs 78 [32–91] pmol/L, respectively, p = 0.014, and 0.75 [0.47–0.92] nmol/l vs 0.5 [0.4–0.6] nmol/L, p= 0.012). However, there was no significant difference between the LHD-PH and the PAH groups.

Conclusion: SSc-associated PH is heterogeneous. RHC is essential to determine the underlying cause. The most frequent cause of PH is LHD, not PAH. Levels of MR-proANP and MR-proADM, but not NT-proBNP, were increased in LHD-PH, and may be more reliable markers than NT-proBNP in this subgroup of patients. This study is the first to identify such a high frequency of LHD-PH correlating with normal NT-proBNP levels but increased MR-proANP and MR-proADM in SSc.

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Measurement of Pulmonary Arteries by Cardiac Magnetic Resonance Imaging: A Simple and Useful Tool for the Detection of Pulmonary Hypertension in Systemic Sclerosis Patients without Overt Cardiac Microvascular Perfusion Defects or Fibrosis. Sandra Chartrand[1], Lada Miller[1], Martial Koenig[1], Jean-Richard Goulet[1], Eric Rich[1], Anne S. Chin[2], Yves Provost[2], Carl Chartrand-Lefebvre[2], Pauline Gou[1], Jean-Luc Senécal[1] and Tamara Grodzicky[1]. [1]Hôpital Notre-Dame du CHUM, Montréal, QC, [2]Hôtel-Dieu de Montréal du CHUM, Montréal, QC

Background/Purpose: Pulmonary hypertension (PH) is a major complication of systemic sclerosis (SSc). We observed that a significant proportion of our SSc patients with PH as diagnosed by right heart catheterization (RHC) had PH due to causes other than pulmonary arterial hypertension (PAH), notably left heart disease (LHD) (15/26, 58%). We hypothesized that LHD in these patients could be explained by cardiomyopathy secondary to microvascular disease and/or fibrosis. The aim of our study was to detect microvascular perfusion defects and/or fibrosis, as well as useful parameters for PH diagnosis, by cardiac magnetic resonance imaging (MRI) in SSc patients with and without PH.

Methods: A retrospective analysis of our cohort of 432 SSc patients was performed. All patients routinely underwent screening for PH, and diagnosis of PH was proven by RHC in all suspected cases. Data from clinical, cardiopulmonary and serological investigations were analyzed. All living patients with PH (n=18) as well as a control group of 19 consecutive SSc patients without clinical suspicion of PH underwent a cardiac MRI (a morphologic and functional study with steady state free precession technique in static and cine imaging, and a T2 short-term inversion recovery (STIR) study, followed by a delayed contrast-enhanced imaging acquisition).

Results: Twenty-six SSc patients (26/432; 6%) had PH diagnosed by RHC. Eighteen of these patients (11 with PH due to LHD [61%], 4 with PAH [22%], 3 from other causes) and 19 without clinical suspicion of PH (control group) underwent cardiac MRI. Age, disease duration, gender, ethnicity, disease subtypes and autoantibody profiles were similar between the two groups. Systolic pulmonary artery pressure by transthoracic echocardiography (48,3±7,5 mmHg vs 30,3±5,7 mmHg, p<0,001) as well as the carbon monoxide transfer factor (TLCO) (54,3±15,4% of predicted value vs 69,1±22,8% of predicted value, p=0,043) were statistically significantly different between SSc patients with and without PH, respectively. Cardiac MRI showed statistically significant differences between SSc patients with and without PH, respectively, for the measurement of the diameter of the main pulmonary artery (PA) (30,90±5,03 mm vs 26,30±3,86 mm, p=0,006), the right PA (23,50±4,11 vs 18,60±2,90 mm, p=0,001), and the ratio of the main PA to the ascending aorta (0,97±0,10 vs 0,84±0,10, p=0,002). There was a trend toward significance for the measurement of the left PA (21,60±3,52 mm vs 19,80±1,98 mm, p=0,07). None of the 37 patients had significant myocardial hypersignal in T2 STIR nor delayed gadolinium enhancement.

Conclusion: Cardiac MRI investigation did not show overt evidence of myocardial perfusion defects nor fibrosis to explain PH secondary to LHD in our SSc cohort. Newer more sensitive cardiac MRI modalities may be more useful and should be evaluated in future studies. However, cardiac MRI measurement of the diameter of the main PA, the right PA and possibly of the left PA, as well as the ratio of the main PA to the ascending aorta, seem to be simple and reliable methods for PH diagnosis in SSc patients, and may prove to be useful noninvasive tools in the investigation of PH.

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Systemic Sclerosis Associated Pulmonary Hypertension - Is Pulmonary Veno-Occlusive Disease As Common As They Say? Benjamin E. Schreiber[1], Greg Keir[2], D. Dobarro[3], Clive Handler[1], Svetlana Nihtyanova[4], Jay Suntharaligam[5], Nicola Sverzelatti[6], Graham Robinson[5], David Hansell[7], Athol U. Wells[2], Christopher P. Denton[8] and John G. Coghlan[1]. [1]Royal Free Hospital, London, London, United Kingdom, [2]Royal Brompton Hospital, United Kingdom, [3]Royal Free Hospital, London, United Kingdom, [4]Royal Free Hospital, Medical School, London, England, [5]Royal United Hospital, Bath, United Kingdom, [6]University of Parma, Parma, Italy, [7]Royal Brompton Hospital, London, United Kingdom, [8]UCL, London, United Kingdom

Background/Purpose: Recent reviews have suggested a high prevalence of pulmonary veno-occlusive disease (PVOD) amongst patients with systemic sclerosis (SSc) associated pulmonary hypertension (PH). Interlobular septal thickening (IST) and centrilobular nodules (CLN) are reported to correlate with presence of PVOD, which is associated with worse outcomes in small series. We tested this hypothesis on a large series of systemic sclerosis patients who underwent evaluation for pulmonary hypertension.

Methods: A retrospective study of patients with systemic sclerosis who underwent CT of the chest within six months of a diagnostic right heart catheterisation. The CTs were blindly scored by two independent radiologists including detailed assessment for extent of interstitial lung disease (using the Goh et al. AJRCCM 2008 staging system), IST and CLN. Each lung quadrant was scored separately for interlobular septal thickening (IST) with score 0–5 and centrilobular nodules (CLN), score 0–3. Survival data were collected on all patients.

Results: Mean age was 57.8 (range 22–85). 78% were female. 84 patients had LcSSc, 32 had DcSSc and 1 had MCTD. CT scans were performed a mean of 2.7 months from the RHC.

There was limited or no ILD extent (<20%) in 46 patients (43%), 20% in 28% and extensive (>20%) in 30%. On right heart catheterisation 53% had precapillary PH while 47% did not.

95 scans were reported independently in a blinded fashion by two radiologists. Of the remaining 95 patients, 49 had PAH and 46 did not. Of those with PH, 18 had <20% ILD, 18 had 20% ILD and 13 had >20% ILD. Amongst patients with PH, there was a weak trend towards worse survival in patients with more lung disease (HR 1.5, 95% CI 0.89,2.52, p=0.13).

IST of any degree was observed in 15% of patients and CLN in 18%. Mean IST score was 1 (on a scale of 0–4) and mean CLN score was 0.63 (scale of 0–2). IST was not associated with extent of ILD (p=0.19 by chi-square), and nor was CLN (p=0.74, by chi-square). IST did not correlate with PVR (R2=2%) whereas CLN did correlate with PVR (R2=15.7%).

By Cox proportional hazards analysis, PVR was a strong predictor of death (p=0.001). Increasing IST was associated with worse survival on univariate analysis (p=0.038) however statistical significance is lost (p=0.11) after adjustment for age.

Increasing CLN is strongly associated with higher mortality (p=0.013) even after adjustment for age, gender, extent of interstitial lung disease and mean pulmonary artery pressure (p=0.047). This is particularly observed in patients without PH (p=0.004 on this multivariate analysis) rather than in patients with PH (where p=0.19 on multivariate analysis). However, CLN is not a significant predictor for PVR after adjustment for age (p=0.18).

Conclusion: Interlobular septal thickening and centrilobular nodules are frequently seen in patients with systemic sclerosis and are each associated with worse survival. However, IST increases with age and CLN increases with worsening pulmonary vascular resistance. In our study they were not independent predictors of worse outcome in systemic sclerosis. It is therefore possible that the significance of these radiological findings is primarily as markers of known prognostic risk factors.

Disclosure: B. E. Schreiber, Actelion Pharmaceuticals US, 8, 9, GSK, 5; **G. Keir**, None; **D. Dobarro**, Eli Lilly and Company, 9; **C. Handler**, Actelion Pharmaceuticals US, 9, Pfizer Inc, 9; **S. Nihtyanova**, None; **J. Suntharaligam**, GSK, 8, Actelion Pharmaceuticals US, 8, Novartis Pharmaceutical Corporation, 8; **N. Sverzelatti**, None; **G. Robinson**, None; **D. Hansell**, Astra Zeneca, 5, Boehringer Ingelheim, 5; **A. U. Wells**, None; **C. P. Denton**, Actelion Pharmaceuticals US, 5, GlaxoSmithKline, 5, Pfizer Inc, 5, United Therapeutics, 5; **J. G. Coghlan**, GSK, 9, Bayer, 9, Pfizer Inc, 9, Eli Lilly and Company, 9.

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Renal Dysfunction and Disease Severity in Scleroderma-Associated Pulmonary Arterial Hypertension. Stephen C. Mathai[1], Laura K. Hummers[1] and Virginia D. Steen[2]. [1]Johns Hopkins University, Baltimore, MD, [2]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Renal disease is a common complication of scleroderma (SSc). Isolated reduction in glomerular filtration rate (GFR), a marker of impaired renal function, can occur in patients with normal serum creatinine. A recent single-center study of patients with SSc and pulmonary arterial hypertension (SSc-PAH) suggests that an estimated GFR (eGFR) < 60 ml/min/1.73m^{2}at baseline occurs in over 40% of patients and portends a three-fold increased risk of death in this population. Therefore, we sought to determine the prevalence and clinical correlates of renal dysfunction in a large, multi-center observational cohort using the PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) registry.

Methods:: We identified patients with SSc-PAH, defined according to the Dana Point criteria. eGFR was calculated using the 4-variable Modified Diet in Renal Disease equation (MDRD); eGFR< 60 ml/min/1.73m^{2}was considered abnormal. Demographic, serologic, physiologic, and hemodynamic parameters were compared between groups using t-tests or chi-squared analyses where appropriate.

Results: 133 SSc-PAH patients were included in this study (Table 1). Overall, 33% (44/133) of subjects had an eGFR<60 ml/min/1.73m^2(low eGFR group). In general, the low eGFR group was older and was more likely to have diffuse disease, but there was no difference in gender, race, duration of SSc, or antibody profiles between groups. Pulmonary function and New York Heart Association functional class were similar between groups, however, six minute walk distance was significantly lower in the low eGFR group. Patients in the low eGFR group were more likely to have had a renal crisis and to have worse hemodynamics (higher mean pulmonary artery pressure, lower cardiac output, and higher pulmonary vascular resistance).

Table 1. Patient Population

Parameter	Overall (n=133)	eGFR<60 (n=44)	eGFR>60 (n=89)	p-value
Age (years)	60 (11)	64 (9)	59 (11)	<0.01
Gender (n,%women)	109 (83)	38 (86)	71 (82)	0.49
Race (n,% Caucasian)	120 (90)	42 (95)	78 (88)	0.15
Limited vs. Diffuse (n,% limited)*	54 (60)	13 (40)	41 (71)	<0.01
Duration of SSc (yrs)	8.2 (9.5)	7.7 (9.5)	8.9 (9.4)	0.68
First Raynaud's symptom (yrs)	14.3 (12.0)	14.9 (13.3)	13.9 (11.4)	0.69
History of renal crisis (n,%)	6 (5)	5 (13)	1 (1)	<0.01
FVC (% predicted)	81.7 (15.7)	84.9 (15.4)	79.9 (15.7)	0.10
FEV1/FVC (% predicted)	81.7 (9.9)	82.0 (11.1)	80.7 (9.9)	0.51
TLC (%predicted)	79.0 (18.5)	79.3 (19.3)	78.9 (18.2)	0.90
DLCO (%predicted)	40.1 (17.5)	37.5 (19.9)	41.5 (16.1)	0.22
FVC/DLCO (% predicted)	2.2 (0.9)	2.2 (0.7)	2.2 (0.9)	0.86
Home oxygen use (n,%)	39 (32)	13 (33)	26 (32)	0.86
6MWT (m)	332 (127)	291 (134)	355 (119)	0.02
NYHA class (I/II vs III/IV)	62/57	20/23	42/34	0.52
Mean PAP (mmHg)	37 (19)	40 (11)	36 (9)	0.02
CO (L/min)	5.0 (1.6)	4.4 (1.2)	5.4 (1.6)	<0.001
PCWP (mmHg)	10 (3)	9 (3)	11 (3)	0.03
PVR (Wood units)	5.8 (3.9)	7.2 (3.5)	5.1 (3.9)	<0.01

Conclusion: In this large cohort of patients with SSc-PAH, renal dysfunction was common and associated with more severe functional and hemodynamic impairments. Interestingly, there was no association between antibody profiles or race and prevalence of renal dysfunction. The determinants of renal disease and the relationship between renal dysfunction and mortality in this cohort will be the focus of future studies in the PHAROS registry.

Disclosure: S. C. Mathai, None; **L. K. Hummers**, None; **V. D. Steen**, Gilead, 5.

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Survival, Hospitalization or Need for Combination Therapy At One Year in Patients with Scleroderma-Associated Pulmonary Arterial Hypertension. Robyn T. Domsic[1], Lorinda Chung[2], Jessica K. Gordon[3], Yona Cloonan[1], Virginia D. Steen[4] and PHAROS Investigators[5]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Stanford Univ Medical Center, Palo Alto, CA, [3]Hospital for Special Surgery, New York, NY, [4]Georgetown Univ Medical Center, Washington, DC, [5]Washington, DC

Background/Purpose: Pulmonary arterial hypertension (PAH) is a leading cause of death in patients with systemic sclerosis (SSc). Although survival has improved with PAH-specific medications in the last decade, the optimal

therapy remains unknown. We sought to compare the one year outcome of SSc-PAH patients with different therapeutic classes of PAH-specific medications.

Methods: Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a multi-center prospective registry of SSc patients at high risk for PAH or with definite PH diagnosed by right heart catheterization (RHC) within 6 months of enrollment. To be included in this analysis, patients had to have World Health Organization (WHO) Group I PAH, and have received a PAH-specific medication for > 3 months duration. We assessed patient outcomes for four therapeutic classes: endothelin receptor antagonists (ERA), phosphdiesterase type 5 inhibitors (PDE-5), prostacyclins (PCA) and those started immediately on combination therapy ($\geq$2 of the other classes). A Kaplan-Meier curve was estimated for 1 year survival from the time the PAH treatment was started, and differences between the drug classes were assessed by the log-rank test. Rates of hospitalizations at one year were compared by chi-square tests.

Results: In the PHAROS registry 160 individuals have PAH, of whom 120 either had$\geq$ 1 year of follow-up or had died prior to 1year of follow-up. Of these, 101 had been treated with a PAH medication for > 3 months and comprised the analysis population. The mean age was 59.0 $\pm$ 10.4 years, 85% were female, 80% Caucasian and 11% African-American. 67% were classified as limited cutaneous SSc. Overall, initial therapy was a PDE-5 in 47%, ERA in 30%, PCA in 13% and combination therapy in 10%. In the PCA group 85% started inhaled, and 15% started parental therapy. With those with a baseline NYHA class within two months of therapy initiation, 25% of the PCA group were class IV, as compared to 20% in the combination, 0% ERA and 7% PDE5. At one year 7% (n=7) on medications had died, whereas 10% had died at one year in the entire PHAROS cohort. There was a statistically significant difference between the drug classes with 98% of PDE-5, 97% of ERA, 69% of PCA and 90% of combination therapy alive at one year (p=0.002). At one year 28% of patients had been hospitalized, but there was no difference in rate of all-cause hospitalization (p=0.78) or PAH-related hospitalizations (p=0.91) between the drug classes. Similarly, there was no difference in progression to combination therapy with 27% of PDE5, 23% of ERA and 13% of PCA (p=0.67).

Conclusion: At one year there is no difference in rates of hospitalization or progression to combination drug therapy among the PAH-specific drug classes. However, there was a difference in one-year survival between the drug classes, with those started on PCAs clearly having the lowest survival. This may reflect that those patients had more severe pulmonary vascular disease at baseline. Further follow-up is needed to determine whether long-term outcomes differ between the PAH therapeutic drug classes.

Disclosure: **R. T. Domsic**, None; **L. Chung**, Gilead and Actelion, 5, Gilead, Actelion, Pfizer, United Therapeutics, 2; **J. K. Gordon**, None; **Y. Cloonan**, None; **V. D. Steen**, Gilead, 5.

ACR Plenary Session I
Discovery 2012
Sunday, November 11, 2012, 11:00 AM–12:30 PM

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The Role of Interleukin-23 in Spondyloarthropathy. Jonathan Sherlock[1], Barbara Joyce-Shaikh[1], Scott Turner[1], Cheng-Chi Chao[1], Manjiri Sathe[1], Jeff Grein[1], Dan Gorman[1], Eddie P. Bowman[2], Terrill McClanahan[1], Jennifer Yearley[1], Gerard Eberl[3], Christopher D. Buckley[4], Robert Kastelein[1], Robert Pierce[1], Drake LaFace[1] and Daniel Cua[5]. [1]Merck, Palo Alto, CA, [2]Merck, Palo Alto, [3]Institut Pasteur, Paris, France, [4]School of Immunity and Infection, MRC Center for Immune Regulation, Birmingham, United Kingdom, [5]Merck Research Laboratory, Palo Alto, CA

Background/Purpose: Spondyloarthropathy is characterized by inflammation and bony pathology at the entheseal insertion of tendons to bone. Recent investigations have converged upon interleukin(IL)-23, demonstrating firstly that genetic variants in its receptor are associated with disease and secondly that HLA-B27, which is present in 90% of patients with ankylosing spondylitis, has a tendency to misfold and form cell surface homodimers resulting, respectively, in production of IL-23 and stimulation of IL-23R+ cells. However why such dysregulation of IL-23 should result in inflammation primarily at the enthesis has remained deeply enigmatic.

We have hypothesized that tissue resident cells fundamentally determine disease localization (Cua and Sherlock, Nature Medicine 17(9): 1055–6) and herein extend our previous observations (Sherlock *et al.* in press) to demonstrate the presence of IL-23R+ cells in the uvea and to further characterize these cells and their effects.

Methods: We used GFP reporter mice to investigate the tissue distribution of IL-23R+ cells in the main tissues inflamed in spondyloarthropathy: the enthesis, aortic valve and uvea. Flow cytometric analysis and multiphoton microscopy was employed to characterize the location of such cells and the reactivity of this tissue to IL-23 was determined in vitro and in vivo.

Results: Entheses, the aortic root and the uvea all contain a novel tissue resident IL-23R+ T lymphocyte, negative for both CD4 and CD8, which allows the tissue to respond to IL-23. Multiphoton microscopy confirms an extremely precise entheseal localization of the IL-23R+ cell type. These cells are RAG dependent, but express the PLZF transcription factor which confers an 'innate like' responsiveness on T cells, allowing them to immediately respond to cytokines. Entheses can respond within hours to IL-23 *in vitro* in the absence of further cellular recruitment. Moreover, IL-23 expression in mice is sufficient by itself to induce hallmark features of spondyloarthropathy, with severe inflammation developing very specifically at the enthesis and aortic root. Entheseal bone erosion, new bone formation and periostitis are likewise present.

Conclusion: The highly restricted anatomical distribution of IL-23R+ cells explains both the exquisitely precise tissue localization of disease in spondyloarthropathy, as well as the known genetic associations with IL-23, and gives a very clear mechanism whereby HLA-B27 and its tendency to cause IL-23 elaboration may predispose to pathology. These IL-23R+ tissue resident cells thus form the point of integration between the specific immunological dysregulations known to be associated with disease, and the very precise anatomical sites affected. The importance of these tissue resident cells is emphasized by the ability of IL-23 to drive enthesitis despite depletion of the conventional IL-23 responsive Th17 cells. Neutralization of IL-23 therefore represents an excellent therapeutic strategy in spondyloarthropathy since it will inhibit a potent molecule associated with known genetic factors, and do so directly at the site of pathology.

Disclosure: **J. Sherlock**, Merck, 3; **B. Joyce-Shaikh**, Merck, 3; **S. Turner**, Merck Pharmaceuticals, 3; **C. C. Chao**, Merck Pharmaceuticals, 3; **M. Sathe**, Merck, 3; **J. Grein**, Merck Pharmaceuticals, 3; **D. Gorman**, Merck Pharmaceuticals, 3; **E. P. Bowman**, Merck Pharmaceuticals, 3; **T. McClanahan**, Merck Pharmaceuticals, 3; **J. Yearley**, Merck Pharmaceuticals, 3; **G. Eberl**, None; **C. D. Buckley**, None; **R. Kastelein**, Merck Pharmaceuticals, 3; **R. Pierce**, Merck Pharmaceuticals, 3; **D. LaFace**, Merck Pharmaceuticals, 3; **D. Cua**, Merck Research Laboratory, 3.

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Dynamic *in Vivo* Imaging of Th17-Mediated Osteoclastic Bone Resorption in Live Bones by Using Intravital Multiphoton Microscopy. Junichi Kikuta and Masaru Ishii. Immunology Frontier Research Center, Osaka University, Osaka, Japan

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint synovial inflammation and progressive cartilage/bone destruction. Although various kinds of cell types, such as T/B lymphocytes, macrophages and synovial fibroblasts, are involved in the pathogenesis of chronic inflammation in RA, bone destruction is considered to be mainly mediated by enhanced activation of osteoclasts. Recently CD4+ T helper 17 (Th17) cells have been reported to express RANKL on the cell surface, which were suggested to be important for osteoclastic bone destruction in arthritic joints. However, the RANKL expressed on the surface of Th17 possesses little ability for inducing differentiation, and the practical function of RANKL and Th17 on bone erosion remained elusive. This study aimed to investigate how the bone-resorptive functions of osteoclasts are regulated *in situ* and how Th17 cells control the osteoclastic bone resorption *in vivo*.

Methods: To examine *in vivo* behaviors of mature osteoclasts and Th17 cells, we utilized advanced imaging system for visualizing live bone tissues with intravital multiphoton microscopy that we have originally established. To identify mature osteoclasts in fluorescent microscopy, we utilized the mice in which GFP is expressed under the promoter of a vacuolar type H+-ATPase a3 subunit, those are preferentially and abundantly expressed in mature osteoclasts (a3-GFP mice). Polyclonally differentiated Th17 cells were labeled with fluorescent dye and then

adoptively transferred into a3-GFP mice. We observed calvaria bone tissues of a3-GFP mice by using intravital multiphoton microscopy.

Results: We succeeded in visualizing live mature osteoclasts on the bone surface *in situ*. By using this imaging system, we could identify different populations of live mature osteoclasts in terms of their motility and function, i.e., 'static – bone resorptive (R)' and 'moving – non resorptive (N)'. Treatment with recombinant RANKL or bisphosphonate changed the composition of these populations as well as total number of mature osteoclasts. We also found that rapid RANKL injection converted the moving (N) osteoclasts to static (R) ones without any changes in total number of osteoclasts, suggesting a novel action of RANKL in controlling mature osteoclast function. Furthermore, we could demonstrate that Th17 cells had potency for inducing rapid N to R conversion of mature osteoclasts by RANKL expressed on their cell surface *in situ*.

Conclusion: By visualizing *in vivo* behaviors of mature osteoclasts, we for the first time identified different functional subsets of live osteoclasts on the bone surface, from 'static – bone resorptive' to 'moving – non resorptive'. Furthermore, RANKL turned out not only to promote the differentiation of osteoclasts but also to regulate the bone-resorptive function of fully differentiated mature osteoclasts. RANKL-bearing Th17 cells were shown to control bone resorption of mature osteoclasts, demonstrating novel actions of Th17 that may be a novel therapeutic target in RA.

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Effects of Odanacatib On BMD and Overall Safety in the Treatment of Osteoporosis in Postmenopausal Women Previously Treated with Alendronate.

Roland Chapurlat[1], Sydney Bonnick[2], Tobias De Villiers[3], Alberto Odio[4], Santiago Palacios[5], Boyd Scott[6], Celine Le Bailly De Tilleghem[7], Carolyn DaSilva[6], Albert Leung[8] and Deborah Gurner[8]. [1]Hôpital Edouard Herriot, Lyon, France, [2]Cooper Clinic, Dallas, TX, [3]Mediclinic Panorama, Cape Town, South Africa, [4]Alta California Medical Group, Simi Valley, CA, [5]Instituto Palacios, Madrid, Spain, [6]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [7]Merck Sharp & Dohme Corp., Brussels, Belgium, [8]Whitehouse Station, NJ

Background/Purpose: Odanacatib (ODN) is a potent, orally-active cathepsin K inhibitor being developed for the treatment of postmenopausal osteoporosis. This study evaluated the effects of ODN 50mg once weekly (OW) on BMD and biochemical markers of bone turnover in patients previously treated with alendronate (ALN) (dosed daily or weekly) for ≥3years, as well as the safety and tolerability of ODN.

Methods: This was a randomized, double-blind, placebo-controlled, 24-month study. The primary endpoint was % change in femoral neck (FN) BMD from baseline at Month 24. 243 postmenopausal women ≥60 years of age with low BMD T-score (T-score range ≤−2.5 but >−3.5) at the total hip, FN or trochanter but no history of hip fracture and who had been treated with ALN for ≥3years were randomized in a 1:1 ratio to receive ODN 50mg OW or placebo OW for 24 months. All patients received vitamin D_3 5600 IU/wk and calcium supplementation (to 1200 mg/day). BMD was assessed by DXA at baseline, 6, 12 and 24 months. Biochemical markers of bone resorption (s-CTx, u-NTx) and bone formation (s-BSAP and s-P1NP) were measured at baseline and 3, 6, 12, 18 and 24 months. This study was not designed and did not have the power to evaluate the effect of ODN on fractures.

Results: In the placebo group, FN and trochanter BMD were not significantly different from baseline levels for the first 12 months, but declined significantly from baseline by Month 24 (−0.94% and −1.35%, respectively). BMD at the total hip declined in a linear manner from baseline to month 24 (−1.87% at 24 months). BMD at the lumbar spine (LS) was not significantly different from baseline for the entire 24 months of the study. BMD changes from baseline at 24 months in the ODN group were significant vs placebo at all 3 hip sites and the LS. The changes in BMD for the FN, trochanter, total hip and LS from baseline were 1.73%, 1.83%, 0.83% and 2.28%, respectively. ODN 50mg OW significantly decreased the biomarker of bone resorption, u-NTx/Cr, and significantly increased biomarkers of bone formation, s-P1NP and s-BSAP, compared to placebo. The increase observed for the bone resorption marker s-CTx with ODN treatment was unexpected. AEs were comparable between the 2 treatment arms. The overall safety profile appeared similar between ODN 50mg OW and placebo.

ODN effects on BMD

% Change from Baseline in BMD (Least Square Mean +/-SE) at 24 Months — Geometric Mean % Change from Baseline +/- SE at 24 Months
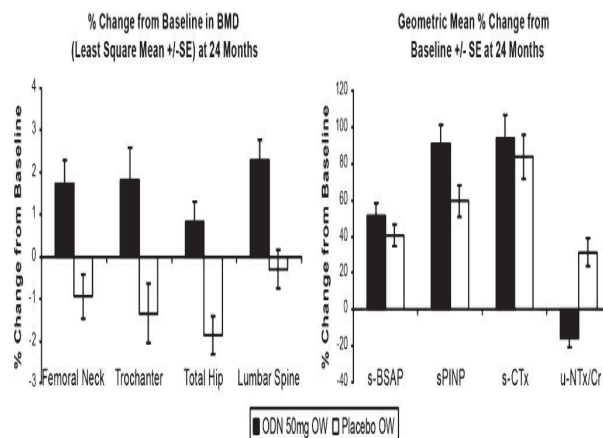
ODN effects on biomarkers

% Change from Baseline in BMD (Least Square Mean +/-SE) at 24 Months — Geometric Mean % Change from Baseline +/- SE at 24 Months
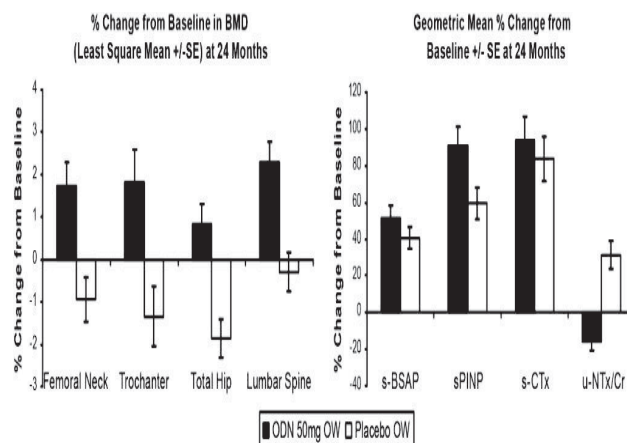
Conclusion: In this study osteoporotic women treated with ODN following ALN treatment show incremental gains in BMD. Biomarker results suggest that ODN decreases bone resorption while preserving bone formation.

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Does the Use of Angiotensin Converting Enzyme Inhibitors Prior to Scleroderma Renal Crisis Affect Prognosis ? – Results of the International Scleroderma Renal Crisis Survey.

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Background/Purpose: Scleroderma renal crisis (SRC) is an infrequent but life-threatening complication of systemic sclerosis (SSc). The outcome of SRC has improved considerably since the advent of angiotensin converting enzyme (ACE) inhibitors. The incidence of SRC has also appeared to have decreased, perhaps in part due to the more liberal use of ACE inhibitors in SSc. However, recent retrospective data suggests that patients with SRC exposed to ACE inhibitors prior to the onset of SRC may have worse outcomes. We undertook a prospective study to verify whether SSc patients with incident SRC on ACE inhibitors at the time of onset of SRC had worse outcomes compared to those who were not on these drugs at that time.

Methods: We designed a prospective, observational cohort study of incident SRC subjects identified through a web-based survey. Every second week, an e-mail was sent to 589 participating physicians from around the world to identify incident cases of SRC. Data on patient demographic and disease characteristics, as well as exposure to ACE inhibitors was collected. A one-year follow-up case report form was sent to all the physicians who identified a case. The primary outcome of interest was death or dialysis at one year after the onset of SRC, comparing patients exposed and unexposed to ACE inhibitors at the time of onset of SRC.

Results: We identified 88 incident cases of SRC, of which 12 were lost to follow up (86% follow up rate). Mean age was 52 years, 67% were women, 76% had diffuse SSc and median disease duration since the onset of the first non-Raynaud's symptom was 1.5 years. The majority of cases had a hypertensive SRC (n=71/76) and only 5 had a normotensive SRC. Eighteen patients (24%) were on an ACE inhibitor immediately prior to the onset of the SRC. At one year follow up, 27 (36%) SRC patients had died and an additional 13 (17%) remained on dialysis.

The crude one-year cumulative incidence of death in those exposed to ACE inhibitors at the time of onset of SRC compared to the unexposed was 1.56 (95% confidence interval [CI] 0.70–3.47) and the crude one-year cumulative incidence of dialysis was 0.61 (95% CI 0.18–2.09). The crude Cox proportional hazard ratio comparing the time to death of SRC patients exposed to ACE inhibitors prior to the onset of SRC to those unexposed was 1.95 (95% CI 0.87–4.35). After controlling for differences in prednisone exposure and history of systemic hypertension in the two groups, the adjusted Cox proportional hazard ratio comparing the time to death of SRC patients exposed to ACE inhibitors prior to the onset of SRC to those unexposed was 2.52 (95% CI 1.05–6.05, p=0.0394).

Conclusion: SRC was associated with poor one-year outcomes. Exposure to an ACE inhibitor prior to the onset of SRC was associated with an increased risk of death during the first year of follow up after SRC. Clinicians caring for patients with early SSc should use ACE inhibitors cautiously.

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Apolipoprotein L1 Risk Variants Underlie Racial Disparities in Lupus Nephritis-Induced End-Stage Renal Disease. Robert P. Kimberly[1], Barry I. Freedman[2], Carl D. Langfeld[3], Devin Absher[4], Kelly K. Andringa[1], Daniel Birmingham[5], Elizabeth E. Brown[1], Mary E. Comeau[6], Karen H. Costenbader[7], Lindsey A. Criswell[8], Jeffrey C. Edberg[9], John B. Harley[10], Judith A. James[11], Diane L. Kamen[12], Joan T. Merrill[13], Timothy B. Niewold[14], Neha Patel[15], Michelle A. Petri[16], Rosalind Ramsey-Goldman[17], Jane E. Salmon[18], Mark Segal[19], Kathy Moser Sivils[13], Betty P. Tsao[20], Bruce A. Julian[9] and Lupus Nephritis-ESRD Consortium[21]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, [3]Wake Forest University Health Sciences, Winston-Salem, [4]HudsonAlpha Institute for Biotechnology, Huntsville, [5]Ohio State University Medical Center, Columbus, OH, [6]Wake Forest University Health Sciences, Winston-Salem, NC, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [8]University of California San Francisco, San Francisco, CA, [9]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [10]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [11]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [12]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC, [13]Oklahoma Medical Research Foundation, Oklahoma City, OK, [14]University of Chicago, Chicago, IL, [15]SUNY Downstate Medical Center, Brooklyn, NY, [16]Johns Hopkins University School of Medicine, Baltimore, MD, [17]Northwestern University Feinberg School of Medicine, Chicago, IL, [18]Hospital for Special Surgery, New York, NY, [19]University of Florida, Gainesville, FL, [20]UCLA School of Medicine, Los Angeles, CA, [21]Birmingham, AL

Background/Purpose: The G1 and G2 coding variants in the apolipoprotein L1 gene (*APOL1;* G1: a compound missense allele (glycine-342/methionine-384) and G2: an in-frame deletion (deletion of asparagine-388 and tyrosine-389)), are strongly and reproducibly associated with focal segmental glomerulosclerosis (FSGS), HIV-associated collapsing glomerulopathy, and hypertension-attributed end-stage renal disease (ESRD) in African Americans (AAs) [Genovese G et al. Science 329:841,2010; Tzur S et al. Hum Genet 128:345,2010]. The role of *APOL1* in lupus nephritis (LN) related ESRD is unexplored. We tested for association between *APOL1* risk variants and LN-ESRD in a national sample of unrelated AAs with systemic lupus erythematosus (SLE).

Methods: The study sample included 668 AA cases with LN-ESRD (456 with kidney biopsy documentation; 212 physician-reported) and 697 AA patients with longstanding SLE lacking LN (mean duration of disease: 10.1 years). Genotyping was performed on a Sequenom platform. Allele frequency differences between LN-ESRD cases and SLE non-nephropathy cases were analyzed using multivariable logistic regression models, adjusting for non-muscle myosin heavy chain 9 gene single nucleotide polymorphism rs4821480 using a recessive genetic model.

Results: In cases with LN-ESRD, 87.1% were female, 89% received cytotoxic therapy, mean + SD age at SLE onset was 26.6 + 0.4 years, and duration of SLE to ESRD was 7.2 + 0.3 years with median at 5 years. In non-nephritis SLE patients, 93.5% were female with age at SLE onset 35.2 + 0.8 years. Contrasting all cases with and without ESRD, *APOL1* risk variants were significantly associated with LN-ESRD (odds ratio 2.35 (1.77–3.3 95% CI); p=4.25E^{-9}); significant differences in association were not observed when comparing cases with or without kidney biopsy documentation to SLE patients without LN. The duration of SLE onset to ESRD for those with the G1/G2 variants was 5.49+/−0.54 (median=4) years, while that for those without the variants was 7.78+/−0.37 (median=6) years, p<0.05.

Conclusion: This study demonstrates strong association between both *APOL1* G1 and G2 variants and LN-associated ESRD in AAs. It appears likely that *APOL1* G1 and G2 coding variants, which are rare in European populations, contribute to nephropathy progression in LN-ESRD, as well as in FSGS and other non-diabetic etiologies of ESRD. These variants, and their higher prevalence in individuals with African ancestry, may explain, in part, disparities in clinical outcomes in LN with there being a higher prevalence of severe LN in AA.

ACR Concurrent Abstract Session
Biology and Pathology of Bone and Joint: Osteoarthritis
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Disease Modifying Effect of Strontium Ranelate in Experimental Dog Osteoarthritis: Inhibition of Major Catabolic Pathways. Jean-Pierre Pelletier, Mohit Kapoor, Daniel Lajeunesse, Hassan Fahmi and Johanne Martel-Pelletier. Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC

Background/Purpose: To assess the disease modifying (DMOA) effect of strontium ranelate (SrRan) under therapeutic conditions on the progression of structural changes and on the major pathways involved in these changes in an experimental osteoarthritis (OA) dog model.

Methods: Dogs were divided into 4 therapeutic groups and underwent sectioning of the anterior cruciate ligament of the right knee and, 4 weeks after surgery, received oral treatment with SrRan 25, 50 or 75 mg/kg, or placebo for 12 weeks. Severity of cartilage lesions was scored macroscopically, and specimens of cartilage, subchondral bone and synovium were processed for histology, including picrosirius red staining and quantitative PCR (RT-PCR). Specific probes were used to quantify the messenger RNA of MMP-1, MMP-13, ADAMTS5, cathepsin K and interleukin-1β (IL-1β). Histomorphometry of the subchondral bone and a pharmacokinetic analysis of strontium (Sr) blood levels were also performed. The level of CTX-II in serum was quantified by ELISA.

Results: At steady state, Sr blood exposures were found to be within the clinical therapeutic range of OA patients treated with 1 or 2 g/day of SrRan, and Sr concentrations in synovial fluid correlated with Sr blood concentrations. SrRan treatment significantly reduced the progression of

OA cartilage lesions at all dosages tested (p<0.05). Picrosirius staining also showed a significantly better preservation of the collagen network in dogs treated with SrRan at 50 and 75 mg/kg/day (p<0.03). The thickening of the subchondral plate found in the OA placebo treated dogs was reduced by SrRan treatment (50 mg/kg/day, p<0.02). The increased gene expression levels of MMP-1, MMP-13, ADAMTS5 and cathepsin K found in OA cartilage were all reduced by SrRan treatment (75 mg/kg/day, p=0.02, p=0.03, p=0.06, p<0.0001, respectively). A significant suppression of the increased levels of IL-1β in OA synovium by SrRan was also found (50 and 75 mg/kg/day, p=0.05). The serum level of CTX-II was significantly reduced at sacrifice in dogs treated with 50 and 75 mg/kg SrRan.

Conclusion: This study is the first to demonstrate that SrRan globally reduced the progression of OA structural changes, both cartilage lesions and subchondral bone sclerosis, in an *in vivo* animal model. The inhibition of the synthesis of several key pathophysiological pathways may have contributed to the protective effect of SrRan.

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A Systems Biology Approach to Elucidating Pathways Active During the Development of Osteoarthritis. Richard F. Loeser[1], Amy L. Olex[2], Brian Westwood[2], Margaret A. McNulty[3], Cathy S. Carlson[3], Michael Callahan[4], Cristin Ferguson[4] and Jacquelyn S. Fetrow[2]. [1]Wake Forest School of Medicine, Winston-Salem, NC, [2]Wake Forest University, Winston-Salem, NC, [3]University of Minnesota, St. Paul, MN, [4]Wake Forest School of Medicine, Winston-Salem

Background/Purpose: OA affects the entire joint but most studies have focused on the disease process in a single tissue. In this study, we identified genes regulated during different stages of the development of surgically-induced OA by microarray using RNA isolated from the joint "organ" and analyzed the data using an unbiased computational modeling approach to discover the pathways active in the disease process.

Methods: 12 week-old male C57/BL6 mice underwent surgical destabilization of the medial meniscus (DMM) to induce OA or sham surgery as control. Joint tissues were collected for isolation of RNA (n=9 mice per group per time point) pre-surgery (time 0) and at 2, 4, 8, and 16 weeks after surgery and for histological analysis of OA severity (n=6 mice per group per time point). RNA was isolated from joint tissue collected from the medial half of the joint, including cartilage, meniscus, subchondral bone, and joint capsule with synovium. RNA was pooled from 3 mice for each Affymetrix microarray and 3 arrays were performed for each group at each time point. Signal log ratios (SLR) of DMM/sham were calculated using normalized array data. Genes passing detection, SLR ($\geq$0.5 or $\leq$0.5 for at least one time point in all 3 pools), and consistency filters were used for computational modeling to identify patterns of gene expression by consensus clustering, network analysis using jActiveModules (JAM) and functional classification using DAVID and KEGG.

Results: Histological lesions of OA were present in the medial tibial plateaus (MTP) of the DMM knees beginning at the earliest (2 week) time point and became progressively more severe by 16 weeks. Osteophytes were cartilaginous at 2 weeks and became progressively ossified. A total of 427 genes passed the consistency and significance filters. There were more upregulated than downregulated genes at all time points except at 8 weeks (17 up, 53 down) with the most upregulated at 4 weeks (336 up,33 down) followed by 2 weeks (174 up,12 down) and 16 weeks (84 up,2 down). Clustering identified 27 clusters with 2 or more genes and DAVID analysis of clusters upregulated at 2 and 4 weeks included morphogenesis, differentiation, development, collagen, and ECM genes as well as transcription regulatory genes. Cell division and cytoskeleton genes were in a cluster highly down-regulated at 8 weeks while genes upregulated at 16 weeks included Prelp (involved in collagen binding), Col3a1 and fibromodulin. JAM analysis revealed 13 subnetworks with gene expression activity during the time course where the majority of up-regulated genes were up at 4 weeks. Prominent sub-networks included the TGF-β signaling pathway, ECM-receptor interactions (including thrombospondins, syndecans, and collagens) and Wnt and hedgehog signaling.

Conclusion: The results support a phasic development of OA. Early matrix remodeling was associated with activation of TGFβ and Wnt/hedgehog signaling which may be drivers of cartilage degradation and osteophyte formation. The quiescent stage at 8 weeks suggests a tempo-

rary stabilization of the joint followed by activation of a more fibrotic process at 16 weeks. The findings suggest that specific therapies intended to slow disease progression may be most effective at specific stages of the disease.

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Changes in Subchondral Bone Provide a Sensitive Marker for Osteoarthritis and Its Progression: Results From a Large Osteoarthritis Initiative Cohort. Michael A. Bowes[1], Christopher B. Wolstenholme[1], Devan Hopkinson[1], Graham R. Vincent[1] and Philip G. Conaghan[2]. [1]Imorphics Ltd, Manchester, United Kingdom, [2]University of Leeds, Leeds, United Kingdom

Background/Purpose: Change in subchondral bone has been clinically associated with progression of osteoarthritis (OA). Modern image analysis techniques allow accurate, automated identification of bone in MR images, facilitating the use of 3D changes in the bone to characterise and monitor OA. Objective was to compare rate of change in bone area of all the knee bones from all subjects in the OAI dataset with definite medial OA with a control group absent of radiological OA over a 4 year period.

Methods: 933 subjects with medial OA and MR images at baseline, 12, 24, 36 and 48 month were selected from the Osteoarthritis Initiative dataset; medial OA was defined as KL$\geq$ 2 and presence of medial osteophytes. 904 control subjects with absence of radiographic OA were also identified, defined as KL=0 at all time-points. One index knee was analyzed per subject. Femur, tibia and patella bones were automatically segmented from MRIs using active appearance models[1]. Anatomical areas were automatically identified within the model[2] and were measured at each time-point. All regions of the articulating surface of the femur, tibia and patella were included in the analysis.

Results: Mean age (SD) of the case group was 62 years (8.8); control group 59 (8.9); mean (SD) BMI for case/control 29.7 (4.9)/ 26.9 (4.3); %females for case/control 35%/47%. Rate of change of bone area in the medial compartments was typically 0.5% per annum in the case group with significantly lower change in the controls. Lateral compartments exhibited around half this amount of change, and showed less difference in the rates of change between cases and controls (though still highly significant). ANCOVA analysis demonstrated that age, BMI and gender could explain only a small amount of the variance in bone change.
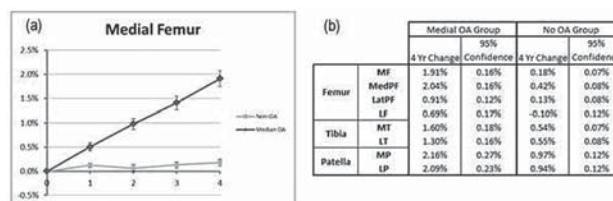
Conclusion: Change in bone area within all knee compartments discriminated significantly between OA and control subjects. Discrimination was strongest in medial compartments, and particularly in the femur. The patella-femoral joint is an important component of OA disease, and discriminates between the groups as strongly as the femorotibial joint. Measurement of bone change provides a valuable tool for monitoring OA progression.

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Intra-Articular Injection of Adipose-Derived Stem Cells Inhibits Activation of the Synovium and Protects Against Cartilage Damage and Enthesophyte Formation in Murine Experimental Osteoarthritis. Peter L.E.M. van Lent[1], Menno C. ter Huurne[1], Arjen B. Blom[1], Rik Schelbergen[1], Louis Casteilla[2], Thomas Vogl[3], Johannes Roth[3], Roxane Blattes[2], Christian Jorgensen[4] and Wim B. van den Berg[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]INSERM U1031, Toulouse, France, [3]University of Muenster, Munster, Germany, [4]Hospital Lapeyronie, Montpellier, France

Background/Purpose: OA lesions are treated with mesenchymal stem cells aiming to enhance tissue repair by transformation to eg. chondrocytes. Recently it has been shown that adipose derived stem cells (ADSC) express strong immunosuppressive characteristics which might impair the activated phenotype of synovial OA macrophages. Previous studies have shown that synovial macrophages are crucial in mediating cartilage destruction and enthesophyte formation in murine collagenase-induced osteoarthritis (CiOA). In the present study we explored the effect of intra-articular injection of ADSCs on synovium, cartilage destruction and enthesophyte formation during murine CiOA.

Methods: Adipose derived stem cells (ADSCs) were isolated from fat surrounding the popliteal lymph nodes and were injected into knee joints at day 7 after induction of CiOA. CiOA was induced by injection of collagenase into murine knee joints, which causes instability and joint destruction and is characterized by synovial lining thickening. Mediators present in washouts of synovium were measured using Luminex. OA phenotypes were measured within 8 weeks after induction. Total knee joints were isolated and performed for histology. Synovial activation was measured using an arbitrary scale of 0–3, cartilage destruction according to the scorings method of Pritzker et al (2006) and enthesophyte formation in cruciate and medial collateral ligaments using image analysis.

Results: A single dose of ADSCs (20×10^3 in mouse serum) was injected into the knee joint of mice, 7 days after induction of collagenase-induced osteoarthritis. Histology showed that thickness of the synovial lining layer, which is characteristic for this model, was significantly inhibited by ADSCs treatment at day 14 (9%) and day 42 (35%) when compared to control (serum) treated OA joints. This was in line with significant lower levels of IL-1β (53%) and S100A8/A9 (51%) (no effect on TNFα and IL-6) in synovial washouts measured at day 14 after treatment. Destruction of cartilage was significantly lower both at day 14 (55%) and day 42 (35%) and was particularly found in the medial tibia. Strikingly, ADSCs treatment had a protective effect on enthesophyte formation assiocated with ligaments. At day 42, the formation of enthesophytes in medial collateral and cruciate ligaments was inhibited by 92% and 43% respectively. Intra-articular injection of GFP-labeled ADSCs into day 7 OA knee joints, showed that stem cells were clearly detected within the synovial intima in close interaction with macrophages.

Conclusion: Our study indicates that a single injection of ADSCs into the knee joints of mice with CiOA gives protection of synovial activation, cartilage destruction and enthesophyte formation when given at day 7 after onset probably by inhibiting the activated phenotype of synovial macrophages.

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Chemokine (C-C Motif) Receptor 2 Signaling Mediates Persistent Pain in Experimental Osteoarthritis. Rachel E. Miller[1], Phuong Tran[1], Rosalina Das[1], Nayereh Ghoreishi-Haack[1], Richard J. Miller[2] and Anne-Marie Malfait[1]. [1]Rush University Medical Center, Chicago, IL, [2]Northwestern University, Evanston, IL

Background/Purpose: To investigate the role of MCP-1/CCR2 in the development of pain in osteoarthritis (OA) using a mouse model, destabilization of the medial meniscus (DMM). The protracted nature of this model enables longitudinal analysis of pain-dependent behaviors and concomitant molecular changes in the innervating dorsal root ganglia (DRG).

Methods: DMM or sham surgery was performed in the right knee of 10-week old male C57BL/6 or *Ccr2* null mice (Taconic) (total number used = 225). Pain-dependent behaviors were assessed at 0, 4, 8, and 16 weeks post surgery. Mechanical allodynia in the hind paw was assessed with von Frey fibers. Locomotion was assessed using a LABORAS platform. At the same time points, innervating dorsal DRG, L3-L5, from DMM or sham-operated and age-matched naïve mice were collected for qRT-PCR of monocyte chemoattractant protein (MCP)-1 and its receptor, CCR2. The response of DRG neurons to MCP-1 was recorded through intracellular Ca^{2+}-imaging. In brief, neurons were isolated, cultured for 3 days, and loaded with a calcium indicator dye. The number of cells responding to MCP-1 was counted. Cell culture supernatants were analyzed for MCP-1 protein via ELISA. For immunohistochemistry of DRG, mice were perfused transcardially with paraformaldehyde and DRG were collected for staining with anti-F4/80 (macrophage marker). Histopathology of the knees was evaluated according to OARSI recommendations.

Results: Joint pathology after DMM progresses slowly over 16 weeks. We documented pain-dependent behaviors longitudinally over this period, and found two stages of OA-associated pain: early-onset mechanical allodynia progressed to week 4, and was maintained for 16 weeks. Locomotive changes indicative of chronic pain (decreases in distance traveled and climbing) were first apparent 8 weeks after DMM, and maintained up to week 16. These changes were reversible with buprenorphine; DRG mRNA levels of MCP-1 and CCR2 were increased compared to naïve and sham controls, peaking at week 8 post DMM (p<0.01); Exposure of DRG neurons isolated 8 weeks post DMM to MCP-1 resulted in an increased calcium mobilization response compared to naïve and sham controls, indicating a functional role for MCP-1/CCR2 signaling in DRG neurons (p<0.0001); Protein levels of MCP-1 were increased in the supernatants of these cultured DRG cells compared to naïve and sham (p<0.0001); DRG may be infiltrated by immune cells, particularly macrophages, which may contribute to pain signaling. Therefore, we examined changes in the DRG macrophage population following DMM and found that by week 8, macrophages infiltrated the DRG and this was maintained through week 16; *Ccr2* null mice developed comparable joint damage 8 weeks post DMM to wild types, but showed altered pain behavior: i) Similar levels of mechanical allodynia developed up to week 8, but the allodynia completely resolved by week 16 weeks; ii) *Ccr2* null mice were protected from decreases in locomotion at 8 and 16 weeks. Macrophage infiltration was not noted in *Ccr2* null DRG at 8 weeks post DMM.

Conclusion: These data support a role for MCP-1/CCR2 in the persistence of experimental OA-associated pain. This pathway merits further exploration as a target for pain in OA.

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Mass Spectrometry Assays of Plasma Biomarkers to Predict Radiographic Progression of Knee Osteoarthritis. Susan Y. Ritter[1], William M. Reichmann[1], Jamie E. Collins[1], Alejandra Garces[2], Bryan Krastins[2], David Sarracino[2], Mary Lopez[2], Elena Losina[1] and Antonios O. Aliprantis[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Thermo Fisher Scientific BRIMS Center, Cambridge, MA

Background/Purpose: Biomarkers to identify osteoarthritis (OA) patients at risk for disease progression are needed. Recently, we performed a proteomic analysis of knee synovial fluid from normal and OA patients to identify differentially expressed proteins that could represent biomarkers of disease activity. Mass spectrometry assays were developed to identify representative peptides from several of these proteins in both synovial fluid and peripheral blood. We tested a panel of these putative biomarkers in a cohort of OA patients followed prospectively for 30 months to identify those peptides that correlate with radiographic progression.

Methods: Multiplexed high throughput selected reaction monitoring (SRM) assays were developed to measure multiple peptides representative of the following 9 proteins identified in previous discovery experiments: afamin, clusterin, insulin-like growth factor binding protein, acid labile subunit, lumican, pigment epithelium-derived factor, lubricin, hepatocyte growth factor, kallistatin, cartilage oligomeric matrix protein. Plasma samples obtained from baseline visit of 173 subjects in an observational OA progression cohort were trypsin digested and SRM assays were performed. Linear regression was used to determine association between each biomarker level at the baseline and maximal joint space narrowing from baseline to 30 months. Correlation matrixes and linear regression models were then performed for the biomarkers, adjusting for age and sex. Finally, a biomarker score was developed for 2 peptides to examine the amount of progression explained by a combination of biomarkers.

Results: For this progression cohort, average age was 61 and average joint space narrowing over 30 months was 0.68 mm. A good correlation between multiple peptides for each individual protein was observed, indicating our assays were correctly measuring their target proteins. From our panel of putative biomarkers, peptides representative of clusterin, lumican and lubricin showed statistically significant associations with joint space narrowing after adjustment for age and sex. Partial R^2 values from these linear regression models show the clusterin FMETVAEK peptide and lubricin LVEVNPK peptide biomarker explains about 2–3% of the variability of JSN, values similar to the amount explained by age **(Table)**. A biomarker score was developed combining normalized data for both lubricin and clusterin peptides, which increased the model R^2 to 0.079.

Table. Linear regression models adjusting for age and sex

Model #	Model R^2	Parameter	Parameter Estimate	Partial R^2	p-value
1	0.063	Clusterin(F)	−1.64	0.022	0.05
		Age	−0.01	0.028	0.03
		Sex	0.26	0.026	0.03
2	0.075	PRG4(L)	−20.96	0.033	0.01
		Age	−0.01	0.030	0.02
		Sex	0.24	0.024	0.04
3	0.079	Biomarker score*	−0.13	0.038	0.01
		Age	−0.01	0.031	0.02
		Sex	0.28	0.030	0.02

*Normalized values for Clusterin(F) and PRG4(L) using beta estimates from models 1 and 2

Conclusion: Targeted mass spectrometry assays provide a rapid means to validate novel biomarkers in human samples. Our results suggest that when combined, clusterin and lubricin levels in plasma are as predictive of OA progression as age. Replication of these findings in other prospective OA cohorts is planned.

Disclosure: S. Y. Ritter, None; **W. M. Reichmann**, None; **J. E. Collins**, None; **A. Garces**, None; **B. Krastins**, None; **D. Sarracino**, None; **M. Lopez**, None; **E. Losina**, None; **A. O. Aliprantis**, None.

ACR Concurrent Abstract Session
Cytokines, Mediators, and Gene Regulation I
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Inhibition of Interleukin-17 Signaling Via De-Ubiquitinatio. Sarah L. Gaffen and Abhishek Garg. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: IL-17A (IL-17) is a proinflammatory cytokine that contributes to the pathogenesis of various autoimmune diseases, including rheumatoid arthritis (RA), multiple sclerosis (MS) and psoriasis. Despite limited homology with the toll-like receptors, IL-17 receptor subunits (IL-17RA and IL-17RC) do not recruit TLR-associated adaptors such as MyD88, but instead associate with the adaptor protein Act1/CIKS. Upon recruitment, Act1 activates pro-inflammatory signaling pathways including TRAF6/NF-kappaB, MAPK and CCAAT Enhancer Binding Proteins (C/EBP) Despite advances in identifying molecular events downstream of IL-17 signal transduction, mechanisms by which IL-17 signaling is constrained remain poorly understood. Ubiquitination is a central post-translational signaling mechanism involved in activation of inflammation, particularly the NF-kappaB pathway. Notably, both Act1 and Traf6 exhibit E3 ubiquitin ligase activity. Genome analysis has identified over 100 deubiquitinases (DUBs) in humans but their role in IL-17 signaling is unknown. Polymorphisms in the gene encoding the DUB A20 (Tnfaip3) are associated with autoimmune diseases including RA and psoriasis. A20 was originally defined as an inhibitor of the TNF signaling pathway. Here, we show that A20 also participates in downregulating the IL-17 signaling pathway.

Methods: IL-17 signaling was assessed in the stromal cell line ST2. Regulation of IL-17-induced genes was assessed by combinations of siRNA silencing, quantitative real-time RT-PCR (qPCR), immunoblotting and luciferase analyses. Association of receptor-associated proteins was determined by co-immunoprecipitation.

Results: IL-17 induced A20 expression, and transient knockdown of A20 resulted in increased IL-17-dependent proinflammatory target gene expression. Consistently, overexpression of A20 inhibits IL-17 target gene expression, which was associated with reduced NF-κB activity. Interestingly, A20 associated with IL-17RA at a motif that was previously linked to negative regulation of the IL-17 signaling pathway.

Conclusion: We show for the first time that A20 is an inhibitor of the IL-17 signaling pathway. This provides a new mechanistic explanation for the role of A20 in regulating autoimmune disease. Moreover, regulation of A20 could serve as a potential target for pharmacologic manipulation of inflammatory signaling in autoimmunity.

Disclosure: S. L. Gaffen, None; **A. Garg**, None.

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Citrullination of ENA-78/CXCL5 Results in Conversion From a Non-Monocyte Recruiting to a Monocyte Recruiting Chemokine. Ken Yoshida[1], Olex Korchynskyi[2], Paul P. Tak[3], Takeo Isozaki[1], Jeffrey H. Ruth[1], Phillip Campbell[1], Dominique L. Baeten[4], Danielle M. Gerlag[4], M. Asif Amin[1] and Alisa E. Koch[5]. [1]University of Michigan, Ann Arbor, MI, [2]Institute of Cell Biology, Lviv, Ukraine, [3]GlaxoSmithKline U.K. and Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [5]University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: Citrullination is a post-translational modification that is the conversion of arginine to citrulline in proteins mediated by peptidylarginine deiminase (PAD). Antibodies directed towards the citrullinated proteins are highly specific for rheumatoid arthritis (RA). We and others have shown that some chemokines including ENA-78/CXCL5 play important roles in the development of RA. We undertook this study to examine whether citrullinated ENA-78/CXCL5 (citENA-78/CXCL5) is detected in RA biological fluids, and if so, what its biological activity is.

Methods: An expression plasmid containing polyhistidine tagged human ENA-78/CXCL5 was transfected into the human embryonic kidney 293T cell line for ENA-78/CXCL5 production. After citrullination of the ENA-78/CXCL5 with rabbit PAD, citENA-78/CXCL5 was used as standard for enzyme linked immunosorbent assay (ELISA). The concentrations of citENA-78/CXCL5 in synovial fluids (SFs) or sera were measured by ELISA using anti-modified citrulline antibody. The citENA-78/CXCL5 levels in RA were compared with osteoarthritis (OA) and other inflammatory rheumatic diseases, and the correlation between the citENA-78/CXCL5 levels and clinical data was analyzed. Monocyte and polymorphonuclear neutrophil (PMN) chemotaxis assays were performed using a 48-well Boyden chamber system to examine the biological activity of citENA-78/CXCL5 compared to ENA-78/CXCL5. C57BL/6 mice were injected intra-articularly with ENA-78/CXCL5 or citENA-78/CXCL5 to induce inflammation and the severity of inflammation was evaluated to compare the biological activity of citENA-78/CXCL5 to ENA-78/CXCL5.

Results: CitENA-78/CXCL5 was significantly higher in RA (n=11, mean±SE; 286.3±68.0 pg/ml) than NL sera (n=15, 1.2±2.6 pg/ml) and higher in RA (n=20, 1126.4±296.6 pg/ml) compared to other inflammatory diseases (n=14, 14.1±8.2 pg/ml) and OA (n=15, 2.3±1.0 pg/ml) SFs. There was no significant correlation between ENA-78/CXCL5 levels and clinical data. On the other hand, there were significant positive correlations between citENA-78/CXCL5 and C-reactive protein (CRP) levels (RA; n=14, r=0.69, p<0.05, RF positive RA; n=10, r=0.86, p<0.05), citENA-78/CXCL5 and erythrocyte sedimentation rate (ESR) (RA; n=15, r=0.77, p<0.05, RF positive RA; n=11, r=0.71, p<0.05). Chemotaxis assays showed that PMN migration in response to citENA-78/CXCL5 was similar to that induced by ENA-78/CXCL5. However, citENA-78/CXCL5 induced monocyte migration, but ENA-78/CXCL5 did not. *In vivo*, citENA-78/CXCL5 induced more intraarticular inflammation compared to ENA-78/CXCL5.

Conclusion: CitENA-78/CXCL5 was detected in RA biological fluids and the concentrations were significantly higher in RA than OA or other diseases, and correlated with the inflammatory markers CRP and ESR. CitENA-78/CXCL5 induced monocyte migration while ENA-78/CXCL5 did not. CitENA-78/CXCL5 induced more severe joint inflammation compared to ENA-78/CXCL5. This may be attributed to the fact that citENA-78/CXCL5 acquired a monocyte recruiting function that ENA-78/CXCL5 does not have. These results indicate that citENA-78/CXCL5 may have novel inflammatory properties compared to ENA-78/CXCL5 in RA pathogenesis.

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A Novel Orally Active Phosphatidylinositol 3-Phosphate 5-Kinase (PIK-fyve) Inhibitor Ameliorates Mouse Psoriasis-Like Model by Inhibition of Interleukin-12 and Interleukin-23 Production From Macrophages. Ayatoshi Andou, Eviryanti Agung, Yukie Seki, Yoichiro Shima, Sen Takeshita, Takashi Yamamoto and Hiroyuki Eda. Ajinomoto Pharmaceuticals Co., Ltd., Kanagawa, Japan

Background/Purpose: Phosphatidylinositol (3,5)-bisphosphate $(PI(3,5)P_2)$ is the most recently-identified phospholipid component of cellular membrane. Phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) is a critical enzyme for the synthesis of $PI(3,5)P_2$ from phosphatidylinositol 3-monophosphate (PI3P), which has been implicated in intracellular trafficking events, but little is known about its biological function. We discovered a lead-compound APY0201 which is a potent, highly selective PIKfyve kinase inhibitor. In this study, we characterized anti-inflammatory properties of APY0201 *in vitro* and *in vivo*.

Methods: *In vitro* study: Mouse macrophages (thioglycolate-induced peritoneal exudate cells) and human peripheral blood mononuclear cells (PBMCs) stimulated by IFN-γ and heat-killed whole bacteria (*Staphylococcus aureus*Cowan strain I (SAC)) were used in this assay.

In vivo study: The imiquimod (IMQ)-induced psoriasis model was used. Female Balb/c mice received daily topical application of approx. 16 mg 0.5% IMQ cream & Vaseline mix (1:1, equivalent to 0.4 mg IMQ) on the right ear for 4 days. APY0201 or vehicle was orally or topically administered once daily. The severity of inflammation was assessed by daily ear thickness and ear weight after 4 days of IMQ-treatment.

Results: APY0201 inhibited the conversion of PI3P to $PI(3,5)P_2$ in the presence of recombinant human PIKfyve with an IC_{50} value of 8.9 nM. It is highly selective for PIKfyve compared to various receptors, channels and enzymes including 25 lipid kinases and 83 protein kinases. Interestingly, APY0201 demonstrated potent *in vitro* inhibitory activity against interleukin(IL)-12p70 production from mouse macrophages and human PBMCs with an IC_{50} value of 8.4 nM and 9.9 nM, respectively. Furthermore, IL-12/23 production but not other inflammatory mediators, such as TNF-α and MCP-1 from these cells were inhibited by APY0201. Downregulation of PIKfyve using siRNA of PIKfyve inhibited expression of IL-12 subunit mRNA in IFN-γ/SAC-activated mouse macrophages. These results indicate APY0201 exerts its inhibitory activity of IL-12/23 production *via* PIKfyve inhibition. In *ex vivo*study, IL-12p70 production was significantly inhibited in IFN-γ/SAC-activated whole blood from mice orally administered with APY0201. Finally, daily oral or topical administration of APY0201 significantly ameliorated skin inflammation in mouse psoriasis-like model.

Conclusion: The therapeutic potential of IL-12/23 inhibition in Th1/Th17-mediated immunological disorders, such as psoriasis has been clinically validated on the efficacy of ustekinumab, anti-IL-12/23 antibody. Our results clearly indicate that PIKfyve inhibition contribute to the suppression of inflammation in both *in vitro* and *in vivo*. Consequently APY0201, highly selective PIKfyve kinase inhibitor might be a promising medication for the treatment of patients with psoriasis.

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The Serine Arginine Protein SF2/ASF Is a Novel Regulator of IL-2 Transcription and Restores IL-2 Production in T Lymphocytes From SLE Patients. Vaishali R. Moulton, Alexandros P. Grammatikos and George C. Tsokos. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease which afflicts mainly women in the reproductive years, and causes painful arthritis, skin disease and complications in the kidneys and brain. Abnormal T lymphocytes in SLE not only regulate autoantibody-producing B cells, but are also responsible for target organ infiltration. Currently, no specific therapies target T cell defects. Moreover, there are no known molecular markers to predict disease activity. Aberrant molecular mechanisms responsible for SLE T cell defects are thus promising targets for therapy, as well as potential biomarkers for disease. A key defect of T cells from lupus patients is that they produce insufficient amounts of the vital cytokine interleukin (IL)-2. Reduced IL-2 production is linked to reduced cytotoxicity, defective regulatory T cell function, and impaired activation-induced cell death leading to persistence of autoreactive T cells. We previously showed that T cells from SLE patients express decreased levels of the T cell receptor (TCR) - associated CD3 zeta (ζ) chain, a feature directly linked to their poor IL-2 production. We recently showed that the serine arginine (SR) protein splicing factor 2/alternative splicing factor (SF2/ASF) enhances the expression of CD3ζ chain by limiting the production of an unstable mRNA splice variant. In this study we asked whether the expression of SF2/ASF is aberrant in T cells from SLE patients and if SF2/ASF regulates T cell function, specifically IL-2 production.

Methods: T cells were isolated by negative selection from peripheral blood of SLE patients and healthy controls. SF2/ASF mRNA and protein expression was assessed using real time pcr and immunoblotting respectively. T cells were transiently transfected with siRNA or plasmids using electroporation. T cells were activated with anti-CD3 and anti-CD28 antibodies. Transcriptional activity was studied using the dual luciferase reporter assay system. IL-2 production was measured in supernatants by enzyme linked immunosorbent assay (ELISA). Chromatin immunoprecipitation assays were used to assess transcription factor binding to the IL-2 promoter.

Results: We show that SF2/ASF expression levels are decreased in T cells from SLE patients, and correlate inversely with patients' SLE disease activity index (SLEDAI). Importantly, overexpression of SF2/ASF in SLE T cells enhances their IL-2 production. In parallel, silencing SF2/ASF expression in normal T cells reduces their IL-2 secretion. Using reporter assays, we show that SF2/ASF increases transcriptional activity of the IL-2 promoter. Further, SF2/ASF induces the expression of the nuclear factor of activated T cells (NFAT) and c-fos transcription factors, and induces increased binding of NFAT and c-fos to the IL-2 promoter. Finally, we show recruitment of SF2/ASF to the IL2 promoter indicating its direct role in IL-2 transcription.

Conclusion: Our results identify SF2/ASF as a novel regulator of IL-2 expression in human T cells and a potential molecular mechanism underlying the altered T cell defect in SLE.

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Select Soluble Inflammatory Mediators Are Detected Prior to and Increase At Systemic Lupus Erythematosus Classification. Melissa E. Munroe[1], Jourdan R. Anderson[1], Julie M. Robertson[1], Timothy B. Niewold[2], George C. Tsokos[3], Michael P. Keith[4], John B. Harley[5] and Judith A. James[6]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Chicago, Chicago, IL, [3]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]Walter Reed National Military Medical Center, Bethesda, MD, [5]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [6]Oklahoma Medical Research Foundation; Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: The processes that lead to clinical illness in systemic lupus erythematosus (SLE) years before diagnosis are not well characterized. Several cytokines have been associated with increased activity in established disease after diagnosis. This study evaluates the temporal relationship between autoantibody production, cytokine levels and the onset of SLE clinical disease.

Methods: Serial sera from 60 SLE cases before diagnosis with no ACR criteria to SLE classification (average timespan= 4.4 years) were obtained from the Department of Defense Serum Repository (DODSR). Sera samples were tested for C-reactive protein (hs-CRP), Von Willebrand's Factor (VWF) and 32 soluble inflammatory mediators, including cytokines, chemokines, and soluble receptors using xMAP multiplex bead-based assays or sandwich ELISA (BLyS, APRIL, hs-CRP, and VWF). In addition, samples were assessed for the presence of SLE-associated autoantibodies, including Ro, La, nRNP, Sm, Ribosomal P, dsDNA, and ANA by ELISA and immunofluorescence. Interferon (IFN) activity was assessed by a cell reporter assay measuring interferon responsive gene expression (MX1, PKR, and IFIT1) by serum.

Results: Patient samples before ACR classification had significant ($p \leq 0.01$) alterations in 16 soluble mediators of inflammation, as well as VWF and hs-CRP. Levels of particular TNF Receptor (TNFR) family members, TNFRI, TNFRII, BLyS, and APRIL, dramatically increased as lupus classification approached (levels at clinical symptoms versus pre-clinical sera, $p \leq 0.001$). The increase in these TNFR mediators affecting B-lymphocyte activation parallels the accumulation of autoantibodies seen leading up to diagnosis in SLE cases. Interferon (IFN)-associated mediators of inflammation are also of particular interest and were assessed. An initial evaluation of 20 SLE cases from this study revealed a significant increase in IFN activity leading up to diagnosis ($p = 0.0279$). We find a similar pattern of increased IFN-γ, IP-10, MIG, and MIP-1α ($p \leq 0.01$) leading up to diagnosis. Mediators such as VWF, hs-CRP, stem cell factor and resistin also increase over the pre-clinical course to SLE transition ($p \leq 0.01$). Inflammatory mediators IL-12 and IL-17 were significantly elevated ($p \leq 0.01$) in pre-clinical samples compared with first ACR criterion and lupus classification.

Conclusion: Before SLE patients transition to clinical disease, they have significantly elevated levels of soluble inflammatory mediators. Further elevation of select markers occurs between early clinical symptoms and classified disease. That these alterations are present prior to the transition to active SLE suggests that multiple perturbations in immune-mediated inflammatory processes occur long before clinical classification and suggest that high-risk, pre-clinical individuals, destined to become SLE patients, can be identified before their illness is clinically manifested and damaging.

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ACR Concurrent Abstract Session
Epidemiology and Health Services Research I: Epidemiology and Outcomes in Rheumatic Disease
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Increased Risk of Recurrent Gout Attacks During Hospitalization.
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Background/Purpose: While anecdotal evidence suggests that risk of recurrent gout attack increases during hospitalization and gout is one of the most common reasons for in-patient rheumatology consultations, to our knowledge no study has formally tested this hypothesis. Understanding the magnitude of risk conferred by hospitalization on recurrent gout attacks would provide clinical guidance as to whether prophylactic therapy should be provided to prevent gout attacks in patients with existing gout during hospitalization, particularly since such attacks contribute to increased length of hospital stay.

Methods: We conducted an online case-crossover study to assess putative risk factors, including hospitalization, for recurrent gout attacks among persons with pre-existing gout. Those who had experienced at least one gout attack within the previous year were recruited online and underwent verification of gout diagnosis through medical records review. Participants logged onto the study website when they experienced a gout attack and provided exposure information (including hospitalization) over the two-day period prior to an acute gout attack (case period) using an online questionnaire. The same questionnaire was collected for a two-day period during an intercritical period (control period) in a 3-month interval for up to four times. We examined the relation of hospitalization and reasons for hospitalization over a 2-day period to the risk of recurrent gout attacks using conditional logistic regression.

Results: Our analysis included 724 subjects who experienced recurrent gout attacks during the study period (mean age 54.5, mean BMI 32.1, 78.5% male). Over the one-year follow-up period, 35 hospitalizations occurred. Of these, 3 hospitalizations were due to gout-related conditions and were excluded from the analysis. Of the remaining, 10 were for surgery, 9 for acute infections, and 13 for other conditions. The proportion of hospitalization was 5.2 and 15.4 per 1000 person-periods during the control and case periods, respectively. Adjusting for alcohol consumption, purine intake, and use of diuretics, allopurinol, colchicine, and NSAIDs, the odds of recurrent gout attacks during hospitalization increased by more than 3-fold (odds ratio=3.86, 95% confidence interval: 1.69–8.84) compared with periods without hospitalization (Table).

Table. Hospitalization and Risk of Recurrent Gout Attacks

Hospitalization Over 2 Days	No. Control Periods	No. Hazard Periods	Adjusted OR (95% CI)
No	1931	1402	1.00 (referent)
Yes	10	22	3.86 (1.69–8.84)

Conclusion: Our study confirmed that the risk of gout attacks increases during hospitalization. These data support the consideration of the provision of appropriate prophylaxis to patients with pre-existing gout during hospitalization.

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Utility of HLA-B5801 Genotyping and Renal Dosing of the Starting Dose of Allopurinol in Preventing Allopurinol Hypersensitivity Syndrome: A Cost-Effectiveness Analysis. Yanyan Zhu[1], Ada Man[2], Tuhina Neogi[3] and Hyon K. Choi[4]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University, Boston, MA, [3]Boston Univ School of Medicine, Boston, MA, [4]Boston University School of Medicine, University of British Columbia, Arthritis Research Centre of Canada, Boston, MA

Background/Purpose: Allopurinol is the leading choice of urate-lowering therapy (95%) for gout which affects 8.3 million US adults. However, allopurinol is associated with a rare but potentially fatal reaction: allopurinol hypersensitivity syndrome (AHS). Studies have shown that HLA-B5801 allele carriage and renal impairment are strongly associated with AHS, suggesting utility of considering these factors in treatment decisions to prevent AHS and AHS-related deaths. We examined the cost-effectiveness of HLA-B5801 genotyping and renal dosing in preventing AHS and AHS-related deaths.

Methods: We built a decision model to compare 4 treatment strategies for 1 million hypothetical patients starting allopurinol in the US. All key parameters and costs were derived from the literature, including the risk of AHS: 0.163%, the risk of death among AHS cases: 26%, the probabilities of HLA-B5801 allele carriage: 0.01 (Caucasians) and 0.07 (Asians), relative risk (RR) of AHS among HLA-B5801 positive patients: 96.6, sensitivity for predicting AHS by renal dosing: 90% [1], HLA-B5801 genotyping cost: $45.11 and the average AHS hospitalization cost: $50,152. Sensitivity analyses were conducted by varying the risk of AHS, RR of AHS among HLA-B5801 positive patients, sensitivity for predicting AHS by renal dosing, and AHS hospitalization cost.

Results: Initiating treatment in all patients with the standard dose resulted in 1630 AHS cases and 424 AHS related deaths. Compared with the standard dose strategy, the combined use of HLA-B5801 genotyping and renal dosing prevented 95% of AHS cases and AHS-related deaths, and saved $32,500,684. It led to incremental cost-effectiveness ratios (ICERs) of −$21,009 per AHS case avoided and −$80,647 per death avoided among Caucasians (i.e., cost-saving). Compared with renal dosing alone, the combined use of HLA-B5801 genotyping and renal dosing avoided 80 more AHS cases and 21 more AHS-related deaths at an incremental cost of $41,072,740, resulting in ICERs of $513,409 per AHS case avoided and $1,955,845 per death avoided among Caucasians. The corresponding effectiveness and ICERs were more favorable among Asians (**Table**). Sensitivity analyses suggested the results were robust to variation in these model parameters.

Table. Results of the Base Case Analysis*

Population	Strategy	Incremental cost (per million patients)	AHS Cases avoided	ICER (per case)	Deaths avoided	ICER (per death)
		Compared with the standard starting dose for all patients strategy				
US Caucasians	1. Standard starting dose (300mg/day) for all patients	–	–	–	–	–
	2. Renally-adjusted starting dose (1.5 mg allopurinol per unit eGFR (mg/ml/min)) for all patients	–$73,573,424	1467	–$50,152	382	–$192,601
	3. Standard starting dose for HLA-B5801 negative patients	$4,737,399	805	$5,885	209	$22,667
	4. Renally-adjusted starting dose for HLA-B5801 negative patients	–$32,500,684	1547	–$21,009	403	–$80,647
US Asians	1. Standard starting dose for all patients	–	–	–	–	–
	2. Renally-adjusted starting dose for all patients	–$73,573,424	1467	–$50,152	382	–$192,601
	3. Standard starting dose for HLA-B5801 negative patients	–$26,754,490	1433	–$18,670	373	–$71,728
	4. Renally-adjusted starting dose for HLA-B5801 negative patients	–$35,649,873	1610	–$22,143	419	–$85,083
		Compared with the renally-adjusted starting dose for all patients strategy				
US Caucasians	2. Renally-adjusted starting dose for all patients	–	–	–	–	–
	4. Renally-adjusted starting dose for HLA-B5801 negative patients	$41,072,740	80	$513,409	21	$1,955,845
US Asians	2. Renally-adjusted starting dose for all patients	–	–	–	–	–
	4. Renally-adjusted starting dose for HLA-B5801 negative patients	$37,923,551	143	$265,200	37	$1,024,961

*Negative dollar amounts = cost-saving

Conclusion: The combined use of the HLA-B5801 genotyping and renal dosing of the starting dose of allopurinol was able to avert the majority of AHS cases and AHS-related deaths. The ICERs were especially favorable among Asians due to a higher probability of HLA-B5801 allele carriage. Since renal dosing was responsible for the majority of the reduction of AHS and AHS-related deaths at no incremental costs, this strategy alone was the most cost-effective. However, the combined use of the HLA-B5801 genotyping and renal dosing was considered cost-effective given that $7 million in the US is the median acceptable cost per life saved [2].

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Anemia and the Onset of Gout in a Population-Based Cohort of Adults: Atherosclerosis Risk in Communities Study. Mara McAdams DeMarco[1], Janet W. Maynard[2], Josef Coresh[1] and Alan N. Baer[2]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, MD

Background/Purpose: There is a growing prevalence of gout in the US and worldwide. Gout is a recognized risk factor for cardiovascular disease (CVD). It is unclear whether other risk factors for CVD are also associated with increased risk of gout. Anemia is one such CVD risk factor. No studies have evaluated the relationship between anemia and gout. We tested whether anemia was associated with incident gout independent of comorbid conditions in Atherosclerosis Risk in Communities (ARIC).

Methods: ARIC is a prospective population-based cohort recruited in 1987–1989 from 4 US communities, consisting of 4 visits over 9 years. Participants were included in this analysis if they answered the gout query and were free of gout at baseline. Incident gout was defined as self-reported onset after baseline. Anemia was defined as hemoglobin <13.5 g/dL for men and <12 g/dL for women. Using a Cox Proportional Hazards model (age as time scale), we estimated the hazard ratio (HR) and confidence intervals (CI) of incident gout by baseline anemia, adjusted for confounders (sex, race, eGFR, BMI, and alcohol intake) and clinical factors (coronary heart disease, CHF, diabetes, hypertension, diuretic use, and serum urate level).

Results: A total of 10,791 ARIC participants met the study criteria. The study population was 43% male, 21% African American and the mean age at cohort entry was 54 years (SD=5.7). The mean hemoglobin level was 13.9 g/dL (SD=1.37); for men 14.9 g/dL (SD=1.1) and for women 13.1 g/dL (SD=1.1). At baseline, 1,084 (10%) participants were classified as having anemia; 66% of the participants with anemia were women. There were 271 cases of incident gout. The results are presented in the table. Patients with anemia had a 2-fold increased risk of developing gout (HR=2.01, 95% CI: 1.46, 2.76). Anemia was associated with incident gout independent of known gout risk factors, confounders and clinical risk factors (HR=1.73, 95% CI: 1.24, 2.41) and after additionally adjusting for serum urate level (HR=1.83, 95% CI: 1.30, 2.57). There was no evidence of effect measure modification by race (p=0.83) or kidney function (p-value=0.29) and limited support for an interaction by sex (p=0.06). Among female participants, the HR of incident gout by baseline anemia status was 2.38 (95% CI: 1.47, 3.84) compared to 1.43 (95% CI: 0.88, 2.30) for male participants.

Table. HR of incident gout by baseline anemia in ARIC

Model	HR (95% CI)
Unadjusted	2.01 (1.46, 2.76)*
Sex and race adjusted	1.52 (1.10, 2.12)*
Sex, race and eGFR adjusted	1.54 (1.11, 2.14)*
Adjusted for confounders[1]	1.64 (1.18, 2.28)*
Additionally adjusted for clinical factors[2]	1.73 (1.24, 2.41)*
Additionally adjusted for serum urate	1.83 (1.30, 2.57)**

[1] Confounders: Sex, race, categorical eGFR, BMI and alcohol intake.
[2] Clinical factors: Baseline hypertension, diuretic use, CHD, and CHF.
* p< 0.05
** p<0.001

Conclusion: We identified anemia as a novel risk factor for gout. Anemia was associated with an approximately 2-fold increased risk of gout independent of kidney function and serum urate. These findings suggest that anemia is a risk factor for gout on par with other chronic conditions such as obesity and diabetes. The biological mechanism linking anemia to gout remains unclear.

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Racial Differences in Reported Knee Pain Severity Persist Even After Adjustment for Knee Examination and Radiographic Findings: Data From the Osteoarthritis Initiative. Paige Luneburg[1], Laura Yerges-Armstrong[2], Braxton D. Mitchell[2] and Marc C. Hochberg[1]. [1]University of Maryland, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: African Americans have a higher prevalence of both radiographic and symptomatic radiographic knee osteoarthritis (OA) than Caucasians. In addition, African Americans with knee OA report more pain than Caucasians. While the reasons for these disparities are poorly understood, differences in risk factor patterns and/or pathoanatomic characteristics have been suggested. We hypothesized that these racial differences might be explained by differences in findings found upon physical examinations, even while stratifying by radiographic severity.

Methods: Racial differences in pain reporting and severity as well as radiographic and physical examination findings of the knees were assessed using baseline data from subjects enrolled in the Osteoarthritis Initiative (OAI), a multicenter, longitudinal observational study initiated in 2004 to

examine biomarkers and risk factors for clinically significant knee OA. This analysis was limited to 690 African Americans and 3,337 Caucasians with complete data from the baseline visit for knee pain, clinical knee exam features, covariates of interest and bilateral fixed-flexion knee radiographs that had been centrally read for OA using the Kellgren-Lawrence (KL) scale. Three measures of pain severity (KOOS, WOMAC and NRS) were analyzed for each knee. We first evaluated racial differences in clinical exam findings using logistic regression models. We next used ANCOVA to determine if race was associated with pain severity while adjusting for anthropometric and demographic variables (body mass index, age, gender, income, depression score, and education level). Analyses were stratified into two groups by radiographic severity (KL=0 or 1 and KL ≥ 2). Finally, we additionally adjusted for clinical exam features that were significantly different between the racial groups.

Results: Patellar quadriceps tendinitis, lateral and medial tibiofemoral joint line tenderness, patellofemoral crepitus and grind, and pain on knee flexion were more common in blacks than whites (p<0.008 for all). No significant differences between racial groups were observed for static alignment, anserine bursa pain or presence of effusion. Blacks reported more knee pain for all three measures of pain severity (p<0.0001) regardless of radiographic severity. After adjusting for differences in knee examination, blacks still reported more knee pain for all three measures of pain severity: adjusted means and P-values are reported in Table 1.

Table.

Dependent	KL Grade	Right Knee Whites N	Right Knee Whites Adj. Mean	Right Knee Blacks N	Right Knee Blacks Adj. Mean	P-value	Left Knee Whites N	Left Knee Whites Adj. Mean	Left Knee Blacks N	Left Knee Blacks Adj. Mean	P-value
Knee Pain Severity in Past 7 Days	0–1	1885	2.0	282	2.5	<0.0001	1942	1.8	305	2.3	0.0001
	2–4	1398	2.9	392	3.5	<0.0001	1349	3.0	363	3.4	0.0138
KOOS Pain Score	0–1	1885	88.6	282	83.5	<0.0001	1942	90.2	305	85.7	<0.0001
	2–4	1398	81.1	392	76.3	<0.0001	1349	81.0	363	75.6	<0.0001
WOMAC Pain Score	0–1	1885	1.7	282	2.7	<0.0001	1942	1.4	305	2.4	<0.0001
	2–4	1398	2.9	392	4.0	<0.0001	1349	3.0	363	4.2	<0.0001

Adjusted for for body mass index, age, gender, income, depression score, and education level and clinical exam features.

Conclusion: These results demonstrate that African Americans report more knee pain than Caucasians and that this finding cannot be explained by features found upon knee examination or differences in radiographic severity. Further analyses will examine the potential role of coping mechanisms, psychosocial health and findings on magnetic resonance imaging of the knees.

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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data From the Osteoarthritis Initiative.
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Background/Purpose: Soft drink consumption has been associated with weight gain and obesity which is a significant risk factor of osteoarthritis (OA), but its role in the progression of OA is unclear. We examine the prospective association of soft drink consumption with radiographic progression of OA.

Methods: In the Osteoarthritis Initiative (OAI), 2149 participants (3066 knees) with radiographic knee OA and having dietary data at baseline were followed up to 12, 24, 36 and 48 months. The frequency of soft drink (not including diet drinks) consumption was assessed with a Block Brief Food Frequency Questionnaire that was completed at baseline. To measure the OA progression, we used the change of a precise quantitative joint space width (JSW) in medial compartment over time between the adjacent bones of the knee based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between soft drink

intake and the change in JSW over time, while adjusting for Body Mass Index (BMI) and baseline disease severity and potential confounding factors.

Results: In stratified analyses by gender, we observed a significant dose-response relationship between soft drink intake and adjusted mean changes of JSW in men (p trend<0.001) after controlling for BMI and potential confounding factors. With increasing levels of soft drink intake, the mean changes in JSW were 0.29mm, 0.39mm, 0.36mm and 0.59mm respectively. When we further stratified by BMI tertiles, stronger dose-response relationship was found (changes in JSW were 0.21mm, 0.38mm, 0.40mm, 0.75mm respectively) in the lowest BMI tertile (BMI<27.5 kg/m^2). In men with BMI ≥27.5 kg/m^2, only highest soft drink level (≥5 times/week) was associated with increased JSW compared to no use. By contrast in women, a significant association and dose-response relationship was only observed with the lowest BMI tertile (BMI<27.3 kg/m^2, p trend <0.001).

Table. Adjusted mean (SE) changes of Joint Space Width (JSW) by soft drink intake*

BMI tertiles†	Soft drinks, times/week	Men N	Men ΔJSW, mm*	Men P value	Men P trend	Women N	Women ΔJSW, mm*	Women P value	Women P trend
Total**	None	202	0.29 (0.03)	Referent		485	0.34 (0.02)	Referent	
	≤1	439	**0.39 (0.02)**	0.012		537	0.37 (0.02)	0.343	
	2–4	140	0.36 (0.04)	0.191		145	0.40 (0.04)	0.192	
	≥5	107	**0.59 (0.05)**	<0.001	<0.001	94	0.34 (0.05)	0.984	0.499
T1	None	62	0.21 (0.06)	Referent		181	0.29 (0.04)	Referent	
	≤1	166	**0.38 (0.04)**	0.012		191	**0.42 (0.04)**	**0.007**	
	2–4	38	**0.40 (0.08)**	0.043		30	**0.52 (0.08)**	**0.009**	
	≥5	29	**0.75 (0.09)**	<0.001	<0.001	17	0.41 (0.11)	0.319	**<0.001**
T2	None	62	0.30 (0.06)	Referent		168	0.38 (0.04)	Referent	
	≤1	140	0.43 (0.04)	0.076		170	0.31 (0.04)	0.170	
	2–4	51	0.33 (0.07)	0.733		51	0.40 (0.06)	0.743	
	≥5	39	0.49 (0.08)	0.050	0.313	27	0.31 (0.09)	0.465	0.713
T3	None	78	0.38 (0.05)	Referent		136	0.36 (0.04)	Referent	
	≤1	133	0.39 (0.04)	0.789		176	0.40 (0.04)	0.516	
	2–4	51	0.38 (0.07)	0.923		64	0.34 (0.06)	0.721	
	≥5	39	**0.62 (0.08)**	0.007	0.022	50	0.35 (0.07)	0.876	0.766

* Adjusted for age, race, education, marital status, household income, employment, follow-up time, depression, knee injury and knee surgery, smoking, milk intake, total energy intake, baseline K-L grade and JSW, weight change, the changes of rim distance and beam angle.
** Adjusted for BMI as well
† BMI tertiles: Man: T1: <27.5, T2: 27.5–30.8, T3 30.9+; Women: T1: <27.3, T2: 27.3–32.0, T3 32.1+

Conclusion: Our results suggest that frequent consumption of soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other prospective studies demonstrating the reduction in soft drink consumption leads to delay in OA progression are needed to test this hypothesis.

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Increased Risk of Acute and Chronic Renal Comorbidity in Ankylosing Spondylitis: Results From a Population-Based Study.
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Background/Purpose: Clinical evidence points to an increased risk of renal comorbidity in ankylosing spondylitis (AS) compared to the general population. However, there are no population-based estimates available in the literature. An increased risk of renal comorbidity would have substantial implications for the monitoring and treatment of AS because the mainstay of pharmacological treatment is the use of non-steroidal anti-inflammatory agents (NSAIDs). We estimated the prevalence and age- and sex-standardized increased risk of renal comorbidity, including acute and chronic kidney disease and amyloidosis in a population-based cohort of persons diagnosed with AS in Québec between 1996 and 2006, compared to the general population.

Methods: A retrospective cohort study was conducted using the administrative physician-billing database of the Régie de l'Assurance Maladie du Québec. The cohort included individuals with at least one International Classification of Diseases, 9th Revision (ICD-9) billing code for AS between 1996 and 2006. A comparison cohort was generated using a 1% random sample of individuals without AS. Renal complications were identified by ICD-9 codes for amyloidosis, hypertensive chronic renal disease, acute and chronic renal disease. Age- and sex-stratified prevalence, and standardized prevalence ratios with 95% confidence intervals (CI), of renal complications

in AS compared with the general population were calculated. Sensitivity analysis was conducted using two ICD-9 codes for AS.

Results: There were 8,616 individuals identified with AS; 56% were male and the median age at diagnosis was 42 years. Overall, renal complications were diagnosed among 3.4% and 2.1% of males and females with AS, compared to 2.0% and 1.6% of males and females in the general population cohort, respectively. Prevalence of renal complications increased with age in both the AS and general population cohort. Age- and sex-stratified prevalence ratios, comparing the risk of renal complications among those with AS to the general population, demonstrated a significantly excess risk of renal complications that was highest among younger individuals with AS. Overall, individuals with AS were at a significantly increased risk of renal complications compared to members of the general population (irrespective of a coding for hypertension), with a standardized prevalence ratio of 1.7 (1.5–2.0). Standardized prevalence ratios were 6.0 (2.0–18.0) for amyloidosis, 1.7 (1.4–2.0) for chronic kidney disease, 3.2 (0.8 – 12.4) for hypertensive kidney disease, and 1.9 (1.5 – 2.3) for acute kidney disease. The excess risk was highest among younger individuals with AS, and results were similar when two ICD-9 codes were used to identify AS.

Conclusion: This population-based analysis shows that individuals with AS are at increased risk of many types of renal complications, including acute kidney disease, with the excess risk being greatest among younger individuals. These data highlight the importance of careful monitoring for renal complications among those with AS, particularly during long-term continuous use of NSAIDs.

Disclosure: W. P. Maksymowych, Abbott Laboratories, 5, Abbott Laboratories, 2, Abbott Laboratories, 8; **S. Szabo**, Oxford Outcomes, 3; **S. Rao**, Abbott Laboratories, 1, Abbott Laboratories, 3; **M. A. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1; **A. R. Levy**, Abbott Laboratories, 5.

ACR Concurrent Abstract Session
Miscellaneous Rheumatic and Inflammatory Diseases: Periodic Fever Syndromes
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Familial Mediterranean Fever: Inhibition of IL-6 Signalling As a New Therapeutic Option in a Frequent Autoinflammatory Syndrome.
Nicola Stein[1], Matthias Witt[1], Michael Baeuerle[2], Fabian Proft[1], Hendrik Schulze-Koops[3] and Mathias Gruenke[1]. [1]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany, [2]Klinikum Nürnberg, Nuernberg, Germany, [3]University of Munich, Munich, Germany

Background/Purpose: Familial Mediterranean Fever (FMF) is the most prevalent episodic fever syndrome with more than 100.000 affected individuals worldwide. Colchicine is the established first-line therapy to control disease activity, to achieve remission and to prevent secondary amyloidosis, a significant complication of an inadequately controlled disease and the major cause of mortality in FMF patients. One third of patients with FMF are non- or only partial responders to colchicine and therewith call for experience with other immunosuppressive agents in FMF. Here, we present the first case series of five patients with Familial Mediterranean Fever (FMF) refractory to treatment with colchicine and/or anakinra, who have been switched to monthly treatment with tocilizumab.

Methods: Up to date, eight FMF-patients have been screened for receiving tocilizumab because of inadequate clinical and/or serological response to colchicine and inadequate response or intolerance of anakinra. Treatment has been started in five FMF-patients and is administered with 8 mg/kg bodyweight tocilizumab every 28 days. Colchicine was continued in four patients and discontinued in one patient. Treatment with anakinra, previously given in two patients, was discontinued.

Results: Three patients showed a good clinical and serological response to tocilizumab. In these patients remission of FMF symptoms was achieved with the first application of tocilizumab. A normalization of SAA- and CRP-level was documented after the first application of tocilizumab in one patient and after the third application in another patient. The therapy was well tolerated in four patients with no relevant side effects (one uncomplicated urinary tract infection). In one patient with no acute FMF-attack after the first application of tocilizumab, the therapy had to be discontinued because of an anaphylactic reaction during the second infusion. The first treated patient achieved prolonged remission with tocilizumab-treatment and has been switched back to colchicine alone for maintenance therapy after the ninth

infusion. He still is in remission, now 18 months after initiation of tocilizumab therapy. Patient 2 is still on tocilizumab. The request for a self-administerable drug led to a switch back to anakinra after the third infusion of tocilizumab in patient 3. Only patient 4 did not respond to tocilizumab and showed persistent arthralgia and a relapse with abdominal pain after the third infusion. The non-responding patient and the patient with the anaphylactic reaction were switched to anakinra. Three additional patients have currently been scheduled for start of tocilizumab therapy in the nearest future.

Conclusion: This is the first documentation of a case series of successful treatment of FMF with tocilizumab. Of note, interference with IL-6 activity did not only result in complete clinical remission in three of the five patients previously resistant to immunosuppressive therapy, but also in complete serological remission as indicated by normalization of SAA in two individuals. These data strongly argue in favour of IL-6 as a main inflammatory cytokine in FMF and, thus, as a promising target in this disease.

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Efficacy and Safety of Canakinumab in Patients with Cryopyrin Associated Periodic Syndrome: Results From Meta-Analysis of 5 Studies.
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Background/Purpose: Canakinumab (CAN) is approved in over 60 countries for the treatment of CAPS. This meta-analysis evaluated the efficacy and safety of CAN and assessed potential differences across age and the 3 CAPS phenotypes (FCAS, MWS and NOMID).

Methods: This meta-analysis pooled data from 5 studies (1 phase II and 4 phase III). Data from 2 of the 4 phase III, open-label, uncontrolled studies with similar efficacy endpoints (n=185, including 128 CAN-naïve patients) were pooled for efficacy analysis (the other studies were of a different design and not included). Patients previously treated with CAN could "roll over" into one of these phase III studies. Step-wise dose escalations from 150 mg or 2 mg/kg (if weight 15–40 kg) every 8 weeks (q8w) up to 600 mg or 8 mg/kg q8w were allowed in patients who did not achieve/remain in complete response (CR; defined as physician global assessment [PGA] ≤ minimal, assessment of skin disease ≤ minimal, serum C-reactive protein and/or serum amyloid A protein < 10 mg/L) in the 2 studies pooled for efficacy. The primary efficacy endpoint, CR was assessed in CAN-naïve patients (n=128). Percentage of patients with relapse assessment and PGA were evaluated in CAN-naïve plus roll-over patients [n=185]). For safety analysis, data from all 5 studies were pooled (n=194).

Results: 85.2% (109/128) of CAN-naïve patients achieved CR; 65.6% (84/128) with 150 mg or 2 mg/kg. 42 patients (32.8%) required dose escalation to 300 or 600 mg (4–8mg/kg) q8w of whom 25 achieved CR at a higher dose, including 7 patients at the highest dose. Of 159 patients assessed for relapse, 142 (89.3%) did not relapse at any dose. CR and relapse data by phenotype and age are shown in Table.

Patients treated with 150mg or 2mg/kg q8w had greater reduction in disease activity (PGA; absent/minimal symptoms) than patients who required dose escalation (91.4% vs 60% to 77.8%) at the End of Study (EOS) (or Week 48). FCAS patients (92%) showed lowest disease activity score at EOS compared to MWS (85.1%) and NOMID (81.8%). Patients as young as 2–<4 yrs had a reduction in disease activity score by Day 8 and EOS (57.1% and 71.4%, respectively, with absent/minimal symptoms). 94.3% (183/194) patients had at least 1 adverse event (AE). Most frequently reported AEs were nasopharyngitis (36.1%), headache (23.7%), rhinitis (17.5%) and upper respiratory tract infection (17.0%). Serious AEs (SAEs) occurred in 13.4% (26/194) patients (infections and infestations; 13 [6.7%]), and no deaths were reported. Incidence of AEs and SAEs was comparable between NOMID and MWS with lower incidence in FCAS (AEs: 98.1% and 96.4% vs 80.6%; SAEs: 13.5% and 16.4% vs 3.2%).

Table. Complete response and relapse assessment to treatment with canakinumab

Parameters	Number of Patients	Phenotype NOMID % (n/N)	MWS % (n/N)	FCAS % (n/N)	Age 2-<4 years % (n/N)	4–11 years % (n/N)	12–17 years % (n/N)	18–59 years % (n/N)	≥60 years %(n/N)
Achieving complete response	N=128[a]	73.7 (28/38[a])*	88.3 (53/60[a])	96.6 (28/29[a])	57.1 (4/7[a])	86.4 (19/22[a])	70.8 (17/24[a])	92.2 (59/64[a])	90.9 (10/11[a])
Patients without relapse	N=159[b]	78.1 (25/32[b])	91.9 (91/99[b])	92.9 (26/28[b])	50.0 (2/4[b])#	87.0 (20/23[b])	94.7 (18/19[b])	90.2 (92/102[b])	90.9 (10/11[b])

[a]Only CAPS-naïve patients; [b]CAPS-naïve and roll-over patients who achieved complete response and had a relapse assessment; *Of the 38 NOMID patients, 21 (55.3%) required dose escalation, 11 of whom later achieved complete response; #3/4 patients were NOMID.

Conclusion: This meta-analysis confirms the efficacy of CAN in CAPS across all phenotypes and also for the youngest patients (2–<4 yrs). Dose escalation was most frequent in younger and NOMID patients who did not respond to initial dose. It did not appear that there was an increase in AEs and SAEs with an increase in dose or decrease in age.

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Efficacy and Safety of Canakinumab in Patients with TNF Receptor Associated Periodic Syndrome. Marco Gattorno[1], Laura Obici[2], Antonella Meini[3], Vincent Tormey[4], Ken Abrams[5], Nicole Davis[6], Christopher Andrews[7] and Helen J. Lachmann[8]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]IRCCS Policlinico San Matteo, Pavia, Italy, [3]Pediatric Immunology and Rheumatology, Brescia, Italy, [4]Galway University Hospitals, Galway, Ireland, [5]Novartis Pharmaceutical Corporation, East Hanover, NJ, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Novartis Pharmaceuticals UK Limited, Surrey, United Kingdom, [8]University College London Medical School, London, United Kingdom

Background/Purpose: TNF-receptor associated periodic syndrome (TRAPS) is a rare dominantly inherited periodic fever syndrome due to mutations of the *TNFRSF1A* gene. It is characterized by recurrent fever attacks associated with rash, musculoskeletal and abdominal pain, conjunctivitis, and periorbital edema. Approximately 10–20% of pts develop renal amyloidosis. The IL-1 receptor antagonist anakinra has been reported to be an efficacious treatment. Canakinumab (CAN) is a fully human monoclonal selective anti-IL-1β antibody with a $T_{1/2}$ of 4 wks. Interim data of open label 4-months CAN therapy and 5-months follow-up in active TRAPS pts is presented.

Methods: 14 adults and 6 children (7 to 78 yrs, median 39 yrs) with active TRAPS entered a 3-part trial: 4 months open-label 150 mg (or 300 mg) CAN every 4 wks followed by up to 5 months treatment withdrawal, and then 24 months open-label CAN. Disease activity was evaluated by a 5-point physician's global assessment (PGA) score and by CRP and SAA levels. Primary endpoint was complete or almost complete response at Day 15. Complete response was defined as clinical remission (PGA of 0 or 1 [absent or minimal signs/symptoms]) and normal CRP and/or SAA. Almost complete response was defined as clinical remission and elevated but ≥70% reduced from baseline CRP and/or SAA. Quality of life was assessed by the SF-36 in adults. Those without response by Day 8 were eligible for another 150 mg dose and then 300 mg thereafter. Pts were observed after last dose until relapse (5 month max) before restarting CAN.

Results: On Day 8, 16 (80%) achieved complete/almost complete response and 18 (90%) achieved clinical remission. Two pts without clinical remission were dose up-titrated to 300 mg. At Day 15, 19 (95%) achieved complete/almost complete response, including all 4 without it at Day 8. Clinical remission was maintained by all from Day 15 onwards except 1 who relapsed at Day 85, responding to that visit's CAN dose. Median time to clinical remission was 4 days (95% CI: 3,8). Median baseline CRP (125 mg/L) and SAA (198 mg/L) both reduced to <5 mg/L from Day 15 onwards. All relapsed after stopping CAN at a median 91.5 days. The relapse graded by the PGA was mild in 11, moderate in 7, and severe in 2. Upon redose, 18 regained complete/almost complete response 8–27 days later and 2 relapsed at final visit with no follow-up available for this analysis. Baseline SF-36 components improved after CAN therapy. All pts reported ≥1 adverse event (AE). Infections, mostly of the upper respiratory tract (URI), was the most common (n=15, 75%) AE category. Headache (n=9) followed by abdominal pain (n=7) were the most common specific AEs reported. Two serious AEs, a URI and a TRAPS relapse, were reported. All pts are active in the 24-month open-label period.

Conclusion: Canakinumab produced a rapid and effective clinical and serological benefit which was maintained with continued dosing. Relapse occurred at a median of 3 months after last dose, was usually mild or moderate, and resolved upon re-dosing. Canakinumab demonstrated a favorable safety and tolerability profile in this small study. Data support IL-1β's pivotal role in TRAPS and further study is needed to better define canakinumab treatment.

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Efficacy and Safety of Canakinumab in Adults with Colchicine Resistant Familial Mediterranean Fever. A. Gul[1], H. Ozdogan[2], B. Erer[1], S. Ugurlu[2], Nicole Davis[3], S. Sevgi[4] and O. Kasapcopur[2]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey, [3]Novartis Pharma Corp, East Hannover, [4]Novartis Pharma, Istanbul, Turkey

Background/Purpose: Familial Mediterranean fever (FMF) is associated with variations in the MEFV gene resulting in proteolytic activation of IL-1β through the inflammasome complex. FMF is characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, and/or erysipelas-like rash. Colchicine is the standard of care to prevent attacks and development of secondary amyloidosis, but there is no established treatment available for those resistant or intolerant to it. Canakinumab, a fully humanized selective anti-IL-1β monoclonal antibody with a half-life of 4-weeks binds to human IL-1β and neutralizes its proinflammatory effects. The aim of this study is to evaluate the efficacy and safety of canakinumab by documenting the FMF attack rate and adverse events (AE) in adolescents and adults with FMF who are resistant or intolerant to colchicine.

Methods: FMF patients describing >1 attack/month in the preceding 3-months despite the highest tolerated colchicine dose were eligible to enter a 30-day run-in period. Those with an attack in the run-in period advanced to a 3-month treatment period to receive canakinumab 150mg sc every 4-weeks starting at the next attack in the following month. Patients then followed-up for up to 2months or until the next attack. Attacks were confirmed by presence of fever, serositis, and elevated CRP. Primary efficacy outcome was the proportion of patients with >50% reduction in time-adjusted attack frequency in the treatment vs pre-treatment periods. Secondary objectives included the percent of patients with no attacks in the treatment period, time to next attack after the last canakinumab dose, and changes in the quality of life by SF-36. Safety was assessed by AEs and laboratory values at each visit.

Results: Thirteen patients entered the run-in period and 9 (median age 22 yrs, range 12–34 yrs) advanced to the treatment period. Only 1 patient had an attack (peritonitis) in the treatment period and all had a ≥50% reduction in their time-adjusted pre-treatment attack rate. Median baseline elevated CRP (58mg/L) and serum AA (162mg/L) levels normalized (CRP, 2.5mg/L; SAA, 5.8mg/L) by Day 8 and remained low throughout the study. The Physical and Mental Component scores of the SF-36 improved from a median baseline of 32 and 38 to 81 and 78 at Day 8 respectively, and continued to improve throughout the treatment period. Five patients had an attack in the follow-up period which occurred a median 71 days (31–78 days) from the last canakinumab dose. Compared to baseline, the physician and patient global assessment of FMF control improved with treatment with overall the response to treatment reported as Very Good by both physicians (9/9) and patients (7/9) at study end. Eight patients reported at least 1 adverse event (AE) with headache (n=4) and upper respiratory tract infection (n=2) being the only AEs reported in more than 1 patient. No one discontinued early from the trial.

Conclusion: In this pilot study, canakinumab was found to be effective at controlling the attack recurrence in FMF patients resistant or intolerant to colchicine. AEs were similar to previous canakinumab trials and were managable. Further studies are warranted to explore the role of canakinumab in the treatment of FMF.

Disclosure: A. Gul, Novartis Pharmaceutical Corporation, 5, Novartis Pharmaceutical Corporation, 2, Xoma Corporation, 2, Xoma Corporation, 5, Servier, 5; H. Ozdogan, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5; B. Erer, None; S. Ugurlu, None; N. Davis, Novartis Pharmaceutical Corporation, 3; S. Sevgi, Novartis Pharmaceutical Corporation, 3; O. Kasapcopur, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5.

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Whole Transcriptome Analysis in Erdheim-Chester Disease: A Multi-center Collaborative Study of 58 Patients. Laurent Arnaud[1], Julien Haroche[1], Lorenzo Dagna[2], Augusto Vaglio[3], Bruno Faivre[4], Karim Dorgham[4], Baptiste Hervier[1], Fleur Cohen-Aubart[1], Guy Gorochov[4] and Zahir Amoura[1]. [1]Hopital Pitié-Salpêtrière, AP-HP & UPMC Univ Paris 06, Paris, France, [2]Vita-Salute San Raffaele University School of Medicine and San Raffaele Scientific Institute, Milano, Italy, [3]University of Parma, Parma, Italy, [4]Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S 945, Paris, France

Background/Purpose: To date, gene expression profiling has not been performed in Erdheim-Chester disease (ECD), a rare, non-Langerhans form of histiocytosis. The aim of this study was to analyze the transcriptome of ECD compared to healthy individuals, as a manner to identify new pathways involved in the pathogenesis of the disease as well as new therapeutic targets.

Methods: Total RNA was extracted from peripheral blood mononuclear cell (PBMC) obtained in 58 patients with biopsy-proven ECD and 36 healthy individuals. Complementary DNA (cDNA) was hybridized in Illumina Human HT-12® v4 Expression Bead Chips. Statistical analysis of Microarray (SAM) algorithm with Benjamini and Hochberg multiple testing correction was used to determine the statistical significance of the differences in gene expression while controlling the false-discovery rate. Cluster analysis was also performed with JMP8 software. Differentially expressed genes were analyzed to identify potential functional pathways using Ingenuity® Pathway Analysis (IPA).

Results: Gene expression analysis using SAM showed 265 significantly down- or up-regulated transcripts between ECD patients and controls. Cluster analysis of these transcripts by similarity on gene expression patterns identified several clusters containing only ECD patients, healthy individuals, or both, underlining the strong heterogeneity of the disease. The set of genes statistically different between ECD and healthy individuals was further analyzed with IPA Analysis, which revealed a role for genes related to growth factor and cytokine activities, cyclin-dependant cell-cycle genes, regulation of phosphate homeostasis, DNA packaging, transcription regulation, and mRNA stability.

Conclusion: This large multicenter collaborative transcriptome analysis of 58 patients with Erdheim-Chester disease reveals that complex gene expression patterns are involved in the pathogenesis of the disease. This may be seen as a significant advance in this rare disease with poor prognosis and non-formally codified therapeutic management.

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IFNg Production Is Intimately Associated with Clinical and Laboratory Features of CpG-Induced Secondary Hemophagocytic Lymphohistiocytosis (sHLH)/Macrophage Activating Syndrome (MAS) in Mice. Vanessa Buatois, Laurence Chatel, Laura Cons, Maureen Deehan, Cristina de Min, Marie Kosco-Vilbois and Walter Ferlin. NovImmune S.A., Geneva, Switzerland

Background/Purpose: Repeated TLR9 stimulation with CpG DNA has been found to result in a sHLH/MAS-like disease in mice (1). CpG-administered mice present with cytopenia, anemia, thrombocytopenia, splenomegaly, hepatitis and hyperferritemia. The use of IFNg deficient mice as well as treatment of wild type mice with the anti-IFNg monoclonal antibody (mAb), XMG1.2, suggested an important role for IFNg in the pathogenesis of sHLH/MAS. Our aim was to extend these findings and perform biomarker studies to correlate the kinetics of IFNg production to sHLH/MAS disease endpoints.

Methods: C57BL/6 mice (n=10) were administered $5 \times 50\mu g$ injections of CpG-1826 over a 10-day period (day 0, 2, 4, 7 and 9). XMG1.2 was administered i.v. at 30mg/kg 24hrs preceding each CpG injection. Quantitative Real-time PCR was used to analyze inflammatory gene expression. Luminex multiplex technology was used to detect serum inflammatory cytokines. Whole blood cell count, red blood cells and haemoglobin were assessed using a haematological counter.

Results: We observe a multi-phasic production of IFNg in serum with peak levels reaching 600pg/ml at day 7. Cytokine mRNA level expression confirms the multi-phasic production of IFNg in the liver and spleen following each exposure to CpG. The initial peak of IFNg production correlates with the rapid appearance of cytopenia and thrombocytopenia, while each additional injection of CpG sustains these symptoms and generates new features such as anemia, hemoglobinemia, splenomegaly, hypercytokinemia and ferritinemia, culminating in induction of acute phase protein SAA and severe disease. IFNg-induced gene signature biomarkers, e.g., CTIIA (MHC class II trans-activator gene) and CXCL10, are upregulated in spleen and liver as too inflammatory cytokines IL-6 and TNFα. Neutralization of IFNg by XMG1.2 reduces body weight loss and splenomegaly, normalizes white blood cell counts, significantly reverses the decrease in other laboratory parameters (e.g., platelets, haemoglobin and red blood cells) and controls hyperferritinemia.

Conclusion: Thus, IFNg production is intimately associated with the clinical and laboratory features in the CpG-induced sHLH/MAS model suggesting the inhibition of this cytokine as a therapeutic target for patients afflicted with this life-threatening disease.

(1) Behrens *et al.*, *J. Clin. Invest.* 2011; 121(6):2264–2277

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ACR Concurrent Abstract Session
Muscle Biology, Myositis and Myopathies: Classification, Treatment and Outcome in Idiopathic Inflammatory Myopathies
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Progress Report On Development of Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies. Anna Tjärnlund[1], Matteo Bottai[2], Lisa G. Rider[3], Victoria P. Werth[4], Clarissa A. Pilkington[5], Marianne de Visser[6], Lars Alfredsson[7], Anthony A. Amato[8], Richard J. Barohn[9], Matthew H. Liang[10], Jasvinder A. Singh[11], Frederick W. Miller[3], Ingrid E. Lundberg[12] and the International Myositis Classification Criteria Project[13]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [2]Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [3]NIEHS, NIH, Bethesda, MD, [4]University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA, [5]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [6]Department of Neurology, Academic Medical Centre, Amsterdam, Netherlands, Amsterdam, Netherlands, [7]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [8]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [9]Department of Neurology, University of Kansas Medical Center, Kansas City, USA, Kansas City, MO, [10]Brigham & Womens Hospital, Boston, MA, [11]University of Alabama at Birmingham, Birmingham, AL, [12]Karolinska Institutet, Stockholm, Sweden, [13]Stockholm

Background/Purpose: In patients with idiopathic inflammatory myopathies (IIM) persisting muscle impairment after treatment underscores the need for improved management. Inadequate classification criteria for IIM are a fundamental limitation in clinical studies of myositis. An international, multidisciplinary collaboration, the International Myositis Classification Criteria Project (IMCCP), with support from ACR and EULAR, seeks to develop and validate new classification criteria for adult and juvenile IIM and its major subgroups.

Methods: *Identification and definition of potential criterion* Candidate variables to be included in classification criteria were assembled from published criteria and inclusion criteria in controlled trials of myositis and refined using Nominal Group Technique. Effort was made to assure content validity. Comparator groups confused with IIM were defined.

Data collection Within this retrospective case control study, clinical and laboratory data from IIM and comparator patients were collected from 47 rheumatology, dermatology, neurology and pediatrics clinics worldwide from 2008–2011.

Analysis Crude pair-wise associations among all variables measured and between each variable and clinician's diagnosis were assessed. Three approaches for derivation of classification criteria were explored:

1. Traditional: case defined by specified number of items from a set

2. Risk score: patient assigned a probability risk score by summing score-points associated with the variables (Model 1)

3. Classification tree: case defined by a decision tree (Model 2)

A random forest algorithm explored the most important variables. Results obtained with each approach were utilized to improve others iteratively.

Validation Internal validation using bootstrap methods was performed.

Results: Data from 973 IIM (74% adults; 26% children) patients and 629 comparators (81% adults; 19% children) were obtained, representing subgroups of IIM (245 polymyositis, 239 dermatomyositis, 176 inclusion body myositis and 246 juvenile dermatomyositis cases). The comparators include other myopathies and systemic rheumatic diseases.

Two models were developed (Table). Model 1 performs better than Model 2 although both models perform equally to, or better, than current published criteria.

Table. New models for classification criteria for IIM and performance of criteria

MODEL 1. RISK SCORE

Variable	Score points
$18 \leq$ Age of onset of first symptom < 40	1.6
Age of onset of first symptom ≥ 40	2.3
Clinical Muscle Variables	
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.6
Neck flexors are relatively weaker than neck extensors	1.6
In the legs proximal muscles are relatively weaker than distal muscles	1.5
Skin Variables	
Heliotrope rash	3.3
Gottronxs papules	2.3
Gottron's sign	3.4
Other Clinical Variables	
Dysphagia or esophageal dysmotility	0.7
Laboratory Variables	
Serum creatine kinase (CK) activity	1.2
Anti-Jo-1 (anti-His) antibodies	4.2
Score-sum from above items*	**0.9**
Muscle Biopsy Variables	
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers	1.6
Perimysial and/or perivascular infiltration of mononuclear cells	1.1
Perifascicular atrophy	1.7

* When muscle biopsies are available, multiply the score-sum of all other variables by 0.9 and then add the scores of the positive biopsies.

MODEL 2. CLASSIFICATION TREE

(a) Heliotrope rash:

If yes then IIM; if no go to step (b)

(b) Objective symmetric weakness, usually progressive, of the proximal lower extremities:

If yes then go to step (c); if no go to step (h)

(c) Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers:

If yes then IIM; if no go to step (d)

(d) Perimysial and/or perivascual infiltration of mononuclear cells:

If yes then IIM; if no go to step (e)

(e) Serum alanine aminotransferase activity:

If yes then IIM; if no go to step (f)

(f) Interstitial lung disease:

If yes then IIM; if no go to step (g)

(g) Dysphagia or esophageal dysmotility:

If yes then IIM; if no then not IIM

(h) Mechanic's hands:

If yes then IIM; if no go to step (i)

(i) Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers:

If yes then IIM; if no then not IIM

PERFORMANCE OF NEW AND EXISITING CLASSIFICATION/ DIAGNOSTIC CRITERIA FOR IIM

Performance (%)	Model 1 Risk Score [a] Without muscle biopsy data	With muscle biopsy data	Model 2 Tree	Peter & Bohan [1][b]	Tanimoto et al. [2]	Targoff et al. [3][b]	Dalakas & Hohlfeld [4][b]	Hoogendijk et al. [5][b]
Sensitivity	91	94	93	98	96	93	6	51
Specificity	82	85	74	55	31	88	99	96
Positive predictive value	90	93	91	85	80	95	92	96
Negative predictive value	84	87	80	90	72	84	43	57
Correctly classified	88	91	88	86	79	91	45	70

[a] Cut point for probability: 50%
[b] Definite and probable polymyositis and dermatomyositis

Conclusion: New classification criteria for IIM with easy-to-access measurements and symptoms have been developed that generally have superior performance compared to existing criteria. External validation is in progress.

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The Functional Index-3 in Adult Dermatomyositis and Polymyositis: Validity and Reliability of an Outcome Measure for Muscle Endurance. Christopher Chong[1], Orla Ni Mhuircheartaigh[1], Helene Alexanderson[2], Tanaz A. Kermani[3], Cynthia S. Crowson[4], Abigail B. Green[4], Ann M. Reed[4] and Floranne C. Ernste[5]. [1]Mayo Clinic, Rochester, [2]Karolinska Institutet, Stockholm, Sweden, [3]University of California Los Angeles, Los Angeles, [4]Mayo Clinic, Rochester, MN, [5]Mayo Clinic Rochester, Rochester, MN

Background/Purpose: Although muscle fatigue is a major source of functional impairment in dermatomyositis (DM) and polymyositis (PM), few valid and reliable methods for efficient evaluation of functional disability exist. The Functional Index (FI) was the first to specifically assess impairment in myositis, and consisted of 14 tasks to determine muscle endurance. The Functional Index-2 (FI-2) was a revision of FI, which decreased the tasks from 14 to 7. However, busy clinical practices may preclude feasibility of use. We developed a Functional Index-3 (FI-3) to streamline content for assessment of muscle endurance in DM and PM patients and tested its validity at a single, large academic center.

Methods: Twenty-eight patients with DM or PM diagnosis were recruited at our institution from 2010–2012. All patients participated in at least one of two sessions which included 3 tasks (shoulder flexion, head lift, hip flexion) performed bilaterally. After each task, participants completed the Borg CR-10 to rate perceived muscle exertion. Self-reported limitations in daily activities were assessed by the Myositis Activity Profile (MAP) and the Health Assessments Questionnaire (HAQ). Intra-class correlation (ICC) coefficients were calculated. Performance results from the tasks were correlated to the MAP, HAQ, and Borg CR-10 using Spearman's correlation coefficient to assess validity.

Results: Fifteen patients with DM, 7 patients with anti-synthetase syndrome, and 6 patients with PM participated. The mean (SD) age was 58 (11) years and mean (SD) disease duration was 6.5 (5.4) years. There were 19 (68%) females. Six patients (21%) had active disease as determined by creatine kinase level and clinician judgment. Twelve patients completed the second session for intra-rater reliability. Consistently high ICC values indicate high intra-rater reliability: ICC (95% confidence interval): shoulder flexion, right 0.90 (0.69, 0.97); shoulder flexion, left 0.88 (0.64, 0.96); head lift, 0.66 (0.19, 0.89); hip flexion, right 0.64 (0.15, 0.88); hip flexion, left 0.84 (0.56, 0.95). Ten patients completed the second session for inter-rater reliability, and the high ICC values show that the raters agreed: shoulder flexion, right 0.81 (0.43, 0.95); shoulder flexion, left 0.94 (0.78, 0.98); head lift, 0.92 (0.74, 0.98); hip flexion, right 0.46 (−0.16, 0.83); hip flexion, left 0.60 (0.03, 0.88). Two patients had large decreases in repetitions in hip flexion during the second session (>8 repetitions). Correlations were significant between MAP, HAQ, and Borg CR-10 in all tasks as shown in the table.

Table. Spearman correlations of disease activity and Borg CR-10 scores with FI-3 task scores in session one

	MAP score (n=28)		HAQ score (n=27)		Borg CR-10 scores (n=28)	
	correlation	p-value	correlation	p-value	correlation	p-value
Shoulder flexion right	-0.62	<0.001	-0.69	<0.001	-0.57	0.002
Shoulder flexion left	-0.54	0.003	-0.54	0.003	-0.45	0.016
Head lift	-0.50	0.006	-0.55	0.003	-0.38	0.046
Hip flexion right	-0.69	<0.001	-0.77	<0.001	-0.46	0.015
Hip flexion left	-0.56	0.002	-0.65	<0.001	-0.40	0.036

Conclusion: The FI-3 is an efficient and valid method for assessment of muscle endurance in DM and PM patients. FI-3's validity is supported by the significant correlations between functional tasks and the MAP, HAQ, and Borg CR-10 scores.

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Sifalimumab, an Anti-IFN-Alpha Monoclonal Antibody Shows Target Suppression of a Type I IFN Signature in Blood and Muscle of Dermatomyositis and Polymyositis Patients. Brandon W. Higgs[1], Wei Zhu[1], Chris Morehouse[1], Wendy White[1], Philip Brohawn[1], Charles Le[1], Anthony A. Amato[2], David Fiorentino[3], Steven A. Greenberg[2], Laura Richman[1], Warren Greth[1], Bahija Jallal[1] and Yihong Yao[4]. [1]MedImmune, LLC, Gaithersburg, MD, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Stanford University School of Medicine, Redwood City, CA, [4]MedImmune, Gaithersburg, MD

Background/Purpose: To assess the pharmacodynamic effects of sifalimumab, an investigational anti-IFN-alpha monoclonal antibody, in the blood and muscle of adult dermatomyositis and polymyositis patients by measuring the suppression of a type I IFN signature following sifalimumab administration.

Methods: A phase 1b randomized, double-blinded, placebo-controlled, dose-escalation, multicenter clinical trial was conducted in adult patients with dermatomyositis or polymyositis. Blood and muscle biopsies were procured before and after administration with sifalimumab. Samples were transcript-profiled using microarray and qRT-PCR. The target modulation in patients following administration with either sifalimumab or placebo was measured by a 13-gene type I IFN signature.

Results: The type I IFN signature was suppressed by a median of 53–66% across the three times points (day 28, 56, and 98) in blood and 47% at day 98 in muscle specimens post sifalimumab administration, with the latter exhibiting dose-dependent target modulation. Patients with ≥15% improvement from baseline manual muscle testing scores showed a greater suppression of the gene signature than those with <15% improvement as measured in both blood and muscle. Pathway/functional analysis of transcripts suppressed by sifalimumab showed that leukocyte infiltration, antigen presentation, and immunoglobulin categories were most suppressed following administration with sifalimumab and were highly correlated with suppression of the type I IFN signature ($r=-0.93$; $p<0.001$ and $r=-0.84$; $p<0.001$, and $r=-0.64$, $p=0.001$, respectively) in muscle tissue.

Conclusion: Administration of sifalimumab resulted in suppression of the type I IFN signature in peripheral blood and muscle tissue in patients with myositis, consistent with this molecule's mechanism of action and a positive trend of correlation between this target suppression and clinical improvement. These observations will require confirmation in a larger trial powered to evaluate efficacy.

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Effect of B Cell Depletion Therapy with Rituximab On Myositis Associated Autoantibody Levels in Idiopathic Inflammatory Myopathy. Rohit Aggarwal[1], Chester V. Oddis[1], Andriy Bandos[1], Danielle Goudeau[2], Diane Koontz[1], Qi Zengbiao[1], Ann M. Reed[3], Dana P. Ascherman[4] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Mayo Clinic, Rochester, MN, [4]University of Miami, Miami, FL

Background/Purpose: Myositis associated autoantibodies (MAA) in idiopathic inflammatory myopathy (IIM) demonstrate unique phenotypic features. In some autoimmune disorders, autoantibody levels correlate with disease activity and are reduced after B cell depletion (BCD). Our aim was to determine the effect of BCD on the serum levels of 3 common MAAs (anti-Jo-1, -TIF1g, -SRP) and to assess whether quantitative changes in MAA levels correlate with IIM core-set measures (CSM) [manual muscle testing (MMT), muscle enzyme, physician global, patient/parent global, extramuscular disease activity and HAQ].

Methods: Treatment-resistant IIM subjects (n=200) received rituximab in a 44-week clinical trial, the Rituximab in Myositis (RIM) Study. CSM were evaluated monthly and serial serum samples were collected. Anti-Jo-1 (n=25), -SRP (n=25) and -TIF1g (n=23) levels were measured using validated ELISAs. Temporal trends in MAA levels and longitudinal relationship between MAA levels and CSM within patients (adjusted for the total immunoglobulin (IgG) levels) was estimated using linear mixed models (SAS v. 9.2). Spearman correlation within each subject longitudinally and median MAA levels and CSM over time were evaluated.

Results: After start of the treatment autoAb levels in Jo-1 subjects decreased by approximately 9 units per week ($p<0.001$). Anti-Jo-1 levels longitudinally correlated with all CSM ($p<0.05$) univariately and after adjusting for IgG levels In contrast, anti-TIF1g and anti-SRP levels do not demonstrate systematic trends with time; there was no significant correlation between anti-TIF1g or anti-SRP levels and any CSM. Median (IQR) Anti-TIF1g levels were unchanged between baseline [34 (11–85)] and the last visit [38 (13–94)]. Post-hoc analysis of anti-SRP levels (n=25) revealed intermediate results as 13/25 (52%) anti-SRP subjects dropped their autoAb level while 9 were unchanged. The 13 subjects with a decrease in anti-SRP levels had significantly higher baseline anti-SRP levels compared to the remaining patients [median 81 (12–208) vs. 5(4–50); p=0.02]. Those 13 subjects demonstrated moderate to strong correlations (rho > 0.35) between anti-SRP levels and CSM except for the HAQ (median rho 0.26).

Longitudinal median Levels of anti-Jo1, muscle enzyme (x upper limit of normal) and IgG (x lower limit of normal) after rituximab
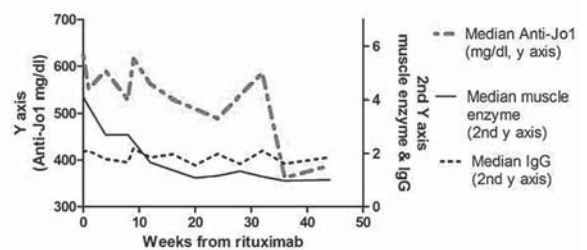
Conclusion: Anti-Jo-1 autoAb levels in IIM patients decreased after BCD with rituximab and longitudinally correlated with changes in all CSM. In contrast, anti-TIF-1g and anti-SRP levels did not change significantly over time and there were no significant correlations with CSM, except a subset of anti-SRP patients with higher baseline levels. The strong association of anti-Jo-1 levels with clinical outcomes suggests that these autoantibodies may have a direct pathogenic role in IIM that is mitigated by B cell depletion with rituximab and may be a good biomarker for disease activity.

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Beneficial Role of Rapamycin in Experimental Autoimmune Myositis.
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Background/Purpose: Idiopathic inflammatory myopathies are a hetero-
geneous group of different diseases, classified into four main categories:
dermatomyositis, polymyositis, immune-mediated necrotizing myopathy, and
sporadic inclusion body myositis. The treatment of polymyositis consists of
corticosteroids frequently associated to other immunosuppressive drugs. The
obligatory and often severe side effects of these drugs, which have to be taken
for several months or years, prompted us to propose alternative treatments,
which have to be tested first in experimental animal models. Rapamycin is a
known potent immunomodulator with less side effects compared to other
immunosuppressants (e.g. ciclosporin). Rapamycin has been used for a
decade in transplant patients to prevent graft rejection. In vivo, rapamycin has
been described to increase the percentage of regulatory T cells. Our objective
was to Study the role of rapamycin in an experimental autoimmune myositis
(EAM) model of polymyositis in mouse (Allenbach Y et al. Am J Pathol,
2009, 174, 989–998).

Methods: EAM is induced by 3 injections of myosin coupled with
complete Freund's adjuvant. Mice received rapamycin (1 mg or 3 mg/kg/day)
during 25 days starting before myosin immunization (preventive treatment),
or during 10 days following the last myosin immunization (curative treat-
ment). Muscle strength and histology, composition of lymphocyte subpopu-
lations, and KLF2 pathway, a transcription factor controlling lymphocyte
homing, were studied.

Results: Under preventive or curative treatment, an increase of muscle
strength was observed with in parallel a decrease of muscle inflammation,
both being well correlated ($R^2=-0.645$, $p<0.0001$). Rapamycin induced a
general decrease in frequency of effector T cells (lymphopenia in draining or
non draining lymph nodes and spleen, harmoniously distributed between
$CD4^+$ and $CD8^+$ T cells, but sparing B cells), and an increase in frequency
of regulatory T cells ($CD4^+CD25^+$) in draining lymph nodes (rapamycin 3
mg/kg/day preventively treated mice compared to controls: $16.9\pm2.2\%$ vs.
$9.3\pm1.4\%$, $p<0.001$), which were mostly activated regulatory T cells
($CD62L^{low}CD44^{high}$: $58.1\pm5.78\%$ vs. $33.1\pm7\%$, treated vs. untreated,
$p<0.001$). Furthermore, during preventive treatment, rapamycin increased the
levels of KLF2 transcript in $CD44^{low}$ $CD62L^{high}$ naive T cell ($2,1\pm0,14$ vs.
$1,05\pm0,09$, treated vs. untreated, $p<0.05$) and in $CD62L^{low}$ $CD44^{high}$
activated T cell ($1,02\pm0,18$ vs. $0,44\pm0,08$, treated vs. untreated, $p<0.05$).

Conclusion: Rapamycin is an effective treatment for EAM, resulting in a
decrease in effector T cells, an increase in regulatory T cells, and upregulation
of KFL2 in naive and activated T cells. Those observations suggest that
rapamycin may represent an effective new therapeutic approach in patients
with polymyositis. This approach may also be beneficial, since a deficiency in
regulatory T cells has been reported during polymyositis.

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None; **O. Benveniste**, None.

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**Cutaneous Ulceration in Dermatomyositis: Association with MDA-5 and
Interstitial Lung Disease.** Neera Narang[1], Livia Casciola-Rosen[2], Antony
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Background/Purpose: Dermatomyositis (DM) is a multisystem auto-
immune disease that affects the muscles and skin and can be associated with
malignancy or interstitial lung disease (ILD). Cutaneous ulceration can be
seen in patients with dermatomyositis, and this has classically been associated
with internal malignancy. We have recently described that ulceration can also
be associated with antibodies against melanoma differentiation-associated
gene 5 (MDA5), a DM-specific autoantigen that is associated with ILD, and
mild or no muscle disease. We sought to better describe cutaneous ulceration
in DM and to specifically identify clinical and serologic correlates of ulcers
and their anatomic location.

Methods: We retrospectively examined a cohort of 131 DM patients
followed in our interdisciplinary rheumatology-dermatology clinic. We col-
lected data on demographics, ANA and DM-associated auto-antibodies (Jo-1,
NXP2, Mi2, TIF-Gamma, SAE1, Ro52, MDA5) and clinical features includ-

ing presence and location of ulcers, ILD (evidence of fibrosis or alveolitis on
computed tomography), and malignancy within 3 years of symptom onset.
The cutaneous ulcer locations were subdivided into three categories: ulcer-
ations over joints (Gottron papules, knees, or elbows); ulcerations of the
digital pulp or periungual region; and ulcers elsewhere on the body including
those in sun-exposed areas. We compared the features of patients with ulcers
to those without ulcers using chi-squared tests. We used univariate and
multivariate logistic regression models to identify significant predictors for
the presence of ulcers and ILD.

Results: In the overall cohort, the mean age was 45 ± 19 years, 31% were
male, and the ethnic distribution was 66% Caucasian, 19% Asian, 5% African
American, and 10% Hispanic. 40 patients had cutaneous ulcers and 91
patients did not have ulcers. 50% of patients had ulcers over the Gottron
papules and extensor surfaces, 40% at the digital pulp or periungual areas, and
62.5% had ulcers located elsewhere. Patients with any cutaneous ulcers were
more likely to be Asian ($p=.006$) or anti-MDA5+ ($p<.0001$). We did not
find a significant association between ulcers and malignancy. In multivariate
analysis MDA5+ remained significant and increased the odds of ulcers by
10-fold (OR=10.1, 95%CI 2.0–51.8, $p=.006$). Examining only the ulcer+
patients, ulcers located at the digital pulp or periungual areas was associated
with a 20-fold increased odds of being MDA5+ (OR= 20.9, 95%CI
3.5–126.5, $p=.0009$). Consistent with previous reports, MDA5+ was asso-
ciated with an increased risk for ILD (OR=5.8, 95%CI 1.8–18.4, $p=.003$),
that was higher in the presence of ulcers (OR=8.3, 95%CI 2.5–28.3,
$p=.0007$), particularly if located at the digital pulp or periungual areas
(OR=14.2, 95%CI 3.4–58.3, $p=.0002$).

Conclusion: We confirmed the strong association between MDA5+ and
cutaneous ulcers, with the novel finding that ulcers located at the digital pulp
and periungual areas are highly predictive of the presence of ILD in these
patients. DM patients who display this cutaneous phenotype should undergo
appropriate evaluation for ILD.

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ACR Concurrent Abstract Session
**Pediatric Rheumatology: Clinical and Therapeutic Disease I:
Juvenile Idiopathic Arthritis I**
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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**Efficacy and Safety of Canakinumab in Patients with Active Systemic
Juvenile Idiopathic Arthritis and Fever: Results From Two Pivotal
Phase 3 Trials.** Hermine I. Brunner[1], Nicolino Ruperto[2], Pierre Quartier[3],
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Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is an
interleukin-1β (IL-1β)-mediated autoinflammatory disease. Canakinumab is
a selective, fully human, anti-IL-1β monoclonal antibody. Two pivotal phase
3 trials evaluated the efficacy and safety of canakinumab in patients (pts) with
active sJIA with fever.

Methods: Pts aged 2–19 yrs with active sJIA (fever, ≥2 active joints,
C-reactive protein >30 mg/L) with inadequate response to standard of care
treatments (NSAIDs, steroids, MTX) were enrolled. Trial 1 was a 4-wk,
double-blind, single-dose study of pts randomized to subcutaneous (SQ)
canakinumab 4 mg/kg or placebo. Trial 2 enrolled 177 pts, including eligible
pts rolling over from Trial 1. In Part I of Trial 2, pts received open-label (OL)
canakinumab 4 mg/kg/4wks SQ for up to 32 wks. Pts with an adapted ACR
Pediatric 30 criteria response (aACR-Ped30) at the end of Part I entered Part
II after randomization 1:1 to continue canakinumab or receive placebo until
37 flare events occurred. The primary endpoint of Trial 1 was the proportion
of aACR-Ped30 responders at Day 15. The primary endpoint of Trial 2 in Part
I was the proportion of steroid-treated pts at entry who successfully tapered
steroids, and in Part II the time to flare. Pts withdrawn due to protocol-driven

discontinuation rules were offered participation in the currently on-going OL long-term extension study.

Results: In Trial 1, 84 pts (canakinumab n=43; placebo, n=41) were enrolled. At Day 15, of the 84 pts, significantly more pts in the canakinumab group (83.7% [36/43]) vs. the placebo group (9.8% [4/41]) achieved an aACR-Ped30 response (P <0.0001). In Trial 2, 177 pts received canakinumab in Part I, 100 of whom were randomized in Part II (canakinumab, n=50; placebo, n=50) and 77 discontinued. During Part I of Trial 2, 44.5% (57/128) of the steroid-treated pts successfully tapered steroids (P <0.0001), with the mean steroid dose lowered to 0.05 mg/kg/d from 0.34 mg/kg/d. Of note, 32.8% (42/128) of the pts stopped steroids completely. In Part II, the median time to flare on placebo was 236 days vs. not observed with canakinumab, corresponding to a statistically significant 63% relative risk reduction of flares (HR 0.37; 95% CI 0.17–0.78; P=0.0043). Inactive disease was achieved by 30.9% (54/175) of the canakinumab-treated pts at the end of Part I and 62% (31/50) upon completion of Part II. 142 (80.2%) of the enrolled pts from Trial 2 entered the OL extension study, which included 48 pts who had withdrawn from the Part I due to efficacy related protocol-driven discontinuation. In both trials, infections were the most common type of adverse event (AE) reported. Most Serious AEs were associated with infections, disease flare, and macrophage activation syndrome (MAS, n=7, including 2 on placebo). Two deaths were reported (1 canakinumab, 1 placebo), both associated with MAS.

Conclusion: These data support that canakinumab is an effective treatment for active sJIA with fever. Canakinumab demonstrated superior efficacy vs. placebo, allowed successful reduction of steroid use, and significantly decreased the risk of sJIA flares, while demonstrating an acceptable safety profile.

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Catch-up Growth During Tocilizumab Therapy for Systemic Juvenile Idiopathic Arthritis: 2-Year Data From a Phase 3 Clinical Trial.
Fabrizio De Benedetti[1], Nicolino Ruperto[2], Graciela Espada[3], Valeria Gerloni[3], Berit Flato[3], Gerd Horneff[4], Barry L. Myones[5], Karen Onel[5], James Frane[6], Andrew Kenwright[7], Terri H. Lipman[8], Kamal N. Bharucha[6], Alberto Martini[3] and D. J. Lovell[9]. [1]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [2]Paediatric Rheumatology International Trials Organisation [PRINTO], Genova, Italy, [3]Paediatric Rheumatology International Trials Organisation–IRCCS [PRINTO], Genova, Italy, [4]Centre of Pediatric Rheumatology, Sankt Augustin, Germany, [5]Pediatric Rheumatology Collaborative Study Group [PRSCG], Cincinnati, OH, [6]Genentech, South San Francisco, CA, [7]Roche, Welwyn Garden City, United Kingdom, [8]University of Pennsylvania School of Nursing, Philadelphia, PA, [9]Cincinnati Children's Hospital, Cincinnati, OH

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA), characterized by chronic arthritis associated with prominent systemic and laboratory features, also has a significant impact on the growing skeleton, resulting in impaired linear growth and systemic osteoporosis. A phase 3 trial (TENDER) demonstrated that the interleukin-6 (IL-6) receptor inhibitor tocilizumab (TCZ) is effective in the treatment of patients with sJIA. Long-term growth responses for children in the TENDER trial (up to week 104) are presented.

Methods: The TENDER trial enrolled 112 patients (ages 2–17 years) with active, refractory sJIA (≥6-month duration with inadequate response to previous nonsteroidal anti-inflammatory drugs and oral corticosteroids). After a 12-week, randomized, placebo-controlled phase, patients received open-label TCZ in the long-term extension. Height parameters, laboratory data, and clinical assessments of disease activity were compared at baseline and through year 2 of the study.

Results: At enrollment in the TENDER trial, the height measurements of study patients revealed profound growth failure (mean height standard deviation score [SDS] of –2.1; n = 107). During treatment, the majority of patients had greater than normal height velocities, with 85% of female patients and 73% of male patients demonstrating catch-up growth (Figure). The height SDS increased significantly from baseline to year 2 of the study, with a mean improvement of 0.61 ($p < 0.0001$, paired t-test). Although the mean corticosteroid dose was higher in the first year (0.13 mg/kg/day compared with 0.05 mg/kg/day in the second year), mean height velocities in the first and second years of the study were comparable at 5.8 and 6.3 cm/y, respectively ($p = 0.32$, paired t-test). During TCZ treatment, a significant increase in insulin-like growth factor 1 (IGF-1) levels was observed, suggesting a normalization of growth hormone axis function (mean baseline IGF-1 SDS of –1.1 [n = 95] compared with year 2 mean IGF-1 SDS of 0.0 [n = 91]; $p < 0.0001$, paired t-test). The osteocalcin/c-telopeptide of type 1 collagen (OC/CTX-1) ratio increased significantly ($p = 0.0045$, paired t-test), suggesting an increase in osteoblast activity relative to osteoclast activity. Patients with greater improvement in JADAS-71 scores during the first year had greater height velocities during that year ($r = -0.35$, $p = 0.0002$; mean decrease in JADAS-71 of 29.2 [n= 107]).
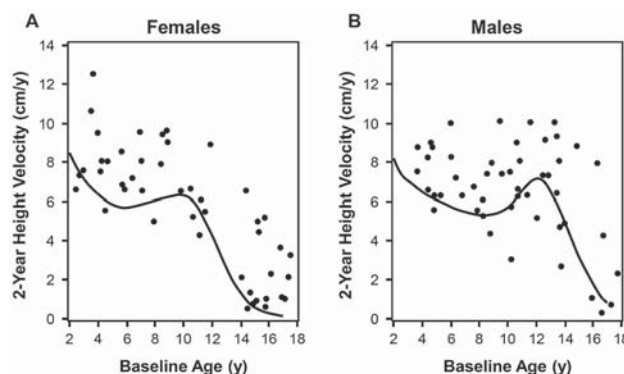
Conclusion: TCZ therapy for sJIA resulted in catch-up growth of study patients. Additionally, TCZ therapy resulted in increased IGF-1 levels and OC/CTX-1 ratios, suggesting beneficial effects on the growth hormone axis and on bone metabolism. Improvement in JADAS scores correlated with increased height velocity. Continued data collection (for a total of 5 years) will allow a comprehensive analysis of growth outcomes in the TENDER study.

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Analysis of Biomarkers in Systemic Juvenile Idiopathic Arthritis Patients On Canakinumab Therapy. Nico Wulffraat[1], Hermine I. Brunner[2], Nicolino Ruperto[1], Pierre Quartier[3], Riva Brik[1], Liza McCann[1], Huri Ozdogan[1], Lidia Rutkowska-Sak[1], Rayfel Schneider[2], Valeria Gerloni[1], Liora Harel[1], Maria Hilário[2], Kristin Houghton[2], Rik Joos[1], Daniel Kingsbury[2], Arndt Brachat[4], Stephan Bek[4], Martin Schumacher[4], Marie-Anne Valentin[4], N.R Nirmala[5], Hermann Gram[4], Ken Abrams[6], Alberto Martini[1] and D. J. Lovell[7]. [1]Paediatric Rheumatology International Trials Organization (PRINTO), Genova, Italy, [2]Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati, OH, [3]Necker-Enfants Malades Hospital, Paris, France, [4]Novartis Institutes for Biomedical Research, Basel, Switzerland, [5]Novartis Institutes for Biomedical Research, Cambridge, MA, [6]Novartis Pharmaceuticals Corporation, New Jersey, [7]Cincinnati Children's Hospital, Cincinnati, OH

Background/Purpose: Systemic Juvenile Idiopathic Arthritis (SJIA) is a severe disabling subtype of Juvenile Idiopathic Arthritis characterized by arthritis plus systemic symptoms, such as high fever, rash, serositis, and lymphadenopathy. Among others, interleukin (IL)-1β is an inflammatory cytokine that plays a dominant role in SJIA and several other autoinflammatory conditions, with anti-IL-1β therapy showing good efficacy in many of these settings. Canakinumab (CAN) is a high-affinity selective human monoclonal antibody targeted against IL-1β. Levels of inflammatory biomarkers and gene expression profiles of patients with active SJIA before and during canakinumab treatment were studied from patients aged 2 to <20 years participating in 2 phase III trials.

Methods: Serial measurements of levels of cytokines and proteins involved in inflammation (IL6; IL18; S100A8, A9 and A12) were made at baseline and at Days 3 and 29 after initiation of CAN treatment. Whole blood samples and DNA microarrays were used to characterize the early (Day 3) transcriptional response to CAN treatment and to predict efficacy.

Results: Protein markers: The median levels of IL-6 were strongly reduced; 7.2 fold reduction in the first trial (*p=0.012*) and 4.9 fold in the second trial (*p=0.000046*) by Day 29, while IL-18 levels remained largely unchanged by Day 29. Among the S100 proteins, median S100A9 levels were reduced by 3.4 fold in the first trial (*p=0.0078)* and 4.3 fold in the second trial (*p=0.016*). S100A8 and S100A9 proteins did not show consistent behaviors across the two trials.

Gene Expression: For all comparisons, the number of down regulated genes was much larger than the number of upregulated genes upon treatment, suggesting that the active disease state was mainly characterized by transcriptional activation of "disease genes". Transcriptional changes upon CAN treatment at Day 3 were highly consistent between the two trials. Subjects who showed strong transcriptional changes (primarily down regulation, >2x, *p=0.05*) also showed a strong adapted pediatric ACR response (≥ACR50) at Day 15, while subjects that did not reach ACR50 by Day 15 showed a much weaker transcriptional response at Day 3. Strongly responsive genes included many known inflammation and neutrophil-related genes, including IL-1β, encoding the CAN target. A set of transcripts was identified for which baseline expression levels predicted a subgroup of strong (≥ACR70) responders at Day 15. However, another subgroup of strong responders was indistinguishable from weak responders (<ACR30) based on transcript levels at baseline.

Conclusion: CAN treatment resulted in a strong reduction of elevated baseline IL6 protein levels in patients with active SJIA, while IL18 protein levels remained largely unchanged until Day 29 of the treatment period. Many patients who showed a strong clinical benefit already at Day 15 were characterized by high baseline expression levels of inflammatory and neutrophil associated genes which were repressed after 3 days of CAN treatment. A second, smaller, group of patients showing good clinical response did, however, not show this pattern, suggesting the existence of mechanistically different subpopulations in this disease.

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Potentially Fatal Pulmonary Complications in Systemic Juvenile Idiopathic Arthritis. Yukiko Kimura[1], Jennifer E. Weiss[1], Kathryn L. Haroldson[1], Tzielan C. Lee[2], Marilynn G. Punaro[3], Sheila K. Feitosa de Oliveira[4], Egla C. Rabinovich[5], Meredith P. Riebschleger[6], Jordi Anton[7], Peter R. Blier[8], Valeria Gerloni[9], Melissa M. Hazen[10], Elizabeth Kessler[11], Karen Onel[12], Murray H. Passo[13], Robert M. Rennebohm[14], Carol A. Wallace[15], Patricia Woo[16], Nico M. Wulffraat[17] and CARRAnet Investigators[18]. [1]JM Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Stanford Univ School of Med, Stanford, CA, [3]Texas Scottish Rite Hospital, Dallas, TX, [4]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [5]Duke University Medical Center, Durham, NC, [6]University of Michigan Health System, Ann Arbor, MI, [7]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [8]Baystate Children's Hospital, Springfield, MA, [9]Gaetano Pini Chair of Rheum, Milan, Italy, [10]Children's Hospital Boston, Boston, MA, [11]Medical College of Wisconsin, Milwaukee, WI, [12]University of Chicago, Chicago, IL, [13]Medical University of South Carolina, Charleston, SC, [14]Alberta Children's Hospital, University of Calgary, Calgary, AB, [15]Seattle Childrens Hospital, Seattle, WA, [16]University College London, London, United Kingdom, [17]University Medical Center Utrecht, Utrecht, Netherlands, [18]Durham

Background/Purpose: Systemic Juvenile Idiopathic Arthritis (sJIA) is characterized by fevers, rash and arthritis, for which IL1 and IL6 inhibitors appear to be effective. Pulmonary artery hypertension (PAH), interstitial lung disease (ILD) and alveolar proteinosis (AP) have been recently reported in sJIA patients with increased frequency and is associated with mortality. The purpose of our study was to identify and characterize these cases and compare them to a larger cohort of sJIA patients.

Methods: A retrospective review of sJIA patients who developed PAH, ILD and/or AP solicited through an electronic listserv was performed. Demographic, sJIA and pulmonary disease characteristics and medication exposure information were collected. These features were compared to a cohort of sJIA patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) pediatric rheumatic diseases registry.

Results: Patients (N=25) were significantly more likely (p<0.05) than the CARRA registry cohort (N=389) to be female and have more systemic features. They were also significantly more likely to have been exposed to the following: an IL-1 inhibitor, tocilizumab, infliximab, corticosteroids, intravenous immunoglobulin, cyclosporine and cyclophosphamide. Eighty% were diagnosed after 2004. Twenty (80%) patients had MAS during their disease course and 16 (64%) had suspected/confirmed MAS at pulmonary diagnosis. Sixteen patients had PAH, 7 AP and 8 ILD. Dyspnea on exertion and shortness of breath were the most common symptoms. One patient was diagnosed at autopsy and did not have any known prior pulmonary symptoms. Pulmonary disease characteristics are shown in the Table. Seventeen (68%) patients were taking or recently (<1 month) discontinued a biologic agent at pulmonary symptom onset, and 12 (48%) were taking anti-IL1 therapy (primarily anakinra). Seventeen (68%) patients died at a mean of 10.2 months from pulmonary diagnosis.

Clinical features at pulmonary disease diagnosis

Total N: 25

Age at start of pulmonary symptoms (years)*	11.7 ± 5.2 (3.5–18.8)
Disease duration at pulmonary diagnosis (months [mos])*	50.6 ± 44.6 (8–160)
Time between pulmonary symptoms to diagnosis (mos)*	3.1 ± 3.2 (0–10)
Time between pulmonary diagnosis to death (mos) (N=17)*	10.2 ± 13 (0–44)
Disease features at pulmonary disease diagnosis	**N (%)**
sJIA manifestations	
Any systemic manifestation**	23 (92)
MAS (suspected or confirmed)	16 (64)
Pericarditis/serositis	11 (44)
Thrombotic thrombocytopenic purpura	1 (4)
Arthritis	16 (64)
Pulmonary symptoms	
Shortness of breath	16 (64)
Dyspnea on exertion	18 (72)
Cough	11 (44)
Clubbing	10 (40)
Chest pain	5 (20)
Pulmonary diagnosis	
Pulmonary artery hypertension	16 (64)
Alveolar proteinosis	7 (28)
Interstitial lung disease	7 (28)

* Mean ± SD (range)
**Includes patients with one or more of the following: fever, rash, lymphadenopathy, hepatomegaly, splenomegaly

Conclusion: Despite recent advances in therapy, sJIA remains a disease with significant morbidity and mortality. This is the first time that a large cohort of sJIA patients who developed PAH, AP and ILD has been described. These are important, largely fatal and under-recognized complications of sJIA which are likely to be the result of severe uncontrolled systemic disease activity and inflammation, but may be influenced by exposure to certain medications. Further prospective studies are needed to determine the factors associated with the development of these complications. Increased awareness regarding these complications in sJIA is needed, and screening for these complications should be considered in sJIA patients with significant and persistent systemic disease activity.

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Incidence of Selected Opportunistic Infections Among Children with Juvenile Idiopathic Arthritis. Timothy Beukelman[1], Fenglong Xie[1], John Baddley[1], Lang Chen[1], Elizabeth S. Delzell[1], Carlos Grijalva[2], Melissa L. Mannion[1], Nivedita M. Patkar[1], Kenneth G. Saag[1], Kevin L. Winthrop[3] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Vanderbilt University, Nashville, TN, [3]Oregon Health & Science University, Portland, OR

Background/Purpose: There may be an increased risk of opportunistic infections among children with juvenile idiopathic arthritis (JIA), especially with exposure to immunosuppressant medications. No controlled studies to address this question have been published. We determined incidence rates of selected opportunistic infections among children with and without JIA and examined the effects of immunosuppressant medications.

Methods: Using U.S. national Medicaid claims data from 2000 through 2005 we identified a cohort of children with JIA based on physician diagnosis codes and dispensed medications. We defined a non-JIA comparator cohort of children diagnosed with attention deficit hyperactivity disorder. All subjects had a 3 month baseline period prior to study follow-up to assess for prevalent opportunistic infections (which excluded patients from analysis) and current medication exposures. All medication exposures to methotrexate (MTX), TNF inhibitors, and systemic glucocorticoids (GC) were considered current for 30 days past the days supplied by the last filled prescription. Hospitalized and outpatient incident opportunistic infections were identified using physician diagnosis or hospital discharge codes. Identification of some infections

(mycoses, tuberculosis, and herpes zoster) also required evidence of treatment with specific antimicrobials within 90 days. We calculated infection incidence rates (IR). The rates in the non-JIA comparator cohort were standardized to the age, sex, and race distribution of the JIA cohort. We calculated incidence rate ratios (IRR) to compare infection rates.

Results: The JIA cohort included 8,503 children with 14,370 person-years of follow-up; 1,392 used TNF inhibitors and 3,491 used MTX during follow-up. The non-JIA comparator cohort included 360,362 children with 490,939 person-years of follow-up. When all opportunistic infections were considered together as a single outcome, there were 42 infections in the JIA cohort (IR 300 [216–406] per 100,000; IRR 2.4 [1.7–3.3] versus non-JIA comparator). Among all children with JIA, there were no identified infections with *Aspergillus*, *Blastomyces*, *Histoplasma*, *Cryptococcus*, *Legionella*, *Listeria*, JC virus, or tuberculosis. We identified 1 infection each (IR 7 per 100,000) with *Nocardia*, non-tuberculous mycobacteria, *Toxoplasma*, and *Pneumocystis*. We identified 3 infections with *Coccidioides* (IR 21 per 100,000; IRR 101 [8.1–5319] versus non-JIA comparator); 5 infections with *Salmonella* (IR 35 per 100,000; IRR 3.8 [1.2–9.5]); and 32 cases of herpes zoster (IR 225 per 100,000; IRR 2.1 [1.4–3.0]). Among children with JIA, herpes zoster was not strongly associated with current use of GC (IRR 1.8 [0.6–4.5] versus no current GC use), MTX (IRR 1.4 [0.5–3.6] versus no current MTX or TNF inhibitor use), or TNF inhibitors (IRR 2.2 [0.7–6.9] versus current MTX use without current TNF inhibitor use).

Conclusion: Opportunistic infections are rare among children with JIA. Nevertheless, children with JIA had a higher rate of opportunistic infections, including *Coccidioides*, *Salmonella*, and herpes zoster, than children without JIA. Herpes zoster was not strongly associated with specific immunosuppressant medications used to treat JIA.

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The Impact of Adalimumab On Growth in Patients with Juvenile Idiopathic Arthritis. D. J. Lovell[1], Nicolino Ruperto[2], Katerina Jarosova[2], Dana Nemcova[2], Veronika Vargova[2], Hartmut Michels[2], Elizabeth Chalom[3], Norman Ilowite[3], Carine Wouters[2], Hermine Brunner[2], Karolyn Kracht[4], Hartmut Kupper[5], Edward Giannini[3], Alberto Martini[2] and Neelufar Mozaffarian[4]. [1]Cincinnati Children's Hospital, Cincinnati, OH, [2]Paediatric Rheumatology International Trials Organisation–IRCCS [PRINTO], Genova, Italy, [3]Pediatric Rheumatology Collaborative Study Group [PRSCG], Cincinnati, OH, [4]Abbott, Abbott Park, IL, [5]Abbott GmbH and Co. KG, Ludwigshafen, Germany

Background/Purpose: Children with juvenile idiopathic arthritis (JIA) often exhibit growth impairments. Treatment with adalimumab (ADA) has been shown to be safe and effective in JIA patients (pts) when dosed every other week (eow) for up to 3 years,[1] but the effect of ADA on growth is not known. The purpose of this post hoc analysis is to describe growth parameters in pts with JIA treated with ADA in a clinical trial setting.

Methods: Pts aged 4–17 with polyarticular course JIA were enrolled in a phase 3, randomized-withdrawal, double-blind (DB), stratified, parallel-group study, which consisted of a 16-wk open-label (OL) lead-in phase, a 32-wk DB phase, and an OL extension (OLE) phase. In the OLE phase, pts were dosed based on body surface area (24 mg/m^2, max 40 mg dose), followed by a switch to 20 or 40 mg eow based on a body weight of ≤30 kg or >30 kg, respectively. To enter the DB phase, pts had to achieve an American College of Rheumatology Pediatric score ≥30% (ACR Pedi 30) during the OL lead-in. Pts could enter the OLE after 32 wks in the DB phase or at time of first flare (whichever came sooner). For this analysis, pts in the DB phase were grouped by baseline weight into 2 groups: ≤33rd percentile and >33rd percentile based on the US Centers for Disease Control and Prevention (CDC) growth charts. All pts who received ≥1 dose of ADA ± methotrexate (MTX) were included in the analysis. Mean CDC percentile changes in height, weight, and body mass index (BMI) percentiles were calculated through 104 weeks. Growth and efficacy data were analyzed using last observation carried forward (LOCF).

Results: Among the 171 pts enrolled in this study, 144 (84%) met ACR Pedi 30 response criteria at week 16, and 133 (78%) entered the DB phase. Of the 133 pts, 77% were female, with a mean age of 11.2 years, and a mean disease duration of 3.8 years; at baseline, 55 pts (41%) were in the ≤33rd percentile for weight and 78 pts (59%) were >33rd percentile. There were no differences between MTX and non-MTX groups in mean changes from baseline in weight, height, or BMI percentiles (*P*>.26). Pts in the lower 33rd percentile climbed to a higher mean growth rate through 104 weeks of ADA treatment (**Figure**). For those who started in the >33rd percentile, growth rates showed an initial increase that remained in the normal range throughout the study (**Figure**). Similar patterns were observed for height and BMI percentiles in these 2 groups. ACR Pedi 30/50/70/90 response rates improved over time in both groups, reaching 85%/76%/60%/36% for the ≤33rd percentile group and 83%/76%/51%/29% for the >33rd percentile group by the end of the DB phase with ADA treatment.

Figure. Mean Height Percentile Change from Baseline[a] (All Subjects Who Received ≥1 Dose of ADA)
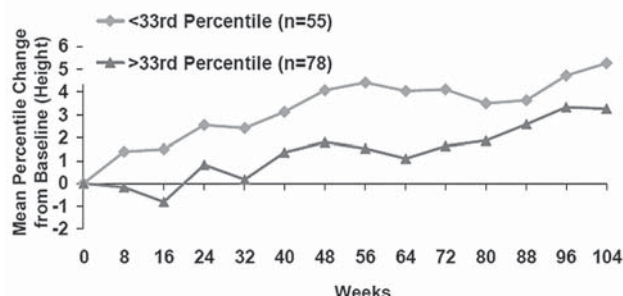
[a]Baseline mean height percentile for pts in the lower 33rd and >33rd percentiles were 25.1 and 55.5, respectively; LOCF analyses.

Conclusion: Long-term ADA treatment ± MTX is associated with improvement and maintenance of growth in children with JIA who had experienced impaired development. ADA treatment improved JIA signs and symptoms in both groups, regardless of baseline growth status.

Reference
[1]Lovell DJ, et al. *NEJM* 2008;359:810–820.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects I: Risk Factors and Prediction of Rheumatoid Arthritis
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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A Prediction Rule for the Development of Rheumatoid Arthritis: A Prospective Cohort Study of Seropositive Arthralgia Patients. Lotte van de Stadt[1], B. I. Witte[2], W.H. Bos[1] and Dirkjan van Schaardenburg[1]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands

Background/Purpose: Patients presenting with arthralgia and a positive test for anti-cyclic citrullinated peptide antibodies (aCCP) and/or IgM rheumatoid factor (IgM-RF) (seropositive) are at risk for developing RA. We aim to predict the development of arthritis in these patients using antibody characteristics and clinical variables.

Methods: A prediction rule was developed using a prospective cohort of 374 seropositive arthralgia patients. Patients were followed biannually in the first year and then annually for the development of arthritis, which was defined as presence of one or more swollen joints at clinical examination. 18 prediction variables were selected based on clinical applicability, biologic plausibility, previous research and expert opinion. Backward stepwise Cox regression was used to create a prediction model (p removal 0.1). Regression

coefficients were rounded to half points to make a prediction rule. Scores were multiplied by 2 for easier clinical applicability. The diagnostic performance of the prediction rule was evaluated using the area under the curve (AUC) of ROC curves.

Results: Patients were followed for a median of 32 months (IQR: 13–48). 131 arthralgia patients (35%) developed arthritis after a median of 12 months (IQR: 6–23), of whom 121 (92%) were diagnosed with RA according to the 2010 ACR/EULAR criteria. The prediction model consisted of 9 variables: antibody status (double positive, or high titer aCCP confers higher risk), RA in a first degree family member, VAS pain over 50, presence of morning stiffness, arthralgia in both upper and lower extremities, duration of symptoms shorter than 12 months, presence of intermittent complaints, history of swollen joints as reported by the patient and alcohol non-use. The variables age, sex, smoking, NSAID use, symmetric symptoms, symptoms in small joints, tender joint count, CRP and Shared Epitope were excluded. Patients scored 0 to 12 points on the prediction rule. The AUC value of the prediction rule was 0.82 (95% CI: 0.75–0.89). According to Cox regression analysis with the prediction rule as categorical variable, patients could be categorized in three risk groups: low risk (0–4 points), intermediate risk (5–6 points) and high risk (7–12 points). 155 (41%) patients had low, 102 (27%) intermediate and 117 (31%) had high risk. The percentages of arthritis development per risk group are depicted in the figure. With the low risk group as a reference, the intermediate risk group had a hazard ratio (HR; 95% CI) of 4.3 (2.3–8.1) and the high risk group had a HR of 14 (7.7–25).

Survival per risk group
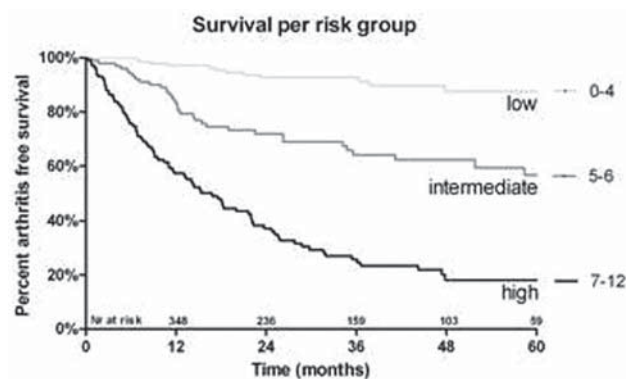
Conclusion: In patients who present with seropositive arthralgia, the risk of developing arthritis and subsequent RA can be predicted. The prediction rule that was made in this patient group can help 1) to inform patients and 2) to select high-risk patients for intervention studies before clinical arthritis occurs.

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Anemia May Provide Clinically Relevant Information Beyond Conventional Disease Activity Assessment to Predict Radiographic Damage Progression in Rheumatoid Arthritis. Burkhard Moller[1], Frauke Förger[2], Peter M. Villiger[3] and Axel Finckh[4]. [1]Inselspital University Hospital, Bern, Switzerland, [2]Inselspital University Hospital of Bern, Bern, Switzerland, [3]Inselspital-University Hospital of Bern, Bern, Switzerland, [4]Geneva University Hospitals, Geneva 14, Switzerland Burkhard Möller, Frauke Förger, Peter M. Villiger, Axel Finckh, on behalf of the Swiss Clinical Quality Management Program for Rheumatic Diseases.

Background/Purpose: Anemia in rheumatoid arthritis (RA) is prototypic for anemia of chronic disease (ACD) and often neglected in clinical practice. Previous studies have shown a relation between this extra-articular manifestation of RA and disease severity. Purpose: To study the relation between anemia and radiographic progression in RA.

Methods: This study is nested in a large prospective RA patient cohort. Data were collected between 1996 and 2007. Anemia was defined according to the WHO criteria (♀ Hb<12, ♂: Hb<13 g/dl). We also used one less (♀ Hb<12.2, ♂ 20–59y: Hb<13.7 g/dl, ♂ 60+y: Hb<13.2 g/dl) and one more severe definition of anemia (♀ Hb<11, ♂: Hb<12 g/dl) in sensitivity analyses. Erosions were assessed with a validated erosion score (Ratingen score) of 38 joints at hands and feet in 11255 radiograph sets from 4005 RA patients, over a mean follow-up of 2.2 years. Radiographic progression was

analyzed using longitudinal regression models for repeated data and adjusted for potential confounding factors, such as age, gender, rheumatoid factor, disease duration and erosion score at inclusion, baseline and time dependent DAS28$_{ESR}$, DMARD, glucocorticoid and anti-TNF therapy. Subgroup analyses were performed in patients starting on methotrexate (n=728) or anti-TNF-therapy (n=938), in patients achieving different stages of severe, moderate, mild disease activity or remission (DAS28$_{ESR}$<2.6, n=1253) at the final visit, and in 508 patients achieving remission after TNF blockade.

Results: Erosions progressed significantly (p<0.001) faster in patients with than without anemia, despite adjusting for clinical disease activity and other important predictors of joint damage. As an example, erosion had progressed by mean 1.36% (95% CI 1.21–1.51) in non-anemic versus 2.66% (2.17–3.14) in anemic patients after one year. Patients with less severe anemia had a less rapid and patients with more severe anemia displayed a more rapid joint damage progression, suggesting a 'dose response effect'. Effect modification by anemia went insignificant in subgroups of patients with persistent clinically detectable disease activity, but remained a significant factor for more rapid erosive progression in patients achieving remission upon any treatment (p<0.001) or upon anti-TNF-therapy (p<0.001).

Conclusion: Anemia appears to capture structural disease processes that remain unmeasured by conventional disease activity measures in patients with or without TNF blockade. Thus, anemia may help to identify patients with more rapid erosive disease.

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Patients with Early Inflammatory Arthritis Who Fulfil the 2010 American College Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis Have Increased Mortality Compared to Those Who Do Not: Results From the Norfolk Arthritis Register.
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Background/Purpose: Mortality is increased in rheumatoid arthritis (RA) in comparison with the general population. The majority of studies have used the 1987 ACR criteria to define RA when investigating mortality. The aims of this study were (i) to examine whether, in a cohort of patients with early inflammatory polyarthritis (IP), the 2010 ACR/EULAR classification criteria for RA identify those with decreased survival; and if this is the case (ii) to identify which components of these criteria are the strongest predictors of mortality.

Methods: Consecutive adults with ≥2 swollen joints for ≥4 weeks were recruited to the Norfolk Arthritis Register (NOAR) between 1990 and 2009. Patients included in this analysis had symptom duration ≤2 years and had not received any disease modifying therapy at initial assessment. Data on the components of the 2010 criteria, along with demographic details, were obtained at baseline visit through a nurse-administered questionnaire and joint examination. Patients also completed the health assessment questionnaire (HAQ). Bloods samples were taken for C-reactive protein (CRP), rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) estimation. All patients registered with NOAR are flagged with the UK Office for National Statistics (ONS) who provide mortality data. Survival analyses were performed using Cox proportional hazards models univariately, then adjusting for age and sex. A multivariate model was then developed including all components of the 2010 criteria as well as baseline smoking status, age and gender.

Results: 1671 patients had complete data for analysis, with 20488 person-years follow up. 1092 (65%) patients were female and there were 471 (28%) deaths reported by the ONS by 31st December 2011. 905 (54%) patients fulfilled the 2010 criteria at baseline, and these patients had a significantly increased risk of death compared to those patients in NOAR who did not fulfil the 2010 criteria, both univariately and in the age and sex

adjusted model, hazard ratio(HR) 1.39 (95% CI 1.15–1.68). Results of the Cox regression models for the different parameters are shown in the table. High titre antibody positivity (more than three times the upper limit of normal) was the strongest predictor of mortality in the multivariate model adjusted for all components of the 2010 criteria, age, sex, and smoking status (HR 1.64 (95% CI 1.34 – 2.01)).

Table 1. Predictors of mortality in the 2010 ACR/EULAR classification criteria for RA

	n (%)	Univariate HR	Univariate 95% CI	Age & sex adjusted HR	Age & sex adjusted 95% CI	Multivariate HR	Multivariate 95% CI
Satisfy 2010 criteria: No	766 (46)	ref	–	ref	–	–	–
Yes	905 (54)	1.56	1.29–1.88	1.39	1.15–1.68	–	–
Joint score 0	173 (10)	ref	–	ref	–	ref	–
Joint score 1	77 (5)	1.09	0.63–1.91	1.31	0.75–2.31	1.55	0.88–2.75
Joint score 2	372 (22)	1.15	0.77–1.74	1.19	0.79–1.79	1.29	0.85–1.95
Joint score 3	357 (21)	1.62	1.09–2.40	1.33	0.90–1.98	1.36	0.92–2.03
Joint score 5	692 (41)	1.60	1.11–2.32	1.42	0.98–2.06	1.40	0.96–2.04
RF/ACPA negative	1086 (65)	ref	–	ref	–	ref	–
RF/ACPA low positive	171 (10)	1.02	0.72–1.45	0.93	0.66–1.33	0.90	0.64–1.28
RF/ACPA high positive	414 (25)	1.84	1.51–2.23	1.75	1.44–2.13	1.6	1.31–1.97
Normal CRP	743 (45)	ref	–	ref	–	ref	–
Abnormal CRP	928 (56)	2.04	1.68–2.46	1.39	1.15–1.69	1.25	1.02–1.52
Disease duration: 6 weeks	88 (5)	ref	–	ref	–	ref	–
≥6 weeks	1583 (95)	0.86	0.60–1.25	0.88	0.61–1.28	0.84	0.58–1.22

Conclusion: In patients presenting with early inflammatory polyarthritis, those who fulfil the 2010 criteria have significantly increased mortality compared to those who did not. The components of the 2010 criteria which appear to be important predictors of mortality are high titre RF or ACPA positivity, and abnormal CRP at baseline.

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An Easy to Use Referral Model for Arthritis From the Rotterdam Early Arthritis Cohort.
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Background/Purpose: The first hurdle general practitioners (GPs) face to identify Rheumatoid Arthritis(RA) is to recognize presence of arthritis. Due to the low incidence of arthritis in primary care it is challenging to differentiate between patients with inflammatory musculoskeletal disease and those without. We set out to create a referral model to aid early referral in primary care based on data from the REACH.

Methods: The REACH cohort includes patients with either arthritis or 2 painful joints with 2 additional inflammatory characteristics. Four hundred and one patients referred to REACH by their GPs were used in this analysis. A prediction model was build by selection of variables from the history, physical examination and laboratory values that were likely available to GPs. The presence of at least one joint with synovitis was used as outcome excluding patients with gout. Variable selection was performed by classifying variables in 8 categories: symptoms, duration of complaints, life style, family history, comorbidity, medication use and systemic complaints (fever, skin disorder) followed by logistic regression with backward selection in each category. A referral model was build with the variables with p<0.1 evaluated in a logistic regression model that was bootstrapped 200 times to elicit the for optimism corrected c-statistic. Performance was also evaluated using ROC-curves and calibration plots. The addition of blood markers to the simple model was also evaluated.

Results: Table 1 shows baseline characteristics for the 401 patients. Arthritis was present at baseline in 182 patients. The referral model based on the REACH data resulted in a model containing the following variables: age, female sex, problems with fitting shoes, self-reported limitation of joint movement, lower number of self-reported painful joints, higher number of self-reported swollen joints, self-reported redness or hot/warm joints, the presence of squeeze pain in hand or feet and delay in presenting to the GP. The AUC was 0.79 (corrected for optimism: 0.72), adding ESR resulted in an AUC of 0.80 and adding RF resulted in 0.81. The simplest model calibrated slightly better (fig 1).

Table 1. baseline characteristics

	case, n=182	non case, n=219		
age (mean, SD)	51 (15)	47 (12)	p<0.05	
gender (%)	69%	66%	p<0.05	
duration of complaints (median, range)	68 (4–370)	122 (1–416)	p<0.05	
delay patient (median, range)	21 (0–328)	43 (0–361)	p<0.05	
tender joint count (median, range)	7 (0–34)	6 (0–38)	ns	
rheumatoid factor positive (%)	25%	11%	p<0.05	
anti-CCP positive (%)	17%	6%	p<0.05	*
ESR (median, range)	18(2–100)	8(0–66)	p<0.05	@
C-reactive proteine (median, range)	6 (1–180)	3 (1–55)	p<0.05	#
Diagnosis RA	0%	29%	p<0.05	$

*n=30 missing, @ n=63 missing, # n=92 missing, $ n=47 missing.

ROC / Calibration
1a Model 1 — Model 1
Model 2
1c Model 3 — Model 3
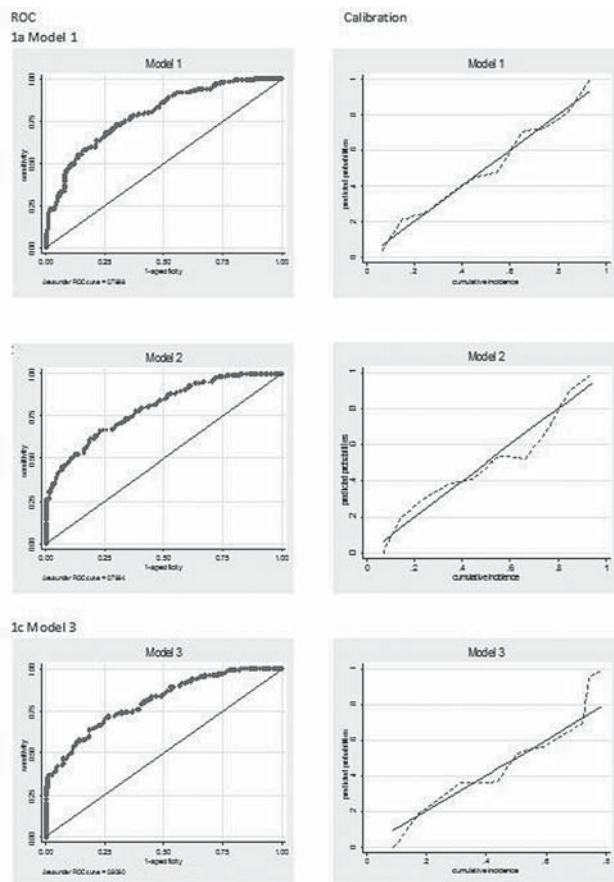
Conclusion: We were able to create a referral model based on history taking and physical examination suitable for referral of patients with arthritis at risk for RA and perhaps other inflammatory diseases in primary care. Adding laboratory values did not improve performance and thus may be omitted based on the resources of the primary care facility.

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2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria Predicts Radiogical, but Not Clinical Outcomes At 18 Months Into Disease in a Canadian Early Arthritis Cohort. Ariel Masetto[1], Arthur J. Fernandes[2], Patrick Liang[3], Pierre Cossette[2] and Gilles Boire[4]. [1]CHUS, Fleurimont, QC, [2]Universite de Sherbrooke, Sherbrooke N, [3]CHUS, Sherbrooke, QC, [4]CHUS - Sherbrooke University, Sherbrooke, QC

Background/Purpose: The potential of the 2010 ACR/EULAR rheumatoid arthritis (RA) classification criteria to discriminate early arthritis patients according to their clinical and radiological outcomes needs to be confirmed.

Methods: Consecutive patients with at least 3 swollen joints (SJC≥ 3) were recruited; duration of disease was more than 1 and less than 12 months; microcrystalline arthritides and connective tissue diseases were actively excluded. All patients were treated with the target of SJC= 0, using whatever DMARDs was required. According to the 2010 RA criteria, our cohort was classified in two groups: RA and non-specific inflammatory arthritis (NSIA). Both groups were compared at baseline and at 18 months into disease according to radiological and clinical outcomes: Sharp erosion score (classified erosive if ≥ 3), Health Assessment Questionnaire (HAQ), Disease Activity Score in 28 joints (DAS28-CRP), and pain (0–100 mm VAS). Remission rates at 18 months were calculated based on DAS 28 and ACR 2011 remission criteria.

Results: A total of 422 patients were available at baseline. Of these, 319 (75.6%) were classified as RA. Based on clinical outcome measures, RA patients had more severe disease than NSA patients at baseline (higher DAS 28, HAQ and pain scores measures – p<0.001). At 18 months, this initial clinical discrepancy had now disappeared, but more RA patients had progressed to erosive status than NSIA patients (54% vs 33%; p<0.001). Using two different definitions of remission, there was no difference in remission rates.

	Rheumatoid arthritis (2010 ACR/EULAR criteria) mean (median)	Non specific inflammatory arthritis mean (median)	P value
Baseline			
HAQ	0.95 (0.875)	0.625 (0.5)	P<0.001
DAS 28 - CRP	5.53 (5.58)	4.61 (4.57)	P<0.001
Pain	59.2 (61)	47.3 (47)	P<0.001
18 months			
HAQ	0.38 (0.25)	0.38 (0.125)	P=0.717
DAS 28 - CRP	2.47 (2.84)	2.64 (2.33)	P=0.238
Pain	29.0 (24)	31.4 (23)	P=0.485
Sharp erosion score	5.67 (3.0)	3.14 (1.0)	P=0.002
Remission at 18 months			
DAS 28 – CRP	53%	58.6%	P=0.316
ACR 2011	16%	18.8%	P=0.964

Conclusion: In this early arthritis cohort actively treated to SJC= 0, there was no difference in the 18-month clinical outcomes (HAQ, DAS 28, Pain, Remission rates) between 2010 ACR/EULAR criteria-defined RA and NSIA patients. Patients with RA had a worse radiological outcome, but significant joint damage occurred in one third of NSIA patients. Early intensive treatment of NSIA patients, and not only of early RA patients, thus appears warranted.

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Is Late Onset Rheumatoid Arthritis (LORA) Really a Distinct Entity of RA? Results From the Swiss Observational Cohort. Ruediger Mueller[1], Toni Kaegi[1], Axel Finckh[2] and Johannes von Kempis[1]. [1]MD, St. Gallen, Switzerland, [2]Geneva University Hospitals, Geneva 14, Switzerland

Background/Purpose: Rheumatoid arthritis (RA) is generally described as a disease with two peaks of onset, either late (late onset RA, LORA) or early (young onset RA, normal 30–55 years, YORA). Considering that the average age of the population is continuously rising, LORA will gain importance in the near future. Despite this growing importance LORA has not been the focus of much interest in the past. This study was set up to analyse disease activity and progression in LORA in comparison to YORA patients with early disease.

Methods: This is a cohort study within the Swiss RA registry SCQM. We included all patients with recent onset arthritis, either RA (disease duration ≤1 year) or undifferentiated, as diagnosed by the data-entering physician. Patients were followed up to 5 years. The cut off between YORA and LORA was operationally set at 60 years of age. Disease progression and activity was assessed based on DAS 28 and the progression of joint erosions using the Ratingen score.

Results: A total of 592 patients with early undifferentiated or RA was analysed. The age at disease onset had a Gaussian distribution, with a single peak at 60 years of age. 366 patients were 60 years or younger (YORA) and 226 patients were older (LORA) at disease onset. DAS 28

scores were significantly higher among LORA as compared to YORA patients (4.8 vs. 4.5, p = 0.049). Corticosteroids were used in 68% of LORA patients as a first line treatment, compared to 25.4% in YORA patients (X^2 test, p < 0.0001). DMARDs, on the other hand, were used in 100% of the YORA patients as first line treatment compared to 91.2% of the LORA patients. During follow up, new glucocorticoid, synthetic, or biologic DMARD were initiated in 32.8%/61.1%/14.1% of all decisions documented among YORA patients and 17.5%/54.6%/6.6% in LORA patients (X^2 test, all p < 0.0001). The DAS28 scores decreased in both groups over the observed time period, and the initial differences in disease activity vanished after 1/2 year and during the subsequent follow up. The Ratingen score was higher in LORA than in YORA patients at inclusion (12.7 vs. 5.6, p < 0.0001). The rate of radiological progression at 5 years was similar comparing LORA and YORA (3.3 vs. 2.6, resp., p=0.64). The level of Ratingen scores at onset and during follow up over 5 years did not clearly separate LORA and YORA into two groups), but rather increased linearly when comparing the patients in groups per decade from 20 to 92 years of age.

Conclusion: Our results do not support the existence of a separate LORA subgroup with a distinct peak of incidence and/or course of the disease.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Comparative Efficacy and Novel Treatment Strategies in Rheumatoid Arthritis
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Discontinuation of Adalimumab without Functional and Radiographic Damage Progression After Achieving Sustained Remission in Patients with Rheumatoid Arthritis (the HONOR study): 1-Year Results. Yoshiya Tanaka, Shintaro Hirata, Shunsuke Fukuyo, Masao Nawata, Satoshi Kubo, Kunihiro Yamaoka and Kazuyoshi Saito. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background/Purpose: Discontinuing anti-TNF therapy after achieving a stable low disease activity (LDA) or remission (REM) state in rheumatoid arthritis (RA) has become an important area of investigation in current rheumatology from the risk-benefit point of view including health-economic considerations. However, there is little information about characteristics of patients in which adalimumab (ADA) can be successfully discontinued in patients with long-standing RA. REM induction was aimed with ADA plus methotrexate (MTX) at patients with long-standing RA encountered during routine clinical practice. In the present HONOR study, we investigated whether the resultant remission was preserved for at least 12 months after discontinuing ADA.

Methods: Sustained REM was defined as persistent DAS28-ESR<2.6 achieved for at least 6 months. Patients with age >18 years who had attained the sustained REM with ADA plus MTX went on ADA discontinuation with their consent and those with follow-up of ≥12 months become subject to evaluation. The primary endpoint was a proportion of patients who maintained the sustained REM for at least another 12 months after the discontinuation. DAS28, SDAI, CDAI, HAQ-DI and DmTSS were analyzed before and after discontinuation of ADA. To predict retaining REM even after withdrawing ADA, a logistic regression/ROC analysis was conducted on clinical variables and cut-off values at the discontinuation were determined.

Results: Of the 197 patients who initiated ADA treatment between July 2008 and April 2011, 69 (35.0%) met the criteria of sustained REM. Fifty-one out of the 69 patients consented to enter the study. The mean age of the 51 patients was 59.5 years with the mean disease duration of 7.1 years. Thirty-six percent of evaluable 42 patients maintained ADA-free remission (DAS28-ESR<2.6) for 12 months. DAS28-ESR at discontinuation was found to be significantly predicting the retention of remission with a cut-off value of 1.98.

ADA-free remission as defined by SDAI ≤3.3 was also maintained for 12 months in 19 (49%) of the 42 patients. A vast majority of patients (94.9%) showed no evidence of radiographic progression at 12 months. Moreover, mean functional improvement observed at the time of ADA discontinuation was almost preserved for 12 months.

Conclusion: Although the sample size is limited, the results of the HONOR study indicated that after reaching REM with ADA plus MTX 36% (DAS28-ESR) and 49% (SDAI) patients could discontinue ADA for ≥12 months without functional impairment and radiographic damage progression. Deep remission at discontinuation was associated with successful biologic-free remission. Hence, "Treatment holiday" of biologics by discontinuing ADA is now feasible in patients with RA following sustained remission.

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Tocilizumab Monotherapy Compared with Adalimumab Monotherapy in Patients with Rheumatoid Arthritis: Results of a 24-Week Study. Arthur Kavanaugh[1], Paul Emery[2], Ronald F. van Vollenhoven[3], Ara H. Dikranian[4], Rieke Alten[5], Micki Klearman[6], David Musselman[6], Sunil Agarwal[6], Jennifer Green[7] and Cem Gabay[8]. [1]UCSD School of Medicine, La Jolla, CA, [2]University of Leeds, Leeds, United Kingdom, [3]Karolinska Institute, Stockholm, Sweden, [4]San Diego Arthritis Medical Clinic, San Diego, CA, [5]Schlosspark Klinik, University Medicine Berlin, Berlin, Germany, [6]Genentech Inc, South San Francisco, CA, [7]Welwyn Garden City, United Kingdom, [8]Geneva University Hospitals, Geneva, Switzerland

Background/Purpose: Approximately one-third of RA pts treated with biologics receive them as monotherapy (ie, without other DMARDs).[1–3] Although tocilizumab (TCZ), an IL-6 receptor inhibitor, has been assessed as monotherapy in 6 trials,[4–9] direct comparison with an anti-TNF agent as monotherapy has not occurred. ADACTA is the first trial specifically designed to determine superiority of one approved biologic vs another (TCZ vs adalimumab [ADA]) as monotherapy for RA.

Methods: ADACTA was a phase 4 randomized, double-blind, 24-wk study in pts with RA of ≥6-mo duration and DAS28 >5.1 who were MTX intolerant or for whom continued treatment with MTX was considered ineffective or inappropriate. Pts received TCZ 8 mg/kg IV every 4 wks (+ placebo [PBO] ADA) or ADA 40 mg SC every 2 wks (+ PBO TCZ) for 24 wks. Primary endpoint was mean change from baseline (BL) in DAS28 at 24 wks.

Results: The ITT population included 325 pts (163, TCZ; 162, ADA). BL characteristics were similar between the TCZ and ADA arms: mean age (54.4 and 53.3 y), mean RA duration (7.3 and 6.3 y), and mean DAS28 (6.72 and 6.76). At wk 24, mean change from BL in DAS28 was significantly greater with TCZ than with ADA ($p<0.0001$; Table). Statistically significantly greater proportions of TCZ than ADA pts achieved DAS28 <2.6, DAS28 ≤3.2, and ACR20/50/70 responses ($p<0.005$; Table). A difference in favor of TCZ was observed in proportions of pts achieving Clinical Disease Activity (CDAI) and Simplified Disease Activity (SDAI) Index remission (≤2.8 and ≤3.3) at wk 24 (post hoc analysis; $p<0.05$; Table). From wk 16 onward, the proportion of pts achieving ACR/EULAR remission (Boolean: SJC ≤1, TJC ≤1, CRP ≤1 mg/dL, pt global VAS ≤10) was numerically greater with TCZ, and by wk 24 it reached 18% compared with 11% for ADA. For exploratory endpoints HAQ-DI, SF-36 MCS, SF-36 PCS, and FACIT Fatigue, differences in mean change from BL at wk 24 were numerically higher for TCZ than ADA. Incidences of AEs, serious AEs, and serious infection were similar between arms (TCZ, 82.1%/11.7%/3.1%; ADA, 82.7%/9.9%/3.1%). Transaminase and LDL elevations and neutrophil count reductions were more common with TCZ. Two deaths occurred in the TCZ arm: 1 due to sudden death, the other due to reported illicit drug overdose.

Table. Selected Endpoints at Week 24 (ITT population[a])

	TCZ, n = 163	ADA, n = 162	p[b]
Primary: change from BL in DAS28	−3.3[c]	−1.8 (diff:−1.5)	<0.0001
Secondary efficacy endpoints			
DAS28 <2.6, %	39.9	10.5	<0.0001
DAS28 ≤3.2, %	51.5	19.8	<0.0001
ACR20, %	65.0	49.4	0.0038
ACR50, %	47.2	27.8	0.0002
ACR70, %	32.5	17.9	0.0023
Exploratory and post hoc efficacy endpoints			
CDAI remission, %	17.2	9.3	0.0389[d]
SDAI remission, %	18.4	8.0	0.0067[d]
ACR/EULAR remission (Boolean), %	18.0	11.0	0.0569[d]
Change from BL in HAQ-DI	−0.7	−0.5 (diff:−0.2)	0.0653[d]

[a]Last-observation-carried-forward and nonresponder imputation were applied to primary and secondary continuous and categorical endpoints, respectively, to handle missing data and data after withdrawal and escape.
[b]p values were adjusted for region and duration of RA for all endpoints. In addition, when evaluating changes from baseline, p values were adjusted for baseline values of the analyzed parameter.
[c]Two pts in the TCZ arm with no post-baseline data were excluded from the primary endpoint analysis.
[d]p value was not adjusted for multiple testing and controlling of type 1 error; therefore, no statistical significance claims can be made.

Conclusion: TCZ as monotherapy was superior to ADA as monotherapy in reducing RA signs/symptoms in MTX-intolerant pts or pts for whom MTX was considered ineffective or inappropriate. The overall AE profiles of the two agents were similar, and lab changes were consistent with previous reports.

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Remission Rates with Tofacitinib Treatment in Rheumatoid Arthritis: A Comparison of Various Remission Criteria.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. This analysis evaluated the rates of remission across five tofacitinib Phase 3 RA trials based on various established and new remission criteria including the ACR/EULAR criteria.

Methods: We analyzed the data from five Phase 3 RA trials of tofacitinib monotherapy (ORAL Solo) or tofacitinib with background DMARD (ORAL Step, Scan, Sync and Standard) and compared remission rates as defined by various remission criteria: a) DAS28-4(ESR) <2.6 (co-primary endpoint in all five Phase 3 studies); b) DAS28-3(CRP) <2.6; c) CDAI ≤2.8; d) index-based ACR/EULAR criteria (SDAI ≤3.3); and e) Boolean-based ACR/EULAR criteria.[1] Remission rates were calculated under each set of criteria for each treatment sequence: tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, placebo (PBO) to 5 mg BID, and PBO to 10 mg BID; PBO sequences were pooled. ORAL Standard also included adalimumab 40 mg sc every 2 weeks as an active control. All trials had an initial PBO period of 3 or 6 months. Here, 3-month LOCF data are presented to illustrate results.

Results: Despite the short treatment duration, rates of remission were 5–30% with tofacitinib treatment (Table). Remission rates were numerically greater for both tofacitinib doses versus placebo, and rates for tofacitinib 10 mg BID were generally greater than with 5 mg BID. Across trials, the DAS28-3(CRP)-based criteria generated markedly higher remission rates compared with other remission criteria.

Table. Remission rates[a] across Phase 3 trials at Month 3

Phase 3 trial	Treatment (N)	DAS28-4(ESR) <2.6	DAS28-3(CRP) <2.6	CDAI ≤2.8	SDAI ≤3.3	Boolean ACR/EULAR
ORAL Solo	Tofacitinib 5 mg BID (241)	5.6	19.1	5.8	5.4	5.0
	Tofacitinib 10 mg BID (242)	9.0	24.8	8.3	9.1	7.4
	PBO (120)	4.5	6.7	1.7	1.7	1.7
ORAL Step	Tofacitinib 5 mg BID (132)	6.7	21.2	6.1	6.8	6.8
	Tofacitinib 10 mg BID (133)	10.4	27.8	7.5	9.0	5.3
	PBO (131)	1.7	4.6	0.8	0	0
ORAL Scan	Tofacitinib 5 mg BID (309)	5.3	21.4	5.8	5.8	4.5
	Tofacitinib 10 mg BID (309)	11.7	28.2	5.5	5.8	7.4
	PBO (154)	1.6	5.2	0	0	0
ORAL Sync	Tofacitinib 5 mg BID (311)	10.0	22.2	5.5	5.8	5.1
	Tofacitinib 10 mg BID (309)	11.2	25.6	7.1	7.1	5.8
	PBO (157)	1.4	5.1	0	0	1.3
ORAL Standard	Tofacitinib 5 mg BID (196)	5.6	15.3	4.6	4.1	2.0
	Tofacitinib 10 mg BID (196)	6.8	18.9	6.1	7.1	5.6
	Adalimumab 40 mg sc Q2W (199)	4.5	14.1	2.5	4.0	2.0
	PBO (106)	2.2	4.8	1.9	1.9	2.8

[a]Last observation carried forward; rates are percentages of patients achieving the respective outcome

Conclusion: Tofacitinib was effective in reaching treatment target[2–4] and inducing remission after 3 months of treatment using various established and new remission criteria including the ACR/EULAR index- and Boolean-based criteria. Remission rates were generally greater with tofacitinib 10 mg BID compared with 5 mg BID.

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A CD4+ T-Cell Gene Expression Signature Predicts Drug Survival On Methotrexate Monotherapy in Early Rheumatoid Arthritis. Arthur G. Pratt[1], Philip M. Brown[1], Simon J. Cockell[2], Gillian Wilson[3] and John D. Isaacs[4]. [1]Newcastle University, Newcastle Upon Tyne, United Kingdom, [2]Newcastle University, Newcastle-upon-Tyne, United Kingdom, [3]Freeman Hospital, Newcastle-upon-Tyne, United Kingdom, [4]Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University and Newcastle upon Tyne NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom

Background/Purpose: The mechanism of action of methotrexate (MTX) in the management of rheumatoid arthritis (RA) remains incompletely understood. It is nonetheless capable of inducing clinical remission as a monotherapy in approximately 30% of cases, being the most cost-effective therapeutic choice in such individuals. We investigated the CD4+ T-cell transcriptome in early RA patients, seeking biomarkers for drug survival on MTX monotherapy and associated pharmacological insights.

Methods: RNA was extracted from highly purified peripheral blood CD4+ T-cells from consenting early RA patients within 4 hours of blood draw, at which time patients had been symptomatic for a median of 12 weeks, and were naïve to immunomodulatory treatments. All patients were subsequently treated with MTX monotherapy, which was continued for as long as this treatment was deemed successful between patient and consulting rheumatologist, over an 18 month follow-up period. Intramuscular steroid bolus administration (but not oral steroid therapy) was permitted during the study at the discretion of the consulting rheumatologist. Transcriptional profiling of baseline samples was undertaken using Illumina WG6v3 BeadChip oligonucleotide array technology and analysed using GeneSpring XI (Agilent).

Results: Of 37 recruited patients, 6 were excluded from analysis because of insufficient or defaulted follow-up. Amongst the remaining 31 patients, 19 (61%) remained on MTX monotherapy at the end of follow-up, but the treatment strategy was unsuccessful (and required modification) for the remaining 12 (39%). Baseline characteristics and final methotrexate doses were comparable between the two groups. 133 CD4+ T-cell transcripts were identified as being differentially expressed between comparator groups at baseline (>1.2 fold-change; p<0.05) and, amongst these, functional analysis identified an over-representation of genes involved in apoptosis (11/133 genes; hypergeometric p=0.000045).
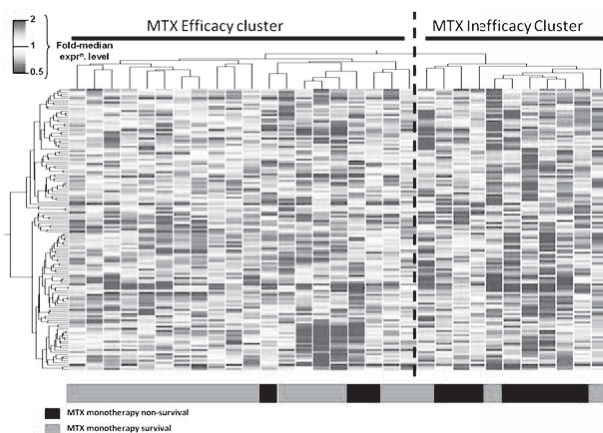
Conclusion: Our pilot study has identified potential transcriptional biomarkers for drug survival on MTX monotherapy amongst early RA patients which, alongside their potential clinical applicability, suggest that the efficacy of this treatment may depend on its ability to regulate CD4+ T-cell survival pathways. Validation amongst a clinically well-characterised, independent early RA cohort is now on-going.

Disclosure: A. G. Pratt, None; **P. M. Brown**, None; **S. J. Cockell**, None; **G. Wilson**, None; **J. D. Isaacs**, None.

Long-Term Outcomes of Early Rheumatoid Arthritis Patients Initiated with Adalimumab Plus Methotrexate Compared with Methotrexate Alone Following a Targeted Treatment Approach. Roy Fleischmann[1], Ronald F. van Vollenhoven[2], Josef S. Smolen[3], Paul Emery[4], Stefan Florentinus[5], Suchitrita S. Rathmann[6], Hartmut Kupper[7] and Arthur Kavanaugh[8]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Karolinska Institute, Stockholm, Sweden, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [4]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [5]Abbott, Rungis, France, [6]Abbott, Abbott Park, IL, [7]Abbott GmbH and Co. KG, Ludwigshafen, Germany, [8]UCSD School of Medicine, La Jolla, CA

Background/Purpose: In rheumatoid arthritis (RA), anti-TNF therapy is considered following 3–6 months of failed methotrexate (MTX) treatment. Some patients (pts), particularly those with many risk factors, may benefit from earlier intervention with anti-TNF+MTX, as this combination maximizes the likelihood of response. This analysis assessed, on a group level, whether there is a long-term advantage for early RA pts treated with initial and continued adalimumab (ADA)+MTX vs those treated with initial placebo (PBO)+MTX and who either continued unaltered therapy or rapidly added ADA following an inadequate response (IR).

Methods: OPTIMA was a 78-week (wk), phase 4, randomized, controlled trial of initial ADA+MTX vs PBO+MTX in MTX-naïve pts ≥18 years, <1 year disease duration, and active RA. Therapy adjustments were made at wk 26 on the basis of achieving a target of stable low disease activity [LDA, defined for this study as DAS28(CRP) <3.2] at wks 22 and 26 (Period 1, P1): ADA+MTX-responders (R) were re-randomized to either withdraw or continue ADA (ADA Withdrawal and Continuation arms, respectively) and PBO+MTX-R continued randomized therapy (MTX Continuation arm) for an additional 52 wks (P2); IR-pts received open-label (OL) ADA+MTX during P2 (OL ADA Carry On and Rescue ADA arms). This post hoc analysis evaluated the proportion of pts who entered P2 and were in LDA, had normal function (HAQ-DI <0.5), and/or the absence of radiographic progression (ΔmTSS ≤0.5) at wk 78 by initial treatment group (ie, the ADA+MTX group includes ADA Withdrawal, Continuation, and OL Carry On arms; the PBO+MTX group includes MTX Continuation and Rescue ADA arms). To account for the full population of P1 ADA+MTX-R, those who withdrew ADA during P2 were replaced by an equivalent proportion of R from the ADA Continuation arm.

Results: Among pts who entered P2 (ADA+MTX, N=466; PBO+MTX, N=460), significantly more were in LDA, had normal function, and/or the absence of radiographic progression following 26 wks of treatment with ADA+MTX vs PBO+MTX (**Table**). Differences in clinical and functional outcomes between initial treatment groups disappeared following an additional 26 or 52 wks of treatment, during which time PBO+MTX-IR (n=348) were switched to OL ADA+MTX. Although the addition of OL ADA to PBO+MTX-IR slowed radiographic progression during P2, more pts who received ADA+MTX from baseline had no radiographic progression at wk 78 than pts who received initial PBO+MTX.

Table. Week 26, 52, and 78 Clinical, Functional, and Radiographic Outcomes in Patients Who Received Continued ADA + MTX Versus Those Who Continued PBO + MTX or Added Open-label ADA Following an Inadequate Response

Outcome	ADA + MTX, n/N (%)[a]			PBO + MTX, n/N (%)[b]		
	Wk 26	Wk 52	Wk 78	Wk 26	Wk 52	Wk 78
DAS28(CRP) <3.2[c]	246/466 (53)	304/465 (65)	303/465 (65)	139/460 (30)***	284/460 (62)	300/460 (65)
HAQ-DI <0.5[c]	211/466 (45)	220/466 (47)	224/466 (48)	150/460 (33)***	203/460 (44)	208/460 (45)
ΔmTSS ≤0.5[d]	402/462 (87)	379/445 (86)	382/443 (86)	330/459 (72)***	318/440 (72)***	318/440 (72)***
DAS28(CRP) <3.2[c] + ΔmTSS ≤0.5[d]	216/462 (47)	260/443 (59)	266/443 (60)	112/459 (24)***	196/440 (45)	211/440 (48)***
DAS28(CRP) <3.2[c] + HAQ-DI <0.5[c] + ΔmTSS ≤0.5[d]	146/462 (32)	168/443 (38)	174/443 (39)	82/459 (18)***	120/440 (27)***	135/440 (31)**

[a]Includes patients from the ADA Continuation (n = 105) and OL ADA Carry On (n = 259) arms, as well as the proportional equivalent number of responders from the ADA Withdrawal arm (n = 102).
[b]Includes patients from the MTX Continuation (n = 112) and Rescue ADA (n = 348) arms.
[c]Last observation carried forward.
[d]Multiple imputations.
*** and ** for P <0.001 and <0.01, respectively, for differences between initial treatments from chi-square.
ADA, adalimumab; MTX, methotrexate; PBO, placebo; Wk, week; DAS28(CRP), 28-joint disease activity score with C-reactive protein; HAQ-DI, disability index of the health assessment questionnaire; ΔmTSS, change in modified Total Sharp score.

Conclusion: Early RA pts treated with PBO+MTX were able to achieve comparable long-term clinical and functional outcomes on a group level to those who began treatment with the combination of ADA+MTX, but only if therapy was optimized by the addition of ADA in PBO+MTX-IR. Still, continued ADA+MTX therapy conferred a radiographic benefit over 78 wks, although the difference did not appear to translate to an additional functional benefit.

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A Multicenter, Randomized, Controlled, Open-Label Pilot Study of the Feasibility of Discontinuation of Adalimumab in Rheumatoid Arthritis Patients in Stable Clinical Remission. Katerina Chatzidionysiou[1], Carl Turesson[2], Annika Teleman[3], Ann Knight[4], Elisabet Lindqvist[5], Per Larsson[6], Lars Cöster[7], Barbro Rydberg[8], Ronald F. van Vollenhoven[9] and Mikael Heimbürger[10]. [1]Karolinska Institute, Stockholm, Sweden, [2]Lund University, Malmö, Sweden, [3]Department of Rheumatology, Spenshult Hospital, Oskarstrom, Sweden, [4]Institution for Medical Sciences, Uppsala University, Uppsala, Sweden, [5]Section for Rheumatology Lund University, Lund, Sweden, [6]Karolinska University Hospital, Stockholm, Sweden, [7]University Hospital, Linköping, Sweden, [8]Kärnsjukhuset, Skövde, Sweden, [9]The Karolinska Institute, Stockholm, Sweden, [10]Abbott Scandinavia, Stockholm, Sweden

Background/Purpose: Treatment with TNF blockers, once started as therapy for RA, is usually continued indefinitely. Information about the possibility to discontinue anti-TNF therapy in RA patients who have obtained remission is limited. If remission could be sustained after cessation of anti-TNF therapy, this would have vast clinical as well as economic implications. The objective of the ADMIRE trial was to assess the possibility of discontinuing adalimumab treatment while maintaining remission in RA patients in stable remission (DAS 28<2.6 for ≥3 months) on combination therapy with adalimumab + methotrexate (MTX).

Methods: A randomized, controlled, open label pilot study of RA patients in stable remission treated with adalimumab + MTX. Patients were randomized in a 1:1 ratio to continue with adalimumab + MTX (arm AM) or to discontinue the biologic agent and continue with MTX monotherapy (arm M) for 52 weeks. Flare was defined as DAS28>2.6 or an increase in DAS28 (DeltaDAS28) of more than 1.2 from baseline at any time. Patients in arm M with a flare restarted adalimumab. The primary endpoint was the proportion of patients in remission at week 28 in both arms. Nonresponder imputation (ie, "flare" imputed) was performed for patients with no available DAS28 at week 28 (this included most patients who had a flare in the M group and restarted adalimumab).

Results: Thirty-three patients were enrolled in the study and were randomized to arm AM (n=17) and arm M (n=16). One patient in arm AM was excluded (did not fulfill inclusion criteria) and one patient in arm M was excluded due to protocol violation. The median (IQR) age of patients was 61 (53–65) years, median (IQR) disease duration was 8 (5–15) years and 67% were female. Median (IQR) DAS28 was 1.86 (1.53–2.39) and MTX dose was 20 mg/w (12.5–20) at baseline. At the end of 28 weeks, 15/16 patients (94%) and 5/15 patients (33%) in arms AM and M, respectively, were in remission (P=0.001). In the M group, 3/15 patients were in remission on MTX only. The proportion of patients with a flare during the first 28 weeks in the AM and M arms was 50% (8/16) and 80% (12/15), respectively (P=0.08). The number of patients in the AM and M arms with at least one DeltaDAS28>1.2 during the first 28 weeks was 1/16 (6%) and 8/15 (53%), respectively (P=0.005). Other results from secondary analyses are shown in Table 1.

Table 1. Primary and secondary efficacy endpoints.

Outcome	Arm AM (adalimumab + MTX) n=16	Arm M (MTX) n=15	Difference between groups*
No. (%) of patients in remission at week 28	15/16 (94%)	5/15 (33%)	0.001
No. (%) of patients with at least 1 flare during first 28 weeks	8/16 (50%)	12/15 (80%)	0.08
No. (%) of patients with at least 1 DAS28>2.6 during first 28 weeks	8/16 (50%)	11/15 (73%)	0.2
No. (%) of patients with at least 1 DeltaDAS28>1.2 during first 28 weeks	1/16 (6%)	8/15 (53%)	0.005
No. (%) of patients with at least 1 DeltaDAS28>0.6 during first 28 weeks	8/16 (50%)	13/15 (87%)	0.04
No. (%) of patients with at least 1 DAS28>2.6 AND DeltaDAS28>1.2 during first 28 weeks	1/16 (6%)	7/15 (47%)	0.01
No. (%) of patients with at least 1 DAS28>2.6 AND DeltaDAS28>0.6 during first 28 weeks	5/16 (31%)	11/15 (73%)	0.02
Relapse-free survival (mean weeks)	22 (95%CI, 18–26)	16 (95%CI, 10–21)	0.05

*Fisher exact test for categorical variables; log-rank (Mantel-Cox) test for survival analysis.

Conclusion: In this pilot study, remission was rarely maintained in patients with long standing RA who discontinued adalimumab. Compared to patients who continued combination therapy, the proportion in sustained remission was significantly lower for the primary and most secondary endpoints. Adalimumab discontinuation may be feasible in only a minority of patients with established RA in stable clinical remission on adalimumab + MTX.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Spondyloarthritis I
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Effect of Certolizumab Pegol On Signs and Symptoms of Ankylosing Spondyltitis and Non-Radiographic Axial Spondyloarthritis: 24 Week Results of a Double Blind Randomized Placebo-Controlled Phase 3 Axial Spondyloarthritis Study. Robert B. M. Landewé[1], Martin Rudwaleit[2], Désirée van der Heijde[3], Maxime Dougados[4], Walter P. Maksymowych[5], Jurgen Braun[6], Atul A. Deodhar[7], Christian Stach[8], Bengt Hoepken[8], Geoffroy Coteur[9], Danuta Kielar[9], Andreas Fichtner[8], Terri Arledge[10] and Joachim Sieper[11]. [1]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [2]Endokrinologikum Berlin, Berlin, Germany, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [5]University of Alberta, Edmonton, AB, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Oregon Health & Science University, Portland, OR, [8]UCB Pharma, Monheim am Rheim, Germany, [9]UCB Pharma, Brussels, Belgium, [10]UCB Pharma, Rtp, NC, [11]Charité Universitätesmedizin Berlin, Berlin, Germany

Background/Purpose: Axial spondyloarthritis (axSpA) includes both ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), as defined by the ASAS criteria.[1] RAPID-axSpA (NCT01087762) is the first report of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, in axSpA,

and the first randomized controlled trial of an anti-TNF to include the entire axSpA population.

Methods: The ongoing 158 week (wk) RAPID-axSpA trial is double-blind and placebo (PBO) controlled to Wk24, dose-blind to Wk48 and then open label to Wk158. Recruited patients (pts) had adult-onset active axSpA as defined by the ASAS criteria,[1] BASDAI ≥4, spinal pain ≥4 on a 10 point scale, CRP > upper limit of normal or sacroillitis on MRI. Pts must have failed ≥1 NSAID. Up to 40% of pts could have experienced secondary failure to 1 previous anti-TNF. The pt population reflected the broad axSpA population, including AS pts meeting the modified New York criteria and nr-axSpA pts who met the ASAS MRI or clinical criteria. Pts were randomized 1:1:1 to PBO, or 400mg CZP at Wk 0, 2 and 4 (loading dose, LD) followed by either 200mg CZP every 2 wks (Q2W) or 400mg CZP every 4 wks (Q4W). Pts receiving PBO who failed to achieve an ASAS20 response at both Wks 14 and 16 were rescued and randomized at Wk16 to receive CZP 200mg Q2W or CZP 400mg Q4W following LD. The primary endpoint was ASAS20 response at Wk12. Non-responder imputation was used for ASAS responses; last observation carried forward was used for BASFI, BASMI and BASDAI.

Results: 325 pts were randomized. Baseline (BL) characteristics were similar between treatment groups (PBO/CZP 200 mg Q2W/CZP 400 mg Q4W) with the exception of higher CRP concentrations, and greater proportion of anti-TNF experienced pts in the PBO group (25.4/17.4/21.2 mg/L; 24.3%/13.5%/10.3%, respectively). AS pts had longer disease and symptom duration at BL compared to nr-axSpA pts. Clinical improvements in ASAS20 responses at Wk12 were statistically significant in CZP 200 mg Q2W and CZP 400 mg Q4W arms vs PBO (Table) and were observed as early as Wk1 (40.5% and 34.6% vs 14.2%, p<0.001). ASAS40 response and ASAS partial remission rates were also higher in the CZP arms vs PBO. At Wks12 and 24, combined CZP arms showed statistically significant improvements vs PBO in BASDAI, BASFI, and BASMI. Similar improvements were reported with CZP vs PBO in both AS and nr-axSpA pts (Table). Adverse events (AEs) occurred in 70.4% vs 62.6%, serious AEs in 4.7% vs 4.7%, and serious infections in 1.1% vs 0 of CZP (combined dose) pts vs PBO pts, respectively. No deaths, TB or malignancies were reported.

Table. Clinical outcomes at Wk12 and Wk24 for axSpA pts in RAPID-axSpA

	AxSpA			AS			nr-axSpA		
Outcome	PBO n = 107	CZP 200mg Q2W n = 111	CZP 400mg Q4W n = 107	PBO n = 57	CZP 200mg Q2W n = 65	CZP 400mg Q4W n = 56	PBO n = 50	CZP 200mg Q2W n = 46	CZP 400mg Q4W n = 51
Week 12									
ASAS20	38.3%	57.7%*	63.6%*	36.8%	56.9%*	64.3%*	40.0%	58.7%	62.7%*
ASAS40	17.8%	43.2%*	48.6%*	19.3%	40.0%*	50.0%*	16.0%	47.8%*	47.1%*
ASAS partial remission	3.7%	23.4%*	24.3%*	1.8%	20.0%*	19.6%*	6.0%	28.3%*	29.4%*
ASAS 5/6	8.4%	45.0%*	41.1%*	8.8%	47.7%*	35.7%*	8.0%	41.3%*	47.1%*
BASDAI CFB	−1.22	−2.82*	−2.80*	−1.02	−2.51*	−2.43*	−1.52	−3.31*	−3.40*
BASFI CFB	−0.53	−2.01*	−2.02*	−0.58	−1.73*	−1.71*	−0.40	−2.29*	−2.26*
BASMI CFB	−0.13	−0.60*	−0.46*	−0.24	−0.57	−0.34	0.02	−0.61*	−0.54*
Week 24									
ASAS20	29.0%	66.7%*	70.1%*	33.3%	67.7%*	69.6%*	24.0%	65.2%*	70.6%*
ASAS40	15.0%	51.4%*	52.3%*	15.8%	47.7%*	58.9%*	14.3%	56.5%*	45.1%*
ASAS partial remission	8.4%	30.6%*	29.9%*	7.0%	30.8%*	25.0%*	10.0%	30.4%*	35.3%*
ASAS 5/6	4.7%	36.9%*	47.7%*	5.3%	33.8%*	46.4%*	4.1%	41.3%*	49.0%*
BASDAI CFB	−1.05	−3.08*	−3.01*	−1.13	−3.00*	−2.98*	−1.01	−3.27*	−3.16*
BASFI CFB	−0.40	−2.36*	−2.20*	−0.74	−2.36*	−2.29*	0.00	−2.40*	−2.07*
BASMI CFB	−0.07	−0.54*	−0.49*	−0.27	−0.62*	−0.56	0.14	−0.48*	−0.41*

*p < 0.05 vs PBO. CFB = change from baseline

Conclusion: CZP effectively and rapidly reduced the signs and symptoms of axSpA, including spinal mobility, with no new safety signals observed. Improvements were similar across CZP dosing regimens, and observed in both AS and nr-axSpA pts.

Reference:
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Spinal MRI Has Little Incremental Diagnostic Value Compared with MRI of the Sacroiliac Joints Alone in Early Spondyloarthritis.

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Background/Purpose: The definition of a positive MRI as major criterion in the Assessment of SpondyloArthritis classification criteria for axial spondyloarthritis (SpA) is based on MRI of the sacroiliac joints (SIJ) alone. It is not known whether additional MRI of the spine may enhance diagnostic certainty over and above SIJ MRI alone. We aimed to assess the incremental diagnostic value of spinal MRI evaluated both separately from and combined with SIJ MRI in early SpA compared to SIJ MRI alone.

Methods: The study sample comprised 2 independent cohorts A/B of 130 consecutive patients with back pain ≤50 years newly referred to 2 university clinics, and 20 healthy controls (HC), in whom both SIJ and spinal MRI were available. Patients were classified according to clinical examination and pelvic radiography as having non-radiographic SpA (nr-axSpA; n=50), ankylosing spondylitis (AS; n=33), or mechanical back pain (MBP; n=47). SIJ and spinal MRI were assessed by 3 blinded readers according to standardized modules. Readers recorded presence/absence of SpA and their level of confidence in this conclusion by global evaluation of the MRI scans on a 0–10 scale (0 = definitely not SpA; 10 = definite SpA). SIJ alone and spinal MRI alone were read independently 6 months apart, with another interval of 1–3 months to the combined assessment of both SIJ and spinal MRI (combined read). We analysed differences between SIJ alone versus spinal MRI alone, and SIJ alone versus combined read of SIJ and spinal MRI. This was done descriptively by the number/percentage of subjects recorded concordantly by any 2 readers for each group and for the 2 cohorts.

Results: For cohorts A and B, respectively, and for assessment of SIJ and spinal scans independently there were 0% and 16.1% of nr-axSpA patients who showed spinal lesions in the absence of SIJ lesions, while 15.8% and 19.4% of nr-axSpA patients considered having a negative SIJ MRI showed a positive spinal MRI according to global assessment. Low confidence (5–7) in a diagnosis of SpA by global evaluation of SIJ MRI increased to high confidence (8–10) by global evaluation of spinal MRI in only 0% and 3.2% of nr-axSpA patients in the 2 cohorts. For cohorts A and B, 5.3% and 3.2% of nr-axSpA patients considered negative for SpA by SIJ MRI scan alone were re-classified as being positive for SpA by global evaluation of combined SIJ and spinal scans. 57.1% and 30.3% of the MBP patients (cohort A/B) showed lesions only on spinal MRI. Up to 15.0% and 18.2% of all controls were considered as having SpA by spinal MRI scan alone, based on spinal BME in 60.9% and on fat infiltration in 26.1% of these subjects.

Number (percentage) of subjects as recorded concordantly by any 2 readers for comparisons of SIJ alone versus spinal MRI alone, and SIJ alone versus combined SIJ and spinal read

Cohort	Cohort A (n=62)				Cohort B (n=88)		
Group	nr-axSpA	AS	MBP	HC	nr-axSpA	AS	MBP
Number of subjects	19	9	14	20	31	24	33
Lesions SIJ-/Spine+	0 (0)	0 (0)	8 (57.1)	7 (35.0)	5 (16.1)	0 (0)	10 (30.3)
Global SIJ-/Spine+	3 (15.8)	0 (0)	1 (7.1)	3 (15.0)	6 (19.4)	0 (0)	6 (18.2)
Global SIJ-/Combination read+	1 (5.3)	0 (0)	0 (0)	0 (0)	1 (3.2)	0 (0)	0 (0)
Global Spine-/Combination read+	7 (36.8)	2 (22.2)	0 (0)	1 (5.0)	5 (16.1)	6 (25.0)	4 (12.1)

Conclusion: Spinal MRI adds little incremental value compared to SIJ MRI alone in terms of lesion detection and classification of early SpA patients.

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Changes in Active Inflammatory Lesions Assessed by Magnetic Reso-nance Imaging: Results of the Infliximab As First Line Therapy in Patients with Early Active Axial Spondyloarthritis Trial. Joachim Sieper[1], Jan Lenaerts[2], Jürgen Wollenhaupt[3], Vadim Mazurov[4], L. Myasou-tova[5], Sung-Hwan Park[6], Yeong W. Song[7], Ruji Yao[8], Denesh Chitkara[8] and Nathan Vastesaeger[9]. [1]Charité, University Medicine Berlin, Berlin, Ger-many, [2]Reuma-instituut, Hasselt, Belgium, [3]Schön-Klinik, Hamburg, Ger-many, [4]St. Petersburg Medical Academy, St. Petersburg, Russia, [5]Kazan State Medical University, Kazan, Russia, [6]Catholic University of Korea, Seoul, South Korea, [7]Seoul National University, Seoul, South Korea, [8]Merck Sharp and Dohme, Kenilworth, NJ, [9]Merck Sharp and Dohme, Brussels, Belgium

Background/Purpose: Few studies have evaluated changes in active inflammation of spine and sacroiliac (SI) joints by MRI during long-term treatment for axial SpA, and no data are available comparing TNF-blockers with NSAIDs.

Objectives: To determine whether combination infliximab (IFX)+NSAID therapy is superior to NSAID monotherapy for improvement in inflammatory lesions in patients with early, active axial SpA who were naïve to NSAIDs or treated with a submaximal dose of NSAIDs and to measure changes in lesions during follow-up with either NPX or no treatment in patients who achieved ASAS partial remission.

Methods: Part I of the INFAST study was a double-blind, randomized controlled trial of IFX in biologic-naïve patients 18–48 years of age with early (<3 years symptom duration), active axial SpA with signs of active sacroiliitis on MRI. Patients were randomized (2:1) to receive 28 weeks of treatment with either IV IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24)+NPX 1000 mg/d or IV PBO+NPX 1000 mg/d. In Part II of INFAST, patients who had achieved ASAS partial remission at week 28 continued in Part II with no IFX treatment and were randomized (1:1 ratio) to continue on NPX or to stop NPX until week 52. MRIs of spine and SI joints at baseline, week 28, and week 52 were used to assess active, inflammatory lesions. Group differences were analyzed descriptively or using Fisher exact tests.

Results: ASAS partial remission at week 28, the primary outcome, was achieved by more patients treated with IFX+NPX (61.9%) than PBO+NPX (35.3%), $P=0.0021$. At week 52, similar percentages of patients in the NPX and no-treatment groups maintained partial remission (47.5 vs 40%). 88% of patients had readable MRIs showing active SI lesions at baseline; 59% had spine lesions. A change from presence at baseline to complete absence of lesions at week 28 occurred more often with IFX+NPX than PBO+NPX for the SI joint (21.9% vs 3.9%, $P=0.0043$) and spine plus SI joints (16.2% vs 0%, $P=0.0016$), but not for spine alone (29.5% vs 15.7%, $P=0.0764$). In Part II, no treatment group differences were observed on these measures. Scores from Part I and II are shown in Table 1 and Table 2, respectively.

Table 1. MRI Scores in Part I

Outcome	IFX+NPX (N=105)			PBO+NPX (N=51)		
	Baseline	Week 28	Change, Median (% Change)	Baseline	Week 28	Change, Median (% Change)
Berlin MRI spine score						
Mean	2.9	0.5		4.2	1.5	
Median	0.8	0.0	–0.5 (–66.7)	1.0	0.5	0.0
SI joint score						
Mean	5.6	1.3		6.6	3.0	
Median	4.0	0.5	–2.0 (–50.0)	6.5	2.5	–3.0 (–46.2)

Table 2. MRI Scores in Part II (Patients in ASAS Partial Remission at Week 28)

Outcome	NPX (N=40)			No Treatment (N=40)		
	Week 28	Week 52	Change, Median (% Change)	Week 28	Week 52	Change, Median (% Change)
Berlin MRI spine score						
Mean	0.3	1.2		1.0	3.2	
Median	0.0	0.0	0.0	0.0	1.0	0.0
SI joint score						
Mean	1.9	4.0		1.6	3.3	
Median	1.3	3.5	1.1 (90.0)	0.5	2.5	1.0 (200.0)

The safety profile was consistent with that of other anti-TNF biologics.

Conclusion: Patients with early, active axial SpA who were treated with IFX+NPX had greater MRI improvement and a greater percentage achieved MRI remission than patients treated with NPX alone. During follow-up, no differences were observed in MRI measures for patients who received NPX vs no treatment.

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The Relationship of Inflammation, Fatty Degeneration and the Effect of Long-Term TNF-Blocker Treatment On the Development of New Bone Formation in Patients with Ankylosing Spondylitis. Xenofon Baraliakos[1], Frank Heldmann[2], Joachim Listing[3], Johanna Callhoff[3], Juergen Braun[1] and EASIC[4]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Ghana, [3]German Rheumatism Research Center, Berlin, Germany, [4]Herne, Germany

Background/Purpose: Clinical trial results suggest that new bone for-mation is neither inhibited nor augmented by anti-TNF agents in ankylosing spondylitis (AS). Recently, a potential role of different inflammatory lesions such as inflammation (INF) and fatty degeneration (FD) to predict new bone formation in patients with active AS was suggested. This is the first study to analyze the relationship between INF and FD as assessed by magnetic resonance imaging (MRI) and syndesmophyte formation as assessed by conventional radiography in vertebral edges (VE) of AS patients under long-term anti-TNF treatment.

Methods: Images were scored blinded for the time point of investigation of MRIs and x-rays of patients who participated in the EASIC Registry. Most patients were treated with infliximab. Presence or absence of INF, FD and syndesmophytes was documented on the level of VEs in the anterior part of the spine at each time point. Data were compared using Fisher′s exact test after adjustment for within-patient variation. Relative risk (RR) calculation based on a general linear model and Poisson variation.

Results: Complete sets of MRIs of 73 AS patients were evaluated at BL and 2y (1,526 VEs, 89 with and 1,437 without syndesmophytes or ankylosis at BL) and were related to complete sets of conventional radiographs of the same patients at BL, 2y and 5y. The amount of VEs with INF decreased significantly from 22.5% at BL to 1.5% after 2y, while in contrast, the amount of VEs with FD increased from 23.9% (n=364) at BL to 32.4% at 2y. In parallel, the VEs with syndesmophytes increased from 5.3% to 7.7% between BL and 2y. Overall, 35 and 60 new syndesmophytes developed after 2y and 5y, respectively, from VEs without baseline radiographic damage. The most frequent MRI pathology for syndesmophyte development at BL was the parallel occurrence of both MRI lesions, INF and FD: 22.9% and 16.7% at 2y and 5y, respectively. On the other hand, most of the new syndesmophytes (57.1% after 2y and 58.3% after 5y) seen on radiographs showed neither FD nor INF at BL. Syndesmophyte occurrence at baseline was the only significant predictor for development of these new syndesmophytes. The RR for syndesmophyte development was significant for the occurrence of the FD/INF combination at both follow-up time points, with a RR of 5.0 (p=0.002) after 2y and RR of 3.3 (p=0.009) after 5y, but only if FD lesions remained unchanged under anti-TNF treatment at 2y. On the other hand, no new syndesmophyte developed after 2y or 5y when INF was resolved. Importantly, we saw no new syndesmophyte developing after resolution of inflammation and evolution of new FD at the same VE.

Conclusion: Both spinal inflammation and fatty degeneration were associated with syndesmophyte development but fatty degeneration showed the highest risk for new syndesmophytes. However, >50% of the new bone formation observed in under anti-TNF treatment over 5 years was not preceded by either one of those. Overall, rather few syndesmophytes developed over 5 years in AS patients treated with anti-TNF. The sequence of INF – FD – new bone formation under anti-TNF was not seen at all. It seems that anti-TNF treatment has a more beneficial effect in the process of bone formation in patients with early (INF) but not late (FD) stages of the disease.

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Ankylosing Spondylitis Is Associated with an Increased Risk of Osteoporotic Fractures: A Population-Based Cohort Study. Juan Muñoz-Ortego[1], Peter Vestergaard[2], Josep Blanch[3], Paul Wordsworth[4], Andrew Judge[5], M. Kassim Javaid[6], Nigel K. Arden[6], Cyrus Cooper[7], Adolfo Díez-Pérez[8] and Daniel Prieto-Alhambra[9]. [1]Hospital Sagrat Cor, Barcelona (Spain), Barcelona, Spain, [2]Aarhus University Hospital THG, Aarhus (Denmark), Aarhus, Denmark, [3]Hospital del Mar, Parc de Salut Mar, Barcelona, Spain, [4]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [5]Oxford University, Oxford, United Kingdom, [6]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Oxford, United Kingdom, [7]University of Oxford; Southampton General Hospital, Southampton, United Kingdom, [8]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona, Barcelona; and RETICEF, ISCIII Madrid; Spain, Barcelona, Spain, [9]URFOA-IMIM, Parc de Salut Mar; Idiap Jordi Gol; University of Oxford; University of Southampton, Barcelona, Spain

Background/Purpose: Patients with Ankylosing Spondylitis (AS) have reduced bone mass, and altered biomechanics at the spine, but their fracture risk remains unclear. We have used a large population-based public health database to study the association between AS and incident fractures.

Methods: We screened the SIDIAP Database (www.sidiap.org) to identify those aged 15 years or older with a diagnosis of Ankylosing Spondylitis (ICD-10 M45), and ascertained incident osteoporotic (OP) fractures (any but skull, fingers and toes) in this population in the period 2006–2011. Five controls with no AS or other inflammatory arthritis were matched on gender, age and General Practitioner (GP). SIDIAP contains the anonymised medical records and pharmacy invoice data of a representative >4.9 million people (80% of the total population). Cox regression stratified on matched sets was used to estimate adjusted (body mass index, smoking, alcohol and oral corticosteroids) hazard ratios (HR) according to AS status. We tested for a priori defined interactions with age, gender, inflammatory bowel disease (IBD) and regular NSAID use.

Results: We identified 6,474 AS patients (0.14% of the population) and 32,346 controls and observed them for a median (inter-quartile range) of 5.98 (2.67–5.99) years. OP and clinical spine fracture rates were 9.64/1,000 person-years (8.52–10.90) and 2.12(1.63–2.76) among AS compared to 8.05 (95%CI 7.57–8.56) and 1.05(0.88–1.24) in controls respectively [Figure]. Adjusted HRs for OP and clinical spine fractures were 1.18 (95% CI 1.02–1.36; p=0.02) and 1.90 (1.37–2.63; p<0.001) respectively for AS patients. Further adjustment for oral corticosteroid use attenuated the association with OP fractures (HR 1.15 (0.99–1.32; p=0.06) but not with clinical spine fractures (HR 1.80 (1.30–2.51); p<0.001). No interactions were present with IBD. By contrast, there were relevant interactions with NSAID use (p=0.001) and gender (p=0.07) on OP fracture: adjusted HRs 1.20 (1.02–1.42; p=0.002) and 0.75 (0.55–1.02; p=0.07) for NSAID non-users VS users respectively [Figure]; and 1.01 (0.80–1.26; p=0.95) for females and 1.28 (1.08–1.53; p=0.006) for males. Similar interactions were found for NSAID use and age on clinical spine fractures (p=0.02 and p=0.03 respectively) [Figure].
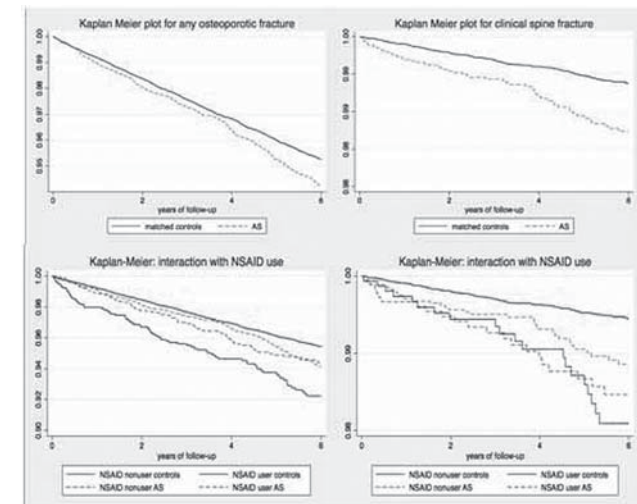
Figure.

Conclusion: Patients with AS are at 18% higher risk of osteoporotic fracture related to use of oral corticosteroids, and at almost double risk of clinical spine fractures, independently of oral corticosteroids. The excess risk associated with AS is biggest in younger males who do not take oral NSAIDs regularly.

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Anti-TNF Therapy Slows Radiographic Progression of Ankylosing Spondylitis. Nigil Haroon[1], Robert D. Inman[2], Thomas J. Learch[3], Michael H. Weisman[4], Michael M. Ward[5], John D. Reveille[6] and Lianne S. Gensler[7]. [1]University Health Network, Toronto Western Research Institute, University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [3]Cedars-Sinai, Los Angeles, CA, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]NIAMS/NIH, Bethesda, MD, [6]Univ of Texas Health Science Center at Houston, Houston, TX, [7]UCSF, San Francisco, CA

Background/Purpose: The influence of anti-TNF therapy on radiographic progression in ankylosing spondylitis (AS) is not well established. We studied this effect on radiographic progression in AS patients.

Methods: Three-hundred-and-seventy-six patients were included with at least 2 sets of radiograph at least 1.5 years apart (range 1.5 to 9 years) from a multicenter longitudinal cohort of 1600 AS patients. Patients with total spinal ankylosis at baseline were excluded. Patients were assessed at least annually on a protocol format. Time-averaged BASDAI, ESR and CRP, NSAID and anti-TNF indices were calculated. Full recommended dose of NSAID/anti-TNF taken for the entire period between x-rays were assigned a score of 100. Total anti-TNF exposure was calculated from the anti-TNF index and the years of exposure. Patients with mSASSS increase at a rate of $\geq$ 1 unit/year were considered progressors. T-test, Chi-square and logistic regression were performed. For multivariate analysis, variables were selected from those that were significant in the univariate analysis. Variables were separated in different models based on the correlation matrix.

Results: The mean age of patients was 40.8 $\pm$ 13.8 years (75% males and 92% HLA-B27 positive) and the mean disease duration was 16.5 $\pm$ 12.9 years. Among patients enrolled, 60% had never smoked and 17% stopped smoking in the period between radiographs. No baseline radiographic abnormality was seen in 44% patients and 35% showed progression $\geq$ 1 mSASSS unit/year.

In the univariate analysis, males progressed faster (1.2 vs 0.8 mSASSS unit/year) with an odds ratio (OR) of 1.9 (95% CI: 1.09–3.39; p=0.02). Smokers had an odds of progression of 1.6 (95% CI: 1.02–2.54; p=0.04). Other significant variables included age of onset, baseline and time-averaged CRP and ESR and cumulative dose of anti-TNF received (Table 1A). The NSAID index was not significant in the univariate analysis. In multivariate analysis (Table 1B), the following variables remained significant: Gender (β=3.7;p=0.003), baseline ESR (β=1.03;p=0.001), baseline mSASSS (β=1.05;p=2 $\times$ 10^{-5}) and cumulative anti-TNF exposure (β=0.99;p=0.006). To estimate the effect with any exposure to biologics, cumulative anti-TNF exposure was substituted with the dichotomous variable: history of anti-TNF exposure. Anti-TNF use was protective against progression with an OR of 0.4 (p=0.006). The other variables remained significant as in the previous model.

Table 1A. Univariate and Multivariate Regression Analysis for radiographic progression

A. Univariate Regression

Covariate	p value	Odds Ratio	Confidence Interval
Male Gender	0.02	1.93	1.10–3.39
Age of Onset	0.004	1.03	1.01–1.06
Disease Duration	2 $\times$ 10-5	1.04	1.02–1.06
Smoking History	0.04	1.61	1.02–2.54
Baseline CRP	0.004	1.03	1.01–1.05
Time-Averaged CRP	0.002	1.05	1.02–1.08
Baseline ESR	0.0001	1.03	1.01–1.04
Time-Averaged ESR	0.006	1.02	1.01–1.04
Baseline mSASSS	1 $\times$ 10-11	1.07	1.05–1.09
Total Biologic Exposure	0.04	0.99	0.99–1.00

Table 1B. Univariate Regression

Model 1

Variables included: Gender, Disease Duration, Baseline ESR, Baseline mSASSS & Total Anti-TNF Exposure

Male Gender	0.003	3.70	1.57–8.70
Baseline ESR	0.001	1.03	1.01–1.04
Baseline mSASSS	2×10^{-5}	1.05	1.03–1.08
Total Anti-TNF Exposure	0.006	0.998	0.997–0.999

Model 2

Variables included: Gender, Age of Onset, Baseline ESR, Baseline mSASSS & Total Anti-TNF Exposure

Male Gender	0.01	2.7	1.3–5.9
Baseline ESR	0.0004	1.03	1.01–1.04
Baseline mSASSS	1×10^{-8}	1.06	1.040–1.09
Total Anti-TNF Exposure	0.04	0.99	0.99–1.000

Model 3

Variables included: Gender, Disease Duration, Baseline ESR, Baseline mSASSS & Anti-TNF (Y/N)

Male Gender	0.01	2.6	1.2–5.4
Baseline ESR	5×10^{-5}	1.03	1.01–1.04
Baseline mSASSS	3×10^{-9}	1.07	1.04–1.09
Anti-TNF Use (Yes/No)	0.006	0.44	0.24–0.79

Age of onset and Disease duration were strongly correlated in the matrix (R=0.98) and so they were included in separate models. Only one inflammatory parameter (Baseline ESR) was used for the same reason. Model 3 was used to calculate the Odds of progression in patients who took anti-TNF at some time compared to those with no exposure.

Conclusion: Inflammation is associated with radiographic progression. Anti-TNF therapy slows the rate of radiographic progression in AS.

ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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The Wnt Inhibitors DKK1 and SFRP1 Are Downregulated by Promoter Hypermethylation in Systemic Sclerosis. Clara Dees[1], Inga Schlottmann[1], Robin Funke[1], Alfiya Distler[1], Katrin Palumbo-Zerr[2], Pawel Zerr[2], Oliver Distler[3], Georg A. Schett[2] and Joerg HW Distler[2]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Tissue fibrosis caused by pathological activation of fibroblasts is a major hallmark of systemic sclerosis (SSc). Epigenetic gene silencing of anti-fibrotic genes such as FLI1 by DNA methylation has been implicated in the pathogenesis of SSc. Also increased activation of the Wnt pathway with decreased expression of endogenous inhibitors has recently been shown to play a prominent role in tissue fibrosis in SSc. However, the molecular mechanisms leading to the decreased expression of Wnt inhibitors is incompletely understood. In the present study, we evaluated whether the expression of endogenous Wnt inhibitors might be silenced through DNA methylation.

Methods: The methylation status of endogenous Wnt inhibitors in leukocytes and fibroblasts was evaluated by methylation-specific PCR. Gene expression in fibroblasts and human skin was analyzed by real-time PCR and immunohistochemistry. The expression of endogenous Wnt inhibitors was also evaluated in the mouse model of bleomycin-induced dermal fibrosis. 5-aza-2-deoxycytidine (5-aza) was used to inhibit DNA methyltransferases (Dnmts) in cultured fibroblasts and mice.

Results: Significant hypermethylation of the promoters of DKK1 and SFRP1 was observed in leukocytes isolated from blood samples of SSc patients. Increased methylation in the promoter region of DKK1 and SFRP1 was also found in cultured fibroblasts from SSc patients. This hypermethylation resulted in decreased gene transcription by 56 ± 5 % for DKK1 and by 89 ± 3 % for SFRP1 (p < 0.05 for both) compared to fibroblasts from healthy

subjects. Of note, treatment with 5-aza re-activated the transcription of SFRP1 in SSc fibroblasts from 11 ± 3 % to 52 ± 16 % of control levels and the expression of DKK1 was completely reversed to control levels (p < 0.05 each). Consistent with the reduced mRNA levels, the protein levels of both DKK1 and SFRP1 were severely decreased in skin of SSc patients as analyzed by immunohistochemistry. In addition, decreased expression of DKK1 and SFRP1 was also found in experimental fibrosis. In the model of bleomycin-induced dermal fibrosis, the mRNA levels of DKK1 decreased by 73 ± 5 % (p = 0.036) upon bleomycin challenge and those of SFRP1 by 35 ± 3 % (p = 0.004). Both genes were re-activated by treatment of bleomycin-challenged mice with 5-aza. Compared to untreated mice injected with bleomycin, the mRNA levels increased upon treatment with 5-aza by 504 ± 42 % (p = 0.024) for DKK1 and by 131 ± 23 % (p = 0.015) for SFRP1. Similar results were obtained for protein levels. Consistently, 5-aza significantly reduced bleomycin-induced dermal fibrosis with decreased dermal thickening and reductions in hydroxyproline content and myofibro-blast counts.

Conclusion: We demonstrate that the endogenous Wnt inhibitors DKK1 and SFRP1 are downregulated by promoter hypermethylation in SSc. Inhibition of Dnmts by 5-aza re-activated gene expression in SSc fibroblasts and in experimental fibrosis. As different inhibitors of Dnmts are already approved for other diseases and are well tolerated, our findings might have direct translational implications and provide a novel approach to inhibit Wnt signaling in SSc.

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Neutralization of Plasminogen Activator Inhibitor-1 Resolves Skin Fibrosis and Vascular Injury in a Murine Model of Human Scleroderma. Raphael Lemaire[1], Tim Burwell[1], Tracy Delaney[1], Cindy Chen[1], Julie Bakken[1], Lily Cheng[1], Philip Brohawn[1], Isabelle de Mendez[2], Dominic Corkill[2], Anthony Coyle[3], Ronald Herbst[1] and Jane Connor[1]. [1]MedImmune LLC, Gaithersburg, MD, [2]Medimmune, LLC, Cambridge, England, [3]Pfizer, Inc., Cambridge (formerly at MedImmune LLC, Gaithersburg, MD, USA)

Background/Purpose: Scleroderma is a systemic autoimmune disease in which thrombosis and fibrosis contribute to skin pathology. Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of pro-fibrinolytic plasminogen activators uPA and tPA and its expression has been shown to be increased in the skin of scleroderma patients. The purpose of this study was to evaluate the contribution of PAI-1 inhibition of PAs to pathological changes in the skin in an animal model that recapitulates both the fibrosis and occlusive vasculopathy of human scleroderma.

Methods: B10D2 splenocytes were injected into BALB/c Rag-2$-/-$ mice resulting in a model of graft-vs-host disease-induced skin fibrosis (GVHD). A monoclonal antibody that selectively prevents the binding of PAI-1 to its target PAs was administered ip two times per week beginning either at time of engraftment or at week 3 post-engraftment. Effect of PAI-1 neutralization was assessed on clinical skin score, gene expression and histological changes in the skin. In addition, the effect of blocking PAI-1 on MMP-1 activation was evaluated in vitro in human dermal microvascular endothelial cells (HMVECs).

Results: In this model fibrosis peaks at week 6 post-graft, following the inflammation peak at week 4. PAI-1 expression is increased in the skin beginning at week
2. Prophylactic neutralization of PAI-1 significantly reduced the clinical skin score in a dose-dependent manner as early as week 2 post-graft. Clinical benefits were associated with normalization of fibrinolysis genes (plasmin, PAI-1- uPA, uPAR, KLK6) and this correlated with resolution of vascular injury markers (VCAM-1, MMP-12), T cell infiltration and TNF-α levels in skin, as assessed over the inflammatory phase of the disease (week 1–4). Administration of the antibody in a therapeutic regimen also resulted in significant reduction of the clinical skin score. Clinical benefits were associated with normalization of fibrinolysis along with resolution of skin fibrosis over the chronic phase of the disease (week 4–6) as shown by reduction of dermal thickness and extracellular collagen which correlated with reduction of expression of pro-fibrotic cytokines (TGF-β, IL-13) and matrix turnover regulators (TIMP-1). The matrix turnover component of PAI-1 inhibition was

further supported where neutralization of PAI-1 in cultured dermal HMVECs decreased MMP-1 activation in a concentration-dependent manner.

Conclusion: These data suggest that PAI-1 plays a key role in both the skin vasculopathy and fibrosis observed in this murine model of human scleroderma and that inhibition of the binding of PAI-1 to PAs resolves fibrosis via two distinct plasmin-based mechanisms: (1) directly via reducing MMP activation and (2) indirectly via reducing infiltration of profibrotic cytokine-secreting inflammatory cells following thrombolysis-based resolution of vascular injury and activation.

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Resident Lung Fibroblast Gene Expression Signatures Predict Susceptibility or Resistance to Experimental Lung Fibrosis. Emma Derrett-Smith[1], Rachel Hoyles[1], Korsa Khan[1], David J. Abraham[1] and Christopher P. Denton[2]. [1]UCL Medical School, London, United Kingdom, [2]UCL, London, United Kingdom

Background/Purpose: In scleroderma (SSc), lung fibrosis is linked to epithelial damage and dysregulated repair mechanisms. Resident lung fibroblasts may affect multiple cell types including epithelium, endothelium, smooth muscle cells and fibrocytes. We have used two complementary transgenic mouse strains with altered TGFβ signalling to better understand the regulatory role of resident lung fibroblasts in defining susceptibility to fibrosis.

Methods: The TβRIIΔk-fib mouse model of SSc, in which TGFβ signalling is upregulated in fibroblasts, is susceptible to fibrotic lung injury whereas the TβRII-null-fib strain, in which TβRII is conditionally knocked out in fibroblasts, is resistant to bleomycin-induced lung fibrosis. We have used an illumina® microarray platform to profile lung or skin fibroblasts from these two strains and identified a cohort of genes that determine susceptibility or resistance to experimental lung fibrosis, comparing to a control group using whole lung from TβRIIΔk-fib animals and wildtype littermates (n=3) on the same microarray platform. Technical validation of data and additional quantitation of gene expression was performed using quantitative RT-PCR assays with replicate samples.

Results: The TβRIIΔk-fib lung fibroblast gene expression signature includes key genes that are implicated as pathogenic drivers of fibrosis and inflammation and potential biomarkers in SSc. Conversely, many of these genes are downregulated in TβRII-null-fib mice (figure 1), including BMP4 (fold reduction in TβRII-null-fib 31.8, p<0.02; fold upregulation in TβRIIΔk-fib compared with WT 2.01, p<0.6); elastin (TβRII-null-fib 17.8, p<0.14; TbRIIΔk-fib 1.86, p<0.09); CCL2 (TβRII-null-fib 56.8, p<0.09; TβRIIΔk-fib 1.72, p<0.03)and MMP13 (TβRII-null-fib 13.2, p<0.08; TβRIIΔk-fib 3.6, p<0.4). CTGF (CCN2) was strongly upregulated in TβRIIΔk-fib lung fibroblasts, but showed less downregulation than other genes in the TβRII-null-fib, probably reflecting multiple pathways of activation. No signature of overexpression was present in the whole lung analysis suggesting that fibroblast-specific differences in gene expression determine altered fibrotic response.

Fibroblast gene expression ranked for differential expression in TβRIIΔk fibroblasts.

Representative gene data in text.
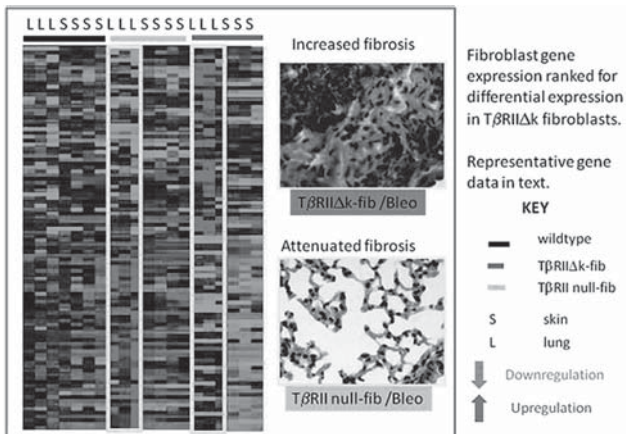
Conclusion: These data define a cohort of genes differentially expressed in fibroblasts that associate strongly with susceptibility or resistance to experimental lung fibrosis. These transcripts include many that are important

in tissue repair and that have previously been shown to be over expressed in SSc skin samples. They suggest that resident fibroblast gene expression signature may govern fibrosis in lung and skin.

Disclosure: E. Derrett-Smith, None; **R. Hoyles**, None; **K. Khan**, None; **D. J. Abraham**, None; **C. P. Denton**, None.

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Crosstalk Between Integrins and TGFβ in the Pathogenesis and Treatment of Multiple Presentations of Scleroderma Elizabeth E. Gerber[1], Fredrick M. Wigley[2], Elaine C. Davis[3], David L. Huso[1] and Harry C. Dietz[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]McGill University, Montreal, QC

Background/Purpose: Scleroderma, defined as pathologic fibrosis of the skin, has many clinical presentations. In the most commonly recognized form, systemic sclerosis (SSc), previously healthy individuals acquire fibrosis of the skin and viscera associated with autoantibodies. Although a genetic contribution to SSc has been established, familial recurrence is rare and causal genes have not been found. The study of SSc is hindered by a lack of animal models that faithfully recapitulate this complex disease. In contrast, a rare disorder, stiff skin syndrome (SSS), shows childhood onset of diffuse skin fibrosis with autosomal dominant inheritance and no visceral fibrosis or autoimmunity. Both disorders have been linked to TGFβ. SSS is caused by heterozygous missense mutations in the gene encoding fibrillin-1, a major constituent of extracellular microfibrils. SSS mutations localize to the only domain that harbors an Arg-Gly-Asp motif that mediates cell-matrix interaction by integrin-binding.

Methods: Two SSS mouse models were generated by homologous recombination and either bred to $Itgb3+/-$ mice or treated with antibodies by IP injection. Primary human dermal fibroblast cultures were derived from forearm biopsies and stimulated with 2 ng/mL TGFβ1. Analyses included skin stiffness scoring, histology, flow cytometry, Western and Northern blotting, and qPCR. Data are shown as standard boxplots (R statistical software) and analyzed with 2-tailed t tests.

Results: Knock-in mutations in $Fbn1$ in mice that either reproduce a naturally-occurring SSS mutation ($Fbn1^{W1572C/+}$) or impose an obligate loss of integrin binding ($Fbn1^{D1545E/+}$), are sufficient to initiate and maintain dermal fibrosis. This associates with upregulation of surface expression of β1 and αvβ3 integrins by dermal cells. Treatment with β1 integrin activating (β1aAb) for 12 weeks reduces active αvβ3 in the dermis and prevents stiffness and skin fibrosis (Fig.1). Notably, genetic ablation of integrin β3 also prevents the phenotype and TGFβ antagonism, commenced at a later age, completely reverses it. In vitro, SSc patient cells also show aberrant integrin expression and function that contributes to a fundamental change in the signaling properties of ligand-activated TGFβ receptors, favoring activation of extracellular-regulated kinase (ERK). Integrin- or ERK-modulating treatments normalized the pro-fibrotic repertoire in SSc cells, increasing levels of matrix-inhibiting microRNA-29, and reducing both ERK activation and collagen expression (Fig.2).

Conclusion: This work demonstrates the potential to reverse established dermal fibrosis in a model of human disease and shows that despite the phenotypic differences between SSS and SSc, study of SSS animal models has offered a pathogenic sequence for scleroderma that suggests therapies for SSc, including β1 integrin activation and blockade of β3 integrin, TGFβ or ERK signaling.

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Aberrant Adipogenesis in the Pathogenesis of Scleroderma. Roberta Goncalves Marangoni, Jun Wei, Monique E. Hinchcliff, Feng Fang, Warren Tourtellotte and John Varga. Northwestern University Medical School, Chicago, IL

Background/Purpose: Skin fibrosis in systemic sclerosis (SSc) is associated with loss of subcutaneous adipose tissue (SCAT) and reduction in adiponectin. The mechanism underlying SCAT atrophy and its significance in pathogenesis are not known. In light of emerging insights into adipogenesis and the plasticity of adipogenic progenitor cells, we investigated the mechanistic basis of adipose atrophy and its relation to fibrosis in the skin.

Methods: The kinetics of SCAT loss was investigated in mouse models of dermal fibrosis. Transgenic mice were used for adipocyte lineage tracing. Modulation of adipogenic differentiation was evaluated in mouse and human stem cells and skin fibroblasts by real-time qPCR, immunoblotting, cytochemistry, and DNA microarrays.

Results: Skin biopsies from a cohort of well characterized patients with diffuse cutaneous SSc showed variable but consistent SCAT atrophy. Moreover, striking loss of SCAT was observed in mouse models of scleroderma induced by bleomycin. Careful time-course studies demonstrated that loss of SCAT preceded the onset of dermal fibrosis. Furthermore, loss of adipogenic markers preceded the increase in fibrogenic markers in the lesional skin. These observations suggest that adipogenic progenitor cell differentiation was redirected towards fibrogenic fates. Indeed, TGF-beta was able to preferentially promote fibrogenic differentiation of mouse 3T3L1 preadipocytes in vitro. Remarkably, the tyrosine kinase abl prevented adipogenesis, which was rescued by the putative antifibrotic drug imatinib. Moreover, in normal skin fibroblasts imatinib caused dramatic induction of adipogenic genes. The potential significance of preadipocyte-fibroblast transitions in fibrogenesis is directly addressed by fate-mapping studies using adipocyte-labeled transgenic reporter mice.

Conclusion: Our studies indicate that SCAT atrophy is consistently associated with human and mouse scleroderma, and appears to precede the onset of dermal fibrosis. Cellular adipocyte/fibroblast plasticity, readily induced in vitro and manipulated by imatinib, may directly contribute to fibrogenesis. We conclude that loss of SCAT might be a primary event in the pathogenesis of SSc, and adipogenic progenitor cell differentiation may be a potential target of therapeutic manipulation.

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Tenofovir, a Potent Anti-Viral Agent, Is an Ecto-5'Nucleotidase (CD73) Inhibitor That Prevents Dermal Fibrosis in a Murine Model of Scleroderma. Jessica L. Feig[1], Doreen Tivon[1], Miguel Perez-Aso[1], Timothy Cardozo[1] and Bruce N. Cronstein[2]. [1]New York University School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Acyclic nucleoside phosphonates are a key class of antivirals commonly used in the treatment of both DNA and retroviral infections. Adefovir and tenofovir are AMP analogues that resemble substrates of CD73. We have previously reported that adenosine, generated by the CD73-mediated dephosphorylation of AMP, acting at A_{2A} receptors, plays a critical role in development of both hepatic and dermal fibrosis in murine models of cirrhosis and scleroderma, respectively. A recent clinical trial demonstrated that tenofovir, but not other antiviral agents, reverses hepatic fibrosis/cirrhosis in patients with hepatitis B. We therefore proposed the hypothesis that tenofovir's antifibrotic effects are mediated by inhibition of adenosine production by CD73-mediated dephosphorylation of AMP.

Methods: In silico modeling and docking studies were performed using an ICM-Browser downloaded from www.molsoft.com. Active site docking with an energy score of less than -32 kcal/mol was considered favorable. CD73 enzyme activity was quantitated by malachite green using 75–100 uM AMP substrate with CD73 transfected 293T cells or recombinant human enzyme. Bleomycin (0.25 U, SubQ)-treated mice were treated with vehicle or Tenofovir (75mg/kg, IP) [n=5 per group]. Skin breaking strength was measured using a tensiometer. Histologic samples of H&E or picrosirus red-stained slides were imaged, and pixel quantification was performed with SigmaScan software. Scar index was determined as the ratio of red/green pixels representing compact/filamentous fibers; higher numbers indicate more fibrosis. Dermal hydroxyproline content was quantified by colorimetric assay.

Results: In silico modeling data suggested that both adefovir and tenofovir bound to the enzymatic pocket of CD73. Tenofovir, but not adefovir, inhibited CD73 activity of 293T cells overexpressing CD73 (38+7.4%, at 10 uM) and of recombinant enzyme (72+1.0%, at 10uM). Tenofovir (75mg/kg) diminished bleomycin-induced dermal fibrosis in bleomycin-treated mice (73.7+3.1% reduction of hydroxyproline content

[p<0.05]; 33.5+3.8% reduction of dermal thickness [p<0.06] and reduction of breaking tension by 66.8+1.4% [p<0.05]). Picrosirius red staining showed dramatic altering of collagen quality (scar index of 1.2+0.1 vs 22.2+0.7 [p<0.001], normal skin is 2.5).

Conclusion: These results provide strong support to the hypothesis that Tenofovir reduces fibrosis via inhibition of adenosine production from AMP by CD73. Moreover, these results suggest that tenofovir may have therapeutic potential in treating fibrosis in patients suffering from non-viral fibrosing diseases such as scleroderma.

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ARHP Concurrent Abstract Session
Foot and Gait Disorders
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Foot Disorders Associated with Over-Pronated and Over-Supinated Foot Types: The Johnston County Osteoarthritis Project. Yvonne M. Golightly[1], Marian T. Hannan[2], Alyssa B. Dufour[3], Howard J. Hillstrom[4] and Joanne M. Jordan[5]. [1]University of North Carolina, Chapel Hill, NC, [2]Hebrew SeniorLife & Harvard Med Sch, Boston, MA, [3]Hebrew Senior-Life & Boston Univ, Boston, MA, [4]Hospital Special Surgery (HSS), New York, NY, [5]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC

Background/Purpose: Based on clinical observations, musculoskeletal foot disorders, such as hallux valgus or plantar fasciitis, appear to occur more frequently in a pronated foot type. Other disorders, like hammer toes or Tailor's bunions, may occur more often in a supinated (high arch) foot type. The purpose of this cross-sectional analysis was to determine whether specific foot disorders were associated with over-pronated and over-supinated foot types in a large, biracial community-based cohort of men and women 50 years of age or older.

Methods: Of 1,695 Johnston County Osteoarthritis Project participants clinically evaluated for foot disorders in 2006–2010, complete foot pressure data were available for 1,466 (1,425 with bilateral and 41 with unilateral foot data; mean age 68.5 years, mean body mass index [BMI] 31.2 kg/m^2, 67.2% women, 29.5% African American). Two trained examiners used the validated Foot Assessment Clinical Tool to determine the presence or absence of foot disorders. Foot pressure scans were recorded for both feet as participants walked at a normal pace over a Tekscan Matscan system (Tekscan Inc., Boston, MA). The center of pressure excursion index (CPEI) was calculated for each foot. CPEI cutoff values were set a priori to create a 3-category foot type variable: over-pronated (≤ 7.3), over-supinated (≥ 21.0), and neutral (> 7.3 to < 21.0; referent). With the foot as the unit of analysis, separate multivariate logistic regression models using generalized estimating equations were performed to examine the association between foot type and each foot disorder, adjusting for age, BMI, gender, and race. Effect modification between foot type and age, BMI, gender, or race were examined (p<0.10 for interaction was considered statistically significant).

Results: Of 2,891 feet available for analysis, 66.5% had a neutral foot type, 13.9% were over-pronated, and 19.7% were over-supinated. Hallux valgus was the most common foot disorder (57.1%), followed by overlapping toes (27.1%), hammer toes (25.9%), Morton's neuroma (6.0%), Tailors' bunions (5.4%), plantar fasciitis (3.4%), and claw toes (2.1%). Table shows results of adjusted models. Compared to a neutral foot type, an over-pronated foot type was associated with hallux valgus (adjusted odds ratio [aOR]=1.36, 95% confidence interval [CI]=1.13–1.65) and overlapping toes (aOR=1.36, 95% CI=1.12–1.64), while an over-supinated foot type was inversely associated with hallux valgus (aOR=0.85, 95% CI=0.74–0.97). These associations did not differ by age, BMI, gender, or race.

Table.

Foot Disorder	Foot Type	Foot disorder/ Foot Type (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Hallux Valgus	Over-Pronated	277/401 (69.1)	1.41 (1.17–1.70)	1.36 (1.13–1.65)
	Neutral	1095/1922 (57.0)	1.00	1.00
	Over-Supinated	279/568 (49.1)	0.85 (0.74–0.96)	0.85 (0.74–0.97)
Overlapping Toes	Over-Pronated	136/401 (33.9)	1.38 (1.15–1.67)	1.36 (1.12–1.64)
	Neutral	500/1922 (26.0)	1.00	1.00
	Over-Supinated	148/568 (26.1)	0.97 (0.80–1.18)	0.97 (0.80–1.18)
Hammer Toes	Over-Pronated	107/401 (26.7)	0.96 (0.75–1.22)	0.89 (0.69–1.15)
	Neutral	489/1922 (25.4)	1.00	1.00
	Over-Supinated	152/568 (26.8)	0.98 (0.80–1.20)	1.00 (0.81–1.23)
Morton's Neuroma	Over-Pronated	19/401 (4.7)	0.76 (0.48–1.20)	0.79 (0.49–1.25)
	Neutral	115/1922 (6.0)	1.00	1.00
	Over-Supinated	40/568 (7.0)	1.14 (0.84–1.53)	1.11 (0.82–1.50)
Tailor's Bunions	Over-Pronated	36/401 (9.0)	1.14 (0.86–1.51)	1.23 (0.93–1.62)
	Neutral	93/1922 (4.8)	1.00	1.00
	Over-Supinated	26/568 (4.6)	0.85 (0.59–1.22)	0.85 (0.60–1.22)
Plantar Fasciitis	Over-Pronated	14/401 (3.5)	0.92 (0.50–1.70)	0.98 (0.53–1.82)
	Neutral	64/1922 (3.3)	1.00	1.00
	Over-Supinated	20/568 (3.5)	1.14 (0.78–1.67)	1.13 (0.76–1.67)
Claw Toes	Over-Pronated	7/401 (1.8)	0.75 (0.37–1.52)	0.69 (0.34–1.42)
	Neutral	42/1922 (2.2)	1.00	1.00
	Over-Supinated	11/568 (1.9)	0.93 (0.51–1.69)	0.89 (0.48–1.64)

*Adjusted for age, BMI, gender, race.

Conclusion: Hallux valgus and overlapping toes were the only foot disorders strongly related to foot type in this sample. Future studies should determine the longitudinal association between foot types and foot disorders as well as examine shoe and orthotic interventions for specific foot types as preventive approaches for foot disorders.

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Biomechanical Function Agrees with Clinical Implications of Foot Disorders in a Population-Based Study. Thomas J. Hagedorn[1], Alyssa B. Dufour[2], Jody L. Riskowski[3], Howard J. Hillstrom[4], Virginia A. Casey[1] and Marian T. Hannan[5]. [1]Hebrew Senior Life, Boston, MA, [2]Hebrew SeniorLife & Boston Univ, Boston, MA, [3]Hebrew SeniorLife & Harvard Med School, Boston, MA, [4]Hospital Special Surgery (HSS), New York, NY, [5]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: Foot disorders are thought to be associated with foot structure and function. However, no population-based studies have objectively evaluated this question. Insights into the relations of foot structure and function with specific foot disorders may further our understanding of their impact. The purpose of this study was to evaluate the relation of foot disorders to foot structure and function in a population-based study.

Methods: The Framingham Foot Study is a cross-sectional population-based study of ambulatory adults (aged 36–100) examined from 2002–08. A podiatric-trained examiner performed a validated foot exam to record presence of specific foot disorders (hallux valgus, hammer toes, claw toes, hallux rigidus, plantar fasciitis, Morton's neuroma, tailor's bunion, and overlapping toes). A Tekscan Matscan pressure mat was used to collect loading data from each foot while walking, and during bipedal standing. From these data, center of pressure excursion index (CPEI), a measure of foot function during walking, and modified arch index (MAI), a measure of foot structure while standing, were calculated for each foot. Participants with valid foot pressure and examination data were included in this analysis. Feet in the top and bottom 20% of CPEI values were classified as supinators and pronators respectively; the middle 60% was the referent. High-arch feet were defined as the bottom 20% of MAI values, while low-arch feet were defined as the top 20%; referent was the middle 60%. Logistic regression, using generalized estimation equations to account for correlations between feet, was used to estimate odds ratios and 95% confidence intervals between foot function, structure and each foot disorder.

Results: There were 3145 participants contributing 5517 feet (Table 1). Hallux valgus and hammer toes were the most common foot disorders. Prevalence of hallux valgus and overlapping toes was higher among prona-

tors, while prevalence of hallux valgus and hallux rigidus was lower among supinators (Table 2). Low arches were associated with a higher prevalence of Morton's neuroma and hammer toes.

Table 1. Population characteristics and prevalence of foot disorders in the study sample. Prevalence by foot (N=5517)

Characteristic	Mean ± Std Dev
Age (years)	66.2 ± 10.5
BMI (kg/m^2)	28.3 ± 5.5
Weight (lbs)	174.1 ± 39.3
Height (in)	65.5 ± 3.9
Foot Disorder	**Prevalence N (%)**
Hallux Valgus	1472 (26.3)
Hammer Toes	894 (16.2)
Morton's Neuroma	439 (8.0)
Overlapping Toes	294 (5.3)
Tailor's Bunion	197 (3.6)
Plantar Fasciitis	177 (3.2)
Hallux Rigidus	173 (3.1)
Claw Toes	74 (1.3)

Table 2. Odds ratios and 95% confidence intervals for GEE analysis of foot structure, function, and disorders.

	Foot Function (defined by CPEI)		Foot Structure (defined by MAI)	
	Pronator	Supinator	Low Arch	High Arch
Hallux Valgus	1.15 (1.01, 1.30)*	0.78 (0.69, 0.89)†	0.95 (0.83, 1.10)	0.95 (0.83, 1.09)
Hammer Toes	0.91 (0.78, 1.05)	0.93 (0.79, 1.09)	1.33 (1.14, 1.57)†	0.99 (0.83, 1.19)
Morton's Neuroma	0.83 (0.66, 1.06)	0.97 (0.77, 1.23)	1.29 (1.01, 1.65)*	1.15 (0.90, 1.47)
Overlapping Toes	1.48 (1.15, 1.91)†	0.99 (0.75, 1.32)	1.27 (0.96, 1.69)	1.03 (0.77, 1.38)
Tailor's Bunion	1.07 (0.79, 1.46)	0.80 (0.60, 1.07)	1.19 (0.85, 1.69)	1.17 (0.88, 1.55)
Plantar Fasciitis	0.98 (0.68, 1.41)	1.22 (0.89, 1.68)	1.16 (0.79, 1.69)	1.10 (0.75, 1.61)
Hallux Rigidus	1.17 (0.92, 1.48)	0.58 (0.41, 0.83)†	1.24 (0.93, 1.65)	0.86 (0.59, 1.25)
Claw Toes	1.06 (0.67, 1.69)	0.85 (0.49, 1.47)	0.84 (0.49, 1,44)	0.79 (0.42, 1.50)

* 0.01 < p < 0.05
† p < 0.01

Conclusion: Foot structure and function were related to prevalence of specific foot disorders in this population. The results are in agreement with biomechanical theory of and clinical implications from specific foot disorders. However, these cross-sectional data cannot confirm a causal relation. These results underscore the utility of clinical input in understanding the relations between foot structure, function, and disorders and may provide insights for interventions to improve function.

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Leg Muscle Mass Is Not Affected by Foot Pain, Structure or Function: The Framingham Foot Study. Alyssa B. Dufour[1], Marian T. Hannan[2], Patricia P. Katz[3], Jody L. Riskowski[4], Thomas J. Hagedorn[5], Virginia A. Casey[5] and Robert R. McLean[6]. [1]Hebrew SeniorLife & Boston Univ, Boston, MA, [2]Hebrew SeniorLife & Harvard Med Sch, Boston, MA, [3]Univercity of California San Francisco, San Francisco, CA, [4]Hebrew SeniorLife & Harvard Med School, Boston, MA, [5]Hebrew Senior Life, Boston, MA, [6]Hebrew Senior Life/Harvard Medical School, Boston, MA

Background/Purpose: While foot pain has been linked to poor outcomes, little is known about how the foot might affect physical functioning or, specifically, leg muscle mass. As no studies have examined the association between leg muscle mass and foot pain, structure or function, the purpose was to evaluate the relation of leg muscle mass to these characteristics, in a population-based study of older men and women. We hypothesized that foot pain and poor foot function/structure (e.g. supination or pronation) would be linked to low leg muscle mass.

Methods: Framingham Foot Study participants with complete data on leg muscle mass as well as foot pain, structure and function (2002–08) were included in this study. Whole body DXA (Lunar DPX-L) was used to measure leg muscle mass (kg). Foot pain (y/n) was present if pain, aching or stiffness was reported on most days of the month. Data from a Tekscan Matscan pressure mat were used to calculate foot structure, as the modified arch index (MAI) during bipedal standing, and foot function, as the center of pressure excursion index (CPEI) while walking using the two-step method. Feet in the top or bottom 20% of CPEI values were classified as supinators or pronators, respectively, and feet in the middle 60% were the referent group. The bottom and top 20% of MAI values were considered high and low arched

feet, respectively, with the referent the middle 60%. The foot with CPEI or MAI value farthest from the respective median value was chosen as the foot of interest for each participant. Crude and adjusted (age, body mass index (BMI, kg/m^2), sex) multinomial (for foot structure and function outcomes) logistic regression was used to determine the association of a 1 standard deviation (SD) increase in leg muscle mass, both crude and normalized to height, with foot pain, structure and function. Sex-specific models were also examined.

Results: Of the 1798 participants (age: 67 $\pm$ 10 years; BMI: 28 $\pm$ 4.9 kg/m^2; 57% women), the average leg muscle mass was 17.51 $\pm$ 2.23 kg in men and 11.60 $\pm$ 1.51 kg in women. 21% reported foot pain. A 1 SD increase in leg muscle mass was associated with 18% lower odds of foot pain, 25% lower odds of pronation and 19% higher odds of supination, compared to the referent. A 1 SD increase in muscle mass was associated with 14% higher odds of low arch and 15% lower odds of high arch. Adjustment for age and BMI did not change the results, but associations were attenuated after adding sex to the model. Results were similar for muscle mass normalized to height and sex-specific models.

Table. Odds ratios and 95% confidence intervals for the associated between one standard deviation increase in leg muscle mass and foot pain, foot structure (MAI), and foot function (CPEI)

	n (%)	Crude Model OR (95% CI)	p-value	Adjusted Model (age, BMI, sex) OR (95% CI)	p-value
Foot pain	385 (21)	0.83 (0.74, 0.94)	0.0023	0.93 (0.74, 1.18)	0.5727
Foot Structure (MAI)					
low arch	474 (26)	1.13 (1.01, 1.27)	0.0296	0.90 (0.71, 1.13)	0.3671
high arch	548 (30)	0.85 (0.76, 0.95)	0.0048	0.82 (0.65, 1.03)	0.0949
Foot Function (CPEI)					
pronator	559 (31)	0.74 (0.66, 0.83)	<.0001	0.96 (0.76, 1.21)	0.7233
supinator	535 (30)	1.17 (1.05, 1.31)	0.0055	0.84 (0.67, 1.05)	0.1197

Conclusion: Our results suggest that although leg muscle mass was associated with foot pain, foot structure and foot function in our population of middle-aged and older adults, these relations are confounded by sex. Leg muscle mass is likely not a determinant of foot pain, structure or function. These results highlight the need for future work to examine the role of foot pain, structure and function in understanding other aspects of impairment and physical function.

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Associations of Foot Structure and Function to Low Back and Lower Extremity Pain. Jody L. Riskowski[1], Alyssa B. Dufour[2], Thomas J. Hagedorn[3], Howard J. Hillstrom[4], Virginia A. Casey[3] and Marian T. Hannan[1]. [1]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [2]Hebrew SeniorLife & Boston Univ, Boston, MA, [3]Hebrew SeniorLife, Boston, MA, [4]Hospital Special Surgery (HSS), New York, NY

Background/Purpose: Common risk factors of low back/lower extremity (LB/LE) joint pain are age, gender and body mass index (BMI), with women, older adults and overweight/obese individuals at increased risk. However, as foot motion during gait influences the movement pattern through the kinetic chain, foot structure and function may also be associated with lower extremity joint pain. Thus, the aim was to evaluate the relations of LB/LE pain to foot structure and function in a population-based study.

Methods: Framingham Foot Study members with complete data on pain in the LB/LE joints as well as foot structure and function were included.

LB/LE joint pain was determined by the response to the NHANES-type question, "On most days do you have pain, aching or stiffness in your [low back, hips, knees, ankles, or feet]?" Bilateral and unilateral pain were weighted the same; responses were dichotomized to yes or no.

A pressure mat (Matscan, Tekscan Inc.) yielded foot structure and function data during bipedal standing, and while walking, using the two-step method. From these data, modified arch index (MAI), a measure of foot structure, and center of pressure excursion index (CPEI), a measure of foot function, were calculated.

Foot structure classification used MAI, with participants who had a foot in the top or bottom 20% of these values considered low arch or high arch, respectively, with the middle 60% the referent. Foot function classification used CPEI, with those who had a foot in the top or bottom 20% of these

values denoted as supinators or pronators, respectively, with the middle 60% the referent.

Crude and adjusted (age, gender, BMI) logistic regression analysis (SAS, v. 9.3) determined associations of LB/LE pain to foot structure and function. Alpha was set to $p \leq 0.05$.

Results: There were 1856 participants (age: 63.8 $\pm$ 8.9 years; BMI: 28.6 $\pm$ 5.6 kg/m^2; 56% women). Of the sites assessed, low back pain was the most common at 34.1%, followed by knee pain at 29.4%; ankle pain was the least prevalent at 11.2% (Table 1).

Those with high arch foot structure had 26% lower odds of low back pain, whereas those with low arch structure had higher odds of knee (57%) and ankle (47%) pain. Supinated foot function during gait was associated with a 31% reduced odds of hip pain. After adjustment, odds ratios were attenuated and confidence intervals widened.

Table 1. Crude and adjusted odds ratios (with 95% confidence intervals) of associations of lower extremity joint pain to foot structure, assessed using modified arch index (MAI), and to foot function, assessed using center of pressure excursion index (CPEI).

Region of Interest	N, % with Pain	MAI – Crude Model Low Arch	MAI – Crude Model High Arch	MAI – Crude Model Low Arch	MAI – Crude Model High Arch
Low Back	632, 34.1%	1.08 (0.85, 1.35)	**0.74 (0.57, 0.95)**	0.94 (0.74, 1.21)	0.80 (0.61, 1.03)
Hips	325, 17.5%	1.25 (0.94, 1.66)	0.98 (0.71, 1.34)	1.04 (0.83, 1.53)	1.12 (0.83, 1.53)
Knees	546, 29.4%	**1.57 (1.24, 1.99)**	0.86 (0.66, 1.13)	1.17 (0.91, 1.52)	1.05 (0.80, 1.39)
Ankles	207, 11.2%	**1.47 (1.05, 2.06)**	1.00 (0.68, 1.47)	1.14 (0.79, 1.64)	1.16 (0.78, 1.71)
Feet	487, 26.2%	1.22 (0.95, 1.56)	0.84 (0.64, 1.11)	1.04 (0.80, 1.35)	0.92 (0.70, 1.22)

Region of Interest	N, % with Pain	CPEI – Crude Model Pronators	CPEI – Crude Model Supinators	CPEI – Adjusted Model* Pronators	CPEI – Adjusted Model* Supinators
Low Back	632, 34.1%	1.20 (0.96, 1.51)	0.91 (0.72, 1.16)	1.19 (0.94, 1.49)	0.98 (0.77, 1.25)
Hips	325, 17.5%	0.82 (0.62, 1.08)	**0.69 (0.51, 0.93)**	0.76 (0.57, 1.02)	0.78 (0.57, 1.05)
Knees	546, 29.4%	0.92 (0.72, 1.16)	0.90 (0.70, 1.14)	0.94 (0.73, 1.20)	0.97 (0.75, 1.26)
Ankles	207, 11.2%	0.86 (0.61, 1.22)	0.92 (0.65, 1.30)	0.86 (0.61, 1.23)	0.99 (0.69, 1.42)
Feet	487, 26.2%	1.10 (0.87, 1.41)	0.89 (0.69, 1.15)	1.08 (0.84, 1.39)	0.97 (0.74, 1.26)

* Model adjusted by age, gender, body mass index

Conclusion: A low arch structure, but not high arch structure or foot function, is associated with greater odds of lower extremity joint pain. The results suggest that differences in the kinetic chain may exist between those with high, low, and normal arch structure, and future studies should evaluate if differences in movement patterns are related to foot structure. Further, as this study is cross-sectional, longitudinal studies are needed to determine the cause-effect relations between foot structure and function to LB/LE pain.

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Associations of Foot Forces and Pressures to Regional Foot Pain: The Framingham Foot Study. Jody L. Riskowski[1], Thomas J. Hagedorn[2], Alyssa B. Dufour[3], Virginia A. Casey[4] and Marian T. Hannan[1]. [1]Hebrew SeniorLife & Harvard Med School, Boston, MA, [2]Hebrew SeniorLife, Boston, MA, [3]Hebrew SeniorLife & Boston Univ, Boston, MA, [4]Hebrew Senior Life, Boston, MA

Background/Purpose: Foot pain is a risk factor for disability; however, not all foot pain is the same. Foot pain etiology can vary by region (e.g., toe pain may arise from overlapping toes, forefoot pain from hallux valgus), suggesting its effects on foot biomechanics may differ as well. Therefore, the aim of this study was to evaluate differences in foot biomechanics during gait by region of foot pain.

Methods: Framingham Foot Study participants with complete data on regional foot pain, foot biomechanics, and foot disorders were included in this study.

A trained examiner conducted a validated foot exam to determine presence of the following structural foot disorders: hallux valgus, hallux rigidus, claw toes, overlapping toes and hammer toes.

Biomechanical data were collected using a pressure mat (Tekscan Matscan) as participants walked barefoot at a self-selected pace. Data were processed (Novel Automask) to extract maximum force and peak pressure at the toes, forefoot, midfoot, and rearfoot.

Participants selected location(s) of foot pain from a graphic, with location options including toe, nail, ball of foot, forefoot, arch, heel and hindfoot. The eight locations of pain were collapsed into four regions: toes (toe and nail pain); forefoot (forefoot and ball pain); midfoot (arch pain); and rearfoot (heel and hindfoot pain).

Each foot was classified into one of seven groups: 1) toe pain only; 2) forefoot pain only; 3) midfoot pain only; 4) rearfoot pain only; 5) pain in two regions; 6) pain in three or more regions; and 7) no regional pain (referent).

A per-foot analysis using General Estimating Equations (SAS, v. 9.3) determined associations between regional foot pain and biomechanical measures, adjusting for age, gender, weight and presence of structural foot disorders. Alpha was set to p≤0.05.

Results: There were 3158 participants (6280 feet) included (age: 66 ± 10.5 years; BMI: 28 ± 5.5 kg/m^2; 56% women), with 2634 (42%) feet having one or more structural foot disorder.

After adjustment, individuals with midfoot pain had higher midfoot force with greater toe pressure (Figure 1), while those with forefoot pain had greater rearfoot force and less toe force, compared to the referent. Individuals with pain in toes, rearfoot, and multiple regions typically displayed lower rearfoot pressure and force relative to the referent.

Regional peak pressure relative to referent

Regional maximum force relative to referent

Toe Pain · Forefoot Pain · Midfoot Pain · Rearfoot Pain · Pain in 2 regions · Pain in 3 regions
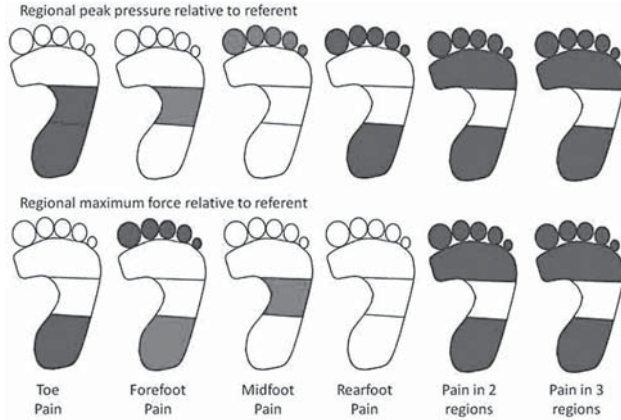
Conclusion: Region of foot pain is associated with biomechanical differences at the pain locale and other foot regions. These results suggest that region of foot pain may be associated with biomechanical differences during gait at other lower extremity joints (e.g., knee and ankle). As changes in gait affect mobility and fall risk, future work should evaluate how region of foot pain affects lower extremity function, falls and disability.

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How Many Steps/Day Are Associated with a Community Level Gait Speed Among Older Adults with or At High Risk of Knee OA? Daniel K. White[1], Roger Fielding[2], Tuhina Neogi[3], Michael P. LaValley[4], K. Douglas Gross[5], Michael C. Nevitt[6], C.E. Lewis[7], James Torner[8] and Catrine Tudor-Locke[9]. [1]Boston University, Boston, MA, [2]Tufts Medical Center, [3]Boston Univ School of Medicine, Boston, MA, [4]Boston University School of Public Health, Boston, MA, [5]MGH Institute of Health Professions, Boston, MA, [6]University of California-San Francisco, San Francisco, CA, [7]University of Alabama, Birmingham City, AL, [8]University of Iowa, Iowa City, Iowa City, IA, [9]Pennington Biomedical Research Center, Baton Rouge

Background/Purpose: While recommended levels of physical activity associated with reducing the risk of poor health outcomes are well known, it is unclear what minimal level of walking is associated with functional benchmarks specific to older adults. The purpose of this study was to examine the minimal number of steps/day associated with walking at a community level gait speed in older adults with or at high risk of knee osteoarthritis (OA).

Methods: The Multicenter Osteoarthritis Study (MOST) is an NIH funded longitudinal study of older men and women who have or are at high risk for knee OA. Participants at the 60-month visit wore a StepWatch Activity Monitor to record walking behavior over 7 days. Usual gait speed (m/s) during a 20 meter walk was determined at the same clinic visit. Walking behavior (steps/day) that best discriminated a gait speed of ≥1.2 m/s (speed needed to cross the street) was determined using a Receiver Operator Curve (ROC). Sensitivity, specificity, and positive predictive value (PPV) was calculated to quantify how well the identified steps/day predicted walking at least 1.2 m/s.

Results: Among 1,757 participants considered (67 ± 8 yrs, BMI 31 ± 6 kg/m^2, female 59%), mean walking behavior was 7,094 ± 2,917 steps/day [range 640–21,593] and mean gait speed was 1.22 m/s ± 0.21 [range 0.4 – 2.1]. Walking at least 6,500 steps/day discriminated meeting a gait speed of ≥1.2 m/s (sensitivity = 70%, specificity = 64%, PPV = 71%).

Conclusion: Most older adults with or at high risk of knee OA who walk at least 6,500 steps/day have gait speeds associated with walking in the community. While further confirmation is needed, at present clinicians may consider setting a goal of 6,500 steps/day as a minimal level of walking for older adults with or at high risk of knee OA.

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ARHP Concurrent Abstract Session
Osteoarthritis
Sunday, November 11, 2012, 2:30 PM–4:00 PM

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Racial Differences in Pain Coping Efficacy in Patients with Hip and Knee Osteoarthritis. Kelli D. Allen[1], Hayden B. Bosworth[1], Cynthia Coffman[1], Jennifer H. Lindquist[1], Nina R. Sperber[1], Morris Weinberger[2] and Eugene Z. Oddone[1]. [1]Duke and Durham VA Medical Center, Durham, NC, [2]University of North Carolina at Chapel Hill & Durham VA Medical Center, Durham, NC

Background/Purpose: Studies have shown that African Americans with osteoarthritis (OA) have greater pain than Caucasians. However, little is known about whether there are racial differences in patients' perceived ability to cope with OA-related pain (coping efficacy). This study examined relationships among race, pain coping efficacy, and pain severity in patients with hip and knee OA.

Methods: We analyzed baseline data from 515 participants in a randomized controlled trial of a telephone-based OA self-management program (mean age = 60 years; 93% male; 46% non-white − 43% African American, 3% other racial/ethnic minorities). Pain coping efficacy was assessed with two questions: "Based on all the things you did to cope, or deal, with your arthritis pain during the last week, 1.) how much **control** do you feel you had over it and 2.) how much were you able to **decrease** it?" Responses used a 7-point Likert scale (0=no control/can't decrease it at all to 6 = complete control/can decrease it completely). Pain severity was assessed with the Arthritis Impact Measurement Scales-2 (AIMS2) pain subscale, which includes 5 items; total scores range from of 0 (least) to 10 (worst) pain. We first fit simple linear regression models to examine the associations of pain severity (AIMS2) and race with the two pain coping efficacy questions. We then used multiple linear regression modeling to examine associations of pain coping efficacy with race and pain severity, as well as whether the relationship between pain coping efficacy and pain severity differed by race (interaction term).

Results: More severe pain was associated with lower pain coping efficacy (regression coefficient = −0.22, p <0.0001 for ability to **decrease** pain, regression coefficient = −0.28, p<0.0001 for perceived **control** over pain). There was no racial difference in perceived ability to **decrease** pain (regression coefficient = −0.13, p=0.37). However, mean perceived **control** over pain was 0.36 points lower for non-whites compared to whites (2.99 vs. 3.35, p = 0.01). In the multiple linear regression model, perceived **control** over pain was 0.76 points lower for non-whites compared to whites (p = 0.09), and more severe pain was associated with lower perceived **control** (regression coefficient = −0.21, p<0.001). In addition, there was some evidence that the relationship between perceived pain control and pain severity differed by race (interaction term p=0.05); specifically, the slope was steeper for non-whites, so that the racial difference in perceived pain control was greater at higher levels of pain (with non-whites perceiving less pain control at higher pain levels).

Conclusion: Non-white patients with OA perceived less control over their pain than whites, and this difference appears to be particularly accentuated at greater pain levels. These results highlight the importance of building our understanding of effective mechanisms to reduce racial differences in both pain severity and pain coping efficacy among individuals with OA.

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African American Adults Less Willing to Undergo Joint Replacement Surgery: The Multicenter Osteoarthritis Study. Julie J. Keysor[1], Huan J. Chang[2], Tianzhong Yang[3], Cora E. Lewis[4], James Torner[5], Michael C. Nevitt[6] and David T. Felson[3]. [1]Boston Univ Sargent College, Boston, MA, [2]The Journal of the American Medical Association, Chicago, IL, [3]Boston Univ School of Medicine, Boston, MA, [4]University of Alabama, Birmingham City, Birmingham, AL, [5]University of Iowa, Iowa City, Iowa City, IA, [6]University of California-San Francisco, San Francisco, CA

Background/Purpose: "Willingness" to undergo joint replacement surgery (JRS) is predictive of subsequent JRS among community-dwelling older adults and could, at least in part, explain the noted ethnic disparity in JRS utilization. Differences between African Americans and whites in JRS "willingness" have not been explored nor have other factors that affect willingness.

Methods: The Multicenter Osteoarthritis Study (MOST) is a prospective community-based study of 3026 adults 50–79 years old with or at risk of developing symptomatic knee or hip osteoarthritis (OA). Participants were from Birmingham, Alabama and Iowa City, Iowa. "Willingness to undergo JRS" was ascertained among participants at the 60-month visit as follows: "based on your understanding of the risks and benefits of hip and knee joint replacement surgery and if your symptoms were severe enough, would you be willing to have joint replacement surgery for your hips or knees?" Responses were coded "willing" or "not willing". The following risk factors for willingness were assessed at the same time: age, gender, education, and race (African American and white); living situation (alone vs. with someone), comorbidity, OA radiographic severity, pain severity, function, depressive symptoms, pain catastrophizing, and study site. We excluded participants who already had a knee or hip replacement (N=438). We used logistic regression to examine the association of ethnicity with JRS willingness after adjusting for covariates.

Results: 1808 subjects who participated in the 60 month exam were included. The mean age of the sample was 67.7 (SD 7.8); 60% were female, 14% were African American, 27% did not have education beyond high school;18.4% lived alone; 11% had high depressive symptoms; 25% reported high pain catastrophizing. In crude and adjusted models, African Americans were significantly less likely to report being "willing" to undergo JRS (Table 1). Willingness declined with age and those from Alabama were less willing than subjects from Iowa. Men and persons with depressive symptoms tended to be less willing (p=0.06). Knee OA severity, pain severity, function, pain catastrophizing, andr living situation were not associated with willingness.

Table 1. Risk Factors Associated with "Willingness" to Have a Total Joint Replacement (Odds Ratios below one signify decreased willingness to undergo THR or TKR; Bold highlight indicates p=0.05 significance)

Variable (range)	Unadjusted Odds Ratio	Unadjusted 95% Confidence Interval	Adjusted Odds Ratio	Adjusted 95% Confidence Interval
Race (African American vs. White)	**0.27**	**0.20, 0.35**	**0.32**	**0.23,0.45**
Age 50–59 years			1	referent
Age 60–69 years			**0.81**	**0.59, 1.11**
Age 70–79 years			**0.50**	**0.36, 0.69**
Age 80+ years			**0.37**	**0.22, 0.60**
Alabama site (referent Iowa)			**0.68**	**0.53, 0.89**
Male (referent female)			1.3*	1.00, 1.64*
Lives alone (referent lives with someone)			1.0	0.75, 1.34
OA Severity			0.93	0.85, 1.04
Education (referent: some high school)			1.14	0.63, 2.06
Comorbidity			1.04	0.95, 1.14
Pain Severity (1–10)			0.98	0.92, 1.05
WOMAC function (lowest tertile: best)			1.0	referent
WOMAC function (middle tertile)			1.16	0.85, 1.58
WOMAC function (highest tertile: worst)			1.10	0.74, 1.62
Depressive symptoms (referent no symptoms)			0.71*	0.50, 1.02*
Pain catastrophizing			0.81	0.62, 1.07

* Approached significance at p=.06

Conclusion: "Willingness" may explain some of the disparities in TKR utilization between African Americans and whites. Older and depressed persons and persons from certain locale's may also be less willing to have TKRs and THRs. Longitudinal studies are needed to establish causality.

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Clinical and Biomechanical Characteristics of Total Hip Arthroplasty Responders and Nonresponders. Genna Waldman[1] and Kharma C. Foucher[2]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical Center, Chicago, IL

Background/Purpose: In a recent study, 14% of total hip arthroplasty (THA) patients were classified as nonresponders, using osteoarthritis (OA) treatment response criteria[1]. Identifying characteristics of responders and nonresponders could lead to better ways to identify and manage likely nonresponders. The purpose of this study was to test the hypothesis that responders have different preoperative and postoperative clinical and gait characteristics than nonresponders. A secondary goal was to evaluate the utility of the Harris hip score (HHS) for calculating response.

Methods: We identified 132 THA patients with pre- and one year postoperative gait and HHS data from our IRB-approved data repository. We calculated responder criteria in three ways based on the literature[1]: (i) Return to Normal (RTN): follow-up HHS ≥ 2 standard deviations above baseline; (ii) a modified version of OMERACT-OARSI responder criteria: relative change $\geq 20\%$; and (iii) Minimally Important Different (MID): follow-up HHS score ≥ 0.5 standard deviation above baseline. Gait variables of interest were self-selected normal walking speed, sagittal plane dynamic range of motion (ROM) and the 3D peak external moments. We used t-tests to compare pre- and postoperative gait variables for responders and nonresponders.

Results: 20%, 13% and 7% of patients were classified as nonresponders based on RTN, modified OMERACT-OARSI, and MID criteria, respectively. Using the modified OMERACT-OARSI criteria, baseline physical characteristics were similar for both groups (table). Preoperatively, nonresponders had 35% higher HHS (p<0.001) and 25% higher ROM (p=0.021) compared to responders. After surgery, nonresponders had significantly lower HHS compared to responders (p<0.001), as well as lower adduction and external rotation moments (p=0.038). Findings were similar when comparisons were done using the other responder criteria.

Table. Characteristics of THA subjects classified as responders and nonresponders

		Responders (87%)	Nonresponders (13%)	p value
Baseline Physical Characteristics	Age (yrs)	60 ± 10	61 ± 10	0.868
	BMI (kg/m2)	29 ± 5	28 ± 4	0.475
	Sex	58 F/57 M	8 F/9 M	0.795
Clinical Characteristics	*Preoperative HHS	**55 ± 13**	**74 ± 14**	**<0.001**
	*Postoperative HHS	**93 ± 8**	**80 ± 17**	**<0.001**
	*Absolute Change	**39 ± 12**	**6 ± 8**	**<0.001**
	*Relative Change (%)	**80 ± 44**	**9 ± 11**	**<0.001**
Preoperative Gait Biomechanics	'Normal' walking speed (m/s)	1.01 ± 0.24	1.02 ± 0.20	0.930
	*Dynamic sagittal plane range of motion (degrees)	**16 ± 6**	**20 ± 6**	**0.021**
	Peak Flexion Moment (%Body Weight × Height)	4.19 ± 1.49	4.97 ± 1.98	0.140
	Peak Extension Moment (%Body Weight × Height)	1.79 ±0.86	1.80 ± 0.67	0.954
	Peak Adduction Moment (%Body Weight × Height)	3.45 ± 1.02	3.23 ± 1.30	0.423
	Peak Abduction Moment (%Body Weight × Height)	1.60 ± 0.86	1.73 ± 0.75	0.548
	Peak External Rotation Moment (%Body Weight × Height)	0.33 ± 0.21	0.34 ± 0.26	0.818
	Peak Internal Rotation Moment (%Body Weight × Height)	0.37 ± 0.22	0.37 ± 0.15	0.994
Postoperative Gait Biomechanics	'Normal' walking speed (m/s)	1.19 ±0.19	1.13 ± 0.19	0.249
	Dynamic sagittal plane hip range of motion (degrees)	25 ± 6	25 ± 6	0.915
	Peak Flexion Moment (%Body Weight × Height)	5.91 ± 2.03	5.82 ± 2.17	0.852
	Peak Extension Moment (%Body Weight × Height)	2.70 ± 1.10	2.82 ± 0.83	0.664
	*Peak Adduction Moment (%Body Weight × Height)	**3.54 ± 0.94**	**3.03 ± 0.91**	**0.038**
	Peak Abduction Moment (%Body Weight × Height)	1.88 ± 0.84	1.87 ± 0.97	0.921
	*Peak External Rotation Moment (%Body Weight × Height)	**0.43 ± 0.23**	**0.31 ± 0.21**	**0.038**
	Peak Internal Rotation Moment (%Body Weight × Height)	0.51 ±0.21	0.44 ±0.18	0.201

*bold text indicates t-test or chi-square test p<0.05

Conclusion: Although a different score was used, a similar proportion of THA patients were classified as nonresponders here as in a previous study[1]. This suggests that the HHS can be used to calculate response criteria if WOMAC scores are unavailable. HHS and ROM were initially higher in patients who would become nonresponders, but after surgery the nonresponders were left with lower mean HHS and lower adduction and external rotation moments. These gait moments reflect net activity of hip abductors. More work is needed to determine whether addressing the abductor impairment suggested by the biomechanical data would improve response. These results demonstrate that some patients who would appear to be more highly functioning before surgery may have both poorer responses and poorer final outcomes.

Reference

1. Judge et al., Arthritis Care Res. 62:480–8, 2010.

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A Rich Description of Clinical Exam Features in Patients with Knee Osteoarthritis and Their Correlation with Functional Outcomes.

Maura D. Iversen[1], Kelli Sylvester[2], Abigail Grader[2], Michelle A. Frits[3], Marie Boneparth[4], Megan Whitmore[4], Jane Lucas[5], Fatima Shahzad[6], Jeffrey B. Driban[6] and Chenchen Wang[6]. [1]Northeastern University, Department of Physical Therapy, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [2]Department of Physical Therapy, Northeastern University, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Tufts Medical Center, Boston, [5]Back Bay Physical Therapy, Boston, [6]Tufts Medical Center, Boston, MA

Background/Purpose: Assessments of symptomatic knee osteoarthritis (KOA) rely on physical measures for clinical decision-making. However, there is limited literature on the association between examination procedures and reported KOA symptoms and activity limitations. This study aims to: (1) provide a rich clinical description of patients with KOA and (2) correlate examination findings with self-reported measures to determine the most efficient exam procedures to classify disease severity.

Methods: This is a secondary analysis of baseline data from 47 patients with symptomatic and radiographic KOA recruited for a randomized clinical trial comparing tai chi and physical therapy. Patients completed self-reported outcome surveys (e.g., WOMAC Osteoarthritis Index [VAS scale]), performance tests (Timed Walk, repeated Sit-to-Stand, 6-min Walk Test, Berg balance), and a standardized physical examination by a physical therapist. The exam included: an interview, muscle flexibility (Ober and Ely), muscle strength testing, ligamentous stability and meniscus integrity tests (e.g., Lachman, McMurray), pain provocation (patella compression), range-of-motion and functional assessments (Waldron squat test). Descriptive statistics and correlations were used to characterize the sample and determine associations between exam procedures, performance tests and outcome measures.

Results: Patients were 58 years of age (SD=9.8), 68% were female, 54% were Caucasian. Most (78%) had a high school education/some college and 30% were employed. 83% had unilateral knee involvement and 25% used an ambulatory device. Patients reported limited function (mean WOMAC function =879.5 [SD= 376]) and pain (mean WOMAC pain = 254.5 [SD=99]) and were at low fall risk (mean Berg= 53.8[SD=2.7]). Few patients tested positive for ligament instability and 2/3 tested positive for patellofemoral involvement. There was a low to moderate correlation between self-reported pain and subject performance on tests of functional strength, aerobic fitness and walking speed. Iliotibial band tightness (based on a positive Ober test) was significantly correlated with increased pain, stiffness and self-reported functional limitations **(TABLE 1)**.

Table 1. Correlations with Self-reported KOA Symptoms and Clinical Test Performance and Physical Examination Procedures

Clinical and Performance Tests	M ± SD N (%)	WOMAC pain	WOMAC stiffness	WOMAC function
6-minute Walk Test (meters)	403.6 ± 83.5	**r=−0.37**	r=−0.20	**r=−0.42**
		p=0.01	p=0.18	**p=0.004**
Timed Walk (20m; sec)	18 ± 3.5	**r=0.32**	r=0.20	**r=0.44**
		p=0.03	p=0.18	**p=0.002**
Timed Chair Stand Test (sec)	31.2.3±11.3	r=0.20	r=0.29	**r=0.37**
		p=0.20	p=0.06	**p=0.01**
Positive Ely	43 (92)	r=−0.05	r=0.24	r=0.03
		p=0.70	p=0.10	p=0.80
Positive Ober	17 (36)	**r=−0.35**	**r= −0.37**	**r=−0.44**
		p=0.02	**p=0.008**	**p=0.002**
Positive Lachman	4 (9)	r=−0.09	r=−0.14	r=−0.07
		p=0.50	p=0.3	p=0.60
Positive McMurray	20 (43)	r=0.07	r=−0.07	r=−0.02
		p=0.60	p=0.6	p=0.90
Positive Waldron Test (pain and crepitus with squat)	8 (17)	r=−0.09	r=−0.15	r=−0.10
		p=0.50	p=0.3	p=0.40
Grind Test (pain with patella compression)	31 (66)	r=0.10	r=−0.17	r=−0.02
		p=0.50	p=0.25	p=0.90

Note: M = mean, SD = standard deviation WOMAC= Western Ontario and McMaster Index

Conclusion: Patients with symptomatic KOA had varied clinical presentations. Those with iliotibial band tightness reported more knee pain, stiffness, and functional limitations. Pain provocation tests were not associated with greater dysfunction or symptoms although most patients tested positive with these tests. Self-reported pain correlated significantly with physical performance test outcomes. The Ober test appears to be a useful clinical maneuver that is associated with KOA related functional difficulties and symptoms. Clinical performance tests of gait speed and aerobic capacity may help identify patients with more severe disease and are less costly than radiographic tests.

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Does Unpredictable Intermittent Knee Pain Limit Functional Ability and Walking Frequency in Knee OA?

Daniel K. White[1], Gillian A. Hawker[2], David T. Felson[1], K. Douglas Gross[3], Jingbo Niu[4], Michael C. Nevitt[5], C.E. Lewis[6], James Torner[7] and Tuhina Neogi[4]. [1]Boston University, Boston, MA, [2]Women's College Research Institute, University of Toronto, Toronto, ON, [3]MGH Institute of Health Professions, Boston, MA, [4]Boston Univ School of Medicine, Boston, MA, [5]University of California-San Francisco, San Francisco, CA, [6]University of Alabama, Birmingham City, AL, [7]University of Iowa, Iowa City, Iowa City, IA

Background/Purpose: People with knee osteoarthritis (OA) reported that unpredictable pain restricts their ability to engage in physical activities in a qualitative study. Since walking is the most common physical activity employed by older adults, it would be important to understand if unpredictable pain impacts walking frequency, which would have important health implications. It is also not clear if unpredictable pain contributes to other functional limitations or restrictions in health-related quality of life (HRQOL). We therefore evaluated the association of unpredictable pain with walking frequency, more general function, and physical health related quality of life in people with or at high risk of knee OA.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of people who have or are at high risk for knee OA. Participants at the 84-month visit who indicated they had intermittent knee pain were asked to rate the frequency of unpredictable pain, i.e., starts without warning, and the frequency of predictable pain, i.e., starts with a trigger. Both were rated on a Likert scale (Never to Very Often). Participants were categorized as having no pain, predominantly unpredictable pain, predominantly predictable pain, or both types according to the worst knee. At the same visit, gait speed over 20 meters, the WOMAC physical function (PF) subscale, and the SF-12 physical function (as a measure of HRQOL) subscale were collected. Steps/day was also collected using a pedometer (Stepwatch) over the next 7 days. We calculated study outcomes according to the presence of unpredictable and/or predictable pain, adjusting for age, sex, BMI, comorbidities, frequency of pain, and depressive symptoms using linear regression.

Results: Of data from the 84-month study visit to date, 664 people had intermittent knee pain (Age 68.5 ± 7.6 yrs, BMI 31.3 ± 6.6 kg/m^{2}, female 70%). Predominantly unpredictable pain was reported in 12%; these subjects had significantly more self-reported functional limitation (WOMAC-PF). However, other outcomes were not statistically significantly different compared with those with no pain. Subjects with predictable pain and both pain types also had worse WOMAC-PF compared with those with no pain, however all other outcomes had values similar to those with no pain. See Table.

Table. Mean and standard error values stratified by pain categories. Mean values are adjusted for age, sex, BMI, comorbidities, frequency of knee pain and depressive symptoms. * indicates p<0.01 compared with 'None' Pain type

Pain type	N (%)	Outcome	Mean	Standard Error
None (i.e., never or seldom predictable	40 (6)	Steps/day	6765.4	484.2
and/or unpredictable pain)		Gait speed (m/s)	1.17	0.02
		WOMAC PF	13.9	1.5
		SF-12	42.3	1.5
Predominantly Unpredictable Pain	80 (12)	Steps/day	7339.2	383.6
		Gait speed (m/s)	1.15	0.02
		WOMAC PF*	15.7	1.1
		SF-12	42.2	1.1
Predominantly Predictable Pain	375 (56)	Steps/day	7353.1	185.0
		Gait speed (m/s)	1.17	0.01
		WOMAC PF*	18.4	0.6
		SF-12	40.8	0.6
Both Unpredictable and predictable pain	169 (25)	Steps/day	7036.1	278.1
		Gait speed (m/s)	1.15	0.02
		WOMAC PF*	21.1	0.8
		SF-12	40.5	0.8

Conclusion: While unpredictable knee pain was associated with more self-reported functional limitation, it was not associated with walking ability and frequency, or HRQOL. Similar findings were noted for those with predictable pain. Pain, regardless of its predictability, may not necessarily adversely affect engagement in walking, but does appear to affect self-perceived function.

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BMI, Occupational Activity, and Leisure-Time Physical Activity: an Exploration of Risk Factors and Modifiers for Knee Osteoarthritis. Kathryn Remmes Martin[1], Diana Kuh[2], Tamara B. Harris[1], Jack M. Guralnik[3], David Coggon[4] and Andrew K. Wills[5]. [1]NIA/NIH, Bethesda, MD, [2]Medical Research Council, London, United Kingdom, [3]University of Maryland, Baltimore, [4]University of Southampton, Southampton, United Kingdom, [5]University of Bristol, Bristol, United Kingdom

Background/Purpose: Risk of knee osteoarthritis (OA) is increased by obesity, and also by physical activities which mechanically stress the joint. The few studies which have examined the interaction between body mass index (BMI) and activity have yielded inconsistent findings. We examined whether the association of BMI across adult life on midlife knee OA was modified by occupational activity and/or leisure-time physical activity (PA).

Methods: Data came from a nationally representative British birth cohort in which 2597 participants underwent clinical examination and assessment of knee OA at 53y. Main exposures at 36, 43 and 53 years: BMI (kg/m²), self-reported leisure-time PA (inactive, less-active, and most-active) and occupational activity – kneeling/squatting; lifting; climbing; or sitting, with likelihood of exposure (unlikely, somewhat-likely and most-likely) assigned using a job-exposure matrix. Odds ratios (OR) for knee OA were estimated at each time-point using logistic regression. Interactions between BMI and occupational or leisure-time PA were tested using a likelihood ratio test (LRT); where p was<0.05, we identified elevated risk by examining BMI in each activity-level, and activity in each BMI-stratum based on standard deviations (-1SD, 0SD, and 1SD). Analyses were stratified by sex, and adjusted models included socioeconomic position and health status variables.

Results: For men, evidence of an interaction between BMI and lifting (LRT p=0.01) occurred only at 43y. BMI increased knee OA risk for men who were most-likely to lift at work (OR per z-score of BMI: 3.55, 95%CI: 1.72–7.33). Interestingly, among those men most-likely to lift at work, those with lower BMI (≤0SD) were at lower risk of knee OA than those somewhat-likely to lift (-1SD - OR: 0.14, 95%CI: 0.03–0.60; 0SD - OR: 0.30, 95%CI: 0.11–0.84). For women, evidence of an interaction between BMI and leisure-time PA (LRT: p=0.005) occurred only at 43y. BMI increased knee OA risk at higher levels of PA (OR per z-score of BMI: 1.59, 95%CI: 1.26–2.00 in inactive; 1.70, 95%CI: 1.14–2.55 in less-active; and 4.44; 95%CI: 2.26–8.36 in most-active). Interestingly, among those women who were most-active, those with lower BMI (≤0SD) were at lower risk of knee

OA than those less-active (-1SD - OR: 0.14, 95%CI: 0.04–0.48; 0SD - OR: 0.36, 95%CI: 0.18–0.73).

Conclusion: Our results suggest that high BMI may be more detrimental to joint health among individuals exposed to greater levels of activity. A better understanding of these relationships may be required to optimize the potential benefits of PA and identify high risk groups within particular occupations.

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ACR Concurrent Abstract Session
Fibromyalgia and Soft Tissue Disorders I
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Symptom Improvement in Fibromyalgia Patients Is Related to Reduced Network Connectivity As Measured by EEG Coherence. Jeffrey B. Hargrove[1], Robert M. Bennett[2], Daniel J. Clauw[3], George Mashour[3] and Lauren Briggs[4]. [1]Kettering University, Flint, MI, [2]Oregon Health & Science Univ, Portland, OR, [3]University of Michigan, Ann Arbor, MI, [4]Grand Valley State University, Allendale, MI

Background/Purpose: To assess changes in brain functional network connectivity (FC) in fibromyalgia (FM) patients treated with Reduced Impedance Noninvasive Cortical Electrostimulation (RINCE). Previous studies using fMRI have reported increased FC in FM, and pain reduction has been shown to correlate with reduced FC following intervention (Arthritis Rheum. Epub 2012). Herein, we explored the notion that FC, as evaluated by electroencephalography (EEG) coherence, would be reduced by treatment with RINCE and associated with clinical improvements.

Methods: Changes in EEG coherence in subjects receiving RINCE (N=37) were compared to subjects receiving sham (N=35). Coherence is a correlation of relative amplitude and phase between pairs of EEG signals that provides information about FC across brain regions. Under IRB-approval, eyes-closed resting EEG was collected for each subject at baseline and within one week of RINCE therapy completion. EEG was collected at 19 International 10–20 electrode sites using a linked-ear reference, sampled at 16-bits, 512 samples per second. EEG files were edited to remove non-EEG artifact. To reduce coherence biasing due to cortical volume conduction over short spatial distances, only non-neighboring electrode pairings (N=118) were analyzed. Coherence was calculated using NeuroGuide 2.0 software and low frequency (1–4Hz) signal components were analyzed and compared between groups. FM symptomatology was assessed with the Fibromyalgia Impact Questionnaire (FIQ) and the SF-36.

Results: Baseline coherence was consistent between groups in 112 of 118 electrode pairs (95%, P<0.05). Following RINCE treatment, a number of significant positive correlations in both inter- and intra-hemispherical electrode pairings were found between change from baseline coherence and improvements in total FIQ and SF-36 domains (see Figure 1). Subjects experiencing reduced coherence in the electrode pairs correlating to FIQ improvement had significantly greater improvements in FIQ total score and pain VAS scale when compared to those with stable or increased coherence (see Table 1).

Table 1. Changes in FIQ total score and pain VAS scale as a function of coherence response

	Intragroup Comparisons			
	RINCE Group		SHAM Group	
	Reduced Coherence	Increased Coherence	Reduced Coherence	Increased Coherence
Baseline FIQ	58.9	64.1	57.2	59.1
End-of-Study FIQ	35.4	53.0	49.1	57.2
P-Value	<0.001	0.023	<0.01	0.80
Baseline Pain VAS	6.9	6.6	6.7	5.5
End-of-Study Pain VAS	3.9	4.9	5.6	5.8
P-Value	<0.01	0.02	0.02	0.87

	Intergroup Comparisons					
	RINCE Group			SHAM Group		
	Reduced Coherence	Increased Coherence	P-Value	Reduced Coherence	Increased Coherence	P-Value
MCFB FIQ	−45%	−19%	<0.001	−14%	−1%	0.07
MCFB Pain VAS	−41%	−20%	0.03	−19%	+7%	0.01

MCFB = mean change from baseline

FIQ Total Score
R-values 0.37-0.38
P-values 0.026-0.034

FIQ Sleep Index
R-values 0.35-0.43
P-values 0.012-0.043

FIQ Fatigue Index
R-values 0.33-0.41
P-values 0.016-0.05

SF-36 Emotional
Wellbeing Domain
R-values 0.33-0.45
P-values 0.007-0.05

SF-36 Social
Functioning Domain
R-values 0.33-0.48
P-values 0.007-0.05
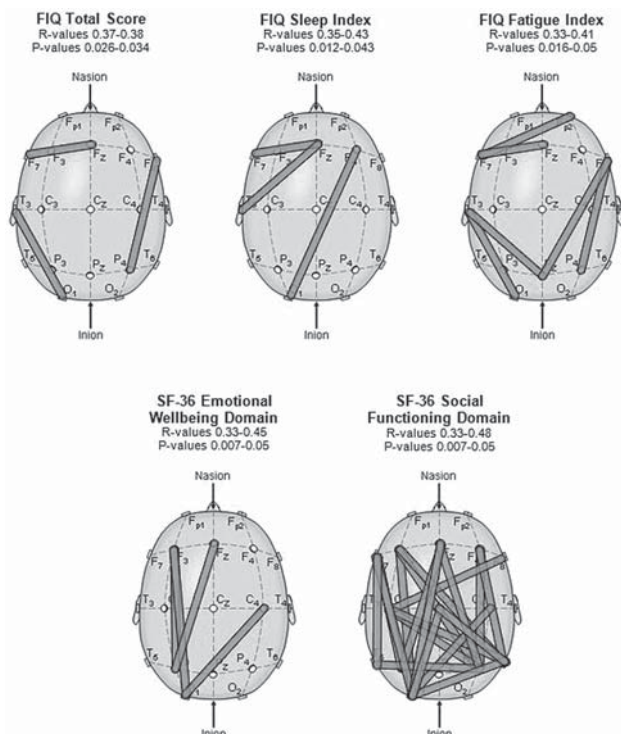
Conclusion: In this study, improvements in FIQ total score and pain VAS scale were greatest in FM subjects showing reductions in brain functional network connectivity based on changes in EEG coherence. This result strengthens previous claims that reduced connectivity may be an objective biomarker of improvement in FM clinical trials. Importantly, it expands the methodology to the use of EEG, which is less costly than fMRI and more generally practical for use in point of care settings.

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Milnacipran Reduces Brain Activity During Pain in Fibromyalgia. Anson E. Kairys, Richard E. Harris, Eric Ichesco, Johnson P. Hampson, Steven Harte, Daniel J. Clauw and Tobias Schmidt-Wilcke. University of Michigan, Ann Arbor, MI

Background/Purpose: Fibromyalgia (FM) is a chronic pain condition characterized by widespread musculoskeletal pain and a number of concomitant symptoms such as fatigue, sleep disturbance, cognitive dysfunction, anxiety, and depression. Milnacipran is a dual serotonin-norepinephrine reuptake inhibitor which has been shown to reduce pain and improve function in FM, however its clinical mechanism of action is largely unknown. Based on its neurotransmitter action in preclinical models, we hypothesized that milnacipran may decrease pain related brain activity in patients with FM.

Methods: 15 FM patients completed a randomized double-blind two-period cross-over study of milnacipran versus placebo. Each 7-week period (drug or placebo) was followed by a 14 day taper and washout.Prior to and following each period, fMRI scans were acquired for each patient. During the fMRI scanning session, pressure was applied to the patient's thumbnail bed. Two pressure intensities were delivered to all subjects in a pseudo-random sequence. One pressure intensity was individually calibrated for each subject to elicit a perceived pain rating of approximately 50/100 (moderate pain).The other pressure intensity was held constant for all subjects at 1.5 kg/cm^2. All fMRI data were pre-processed using SPM5. Regressors of interest (two pressure intensities) were convolved with the hemodynamic response function and applied to voxel-wise statistics. Images were then analyzed using a flexible factorial design within SPM5 to investigate changes in brain activations pre and post drug/placebo treatment. Regions of interest (ROIs) showing

significant changes in blood-oxygen-level-dependent (BOLD) activation during either placebo or drug were extracted and analyzed using SPSS 19.

Results: During milnacipran treatment, FM patients displayed a significant reduction in pain-evoked BOLD activity within the right posterior and left mid-insula (post- minus pre- milnacipran percent BOLD change -0.727 ± 1.09 and -0.485 ± 0.837 respectively) and left inferior parietal lobule (IPL) (mean difference $\pm$ SD: -1.08 ± 1.27; all p<0.05 corrected). None of these changes were seen during treatment with placebo, and in fact an increase in insula BOLD activity during placebo was detected (0.707 ± 0.766 and 0.630 ± 0.581 respectively). The increase in right insula BOLD during placebo appeared to be due to incomplete washout of milnacipran during the cross-over as evidenced by decreased BOLD activity pre-placebo for those taking drug first (n=8; -0.651 ± 0.489; p<0.05).No significant correlations between changes in BOLD activation for any region and improvements in clinical pain were detected (all p>0.10).

Conclusion: Milnacipran reduces pain-evoked BOLD activity within the insula and IPL. Additionally; we find a sustained decrease in insular BOLD activation which persists following the removal of the drug. Although we did not detect a relationship with pain improvement in this small sample, larger samples may be needed to associate brain activity with the clinical mechanism of action of milnacipran.These findings have implications for randomized controlled trials of milnacipran in chronic pain populations.

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Frontal Brain Connectivity to the Default Mode Network Is Associated with Subjective Fatigue Irrespective of Pain and Depression. Johnson P. Hampson[1], Daniel J. Clauw[1], Jieun Kim[2], Vitaly Napadow[3] and Richard E. Harris[1]. [1]University of Michigan, Ann Arbor, MI, [2]Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, [3]Martinos Center for Biomedical Imaging, Charlestown, MA

Background/Purpose: Chronic pain patients report increased levels of fatigue; however, very little is known about the underlying mechanisms of this symptom. Previous work by our group found that chronic pain patients diagnosed with fibromyalgia (FM) have elevated levels of intrinsic connectivity between the insula and the Default Mode Network (DMN) [1], a network thought to be engaged in self-referential thinking.Moreover reductions in DMN to insula connectivity were associated with concomitant reductions in clinical pain [2]. In this exploratory analysis, we investigate the relationship between longitudinal changes in fatigue levels and variation in DMN connectivity, while controlling for pain and depression.

Methods: 17 FM patients underwent resting state fMRI at baseline and at 4 weeks following non-pharmacological intervention. Within-subject resting fMRI data analysis was performed using FSL dual-regression Independent Component Analysis as reported previously [1, 2]. Group level multiple linear regression was done with FSL using change in resting DMN connectivity from baseline to post therapy versus change in fatigue scores, correcting for age and pain or depression. Clinical fatigue, pain, and depressive symptoms were assessed with Multidimensional Fatigue Inventory, the Short Form of the McGill pain questionnaire, and the Center for Epidemiologic Studies Depression questionnaires respectively.

Results: Following therapy there was a trend for reduced fatigue levels (difference mean $= -1.37$; SD $= -0.09 \pm 2.84$; p=0.06). No significant correlation was seen between change in fatigue and pain scores (p=0.92), but a trend towards positive correlation between change in fatigue and depression (p=0.07). FM patients demonstrated significant (p<0.05 corrected) positive correlations between changes in resting DMN connectivity to multiple brain regions and changes in self reported fatigue, even after adjusting for pain and depression.These regions included the bilateral superior frontal gyrus (pain corrected r=0.79 and depression corrected r=0.80), insula (pain corrected r=0.50 and depression corrected r=0.62), and thalamus (pain corrected r=0.63 and depression corrected r=0.72).

Conclusion: This study suggests that connectivity of multiple brain regions to the DMN is associated with subjective reports of fatigue. While the insula and thalamus are known to be involved in pain processing and modulation, the superior frontal gyrus is more typically involved in cognitive function. We speculate that enhanced connectivity of this structure to the

DMN could signify altered cognitive function specifically during periods of elevated fatigue.

References

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A Comparison of the Nociceptive Flexion Reflex, Pressure Algometry and Summated Widespread Pain in the Diagnosis of Fibromyalgia. Robert M. Bennett[1], Kim D. Jones[2] and Janice Hoffman[3]. [1]Oregon Health & Science Univ, Portland, OR, [2]Oregon Health Sciences University, Portland, OR, [3]Oregon Health & Science University, Portland, OR

Background/Purpose: To reevaluate the usefulness of the nociceptive flexion reflex (NFR) in distinguishing between FM patients and healthy controls, compared to computerized algometry and a summated measure of pain in 24 anatomical sites. NFR is a reflex contraction of the biceps femoris muscle elicited by progressive electrical stimulation of the sural nerve. It is measured as the least current (mA) required to stimulate the biceps contraction. Previous studies have reported that FM patients required less current to elicit biceps contraction than healthy controls (HC) *(Arthritis Rheum. 2003 48(5):1420–9, Pain. 2004 Jan;107(1):7–15.)*

Methods: The NFR threshold (NFRz) was evaluated by using a single ascending series of stimulations of 4 mA increments, and the biceps femoris contraction (EMG) was timed in relation to the onset of the stimulus to define the RIII reflex. The evaluation of the NFRz used a computerized NFR Interval z score, defined as NFR Interval Mean-baseline divided by the baseline SD, as previously described *(Pain. 2009 Sep;145(1–2):211–8).* B. Computerized algometry was performed at 4 paired sites (volar forearm, mid trapezius, mid gluteal area and mid-point of anterior thigh) with the average of 3 readings at each site, using an AlgoMed Pressure Algometer (Medoc, Durham, NC.) All subjects estimated their current pain level (VAS 0 –10) at 24 locations representative of widespread pain (Arthritis Res Ther. 2009;11(4); the VASs at the 24 sites were summated into a single figure (0 –; 240).

Results: The study was approved by the OHSU IRB. All subjects were female and FM diagnosis was based on the 1990 ACR criteria. The ages of the FM and HC subjects were similar, but the FM had a higher BMI. In contradistinction to 2 previously reported studies, comparing FM to HC, the NFRz was slightly higher (NS 0.18) in the FM subjects (table 1). As was expected the FM subjects had higher pain ratings on activation of the reflex, but endured more electrical stimulations (NS). Both the mean algometer scores at 4 paired sites and the summated pain at 24 locations provided a very significant discrimination between FM and HC.

	FM N=30	HC N=30	P value
Age	53.2	46.1	0.16
BMI	32.58	28.44	0.039
Current activating biceps reflex NFRz (mA)	24.94	19.10	0.180
Pain VAS at NFRz	68.06	39.66	0.004
Max Current Reached during testing (mA)	33.00	24.48	0.170
Max VAS Rating Given	87.50	66.44	0.002
Number of electrical stimulations	20.57	18.60	0.361
Mean algometer scores at 4 paired sited (kPa)	113.8	465.5	≤0.0001
Summated pain in 24 areas	111	12	≤0.0001

Conclusion: In this study, we were unable to confirm that the nociceptive flexion reflex is decreased in FM patients compared to HC. This difference maybe due to the employment, in the current study, of a computerized evaluation of the NFRz which used a strict definition of the NFRz. On the other hand, 2 less technically demanding methodologies, namely pressure pain at 4 paired sites and a summation of pain VAS at 24 widespread locations, provided a highly significant discrimination between FM and HC. These latter 2 methods need to be studied in a broad variety of rheumatic disorders to evaluate their utility in diagnosing FM in the clinical setting.

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Milnacipran Increases Cortical to Brainstem Connectivity During Pain in Fibromyalgia. Eric Ichesco, Tobias Schmidt-Wilcke, Anson E. Kairys, Johnson P. Hampson, Steven E. Harte, Daniel J. Clauw and Richard E. Harris. University of Michigan, Ann Arbor, MI

Background/Purpose: Fibromyalgia (FM) is a chronic widespread pain disorder characterized by muscle tenderness, fatigue, poor sleep, and mood disturbance.Milnacipran is a dual serotonin-norepinephrine reuptake inhibitor FDA-approved for the treatment of this condition; however its clinical mechanism of action remains unknown.We used functional connectivity magnetic resonance imaging (fcMRI) to examine the effect of milnacipran on brain connectivity during evoked pressure pain.

Methods: 13 patients with FM completed a randomized double-blind two-period cross-over study of milnacipran versus placebo. Each 7-week period (drug or placebo) was followed by a 14 day taper and washout.Prior to and following each period, all subjects underwent fcMRI during which pressure was applied to their thumbnail. Two pressure intensities were delivered in a pseudo-random sequence: an individually calibrated pressure evoking moderate pain (50 on a 100 point Numerical Rating Scale [NRS]) and an equal pressure across all subjects. All fcMRI data were preprocessed and analyzed using Statistical Parametric Mapping 5 and the CONN toolbox-.Seed based functional connectivity analyses included three anterior cingulate cortex (ACC) and bilateral periaqueductal gray (PAG) regions.Paired t-test image comparisons were deemed significant at p<0.05 cluster level corrected. Pearson's r values for connectivity were extracted and correlated with clinical pain from the Brief Pain Inventory (BPI) and "average evoked pain" acquired immediately after the fcMRI run (NRS) for placebo and drug treatments using SPSS 19.

Results: Milnacipran treatment was associated with *increased* connectivity between multiple cortical regions and brain stem areas involved with descending analgesia: the perigenual ACC (seed region) showed greater connectivity to the pons and PAG (both p<0.05 corrected), and the PAG (seed region) showed greater connectivity with the bilateral mid insula cortex and the supplementary motor area/mid cingulate cortex (midCC; all p<0.05 corrected).Milnacipran also significantly *decreased* inter-cortical connectivity between the ACC seed regions and the inferior parietal lobule and midCC (p<0.05 corrected).These effects were not detected during the placebo period (all p>0.05).Interestingly increases in ACC to PAG connectivity following milnacipran were associated with the decreases in clinical pain (BPI interference: r = −0.672, p = 0.012) while decreases in connectivity between the ACC and midCC were associated with reduced levels of average evoked pain (r = 0.648, p = 0.017).

Conclusion: Here we provide the first evidence that milnacipran alters brain connectivity during evoked pain in patients with FM.The increased connectivity between the ACC and the PAG suggests that the analgesic action of milnacipran involves, at least in part, enhanced cortical modulation of brainstem sites implicated in descending antinociception. Conversely, the brain regions that show decreased connectivity during milnacipran therapy are regions where functional connectivity is increased in chronic pain states, and is associated with clinical pain report.

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Posterior Insula Combined Glutamate and GlutamineIs Associated with Pain in Fibromyalgia: A Replication Study. Eric Ichesco, Daniel J. Clauw, Steven E. Harte, Anson E. Kairys, Johnson P. Hampson, Tobias Schmidt-Wilcke and Richard E. Harris. University of Michigan, Ann Arbor, MI

Background/Purpose: Central pain augmentation resulting from enhanced excitatory and/or decreased inhibitory neurotransmission is a proposed mechanism underlying the pathophysiology of functional pain syndromes such as fibromyalgia (FM). Previously, we demonstrated that glutamate (Glu), an excitatory neurotransmitter, and combined Glu and glutamine (Glx) levels are higher within the posterior insula of patients with FM [Harris et al. AnR 2009]. Moreover we also found that reduction in the levels of posterior insula Glx and Glu, following a non-pharmacologic intervention, were also associated with decreased pain [Harris et al. AnR 2008].Here we sought to replicate these findings in a separate sample of FM

patients within the placebo arm of a randomized crossover trial of milnacipran versus placebo.

Methods: Thirteen female individuals (mean age 41.8 yrs, SD = 11.0) satisfying 1990 American College of Rheumatology criteria for FM completed a randomized double-blind two-period cross-over study of milnacipran versus placebo. For the purposes of this analysis, only the placebo periods were studied.Each 7-week period (drug or placebo) was followed by a 14 day taper and washout.Prior to and following each period, proton magnetic resonance spectroscopy (^{1}H-MRS) of the right posterior insula was acquired for each patient at rest.Individual patient spectra were fit with the Linear Combination Model program and the levels of Glx were estimated relative to levels of creatine (Cr) (i.e. Glx/Cr ratio).Immediately prior to each ^{1}H-MRS scan, evoked pressure-pain was delivered to the left thumbnail bed during a functional magnetic resonance imaging (fMRI) run (fMRI data not presented here). Subjects reported their "average pain", during this fMRI run, using a numerical rating scale (0–100; 0=no pain and 100=worst pain imaginable) following each session.This pressure pain rating was correlated with Glx levels.

Results: Cross sectional analysis, prior to placebo administration, demonstrated that Glx/Cr levels were positively related to subjective pain report during evoked pressure pain (r = 0.811, p < 0.001): higher Glx/Cr was associated with greater pain.Moreover the change in Glx/Cr from pre- to post-placebo was also positively correlated with the change in evoked pain report (r = 0.697, p = 0.008): reductions in Glx/Cr were associated with reductions in pain.Glx changes were not related to clinical pain (p < 0.05).

Conclusion: Similar to our previous findings, concentrations of Glx within the right posterior insula were found to be positively correlated with pain report in both cross-sectional and longitudinal analyses. These results add to the growing body of literature indicating that ^{1}H-MRS derived levels of Glx may serve as a marker or surrogate end point for clinical trials of FM.Replication of these findings in other pain states is recommended.

References:

1. Harris et al. AnR 2008

ACR Concurrent Abstract Session
Imaging of Rheumatic Diseases I: Ultrasound and X-ray
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Predictors of Rheumatoid Arthritis: Quantitative and Semiquantitative Sonographic Measurements of Peripheral Joints. Flavia S. Machado, Rita N.V. Furtado, Rogerio D. Takahashi, Ana Leticia P. de Buosi and Jamil Natour. Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Sonographic quantitative and semiquantitative measurements in peripheral joints of normal subjects are yet to be defined, as are sonographic predictors of rheumatoid arthritis (RA). Our objetive was to estimate quantitative and semiquantitative ultrasound measurements predictors of RA in small, medium and large joints.

Methods: A cross-sectional study was carried out involving 78 healthy volunteers (HV) and 60 patients with RA (ACR), matched for age group and gender. A "blind" radiologist used a My Lab 60 XVision machine (Esaote, Biomedica - Genova, Italy) with a linear array (6–18MHz) to evaluate 6.348 joint recesses. Quantitative measurements of synovial recess (QSR) (mm) and semiquantitative measurements of synovial hyperplasia (SSH), Power Doppler (SPD) and bone erosion (SBE) (scores 0–3) were performed. To determine the chance to detect RA, ROC curve analysis for QSR measurements were performed (specificity 98.7%) and, for the semiquantitative measures, an univariate logistic regression (expressed in odds ratio - OR) was carried out. P value <0.05 was set as significant.

Results: The mean age (± SD) was 46.48 (9.14) and 43.89 (9.09), respectively for the HV and RA groups. The sample was homogeneous for gender, age group and skin color. RA group: mean disease duration was 7.89 years (± 6.76) and DAS-28 4.20 (± 1.71). Statistical difference was observed between groups for QSR (p<0.013) for most of the recesses. Mean (±SD) (mm) of QSR, respectively for HV and RA groups (HV/RA), were: radiocarpal: 2.07 (0.56)/3.24 (1.24); distal radioulnar: 1.45 (0.37)/2.28 (1.11); ulnocarpal: 1.37 (0.59)/2.74 (1.76); dorsal 2ndMCP: 1.06 (0.53)/1.51 (0.96);

palmar 2ndMCP: 0.88 (0.60)/1.40 (1.01); dorsal 3rdMCP: 0.81 (0.62)/1.24 (0.99); dorsal 2ndPIP: 0.46 (0.25)/0.76 (0.64); dorsal 3rdPIP: 0.44 (0.32)/0.83 (0.56); palmar 3rdPIP: 0.83 (0.27)/1.11 (0.55); coronoid fossa: 0.97 (1.06)/2.18 (2.27); olecranean fossa: 1.51 (1.17)/2.79 (2.65); posterior GH recess: 2.43 (0.45)/3.03 (1.29); knee: 2.21 (1.65)/3.95 (2.96); talocrural: 2.38 (1.13)/3.34 (1.99); talonavicular: 2.67 (1.10)/3.56 (1.50); subtalar: 2.15 (1.13)/3.07 (1.71); dorsal 5thMTP: 0.72 (0.70)/1.47 (1.11). Cutoff values of QSR specific of RA (AUC>0,700) were: radiocarpal 3.78mm; ulnocarpal 3.07mm; distal radioulnar 2.21mm; dorsal 3rd PIP 1.19mm; knee 6.7mm and dorsal 5th MTP 2.33mm. For semiquantitative measurements, progression from score 0 to 3, at the recesses with greater chance to detect RA were: SSH: ulnocarpal (OR=100, p<0.001); radiocarpal (OR=70, p<0.001); distal radioulnar (OR=43, p<0.001) and knee (OR=28, p<0.001); SPD: radiocarpal (OR=66, p<0.001); SBE: radiocarpal (OR=324, p=p<0.001); lateral 5thMTP (OR=100, p=p<0.001); 2nd MCP (dorsal and radial)(OR= 92, p<0.001) and ulnocarpal (OR=48, p<0.001). Inter-observer reliability for quantitative and semi-quantitative measures ranged from 0.563 to 0.872 and 0.341 to 0.823, respectively.

Conclusion: Quantitative measures specific of RA were found in almost all recesses. Semiquantitative measurements analysis showed that the worst scores found at radiocarpal, ulnocarpal and lateral 5thMTP recesses increases the chance to detect RA.

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Power Doppler Is Predictive of Treatment Failure in Early Rheumatoid Arthritis Patients: A One Year Follow-up Study. Karine R. Luz, Rita N.V. Furtado, Marcelo M. Pinheiro, Giovanna S. Petterle and Jamil Natour. Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: It is known that ultrasound (US) is a useful test to monitor rheumatoid arthritis (RA) patients. However, to date, no study has shown the US parameters to be able to predict treatment failure in RA patients.Thus the aim of the present study was to evaluate the findings of a new ultrasound score (US10) of the hand and wrist joints (US10) to predict treatment failure in early RA patients.

Methods: A 12-months cohort study was carried out in patients with early RA, with less-than-1 year symptom with no previous use of disease-modifying antirheumatic drugs (DMARD). The patients underwent clinical, laboratory assessment and blinded US examination (US10) at baseline, 3, 6, 9 and 12 months. The US10 included the following joints:wrist, second and third metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. This score was composed by the following parameters, a first one was according to inflammation: a qualitative (0–1) and semi-quantitative(0–3) scoring to synovial proliferation(SPQ10,SPSQ10) and to power Doppler (PD) (PDQ10,PDSQ10), and qualitative (0–1) gray scale and PD scores for tenosynovitis/paratendinosis (GSTN10, PDTN). A second US finding was categorised according to joint damage: a qualitative (0–1) and semi-quantitative(0–3) scoring to bone erosions (ERQ10, ERSQ10) and to cartilage damage (CAQ10, CASQ10).All patients were treated by a single rheumatologist following similar treatment protocol performed according to clinical activity criteria of the joint 28-Disease Activity Score (DAS 28) and the Physician's Global Assessment (AGM). Three treatment failures were observed over these 12 months: first DMARD failure (Failure 1), a second DMARD failure (Failure 2) and a first immunobiological failure (Failure 3).

Results: 48 patients completed the study, and 41 (85.41%) hadFailure 1, 25 (52%) had a Failure 2 and five (10.5%) patients had a Failure 3. The respective PDQ10 baseline was a predictor for Failure 1 and Failure 2 with the following cutoff values: 2.5 (S = 87.8%, E = 71.42% PPV = 94.7% and NPV = 50%) and 4.5 (S = 84%, E = 47.82%, PPV = 63.6% and NPV=73.3%). The PDSQ10 baseline was also a predictor for Failures 1 and 2 with the respective cutoff values: 5.0 (S = 90.2%, E = 71.4%, PPV = 94.9% and NPV = 55.6 %) and 9.5 (S = 84%, E = 47.82%, PPV = 63.6% and NPV 73.3%). Furthermore, there was an increase in 1.47 and 1.19 OR per unit increase in score PDQ10 to predict Failures 1 and 2 (p<0,005). The PDSQ10 at baseline also showed an OR of 1.18 and 1.7 (95%, p <0.005) to predict failure for the first and second DMARD, respectively.

Conclusion: US10, with the PDQ10 and PDSQ10 parameters was found to be useful to predict the first and second DMARD failure in early RA patients.

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Ultrasonography Predicts Achievement of Deeper Remission After DAS28-Based Clinical Remission of Rheumatoid Arthritis. Ryusuke Yoshimi, Maasa Hama, Daiga Kishimoto, Reikou Watanabe, Takeaki Uehara, Yukiko Asami, Atsushi Ihata, Atsuhisa Ueda, Mitsuhiro Takeno and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan

Background/Purpose: Although clinical remission is an agreeable goal of treatment in rheumatoid arthritis (RA), the definition is still controversial. Indeed, progressive structural damage is often found even after achieving DAS28-based remission, suggesting the criteria are not satisfactory for true remission. There is accumulating evidence that ultrasonography (US) is helpful for judgment of the disease remission. Here we investigated whether US is useful for predicting Boolean remission in RA patients who had been satisfied with DAS28-based remission criteria.

Methods: Twenty-seven RA patients who had been in DAS28-based clinical remission (DAS28-ESR < 2.6 or DAS28-CRP < 2.3) for more than 2 months were recruited and monitored for 2 years. Patients who had clinical flare-up were excluded, and the remaining patients were divided based on Boolean remission criteria at 2 years. Bilateral wrists and all of MCPs and PIPs were examined by Gray scale (GS) and power Doppler (PD) US at the entry. GS and PD signals were scored in each joint from 0 to 3, respectively. Total GS score and total PD score were calculated by summing up the score of individual joints. Hand X-ray was evaluated by van der Heijde-modified total Sharp score (mTSS) at the entry and end of study.

Results: Five patients dropped out of the study due to clinical flare-up, while DAS28 remission had been maintained for 2 years in 22 patients, including 16 patients (73%) who met Boolean remission criteria at the end of study. Both total GS score and total PD score at baseline were significantly lower in Boolean remission group than non-remission group (*Table*). There was no significant difference in other baseline parameters, including duration of disease, duration of remission, mTSS, and disease activity composite parameters between two groups (*Table*). However, the increase of patient's global visual analogue scale (gVAS) and mTSS were significantly smaller during 2 year study period in Boolean remission group than non-remission group (-4.69 ± 10.3 vs 13.2 ± 20.3, $p = 0.023$, and 0.31 ± 2.36 vs 3.67 ± 3.35, $p = 0.047$, respectively). In US findings at the entry, total GS score, but not total PD score, was associated with clinical stage, mTSS at baseline, and swollen joint count, tender joint count and gVAS at 2 years. Furthermore, Boolean remission was achieved in all of the 11 patients having total GS score 7 or less at the entry, whereas 6 (55%) of the other 11 patients failed to reach Boolean remission. On the other hand, progression of mTSS was rather associated with high total PD score, but not with total GS score, at the entry.

Table. Correlation between Boolean-based remission at 2 years and baseline variables

Baseline variable	Boolean-based Remission (*n* = 16)	Boolean-based non-remission (*n* = 6)	*p*
Age (year)	57.3 ± 11.3	55.3 ± 11.9	0.74
Sex	M: 4 cases, F: 12 cases	M: 0 cases, F: 6 cases	0.29
Duration of RA (month)	87.9 ± 50.7	70.3 ± 22.8	0.96
Duration of remission (month)	21.5 ± 19.0	17.8 ± 13.8	0.93
Clinical stage	2.06 ± 0.97	2.50 ± 0.76	0.28
modified total Sharp score	12.4 ± 11.9	33.8 ± 33.4	0.14
Total GS score	7.75 ± 6.02	16.0 ± 11.3	0.012*
Total PD score	1.06 ± 1.14	6.33 ± 6.99	0.020*
DAS28-CRP	1.59 ± 0.52	1.66 ± 0.34	0.76
DAS28-ESR	1.97 ± 0.59	2.23 ± 0.50	0.38
Boolean-based remission	6 cases (38%)	1 case (17%)	0.62
Swollen joint count	0.38 ± 0.60	1.33 ± 1.11	0.060
Tender joint count	0.25 ± 0.43	0.33 ± 0.47	1.00
Global VAS (mm)	10.6 ± 9.45	10.2 ± 4.74	0.93
ESR (mm/h)	11.6 ± 6.65	16.3 ± 17.7	0.39
CRP (mg/dl)	0.13 ± 0.16	0.04 ± 0.01	0.17
MMP-3 (ng/ml)	98.5 ± 105	51.8 ± 12.1	0.32
RF (U/ml)	85.6 ± 90.7	54.1 ± 52.5	0.49

*$p < 0.05$

Conclusion: This study shows that none or low grade of GS and PD findings in US are associated with the achievement of Boolean remission in near future and that GS findings are implicated in exacerbation of clinical parameters composing Boolean remission criteria. Thus, US is essential for assessment and prediction of "true remission" of RA.

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Assessment of Omeract Global Power Doppler Ultrasonography 44-Joint Scoring System and Reduced Joint Scoring Systems in Rheumatoid Arthritis Patients Treated with Abatacept Plus Background Methotrexate. MA D'Agostino[1], R. Wakefield[2], H. Berner Hammer[3], O. Vittecoq[4], M. Galeazzi[5], P. Balint[6], E. Filippucci[7], I. Moller[8], A. Iagnocco[9], E. Naredo[10], Mikkel Ostergaard[11], C. Gaillez[12], K. Van Holder[13], M. Le Bars[12] and OMERACT-US Task Force[14]. [1]AP-HP Ambroise Pare Hospital, Boulogne-Billancourt, France, [2]University of Leeds, Leeds, United Kingdom, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]University Hospital, Rouen, France, [5]University of Siena, Siena, Italy, [6]National Institute, Budapest, Hungary, [7]University Politecnica delle Marche, Ancona, Italy, [8]Instituto Poal, Barcelona, Spain, [9]Sapienza Università di Roma, Roma, Italy, [10]Hospital Severo Ochoa, Madrid, Spain, [11]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [12]Bristol-Myers Squibb, Rueil Malmaison, France, [13]Bristol-Myers Squibb, Braine-L'Alleud, Belgium, [14]Paris

Background/Purpose: The first international trial using the standardized global OMERACT Power Doppler Ultrasonography (PDUS) synovitis scoring system[1] showed early and significant signs of improvement in synovitis in abatacept-treated pts with RA, demonstrating the sensitivity of this score.[2] This trial evaluated paired MCPs 2–5 for its primary endpoint. However, there is no consensus on the minimum joint count needed to evaluate response with the OMERACT PDUS synovitis score. Additional analyses evaluated the effect of abatacept on the OMERACT global PDUS synovitis score, using a paired 22-joint count and a reduced set of joints defined here as Global Synovitis Score (GLOSS). We compare the responsiveness of GLOSS with two published reduced joint counts.[3,4]

Methods: This 6-month, single-arm, open-label study enrolled RA pts with inadequate response to MTX, and DAS28 (CRP) >3.2 or ≥6 tender and swollen joints and CRP >ULN. Global PDUS paired 22-joint score was assessed at baseline (BL); Days 7, 15, 29, 43, and 57; and then monthly by a PDUS examiner blinded from clinical assessments. A reduced subset of joints (GLOSS) that best represented the global PDUS score for paired 22 joints of all pts over three time points was identified at BL, Days 85 and 169, based on principal component analysis. The number of joints was selected based on Eigen values using a statistical method described by Jolliffe.[5] The three best subsets of paired joints, one for each time point, were identified using two methods, based on values of efficiency measure (EM) of the reduced subset: EM ≥0.6 at all three time points and the subset with the highest minimum EM over the three time points. The sensitivity to change was assessed for GLOSS and the existing 12-joint[3] and 7-joint[4] sets using standardized response mean (SRM) in a *post hoc* analysis.

Results: BL demographics and mean change from BL in global PDUS score (MCPs 2–5) over 6 months have been reported.[2] Mean change (95% CIs) from BL in global paired PDUS 22-joint score was −1.7 (−3.4, −0.1; n=87) at Day 7 and improved up to Day 169 [−15.7 (−19.0, −12.5; n=95)]. The GLOSS that best represented the global paired PDUS 22-joint score of all pts over the three time points was identified as 9 paired joints: shoulder, elbow, wrist, MCP1, MCP4, PIP2, knee, MTP3, and MTP5. When comparing the GLOSS with the published reduced joint sets (bilaterally taken), mean changes from BL improved up to Day 169 for all, with a similar SRM (Table).

Joint count	n	Mean change in joint count (95% CI)	SRM
GLOSS	84	−6.4 (−7.9, −4.9)	−0.949
12-joint set	85	−5.3 (−6.5, −4.2)	−0.994
7-joint set	85	−6.6 (−8.0, −5.3)	−1.053

n=number of pts with BL and post-BL measurements

Conclusion: Abatacept + MTX resulted in early (Day 7, by global PDUS 22-joint score) and continuous reductions in synovitis to Day 169 (with global

PDUS 22-joint score and 9-joint GLOSS). The GLOSS 9-joint subset and the 12- and 7-joint sets all demonstrated a similar sensitivity to change.

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The Relationship Between Power Doppler Ultrasonography Outcomes and Clinical Efficacy in Abatacept-Treated Patients with Rheumatoid Arthritis and in Inadequate Response to Methotrexate.

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Background/Purpose: An exploratory study using the standardized global OMERACT Power Doppler Ultrasonography (PDUS) scoring system[1] in patients (pts) with established RA and inadequate response to MTX treated with abatacept (ABA) + background MTX demonstrated early signs of improvement in synovitis of paired MCPs 2–5 at Day 7 with further improvement up to Day 169 (Mth 6).[2] This analysis investigates the relationship between DAS28 disease status at Day 169 and PDUS improvement at Day 85 (Mth 3) using three joint counts (paired MCPs 2–5, paired 22-joints, and a reduced set of paired 9-joints [Global Synovitis Score; 'GLOSS']); and if changes in PDUS at Day 85 in any of the joint counts can differentiate between early (<3 mths) and late (>3 mths) responders.

Methods: This was a *post hoc* analysis of pts who completed 6 mths of treatment with ABA + MTX in the open-label, exploratory Phase IIIb study.[2] Global PDUS scores for paired MCPs 2–5 (range: 0–24 units), 22 joints (range: 0–132 units), and a reduced subset of 9 joints (GLOSS: shoulder, elbow, wrist, MCP1, MCP4, PIP2, knee, MTP3, and MTP5; range: 0–54 units) were assessed at baseline (BL) and Mths 3 and 6 by a blinded PDUS examiner. Changes in global and component (synovial hypertrophy, power Doppler [PD], and joint effusion) PDUS paired MCPs 2–5 scores at Mth 3 were analyzed according to remission status (DAS28 <2.6) at Mth 6. In pts reaching LDAS (DAS28 ≤3.2) at Mth 6, changes in global PDUS paired MCPs 2–5, 22 joints, and GLOSS from BL to Mth 3 were summarized according to whether pts achieved clinically meaningful improvement (CMI) in DAS28 (≥1.2) or not at Mth 3 (early vs late responders).

Results: Similar mean change from BL to Mth 3 in global PDUS and synovial hypertrophy was observed irrespective of remission status at Mth 6. A numerically greater improvement in PD signal was seen in pts who reached remission at Mth 6 vs those who did not (Table 1). In pts achieving LDAS at Mth 6, the global PDUS paired 22-joint score and GLOSS, but not MCPs 2–5, could discriminate numerically between early vs late responders (Table 2).

Table 1. Mean change (95% CIs) from BL to Mth 3 in global PDUS paired MCPs (2–5) scores and components, according to remission status at Mth 6

N=104	Global PDUS (MCPs 2–5) score	Synovial hypertrophy	Power Doppler	Joint effusion
Remission (n=37)				
Mean change (95% CI)	−4.2 (−5.9, −2.6)	−3.8 (−5.3, −2.3)	**−4.9 (−6.2, −3.7)**	−1.9 (−3.2, −0.7)
No remission (n=43)				
Mean change (95% CI)	−4.0 (−5.2, −2.8)	−3.9 (−5.0, −2.7)	**−2.6 (−3.8, −1.4)**	−1.4 (−2.4, −0.5)

Table 2. Mean change (95% CIs) in global PDUS scores from BL to Mth 3 in pts who achieved LDAS at Mth 6, according to early or late response

Patients in LDAS at Mth 6	Global PDUS (MCPs 2–5) score	Global PDUS 22-joint score	GLOSS
Early responders (at least CMI at Mth 3) (n=37)	−4.2 (−5.8, −2.5)	−12.6 (−17.2, −8.0)	−6.1* (−8.0, −4.1)
Late responders (no CMI at Mth 3) (n=10)	−4.3 (−6.2, −2.4)	−10.6 (−16.7, −4.5)	−4.3 (−6.2, −2.4)

*n=36
n is the number of pts with BL and post-BL measurements

Conclusion: This first international study using the standardized global OMERACT PDUS score showed that abatacept-treated pts demonstrated improvements in PDUS paired MCP 2–5 scores regardless of remission status at Mth 6. However, pts in remission at Mth 6 had numerically greater improvements in PD MCPs 2–5 at Mth 3 than those who were not. In pts reaching LDAS at Mth 6, improvements in all PDUS scores were seen regardless of responder status. Early responders could be identified by numerically greater improvement of either global PDUS paired 22-joint score or GLOSS.

Reference
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Intravenous Golimumab Inhibits Radiographic Progression and Maintains Clinical Efficacy and Safety in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: 1-Year Results of a Phase 3 Trial.

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Background/Purpose: To evaluate long-term clinical/radiographic efficacy of IV golimumab(GLM) 2mg/kg+MTX in pts with active RA despite MTX through wk 52.

Methods: Pts (n=592) with active RA (≥6/66 swollen joints, ≥6/68 tender joints, CRP≥1.0mg/dL, RF and/or anti-CCP positive at screening) despite ≥3months of MTX(15–25mg/wk) participated in this multicenter, randomized, double-blind, placebo(PBO)-controlled study. Pts were randomized to IV GLM 2mg/kg or PBO at wks0&4 and q8wks; all pts continued stable MTX. Pts randomized to PBO with <10% improvement in SJC+TJC at wk16 could early escape to IV GLM 2mg/kg (wks16&20, q8wks). All PBO pts received IV GLM 2mg/kg starting at wk24. Primary study endpoint was wk14 ACR20 response; major secondary clinical efficacy endpoints are reported through wk24. Radiographs of hands and feet were taken at baseline, wk24(wk16 for early escape) and wk52 and were scored by 2 independent readers and adjudicator (as needed) using modified vdHS score.

Results: Baseline demographic and disease characteristics were comparable between grps. 93% of pts (553/592) continued through wk52. 39 pts d/c, mostly due to AEs(18 pts).GLM+MTX-tx pts demonstrated significantly (sig) less radiographic progression (total vdHS+subscores) vs PBO+MTX at wk24. Pts randomized to PBO+MTX who began GLM at wk16/24 demonstrated marked

slowing of radiographic progression, to the same rate as pts randomized to GLM, from wk24 to wk52. At wk14, sig (p<0.001) larger proportions of GLM+MTX vs PBO+MTX pts achieved ACR20,DAS28-CRP good/moderate, ACR50 and ACR70 responses and greater median improvement in HAQ score (0.50vs0.13). Through wk52, ACR20, ACR50, ACR70, and DAS28 good/moderate response rates in pts randomized to GLM+MTX were 66%, 39%, 18%, and 81%, resp. Among pts who achieved ACR20, ACR50, ACR70 and DAS28 good/moderate responses by wk24, 82%, 72%, 61%, and 88%, resp, maintained response through wk52. Through wk52, all GLM-tx pts were followed for an average of 44wks. AEs and serious AEs occurred in 65% and 9%, resp, of GLM-tx pts (vs 43% and 4% at wk24). 1 case of TB and no serious opportunistic infections were reported through wk52. 1 pt receiving GLM+MTX (0.16%) died. Through wk52, the proportions of infusions and pts with infusion reactions were 0.7% and 3.6%, resp, (vs 1.1% and 3.5% at wk24).

Table. Summary of efficacy among randomized pts. Data shown are number (%) of pts or mean±SD/median (interquartile range).

CLINICAL EFFICACY	Placebo + MTX (n=197)	GLM 2mg/kg + MTX (n=395)
Week 14		
ACR20*/ACR50 /ACR70	49 (24.9%)/17 (8.6%)/6 (3.0%)	231 (58.5%)/118 (29.9%)/49 (12.4%)***
DAS28-CRP moderate or good response	79 (40.1%)	321 (81.3%)***
Improvement from baseline in HAQ score	0.50 ± 0.58/0.13 (−0.13, 0.50)	0.19 ± 0.56/0.50 (0.13, 0.88)***
Week 24		
ACR 20 response	62 (31.5%)	248 (62.8%)***
ACR 50 response	26 (13.2%)	142 (35.9%)***
ACR 70 response	8 (4.1%)	69 (17.5%)***
DAS28-CRP moderate or good response	88 (44.7%)	331 (83.8%)***
Improvement from baseline in HAQ score	0.21± 0.55/0.13 (−0.13, 0.50)	0.53 ± 0.64/0.50 (0.13, 0.88)***
Improvement in HAQ≥0.25 from baseline	89 (45.2%)	266 (67.3%)***
Week 52		
ACR20 response	121 (61.4%)	260 (65.8%)
ACR50 response	62 (31.5%)	153 (38.7%)
ACR70 response	29 (14.7%)	72 (18.2%)
DAS28-CRP moderate or good response	149 (75.6%)	321 (81.3%)
Improvement from baseline in HAQ score	0.42 ± 0.59/0.38 (−1.1; 1.9)	0.51 ± 0.65/0.38 (−1.0; 2.5)
Improvement in HAQ≥0.25 from baseline	123 (62.4%)	253 (64.1%)
RADIOGRAPHIC PROGRESSION		
Baseline Total vdHS		
Total score	50.26 ± 59.85/29.00 (8.50, 77.24)	47.59 ± 54.63/28.00 (9.00, 67.50)
Erosion subscore	25.63 ± 32.38/13.00 (4.00, 36.00)	23.89 ± 29.00)/13.50 (4.00, 32.00)
Joint space narrowing subscore	24.63 ± 29.47/12.50 (4.00, 37.50)	23.70 ± 28.26 13.00 (3.00, 35.50)
Total vdHS Change from baseline at wk24		
Total score	1.09 ± 3.19/0.00 (0.00, 1.49)	0.03 ± 1.90/0.00 (−0.50, 0.50)***
Erosion subscore	0.53 ± 2.09/0.00 (0.00, 0.50)	−0.12 ± 1.15/0.00 (−0.50, 0.00)***
Joint space narrowing subscore	0.56 ± 1.73/0.00 (0.00, 0.50)	0.14 ± 1.33/(0.00, 0.00)**
Proportions of pts at wk24		
Progression based on smallest detectable change (SDC)		
Total (SDC=1.91)	38 (19.3%)	34 (8.6%)***
Erosion (SDC=1.57)	21 (10.7%)	15 (3.8%)***
Joint space narrowing (SDC=1.19)	34 (17.3%)	39 (9.9%)**
Change in vdHS ≤ 0	113 (57.4%)	279 (70.6%)***
Total vdHS change from wk24-wk 52#		
	0.12 ± 2.44/0.00 (−0.50, 0.50)	0.15± 1.83/0.00 (−0.50, 0.50)
Total vdHS change from wk0-wk52	1.22± 3.98/0.00 (0.00, 1.50)	0.13 ± 3.11/0.00 (−0.50, 0.50)***

*Primary endpoint, **, ***p-value vs. placebo + MTX < 0.01, 0.001, respectively.
*Pts with missing total vdHS score at wk24 were excluded.

Conclusion: GLM+MTX sig inhibited radiographic progression (for total vdHS and subscores) at wk24&52. Among PBO-tx pts who began GLM at wk16/wk24, marked slowing of radiographic progression, to the rate in pts randomized to GLM, was observed from week 24 to wk52. IV GLM+MTX sig improved and maintained RA signs/symptoms in pts with active RA despite ongoing MTX and continued to demonstrate an acceptable safety profile through wk52.

ACR Concurrent Abstract Session
Metabolic and Crystal Arthropathies: Clinical
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Rilonacept for Gout Flare Prophylaxis in Patients with Chronic Kidney Disease: Analysis of 3 Clinical Trials. Robert Terkeltaub[1], Robert R. Evans[2], Steven P. Weinstein[2], Richard Wu[3] and H. Ralph Schumacher[4]. [1]VA Medical Ctr, San Diego, CA, [2]Regeneron Pharmaceuticals Inc, Tarrytown, NY, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]University of Pennsylvania and VA Medical Center, Philadelphia, PA

Background/Purpose: Gout flare (GF) prophylaxis in patients (pts) with chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m^2) remains challenging, since prophylaxis with NSAIDs or colchicine may not be advisable in these patients. Three phase 3 trials demonstrated that weekly subcutaneous administration of rilonacept, an IL-1 antagonist, reduced GFs in pts initiating urate-lowering therapy (ULT). This post hoc analysis of the 3 trials evaluated rilonacept in pts stratified by presence and absence of CKD.

Methods: PRESURGE-1 and PRESURGE-2 were similar randomized confirmatory efficacy trials with a 16-week treatment period (80 pts per group: placebo [Pbo], rilonacept 80mg/week [R80], rilonacept 160mg/week [R160]); RESURGE was a large 16-week randomized safety trial that also assessed GFs. Pts with eGFR <30ml/min/1.73m^2 were excluded from these studies. In this analysis, only pts with initial serum urate ≥7.5 mg/dL, ≥2 gout flares in the prior year, and initiating ULT were included. GFs/pt, and % of pts with ≥1 and ≥2 GFs were analyzed stratified by baseline eGFR <60 ml/min/1.73m^2 and ≥60 ml/min/1.73m^2, and included pts pooled from PRESURGE-1 and PRE-SURGE-2; RESURGE alone; and pts pooled from all 3 studies. Safety was based on adverse events (AEs) in the overall safety database stratified by eGFR.

Results: While pooled data from PRESURGE-1 and PRESURGE-2 showed that for pts with CKD, R80 (n=21) and R160 (n=19) reduced GFs/pt by 33% and 53% relative to Pbo (n=26), respectively, the effect on the proportion of pts with GFs was variable, likely due to low pt numbers. Results from the much larger RESURGE study showed that for CKD pts (Pbo, n=23; R160, n=63), GFs/pt were reduced by 65%, from 3.13 (Pbo) to 1.11 (R160), with fewer pts reporting ≥1 GF (41% vs 74%) and ≥2 GFs (24% vs 48%); for pts with eGFR ≥60 (Pbo, n=120; R160, n=339), GFs/pt were reduced by 75%, from 1.78 (Pbo) to 0.45 (R160), with fewer pts on R160 reporting ≥1 GF (25% vs 53%) and ≥2 GFs (10% vs 38%). Pooled data from the 3 studies showed a consistent effect of rilonacept to prevent GFs in pts with CKD across the endpoints (Table). In studies of rilonacept for GF prophylaxis, within each eGFR category the incidence of treatment-emergent AEs and serious AEs, respectively, were similar between treatment groups (eGFR <60: placebo, 64.2% and 8.6%; all rilonacept, 67.6% and 6.0%. eGFR ≥60: placebo, 59.0% and 3.3%; all rilonacept 65.6% and 3.0%), although SAEs were more frequent in the eGFR <60 subgroup.

	Placebo (n = 306)	Rilonacept 80 mg (n = 162)	Rilonacept 160 mg (n = 585)
All patients, n	304	162	585
Flares per patient, mean (SD)	1.65 (2.40)	0.51 (1.14)	0.50 (1.11)
Patients with ≥1 flare, %	54.9	28.4	26.7
Patients with ≥2 flares, %	38.2	11.7	11.3
Baseline eGFR < 60 ml/min/1.73m^2, n	49	21	82
Flares per patient, mean (SD)	2.24 (3.63)	0.86 (1.28)	0.96 (1.66)
Patients with ≥1 flare, %	59.2	42.9	39.8
Patients with ≥2 flares, %	36.7	28.6	23.3
Baseline eGFR ≥60 ml/min/1.73m^2, n	255	141	483
Flares per patient, mean (SD)	1.54 (2.08)	0.46 (1.11)	0.43 (0.98)
Patients with ≥1 flare, %	54.1	26.2	24.6
Patients with ≥2 flares, %	38.4	9.2	9.5

Conclusion: Rilonacept demonstrated efficacy and tolerability for GF prophylaxis in pts with CKD for whom other agents might be inadvisable.

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Familial Aggregation and Heritability of Gout in Taiwan: A Nationwide Population Study. Chang-Fu Kuo[1], Matthew J. Grainge[1], Lai-Chu See[2], Kuang-Hui Yu[3], Shue-Fen Luo[3], Ana M. Valdes[4], Weiya Zhang[1] and Michael Doherty[1]. [1]University of Nottingham, Nottingham, United Kingdom, [2]Chang Gung University, Taoyuan, Taiwan, [3]Chang Gung Memorial Hospital, Taoyuan, Taiwan, [4]St. Thomas' Hospital, King's College London, London, United Kingdom

Background/Purpose: Gout has long been recognised to cluster within families. However, formal evidence for familial aggregation is scant and discordant and the magnitude of any genetic component remains unclear. Therefore we undertook the present study to estimate the familial risk of gout in individuals with affected first-degree relatives compared to individuals with no affected first-degree relatives.We also estimated the heritability and population attributable risk to assess the magnitude of genetic contribution to susceptibility to gout.

Methods: Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of data collected from 11,770,921 men and 11,697,080 women in 2004. The case definition of gout consisted of a physician diagnosis and the use of gout-specific treatment. We identified individuals with first-degree relatives affected by gout and compared the prevalence of disease between individuals with and without affected first-degree relatives. The marginal Cox proportional hazard model with an equal follow-up time for all subjects was used to estimate RR and the 95% confidence interval (CI). This model was used to account for shared environment and case clustering within families with robust variance, and to adjust for age, place of residence, income levels and occupation.C:\Users\Users\zandis\Google Drive\Familial aggregation and heritability of gout in Taiwan submitting old.docx - _ENREF_16 The RR was estimated for different first-degree relative categories and for the number of first-degree relatives affected by gout. eritability (h^2) was estimated using the multifactorial polygenic model.

Results: The prevalence of gout was higher in individuals with affected first-degree relatives (6.92%) than those without (4.83%). The overall familial relative risk (RR) was 1.92 (95% CI, 1.90–1.93). The RRs (95% CIs) for an individual with an affected twin, sibling, offspring and parent were 2.89 (2.65–3.16), 2.26 (2.21–2.32), 2.07 (2.05–2.09) and 1.77 (1.75–1.78), respectively. The RR (95% CI) increased with the number of affected first-degree relatives, from 1.86 (1.85–1.88), 3.02 (2.95–3.09) and 4.48 (4.07–4.92) for one, two or three or more affected relatives. The heritability of gout was 0.46 (95% CI, 0.44–0.47). The population attributable risk associated with familial aggregation in Taiwan was 5.77% (95% CI, 5.65%–5.82%).

Conclusion: This first ever population-based study confirms that gout aggregates within families. The heritability of gout is high in the general population in Taiwan and genetic predisposition contributes to a significant proportion of gout development.

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Exploratory Analysis of Radiographic Change in Patients Treated with Intensive Urate-Lowering Therapy. Nicola Dalbeth[1], Anthony Doyle[1], Fiona M. McQueen[1], John S. Sundy[2] and Herbert S. B. Baraf[3]. [1]University of Auckland, Auckland, New Zealand, [2]Duke University Medical Center, Durham, NC, [3]Arthritis & Rheumatism Associates, Wheaton, MD

Background/Purpose: In patients with gout, tophi are strongly associated with radiographic damage.Effective urate-lowering therapy (ULT) reduces tophus size.However, no studies to date have convincingly demonstrated that ULT can inhibit progression or promote healing of radiographic damage.Pegloticase therapy leads to dramatic reductions in serum urate (SU) concentrations and subcutaneous tophi in patients who respond to treatment.The aim of this exploratory analysis was to describe radiographic changes following treatment with pegloticase.

Methods: Serial plain radiographs of the hands and feet were obtained as standard of care from patients with severe chronic gout treated with pegloticase.Paired films at baseline and 12 months were available for nine patients.Five of these patients had films at baseline, 12 and 24 months.Radiographs were analysed sequentially in chronological order by two observers; a musculoskeletal radiologist and a rheumatologist with experience in radiographic scoring.Radiographs were scored for erosion and joint space narrowing according to the modified Sharp-van der Heijde method, validated for gout.Scorers were blinded to each other's scores and to the clinical characteristics of the patients (including the clinical response to pegloticase).Inter-observer ICCs were 0.89 (0.76–0.95) for total scores and 0.83 (0.53–0.94) for change scores.A detailed qualitative site-by-site analysis was also undertaken to define additional changes observed from baseline.

Results: All patients had sustained SU <1 mg/dL during pegloticase treatment.For the entire group, median (range) total radiographic scores reduced from 73 (1.5–138) at baseline to 60.5 (1.5–110) at 12 months, p=0.01.Median (range) erosion scores reduced from 48.5 (1.5–98.5) at baseline to 42.0 (1–71.5) after one year, p=0.003.In contrast, narrowing scores did not change over the one year period; baseline narrowing scores were 24.5 (0–43) and at one year 22.5 (0.5–41.5), p=0.26.Further reductions were observed in total scores and erosion scores in the five patients with films available at 24 months following treatment, but not in narrowing scores (one way ANOVA p=0.009 for total score, 0.02 for erosion and 0.95 for narrowing).Qualitative site-by-site analysis identified regression of soft tissue masses, increased sclerosis, and filling in of erosions in the follow-up films (Figure).

Figure 1. Paired radiographs of the fingers of the right hand in a patient with tophaceous gout A. at baseline, B. after one year of pegloticase therapy.

Conclusion: This exploratory analysis suggests that intensive urate-lowering therapy can lead to improvement in structural damage, particularly bone erosion, in patients with severe chronic gout.

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Glomerular Filtration Rate, Chronic Kidney Disease and Incidence of Physician Diagnosed Gout. Eswar Krishnan. Stanford University, Stanford, CA

Background/Purpose: The kidney is the major organ of urate excretion in humans. Yet, there are few studies that assess whether reduced glomerular filtration and/or kidney damage increases the incidence of gout.

Methods: Seven-year follow up data from the Multiple Risk Factor Intervention Trial, a primary prevention trial for cardiovascular disease among 12,886 men aged 35 to 57 years were analyzed. At each of seven annual visits, participants were assessed for gout by the study physician. Chronic kidney disease was defined as per the National Kidney Foundation guidelines. Standardized incidence ratios (SIR) we computed using data from the Rochester Epidemiology Project.Cox proportional hazards regression analysis was used to assess the association between gout and chronic kidney disease after accounting for the effects of potential confounders (age, race, blood pressure, alcohol and fructose consumption, body mass index, fasting triglycerides, use of aspirin, diabetes status, and diuretic use).

Results: Overall there were 722 cases of incident gout over 76,602 person-years of follow up. The incidence and SIR of goutincreased with decreasing eGFR (**Figure**). The multivariable adjusted hazard ratio for those with chronic kidney disease was 1.9 (1.6, 2.2). Each standard deviation decline in eGFR was associated with a hazard ratio of 1.4 (1.3, 1.5).Addition

of serum urate as well as urate-chronic kidney disease interaction term did not attenuate the hazard ratio.
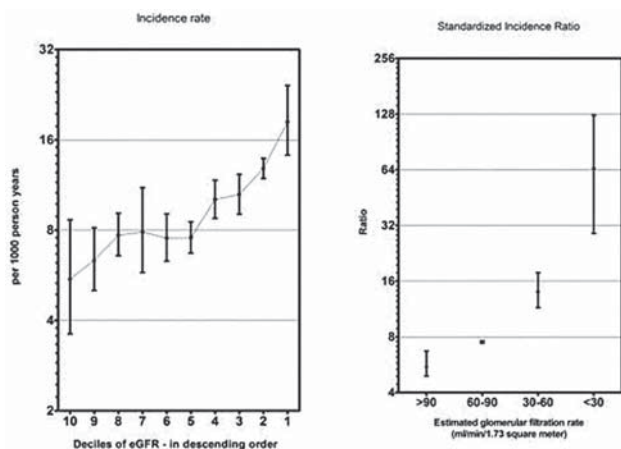
Conclusion: Chronic kidney disease is an independent risk factor for gout. The large magnitude of the metrics of association was not explained by hyperuricemia associated with chronic kidney disease.

Disclosure: **E. Krishnan**, savient, 1, URL, takeda, metbolex,ARDEA, 2, METABOLEX TAKEDA, 5;

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Feasibility of Using a Pharnacist-Based Gout Management Clinic to Improve Serum Uric Acid in Gout Patients an a Large Prepaid Health Plan. Robert D. Goldfien[1], Michele S. Ng[2], Goldie M. Yip[2], Alice Hwe[2], Alice Pressman[2] and Andy L. Avins[2]. [1]Kaiser Permanente, Richmond, CA, [2]Kaiser Permanente, Oakland, CA

Background/Purpose: Effective treatment for recurrent gout has been hampered by a number of problems including outdated treatment approaches, a failure to treat to target, and poor medication adherence by patients. To address these shortcomings, we set up referral-based gout management clinic and made it available to primary care physicians at a single Kaiser Permanente Medical Center. Patients deemed appropriate for uric acid lowering treatment were referred by their primary care physicians to the clinic.

Methods: The gout management clinic is a pharmacist-staffed, protocol-based program. The pharmacist, under the supervision of a Board Certified Rheumatologist, initiates and/or adjusts urate-lowering medications and monitored lab parameters and clinical course. The protocol employs standard gout medications (including medicatons to prevent and treat gout flares) and laboratory monitoring to achieve and maintain a serum uric acid (SUA) level of 6.0 or less. Patients are monitored until a target SUA ismaintained for at least 3 months prior to discharge from the clinic.

Results: Results for the first 100 consecutive patients enrolled in this ongoing clinic are reported here.To date, a SUA of 6.0 or less has been achieved in 67 patients, and no serious adverse reactions have been seen.The mean pre-treatment SUA was 9.3+/− 1.9 mg/dl, and the average (most recent or final) SUA with treatment is 5.9 +/−1.4 mg/dl.Thirty-five patients have already completed the program and have been discharged back to their primary care physicians. Of these, 29 were on allopurinol at a mean dose of 314 mg/day.(Range 100–750 mg).The remaining patients, were on febuxostat (3 patients and probenecid (2 patients).

Conclusion: These results show that recurrent gout can be effectively and safely managed by a protocol based population management program. This approach was efficient and required a minimal time commitment on the part of the supervising rheumatologist.

Disclosure: **R. D. Goldfien**, None; **M. S. Ng**, None; **G. M. Yip**, None; **A. Hwe**, None; **A. Pressman**, None; **A. L. Avins**, None.

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Levotofisopam Has Uricosuric Activity and Reduces Serum Urate Levels in Patients with Gout. Robert J. Noveck[1], Zongyao Wang[1], Ann Forsthoe-fel[1], Kristina Sigmon[1], Pauliana C. Hall[2], John C. Keogh[3] and John S. Sundy[1]. [1]Duke University Medical Center, Durham, NC, [2]PCH Integrated Regulatory Services, Inc., Laguna Niguel, CA, [3]Keogh Medical Writing, Philadelphia, PA

Background/Purpose: The investigational new drug levotofisopam is the S-enantiomer of racemic tofisopam, a 2,3-benzodiazepine derivative approved in over 20 countries outside the US for treatment of anxiety and autonomic instability. Two Phase 1 trials of levotofisopam in healthy volunteers demonstrated acceptable safety and unexpected reductions in serum urate (SUA). This finding raised the possibility that levotofisopam may be an effective urate-lowering therapy (ULT) in patients with gout. The objectives of this proof of concept (POC) study were to evaluate the safety and tolerability of levotofisopam and its effect on SUA in patients with hyperuricemia and gout.

Methods: This was an open-label, inpatient study of levotofisopam 50 mg TID administered for 7 days to men and women with hyperuricemia and gout.Patients were required to have had1+ gout flare in the previous 6 months,1+ chronically swollen joint due to gout, or1+ tophus; and screening SUA $\geq$8.0 mg/dL and $\leq$12 mg/dL after stopping ULT for $\geq$10 days. Key exclusions were estimated GFR <60 mL/min/1.73 m^2 and 24-hour urine uric acid excretion >1000 mg. Patients were admitted for 3 days prior to dosing and received levotofisopam 50 mg as a single dose on Day 1, 50 mg TID on Days 2–6, and 50 mg as single dose on Day 7. The primary efficacy variable was % reduction in SUA from baseline to Day 7. Secondary variables included absolute reduction in SUA, proportion of subjects with SUA <6 mg/dL on Day 7, change in fractional excretion of urate, and 24-hour urinary urate on Day 6. Adverse events (AEs) were assessed during the screening, treatment, and follow-up periods.

Results: Twenty patients were to be enrolled, but after 13 subjects were dosed, the primary objective of confirming urate-lowering potential in gout patients was achieved and the study was stopped. Baseline characteristics: mean age 47.7 years (range 39–64); 11M/2F; mean BMI 28.5 kg/m^2(range 21–33). Baseline mean SUA was 8.0 mg/dL (range 7.0–9.7). At Day 7, the mean percent reduction in SUA was 48.8% (range 31.1%–64.6%). Mean absolute reduction in SUA was 3.9 mg/dL (range 2.3–5.3), and mean treated SUA was 4.1 mg/dL (range 2.9–5.8). All 13 patients achieved a therapeutic SUA of <6.0 mg/dL. Substantial reduction in SUA was observed, to <5 mg/dL in 10/13 and <4 mg/dL in 7/13 patients. Significant increases in fractional excretion of urate and 24-hour urine urate excretion were observed. There were no serious or severe AEs or premature discontinuations due to AEs. Three patients experienced gout flare. Other AEs were musculoskeletal pain/stiffness (7), headache (6), and dizziness, diarrhea, dyspepsia, toothache, rash, and ECG lead dermatitis (2 each). No clinically meaningful changes were observed in other safety assessments.

Conclusion: Monotherapy with levotofisopam led to clinically meaningful reduction of SUA in patients with hyperuricemia and gout. Treatment was generally well tolerated with 23% of the patients experiencing gout flare. Increased fractional excretion of uric acid suggests that levotofisopam reduces SUA primarily through uricosuric activity. These results support further studies to investigate the potential role of levotofisopam for in the treatment of hyperuricemia in gout.

Disclosure: **R. J. Noveck**, Pharmos, 2, Ardea, 2, Metabolex, 2, Novartis Pharmaceutical Corporation, 2, Takeda, 2; **Z. Wang**, None; **A. Forsthoefel**, None; **K. Sigmon**, None; **P. C. Hall**, Pharmos, 5; **J. C. Keogh**, Pharmos, 5, Vela Pharmaceuticals, Inc., 7; **J. S. Sundy**, Ardea Biosciences, 2, Ardea Biosciences, 5, Regeneron, 2, Regeneron, 5, Metabolex, 2, Metabolex, 5, Pharmos, 2, Pharmos, 5, Savient, 5, Savient, 2, Celgene, 2, General Electric, 1, Academic Partners for Medical Education, LLC, 4, Medanta Duke Research Institute, 6, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5.

ACR Concurrent Abstract Session
Osteoporosis and Metabolic Bone Disease
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Trajectories of Change in Physical Function: Effects On Fractures and Mortality. Kamil E. Barbour[1], Li-Yung Lui[2], Deborah E. Barnes[3], Kristine E. Ensrud[4], Anne B. Newman[5], Kristine Yaffe[3], Steven R. Cummings[6] and Jane A. Cauley[5]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]California Pacific Medical Center, San Francisco, CA, San Francisco, [3]University of California San Francisco, San Francisco, CA, San Francisco, CA, [4]University of Minnesota and Minneapolis VAHS, Minneapolis, MN, Minneapolis, MN, [5]University of Pittsburgh, Pittsburgh, PA, [6]San Francisco Coordinating Center, CPMC Research Institute, San Francisco, CA

Background/Purpose: Prior studies have identified poor physical function as a risk factor for fractures and mortality.However, these studies did not consider change in physical function over time.We hypothesized that women

who maintain their physical function would have a lower risk of non-traumatic fracture (hip and any non-vertebral) and death.

Methods: We followed 9704 women enrolled into the Study of Osteoporotic Fractures at four U.S. clinical centers. Physical function was measured a maximum of 8 times over 19 years. The median (range) number of measurements for walking (m/s) and chair stand speed (time/s) were 6 (1–8) and 5 (1–8), respectively. Random slope and intercept models were used to determine a walking and chair stand speed slope for each woman, and for the entire population. Three groups were formed for walking speed: "maintainers" (slope ≥ −1 SD from 0, n=773, 8%); "average decliners" (1 SD below mean ≤ slope <−1 SD from 0, n=7676, 79%); "accelerated decliners" (slope >1 SD below mean, n=1255, 13%). Cox proportional hazards models were used to estimate hazard ratios (HRs; 95% CI) of fracture and mortality and control for age, BMI, physical activity, falls, fracture after age 50, diabetes, stroke, hypertension, calcium intake, health, weight change, smoking, estrogen use, and hip BMD.

Results: The HR of hip and any non-vertebral fracture was 0.64 (0.50, 0.81) and 0.76 (0.67, 0.86) for maintainers of walking speed and 1.52 (1.31, 1.76) and 1.24 (1.13, 1.36) among accelerated decliners of walking speed when compared with the average decliner group. Similar results were shown for chair stand speed. The HR of mortality was 0.49 (0.43, 0.56) for maintainers of walking speed and 0.56 (0.50, 0.64) for maintainers of chair stand speed compared with average decliner group. The HR of mortality was null for accelerated decliners of walking speed, but surprisingly 0.75 (0.70, 0.81) for accelerated decliners for chair stand speed compared with average decliners.
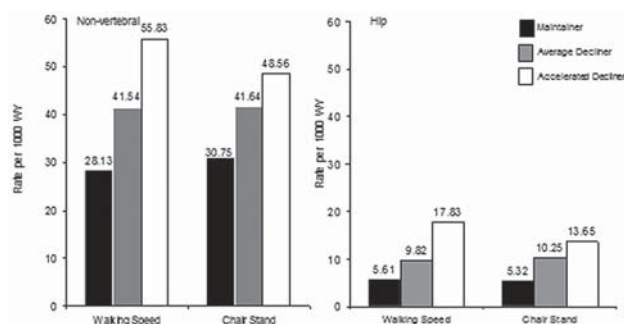
Figure 1. Fracture rate per 1000 women-year

Conclusion: Women who maintained physical function up to 19 years experienced a lower risk of fractures and mortality than average decliners of physical function, suggesting that maintaining physical function may be a marker for healthy aging.

Disclosure: **K. E. Barbour**, None; **L. Y. Lui**, None; **D. E. Barnes**, None; **K. E. Ensrud**, None; **A. B. Newman**, None; **K. Yaffe**, None; **S. R. Cummings**, None; **J. A. Cauley**, None.

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In Rheumatoid Arthritis Incident Fractures Are Associated with an Increased Risk of Cardiovascular Events. Orla Ni Mhuircheartaigh, Cynthia S. Crowson, Sherine E. Gabriel, Veronique L. Roger, L. Joseph Melton III and Shreyasee Amin. Mayo Clinic, Rochester, MN

Background/Purpose: Rheumatoid Arthritis (RA) is associated with an increased risk for both fracture (fx) and cardiovascular disease (CVD) and there is increasing evidence establishing a link between these conditions. In addition to common shared risk factors (e.g., smoking), chronic inflammation may also be key to the pathogenesis of bone loss and CVD. Our aim was to determine whether an incident fx following RA diagnosis increases the risk for subsequent CVD.

Methods: We studied a population-based inception cohort (age ≥18 yrs) who fulfilled 1987 ACR criteria for RA between 1955 and 2007 and an equal number of age- and sex-matched non-RA subjects from the same underlying population. All incident fxs, CVD events (including ischemic heart disease [IHD] and heart failure [HF]) and CVD risk factors (smoking, diabetes mellitus, hypertension, dyslipidemia) were identified through a review of complete (inpatient and outpatient) community medical records. Pathologic fxs and fxs resulting from severe trauma (e.g., motor vehicle accidents) were excluded from analyses. Subjects with prior CVD were also excluded. Adjusting for age, sex, calendar year and CVD risk factors, Cox proportional hazard models were used to examine the risk for CVD following incident fx

(modeled as a time-dependent covariate) in both RA and non-RA subjects. CVD risk factors were also modeled as time-dependent covariates.

Results: We identified 1171 RA and 1171 non-RA subjects (for each group: mean age ± SD, 57 ± 16 yrs; 822 [70%] women), of whom 137 RA and 139 non-RA subjects with prior CVD were excluded. Over a follow-up of 14,125 person-years (py) (median, 10 years) and 16,125 py (median, 12 years) for RA and non-RA subjects, respectively, 406 RA and 346 non-RA subjects had an incident fx and 284 RA and 225 non-RA subjects developed CVD. Among RA subjects, but not non-RA subjects, there was an increased risk for CVD following an incident fx (Table). Results were similar following a fx at a major osteoporotic fx site (hip, spine, wrist, shoulder) [results not shown].

	Hazard Ratio* (95% CI) for CVD following Incident Fx		
	Any CVD	IHD	HF
RA subjects	1.80 (1.35, 2.40)	1.56 (1.10, 2.20)	1.81 (1.32, 2.47)
Non-RA subjects	1.12 (0.77, 1.62)	1.09 (0.71, 1.68)	1.07 (0.70, 1.63)

* adjusted for age, sex, calendar year and CVD risk factors

Conclusion: In women and men with RA, an incident fracture is associated with an increased risk of subsequent CVD. Although the mechanism underlying this association remains to be clarified, a new fx in an RA patient should be considered a sentinel event that prompts further evaluation of their cardiovascular risk.

Disclosure: **O. Ni Mhuircheartaigh**, None; **C. S. Crowson**, None; **S. E. Gabriel**, Pfizer Inc, 2, Roche Pharmaceuticals, 5; **V. L. Roger**, None; **L. J. Melton III**, None; **S. Amin**, Merck Pharmaceuticals, 5.

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Association of Serum Uric Acid and Incident Fractures in Elderly Men. Nancy E. Lane[1], Neeta Parimi[2], Barton Wise[3], Peggy Cawthon[4], Eric Orwoll[5] and MrOS Investigators Group[6]. [1]UC Davis School of Medicine, Sacramento, CA, [2]CPMC Research Institute, SF, CA, [3]UC Davis, School of Medicine, Sacramento, CA, [4]CPMC Research Institute, San Francisco, CA, [5]Portland, OR, [6]Sacramento, CA

Background/Purpose: Normal mineral metabolism is critical for skeletal integrity. Uric acid (UA) is produced from purines by the enzyme xanthine oxidase, and elevated levels may cause gouty arthritis and kidney stones. High uric acid levels result in endothelial damage and play a role in disease processes including hypertension, heart failure and renal disease. Conversely, UA also appears to function as an anti-oxidant and may protect against the oxidative stress associated with aging and disease. Recently, serum uric acid was reported associated with elevated bone mineral density and lower prevalence of fractures in older men (Nabipour, JBMR 2011). To confirm this association, we performed a prospective case-cohort study to understand the relation of uric acid and fracture risk in older men enrolled in the Osteoporotic Fractures in Men (MrOS) study.

Methods: In the cohort of 5994 men 65 and older attending the baseline MrOS examination, we evaluated a subgroup 1,682 men in a case-cohort study design. This group included 387 men with incident non-vertebral fractures (with 73 hip fractures) and a sample of 1385 men randomly selected from the cohort with baseline mineral and calcium hormone measurements. Serum uric acid was measured in baseline serum samples by Unical DxC 800 auto-analyser (Beckman Coulter, Fullerton, CA, USA). All men who experienced any non-vertebral fracture from baseline until February 2007 (average follow-up 4.7 years) were included in the analysis. Incident fractures were confirmed with x-ray reports. Hip bone mineral density was obtained at the baseline. Modified proportional hazards models that account for case-cohort study design were used to estimate the relative hazards (RH) of fracture in men for serum uric acid.

Results: Subjects with incident non-vertebral fractures were older, had lower total hip BMD, and higher serum phosphorus. Cases were more likely to report a history of falls and to be frail (all p<0.01). Overall, there was no difference in risk of hip fracture by baseline uric acid after adjustment for age, clinic site, BMI, race, total hip BMD, vitamin D and PTH. However, there is 19% decrease risk of non-vertebral fractures (95% CI 0.71–0.93; p=0.003) per 1 SD increase of baseline UA after multivariate adjustment. Total hip BMD was significantly higher in the group of men with high uric acid levels and increased continuously across quartiles of uric acid after multivariate adjustment (p for trend=0.009).

Conclusion: Higher serum uric acid levels were associated with a reduction in risk of incident fractures and higher hip bone mineral density.

Disclosure: **N. E. Lane**, None; **N. Parimi**, None; **B. Wise**, None; **P. Cawthon**, None; **E. Orwoll**, None;

822

Greater Than Expected Increased Mortality Following Fragility Fractures in Women and Men with Rheumatoid Arthritis. Shreyasee Amin, Sherine E. Gabriel, Sara J. Achenbach, Elizabeth J. Atkinson and L. Joseph Melton III. Mayo Clinic, Rochester, MN

Background/Purpose: Women and men with RA are at an increased risk for fracture [fx] as well as greater overall mortality. It is recognized that in the general population, overall mortality among those with a fx is increased. We sought to determine whether an incident fx following the diagnosis of RA contributes to an excess mortality beyond what would be expected for an incident fracture in those without RA.

Methods: We studied a population-based inception cohort (age ≥18 yrs), who fulfilled 1987 American College of Rheumatology criteria for RA between 1955–2007, and an equal number of age- and sex-matched non-RA subjects from the same underlying population, who were followed until death or last available follow-up. All incident fxs were identified through a complete review (inpatient and outpatient) of medical records. We excluded from analyses pathologic fxs and fxs resulting from severe trauma (e.g. motor vehicle accidents, etc.). Cox proportional models were used to examine the risk for death following the first incident non-pathologic fracture resulting from no more than moderate trauma [moderate trauma fx] after RA diagnosis, or equivalent index date in non-RA subjects. All analyses were adjusted for age and sex, and fractures were modeled as a time-dependent covariate. In RA subjects, we also examined in separate analyses whether steroid use, being seropositive, or having nodules or erosions (modeled as time-dependent covariates) could account for the risk of death following fracture.

Results: In 1171 RA subjects, (822 women and 349 men, mean age at RA diagnosis ± SD: 56 ± 16 yrs and 58 ± 14 yrs, respectively), followed for 15,707 person-yrs [p-y], 440 had any moderate trauma fx, while 535 died over the available follow-up. In sex- and age-matched non-RA subjects, 374 had any moderate trauma fx and 441 died over 17,643 p-y follow-up. In RA subjects, a moderate trauma fx increased the risk for death (Hazard Ratio [HR], 2.2; 95% CI: 1.8, 2.6). An increased risk for death was also observed in non-RA subjects following a moderate trauma fx (HR: 1.5, 95% CI: 1.2, 1.9) although this risk was significantly lower (p = 0.04) than in RA. In RA subjects, any moderate trauma fracture remained a significant predictor of death even after adjusting for steroid use, being seropositive, or having nodules or erosions (HR: 1.9, 95% CI: 1.6, 2.3).

Conclusion: A moderate trauma fracture in RA is associated with a greater than expected excess mortality. Identifying characteristics or other co-morbidities among those with RA who fracture may help explain this excess risk of death following fractures.

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Positive Effects of Tocilizumab On Bone Remodeling in Patients with Rheumatoid Arthritis. Karine Briot[1], Thierry Schaeverbeke[2], Fabien Etchepare[3], Philippe Gaudin[4], Aleth Perdriger[5], Muriel Vray[6], Stephanie Rouanet[7], Ghislaine Steinberg[7] and Christian Roux[1]. [1]Paris Descartes University, Paris, France, [2]Groupe Hospitalier Pellegrin, Bordeaux, France, [3]G.H. Pitié-Salpêtrière, Paris, France, [4]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [5]Hôpital Sud, Rennes, France, [6]Paris, France, [7]Roche, Neuilly sur Seine, France

Background/Purpose: The anti-IL6-R antibody tocilizumab (TCZ) is an effective treatment of rheumatoid arthritis (RA). Previous studies showed that TCZ has a positive effect on bone turnover. However the effect of TCZ on bone mineral density (BMD) and regulators of bone remodeling pathways are limited. The objective of this ancillary study was to assess prospectively the TCZ effects on BMD and bone remodeling.

Methods: 103 patients with moderate to severe RA were treated with TCZ 8 mg/kg+ methotrexate (MTX) every 4 weeks in the Torpedo study during 12 months. Total hip and lumbar spine BMD were performed at baseline and after 48 weeks by dual energy X ray absorptiometry (DXA). Pro-collagen serum type I N-terminal propeptide (PINP), a marker of bone formation; serum C-terminalcross-linked telopeptide of type I collagen (CTX-I), a marker of bone resorption, and circulating levels of osteoprotegerin, receptor activator of nuclear factor-kappaB ligand, Wnt signalling pathway inhibitors Dickkopf-1 (Dkk-1) and sclerostin, were assessed at baseline, 12 and 48 weeks. Corticosteroid (CS) use was described using the

AUC (Area under the Curve) time weighted of cortisone intake (AUC-CS). Analysis was intent-to-treat. **Results** were presented in median and tested using the Wilcoxon paired signed-rank test.

Results: 103 patients (75 % women, 52±12 years) with active RA and a mean disease duration of 4 ±3 years were included. BMD was available for 73 patients at baseline and end of study. Serum PINP increased from baseline by 22 % (p≤0.001) and 19% (p≤0.001) at week 12 and week 48, respectively. By contrast CTX-I remained stable over the time which led to an improvement in PINP/CTX-I ratio of 14%, (p≤0.001) and 23 % (p≤0.001) at week 12 and 48, respectively. Serum DKK-1 significantly decreased from baseline by −31 % (p≤0.001) and −25 % (p=0.025) at week 12 and 48, respectively. The evolutions of DKK-1 and P1NP were not correlated. Evolutions of serum OPG and sclerostin were not significant over 48 weeks. There was no change in lumbar spine and hip BMD over 48 weeks. However in patients in the highest quartile of AUC-CS (>7.5mg/d), BMD significantly decrease at trochanter (p=0.016). CS dose was not a determinant of bone remodeling markers changes.

Conclusion: in these patients treated with TCZ in combination with MTX, we did not see the expected bone loss related to inflammation. DKK-1, a key determinant of the bone destructive pattern of RA, decreases in patients treated with TCZ which could participate to a rapid and positive effect on bone balance due to an increase in bone formation. From the results of this small sample of patients, it seems that there is no indication for prevention of CS-induced bone loss in patients receiving TCZ and low doses of corticosteroids.

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Progressive Improvements in Cortical Mass and Thickness throughout the Hip Were Observed with Denosumab Treatment in the Freedom Trial. Ken Poole[1], Graham Treece[1], Andrew Gee[1].Jacques P. Brown[2], Michael R. McClung[3], Andrea Wang[4] and Cesar Libanati[4]. [1]University of Cambridge, Cambridge, United Kingdom, [2]CHUQ-CHUL Research Centre, Quebec City, QC, [3]Oregon Osteoporosis Center, Portland, OR, [4]Amgen Inc., Thousand Oaks, CA

Background/Purpose: Denosumab (a RANK ligand antibody) reduces remodeling, increases bone mineral density, and reduces cortical porosity in postmenopausal women with osteoporosis. In FREEDOM, denosumab treatment reduced the relative risk of hip fracture by 62% in those ≥ 75 years (Boonen et al, JCEM 2011). Bone strength at the hip, estimated by FEA from QCT scans, was significantly improved from baseline and compared with placebo (Keaveny et al, ASBMR 2010). To better characterize the changes, we used a novel cortical bone mapping technique on those same serial QCT scans, to determine the extent and distribution of mass and thickness changes at the proximal femur, a key skeletal site for fracture risk.

Methods: Eighty women age 74±5 years who participated in a FREE-DOM substudy underwent hip QCT scanning at baseline, and months 12, 24, and 36 during denosumab (60 mg SC Q6M) or placebo treatment; all subjects received calcium and vitamin D supplementation. For each femur, in addition to overall cortical density, the distributions of cortical mass (in mg per unit cm[2] of periosteal surface) and thickness were measured in a blinded-to-treatment manner. Distributed measures were transferred to an average femur by first registering each individual femur to this surface. Statistical parametric mapping was used to calculate significance of denosumab or placebo effects at each time point in relation to baseline, and between treatments. Distributed results were visualised as a color map over the average femur.

Results: In denosumab-treated women, there was a progressive increase in cortical mass over time, reaching a difference vs placebo of 6% at 3 years (p<0.0001) (Fig. 1). Approximately one-third of this increase was attributed to an increase in cortical density of 7.6±1.8 mg/cm^{3}/year (p<0.0001), which in turn remained unchanged in placebo-treated subjects (p=0.62). With denosumab, cortical thickness was also significantly increased, which may represent in-filling of the cortical compartment. In contrast, average cortical mass and thickness decreased in subjects who received calcium and vitamin D alone. Mass color maps (Fig. 2) reveal the distribution of increases in cortical mass with denosumab, which were significant over an increasingly large area of the proximal femur.
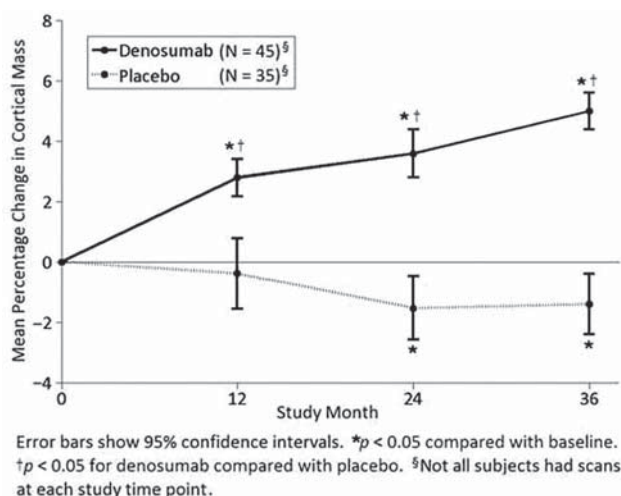
Fig. 1. Mean change in cortical mass, as a percentage of baseline.

Error bars show 95% confidence intervals. *$p < 0.05$ compared with baseline. †$p < 0.05$ for denosumab compared with placebo. §Not all subjects had scans at each study time point.
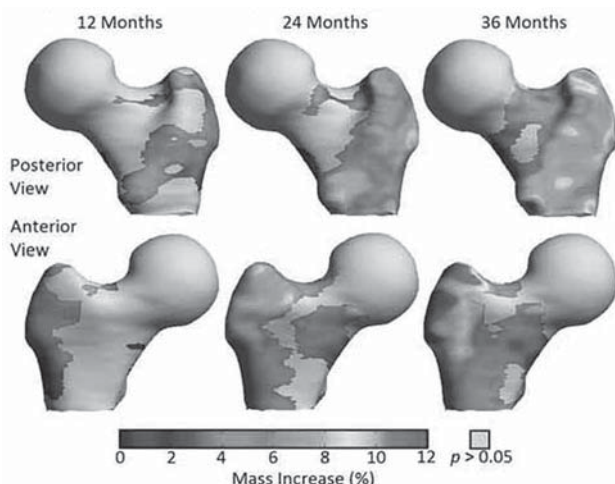
Fig. 2. Additional cortical mass increase from baseline in Denosumab group compared with placebo group, as a percentage of baseline cortical mass.

Conclusion: In postmenopausal women with osteoporosis, administration of denosumab significantly and progressively increased cortical mass and thickness in regions of the proximal femur associated with hip fracture.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects II: Long-term Outcome of Rheumatoid Arthritis, Observational Studies
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Osteoporosis and Vertebral Fractures Are Important Determinants of Cardiovascular Disease in Rheumatoid Arthritis. Ausaf Mohammad[1], Derek Lohan[1], Diane Bergin[1], Sarah Mooney[1], John Newell[2], Martin O'Donnell[1], Robert J. Coughlan[1] and John J. Carey[1]. [1]Galway University Hospitals, Galway, Ireland, [2]National University of Ireland, Galway, Ireland

Background/Purpose: Cardiovascular disease(CVD) represents a major comorbidity and the leading cause of mortality for Rheumatoid arthritis(RA) patients. Unfortunately traditional risk factors for CVD underperform in RA.

Enhanced risk stratification methods are needed. Recently a strong association between osteoporosis and CVD has been recognised in other populations. RA patients are also at increased risk of osteoporosis and thus may undergo DXA scanning as part of their usual care. DXA can diagnose osteoporosis by measuring BMD or by detecting vertebral fractures(VF) using VFA. We assessed the prevalence of osteoporosis by BMD criteria and VF in our RA cohort. We also determined whether osteoporosis increases the risk of CVD in RA patients compared to traditional CVD risk factors and RA disease activity.

Methods: A cross-sectional study of our RA cohort. We evaluated risk factors for, and details of CVD among patients ≥40 years who met 1987 ACR criteria for RA classification. Only those with a prior DXA and VFA scan available for analysis were included. Study was approved by local I.R.B. All scans were evaluated by two blinded musculoskeletal radiologists to determine the prevalence, number and severity of VF using Genant criteria. Patients were diagnosed as 'osteoporosis' using WHO DXA criteria. We compared the prevalence of osteoporosis and VF between RA patients with and without CVD, and using multivariate logistic regression analyses assessed whether VF, osteoporosis, traditional CVD risk factors and RA disease activity were independently associated with prevalent CVD.

Results: 603 patients met inclusion criteria: 74% female mean age 56 years, 76% seropositive. 230 subjects had 1 or more documented CVD event: MI 45, stent 145, CHF 33 and stroke 7. Subjects with CVD were twice as likely to have VF (24% Vs 12%) and 4 times as likely to have osteoporosis (60% Vs 15%) than those without CVD(p <0.05). Low BMD and VF were independently associated with CVD in multivariate regression analyses (P <0.05), and outperformed traditional risk factors for CVD and RA disease activity scores (Table 1).

Table 1. Age/gender adjusted OR for Osteoporosis, VF, RA Disease Activity and Traditional CVD Risk factors for CVD in RA Cohort

Variable	OR (95% Confidence Interval)	p Value
Diabetes Mellitus	1.61 (1.04–2.48)	<0.001
Smoking	1.18 (1.10–1.27)	0.042
Hypertension	1.58 (1.12–1.89)	0.001
Hyperlipidemia	1.02 (1.00–1.05)	0.041
CRP	1.73 (1.41–2.12)	<0.001
DAS28	1.63 (1.30–2.03)	0.001
Vertebral fracture	2.70 (1.50–4.75)	<0.001
Osteoporosis	2.67 (1.87–3.91)	<0.001

Conclusion: BMD and VF among RA patients should alert physicians not just to the presence of osteoporosis, but also to the possibility of CVD. Interventions to reduce the development of CVD in RA patients with osteoporosis may be warranted.

Disclosure: **A. Mohammad**, None; **D. Lohan**, None; **D. Bergin**, None; **S. Mooney**, None; **J. Newell**, None; **M. O'Donnell**, None; **R. J. Coughlan**, None; **J. J. Carey**, None.

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Predictors of Return to Work During 3 Years After Start of First Tumor Necrosis Factor Antagonist in a National Cohort of Biologics-Treated Patients with Rheumatoid Arthritis. Tor Olofsson[1], Ingemar F. Petersson[2], Jonas Eriksson[3], Martin Englund[2], Pierre Geborek[1], Lennart T.H. Jacobsson[4], Johan Askling[3] and Martin Neovius[3]. [1]Department of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden, [2]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Background/Purpose: To estimate predictors of return to work during 3 years following start of anti-TNF therapy in working-age RA patients with total work disability at treatment start.

Methods: RA patients aged 19–61y (n=753; mean age 53y; 80% women) starting their first anti-TNF therapybetween Jan 2006 and Dec 2009 and having total work disability at treatment start (90 days with sick leave or disability pension during the 3 months preceding anti-TNF start) were identified in the Swedish biologics register (ARTIS; 92% nationwide coverage). The mean/median disease duration at bio-start was 11y/8y, 77% were on ≥1 non-biological DMARD (corticosteroids excluded). Days of sick leave and disability pension were retrieved from the Social Insurance Agency

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register covering all inhabitants in Sweden (data available until Oct 2010). Survival analysis was conducted with return to work ≥50% as outcome (defined as the first occurrence of a month with <15 days of sick leave or disability pension during follow-up). Baseline predictors including sex, age, education level, disease duration (counted from symptom onset), HAQ, CRP and use of non-biological DMARDs were estimated using Cox regression. The model was further adjusted for year of bio-start, health care region, unemployment status, depression and anxiety disorders, and malignancies. DAS28 was analysed in a separate model excluding HAQ (due to multi-collinearity) and CRP.

Results: During the 3-year observation period after start of anti-TNF treatment the overall cumulative probability of return to work ≥50% of monthly days was 21%. The corresponding probability for patients with disease duration <5y and ≥5y was 34% and 13%, respectively (Figure; unadjusted hazard ratio [HR] for return to work ≥50% 3.0, 95%CI 2.1–4.2; adjusted HR 2.4, 95%CI 1.5–3.7). Besides this, HAQ (HR 1.6, 95%CI 1.1–2.3, per unit decrease), age at bio-start (1.8, 1.4–2.2, per 10y decrease) and education level (2.1, 1.0–4.2, for >12y vs ≤9y) were also significant predictors in adjusted analysis. This was not the case for sex (p=0.08), CRP (p=0.34) or use of non-biological DMARDs (p=0.61) at bio-start. DAS28, analysed separately, was not a statistically significant predictor after adjustment (p=0.64).
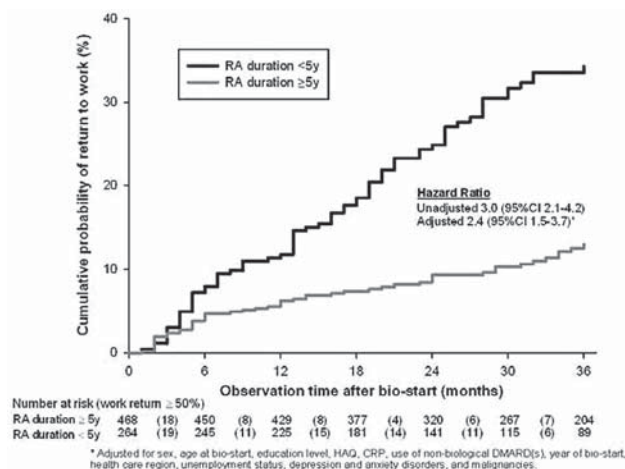
Figure. Cumulative probability of work return ≥50% of monthly days for totally disabled RA patients (19–61 y) after start of first anti-TNF therapy (2006–2009) and 36 months forth, stratified on disease duration at treatment start.

Conclusion: The probability of return to work for totally disabled RA patients was higher for patients initiating anti-TNF therapy within 5 years of symptom onset. HAQ, age at bio-start and education level were also statistically significant predictors, while DAS28 and use of non-biological DMARDs were not. The results suggest that there might be a potential for increasing return to work if biological treatment was started earlier in the disease course in work disabled patients.

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Sustained Development of Cardiovascular Disease in Rheumatoid Arthritis Despite Cardioprotective Treatment: The 10-Year Prospective Carre-Study. Alper M. van Sijl[1], Inge A.M. van den Oever[1], Mike J.L. Peters[2], Vokko P. van Halm[3], Alexandre E. Voskuyl[2], Yvo M. Smulders[2] and Mike T. Nurmohamed[1], [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Academic Medical Centre, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which is associated with an increased cardiovascular (CV) risk. It is still unknown to what extent this is due to CV risk factors or the underlying inflammatory process in RA. With the advent of effective anti-inflammatory and cardioprotective treatment, this riskmight be mitigated or even reduced. The present study compared changes in CV risk factors, RA-related factors and medication use over time in RA-patients who did and did not develop CV disease during follow-up.

Methods: Starting from 2000–2001, 10-year incidence rate of CV disease, CV risk factors, RA-related factors and medication use were assessed in a prospective cohort of 353 RA patients at baseline, at 3-years and at 10-years of follow-up. Associations between the changes in RA related factors and development of CV disease were assessed using generalized estimating equation (GEE) analyses, while changes in all variables were assessed with general linear models (GLM).

Results: After 10 years, there were 58 CV events over 2361 patient years of follow-up, incidence rate (IR) of 25.3/1.000 patientyears. This was similar to the IR between 3-years and 10-years of follow-up: 22.8/1.000 patientyears. GLM analyses showed that use of antihypertensives, statins, TNF inhibitors and general CV risk increased significantly over time, while RA related factors improved significantly. GEE analyses showed that increased use of TNF inhibitors was positively associated with less incident CV disease.

Table 1. Changes in CV risk factors and RA-related factors during follow-up

	Baseline (n=353)	Change 0–3 years (n=226)	Change 3–10 years (n=164)
Changes in CV-risk factors			
Total cholesterol, in mmol/L	5.82 ± 1.11	−0.21	+0.05
LDL-cholesterol, in mmol/L	3.73 ± 1.03	+0.37 *	+0.07
HDL-cholesterol, in mmol/L	1.48 ± 0.48	+0.17 *	−0.07
Triglycerides, in mmol/L	1.3 (1.0–1.8)	0	0
Total-/HDL-cholesterol ratio	4.32 ± 1.48	−0.63 *	+0.10
Statins, %	9	+3 *	+5 *
Systolic BP, mmHg	141 ± 19	0	0
Diastolic BP, mmHg	81 ± 8	0	+5 *
Antihypertensives, %	24	+4	+11 *
Hypertension, %	59	−6 *	+3
DM, %	5	0	+4 *
Current smoking, %	27	−5	−10 *
Packyears	18 (1–34)	−1	+3
Body-mass index, kg/m2	26.7 ± 4.8	+0.4 *	+0.2 *
Markers for CV risk			
Intima-media thickness, mm	0.815 ± 0.136	+0.030	−0.006
10-year CV risk (SCORE)	5.0 (2.4–9.5)	+0.5	+4.4 *
RA-related factors			
ESR, mm/hour	17 (9–31)	−2 *	−1 *
CRP, mg/L	7 (3–18)	−2 *	−2 *
DAS–28	3.91 ± 1.38	−0.72	−0.05
DAS-remission (DAS28 <2.6)	18	+6	−7 *
HAQ	0.75 (0.38–1.13)	−0.12 *	+0.02
Use of biologicals, %	2	+9 *	+14 *
Use of MTX, %	60	–	−14
Use of prednisone, %	15	–	−2
Use of NSAIDs, %	67	–	−40 *

* p < 0.05. Changes in CV- and RA-related factors are investigated by General Linear Models
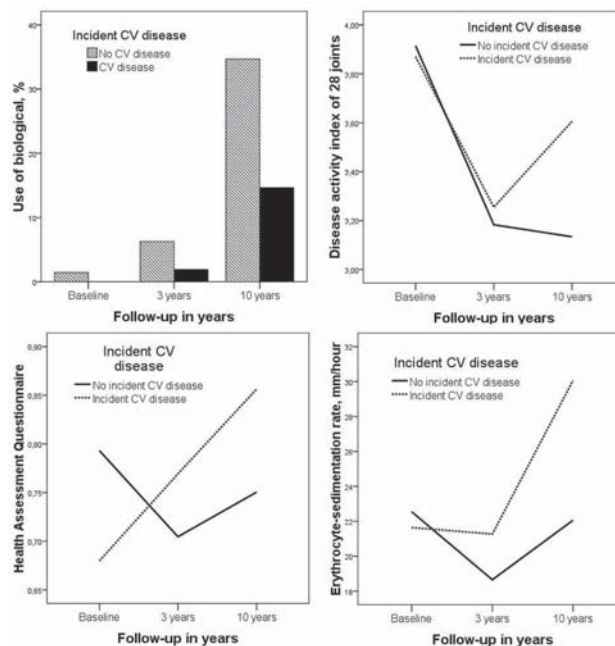
Figures 1–4. Changes in use of biologicals and RA factors over time stratified for incident CV disease

Conclusion: The risk of incident CV disease persists in patients with RA despite the advent of effective anti-inflammatory therapies and increased use of cardioprotective medication in recent years. Patients who used TNF inhibitors and, more indirectly, had a reduction in inflammation or disease activity, were less at risk of developinga CV disease. General CV risk and use of cardioprotective medications did not attenuate this association. A more aggressive cardioprotective and anti-inflammatory treatment of RA might mitigate the burden of CV disease in RA.

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Association between Anti-Tumor Necrosis Factor Therapy and the Risk of Ischemic Stroke in Subjects with Rheumatoid Arthritis. Results From the British Society for Rheumatology Biologics Registers-Rheumatoid Arthritis (BSRBR-RA).

Audrey S. Low[1], Mark Lunt[2], Louise K. Mercer[1], James B. Galloway[1], Rebecca Davies[3], Kath D. Watson[4], British Society for Rheumatology Biologics Register (BSRBR) control centre consortium[1], Deborah P. Symmons[1], William G. Dixon[1], Kimme L. Hyrich[3] and On behalf of the BSRBR[5]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [4]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [5]British Society for Rheumatology, London, United Kingdom

Background/Purpose: Subjects with rheumatoid arthritis (RA) are at increased risk of cardiovascular (CV) morbidity and mortality, with some studies suggesting an increased risk of stroke (CVA). The aim of the analysis was to study the association of anti-TNF therapy with ischemic CVA (isCVA) in routine clinical practice.

Methods: The BSRBR-RA is an ongoing national prospective cohort study of subjects with RA recently started on anti-TNF therapy (etanercept, infliximab, adalimumab). A biologic-naïve comparator cohort of subjects with RA treated only with non-biologic disease modifying anti-rheumatic drugs (nbDMARDs) was also recruited. Both cohorts were recruited from 2001–2008 and were followed by physician and patient questionnaires every six months for the first three years and annual physician questionnaires thereafter, in which data on serious adverse events such as CVAs and drug therapy were reported. All subjects were also linked to the national death register. Further data about reported CVAs were collected from medical records and validated against the World Health Organization criteria for CVA. These were further classified as isCVA using CT brain reports or if isCVA was reported as the underlying cause of death from death certificates using International Classification of Diseases 10 (ICD-10) code I63. Only validated isCVAs were included in the analysis. Subjects with prior CVA were excluded. Subjects were censored at first isCVA, death or date of last physician follow-up, whichever came first. Risk of isCVA was compared between the nbDMARD cohort and subjects ever exposed to anti-TNF using a Cox regression model. Adjustment was made using propensity scores stratified by deciles, which included age, gender, ethnicity, BMI, DAS28, disease duration, HAQ, prior nbDMARD use, steroid use at baseline, year of entry to study, smoking, baseline drugs including NSAIDs, digoxin, warfarin, antiplatelet agents, statins, history of cancer, hypertension, ischaemic heart disease, diabetes, depression and chronic lung disease.

Results: To 10/31/2010, 130 verified incident isCVA (21 in 3271 nbDMARD subjects, 109 in 11642 anti-TNF subjects) occurred during 11973 and 61226 person-years (pyrs) of observation respectively (incidence rate 175 versus 178 per 100,000 pyrs). After adjustment, there was no association between ever exposure to anti-TNF and isCVA risk: hazard ratio (HR) 0.88 (95% CI 0.46, 1.71).

Table.

	nbDMARD (n=3271)	Anti-TNF (n=11642)
Age (years), mean (SD)	60 (12)	56 (12)
Female, %	74	77
Disease duration (years), median (IQR)	6 (1,15)	11 (6, 19)
Baseline DAS28, mean (SD)	5.3 (1.1)	6.6 (1.0)
Baseline HAQ, mean (SD)	1.5 (0.7)	2.0 (0.6)
Number of prior nbDMARDs, median (IQR)	2 (1, 3)	4 (3, 5)
Baseline steroid use, %	22	44
Baseline NSAID/COX2 use, %	55	63
Hypertension at baseline, %	31	30
Person-years of follow-up	11973	61226
Person-years of follow-up per person, median (IQR)	3.9 (2.1, 5.2)	5.6 (3.9, 6.9)
Number of incident fatal & non-fatal isCVA	21	109
Crude incidence rate of isCVA per 100,000 pyrs (95%CI)	175 (128, 297)	178 (151, 221)
Risk of isCVA in subjects ever exposed to anti-TNF therapy	–	–
Unadjusted HR (95% CI)	Referent	1.07 (0.67, 1.71)
Adjusted for age & gender (95% CI)		1.49 (0.92, 2.40)
Fully adjusted-stratified by deciles of propensity score (95%CI)		0.88 (0.46, 1.71)

Conclusion: Exposure to anti-TNF therapy does not appear to be associated with the risk of isCVA over the short term when compared to nbDMARD therapy. Further follow-up is needed to assess time-varying risk.

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Subcutaneous Nodules Are Significantly Associated with Cardiovascular Events in Patients with Rheumatoid Arthritis: Results From a Very Large US Registry.

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Background/Purpose: Cardiovascular Disease (CVD) is now recognized to be a major comorbidity of patients with rheumatoid arthritis.Predictors of CVD have been shown to include a variety of measures of RA disease activity and severity (1). Although subcutaneous nodules (SQN) are associated with more severe RA, until this time there had been no clinical phenotypic characteristic which was immediately recognizable as a marker of increased risk for CVD in patients with RA.

Methods: Data are from the CORRONA database from Oct 2001 to Sept 2011 was evaluated.23327 patients with RA, including 182,201 individual visits who have an average of 3 years of follow-up dataand with 70455 patient-years and 795 CV events are included in this analysis. Presence or absence of SCN have been routinely collected over the entire 11 year history of the registry.CV events (ischemic heart disease including MI, stroke/TIA, CHF and CV death) were defined by MD reported events and exclusion of events not confirmed by the sites completing a follow up form.Cox regression models were used to estimate HR for time to first event with entry into CORRONA as the origin.Unadjusted and adjusted Hazard Ratios (HR) for SCN were estimated. A multivariable model was fit that considered the following factors as possible covariates: age, gender, age of onset of RA, presence of diabetes mellitus (DM), hypertension, smoking, alcohol consumption, use of a lipid lowering agent.Significant factors were retained in the model.

Results: Table 1 shows the estimated HR for SCN unadjusted and then adjusted with the covariates considered in the model. Unadjusted HR for SCN is 1.44, 95% CI: [1.23–1.67].Adjusted HR is 1.25 [1.07–1.46]. An interaction of age and gender provided a better fit of the model, females with a steeper increase in risk with age than males.

Table 1. CV risk associated with subcutaneous nodules adjusted and unadjusted Hazard Ratios (HR)

	HR	95% CI	p-value
Subcutaneous Nodules (unadjusted)	1.44	[1.23–1.67]	<0.0001
Multivariable Model			
Subcutaneous Nodules	1.25	[1.07–1.46]	0.0048
History of CVD	2.89	[2.40, 3.48]	<0.0001
Diabetes	1.72	[1.40,2.10]	<0.0001
Hx of Hypertension	1.47	[1.25, 1.73]	<0.0001
Current Smoker	1.39	[1.16, 1.66]	0.0003
Current Drinker	0.74	[0.63, 0.86]	0.0002
Age Onset of RA (per year)	1.004	[1.001, 1.007]	0.121
Lipids Measured	1.65	[1.21, 2.23]	0.0014
Age (Males)* (per year)	1.01	[1.00, 1.02]	0.049*
Age (Females)* (per year)	1.03	[1.02, 1.04]	
Females vs Males (at age 40)*	0.39	[0.26, 0.60]	
Females vs Males (at age 70)*	0.59	[0.50, 0.70]	

*Age-Gender interaction included in the model; p-value for test of interaction.

Conclusion: We report for the first time, from a very large US observational registry, that SCN confer a significantly increased likelihood of CVD in patients with RA followed for a period of > 3 years. While active RA is a risk factor for CVD the presence of subcutaneous nodules, an immediately assessable and accessible clinical phenotype, confers an increased risk for this major comorbidity.

Reference
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Five-Year Favourable Outcome of Patients with Early Rheumatoid Arthritis in the 2000s: Data From the Espoir Cohort. Bernard G. Combe[1], Nathalie Rincheval[2], Joelle Benessiano[3], Francis Berenbaum[4], Alain G. Cantagrel[5], Jean-Pierre Daurès[2], Maxime Dougados[6], Patrice Fardellone[7], Bruno Fautrel[8], Rene-Marc Flipo[9], Philippe M. Goupille[10], Francis Guillemin[11], Xavier X. Le Loet[12], Isabelle Logeart[13], Xavier Mariette[14], Olivier Meyer[15], Philippe Ravaud[16], Alain Saraux[17], Thierry Schaeverbeke[18] and Jean Sibilia[19]. [1]Hopital Lapeyronie, Montpellier, France, [2]Institut Universitaire de Recherche Clinique, Montpellier, France, [3]Rheumatology, Paris Unervisity Hospital BICHAT, Paris, France, [4]AP-HP, St Antoine Hospital, Paris, France, [5]Hopital Purpan, Toulouse CEDEX 9, France, [6]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [7]C.H.U. D'Amiens, Amiens, France, [8]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [9]Hopital R Salengro CHRU, Lille CEDEX, France, [10]Hopital Trousseau, Tours, France, [11]Faculte de Medecin/BP 184, Vandoeuvre-les-Nancy, France, [12]CHU de ROUEN, Rouen, France, [13]Pfizer, Paris, France, [14]Université Paris-Sud, Le Kremlin Bicetre, France, [15]Hopital Bichat, Paris, France, [16]Hotel Dieu University hospital, Paris, France, [17]CHU de la Cavale Blanche, Brest Cedex, France, [18]Groupe Hospitalier Pellegrin, Bordeaux, France, [19]CHU Hautepierre, Strasbourg, France

Background/Purpose: To report the five-year outcome of a large national multicentre, longitudinal and prospective cohort of patients with very early arthritis and rheumatoid arthritis (RA), the so-called "ESPOIR cohort study".

Methods: Patients were recruited if they had early arthritis of less than 6 months disease duration, a high probability to develop RA, and if they were DMARD and steroids naïve. Patients have been followed every 6 months during the first 2 years then every year. Logistic regression analysis was used to determine predictive factors of outcome.

Results: 813 patients were included. The mean age was 48.1 ± 12.6 years, the main delay for referal was 103.1 ± 52.4 days. DAS28 score was 5.1 ± 1.3, HAQ DI was 1.0 ± 0.7. 44.2 % and 38.8 % had respectively IgM rheumatoid factor or anti-CCP antibodies. These rate remained stable during follow-up. 22 % of the patients had erosions on hand or feet at baseline. 78.5 % of the patients fulfilled the 2010 ACR/EULAR criteria for RA at baseline and 93.8 % during follow-up.573 patients were evaluated at the 5-year follow-up visit. The outcome was rather mild in most of the patients. Disease activity (median DAS28 score: 2.5) and HAQ DI (median: 0.3) were well controlled overtime. The annual rate of radiographic progression was low (2.9 modified Sharp score unit/year). A minority of the patients required joint surgery and no increased risk of co-morbidities was observed. During the 5-year follow-up, 82.7% of the patients received at least one DMARD, which was mainly MTX (n=536; 65.9 %) usually prescribed as monotherapy.18.3 % of the included patients were treated with a biological DMARD and almost 60 % of the whole cohort received at least once, prednisone with a mean dosage of 8.8 ± 7.7 mg/day. Anti-CCP antibodies were the best predictive factor of radiographic progression, prescription of both synthetic or biologic DMARDs or still being followed in the cohort at 5-year

Conclusion: The quite favourable 5-year outcome of this very early RA cohort highlights the need for early referral, early effective treatment and close monitoring in the management of patients with early arthritis in daily practice.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Efficacy and Safety of Novel Entities
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Efficacy of Brodalumab (AMG 827) in Subjects with Rheumatoid Arthritis and an Inadequate Response to Methotrexate. Karel Pavelka[1], Yun Chon[2], Richard Newmark[2], Ngozi Erondu[2] and Shao- Lee Lin[2]. [1]Institute and Clinical of Rheumatology, Charles University, Prague, Czech Republic, [2]Amgen Inc, Thousand Oaks, CA

Background/Purpose: A potential role for IL-17 in rheumatoid arthritis (RA) has been supported by data from clinical studies of inhibitors of the IL-17A ligand. To evaluate efficacy and safety of brodalumab (AMG 827), a human monoclonal antibody inhibitor of the IL-17 Receptor, in subjects with RA.

Methods: Subjects with RA who had an inadequate response to methotrexate (ie, continuing RA symptoms) and were biologic-naïve were randomized 1:1:1:1 to receive brodalumab (70, 140, or 210 mg) or placebo subcutaneously at day 1 and weeks 1, 2, 4, 6, 8, and 10 (Q2WK). Primary endpoint was proportion of subjects achieving an American College of Rheumatology (ACR) 50 response at week 12. Secondary endpoints included proportion with ACR 20 and 70 at week 12 and Disease Activity Score 28 joint (DAS28) at week 12. Safety was assessed by monitoring adverse events (AEs). Analyses were based on intent to treat using non-responder imputation.

Results: Two hundred fifty-two subjects were randomized; 189 to brodalumab and 63 to placebo. Two hundred forty-two subjects (183 [97%] AMG 827; 59 [94%] placebo) completed the study (defined as 16 weeks of study evaluations). Demographics and baseline characteristics were generally balanced among treatment groups. The majority ($> 75\%$) of subjects were female and white. In subjects treated with brodalumab and placebo, respectively, mean (SD) age was 50.6 (11.5) years and 53.3 (10.3) years, mean weight was 72.8 (15.1) kg and 74.8 (16.5) kg, mean duration of RA was 8.1 (7.9) years and 7.5 (6.9) years, mean Disease Activity Score 28 joint (DAS28) was 6.5 (0.8) and 6.4 (0.8), and mean C-reactive protein (CRP) was 12.8 (12.1) mg/L and 14.6 (17.6) mg/L.

ACR 50 at week 12 occurred in 16% (70 mg), 16% (140 mg), 10% (210 mg), and 13% (placebo; all non-significant vs placebo) of subjects. Differences in ACR 20 and 70 were non-significant ($p > 0.05$) for any treatment group as compared with placebo. Mean (SD) change from baseline in DAS28 at week 12 was −1.4 (1.3), −1.3 (1.2), −1.3 (1.2), and −1.3 (1.2) for the 70 mg, 140 mg, 210 mg and placebo groups, respectively. The p-values for DAS28 at week 12 in brodalumab treatment groups compared with placebo were all non-significant ($p > 0.05$). Mean (SD) percent CRP change was 97.5 (345.4), 50.7 (168.7), 45.1 (159.3), and 33.5 (170.3) for the 70 mg, 140 mg, 210 mg and placebo groups, respectively. No differences in efficacy outcomes for subgroup analyses based on sex, age, weight, or region were observed. Incidences of all AEs, including serious AEs (SAEs), were similar across treatment groups. A total of 7 subjects reported SAEs during the study (2 in the placebo group and 5 in the brodalumab groups), none of which was treatment related. There was 1 death (cardiopulmonary failure) 1 week after last dose in the 140 mg group.

Conclusion: There was no evidence of meaningful clinical efficacy or change in CRP with brodalumab treatment in subjects with RA who had an inadequate response to methotrexate. Short-term treatment was well tolerated across a dose range of 70 to 210 mg and these analyses did not suggest any safety risks with brodalumab administration. These preliminary results do not support further evaluation of brodalumab as a treatment for RA.

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Peroxisome Proliferator-Activated Receptor Gamma Agonist Treatment for Rheumatoid Arthritis: A Proof-of-Concept Randomized Controlled Trial. Michelle J. Ormseth, Annette M. Oeser, Andrew Cunningham. Aihua Bian, Ayumi Shintani, S. Bobo Tanner and C. Michael Stein, Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Rheumatoid arthritis (RA), a chronic inflammatory disease, is associated with insulin resistance.Experimental evidence indicates that the relationship between insulin resistance and inflammation is bi-directional: inflammation promotes insulin resistance, and insulin resistance promotes inflammation. Therefore, we examined the hypothesis that improving insulin sensitivity with pioglitazone, a thiazolidinedione PPAR-γ agonist, would decrease inflammation in patients with RA.

Methods: In a single center, randomized, double blind, placebo-controlled cross-over trial of 20 weeks duration, patients with RA (n=34) and moderate disease activity receiving stable disease modifying anti-rheumatic drug therapy were randomized to receive either pioglitazone 45mg daily (n=17) or matchingplacebo (n=17) for 8 weeks in addition to current therapy. This was followed by a 4 week wash-out period and then patients received the alternative regimen for the next 8 weeks.Primary outcome measures were change in DAS28 score; individual components of the DAS28 score including tender and swollen joint count, patient reported disease activity based on visual analog scale (VAS), and acute phase reactants; and change in insulin resistance determined by the homeostatic model assessment for insulin resistance (HOMA). Disease activity variables, inflammatory markers, and fasting insulin and glucose were measured. Analysis was by intention to treat and linear mixed effect models were used to determine the effect of pioglitazone on outcome measures.

Results: Patients had a median [IQR] age of 52.5 years [44.2–59.5 years], 82% were female and baseline median DAS28 CRP was 4.24 [3.62–5.6]. Compared to placebo, the addition of pioglitazone was associated with a 0.368 unit (95% CI, 0.0002–0.735) reduction in DAS28 CRP, (P=0.036), a 48.7% (28.5–63.1%) decrease in CRP (P<0.001), and a 23.7% (1.1–41.1%) decrease in insulin resistance as measured by HOMA (P=0.04). There was no significant reduction in swollen (P=0.83) or tender joint count (P=0.43), and a non-significant trend toward decreased patient reported disease activity VAS by 9.8mm (−0.1–19.7mm) (P=0.05). There was no significant change in ESR (p=0.27) or DAS28 ESR (P=0.92). Lower extremity edema was more common during pioglitazone (16%) treatment than placebo (0%); otherwise, adverse events occurred with similar frequency.

Conclusion: The addition of pioglitazone to current RA treatment improves insulin resistance and modestly reduces RA disease activity measured by DAS28 CRP and CRP levels.

Disclosure: M. J. Ormseth, None; **A. M. Oeser**, None; **A. Cunningham**, None; **A. Bian**, None; **A. Shintani**, None; **S. B. Tanner**, None; **C. M. Stein**, None.

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A Phase 1, Randomized, Double-Blind, Placebo-Controlled Multiple-Dose Study of Intravenous Staphylococcal Protein A in Patients with Active Rheumatoid Arthritis On Methotrexate: Safety, Pharmacokinetics and Efficacy. Edward Bernton[1], Eduard Krantz[2] and William Gannon Jr.[3]. [1]Protalex Inc., Summit, NJ, [2]Parexel Clinical Pharmacology, Bloemfontein, South Africa, [3]Capital City Technical Consulting, Inc., Washington, DC

Background/Purpose: PRTX-100 is highly-purified GMP staphylococcal protein A (SpA) that binds with extremely high affinity to the Vh antibody framework region of Clade Vh3 immunoglobulins.SpA thus binds to human monocytes and Vh3 B-cells and, at concentrations of <50 ng/mL, SpA can inhibit their activation *in vitro*. In 1999 the FDA licensed an immunoabsorbent device for treatment of RA and subsequently it was demonstrated that these treatments exposed patients to low doses of SpA.Phase I studies have characterized the safety of single intravenous doses of SpA up to 0.45 μg/kg.

Methods: This phase I multicenter sequential dose-escalation study enrolled patients with active RA on methotrexate (mean DAS28-CRP of 5.78).Sequential cohorts were treated with 0.15, 0.45, 0.9 or 1.5 μg/kg of PRTX-100 or placebo, administered weekly for 4 weeks.Safety and disease activity were evaluated over 16 weeks following the first dose.The primary disease activity response endpoint was the number of patients with a DAS28-CRP <3.2 at Week 6.Pharmacokinetics were evaluated after the first and last dose.

Results: A total of 37 patients were enrolled.PRTX-100 was generally safe and well-tolerated; 3/29 PRTX-100-treated patients had mild to moderate infusion reactions, which were self-limiting and related to dosing rate.Transient flare of RA occurred in 4/29 of PRTX-100 patients.The relationship of dose to PRTX-100 C_{max} and AUC was linear, but clearance and AUC were extremely variable within dose cohorts.The mean C_{max} at 1.5 μg/kg was 51.9 ng/mL.PRTX-100 elicited anti-drug antibodies (ADAs) in the majority of patients but the incidence or titer of ADAs was not dose-dependent.Higher titer ADAs were associated with an increased plasma clearance after the fourth dose.The development of ADAs did not appear to preclude an effect of PRTX-100 on measures of disease activity. The endpoint of DAS28-CRP <3.2 at Week 6 was met by 3/29 PRTX-100 and 0/8 placebo patients.PRTX-100 treatment did not decrease CRP, even in patients whose swollen and tender joint count and global VAS decreased to low levels after treatment.A post-hoc analysis was performed examining changes in CDAI scores in all patients to remove the influence of the CRP component.At baseline the mean CDAI score for study patients was 36.8.In the placebo, 0.15 μg/kg and 0.45 μg/kg PRTX-100 groups, 1/8 patients attained low disease activity (CDAI ≤10) on two or more consecutive visits.Two of eight and 2/5 patients in the 0.9 and 1.5 μg/kg PRTX-100 groups, respectively, attained this same endpoint and maintained CDAI ≤10 for 12 weeks after the end of treatment.Of the 4/5 responders in the 1.5 μg/kg group, two attained a CDAI ≤6 (remission), one attained a CDAI ≤10 (low activity), and one attained a CDAI of 10.1 over the course of the study.The mean time to peak response in this group was 70 days.

Conclusion: Four weekly doses of intravenous PRTX-100 demonstrated an acceptable safety profile and, at the higher doses, decreased RA activity as scored by CDAI.Results of this pilot study support further clinical trials of PRTX-100 at doses of 1.5 μg/kg and higher.

Disclosure: E. Bernton, Protalex Inc., 1, Protalex Inc., 5; **E. Krantz**, Paraxel, Inc, 3; **W. Gannon Jr.**, Protalex, Inc., 1, Protalex, Inc., 5, Protalex, Inc., 6.

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Cetrorelix, a Gonadotropin-Releasing Hormone Antagonist, Significantly Reduces Tumour-Necrosis-Factor-Alpha and Demonstrates Efficacy in Patients with Active Rheumatoid Arthritis: A Proof-of-Concept, Double-Blind, Randomised Trial. Anita Kåss[1], Øystein T. Førre[2], Morten Fagerland[2]. Hans Christian Gulseth[3], Peter Torjesen[4] and Ivana Hollan[5], [1]University of Oslo, Oslo, Norway, [2]Oslo University Hospital, Oslo, Norway, [3]Betanien Hospital, Skien, Norway, [4]Oslo University Hospital, Norway, [5]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is unclear, and treatment options can be improved. Gonadotropin-releasing hormone (GnRH) stimulates immune responses (1) and therefore might be pro-inflammatory in RA. We investigated the short-term effects of a GnRH-antagonist, cetrorelix (which rapidly decreases luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), in a proof-of-concept study in RA.

Methods: In this double-blinded, single-site study in Norway (ClinicalTrials.gov NCT00667758), 99 patients with active longstanding RA, were randomised to predefined intention-to-treat populations using computer-generated allocation (1:1) in dynamic blocks stratified for sex. Patients were assigned to subcutaneous cetrorelix (n=48) (5 mg days 1–2, 3 mg days 3–5) or placebo (n=51). The primary endpoint was the change in disease activity score (DAS28CRP) by day 5, when the greatest LH and FSH suppression was anticipated. Secondary endpoints included change in tumour necrosis factor-α (TNF-α), American College of Rheumatology (ACR) responses, and DAS28CRP<2.6 remission by day 5. Patients were followed up on days 10 and 15.

Results: By day 5, the change in DAS28CRP was −0.82 (95% CI –1.06, –0.58) in the cetrorelix group and –0.57 (–0.76, –0.37) in the placebo group, between-group difference 0.26 (–0.04, 0.57, p=0.091).By day 5, TNF-α (log pg/mL) was significantly decreased in the cetrorelix group (–0.58) compared with the placebo group (–0.02; difference 0.55 [0.08, 1.01], p=0.023), and more patients on cetrorelix achieved ACR20 responses (40% *vs* 18%; p=0.015) and DAS28CRP<2.6 remission (13% *vs*0%; p=0.009). Serum CRP levels were clinically relevantly reduced in the cetrorelix group versus placebo (−0.28 vs. 0.045mg/dL, p=0.060); followed by a reduction in ESR levels by day 15 (−1.06 vs. 5.04, p=0.051). Disease activity markers rebounded towards baseline after cetrorelix withdrawal, except erythrocyte sedimentation rate, which is slower to change. Adverse event rates were similar between groups.

Conclusion: This study demonstrates antagonizing GnRH with cetrorelix lowers TNF-α, and improves signs and symptoms of RA. The novel association between GnRH and TNF-α may improve insights into the pathogenesis and treatment of RA, and potentially other autoimmune diseases. Larger, long-term studies on the efficacy and safety of GnRH antagonists in RA patients are warranted.

Reference:
1. Chen A et al. The neuropeptides of GnRH-II and GnRH-I are produced by human T cells and trigger laminin receptor gene expression, adhesion, chemotaxis and homing to specific organs. Nat Med 2002; 8: 1421-6.

Disclosure: A. Kåss, None; **T. Førre**, None; **M. Fagerland**, None; **H. C. Gulseth**, None; **P. Torjesen**, None; **I. Hollan**, None.

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Low Doses of Ocaratuzumab, a Fc- and Fab-Engineered Anti-CD20 Antibody, Result in Rapid and Sustained Depletion of Circulating B-Cells in Rheumatoid Arthritis Patients. Adrienne O'Reilly, Tracy Davis and Vinay Jain. Mentrik Biotech, Dallas, TX

Background/Purpose: B-cell depletion provides therapeutic benefits for patients with rheumatoid arthritis (RA). Ocaratuzumab, previously known as AME-133v, is a Fc- and Fab-engineered, humanized, anti-CD20 monoclonal antibody designed for optimized affinity to the CD20 antigen as well as to the CD16 (FcγRIIIa) receptor on effector cells. It demonstrates 13–20 fold higher affinity for CD20 and 6-fold higher antibody-dependent cellular cytotoxicity as compared to rituximab, which is currently approved for RA. Because patients with low affinity FcγRIIIa receptors historically have poor B-cell depletion with rituximab, there is a need for monoclonal antibodies that improve the rate of B-cell depletion in these patients. The ability of ocaratuzumab to deplete B-cells in patients with RA was studied in a dose escalation phase I study.

Methods: Five RA patients were treated with a single intravenous (IV) dose of 5 mg of ocaratuzumab, and three patients received 7.5 mg IV of ocaratuzumab. Patients were followed for B-cell depletion and recovery.

Results: Rapid B-cell depletion was seen in all patients in both the 5 mg and 7.5 mg cohorts (Figure 1). This depletion, with CD20+ cells either absent or very low, was seen as early as 3 hours after the start of infusion. Although most patients began to recover their B-cell counts within seven days of the infusion, at two months, the circulating B-cell counts were less than 50% of baseline in 5 of the 8 patients treated with ocaratuzumab.
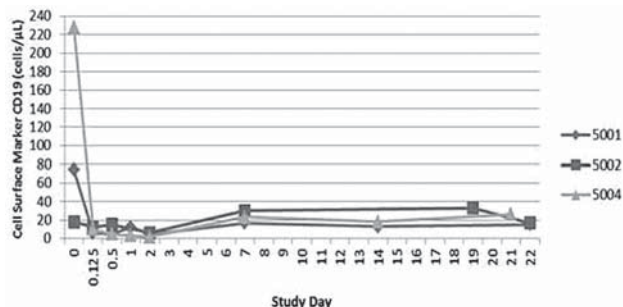
Figure 1. B-cell depletion with a single 7.5 mg IV dose of ocaratuzumab

The subjects were followed beyond the Day 85 visit to monitor the recovery of their B-cells. Four patients had follow-ups up to 3 months after Day 85, two patients up to four months, and two patients up to 6 and 13 months, respectively. Based on review of the adverse events, no suggestion of susceptibility to infection was seen.

As expected, administration of the larger dose led to a greater C_{max}. In the 7.5 mg cohort, C_{max} was 1720 ng/mL and 1620 ng/mL in the 5 mg cohort. The AUC of the drug was 24,000 ng·hr/mL in the 7.5 mg cohort and 4160 ng·hr/mL in the 5 mg cohort.

Conclusion: Even when administered at doses that are less than 100 fold that of rituximab, ocaratuzumab demonstrates rapid and prolonged B-cell depletion in RA patients. The majority of the patients treated with very low doses of ocaratuzumab demonstrated protracted B-cell depletion lasting for three months, with one patient recovering B-cells more than one year after receiving 7.5 mg of drug. Ocaratuzumab may provide a therapeutic option for patients with autoimmune diseases, especially those with the low affinity FcγRIIIa phenotype, who have not received optimal benefit from conventional monoclonal antibodies. Furthermore, ocaratuzumab can potentially be given at doses much smaller than that of the conventional antibodies, possibly permitting subcutaneous administration.

Disclosure: A. O'Reilly, Employee of Mentrik Biotech, 3; **T. Davis**, Employee of Mentrik Biotech, 3; **V. Jain**, CEO of Mentrik Biotech, 4.

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Clinical Responses and Patient Reported Outcomes to NNC0109-0012 (anti-IL-20 mAb) in RheumatoidArthritis (RA) Patients Following 12-Weeks Dosing and 13 Weeks Follow up: Results From a Phase 2a Trial. Ladislav ŠEnolt[1]. Marie Göthberg[2], Xavier Valencia[3] and Eva Dokoupilova[4], [1]Institute of Rheumatology, Prague, Czech Republic, [2]Novo Nordisk, A/S, Soeborg, Denmark, [3]Novo Nordisk, Inc., Princeton, NJ, [4]Medical Plus s.r.o, Uherske Hradiste, Czech Republic

Background/Purpose: NNC0109-0012 (anti-IL-20 mAb) is a novel human monoclonal IgG$_4$ antibody which binds to and neutralizes the activity of IL-20. Data from a phase 1 single-dose trial in healthy volunteers and RA patients, and a multiple-dose trial in RA patients, did not raise any safety concerns. NNC0109-0012 has linear pharmacokinetics in the investigated dose range (1–3 mg/kg) and signs of reduced disease activity were shown in RA patients. Objectives of this phase 2a trial were to evaluate changes in disease activity in RA patients with active disease using the following endpoints: DAS28-CRP, ACR20/50/70, and the patient-reported outcomes physical function (HAQ-DI), pain (Pain VAS) and global disease activity (PtGA VAS) after 12 weeks of treatment and during a 13-week follow up period.

Methods: A total of 67 RA patients (51 females:16 males) with active disease (DAS28 (CRP) >4.5, $\geq$5 swollen and $\geq$5 tender joints) were randomized in a 2:1 ratio (45 NNC0109-0012: 22 placebo) in a multicenter, double-blind, placebo-controlled, parallel group trial. Patients were dosed once-weekly s.c. with 3 mg/kg NNC0109-0012 or placebo for 12 weeks and followed for an additional 13 weeks. Patients were 18 to 75 years old with active RA and on stable methotrexate (MTX) treatment (>7.5 to <25 mg/week for at least 4 weeks). The primary endpoint was change in DAS28 (CRP) at Week 12.

Results: DAS28 (CRP) was significantly decreased compared to placebo at Weeks 12 and 16, and through Weeks 12 – 25 for seropositive (RF and anti-CCP positive) patients (n=29 and 14; 3 mg/kg and placebo, respectively). Significantly more NNC0109-0012 treated seropositive patients compared to placebo achieved ACR20/50 at Week 12 and ACR70 at Weeks 12, 16 and 20. Physical function, pain and global disease activity were significantly improved compared to placebo for seropositive patients for Weeks 12 – 25. Similar trends in NNC0109-0012 effects on most of the secondary endpoints for disease activity were observed in all randomized patients, although not all changes were significant. No deaths, serious adverse events or dose limiting toxicities were reported.

	Week 12	Week 16	Week 20	Week 25
DAS28 (CRP)[a]	−0.88*	−0.72*	−0.51	−0.60
DAS28 (CRP), S+	−1.66†	−1.55†	−1.26**	−1.24**
ACR20 (%), S+	58.6/21.4*	62.1/35.7	58.6/28.6*	58.6/35.7
ACR50 (%), S+	48.3/14.3*	44.8/14.3	44.8/21.4	44.8/21.4
ACR70 (%), S+	34.5/0*	34.5/0*	31.0/0*	31.0/7.1
HAQ−DI, S+	−0.45*	−0.32	−0.42*	−0.47*
Pain (VAS), S+	−30†	−28**	−25**	−29†
PtGA (VAS), S+	−28†	−29†	−25**	−28†

DAS28 (CRP), HAQ-DI, pain (VAS), PtGA (VAS) shown as mean difference for NNC0109-0012 μ placebo; Proportion with ACR20/50/70 for NNC or placebo shown as NNC/placebo. VAS = visual analogue scale (mm).[a]All randomized patients; S+=seropositive; * = p<0.05, ** = p<0.01,† = p<0.001

Conclusion: This phase 2a trial investigating NNC0109-0012 (anti-IL-20 mAb) in patients with RA met its primary endpoint, showing significant improvement in DAS28 (CRP) after 12 weeks. For the sub-group of RF/anti-CCP-positive patients, the treatment effects of NNC0109-0012 on all disease parameters were significantly larger than for all randomized patients at week 12 and were sustained during the 13 weeks after stopping study drug administration. Treatment with NNC0109-0012 revealed no safety concerns. The data from this trial support further clinical development of NNC0109-0012 (anti-IL-20 mAb) in RA.

Disclosure: L. ŠEnolt, None; **M. Göthberg**, Novo Nordisk, 3; **X. Valencia**, Novo Nordisk, Inc, 3; **E. Dokoupilova**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment I: Renal
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Response to MMF Therapy for Lupus Nephritis Is Independent of Genetic Variation of Inosine Monophosphate Dehydrogenase. Noa Schwartz[1], Tejaskumar Patel[1], Ellen M. Ginzler[2], Neil Solomons[3], Jill P. Buyon[4] and Robert M. Clancy[1]. [1]New York University School of Medicine, New York, NY, [2]SUNY-Downstate Medical Center, Brooklyn, NY, [3]Vifor Pharma, [4]NYU School of Medicine, New York, NY

Background/Purpose: The Aspreva Lupus Management Study (ALMS) demonstrated the efficacy of mycophenolate mofetil (MMF-a prodrug of MFA, mycophenolic acid) for both induction and maintenance of response in lupus nephritis. However, response is not uniform and it remains unresolved whether this relates to genetic variation in inosine monophosphate dehydrogenase (*IMPDH*).SNPs in *IMPDH1* (rs2278294) and *IMPDH2* (rs11706052) confer a higher risk of acute rejection in renal transplant recipients, and lymphocytes of mutant carriers (rs11706052) yieldan antiproliferative effect which is half that of subjects who are homozygous common. In addition, the ability of MMF to reduce pathogenic nitric oxide (NO) is attenuated in subjects carrying variant forms of *IMPDH*. Accordingly, this study was initiated to determine whether the clinical response of MMF and phenotype (NO levels) in ALMS associates with variants of I*MPDH*.

Methods: Subjects were 62 ALMS patients randomized to MMF in induction and/or maintenance.DNA and blood samples were obtained for evaluation of genetic variation and serum NO levels (colorimetric method, NO = nitrite + nitrate).Genotyping assignments were made based on a postread of the amplified genomic patient DNA by allelic discrimination and use of probes for *IMPDH1* rs2278294 and *IMPDH2* rs11706052 (Applied Biosystems).The allele calling rate of 62 DNA samples was 98% for rs2278294 and 100% for rs11706052.Assignments were verified by PCR amplification and direct sequencing.Both rs11706052 (*IMPDH2*) and rs2278294 (*IMPDH1*) were tested for departure from Hardy-Weinberg equilibrium (HWE) expectations.

Results: Representation of the two candidate SNPs had no HWE deviation; the relatively frequent minor alleles were comparable to those in the dbSNP database and in agreement with allelic discrimination and direct sequencing.Patients were stratified into two groups: Group I defined as responders to MMF at induction and non-treatment failures at maintenance, and Group 2 non-responders at induction and treatment failures at maintenance.For the *IMPDH2*, rs11706052, the distribution of variant alleles was similar for subjects in both groups (10.5%vs 13.9% MAFfor Groups 1 (N=18) and 2 (N=19), respectively). Similar results were observed when the analysis was restricted to Hispanics (largest ethnic group). For the *IMPDH1,*rs2278294, no association was observed between groups (44.4%vs 44.7% MAF, Groups 1 vs Groups 2).With regard to NO, there was no association between genotypes at rs2278294 and levels (14.5±2.6 uM vs 20.4±2.8, P=0.30, homozygous variant (N=9) versus heterozygous + homozygous common (N=33), respectively).

Conclusion: In distinction to renal transplant, genetic variation at *IMPDH1* and *IMPDH2* does not account for variability in the clinical response to MMF or levels of NO. These results should allay concerns regarding genetic testing of these alleles to predict efficacy of MMF in lupus.

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Association of Urinary and Serum Soluble Fn14 Levels and TWEAK Levels with Lupus Nephritis Disease Activity. Irene Blanco[1], Ping Wu[2], Timothy S. Zheng[3], Shawn Weng[4], Jennifer S. Michaelson[5], Linda C. Burkly[5] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Biogen Idec, Inc, Cambridge, MA, [3]Biogen Idec Inc, Cambridge, MA, [4]Biogen Idec, Inc., Cambridge, MA, [5]Biogen Idec, Cambridge, MA

Background/Purpose: We have showed that the cytokine TWEAK is a biomarker for lupus nephritis (LN). However, soluble receptors for key immune pathways are also potential biomarkers of inflammatory diseases, including SLE. Thus, we hypothesized that a soluble form of TWEAK receptor, Fn14, might be present in human serum or urine and could be a biomarker for LN.

Methods: Serum and urine from 67 patients from the Einstein Lupus Cohort were included in this study. 34 had active LN (renal SLEDAI≥4) and 33 had inactive, non-LN SLE (general SLEDAI≤2). Healthy normals (n=39), age and race matched, were also evaluated. ELISAs were performed on serum and urine samples to determine soluble Fn14 and TWEAK levels.All data was analyzed using STATA 10.1

Results: Of the 106 patients, 47% were Black, 47% were Hispanic and 6% were of another race/ethnicity. 79% were female with a median age of 43y. For the SLE patients the median disease duration was 6.0y. As expected LN patients had higher median protein to creatinine ratios as compared to both inactive SLE patients and normals (1.22 v 0.11 v 0.09, p<0.001).Although the normal group had a higher median GFRs overall, all groups had normal median values (90 v 89 v 115, p=0.02)

Serum Fn14 (sFn14) levels were significantly higher in LN compared to normals (p=0.002) and trended toward significance when comparing LN to the inactive SLE group (p=0.06). Median urine Fn14 levels tended to be higher in the LN group as compared the inactive SLE (p=0.06) and normals (p=0.05) but did not achieve significance with normalization to urine creatinine (p=0.06 and 0.12 for comparison to inactive SLE and normal, respectively). While there was no significant difference between the groups with regard to serum EAK, as previously shown, median urinary TWEAK levels were significantly elevated in the LN group compared to inactive SLE and normal groups when normalized to urine creatinine concentration (LN v inactive SLE (p=0.002) and LN v normal (p=0.002).

We performed an ROC analysis to determine the capability of sFn14 to distinguish between LN and inactive SLE as well as LN and normals. The AUC for sFn14 by itself was fair (LN v inactive SLE, AUC: 0.63; LN v normals, AUC: 0.70) while that of normalized uTWEAK was good (LN v inactive SLE, AUC: 0.77; LN v normals, AUC: 0.72). However, when the AUC for sFn14 and uTWEAK were combined the AUC was increased (LN v inactive SLE, AUC: 0.80; LN v normals, AUC: 0.76).
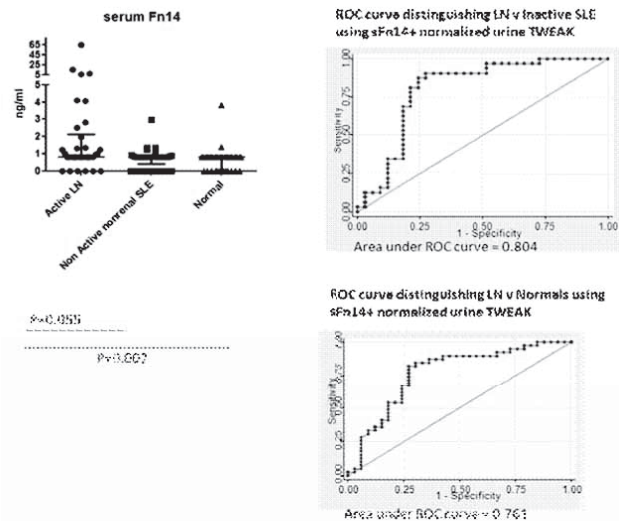
Conclusion: sFn14 levels are significantly elevated in patients with LN. This novel finding contributes to our previous observations that urinary TWEAK is elevated in this patient population. Adding sFN14 levels to urinary TWEAK levels as a combined biomarker has a higher capacity than each alone to distinguish between LN and inactive SLE as well as LN and normals. sFn14 is a promising novel biomarker in LN, further underscoring the TWEAK/Fn14 pathway as a potential therapeutic target that warrants further study.

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Urinary Levels of High Mobility Group Box 1 Protein Are Elevated in Patients with Active Lupus Nephritis, and Correlate with Renal Histopathology. Irene Blanco[1], Neelakshi Jog[2], Chaim Putterman[1], Iris Lee[2] and Roberto Caricchio[3]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Temple University, Philadelphia, PA, [3]Temple Univ Med Office Bldg, Philadelphia, PA

Background/Purpose: High mobility group box 1 protein (HMGB-1) had been implicated in the pathogenesis of SLE and potentially lupus nephritis (LN).There is increased expression in the both the glomerulus and mesangium and is found to be increased in the serum of LN patients compared to controls. To further investigate what happens locally in the kidney, we analyzed the urine of active LN patients for HMGB-1.

Methods: Urine from 61 Einstein Lupus Cohort patients was included in this study. 32 patients had active, biopsy-proven LN, (15 class III or IV, 7 mixed class III/IV+V, 10 class V; all had renal SLEDAI $\geq$4)and 29 had inactive, non-LN SLE (general SLEDAI$\leq$2). HMGB-1 was detected by western blot using a polyclonal antibody against it. Band intensities were measured with ImageJ software and HMGB-1 was normalized to albumin for each sample. Urine was then normalized to urine creatinine to account for the volume of each specimen.All data was analyzed using STATA 10.1

Results: Of the 61 patients, 90.2% are female and 9.8% are male.47.5% are Hispanic, 45.9% are Black and 6.6% are of another race/ethnicity. The median age and disease duration were 39y and 7.5y respectively. Overall, LN patients have lower median serum albumin levels (3.6 v 4.1, p<0.001) and higher median protein to creatinine ratios ("uP/C", 1.22 v 0.11, p<0.001), but there was no statistically significant difference in serum creatinine or GFR when compared to those with inactive SLE.

Median normalized urine HMGB-1 was significantly elevated in LN patients compared to inactive SLE (53.81 v 9.46, p<0.001). A difference in median levels was also seen between the classes.There was a significant difference between proliferative and membranous disease (33.4 v 138.8, p=0.003) and there seemed to be increased levels between mixed and membranous disease (47.5 v 138.8, p=0.07). However there was no significant difference between proliferative and mixed LN (33.4 v 47.5, p=0.21)
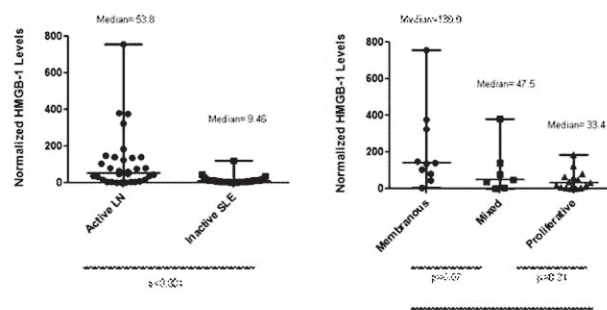
uP/C was associated with urinary HMGB-1 (r=0.52, p<0.001), but across the classes this was true only for membranous disease (r=0.71, p=0.022, proliferative, p=0.63; mixed, p=0.34). This is despite the fact that median uP/C was highest in mixed disease as compared membranous and proliferative (2.82 v 1.75 v 0.70, p=0.06).

Conclusion: This is the first study to look at urinary HMGB-1 levels in lupus nephritis. Levels are significantly higher in active LN patients compared to inactive SLE. Levels may be associated with class where the highest levels were seen in membranous disease. While this was correlated to uP/C in the membranous group, it was neither correlated in the mixed group, despite having higher levels of proteinuria, nor in the proliferative group, where there was also elevated urinary protein though not to the level of the other groups. Therefore it is possible that the same process that drives proteinuria in membranous disease is driving elevated HMGB-1 levels.

Disclosure: I. Blanco, None; **N. Jog**, None; **C. Putterman**, None; **I. Lee**, None; **R. Caricchio**, None.

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Do Serum Hepcidin 25 Levels Predict SLE Renal or Non-Renal Flares? Alexandra Friedman[1]. Nicholas Young[1], Paul Jensen[2], Xiaolin Zhang[2], Wael N. Jarjour[3], Brad H. Rovin[2], Daniel Birmingham[2], Lee Hebert[2] and Stacy P. Ardoin[3]. [1]The Ohio State University Medical Center, Columbus, OH, [2]Ohio State University Medical Center, Columbus, OH, [3]Ohio State University, Columbus, OH

Background/Purpose: Biomarkers are needed which can accurately predict systemic lupus erythematosus (SLE) flare, allowing tailoring of immunosuppressive therapy to minimize disease damage and medication toxicity. Urinary hepcidin-25 levels have been shown to decrease 2 months prior to renal SLE flare and show promise as a biomarker of lupus nephritis flare.This study assessed serum hepcidin-25 levels before, during and after renal and non-renal SLE flares.

Methods: As part of the Ohio SLE Study (OSS), serum and urine were obtained in SLE patients prospectively at every 2 month intervals.We identified 34 renal flare cycles in 21 patients and 22 non renal flare cycles in 17 patients. We measured serum 25 hepcidin levels at baseline, at time of flare and at 2 and 4 month intervals prior to flare and after flare.Renal and non-renal flares were defined and adjudicated by OSS protocol. Serum hepcidin-25 was measured in duplicate by enzyme immune assay kits (Bachem).Descriptive statistics were performed.

Results: Serum hepcidin-25 levels showed substantial inter-patient variability and were presented relative to normalized baseline levels.As shown in Figure 1, serum hepcidin 25 levels decreased significantly 2 months prior to renal flares but did not decrease prior to non renal flares.
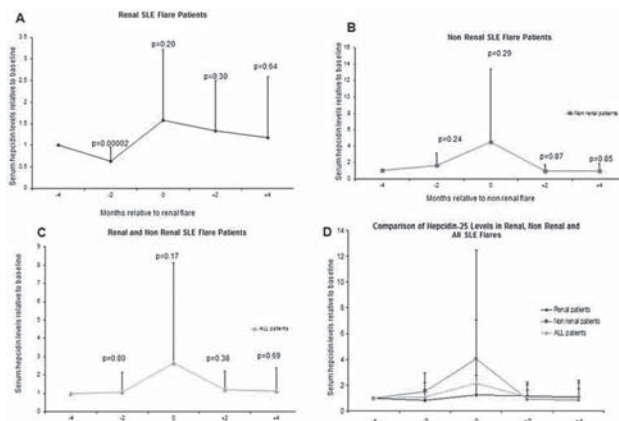
Conclusion: Serum hepcidin-25 levels decrease 2 months prior to renal SLE flare but not prior to non-renal SLE flare. To our knowledge, this is the first study to show that serum hepcidin 25 levels may predict renal SLE flare.These findings need to be confirmed in larger prospective cohorts but support previous evidence that hepcidin 25 may be a biomarker for renal SLE flares.

Disclosure: A. Friedman, None; **N. Young**, None; **P. Jensen**, None; **X. Zhang**, None; **W. N. Jarjour**, None; **B. H. Rovin**, Genentech and Biogen IDEC Inc., 5, Teva Pharmaceuticals, 2, Lilly, 5; **D. Birmingham**, None; **L. Hebert**, None; **S. P. Ardoin**, None.

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Effect of Partial and Complete Proteinuria Recovery in Lupus Nephritis On Long Term Outcomes. Zahi Touma, Murray B. Urowitz, Dominique Ibanez and D. D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: The identification of partial proteinuria recovery (PPR) of$\geq$ 50% allows for the detection of an additional number of patients who improve their proteinuria on standard of care treatment.The long term outcome of patients with$\geq$ 50% PPR at 1 year is not well studied.

To determine the prognostic value of PPR and complete proteinuria recovery (CPR) at 1 year on long term outcomes compared to patients who did not recover proteinuria$\geq$ 50% on standard of care therapy.

Methods: All active lupus nephritis (LN) patients registered at a large lupus clinic from 1970–2011. Proteinuria was defined as >0.5g/24 hours based on a 24 hour urine collection. Patients with proteinuria and at least one of the urinary sediments (hematuria, pyuria or casts) present at entry into the study and persistent on 2 consecutive visits were enrolled.

CPR was defined as proteinuria <0.5g/24 hours based on SLEDAI-2K. PPR was a decrease of $\geq$ 50% in the level of proteinuria from baseline as defined by SLEDAI-2K responder index-50 (SLEDAI-50-RI). Not recovered was defined as less than 50% recovery.Proteinuria recovery was identified if present on 2 consecutive visits within 1 year.

The long term outcomes (death, eGFR<15, dialysis or kidney transplant, SLICC Damage Index (SDI)>0, SDI>3) occurring after the identification of proteinuria related to LN at entry into the study were studied. The mean time to long term outcome was determined

Proportional hazard models were used to determine the hazard ratio (HR) for long term outcomes for the different recovery definitions.

Results: 217 patients (81.8% female) were identified. At 1 year: 45 patients achieved PPR, 48 CPR and 124 not recovered.

Long term outcomes: eGFR< 15 was identified in 14.3% of the patients, dialysis or kidney transplant in 12.8%,.18% of the patient died and 56% developed damage (SDI>0) with 30.7% with SDI >3.

The mean time to event from 1st visit in the study were:7.0 ± 8.3 years for death (n=39),3.7 ± 3.7 years for eGFR< 15 (n=30), 5.5 ± 6.0 for dialysis or kidney transplant (n=20), 3.6 ± 5.6 years for SDI>0 (n=75) and 6.1 ± 7.3 years for SDI>3 (n=57).

Achieving a PPR at 1 year protects from the development of eGFR<15; HR=0.29. Achieving a CPR at 1 year protects from the development of eGFR<15 (HR=0.25), accrual of damage with SDI>3 (HR=0.23) and none with CPR at 1 year subsequently went on to dialysis or transplant. (Table 1).

Table 1. Time to development of event in patient who achieved CPR and PPR at 1 year compared to patients without proteinuria recovery

Outcomes	PPR HR (p-value)	CPR HR (p-value)
Death	0.88 (0.75)	0.35 (0.05)
eGFR<15	0.29 (0.04)	0.25 (0.02)
Dialysis or Kidney Transplant	0.42 (0.17)	No event
SDI>0	1.05 (0.86)	0.70 (0.22)
SDI>3	0.73 (0.35)	0.23 (0.002)
Atherosclerotic events	1.07 (0.93)	0.84 (0.79)

Conclusion: Achieving complete recovery from proteinuria in patients with active lupus nephritis at 1 year from the onset of lupus nephritis protects against comorbidities including end stage kidney disease, dialysis and transplant, organ damage and death. Nonetheless, achieving at least partial recovery in proteinuria, ≥ 50%, at year 1 from the onset of lupus nephritis protects against the development ofeGFR<15.

Disclosure: **Z. Touma**, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **D. D. Gladman**, None.

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Partial and Complete Recovery From Proteinuria in Lupus Nephritis Patients Receiving Standard of Care Treatment. Zahi Touma, D. D. Gladman, Dominique Ibanez and Murray B. Urowitz. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: In the majority of trials on lupus, partial proteinuria recovery (PPR) (≥ 50% decrease in the proteinuria level) is a component of the composite outcome of partial renal remission.

To determine the percentage of patients who achieve complete proteinuria recovery (CPR), PPR and CPR and/or PPR in lupus nephritis (LN) patients receiving standard treatment at 6 months, 1 year and 2 years. The am of this study was to determine if the initial level of proteinuria predicts recovery from proteinuria.

Methods: We studied all active LN patients registered at the Lupus Clinic (1970–2011).Proteinuria was defined as >0.5g/24 hours based on a 24 hour urine collection. Patients with proteinuria and at least one of the urinary sediments (hematuria, pyuria or casts) present at the entry of the study and persistent on 2 consecutive visits were enrolled. Patients were grouped into: group 1 as 0.5–0.9g/day, group 2 as 1–2g/day and group 3 as ≥2g/day.

CPR was defined as proteinuria <0.5g/24 hours based on SLEDAI-2K. PPR was a decrease of ≥ 50% in the level of proteinuria from baseline as defined by by SLEDAI-50 responder index (SLEDAI-50-RI).

We determined the percentage of PPR, CPR and PPR and/or CPR achieved: 1) on 1 visit at 6 months, 1 year and 2 years 2) persistent on 2 consecutive visits at 6 months, 1 year and 2 years. The percentage of patients who recovered from proteinuria was evaluated based on initial proteinuria levels with the Kaplan-Meier estimator.

Results: 217 patients (81.8% female) were identified. The age and duration of lupus at the start of the study was 34.2 ± 12.4 and 5.7 ± 6.3 years.

PPR was achieved by 27% of patients at 6 months, 48.3% at 1 year and 69.4% at 2 years. PPR and/ or CPR was achieved by 31.8% of patients at 6 months, 57.6% at 1 year and 79.3% at 2 years. CPR was achieved by 8.8% of patients at 6 months, 35.2% at 1 year and 60.2% at 2 years (table 1). The percentage of PPR, CPR and PPR and/or CPR decreased when proteinuria recovery was required on 2 consecutive visits (Table 1) (Figure 1).

Based on the level of proteinuria, in group 1, 2 and 3 more patients achieved at least PPR compared to CPR at 6 months (p=0.81), 1 and 2 years (p<0.05).

Table 1. Percentage of PPR, CPR, and PPR or CPR using 1 visit or 2 visits what does this mean

	Percent of patients who have proteinuria recovery					
	@ 6 months		@ 1 year		@ 2 years	
Definitions	1 visit	2 visits	1 visit	2 visits	1 visit	2 visits
Partial recovery	27%	21%	48.3%	35.8%	69.4%	50.9%
Complete recovery	8.8%	6.9%	35.2%	24.8%	60.2%	45.7%
Partial or complete recovery	31.8%	25.5%	57.6%	46.4%	79.3%	65.9%
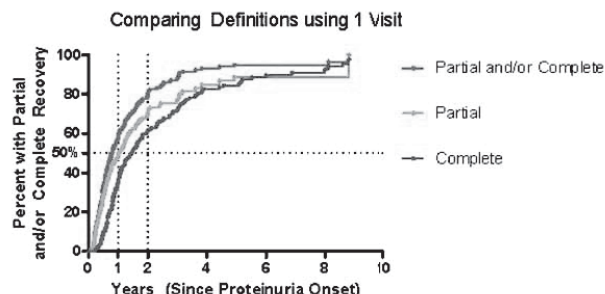
Figure 1. Comparing Complete, Partial, Partial and/or Complete – All Patients— 1 Visit Definition

Conclusion: The identification of partial proteinuria recovery allowed the detection of additional patients who improved their proteinuria on standard of care treatment. 58% of patients achieved at least partial while only 35% achieved CPR at year 1. PPR can serve as an important primary endpoint in research studies and trials.

Disclosure: **Z. Touma**, None; **D. D. Gladman**, None; **D. Ibanez**, None; **M. B. Urowitz**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Interferon Regulatory Factor 5 Associates with Systemic Lupus Erythematosus Through Two Distinct and Independent Effects. Erin Zoller[1], Leah C. Kottyan[1], Bahram Namjou[1], Samuel Vaughn[1], Miranda C. Marion[2]. Carl D. Langefeld[2], Marta E. Alarcon-Riquelme[3], Juan-Manuel Anaya[4], Elizabeth E. Brown on behalf of PROFILE[5], Sang-Cheol Bae[6], Jeffrey C. Edberg[7], Patrick M. Gaffney[8], Diane L. Kamen[9], Robert P. Kimberly[5], Chaim O. Jacob[10], Joan T. Merrill[11], Kathy Moser Sivils[11], Michelle A. Petri[12], Rosalind Ramsey-Goldman[13], John D. Reveille[14], Anne M. Stevens[15], Betty P. Tsao[16], Luis M. Vila[17], Timothy J. Vyse[18] and Kenneth M. Kaufman[1], [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [4]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [7]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [8]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [9]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC, [10]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [11]Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Johns Hopkins University School of Medicine, Baltimore, MD, [13]Northwestern University Feinberg School of Medicine, Chicago, IL, [14]Univ of Texas Health Science Center at Houston, Houston, TX, [15]University of Washington, Seattle, WA, [16]UCLA School of Medicine, Los Angeles, CA, [17]University of PuertoRico Medical Sciences Campus, San Juan, PR, [18]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom

Background/Purpose: Powerful evidence suggests that Systemic lupus erythematous (SLE or lupus) autoimmunity is mediated by disregulation of the IRF5-NFκB signaling pathway. The interferon regulatory factor 5 (IRF5) genomic locus is associated with lupus and seven other autoimmune diseases

in populations of each of the major ancestral groups. While the association of lupus with the IRF5 region has been extensively confirmed, previous publications have not presented a comprehensive analysis of the complete genetic variation of the entire locus including the juxtaposing gene TNPO3.

Methods: In order to fine map the entire IRF5/TNPO3 region, we used an Illumina iSelect custom array to genotype 107 single nucleotide polymorphisms (SNPs) in 8,395 SLE cases and 7,367 controls of European, African American, Asian, Hispanic, and Native American ancestry. Additionally, we imputed genetic variants spanning the IRF5/TNP03 region and performed targeted deep sequencing of lupus cases and controls to identify over 7,000 variants in the region.

Results: Through direct genotyping, imputation, and deep sequencing, we have accounted for all variation within the IRF5/TNPO3 region and identified a set of variants that includes the causative polymorphism(s). In each ancestry group, we confirmed strong association of variants located in the promoter region of IRF5. Furthermore, in Europeans and populations with European admixture, we also observed a strong independent association that spans the IRF5 and TNPO3 genes marked by a large haplotype.Through step-wise conditional analysis of the variation, our model of association using these two independent effects is able to explain the entire association of the IRF5/TNPO3 region. Using an iterative strategy, we limited the list of possible causal polymorphisms to those present in the genetic models with the strongest lupus associations.We further demonstrated evidence for over-transmission of European-derived variants to African American cases by using global and local admixture analysis.

Conclusion: IRF5 association reflects a crucial component in the pathogenesis of lupus in multiple ancestral groups.With these studies, we present a model of association that is superior to other genetic models published to date: we show two distinct and independent effects within the IRF5/TNPO3 locus. Being convinced that we have identified all of the genetic variation relevant to the IRF5 association in the region of IRF5/TNPO3, we have therefore captured the causal variant(s). Identifying the independent genetic effects allows for the separate pursuit of causal polymorphisms within this defined variation and disease mechanisms yet to be described.

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Toll-Like Receptor 9-Independent and Immune Complex-Independent Interferon-α Production by Neutrophils Upon Netosis in Response to Circulating Chromatin. Dennis Lindau[1], Julie Mussard[2], Armin Rabsteyn[1], Matthieu Ribon[2], Ina Kötter[3], Annette Igney[3], Gosse Adema[4], Marie-Christophe Boissier[5], Hans-Georg Rammensee[1] and Patrice Decker[2]. [1]University of Tübingen, Institute for Cell Biology, Tübingen, Germany, [2]University of Paris 13, Sorbonne Paris Cité, Bobigny, France, [3]Department of Internal Medicine II, Rheumatology Division, Tübingen, Germany, [4]Nijmegen Centre for Molecular Life Sciences, Nijmegen, Netherlands, [5]Avicenne Hospital, Rheumatology Department, Bobigny, France

Background/Purpose: Chromatin (which is composed of DNA and histones) represents a major autoantigen in systemic lupus erythematosus (SLE). Interferon-α (IFN-α) plays an important role in lupus development. Although activated plasmacytoid dendritic cells (pDC) are believed to be the main producers of IFN-α in SLE, pDC represent a minor cell population. On the other hand, neutrophils represent 50 % of total blood leukocytes and are activated in SLE, especially by chromatin. Moreover, neutrophils form immunogenic neutrophil extracellular traps (NET) in SLE. Toll-like receptor (TLR) 9 recognizes certain forms of DNA but its role in SLE is still not elucidated. We therefore sought to determine the cellular source of IFN-α as well as the natural stimuli in SLE, the mechanism and the impact of TLR9.

Methods: Chromatin (mono-nucleosomes) was purified from calf thymus. PBMC and neutrophils were isolated from healthy individuals and SLE patients. Mouse neutrophils were purified from the bone marrow. Cells were activated with different stimuli and IFN-α production/secretion was estimated by flow cytometry, ELISA and a bioassay. Gene expression was analyzed by qRT-PCR. Neutrophil activation was verified by flow cytometry and ELISA. NET induction was estimated by confocal microscopy.

Results: Isolated neutrophils produce IFN-α upon stimulation with chromatin. IFN-α secretion by neutrophils was observed with steady-state neutrophils, and not pro-inflammatory neutrophils, from both healthy donors and SLE patients whereas pDC were less efficient. Neutrophil-derived IFN-α was detected in response to free chromatin, and not chromatin-containing immune complexes, as well as TLR9 agonists. Nucleosome-induced IFN-α production by neutrophils was associated with IL-8 secretion, CD66b up-regulation, ROS production and NET formation (NETosis). Neutrophil priming is not required. In low-responders, autologous PBMC sustain IFN-α secretion by chromatin-activated neutrophils in co-cultures. In contrast to TLR9 agonists, chromatin-induced IFN-α secretion occurs independently of TLR9 since neutrophils isolated from both wild-type and TLR9-deficient mice were activated. Finally, chromatin increases gene expression levels of IFN-α and several DNA sensors, e.g. AIM2 and STING.

Conclusion: Neutrophils represent also an important source of IFN-α. IFN-α was detected at the mRNA and protein levels and in an active and secreted form. This is the first report showing both that steady-state neutrophils can secrete IFN-α and identifying a natural lupus stimulus involved. Since both normal and lupus neutrophils have the capability of producing IFN-α, a key event is thus the presence of increased concentrations of circulating nucleosomes in SLE patients. Chromatin-activated neutrophils (in addition to pDC and low-density granulocytes) may secrete IFN-α early during the lupus disease, before immune complexes are produced. The generation of NET and the expression of genes involved in the recognition of DNA may strengthen pDC activation and DNA-mediated activation.

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Systemic Lupus Erythematosus Immune Complexes Upregulate the Expression of CD319 and CD229 On Plasmacytoid Dendritic Cells. Niklas Hagberg[1], Jakob Theorell[2], Gunnar V. Alm[3], Maija-Leena Eloranta[1], Yenan Bryceson[2] and Lars Rönnblom[1]. [1]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [2]Center for Infectious Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Swedish University of Agricultural Sciences, Uppsala, Sweden

Background/Purpose: Patients with SLE have an activated type I interferon (IFN) system due to an ongoing IFN-alpha synthesis by plasmacytoid dendritic cells (pDCs) stimulated by endogenous nucleic-acid containing immune complexes (ICs). The IFN-alpha production by pDC is strongly promoted by NK cells via MIP-1beta and LFA-1-mediated cell contact. In this study we aimed to further identify molecules of importance in the pDC-NK cell cross-talk.

Methods: Healthy donor PBMC were stimulated with medium or IC consisting of purified SLE-IgG and U1snRNP particles (SLE-IC) for 6 h. Surface expression of 45 different molecules was determined on pDCs, CD56^{dim} and CD56^{bright}NK cells by flow cytometry. Regulation of CD319 (CRACC) and CD229 (LY9) was analyzed in isolated or cocultured pDCs and NK cells. Intracellular IFN-alpha was correlated to the expression of CRACC and LY9 on pDCs and the expression of these molecules on different immune cells was compared between SLE patients and healthy controls. Expression of the adaptor molecules SAP and EAT-2 was determined by western blot. The functional role of CRACC and LY9 in pDC and NK cells was investigated.

Results: SLE-IC induced expression of CRACC and LY9 on pDCs, and CRACC on CD56^{dim} NK cells in PBMC (Mean fold increased MFI 3.7, 2.2 and 2.0, respectively). CRACC and LY9 were not regulated in purified pDC but addition of NK cells restored the up-regulation on pDCs. IL-3 or GM-CSF increased the expression of CRACC and LY9 on SLE-IC-stimulated pDCs as efficiently as NK cells. IFN-alpha producing pDCs had a higher expression of CRACC and LY-9 compared to IFN-alpha negative pDCs. Patients with SLE displayed an increased frequency of CRACC+ CD56^{bright} NK cells and B cells (p=0.03; 17±2% vs. 10±2% and p<0.001; 10±3% vs 3±0.3%, respectively, (mean±SEM)) and a decreased frequency of CRACC+ CD56^{dim} NK cells (p=0.01; 59±5% vs. 76±3%, (mean±SEM)). No expression of SAP or EAT-2 was found in pDCs, while NK cells expressed both molecules. Cross-linking CRACC or LY9 by plate-bound mAbs did not affect IFN-alpha production by SLE-IC-stimulated pDCs. Cross-linking CRACC in a redirected cytotoxicity assay resulted in a low frequency of degranulating NK cells, whereas co-ligation of CRACC together with DNAM-1 (CD226) significantly increased the degranulation (4% and 29% CD107a+ CD56^{dim}NK cells, respectively).

Conclusion: SLE-ICs up-regulates the expression of the costimulatory molecules CRACC and LY9 on pDCs and these molecules also have an increased expression on IFN-alpha producing pDCs. Because these SLAM molecules are self-ligands and involved in the activation of several types of immune cells, the expression on both pDCs and NK cells might facilitate the pDC-NK cell interaction and the function of these cells. In contrast to the positive signal delivered by CRACC and LY9 to NK cells, the lack of SAP and EAT-2 adaptor molecules in pDCs suggests an inhibitory function in these cells. The precise roles of CD319 and LY9 in the autoimmune disease process remains to be established, but are important to clarify given the altered expression of CRACC in SLE on both B cells and NK cells.

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Preferential Binding to Elk-1 by SLE-Associated *IL10* Risk Allele up-Regulates *IL10* Expression.
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Background/Purpose: The established association between *IL10* and multiple autoimmune diseases including SLE and elevated levels of IL-10 in SLE patients correlating with disease activity led us to fine-map the *IL10* family locus (*IL10-IL19-IL20-IL24)* to evaluate SLE-associated SNPs for their potential functions in multiple ancestries.

Methods: We genotyped 19 tag SNPs of the 154 kb *IL10* family locus in 15533 subjects including European Americans (EA, 3820 cases vs 3412 controls), African Americans (1670 vs 1904), Asians (1252 vs 1249) and Hispanics (1445 vs 781), and imputed an additional 109 SNPs in EA. Each SNP was assessed for association with SLE, and haplotype-based conditional testing was conducted to distinguish independent signals. Transcript and protein levels of IL-10 were measured by real-time PCR and ELISA. EMSA was performed using nuclear lysates of SLE PBLs to assess differential binding to SLE-associated SNP alleles that might regulate IL-10 expression. Elk-1 activation was detected by Western blot, and co-localization of IL-10 and phospho-Elk-1 by flow cytometry.

Results: Among 19 genotyped SNPs, the 3'UTR downstream SNP of *IL10*, rs3024505, exhibited the strongest independent association with SLE susceptibility in EA only ($P = 2.67 \times 10^{-8}$, OR [95%CI] =1.30 [1.19–1.43]). Lower allelic frequencies of this SNP and lack of other association signals in non-EA led us to focus on EA for imputation, showing association with SLE of 3 additional SNPs: rs3122605 (10kb 5' upstream), rs3024493 (intron3) and rs3024495 (intron4) tagged by rs3024505 ($r^2>0.91$). SLE patients carrying risk-alleles of these 4 SNPs had higher IL10 expression at mRNA ($P=3.8 \times 10^{-6}$) and protein level ($P=4.2 \times 10^{-5}$) than those carrying non-risk alleles. Only the risk allele of rs3122605 exhibited binding to nuclear extracts from SLE PBLs using EMSA. This risk allele was predicted to preferentially bind to transcription factor Elk-1, and was validated by supershift in the presence of ELK-1 antibodies, suggesting it is the likely causal variant. Upon

activation, cytoplasmic Elk-1 is known to be phosphorylated and translocated into the nucleus inducing transcription. Phospho-Elk-1 was detected in nuclear extracts from SLE but not normal PBMCs, and appeared higher in patients with increasing SLEDAI scores (Figure). Co-expression of phospho-Elk-1 and IL-10 in PBLs was elevated in SLE than controls ($P = 0.005$) and active than inactive patients ($P < 0.05$).
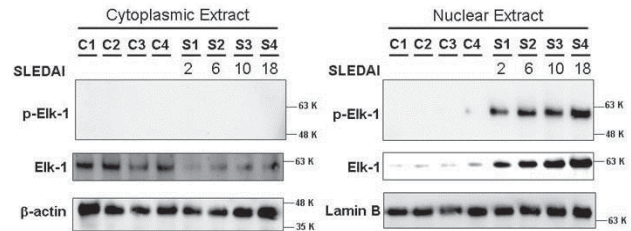
Conclusion: We identified GWAS level association ($P<5\times10^{-8}$) of 4 *IL10* SNPs with SLE in EA. The risk allele of 5' upstream rs3122605 preferentially binding to ELK-1 was associated with elevated IL10 levels. Nuclear localization of activated phospho-Elk-1 was elevated in SLE PBLs that also expressed IL-10, especially during active disease. Taken together, the SLE-associated rs3122605 C allele conferred SLE risk by upregulating ELK-1-mediated IL-10 expression.

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Enhanced ROCK Activation in Patients with Systemic Lupus Erythematosus.
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Background/Purpose: The Rho GTPases, Rac and RhoA, play a key role in immune responses by regulating both cytoskeletal reorganization and gene expression. RhoA exerts many of its effects by activating Rho kinases (ROCKs). Aberrant ROCK activation has been implicated in the pathogenesis of various cardiovascular, renal, and neurological disorders. As such, ROCK inhibitors have emerged as potential treatments for these diseases. Recent studies have demonstrated that, in T cells, Rho kinases can regulate the production of IL-17 and IL-21, two cytokines associated with the development of multiple autoimmune disorders including Systemic Lupus Erythematosus (SLE). ROCK inhibition has previously been shown to ameliorate the cytoskeletal abnormalities of SLE T cells suggesting that SLE patients may exhibit aberrant ROCK activation. The goal of this study was to measure ROCK activity in SLE patients and its relationship with clinical and immunological aspects of SLE.

Methods: We performed a cross sectional study of 28 SLE patients and 25 healthy controls matched for age (31.1 ± 9.1 years vs (31.8 ± 8.2), gender (79% female vs 92%) and race. Mean SLEDAI 4.0 ± 2.4 (Range: 0–10) and physician global assessment 0.8 ± 0.7 (Range: 0–2). Peripheral blood mononuclear cell (PBMC) lysates were used for ROCK kinase activity assays. Cytokine and chemokine profiles in plasma were analyzed via ELISA.

Results: PBMCs from SLE patients expressed significantly higher levels of ROCK activation compared to healthy controls, 1.251 (IQR 0.5–1.6) vs. 0.5645 (IQR 0.5–0.6), respectively (p=0.0015). There were two distinct subgroups of SLE patients: those with high (ROCK^high) and low (ROCK^low) ROCK levels; 16/28 (57%) patients were in the ROCK^high group. Using linear regression models, disease duration, lymphocyte count, and azathioprine use were identified as independent predictors of ROCK activity (p≤0.02). There was no significant difference in IL-17 and IL-21 plasma levels between SLE patients and healthy controls.CCL20 levels from SLE patients were, however, significantly elevated compared to healthy controls, 16.1 pg/ml (IQR 10–23) vs. 10.2 pg/ml (IQR 7.1–15.5), respectively

(p=0.02). Consistent with previous studies, SLE patients expressed significantly higher BAFF levels when compared to controls, 1144 pg/ml (IQR 706–1609) vs. 762.8 pg/ml (IQR 661–829), respectively (p=0.009). There was no correlation between ROCK levels and SLEDAI, cytokine profiles, autoantibodies, or renal disease.

Conclusion: Enhanced ROCK activity was seen in a subgroup of SLE patients and was associated with disease duration, lymphocyte count, and azathioprine use. Given the multiple links between CCL20 and Th17 cells, the elevated levels seen in SLE suggest a role for Th17 cells in the pathogenesis of SLE. These data support the concept that the RhoA/ROCK pathway could represent an important therapeutic target for the treatment of SLE and that measurement of ROCK activation in SLE patients may be utilized to assess the efficacy of therapies, such as ROCK inhibitors, aimed at inhibiting this pathway. Following SLE patients prospectively is necessary to further characterize ROCK levels over time and establish their relationship with disease activity and/or medications.

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Targeting Glycosphingolipid Biosynthesis Normalises T Lymphocyte Function in Patients with Systemic Lupus Eyrthematosus.

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) are characterised by hyperactive T-cells that provide help to autoreactive B-cells. Underlying this hyperactivity are alterations in the lipid and protein composition of membrane lipid microdomains (lipid rafts) that influence the nature, duration and outcome of immune synapse formation between T-cells and antigen presenting cells including B-cells. We examined the profile of lipid raft-associated glycosphingolipids (GSL) in T-cells, the mechanisms underlying their abnormal expression in patients with SLE and whether by normalising GSL expression, T-cell function could be restored in patients.

Methods: High performance liquid chromatography and flow cytometry were used to assess the GSL profile and phenotype of T-cells from 98 patients with SLE compared with 82 healthy controls and 23 patients with other autoimmune rheumatic disease. Western blotting, quantitative PCR and confocal microscopy using fluorescently-labelled GSLs were used to assess levels of proteins controlling GSL expression and GSL location within T-cells. T-cell function was assessed by measuring phosphorylation of proximal and downstream signalling molecules, proliferation and cytokine production.

Results: The expression levels of lipid raft-associated GSL lactosylceramide (LC), Gb3 and GM1 were significantly increased in T-cells from patients with SLE compared to healthy and disease controls. In healthy donors LC^+, $GM1^+$ and $Gb3^+$ T-cells had an activated phenotype, increased expression of proliferation marker Ki-67 and transcription factor RORgT, however, raised GSL expression was not associated with a specific T-cell phenotype in patients with SLE. Increased GSL expression in T-cells from SLE patients was not associated with altered levels of enzymes controlling GSL biosynthesis but was associated with increased GSL recycling from the plasma membrane to intracellular compartments. T-cells from patients with SLE incorporated fluorescently-labelled-LC into intracellular vesicles more rapidly compared to T-cells from healthy controls and this was accompanied by increased expression of the Niemann-Pick 1 and 2 genes that control GSL recycling. *In vitro* culture of T-cells from SLE patients with direct inhibitors of GSL biosynthesis normalised GSL membrane expression and restored their function in terms of lipid raft-associated T-cell signalling, proliferation and cytokine production.

Conclusion: We show that targeting lipid biosynthesis pathways using clinically approved inhibitors can rectify hyperactivity in autoimmune T-cells and restore their function.

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The Risk of Cardiovascular Disease in Systemic Sclerosis: A Population-Based Cohort Study.

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Background/Purpose: Recent studies show that the prevalence of subclinical atherosclerosis is increased in individuals with systemic sclerosis (SSc). An accurate understanding of cardiovascular disease (CVD) risk is crucial in improving the overall outcomes of SSc, a disease associated with high mortality. To further elucidate the association between SSc and CVD, we evaluated the future risk of incident myocardial infarction (MI), stroke, and peripheral vascular disease (PVD) in individuals with SSc in a general population context.

Methods: We conducted a matched cohort study using The Health Improvement Network database, which is derived from electronic medical records from general practices in the UK from 1986 to 2011. SSc diagnoses, covariates, and cardiovascular outcomes were identified from the records. We conducted two cohort analyses: 1) MI and stroke, and 2) PVD, excluding individuals with prevalent disease from each analysis. PVD specifying the upper extremities was not included. We estimated hazard ratios (HRs) using Cox proportional hazards regression models, comparing SSc with age-, sex-, and entry time-matched comparison cohorts, adjusting for BMI, smoking, diabetes, hyperlipidemia, hypertension, atrial fibrillation, aspirin, oral glucocorticoid, and NSAID use. We then estimated the cumulative incidence of each outcome accounting for the competing risk of death.

Results: Mean follow-up time was 5.2 years in the SSc cohorts and 6.0 years in the comparison cohorts. Among 865 individuals with SSc (85.8% female, mean age 58.7 years), the incidence rates (IRs) of MI and stroke were 4.4 and 4.8 per 1000 person-years (PY), versus 2.5 and 2.5 per 1000 PY in the comparison cohort, respectively. The corresponding adjusted HRs were 1.80 (95% CI 1.07 to 3.05) for MI and 2.61 (95% CI 1.54 to 4.44) for stroke. Among 858 individuals with SSc (85.3% female, mean age 58.9 years), the IR of PVD was 7.6 per 1000 PY versus 1.9 per 1000 PY in the comparison cohort, with an adjusted HR of 4.35 (95% CI 2.74 to 6.93).
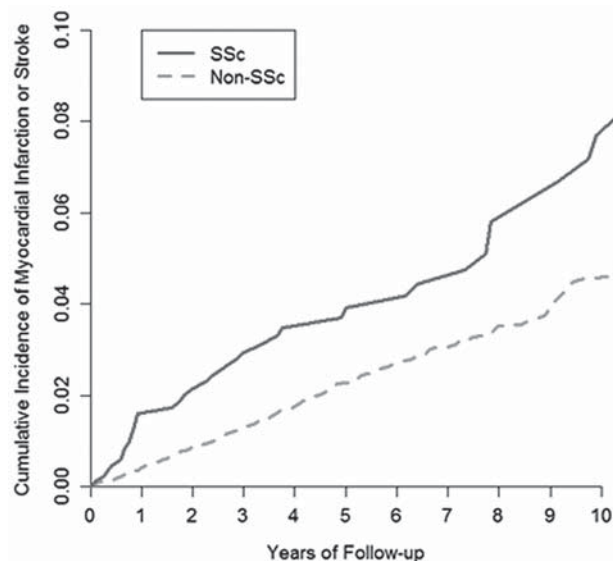
Figure 1. Cumulative incidence of myocardial infarction or stroke in 865 individuals with systemic sclerosis (SSc) as compared to 8643 age-, sex-, entry time-matched, non-SSc individuals. Estimates accounted for the competing risk of death.
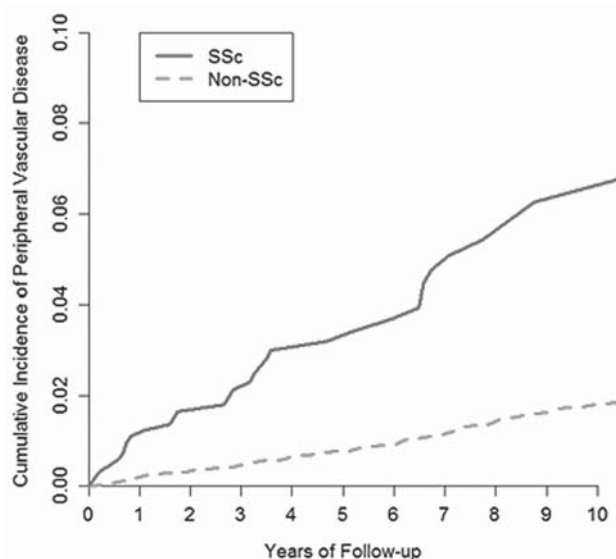
Figure 2. Cumulative incidence of peripheral vascular disease in 858 individuals with incident systemic sclerosis (SSc) as compared to 8580 age-, sex-, entry time-matched, non-SSc individuals. Estimates accounted for the competing risk of death.

Conclusion: These findings provide the first general population-based evidence that SSc is associated with an increased risk of developing MI, stroke, and PVD.Increased awareness of CVD in individuals with SSc is warranted.Further insight into the etiology of CVD in SSc, including the relative contributions of microvascular and macrovascular pathology, as well as how anti-platelet or vasodilating medications may alter this pathology, is needed.

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Elevation of KL-6 At Early Disease Course Predicts Subsequent Deterioration of Pulmonary Function in Patients with Systemic Sclerosis and Interstitial Lung Disease. Masataka Kuwana[1], Tsutomu Takeuchi[1] and Junichi Kaburaki[2]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Shinakasaka Clinic, Tokyo, Japan

Background/Purpose: Interstitial lung disease (ILD) is the leading cause of morbidity and mortality in patients with systemic sclerosis (SSc). However, only a subset of SSc patients with ILD develops end-stage lung disease (ESLD). The presence of significant fibrosis on high-resolution computed tomography and percent predicted forced vital capacity (%FVC) <70% were shown to be variables associated with a greater decline in pulmonary function, but these findings are rarely detected in patients with early SSc. In our institution, we principally did not treat ILD in SSc patients before 2000. Therefore, our cohorts of untreated patients are extremely useful in assessing the natural history of pulmonary function in SSc patients with ILD. Using this cohort, we evaluated initial factors that predict development to ESLD.

Methods: We enrolled 50 patients with SSc, who were diagnosed as having SSc between 1980 and 1995. These patients were selected from our database based on the following criteria: they had ILD as determined by chest radiographs at diagnosis, had disease duration <3 years at diagnosis, were followed for 10 or more years unless death due to ILD-related causes, had at least 4 serial pulmonary function tests, and had never received immunosuppressants, >10 mg daily prednisolone, or other potential disease-modifying drugs. ESLD was defined as having at least one of the following: <50% FVC, required oxygen supplementation in the absence of pulmonary hypertension, or death due to ILD-related causes. We performed statistical analyses stratified by development to ESLD and multivariate analysis to assess factors that predict the ESLD development. Survival analysis was performed using the Kaplan-Meier method combined with log-rank test.

Results: Disease duration at diagnosis was 14.2 ± 7.2 months and %FVC was 83.7 ± 14.2%. The patients were followed for 173.5 ± 64.7 months, and 16 patients (32%) developed ESLD. The decline in %FVC during the 12-month period was 4.6 ± 2.4% in patients who developed ESLD and 0.5 ± 0.8% in patients who did not ($P < 0.0001$). Cumulative survival rates were significantly worse in patients who developed ESLD than in those who did not ($P < 0.0001$). Initial characteristics associated with development to ESLD included diffuse cutaneous SSc ($P = 0.006$), anti-topoisomerase I antibody ($P = 0.004$), exertional dyspnea ($P = 0.03$), elevated KL-6 ($P < 0.0001$), reduced %FVC ($P = 0.007$), and reduced %DLco ($P = 0.001$). Multivariate analysis revealed that elevated KL-6 at diagnosis was the sole parameter independently associated with the ESLD development ($P = 0.0002$, odds ratio = 88). Cumulative rates free of ESLD and death were significantly greater in patients with normal KL-6 than in those with elevated KL-6 ($P < 0.0001$ for both comparisons). Finally, the rate of decline in %FVC was negatively correlated with KL-6 at diagnosis ($r = 0.71$, $P < 0.0001$).

Conclusion: SSc patients with ILD are heterogeneous in terms of deterioration of pulmonary function. Elevated KL-6 at baseline is an independent predictor of %FVC decline and mortality. SSc patients with ILD and elevated KL-6 at early disease course are candidates for aggressive therapeutic intervention.

Disclosure: M. Kuwana, None; **T. Takeuchi**, None; **J. Kaburaki**, None.

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An Evidence-Based Screening Algorithm for Pulmonary Arterial Hypertension in Systemic Sclerosis. James R. Seibold[1], Christopher D. Denton[2], Ekkehard Grünig[3], Diana Bonderman[4], Oliver Distler[5], Dinesh Khanna[6], Ulf Müller-Ladner[7], Janet E. Pope[8], Madelon C. Vonk[9], Martin Doelberg[10], Harbajan Chadha-Boreham[10], Harald Heinzl[4], Daniel M. Rosenberg[10], Vallerie McLaughlin[6] and John G. Coghlan[2]. [1]Scleroderma Research Consultants LLC, Avon, CT, [2]Royal Free Hospital, London, United Kingdom, [3]University Hospital, Heidelberg, Germany, [4]Medical University of Vienna, Vienna, Austria, [5]University Hospital Zurich, Zurich, Switzerland, [6]University of Michigan, Ann Arbor, MI, [7]Kerckhoff-Klinik GmbH, Bad Nauheim, Germany, [8]Western University of Canada, St. Joseph's Health Care, London, ON, [9]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [10]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Background/Purpose: Pulmonary arterial hypertension (PAH) is a leading cause of mortality and late-stage morbidity in systemic sclerosis (SSc). Current PAH screening recommendations are consensus-based and their clinical application results in high false positive rates. The rate of missed diagnoses has never been determined. The DETECT study aimed to develop an evidence-based screening algorithm for PAH in SSc patients that would limit the number of missed PAH diagnoses.

Methods: In this prospective, multicenter, cross-sectional observational cohort study [NCT00706082], adult patients with SSc for >3 years, a diffusing capacity of the lung for carbon monoxide (DLCO) <60% of predicted, and no previous diagnosis of pulmonary hypertension underwent multiple non-invasive screening tests followed by diagnostic right heart catheterization (RHC). Univariable and multivariable analyses selected the best discriminatory variables for identifying PAH, which were assessed for clinical plausibility and feasibility and incorporated into a two-step internally validated screening algorithm.

Results: Of 466 SSc patients, 19% (n=87) had RHC-confirmed PAH and 69% (n=321) had normal pulmonary arterial pressure (PAP). PAH was mild (mean PAP 32.5 [30.7–34.3] mm Hg; 64.4% WHO functional class I or II). Six simple screening tests (forced vital capacity [% predicted]/DLCO [% predicted]; current/past telangiectasias; anti-centromere antibody; N-terminal pro-brain natriuretic peptide; uric acid; right axis deviation on electrocardiography) were used in step 1 of the algorithm to derive a risk prediction score with pre-defined high sensitivity (to minimize the rate of missed PAH diagnoses) and to inform a decision to refer to echocardiography. Right atrial area and tricuspid regurgitation jet velocity were added in step 2 (with pre-defined low specificity) to determine referral to RHC. The DETECT algorithm, with step 1 sensitivity 97% and step 2 specificity 35%, resulted in a rate of missed PAH diagnoses of 4% requiring RHC in 62% of patients. When the current ERS/ESC screening recommendations were applied, the missed diagnoses and the RHC referral rates were 29% and 40%, respectively.

Conclusion: The two-step algorithm is a sensitive non-invasive screening tool for detection of PAH in SSc which addresses resource utilization of RHC, identifies less advanced disease and, most importantly, minimizes missed diagnoses. This is an evidence-based approach to revise standards of care in SSc patients.

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C-Reactive Protein Predicts Long-Term Progression of Interstitial Lung Disease and Survival in Patients with Early Systemic Sclerosis. Xiaochun Liu[1], Maureen D. Mayes[1], John D. Reveille[2], Emilio B. Gonzalez[3], Brock E. Harper[3], Hilda T. Draeger[4] and Shervin Assassi[5]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]Univ of Texas Health Science Center at Houston, Houston, TX, [3]University of Texas Medical Branch, Galveston, TX, [4]Univ of TX Health Sci Ctr, San Antonio, TX, [5]Univ of Texas Health Science Houston, Houston, TX

Background/Purpose: The currently available clinical markers are not reliable predictors of long-term progression of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). In a previous study conducted in the GENISOS (Genes versus Environment in Scleroderma Outcome Study) cohort, none of the baseline clinical variables (including serology and disease type) was predictive of long-term decline in forced vital capacity (FVC). Elevated C-reactive protein (CRP) levels have been reported in a subset of patients with SSc and correlated with disease severity as well as shorter survival. Herein, we examine the predictive significance of CRP for progression of ILD (based on longitudinally obtained serial FVC) and survival in a large early SSc cohort.

Methods: We compared the plasma CRP levels in 266 SSc patients enrolled in the GENISOS cohort (mean disease duration at enrollment 2.5 years, 59% diffuse cutaneous involvement) to that of 97 age, gender and ethnicity-matched controls. Subsequently, the correlation between the plasma CRP levels and concomitantly obtained markers of disease severity was assessed. The primary outcome was decline in FVC over time. A total of 1,016 FVC measurements fulfilled the American Thoracic Society/European Respiratory Society criteria and were included in the analysis. The mean follow-up time was 4.4 years. The predictive significance for long-term change in FVC was investigated by a joint analysis of longitudinal measurements (sequentially obtained % predicted FVC) and survival data. This approach allows inclusion of all FVC measurements and accounts it for survival dependency.

Results: We confirmed that the baseline plasma CRP levels were significantly higher in SSc patients than matched controls (p=0.027). In addition to body mass index and age at baseline, the plasma CRP levels were associated with absence of anti-centromere antibodies ($p=0.043$). Also consistent with previous reports, plasma CRP levels correlated with the concomitantly obtained joint, skin and lung components of the Medsger Severity Index, as well as, FVC, DLco, mRSS. More importantly, baseline CRP levels correlated with shorter survival ($p<0.001$) and predicted the long-term decline in % predicted FVC ($\beta = -0.35$, 95% CI: $-0.61 - -0.09$, $p = 0.006$).The predictive significance of CRP for ILD progression was independent of potential confounders (age at baseline, gender, ethnicity, body mass index, and treatment with immunosuppressive agents) in the multivariable model ($\beta = -0.37$, 95% CI: $-0.63 - -0.11$, $p=0.005$).

Conclusion: In the present study, we show for the first time that the baseline CRP levels are predictive of long-term ILD progression. High CRP levels can identify the subgroup of patients that would benefit from more intensive monitoring and treatment.

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Systemic Sclerosis Classification Criteria: Developing Methods for Multi-Criteria Decision Analysis. Sindhu R. Johnson[1], Raymond P. Naden[2], Jaap Fransen[3], Frank H.J. van den Hoogen[4], Janet E. Pope[5], Murray Baron[6], Alan G. Tyndall[7], Marco Matucci-Cerinic[8] and Dinesh Khanna on behalf of ACR/EULAR Classification Criteria SSc[9]. [1]Toronto Western Hospital, Toronto, ON, [2]Auckland City Hospital, Auckland, New Zealand, Austria, [3]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [4]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [5]St. Joseph Health Care London, London, ON, [6]Jewish General Hospital, Montreal, QC, [7]University of Basel, Basel, Switzerland, [8]Univ Florence, Firenze, Italy, [9]University of Michigan, Ann Arbor, MI

Background/Purpose: Classification criteria for systemic sclerosis (SSc) are being developed. Twenty-three candidate criteria have been identified, but need to be reduced. The objectives of this study were to: 1) develop a SSc-specific instrument for use in a forced-choice study and evaluate its sensibility (comprehensibility, clarity, face and content validity, and feasibility); 2) use forced-choice methods to reduce and weight criteria; and 3) explore the agreement between SSc experts on the probability that cases were classified as SSc.

Methods: A standardized instrument was tested for attributes of sensibility. The instrument was applied to cases of SSc from 20 cohorts covering a range of probabilities that each case had SSc (very likely to not at all). SSc experts rank-ordered cases from 1 (highest probability) to 20 (lowest probability). Experts then reduced and weighted the 23 criteria using forced choice-conjoint analytic methods and subsequently re-ranked the cases. Consistency in both rankings was evaluated using an intraclass correlation coefficient (ICC).

Results: Experts endorsed clarity of the form (83%), comprehensibility of the instructions and response option (100%), face and content validity (100%) and feasibility. Experts identified 'skin thickening of the fingers and proximal to the metacarpophalangeal joints' as a sufficient criterion for SSc classification. Other criteria were reduced and weighted (weight in points): skin thickening of the fingers (14–22), finger tip lesions (9–21), finger flexion contractures (16), telangiectasia (10), abnormal nailfold capillaries (10), puffy fingers (5), calcinosis (12), Raynaud's phenomenon (13), tendon/bursal friction rubs (21), pulmonary fibrosis/pulmonary hypertension (13), renal crisis (11), esophageal dilation (7) and SSc-related antibodies (15). The ICC for agreement across experts was 0.73 (95% CI 0.58, 0.86) and improved to 0.80 (95%CI 0.68, 0.90).

Conclusion: Our SSc-specific instrument for classification has demonstrable sensibility. The number of criteria were reduced by 35% (from 23 to 15) and weighted. The experts had substantial agreement in rank order. The next phase of criteria development will evaluate a threshold. Our methods reflect the rigors of modern psychometric science, and serves as a template for developing classification criteria in other diseases.

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Anti-EIF2B: A Novel Interstitial Lung Disease Associated Autoantibody in Patients with Systemic Sclerosis. Zoe Betteridge[1], Felix Woodhead[2], Christopher Bunn[3], Christopher D. Denton[4], David J. Abraham[5], Sujal Desai[6], Roland du Bois[7]. Athol U. Wells[8] and Neil McHugh[1], [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]University Hospitals Coventry and Warwickshire, Coventry, United Kingdom, [3]Royal Free Hospital, London, United Kingdom, [4]Royal Free and University College Medical School, London, England, [5]UCL Medical School, London, United Kingdom, [6]Kings College Hosptial, London, United Kingdom, [7]National Jewish Health, Denver, [8]Royal Brompton Hospital, United Kingdom

Background/Purpose: Autoantibodies occur in 75–95% of Systemic Sclerosis (SSc) patients. Studies have shown that the presence of particular SSc-specific autoantibodies (anti-centromere, anti-topoisomerase-1, anti-RNA polymerase III, anti-U3RNP, anti-U11/U12 RNP and anti-To/Th) correlates with distinct clinical subsets of patients. Additionally, SSc-related autoantibodies (PmScl, Ku, Ro60, La and U1RNP) can be found in a variety of other connective tissue diseases including SSc patients with overlap features. However, despite this vast array of SSc associated autoantibodies, there still remains a minority of patients that appear to be autoantibody negative. Here we report a novel SSc-specific autoantibody in 7 SSc patients.

Methods: Serum and clinical data were available from 379 patients with SSc investigated for interstitial lung disease (ILD) at the Royal Brompton Hospital and a separate 169 unselected SSc patients (Bath). Serum was also available from a control population consisting of 171 patients with other forms of connective tissue disease (dermatomyositis, polymyositis, systemic lupus erythematosus and rheumatoid arthritis), 141 patients with idiopathic ILD and 88 healthy normal controls. All sera were tested by routine serological techniques followed by radiolabelled protein immunoprecipitation (IPP) for samples negative for anti-centromere, anti-topoisomerase 1 and anti-RNA polymerase III. Patients' sera immunoprecipiating a novel 30 kDa band were further analyzed by indirect immunofluorescence and IPP using depleted cell extracts, to establish a common reactivity. A combination of non-radiolabelled IPP and mass spectrometry (MS) was used to identify the novel autoantigen and findings were confirmed using a commercial antibody in both immunodepletion and IPP-western blotting assays.

Results: A novel autoantigen at 30 kDa was recognized by sera from 7 sera from patients with SSc and by no controls. None of the 7 positive sera contained other known SSc-specific autoantibodies, although one patient co-immunoprecipiated SSc-associated Ro60 autoantigens. All 7 sera resulted in a cytoplasmic speckled pattern on IIF. Immunodepletion experiments indicated that all 7 serum samples immunoprecipitated the same autoantigen and MS analysis identified the novel autoantigen as EIF2B (Eukaryotic Initiation Factor 2B, subunit β). These findings were confirmed by both IPP and IPP-western blotting using a commercial anti-EIF2B antibody. Clinically, 6 anti-EIF2B positive patients had confirmed ILD, whilst the 7th patient did not have a chest CT, but had a reduced pulmonary gas transfer, demonstrating an association between anti-EIF2B and ILD (p=0.018). Six of the patients had diffuse cutaneous involvement (p=0.008) and four had overlap features with other autoimmune diseases (two polymyositis and two RA).

Conclusion: We report the presence of SSc-specific autoantibodies to anti-EIF2B in approximately 1% of SSc/SSc overlap patients. These autoantibodies are associated with the presence of ILD and diffuse cutaneous disease, and may therefore act as a biomarker, aiding in the clinical diagnosis and treatment of this subset of patients.

ACR Concurrent Abstract Session
Vasculitis: Pathogenesis
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Identification of a *Burkholderia* -Like Strain From Temporal Arteries of Subjects with Giant Cell Arteritis. Curry L. Koening[1], Bradley J. Katz[2], Jose Hernandez-Rodriguez[3]. Marc Corbera-Bellalta[4], Maria C. Cid[4], Herbert P. Schweizer[5], Dean Li[2], Jerry Kaplan[2], Gary S. Hoffman[6] and Ivana De Domenico[2], [1]Salt Lake City Veterans Administration, Salt Lake City, UT, [2]University of Utah, Salt Lake City, UT, [3]Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [4]Vasculitis Research Unit. Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [5]Colorado State University, Fort Collins, CO, [6]Cleveland Clinic, Cleveland, OH

Background/Purpose: Giant cell arteritis (GCA) is a granulomatous vasculitis of large- and medium-sized arteries. An infectious organism has been hypothesized to cause GCA. We used 16S rRNA analysis to amplify a bacterial genomic sequence unique to the temporal arteries of GCA subjects. Identification of the bacteria allowed us to detect the organism's lipopolysaccharide (LPS) in the serum of these subjects and isolate the bacteria from temporal arteries of GCA patients.

Methods: Frozen and paraffin-embedded temporal arteries from biopsy-proven GCA subjects and controls were used for analysis.GCA subjects fulfilled the 1990 ACR criteria for GCA.DNA and RNA were isolated from frozen temporal arteries. 16S rRNA analysis was performed using primers to the conserved regions of bacterial 16S rRNA. Multilocus sequence typing (MLST), a PCR-based method of bacterial identification, was performed to type the organism.A *Burkholderia* anti-LPS monoclonal antibody was used to perform immunofluorescence (IF) and ELISA.*Burkholderia* was cultured from a temporal artery and the isolate was injected into C3H/HeSnJ mice. Infected mice were sacrificed and organs were analyzed by light microscopy for vasculitis.Student's t-test was used to compare mean values.

Results: 16S rRNA analysis identified a genomic sequence within an affected artery that was 100% homologous to the genus *Burkholderia*. Primers specific for the bacteria identified the organism in 9/10 GCA arteries but in none of the controls (0/11).MLST analysis identified the organism as *B. pseudomallei-like* (BpGCA).RT-PCR confirmed the absence of type III secretion factors, a genetic profile that confers an attenuated phenotype for many species of *Burkholderia*. IF of paraffin-embedded temporal arteries identified BpGCA-LPS in GCA arteries but not controls.ELISA detected BpGCA-LPS at high levels in the serum of GCA subjects (n=61, mean 437.8 pg/ml, SEM 36.7) but not healthy controls (n=102, mean 28.1 pg/ml, SEM 3.8, p<0.0001).BpGCA was cultured from the temporal artery of a subject with GCA and the isolate was used to infect C3H/HeSnJ mice. Mice injected with the organism developed inflammation of pulmonary blood vessels.

Conclusion: An attenuated newly identified species of *Burkholderia* has been isolated from temporal arteries of GCA subjects.LPS of the organism is detectable in the serum of GCA subjects. Mice infected with the organism develop vasculitis. BpGCA appears to be a critical factor in the pathogenesis of GCA.

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Am80, a Retinoic Acid Receptor Agonist, Ameliorates Murine Vasculitisthrough the Suppression of Neutrophil Migration and Activation. Chie Miyabe[1], Yoshishige Miyabe[1], Noriko Miura[2], Kei Takahashi[3], Yuya Terashima[4], Etsuko Toda[4], Fumiko Honda[1], Tomohiro Morio[1], Naohito Ohno[2], Jun-ichi Suzuki[4], Mitsuaki Isobe[1], Kouji Matsushima[4], Ryoji Tsuboi[5], Nobuyuki Miyasaka[1] and Toshihiro Nanki[1]. [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]School of Pharmacy, Tokyo University of Pharmacy and Life Science, Tokyo, Japan, [3]Toho University Ohashi Medical Center, Tokyo, Japan, [4]The University of Tokyo, Tokyo, Japan, [5]Tokyo Medical University, Tokyo, Japan

Background/Purpose: Vasculitis is characterized by leukocyte infiltration in the vessel walls with destructive damage to mural structures. Retinoids are compounds that bind to retinoic acid receptors (RARs)and have biological activities of vitamin A, including modulatory effects on cell proliferation and differentiation. Synthetic retinoid, Am80, is a specific ligand for RAR-α/β but not RAR-$\gamma$and is characterized by higher stability, fewer potential adverse effects, and superior bioavailability compared with all-*trans* retinoic acid. Previously we showed that Am80 ameliorated murine collagen-induced arthritis and experimental autoimmune*myositis*. In this study, we examined the therapeutic effects of Am80 on a murine model of vasculitis induced by *Candida albicans* water-soluble fraction (CAWS).

Methods: Vasculitis was induced in BALB/c mice by intraperitoneal injection of CAWS from day 1 for 5 days. Neutrophils were depleted by injection of anti-neutrophil serum. Am80 was administrated orally once dailyfrom day 1 for 5 weeks or from day 8 for 4 weeks. Vasculitis was histologically evaluated. Number of migrated cells of labeled-adaptively transfer cells was counted. Chemotaxis was analyzed using cell mobility analysis device. Production of reactive oxygen species (ROS) and phosphorylation of mitogen-activated protein kinases was measured by flow cytometry. Concentrations of elastase, CCL2 and IL-6 were measured by enzyme-linked immunosorbent assays.

Results: Administration of CAWS induced vasculitis in the coronary arteries and aortic root with abundant neutrophil infiltration. Depletion of neutrophils reduced CAWS-induced vasculitis. Treatment with Am80 from day 1 significantly attenuated the experimental vasculitis. In addition, administration of Am80 from day 8, after the onset of vasculitis, also ameliorated the vasculitis. Am80 inhibited migration of transferred neutrophils into the site of vasculitis. *In vitro*, Am80 suppressed N-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced chemotaxis of human peripheral blood neutrophils. Am80 reduced ROS production by phorbol 12-myristate 13-acetate, Pam3CSK4 or lipopolysaccharide (LPS)-stimulated peripheral blood neutrophils. Elastase release by fMLP and cytochalasin B-stimulated neutrophils was inhibited by incubation with Am80. Am80 also inhibited phosphorylation of extracellular signal-regulated kinase 1/2 and p38 in neutrophils-stimulated with fMLP and LPS. Moreover, Am80 reduced CCL2 and IL-6 production from human umbilical vein endothelial cells-stimulated with TNF-α or IL-1β.

Conclusion: Am80 significantly suppressed CAWS-induced vasculitis presumably through inhibition of neutrophil migration and activation.

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Impairment of the Inhibitory PD-1-PD-L1 Axis in Giant Cell Arteritis (GCA). Mazen Nasrallah[1], Augusto Vaglio[2], Shalini Mohan[1], Bjorn Hartmann[1], Joyce Liao[3], Kenneth J. Warrington[4], Jorg J. Goronzy[5] and Cornelia M. Weyand[6]. [1]Stanford University, Stanford, CA, [2]University of Parma, Parma, Italy, [3]Stanford University, Palo Alto, CA, [4]Mayo Clinic, Rochester, MN, [5]Stanford Univ School of Medicine, Stanford, CA, [6]Stanford University School of Medicine, Stanford, CA

Background/Purpose: Giant cell arteritis (GCA) is an autoimmune syndrome characterized by granuloma formation in the media of medium and large arteries. In a healthy immune system, excessive immune stimulation is counteracted by negative costimulatory signals which oppose T cell activation and protect tissue tolerance. An important inhibitory molecule within the B7/CD28 family is the programmed death-1 receptor (PD-1), with its ligand PD-L1. We have screened T cells from GCA patients for molecular elements that regulate inhibitory pathways and have tested the functional role of co-inhibitory molecules in in vitro and in vivo models of vasculitis.

Methods: Peripheral blood T cells from 45 patients with biopsy-proven GCA and 54 age-matched controls were profiled for the expression of positive and negative costimulatory receptors which critically adjust T cell-responsiveness. Transmural migration of activated T cells was studied in 3-dimensional cellulose fiber-based scaffolds populated with endothelial cells or vascular smooth muscle cells and assembled into walls mimicking human medium arteries. Disease-relevant functions of patient-derived CD4 T cells were studied in vivo in humanized chimera mice engrafted with human arteries.

Results: GCA patients have significantly increased frequencies of PD-1$^+$ CD4 T cells when compared to controls (30.3 % vs. 19.7 %; p=0.02). The PD-1 ligand PD-L1, normally strongly expressed on endothelial cells of the vasa vasorum was barely detectable in GCA-affected temporal arteries. PD-1-PD-L1 interactions were critically involved in regulating transfer of T cells across the endothelial barrier in the 3D-custom made arterial walls. Antibody-mediated blockade of PD-1 doubled the number of CD4 T cells crossing the endothelial layer (n=7 distinct T cell donors; p=0.04) and enhanced pooling of intrawall T cells. To explore the significance of negative signaling in arteritis, human artery-SCID chimeras were treated with the PD-1 blocking PD-L1 fusion protein. Disrupting PD-1 signaling effectively accelerated vessel wall inflammation; by enhancing T cell pooling and DC activation and boosting the production of innate and adaptive cytokines.

Conclusion: The PD-1-PD-L1 pathway protects the vessel wall from inflammatory attack. Several steps of the immune activation cascade relevant for GCA underlie regulation by this negative signaling pathway. T cells from GCA patients receive insufficient inhibitory signals due to a lack of PD-L1 expression. Reestablishing negative signaling may be necessary to prevent detrimental immune responses in GCA and to restore the immune privilege of the arterial wall.

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Dense Genotyping, Imputation, and Regression Analysis Identifies Multiple Independent Genetic Susceptibility Loci within the HLA Region in Behcet's Disease. Travis Hughes[1], Adam Adler[2], Patrick S. Coit[1], Vuslat Yilmaz[3], Kenan Aksu[4], Nursen Duzgun[5], Gokhan Keser[4], Ayse Cefle[6], Ayten Yazici[6], Andac Ergen[7]. Erkan Alpsoy[8], Carlo Salvarani[9], Bruno Casali[10], Ina Koetter[11], Javier Gutierrez-Achury[12], Cisca Wijmenga[12], Haner Direskeneli[13], Guher Saruhan-Direskeneli[14] and Amr H. Sawalha[1]. [1]University of Michigan, Ann Arbor, MI, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Istanbul University, Istanbul Faculty of Medicine, Department of Physiology, Istanbul, Turkey, [4]Ege University, Izmir, Turkey, [5]Ankara University, Ankara, Turkey, [6]Kocaeli University, Kocaeli, Turkey, [7]Okmeydaný Research and Education Hospital, Istanbul, Turkey, [8]Akdeniz University, Antalya, Turkey, [9]Arcispedale S Maria Nuova. IRCCS, Reggio Emilia, Italy, [10]Molecular Biology Laboratory, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [11]University Hospital, Tuebingen, Germany, [12]University Medical Hospital Groningen, University of Groningen, Groningen, Netherlands, [13]Marmara University, School of Medicine, Istanbul, Turkey, [14]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Background/Purpose: The genetic association between *HLA-B51* and Behcet's disease is well established. However, localizing this genetic effect and exploring additional susceptibility loci within the HLA has been limited by the complexity and the strong linkage disequilibrium in this region. Herein, we provide evidence for multiple independent genetic effects within the HLA region in Behcet's disease, using two independent and ethnically divergent cohorts.

Methods: A total of 503 Turkish patients and 504 controls, and 144 Italian patients and 1270 controls were genotyped across 8,572 SNPs in the HLA extended region (Chr6: 28,889kb-33,000kb, HG19) using a custom platform (Immunochip). After applying quality control and tests for autosomal heterozygosity, identity by descent, and population stratification by principal component analysis, 467 Turkish patients and 472 controls, and 127 Italian patients and 1266 controls were included in the final analysis. Additional variants from the 1000 Genomes Project were imputed in both cohorts using Impute 2 with a combined reference panel of 1,092 individuals. Meta-analysis was then performed among 24,834 markers conserved between the two cohorts and genetic analysis performed. Next, logistic regression and pairwise conditional analysis was performed to identify independent effects among the associations detected.

Results: Three independent genetic association effects were detected between the HLA region and Behcet's disease ($r^2<0.30$).The most significant association was with rs116799036 (meta-analysis: OR= 3.88, P= 9.42×10^{-50}; Turkish: OR= 3.74, P= 5.75×10^{-33}; Italian: OR= 4.14, P= 4.93×10^{-23}) which is located approximately 24kb upstream of *HLA-B* and 18kb upstream of *MICA*. A second independent genetic association tagged by rs12525170 located within *PSORS1C1* (meta-analysis: OR= 3.01, P= 3.01×10^{-26}; Turkish: OR= 2.90, P= 1.35×10^{-17}; Italian: OR= 3.22, P= 4.51×10^{-12}), and a third tagged by rs114854070 located 1.4kb upstream of *HLA-F-AS1* (meta-analysis: OR= 1.95, P= 7.84×10^{-14}; Turkish: OR= 1.97, P= 2.34×10^{-9}; Italian: OR= 1.91, P= 3.74×10^{-6}) were also detected. Each of these three genetic associations in the HLA region maintained significance after controlling for the effects of the other two using regression analysis, in both cohorts independently and in the meta-analysis. This was confirmed using pairwise conditional analysis.

Conclusion: Multiple independent genetic associations are observed in the HLA region for Behcet's disease. While the most significant association resides upstream of *HLA-B* and *MICA* genes, two genetic associations in *PSORS1C1* and in *HLA-F-AS1* appear to be independent.

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Endothelin-1 (ET-1) Induces Extracellular Matrix Protein Production by Human Temporal Artery Derived Myointimal Cells. A Mechanism Potentially Leading to Intimal Hyperplasia and Vascular Occlusion in Giant-Cell Arteritis. Ester Planas-Rigol[1], Marc Corbera-Bellalta[2], Marco A. Alba[2], Itziar Tabera-Bahillo[2], Sergio Prieto-Gonzalez[2], Georgina espigol-Frigole[2], Jose Hernandez-Rodriguez[3]. Ester Lozano[4] and Maria C. Cid[1], [1]Vasculitis Research Unit. Hospital Clínic. University of Barcelona. IDI-BAPS, Barcelona, Spain, [2]Hospital Clinic University Barcelona, Barcelona, Spain, [3]Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [4]Hospital Clinic University Barcelona

Background/Purpose: Endothelin-1 (ET-1) is the main isoform of the Endothelin family. It is also the most powerful vasoconstrictor identified. ET-1 is constitutively produced in blood vessels by endothelial cells and vascular smooth muscle cells (VSMC). VSMC express two endothelin receptors: Endothelin receptor A and B (ETAR and ETBR) but the main effect of vasoconstriction may be the result of the interaction between ET-1 and ETAR. Transforming Growth Factor β1 is a fibrogenic cytokine and recent studies suggest that ET-1 contributes to the fibrogenic effect of TGFβ by fibroblasts.

To investigate whether ET-1 and TGFβ may contribute to vascular occlusion by inducing pro-fibrotic responses in cultured vascular myointimal cells.

Methods: VSMC were obtained from cultured human temporal artery sections obtained for diagnostic purposes as described (Ann Rheum Dis. 2008 Nov; 67(11):1581–8). ET-1, TGFb, collagen type I (COL1) and type III (COL3) expression was assessed by quantitative real-time PCR (Taqman[R] Gene Expression Assay) from Applied Biosystems. COL1 and COL3 protein production was determined by ELISA (Takara and USNC Biological) kits respectively.

Results: ET-1 and TGFb up regulated COL1, COL3 expression by VSMC at the mRNA and protein level. This increase was inhibited by ETAR receptor antagonist BQ123 and partially abrogated by ALK5 inhibitor SB525334.

ET-1 induced indeed a remarkable early expression of TGFβ and TGFb induced, in turn, a later induction of ET-1. A double blockade of these cytokines enhanced the inhibition of COL1 and COL3 expression suggesting that collagen production by VSMC may be dependent of both ET-1 and TGFβ.

Phenotypic changes in ET-1-treated-VSMC were also observed. These cells became adherent earlier than untreated ones. Treatment with BQ123 reverted this phenotype suggesting that ET-1 may have an important role in the regulation of VSMC adhesion and migration

Conclusion: ET-1 may contribute to intimal hyperplasia directly by inducing collagen type I and III by human medium-size artery derived myointimal cells. Since ET-1 and TGFb are expressed in GCA lesions these preliminary results suggest that ETAR and ALK5 receptor antagonists may prevent intimal hyperplasia and vascular occlusion in GCA.

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Interleukin-21, B Cell Activating Factor and Unmethylated CpG Oligodeoxynucleotides Synergize in Promoting Anti-Proteinase 3 Autoantibody Production *in Vitro*. Nikola Lepse[1], Judith Land[1]. Abraham Rutgers[1], Cees G.M. Kallenberg[1], Coen A. Stegeman[1], Peter Heeringa[2] and Wayel H. Abdulahad[1], [1]University Medical Center Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Netherlands

Background/Purpose: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are characterized by the presence of circulating autoantibodies that are often directed against proteinase 3 (PR3). Although the mechanisms that lead to ANCA production in AAV are not clear, bacterial infections have been linked to disease development. We have reported that unmethylated CpG oligodeoxynucleotides (CpG-ODN), which resemble bacterial DNA, in combination with IL-2 enhance ANCA production *in vitro*. Recent studies have highlighted the role of IL-21 in plasma cell formation and antibody production by synergizing with B cell activating factor (BAFF). This study aimed to assess the involvement of CpG-ODN, IL-21, and BAFF in the mechanisms that contribute to ANCA production in AAV patients.

Methods: Twenty two patients with PR3-AAV (18 in clinical remission, 4 with active disease) and 8 healthy controls (HC) were included in the study. Peripheral blood mononuclear cells (PBMC) were isolated and cultured *in vitro* for 12 days in the presence of BAFF and IL-21, with or without CpG-ODN. IgG production was measured in culture supernatants by ELISA and PR3-ANCA production was quantified by Phadia EliA and expressed in response units (RU). The percentage of circulating IL-21 producing CD4+ T cells was analyzed by flow cytometry in blood samples stimulated *ex vivo* with phorbol-myristate-acetate and calcium ionophore in the presence of brefeldin A. CFSE Cell Proliferation Kit was used to assess the effect of BAFF, IL-21, and CpG-ODN on B cell proliferation.

Results: PBMC stimulation with CpG-ODN and IL-2 significantly increased *in vitro* production of IgG in both HC and patients (P=0,0004) whereas PR3-ANCA production was detected in patient samples only (RU median 0,85 (range 0,00–36,72), compared to 0,10 (0,00-0,14) in HC). Stimulation with BAFF and IL-21 also significantly increased IgG production in HC and patients (P=0,0001) and ANCA production in patient samples (median 0,90 (range 0,00–58,80) versus 0,11 (0,00-0,12) in HC), which could be further augmented by addition of CpG-ODN (median 1,06 (range 0,00–140,00) versus 0,17 (0,10–0,26) in HC). Compared to HC, the proportion of IL-21 producing CD4+ T cells was significantly increased in the circulation of AAV patients. Preliminary data indicate that stimulation with BAFF, IL-21 or the combination of BAFF/IL-21 does not induce B cell proliferation. In contrast, stimulation with CpG-ODN alone induced proliferation in 11,6% of B cells, whereas the combined treatment with BAFF, IL-21 and CpG-ODN induced proliferation in 57,8% of B cells.

Conclusion: IL-21, BAFF and CpG ODN synergize in promoting IgG and PR3-ANCA production from PBMCs of AAV patients *in vitro*. This effect was associated with substantial B cell proliferation. The increased percentage of IL-21 producing CD4+ T cells in AAV patients suggests the involvement of IL-21 in ANCA production *in vivo*. Overall, these data indicate that the interplay between endogenous B cell stimuli and bacterial products may contribute to PR3-ANCA reactivation in AAV via B cell activation and proliferation.

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ARHP Concurrent Abstract Session
Pediatrics: Disease Flares
Sunday, November 11, 2012, 4:30 PM–6:00 PM

A Family Based Pedometer Walking Program in an Adolescent Population with Juvenile Idiopathic Arthritis. Sara M. Stern, Jill R. Blitz, Amber Richards and Katherine AB Marzan. Children's Hospital Los Angeles, Los Angeles, CA

Background/Purpose: Walking programs are effective in adult arthritis but have not been studied in adolescents with arthritis.The study's objective was to evaluate the impact of a family based pedometer (PED) walking program and an educational program on the exercise tolerance of adolescent juvenile idiopathic arthritis (JIA) patients (Pts) with lower extremity involvement.

Methods: 27 Pts with lower extremity JIA were prospectively studied in a 2 phase exercise program.In the 1st 6 week (wk) phase Pts were given typical guidance from a rheumatologist and physical therapist to increase their activity with daily walking.Data was obtained at baseline, and after the 1st and 2nd 6 wk phases.In the 2nd 6wk phase all Pts and family members received a PED to record their daily steps and were randomized into 2 groups.One group attended a 30 min Arthritis Foundation *Walk with Ease* (WWE EP) educational program specifically adapted for adolescents and the other did not.The 6 minute walk test (MWT) was the primary outcome measure to assess program effectiveness.Secondary outcome measures included body mass index (BMI), Childhood Health Assessment Questionnaire (CHAQ), and visual analogue scale (VAS) for pain.

Results: 27 Pts (23 F: 4M) 11–19 yrs old (mean 16 yrs) participated.19 were Latino (Lat) reflecting the population of the center.13 completed the study.All but 1 of the 14 Pts (12 Lat, p = 0.1) that discontinued the study did so between the 1st and 2nd visit prior to receiving a PED primarily due to 2nd thoughts about participating in an exercise program.While no statistically

significant differences were noted between Pts that discontinued and completed the study, those that discontinued had a trend towards higher BMI, shorter 6MWT, smaller HR change and higher VAS scores possibly reflecting a less motivated group.

13 pts (7 Lat) with mean age of 16 ± 2 yrs completed the study (12F: 1M).They generally had mild disease with a mean CHAQ of 0.65 ± 0.79 and mean VAS of 2.5 ± 3.6 cm.5 Pts had active JIA at the initial visit and 3 other Pts had active JIA over the course of the study.There was a significant increase in 6 MWT distance from baseline (458.0 ± 70.8 m) to the end (501.4 ± 59.8 m) of the 6wk initial phase (p = 0.029).During the interventional 2nd phase, Pts maintained their improved exercise tolerance with a modest trend toward increased 6 MWT from 501.4 ± 59.8 mto 504.7 ± 60.6 m (p = 0.76).There were no differences in the 6 MWT between the Pts that received the education program (n=9) to those that did not (n=4) possibly due to small sample size (p = 0.93).However, the WWE EP group at baseline visit appeared to have an overall higher exercise tolerance (6 MWT 478.1 ± 78.5 m vs 417.8 ± 27.2 m) and had a healthier initial BMI (23±5 vs 26±3).In addition, Pts in the WWP EP group overall walked more steps per day while using their PED (2978 ± 3002 steps vs 1968 ± 1472 steps), although this was not statistically significant.

Conclusion: In motivated adolescents with JIA, an exercise program with consistent support from a physical therapist and rheumatologist significantly increased exercise tolerance.The addition of a PED and modified WWE EP to a walking program helped Pts maintain or increase exercise tolerance.

Disclosure: S. M. Stern, Arthritis Foundation, 2; **J. R. Blitz**, None; **A. Richards**, None; **K. A. Marzan**, None.

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What Is the Impact of a Transition Program On Adolescents with Juvenile Idiopathic Arthritis and Their Parents ? Deborah Hilderson[1], Rene Westhovens[2], Rik Joos[3], Carine H. Wouters[2] and Philip Moons[4]. [1]University Hospital Leuven, KU Leuven, Leuven, Belgium, [2]University Hospital KU Leuven, Leuven, Belgium, [3]University Hospital Gent, Ghent, Belgium, [4]KU Leuven, Leuven, Belgium

Background/Purpose: To date, there is no structured or systematic approach in Belgium for transferring adolescents with juvenile idiopathic arthritis from pediatric rheumatology to an adult rheumatology setting. We explored the impact of a transition program for adolescents with JIA on patient- and parent-related outcomes.

Methods: Using a one-group pretest-posttest design with a non-equivalent posttest only comparison group, we included literate, Dutch-speaking adolescents (14–16 years of age) with JIA, treated and followed-up at the department of pediatric rheumatology of the University Hospitals of Leuven in the experimental group. The intervention consisted of five key components: introduction of the transition coordinator (TC), focus upon health behavior, adolescent-information day, transfer plan and transfer to adult rheumatology care under the guidance of the TC. The comparison group comprised adolescents aged 17–23 years, who have recently been transferred to the adult rheumatology program without a specific transition program. Outcomes were operationalized in terms of medication adherence (VAS, SHCS-AQ), illness related knowledge (modified PKQ), functional status (CHAQ), health status (PedsQL), global quality of life (LAS), fatigue (MVI-20), and patients' knowledge (modified PKQ). In parents, we measured promotion of independence (PI Scale), support of autonomy (Autonomy Support Scale), psychological control (Psychological Control Scale), health status (PedsQL for parents) and functional status of their child (CHAQ). A total of 33 patients in the intervention group and 45 patients in the comparison group participated. Overall, 23 patients could be matched with controls on gender, JIA subtype, clinical remission, medication prescription and disease activity with comparison patients. Effect sizes in outcomes of the experimental group were measured at baseline and after transfer to the adult program (longitudinal study). Effect sizes in outcomes between the experimental group and the matched comparison group of patients transferred to the adult program without a specific self-management/transition program were measured (comparative study).

Results: *Longitudinal study*: A large positive effect was calculated for the improved psychosocial health. A medium positive effect was found in the improvement of quality of life of patients. Medium negative effects were found in improved health status rheumatology, perceived by parents. *Comparative study:* For patients in the experimental group, a large positive effect was found in reduction of parental expectations. Medium positive effects were found in improved psychosocial health and reduction in behavioral control. Medium negative effects were found in reduction of psychological control.

Conclusion: Implementation of a transition program can improve the psychosocial health and quality of life of adolescents with JIA during the transition process. It is important to involve the parents into the transition process in order to promote self-management of the adolescent with JIA.

Disclosure: D. Hilderson, None; **R. Westhovens**, None; **R. Joos**, None; **C. H. Wouters**, None; **P. Moons**, None.

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Employment of a Needs Assessment Survey to Shape a Novel Web-Based Pediatric Rheumatology Curriculum for Primary Care Providers. Amy L. Woodward and Z. Leah Harris. Vanderbilt University School of Medicine, Nashville, TN

Background/Purpose: Pediatric rheumatology faces many challenges due to the shortage of board certified physicians in the field and the imbalance in their geographic distribution.This shortage has required primary care physicians and adult rheumatologists to assume the care of children with rheumatologic diseases, though these physicians report significant discomfort doing so. We are addressing this issue through the development of a novel web-based curriculum aimed at primary care physicians, employing a needs assessment survey to help guide the curriculum.

Methods: Tenants of adult learning theory stress activating the learners' prior knowledge and engaging the learner in determining personal educational goals. We therefore distributed a needs assessment survey to Vanderbilt Pediatric residency graduates (1981–2010) working in primary care who kept an address on file with the Vanderbilt Medical Alumni Association. Our goals were to understand perceptions of what the needs are and what educational interventions would be most effective.

Results: Of 152 surveys sent successfully via Survey Monkey, we received 28 responses (18.4%). When asked the question "On completion of your residency training were you comfortable recognizing the following diseases in children?", the self-reported ability to recognize chronic arthritis on completing residency was high (71.4%), while confidence in recognizing other chronic autoimmune diseases was low, with only 64.3% comfortable recognizing lupus, the majority uncomfortable recognizing juvenile dermatomyositis (53.6%), localized scleroderma (75%), systemic sclerosis (82.1%), Behcet's Disease (75%) and sarcoidosis (82.1). (Figure 1) We also found primary care physicians to have interest in practical, problem oriented educational resources, including action plans for common rheumatologic complaints (71.4%) and emergencies by specific disease (67.9%) (Figure 2).

Specific autoimmune disease	Yes	No
Chronic arthritis	71.4% (20)	28.6% (8)
Systemic lupus erythematosus	64.3% (18)	35.7% (10)
Juvenile dermatomyositis	46.4% (13)	53.6% (15)
Henoch-Schonlein purpura	100% (28)	00.0% (0)
Kawasaki Disease	92.9% (26)	7.1% (2)
Localized Scleroderma	25.0% (7)	75.0% (21)
Systemic sclerosis (systemic scleroderma)	17.9% (5)	82.1% (23)
Behcet's Disease	25.0% (7)	75.0% (21)
Sarcoidosis	17.9% (5)	82.1% (23)

Possible Intervention

Intervention	% favorable response
Additional education in Pediatric Rheumatology	78.6%
Proactive plan of approach for common rheum problems	71.4%
Action plan for emergencies by specific disease	67.9%
Action plan for emergencies for specific patients	60.7%
Improved access to peds rheumatologist for questions	57.1%
Improved access to peds rheumatologist for urgent visits	39.3%

Conclusion: Our needs assessment survey of primary care physicians found a high self-reported ability to recognize chronic arthritis when leaving

residency training, though low confidence in recognizing rarer but potentially more serious or life-threatening autoimmune diseases. Our results also indicate that primary care physicians have interest in practical, problem oriented educational resources to assist them in caring for children with rheumatologic diseases. We will utilize our survey results to develop a learner centered web-based curriculum in pediatric rheumatology, with the ultimate goal of improving care for children with autoimmune diseases.

Disclosure: **A. L. Woodward**, None; **Z. L. Harris**, None.

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Will I Waste Your Time? Delays in Help-Seeking for RA Flares. Caroline A. Flurey[1], Marianne Morris[1], Jon Pollock[1], Rodney A. Hughes[2], Pamela Richards[3] and Sarah Hewlett[1]. [1]University of the West of England, Bristol, United Kingdom, [2]St. Peters Hospital, Chertsey Surrey, United Kingdom, [3]University of Bristol, Bristol, United Kingdom

Background/Purpose: Anecdotal evidence suggests that patients vary in how long they wait before seeking medical help for an RA flare. The aim of this research is to explore why, and their tipping points for seeking help.

Methods: Q-Methodology: 29 RA patients sorted 23 statements (generated in previous qualitative interviews) about their help seeking behaviours when in a flare, across a forced distribution in ranked order of agreement. Data were analysed using centroid factor analysis with varimax rotation (i.e. the participants and not the items are the variables). Demographic and clinical data were collected and patients completed comments booklets about their rationale for sorting the statements.

Results: Consensus was reached on 9 statements and two factors were produced, which explained 51% of the study variance and accounted for 22 of the 29 participants. None of the Q-sorts were confounded (loading on more than one factor). A participant loading of 0.54 reached significance at p<.01.

Consensus: "When I just don't know what to do anymore": The top 3 of the 9 consensus statements are 'when the pain becomes too intense', 'when the Flare has gone on longer than expected' and 'when the symptoms become uncontrollable', suggesting these are the tipping points for seeking help.

Factor A: Definite Decision: "It won't go away, so I won't wait": Sixteen participants: mean disease duration 15.2yrs (SD 10.3), age 54.8yrs (SD 9.6), HAQ score 1.360 (SD 0.8), 69% female, 69% on biologic therapies.

These patients will seek help quickly when they are in a flare, they know that their medical team can help and that their flare won't go away on its own. They don't worry about wasting their own or the Rheumatologist's time and will not wait until their next scheduled appointment for help. Tipping points for seeking help for these patients are worries about long term damage to their joints, knowing their flare needs to be controlled by new medication and their quality of life being affected.

Factor B: Cautious Indecision: "Lying down and not moving until it goes": Six participants: mean disease duration 18.7yrs (SD 13.9), age 50.5yrs (SD 15.4), HAQ score 1.23 (SD 0.9) 67% female, 0% on biologic therapies.

These patients wait to contact the medical team when they are in a flare. They are reluctant to seek help as they hope the flare will go away on its own and do not believe it will last until they seek medical help. They don't like asking for help and worry about wasting the Rheumatologist's time. They may wait until their next scheduled appointment before seeking help and will try to manage their symptoms themselves. These patients need to be prompted by a friend or family member to seek help.

Conclusion: Whilst consensus indicates pain is a tipping point, for some patients a complex interaction of beliefs hinders their help-seeking behaviour. Health care professionals should be aware that some patients delay help-seeking due to fears of time wasting, thus potentially risking further damage.

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865

A Methodology for Estimating Disease State Transitions: Repeated Measures Markov Models with Covariate Dependence. George W. Reed[1], Andrew S. Koenig[2]. Katherine C. Saunders[3], David H. Collier[4], Joel M. Kremer[5] and Sameer Kotak[6], [1]University of Massachusetts Medical School, Worcester, MA, [2]Pfizer Inc., Collegeville, PA, [3]CORRONA, Inc., Southborough, MA, [4]Amgen Inc., Thousand Oaks, CA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY, [6]Pfizer Inc., New York, NY

Background/Purpose: Many RA patients have variable disease activity over time due to disease flare, reduction in efficacy of current medications and other disease mediating changes. Understanding these transitions and the factors associated with these transitions are important in the treatment of RA. Appropriate analytic models for estimating these transitions are needed.

Methods: Modeling methods were explored for estimating transitions from various disease states defined by low, moderate and severe using CDAI. The framework needed to provide intuitive estimates of the probability of transitioning between states, stability using variable time intervals, allow repeated measures within patients, and a method of estimating associations of patient and treatment characteristics with transition probabilities. A Markov modeling framework was examined. To test the models we used RA patient disease activity data from the CORRONA RA registry and examined multiple visits per patient. There were over 160,000 visits from over 24,000 RA patients available for analysis.

Results: Starting with a simple transition model (Figure 1a), a first order Markov process was assumed and a logistic regression model that incorporates a single prior state produced stable estimates for variable time between visits. Transition probabilities differed by 0.07 for large differences in visit intervals, 3 mos vs 1 yr. A single logit equation can estimate the impact of the prior state ($Y_{i,\,j-1}$), covariates (x_{ij}) associated with the transitions and test if different covariate associations are dependent on prior state:

$$\text{logit Pr}(Y_{ij} = |Y_{ij} = y_{ij}) = \beta_0 x_{ij} + y_{ij-1}\alpha_{ij},$$

where

$$\pi_{j-1,1} = \text{Pr}(Y_{ij} = 1 | Y_{ij-1} = y_{ij-1}).$$

Figure 1b illustrates estimated transition probabilities.

The modeling framework is able to accommodate additional complexities. A multinomial logistic model provides estimates for more than two states. The models allow the use of higher order Markov processes to estimate the influence of disease state at earlier visits.

π_{00}=probability low to low
π_{01}=probability low to mod/sev
π_{10}=probability mod/sev to low
π_{11}=probability mod/sev to mod/sev
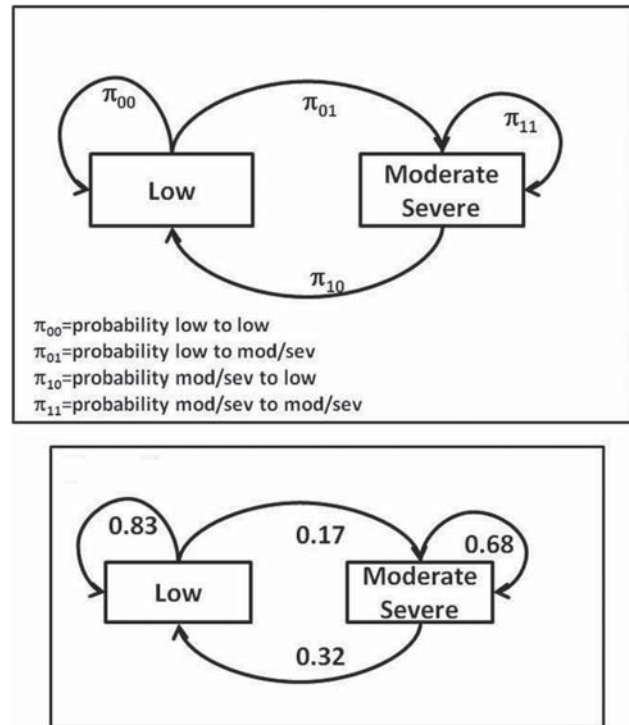
Conclusion: Markov models and logistic or multinomial models of the transition probabilities provides a framework for analyzing patient disease states, the population transition probabilities and covariates associated with those transitions.

Disclosure: **G. W. Reed**, Corrona, 2, University of Massachusetts Medical School, 3, Corrona, 5, Harvard Medical School,; **A. S. Koenig**, Pfizer Inc, 3, Pfizer Inc, 1; **K. C. Saunders**, Corrona, 3; **D. H. Collier**, Amgen Inc., 1, Amgen Inc., 3; **J. M. Kremer**, Bristol-Myers Squibb, Genentech, Pfizer, HGS, UCB, 2, Amgen, Abbott, Genentech, Pfizer, 5, Amgen, Abbott, BMS, 8, Corrona, 4; **S. Kotak**, Pfizer Inc, 1, Pfizer Inc, 3.

ARHP Concurrent Abstract Session
Psychological Aspects of Rheumatologic Disease
Sunday, November 11, 2012, 4:30 PM–6:00 PM

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Pain Is Associated with Telomere Shortening in Women with Fibromyalgia. Afton L. Hassett[1], Daniel J. Clauw[1], Richard E. Harris[1], Steven E. Harte[1], Anson E. Kairys[1], Steven Buyske[2] and David A. Williams[1]. [1]University of Michigan, Ann Arbor, MI, [2]Rutgers University, Piscataway, NJ

Background/Purpose: Telomere length is considered a marker of cellular aging and has been linked to an increased risk for morbidity and mortality. Psychosocial factors associated with shortened telomeres (e.g., obesity, depression, anxiety, trauma) are also common in chronic pain; yet, little is known about telomere length in pain populations. Thus, a preliminary investigation was conducted in fibromyalgia.

Methods: Leukocyte telomere length was evaluated in 66 women with fibromyalgia and 22 healthy female controls. Participants were from a convenience sample of individuals who underwent a blood draw and completed questionnaires including the Brief Pain Inventory (BPI) and Center for Epidemiologic Studies Depression Scale (CESD). A subgroup of fibromyalgia patients underwent quantitative sensory testing (QST; n=12) and neuroimaging (voxel-based morphometry; n=12). Telomere length was measured using the quantitative polymerase chain reaction method.

Results: Although patients had shorter telomere length than controls, the difference was not statistically significant. However, higher levels of pain within fibromyalgia were associated with shorter telomere length ($r_{partial} = -.267$, $p = 0.039$). In a comparison of patients categorized as having higher levels of pain (BPI $\geq 5/10$; n = 30) and lower levels of pain (BPI $< 5/10$; n = 31), those with higher levels of pain were more likely to have shorter telomere length than those with low levels of pain despite chronological age ($F = 5.39$, $p = 0.024$). In a similar comparison of telomere length between those with likely depression (CESD scores $\geq$ 19; n = 24) and those likely without depression (CESD scores $<$ 19; n = 42), no significant group differences were detected ($p = 0.175$). However, when pain and depression were combined, patients categorized as high-pain/high-depression had an age-adjusted telomere length 265 base pairs shorter than those with low-pain/low-depression ($p = 0.043$); a difference consistent with over six years of chronological aging. In the subset tested, telomere length was also related to experimentally-induced pain threshold ($r_{partial} = .728$, $p = 0.017$), mild pain ($r_{partial} = .642$, $p = 0.045$) and slightly intense pressure pain ($r_{partial} = .706$, $p = 0.023$), as well as gray matter volume (e.g., primary somatosensory cortex: $r = .725$, $p < 0.05$ corrected), such that patients with shorter telomeres tended to be more sensitive to evoked pressure pain and have less gray matter volume in pain processing regions of the brain.

Conclusion: Our data suggest that pain in fibromyalgia is associated with shortened telomere length. These effects are largely independent of other factors commonly associated with telomere shortening.Interestingly, short telomere length was directly related to evoked pain sensitivity and altered brain structure. Although these findings are preliminary, they suggest that pain may accelerate cellular aging.

Disclosure: **A. L. Hassett**, None; **D. J. Clauw**, None; **R. E. Harris**, None; **S. E. Harte**, Analgesic Solutions, Natick, MA,; **A. E. Kairys**, None; **S. Buyske**, None; **D. A. Williams**, None.

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Events That Triggerthe Onset of the Fibromyalgia Syndrome (FMS). Robert S. Katz[1], Sharon M. Ferbert[2], Alexandra Small[3] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL, [3]University of Illinois Medical School

Background/Purpose: Triggering events – those that are followed by the onset or rapid increase in FMS symptoms – have a significant impact in some cases.In order to learn more about the nature and impact of triggering events, we asked FMS patients about traumatic experiences in their lives, and whether these events affected the onset of their FMS symptoms.

Methods: As a part of an Internet survey administered by the volunteer community fibromyalgia organization, AFFTER, 763 female self-identified FMS patients and 115 female controls without FMS responded to questions about emotionally stressful or life-changing events and whether any of these events suddenly triggered FMS, as well as follow-up questions on the pace of onset of FMS symptoms before and after triggering events. Only women's responses were analyzed to eliminate confounding by gender.

To validate the Internet Survey, an identical rheumatology office questionnaire was administered to 115 FMS patients and 63 control patients with other rheumatic diseases.The chi-square test of association and Fisher's exact test were used to compare percentages, and the Mann-Whitney test was done to compare FMS and control patients with respect to age. A 0.05 significance level was used and all tests were two-sided.

Results: In the Internet survey the mean respondent age was 49.8 ± 11.4 years. 78.0% of FMS respondents reported that they had experienced a significant life-changing event or emotional stressor, vs. 35.7% of controls ($p < 0.001$). Specific traumatic events experienced by FMS patients vs. controls included major surgery (70.4% vs. 43.5%, $p < 0.001$), major or long lasting illness (44.7% vs. 18.3%, $p < 0.001$), and accidents 26.9% vs. 12.2, $p = 0.001$).

Post-traumatic symptoms included startling easily (32.2%), intrusive memories of the trauma (18.1%), nightmares (17.7%), reluctance to speak or think about the trauma (14.5%), and symptoms of hypervigilance and post-traumatic stress disorder.30.2% indicated that their FMS began suddenly after one of these events. These post-traumatic episodes generally began as either back pain (50.4%), neck pain (50.0%) or both.

In the rheumatology office practice questionnaire 81.7% of FMS patients and 61.9% of control patients were women ($p = 0.004$). The mean age was 48.1 ± 12.3 years for FMS patients and 50.7 ± 13.6 for control patients ($p = 0.092$). 88.7% of FMS patients and 76.2% of control patients reported that they had experienced at least one very stressful or life-changing event ($p = 0.028$). Some of the FMS patients who reported a traumatic FMS trigger also reported other post-trauma symptoms: startling easily (15.4%), intrusive memories of the trauma (10.3%), reluctance to speak or think about the trauma (10.3%), and nightmares (7.7%).

Conclusion: Surgery, severe illness, and accidents precipitated the onset of fibromyalgia in some patients. In the Internet survey, 30.2% of fibromyalgia patients experienced FMS onset after a traumatic event.Fibromyalgia symptoms usually began with neck or back pain. Some of the FMS patients experienced symptoms consistent with hypervigilance and post-traumatic stress disorder.

Disclosure: **R. S. Katz**, None; **S. M. Ferbert**, None; **A. Small**, None; **S. Shott**, None.

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Illness Perceptions Among Patients with Different Forms of Vasculitis. Peter C. Grayson[1], Naomi Amudala[1], Carol McAlear[2], Renée Leduc[3], Denise Shereff[3], Rachel Richesson[3], Liana Fraenkel[4] and Peter A. Merkel[5]. [1]Boston University Medical Center, Boston, MA, [2]Vasculitis Clinical Research Consortium, University of Pennsylvania, Philadelphia, [3]University of South Florida, Tampa, FL, [4]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [5]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Patient-held beliefs about their illness are central for understanding patient reactions to specific diseases. This study aimed to compare illness perceptions, defined as the organized cognitive beliefs patients hold about disease, among different forms of vasculitis and to identify risk factors for negative illness perceptions.

Methods: Participants were recruited from an online registry in vasculitis to complete the revised Illness Perception Questionnaire (IPQ-R) which measures dimensions of illness perception. High scores on the *identity, timeline, cyclical, consequences,* and *emotional representations* dimensions represent strongly held beliefs about the number of symptoms attributed to illness, the chronicity and cyclical nature of the condition, the negative consequences of illness, and the negative emotional impact of disease. High scores on the *personal control, treatment control* and *illness coherence* dimensions represent positive beliefs about the controllability of the illness and personal understanding of the condition. Mean scores in IPQ-R dimensions were compared across types of vasculitis where n>30 and to literature-reported IPQ-R scores in diabetes mellitus, hypertension, and osteoarthritis using ANOVA with post-hoc Scheffe tests. Cluster analysis of IPQ-R scores was used to identify a group with negative illness perceptions, and stepwise regression was used to identify clinical variables (age, sex, race, ethnicity, place of birth, education, income, depression) and disease characteristics (activity status, severity, duration, overall health) associated with negative illness perception.

Results: 692 participants with 9 forms of vasculitis completed the IPQ-R. For 6 dimensions, there were no significant differences in mean IPQ-R scores between the different vasculitides.Scores in *identity* and *cyclical* dimensions

were significantly higher in Behçet's disease compared to other types of vasculitis (13.5 vs 10.7; 4.0 vs 3.2, p<0.05). Compared to other chronic diseases, patients with vasculitis perceived greater negative disease impact on function and emotional well-being (**Table**). Younger age (OR=1.04; 95%CI 1.02–1.06), depression (OR=4.94; 95%CI 2.90–8.41), active disease status (OR=2.05; 95%CI 1.27–3.29), and poor overall health (OR=3.92; 95%CI 0.88–17.56) were significantly associated with negative illness perception.

Table 1. Mean IPQ-R Dimension Scores in Vasculitis and Other Chronic Diseases

	Vasculitis* n = 692	Diabetes[a] n = 164	Hypertension[b] n = 514	Osteoarthritis[c] n = 241
*Identity***	10.7 (±5.1)	NC	NC	NC
Timeline	4.1 (±0.8)	3.9 (±0.8)	3.6 (±0.4)	4.2 (±0.8)
Cyclical	3.2 (±1.0)	2.8 (±0.7)	3.2 (±0.8)	3.6 (±0.8)
*Consequences****	3.8 (±0.8)	2.9 (±0.6)	2.6 (±0.6)	2.8 (±0.8)
*Emotional repr.****	3.1 (±1.0)	2.0 (±0.6)	2.6 (±0.7)	2.4 (±0.8)
Personal control	3.3 (±0.8)	3.9 (±0.6)	3.5 (±0.7)	3.1 (±0.6)
Treatment control	3.3 (±0.7)	4.6 (±0.9)	3.5 (±0.6)	2.8 (±0.6)
Illness coherence	3.4 (±1.0)	3.5 (±0.9)	NR	3.6 (±0.8)

* Vasculitis types include Behçet's disease (n=48), central nervous system vasculitis (n=12), Churg-Strauss syndrome (n=121), giant cell arteritis (n=32), Henoch-Schönlein purpura (n=12), microscopic polyangiitis (n=42), polyarteritis nodosa (n=36), Takayasu's arteritis (n=57), and granulomatosis with polyangiitis (n=332). ** Identity was scored on scale from 0–22. All other dimensions were scored on a scale from 1–5. *** Difference between vasculits and all other diseases (p<0.05). NC = not comparable across diseases due to disease-specific modifications to IPQ-R. NR = not reported. [a] = Searle, *J of Psych Res*, 2007; [b] = Ross, *J of Hum Hypertension*, 2004; [c] = Bijsterbosch, *A&R*, 2009.

Conclusion: Patients with vasculitis have a unique set of illness perceptions. Clinicians should be aware that younger age, a history of depression, active disease status, and poor overall health are risk factors for negative illness perceptions in systemic vasculitis. Given the similarities in illness perceptions across the vasculitides, ongoing efforts to derive patient-reported outcome measures in vasculitis should focus on measures that are universally applied to different types of vasculitis.

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Concepts Which Determine Health in a Positive Way Are Important to People with Rheumatoid Arthritis and Are Covered by Some Patient-Reported Outcome Instruments. Mona Dür[1], Michaela Coenen[2], Josef S. Smolen[3] and Tanja A. Stamm[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Ludwig-Maximilians-University, Munich, Germany, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Rheumatoid arthritis is a chronic autoimmune disease that has a major impact on functioning, health and well-being. Concepts which determine health in a positive way are often not addressed in a busy clinical setting. The aim of this study is to explore which concepts determine health in a positive way and are meaningful to patients with RA. Furthermore we wanted to analyse whether they are covered by patient-reported outcome (PRO) instruments, and which of them could be recommended for clinical use and/or research.

Methods: We conducted a qualitative narrative biographic study consisting of three steps (see figure): people with RA were asked to tell their life stories which were analysed with the biographical narrative interpretative method afterwards. Hereinafter, we linked concepts which determine health in positive way derived from a systematic literature search to the perspective of patients. Finally, we explored whether these concepts were covered by PROs identified in another systematic literature search. The evaluation of the PROs' coverage was based on the model of the WHO International Classification of Functioning, Disability and Health (ICF).

Results: 15 people with RA with a median age of 52,5 years (IQR 35.75 – 62,5) and median disease duration of 24.50 months (IQR 10 – 59,25) participated in the qualitative study. Occupational balance, social support, participation and coping were the most frequently mentioned meaningful concepts (see table). While coping was mentioned by a higher number of men (83% of all men), optimism and vocational gratification were only important for women (78 resp. 67%). The concept of work-life balance did not appear in the qualitative data. Secondary gain from illness was found in only in 2 participants (13%). 28 PROs were derived from the systematic literature search. The concepts coping, self-efficacy, participation, optimism and social

support were covered particularly.
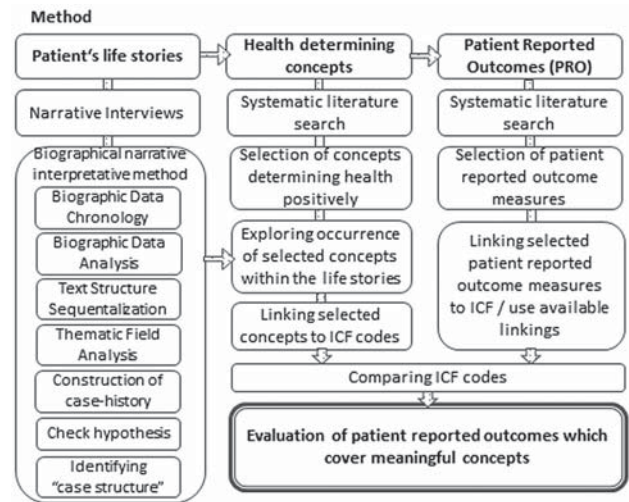
Table 1. Frequency of concepts in a ranked der per sex

Concepts	RA %	Women %	Men %
Occupational Balance	80	89	67
Social support	67	67	67
Participation	63	22	50
Coping	60	44	83
Optimism	47	78	0
Self-efficacy	47	67	17
Vocational gratification	40	67	0
Sense of Coherence	40	44	33
Job satisfaction	33	56	0
Resilience	27	22	33
Social acceptance	27	33	17
Secondary illness gain	13	22	0
Work-Life Balance	0	0	0
n per group	15	9	6

Conclusion: Several concepts which determine health in a positive way show a gender difference. Social support and coping should get more attention in clinical routine and research of people with RA. Therefore the use of MOS social support survey (Sherbourne & Stewart 1991) and the arthritis self-efficacy scale (Lorig et al. 1989) is recommended.

Disclosure: M. Dür, None; **M. Coenen**, None; **J. S. Smolen**, None; **T. A. Stamm**, None.

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To Love and to Hold: Men Describe Parenting in the Presence of Inflammatory Arthritis. Catherine L. Backman[1] and Alana Longson[2]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Vancouver, BC

Background/Purpose: Inflammatory arthritis (IA) may limit participation in life roles such as parenting. Surprisingly little research has investigated the impact of IA on parenting tasks and experiences of fathers. This descriptive pilot study adapted a mail survey used in a cross-sectional study of mothers to an online format to (a) examine feasibility of the tool and items for use with men, and (b) assess self-reported performance of parenting tasks, parenting satisfaction, and parenting efficacy in fathers with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS).

Methods: Men with IA were recruited through rheumatologists' offices, arthritis consumer newsletters and web sites, and public education forums on arthritis. Eligibility criteria included a diagnosis of IA confirmed by a rheumatologist and at least one child ≤18 yrs living with them. Volunteers were sent a web link and password to access the survey. The Parenting Disability Index (PDI) and Parenting Sense of Competency Scale (PSOC) were used to measure parenting outcomes. Surveys also inquired about employment, household work, social support, family quality of life, health status, demographics, and survey feasibility questions. Descriptive statistics

were used to assess numeric responses and thematic content analysis used to examine text responses.

Results: Twelve men volunteered and 10 submitted complete surveys, and reported taking 15 to 60 minutes to do so. They ranged in age from 38 to 59 years, and had 1 to 5 children ranging in age from 4 months to late 20s. Eight were married, 2 were separated/divorced. Four had RA, 4 had AS, and 2 had PsA, from 1 to 32 years in duration (mean = 17.5). Seven were employed. Health Assessment Questionnaire II scores ranged from 0 to 1.5 (mean =.53, median =.40); the common functional limitation was lifting and moving heavy objects. They reported few limitations in parenting tasks, with PDI scores ranging from.20 to 1.26 (0 to 3 scale), mostly related to having energy to be patient with their child, getting up during the night or early morning, and playing (on the floor or outdoors). PSOC total scores ranged from 2.0 to 2.82 (0 to 6 scale; mean = 2.28, SD =.29), while parenting sense of efficacy subscale ranged from 1.67 to 3.56 (mean = 2.32, SD =.60) and parenting satisfaction subscale ranged from 1.50 to 2.75 (mean = 2.22, SD =.38). Men reported many joys in parenting ("to love and to hold" their children), and several challenges ("communicating the fact I'm in pain in a way that doesn't make my 7 year old worried or overly protective; I also don't want to downplay it"). A key motivator for participating in the survey was "most seminars and clinics are directed at or attended by women, so a men's questionnaire is a must!"

Conclusion: The online parenting survey was relevant to the participating men. Although this sample is too small to generalize, findings suggest men with IA experience specific limitations in parenting, but experience great satisfaction with this role. Assessment of parenting task performance may be important to assess in both practice and research settings when selecting outcomes that are meaningful to people living with arthritis.

Disclosure: C. L. Backman, None; **A. Longson**, None.

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Depression Predicts Mortality in RA. Christina Bode[1], Chris Tonner[2], Laura Trupin[3] and Patricia P. Katz[4]. [1]University of Twente, Enschede, Netherlands, [2]UCSF, San Francisco, CA, [3]UC San Francisco, San Francisco, CA, [4]Univercity of California San Francisco, San Francisco, CA

Background/Purpose: Depression rates are elevated among individuals with rheumatoid arthritis (RA).Studies in cardiovascular disease and among elderly populations have found that depression is a risk factor for mortality, but the risk of mortality from depression in RA has received little attention.

Methods: Data were derived from a longitudinal cohort study of individuals with RA recruited from community rheumatology practices and interviewed annually by telephone.To be eligible for the current analysis, participants had to have an interview in either 2002 or 2003 and have at least one follow-up interview (n=530).Subjects were followed until 2009. Cox regression models estimated the association of depression with the risk of all-cause mortality.Depression was defined as a score ≥5 on the 15-item Geriatric Depression Scale (GDS). Using a time-dependent value, depression was

defined as GDS≥5 in the last interview prior to death or censorship. In separate analyses we also examined the risk of a 2-point increase in GDS score from the penultimate to the last interview prior to death or censorship. Analyses controlled for age, gender, disease duration, and presence of any cardiovascular disease risk factors.Separate analyses also examined the conjoint effects of gender and depression.

Results: Mean age (±SD) was 60 (±13), mean disease duration was 19 (±12) years, 84% were female, and 46% reported at least one cardiovascular risk factor. Subjects were followed for a mean of 4.9 (±1.6) years until death or censorship.63 (12%) participants died during the follow-up period. In bivariate analyses, depression was associated with an increased risk of death (HR=3.5 [95% CI 2.1, 5.8]).Worsening of GDS score by ≥2 points was also associated with an increased mortality risk (HR=2.5 [1.5, 4.2]).Controlling for covariates, both depression and an increase in GDS remained significant predictors of mortality (see Table). Interaction models showed men with depression had 5 times the risk of death compared to women with no depression.Men without depression also had a greater mortality risk than women with no depression after controlling for covariates.

Table 1. Depression and increase of depression proximal to death as a risk factor for death among individual with RA

		Hazard Ratio (95% CI)
Model 1	Baseline GDS< 5	(referent)
	Baseline GDS≥5	2.3 (1.4, 3.9)
Model 2	GDS increase < 2 points	(referent)
	GDS increase ≥ 2 points	1.9 (1.1, 3.3)
Model 3	Baseline GDS <5 Women (ref)	(referent)
	Baseline GDS ≥ 5 Women	2.5 (1.4, 4.6)
	Baseline GDS < 5 Men	3.1 (1.4, 6.5)
	Baseline GDS ≥5 Men	5.9 (2.7,13.1)
Model 4	GDS increase < 2 points Women (ref)	(referent)
	GDS increase ≥ 2 points Women	2.1 (1.1, 3.9)
	GDS increase < 2 points Men	3.0 (1.5, 6.0)
	GDS increase ≥ 2 points Men	5.1 (2.2,11.8)

All models controlled for age, disease duration, cardiovascular disease risk factors. Models 1 and 2 also controlled for gender.

Conclusion: Depression and increase in depressive symptoms are significant risk factors for all-cause mortality in RA.Men with either of these characteristics are particularly at risk. These findings provide additional evidence of the importance of identifying and treating depression among persons with RA.Strategies to motivate men for treatment of depression are especially needed.

Disclosure: C. Bode, None; **C. Tonner**, None; **L. Trupin**, None; **P. P. Katz**, None.

affection and indicate that CC chemokines should be further studied to clarify a role as biomarkers or novel therapeutic targets in JDM.

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Monocyte Chemoattractant Protein-1 and Eotaxin Are Associated with Parameters of Cardiac Dysfunction in Juvenile Dermatomyositis. Thomas Schwartz[1], Ivar Sjaastad[2], Berit Flatø[1], Maria Vistnes[1], Geir Christensen[1] and Helga Sanner[1]. [1]Institute for Clinical Medicine, University of Oslo, Oslo, Norway, [2]Institute for Experimental Medical Research, Oslo University Hospital, Oslo, Norway

Background/Purpose: Juvenile dermatomyositis (JDM) is a vasculopathic disease affecting not only skeletal muscle and skin, but other organs as well. Previously we have shown that JDM patients can have cardiac dysfunction (measured by E/e'). Considering the systemic nature of the disease, it is reasonable to believe that inflammation of the myocardium can occur, similar to what is seen in skeletal muscle. Increased abundance of pro-inflammatory cytokines has been shown in cardiac and rheumatic diseases. We examined associations between cytokine levels and cardiac parameters in patients with JDM and matched controls.

Methods: 54 JDM patients (estimated to represent the vast majority of known cases in Norway diagnosed from 1970–2006) were clinically examined, follow-up time median 16.8 years (range 2–38 years) after disease onset, and compared with 54 age- and sex-matched controls. Disease activity score (DAS) and myositis damage index (MDI) were assessed at follow-up by clinical examination and at 1 year post-diagnosis by chart review (DAS and MDI 1 year). Cytokines were analyzed by Luminex technology. Echocardiography with tissue Doppler was performed and analyzed blinded to patient information.

Results: Early diastolic tissue velocity (e') that reflects diastolic cardiac function, was lower in JDM patients than in controls (11.2 vs.12.6 cm/s, p=0.004), suggesting diastolic dysfunction in JDM. E' correlated with MDI 1 year, MDI at follow-up and DAS 1 year (rsp=0.46, rsp=0.59 and rsp=0.60, all p<0.001). Also, DAS 1 year predicted a low e' (diastolic dysfunction), at follow up after correcting for gender and age in a linear regression model (standardized β=0.38, p<0.001). In patients, the serum level of the two CC chemokines, monocyte chemoattractant protein-1 (MCP-1) and eotaxin, correlated with e' (rsp=0.65 and rsp=0.59, both p<0.001) (Figure). For MCP-1, association with e' was also present after adjusting for disease duration and gender in a linear regression model (standardized β=0.36, p=0.001). No correlations were seen between the two CC chemokines and systolic parameters. MCP-1 and eotaxin also correlated with diastolic blood pressure (rsp=0.46 and rsp=0.50 both p<0.001). In controls, the CC chemokines did not correlate with any echocardiographic or clinical parameters.
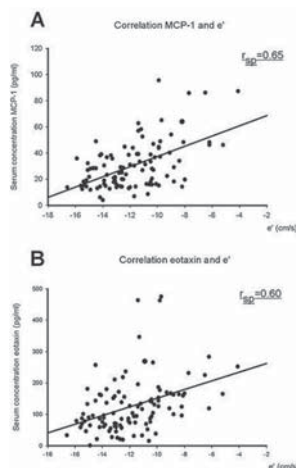
Figure.

Conclusion: Patients with JDM had subclinical diastolic dysfunction (measured by e') compared to controls, and those with sustained early disease activity seemed to be at risk later in life to develop diastolic dysfunction. Considering the correlation with e', MCP-1 and eotaxin might be involved in an inflammatory response in JDM, leading to myocardial fibrosis and subsequently diastolic dysfunction. The findings give new insight in the mechanism of myocardial

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Imbalance Between Histone Acetyl Transferase and Histone Deacteylase Activities and Modulation of HDAC Activity and Tnfa Production by HDAC Inhibitors in Patients with Ankylosing Spondylitis or Rheumatoid Arthritis. Eric Toussirot[1], Wasim Abbas[2], Kashif Aziz Khan[3], Marion Tissot[2], Alicia Jeudy[2], Lucile Baud[2], Ewa Bertolini[4], Daniel Wendling[5], Georges Herbein[6] and CIC Biotherapy[7]. [1]CIC Biotherapy 506 and Rheumatology and EA 4266 Pathogens and Inflammation, Besançon, France, [2]EA 4266 Pathogens and Inflammation, Besançon, France, [3]EA Pathogens and Inflammation, Besançon, France, [4]Rheumatology, Besançon, France, [5]Minjoz University Hospital, Besancon, France, [6]Virology and EA 4266 Pathogens and Inflamamtion, Besançon, France, [7]University Hospital, Besançon, France

Background/Purpose: TNFa is a major cytokine involved in conditions such as ankylosing spondylitis (AS) and rheumatoid arthritis (RA). Epigenetic regulation corresponds to different processes including modifications in histone proteins. These mechanisms regulate the transcription of genes coding for inflammatory cytokines such as TNFa. The acetylation of histone proteins (dependent on histone acetyl transferase-HAT-) promotes gene transcription while deacetylation (controlled by histone deacetylase) prevents this reaction. Limited data are available on HAT and HDAC activities in AS or RA. HDAC inhibitors (HDACi) are currently in development and may be of interest in modulating TNFa production in RA or AS.

Objectives: To determine the levels of HAT and HDAC activities in patients with AS or RA compared to healthy controls (HC) and to evaluate the *ex vivo* effects of HDACi (trichostatin A-TSA- and sirtinol -Sirt-) on HAT and HDAC activities and TNFa production by PBMC.

Methods: 21 patients with AS (New York criteria, 18 M, mean age ±SEM 44.3 ± 3.2 years, disease duration 14.1 ± 2.2 years), 52 patients with RA (ACR 1987 criteria, 16 M, mean age 56.9 ± 1.6, disease duration 11.3 ± 1.2) and 38 healthy controls (HC) (12 M, mean age: 34.6 ± 1.8) were evaluated.No patient received biologics. HAT and HDAC activities were assessed on nuclear extracts of PBMC isolated by Ficoll hypaque using a colorimetric assay (EpiQuick HAT Activity/inhibition Assay kit, and EpiQuick HDAC Activity/inhibition Assay kit, Epigentek). These activities were measured prior and after *ex vivo* treatment of PBMC by HDAC inhibitors. TNFa was evaluated in PBMC culture supernatants after 1 and 3 days (TNFalpha Quantikine ELISA kit, R&D Systems).

Results: HAT activity was decreased in patients with AS compared to HC (68.2 ± 8.1 *vs* 111.3 ± 15.5 ng/h/mg) (p= 0.05) while RA patients had increased HAT activity (126.8 ± 16.4 *vs* 111.3 ± 15.5 ng/h/mg; NS). Compared to HC, HDAC activity was decreased in both AS (p=0.01) andRA (NS) (HC vs AS *vs* RA: 4778.9 ± 752 *vs* 1984. 6 ± 249 *vs* 3915.9 ± 790 pmol/min/mg). No correlation was observed between clinical disease assessment in RA or AS and HAT or HDAC activity. *Ex vivo* addition of TSA or Sirt to PBMC reduced HDAC activity by 51.1% in HC and by 37.7% in RA but had no effect in AS.HAT activity was not modulated by HDACi. TNFa production by PBMC was down regulated by the addition of TSA or Sirt to cell culture in HC and RA but this regulation was only obtained with Sirt in PBMC culture from patients with AS.

Conclusion: HAT and HDAC activities are dysregulated in AS and RA with a balance between HDAC and HAT favoring HAT activity and promoting gene transcription. *Ex vivo* treatment of PBMC by HDAC inhibitors may regulate HDAC activity and TNFa production especially in HC and RA but seems less effective in AS.

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TNFα Induces Sustained Signaling and a Prolonged and Unremitting Inflammatory Response in Synovial Fibroblasts. Angela Lee, Galina Grigoriev, Janice Chen, Lionel B. Ivashkiv and George D. Kalliolias. Hospital for Special Surgery, New York, NY

Background/Purpose: The non resolving character of synovial inflammation in rheumatoid arthritis (RA) is a conundrum. To identify the

contribution of fibroblast-like synoviocytes (FLS) to the perpetuation of synovitis, we investigated the molecular mechanisms that govern the TNFa-driven inflammatory program in human FLS.

Methods: FLS obtained from synovial tissues of patients with RA or osteoarthritis were stimulated with TNFa and assayed for gene expression and cytokine production by qPCR and ELISA. NF-kB signaling and chromatin accessibility were evaluated using Western blotting and restriction enzyme accessibility (REA) assays.

Results: In FLS, TNFa induced prolonged transcription of *IL-6* and progressive accumulation of IL-6 protein over four days (Figure 1A). Similarly, induction of IL-8, CCL5, MMP1 and MMP3 mRNA, after TNFa stimulation, was sustained for several days (data not shown). This contrasted with the macrophage response to TNFa, which characteristically involved a transient increase in the expression of pro-inflammatory genes (Figure 1B). In FLS, TNFa induced prolonged activation of NF-kB signaling (Figure 2A) and a sustained increase in chromatin accessibility at the *IL-6* promoter (Figure 2B).Furthermore, FLS expressed low levels of the feedback inhibitors ABIN3, IRAK-M, ATF3 and SOCS3 that terminate inflammatory responses in macrophages (Figure 3).
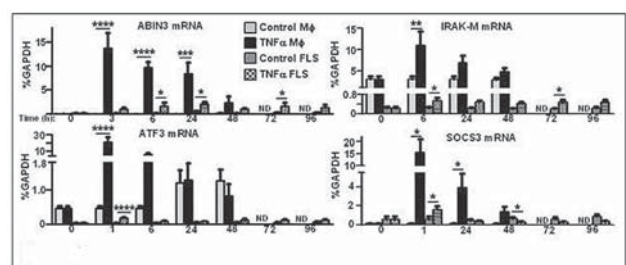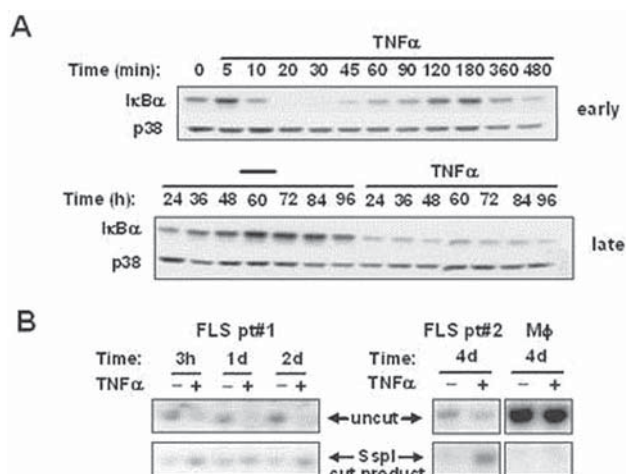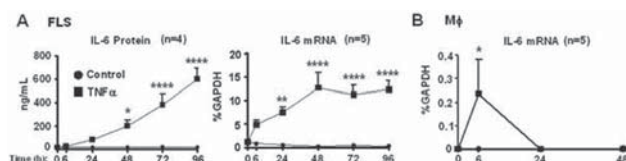
Conclusion: TNFa signaling is not effectively terminated in FLS, leading to an uncontrolled inflammatory response. The results suggest that prolonged and sustained inflammatory responses by FLS, in response to synovial TNFa, contribute to the persistence of synovial inflammation in RA.

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Discovery of Pharmacologic MIF Antagonists by Structure-Based Molecular Design. William L. Jorgensen[1], Alissa A. Hare[1], Zoe Cournia[1], Sunilkumar Gandavadi[1]. Xin Du[1], Lin Leng[1] and Richard J. Bucala[2], [1]Yale University, New Haven, CT, [2]Yale University School of Med, New Haven, CT

Background/Purpose: Cytokine inhibition is becoming a mainstay for the therapy of autoimmunity but current antibody-based approaches remain limited by high cost, parenteral administration, and anti-idiotype responses. Orally available, small molecules offer considerable advantages, yet the discovery of molecules that effectively disrupt the molecular interactions between cytokines and their receptors remains to be achieved. Macrophage migration inhibitory factor (MIF) is an attractive drug target because of its genetic association with autoimmunity and its role in counter-regulating glucocorticoid immunosuppression. The discovery of the MIF receptor (CD74) together with X-ray crystallography of MIF has enabled structure-based design using ligand docking, moleculegrowing computational methodologies, and receptor binding assessment. By this approach, we are pursuing the discovery of potent and selective MIF antagonists with auspicious pharmacologic properties.

Methods: Utilizing a high resolution MIF crystal structure, virtual screening was performed by docking 2.1 million compounds into the MIF tautomerization site, which was judged to interface with the MIF receptor. Validation by in vitro functional analyses revealed novel compounds with μM inhibitory activity in several molecular series. Structure optimization was pursued by synthesis of substituted benzoxazol-2-ones and MIF receptor binding, MIF ligand selectivity, and MIF-dependent signal transduction evaluated in vitro.

Results: Binding analysis of MIF interaction with the MIF receptor ectodomain revealed 11 novel compounds with IC50s in the μM range. Beginning with a 1 μM candidate, substituted benzoxazol-2-ones were discovered with IC50 values as low as 80 nM for MIF receptor antagonism. One such molecule: 3-(3-hydroxybenzyl)-5-methylbenzo[**d**]oxazol-2(3**H**)-one (Debio 1036) was evaluated more closely and functional inhibition established in synovial fibroblasts for MIF-dependent ERK1/2 phosphorylation (IC50=5 nM) and invasive phenotype. Debio 1036 also was 1000-fold more selective for MIF than for its close structural homolog, DDT (MIF-2).

Conclusion: Several highly potent, small molecule MIF receptor antagonists have been identified by a combination of structure-based molecular design and functional analysis. Compounds with oral bioavailability and auspicious pharmacologic properties are anticipated to provide promising candidates for the treatment of human autoimmunity.

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Xanthine Oxidase-Derived ROS Direct Context-Dependent Action of NFAT5 Toward Inflammatory Response in Macrophages. Nam Hoon Kim. Catholic university of Korea, Seoul of Korea, Seoul, South Korea

Background/Purpose: NFAT5, a well known osmo-protective factor, can be activated by isotonic stimuli, such as Toll-like receptor (TLR) triggering. Here, we identified a novel signal pathway activated in macrophages upon TLR ligation.

Methods: We demonstrated that high salt and TLR ligation activate distinct sets of downstream target genes in a NFAT5-dependent manner. While ROS are essential for this, their source differs depending on the context; mitochondria for high salt and xanthine oxidase for TLR. The two pathways are mutually suppressive. Moreover, the xanthine oxidase-NFAT5 pathway is required for TLR-mediated inflammatory arthritis, inducing the proinflammatory cytokine production.

Results: we identified a novel xanthine oxidase- reactive oxygen species (ROS)-p38-NFAT5 pathway activated in macrophages upon TLR ligation.

Conclusion: Together, xanthine oxidase-derived ROS function as molecular sensors to discriminate TLR ligation from osmotic stimulus in macrophages, directing NFAT5 action toward innate immunity.

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Aberrant Expression of BAFF Receptor (BR3) in Peripheral Monocytes of Patients with Primary Sjögren's Syndrome Impacts Abnormal Activation of BAFF Signaling Through IKK-Alphaand IKK-Beta. Keiko Yoshimoto[1], Maiko Tanaka[1], Masako Kojima[1], Hideko Ogata[1], Hideto Kameda[1], Katsuya Suzuki[1], Tohru Abe[2] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Saitama Medical School, Kawagoe-shi Saitama, Japan

Background/Purpose: B cell activating factor belonging to the TNF superfamily (BAFF) regulates proliferation, differentiation and survival of B cells and plays a pivotal role in the pathogenesis of autoimmune diseases such as primary Sjögren's syndrome (pSS). BAFF is a ligand for three TNF-receptor family members; i.e., BAFF receptor (BR3), TACI and BCMA. Several lines of evidence demonstrate that BR3 is the receptor that mediates BAFF-dependent B cell biology and that BAFF activates alternative NF-kB signaling in B cells. However, the regulatory mechanisms of BAFF signaling in other immune cells, such as monocytes, are not well understood. In our previous study, we revealed that BAFF induced robust increase in the production of IL-6 by pSS monocytes. We also found that the expression levels of BR3 and several transcription factors such as NF-IL-6 and NF-kB2 were enhanced in pSS monocytes compared to normal monocytes. These data suggest that BAFF signaling is abnormal in pSS monocytes. The purpose of the present study is to elucidate these possible abnormalities.

Methods: Whole blood was prepared from pSS patients and age-matched normal individuals, and the expression level of BR3 on monocytes was analyzed by FACS. Peripheral monocytes were stimulated in vitro with soluble BAFF (sBAFF), and the production of IL-6 by the cells was measured by ELISA. The expression levels of IKK-alpha and IKK-beta, which are involved in NF-kB pathways, were analyzed by western blotting analysis.

Results: In accordance with our previous findings with quantitative PCR, FACS analysis showed that the expression level of BR3 was significantly elevated in pSS monocytes compared to normal monocytes.Interestingly, the expression level of BR3 on monocytes was positively correlated with the amount of IL-6 produced by pSS monocytes triggered by sBAFF. When the monocytes were cultured with sBAFF in the presence of NF-kB activation inhibitor, the production of IL-6 by the cells was strongly suppressed in a dose-dependent manner. In addition, phosphorylation level of IKK-alpha was elevated in pSS monocytes compared to normal monocytes without stimulation, whereas that of IKK-beta was not significantly different between pSS and normal monocytes. Moreover, phosphorylation levels of IKK-alpha and IKK-beta in the monocytes were enhanced upon stimulation with sBAFF.

Conclusion: BAFF acts through BR3 to activate the expression of the IL-6, and that IKK-alpha and IKK-beta are involved in the signal transduction pathway triggered by sBAFF.

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Differential Regulation of Cytokines by Extracellular-Signal Regulated Kinase and c-Jun N-Terminal Kinase in Map Kinase Kinase-3 and -6 Deficiency. Deepa Hammaker, Katharyn Topolewski, Monica Guma, David L. Boyle and Gary S. Firestein. UCSD School of Medicine, La Jolla, CA

Background/Purpose: p38 inhibitors have limited efficacy in rheumatoid arthritis (RA), possibly because p38 blockade suppresses IL-10 production and increases JNK and ERK phosphorylation in macrophages. This positive feedback mechanism elevates IL-6 levels and decreases IL-10 production. In contrast, bone marrow derived macrophages (BMDM) deficient in upstream p38 regulators (MKK3 or MKK6) have normal ERK and JNK responses and near normal IL-10 gene expression. The goals of this study were (1) to determine if dual ERK and JNK inhibition avoids reflex increases in pro-inflammatory cytokine expression and (2) to dissect the mechanisms of IL-10 regulation in MKK-deficient and p38 inhibitor treated BMDM.

Methods: Bone marrow derived macrophages from wild type (WT), MKK3−/− and MKK6−/− mice were pre-treated with p38 inhibitor SB203580 (SB), JNK inhibitor SP600125 (SP) and/or ERK inhibitor PD98059 (PD) and stimulated with LPS. Supernatant IL-6 and IL-10 levels were measured by immunoassay. IL-10 mRNA half-life was measured using LPS-stimulated BMDM treated with actinomycin D and qPCR. IL-10 promoter activity was determined in BMDM transfected with a mouse IL-10 promoter luciferase construct and normalized to a Renilla construct.

Results: We evaluated the role of JNK and ERK in BMDM IL-6 and IL-10 production. SB increased IL-6 production induced by LPS while SP and PD significantly reduced IL-6 levels in WT, MKK3−/−, and MKK6−/− cells (Figure 1, SP % inhibition: WT (91±1%), MKK6−/− (81±8%), and MKK3−/− (84±4%, n=3/group, p<0.008) (PD % inhibition: WT (85±3%), MKK6−/− (65±3%), and MKK3−/− (65±1%, n=3, p<0.02). SP or PD alone or in combination with SB reduced IL-6production, indicating that blocking JNK and/or ERK overcame thepro-inflammatory effect of p38 inhibition.IL-10 levels were significantly reduced by SB in WTBMDM (62±9%), MKK6−/− (62±6%), and MKK3−/− (57±4%) (n=3/group, p<0.034). SP also inhibited IL-10 levels while PD had no effect. Surprisingly, the combination of SB and SP prevented the p38-mediated reduction in IL-10 production suggesting that JNK and p38 pathways have opposing effects on this cytokine. We then looked at the effect of SB and MKK-deficiency on IL-10 promoter activity in BMDM treated with LPS. IL-10 promoter activity in WT cells was reduced by 43±6% by SB (n=3/group, p=0.02). However, MKK3- and MKK6-deficient cells had normal promoter activity, indicating that IL-10 transcription is not impaired in MKK-deficient cells. IL-10 mRNA half-life was unaffected by MKK-deficiency or SB-treatment in LPS-stimulated BMDM.
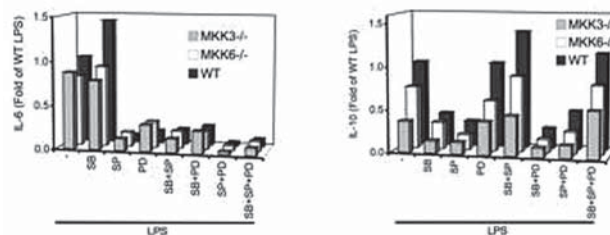
Conclusion: Increased JNK and ERK activation, along with suppressed IL-10 production contribute to the pro-inflammatory effects of p38 inhibition in BMDM. Combining a p38 inhibitor with a JNK inhibitor might be more effective than a selective p38 inhibitor by preserving anti-inflammatory responses and blocking the reflex pro-inflammatory response.

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Fucosyltransferase 1 (fut1) Is Overexpressed in Rheumatoid Arthritis Synovial Tissue and Modifies Cytokine Production. Takeo Isozaki[1], Jeffrey H. Ruth[1], M. Asif Amin[1], Phillip L. Campbell[1], Steven E. Domino[1], G. Kenneth Haines III[2] and Alisa E. Koch[3]. [1]University of Michigan, Ann Arbor, MI, [2]Yale University, New Haven, CT, [3]University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: Rheumatoid arthritis (RA) is a systemic auto-immune disease characterized by inflammation and joint destruction. Angiogenesis and cytokine production are involved in the pathogenesis of RA. We have shown that soluble H and Lewis[y] antigens are mediators of angiogenesis and are upregulated in the RA joints compared to normal (NL) or osteoar-thritis (OA) joints. Fucosyltranseferase 1 (fut1) is an $\alpha(1,2)$-fucosyltransferase responsible for synthesis of the H blood group and Lewis[y] antigens. However, a direct role for fut1 in RA has not been demonstrated. In this study, we examined the expression of fut1 in RA synovial tissue (ST) and deter-minedthe functional consequences of fut1 expression.

Methods: Fut1 expression was determined in RA, OA and NL ST samples by immunohistological staining. To determine whether fut1 was expressed by the human microvascular endothelial cell line (HMEC-1) and human dermal microvascular endothelial cells (HMVECs), real time poly-merase chain reaction (RT-PCR) was performed. To block the expression of fut1, HMEC-1s and HMVECs were transfected with fut1 sense or antisense oligonucleotides (ODNs). After treatment, cells were stimulated with interleukin-1β (IL-1β), IL-17 or phorbol 12-myristate 13-acetate (PMA) to stimulate cytokine expression. We examined monocyte chemotactic protein (MCP)-1/CCL2 expression as this chemokine has been shown to be decreased in mouse KRN arthritis induced fut1 knockout joints. We also examined angiogenic vascular endothelial growth factor (VEGF) and regulated upon activation and normal T-cell expressed, and secreted (RANTES)/CCL5 expression, as these cytokines have been shown to be important in RA pathogenesis. In addition, we isolated endothelial cells (ECs) from wild type (wt) and fut1 knockout mice. To confirm the role of fut1 in angiogenesis, we

performed EC chemotaxis using wt and fut1 knockout ECs in modified Boyden chambers.

Results: RA STs contained a greater percentage of fut1 ECs than did OA or NL STs [mean ± SEM; RA ST (n=18) 34 ± 8%; OA ST (n=18) 14 ± 6% and NL ST (n=18) 11 ± 4%, p<0.05 between RA ST and OA ST; RA ST and NL ST]. To determine if fut1 expression was inducible by inflammatory cytokines, we stimulated ECs with IL-1β and found that fut1 messenger RNA (mRNA) was IL-1β inducible in HMEC-1s and HMVECs.Fut1 antisense ODN transfected HMEC-1s and HMVECs had significantly decreased expression of MCP-1/CCL2 and RANTES/CCL5 compared to fut1 sense ODN transfected cells stimulated withIL-1β, IL-17 or PMA at the mRNA and protein levels (p<0.05). Fut1 knockout mouse ECs stimulated with IL-1β expressed less VEGF mRNA than wt ECs (p<0.05). These results indicate that fut1 regulates EC expression of cytokines important in RA pathogenesis. Finally, fut1 knockout mouse ECs had decreased migration to VEGF compared with wt mouse ECs (10 ± 1 vs. 16 ± 1 cells migrated, n=6 experiments, p<0.05).

Conclusion: These data show that fut1 is overexpressed in RA ST, and that by blocking fut1 expression, we can modify the production of many proinflammatory cytokines. In addition, we show that fut1 regulates EC migration, a facet of angiogenesis in response to VEGF. Hence, fut1 may be an important new target for RA therapy.

Disclosure: **T. Isozaki**, None; **J. H. Ruth**, None; **M. A. Amin**, None; **P. L. Campbell**, None; **S. E. Domino**, None; **G. K. Haines III**, None; **A. E. Koch**, None.

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Interferon Regulatory Factor 8 Regulates BAFF Production in Murine Macrophages and Is a Nexus for Cross Talk Between IFN-γ and TGF-β.
Weijia Yuan, Sanjay Gupta, Jane E. Salmon and Alessandra B. Pernis. Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

Background/Purpose: Lupus is a systemic autoimmune disease that can lead to severe end-organ damage characterized by unabated inflammation and aberrant tissue repair. Macrophage dysregulation plays a key role in mediating this tissue damage. Interferon regulatory factor 8 (IRF8) is a crucial controller of macrophage function and has been identified as a susceptibility locus for lupus. The cellular pathways regulated by IRF8 may be important in tissue damage in lupus. IRF8 is known to mediate macrophage activation in response to IFN-γ.Infiltrating macrophages stimulated by IFN-γ produce B-cell activating factor (BAFF) which may perpetuate local immune responses. TGF-β, a cytokine linked to tissue repair via Rho-kinase (ROCK), can augment BAFF production. Here we use the regulation of BAFF as a model to dissect the cross talk between IFN-γ and TGF-β and identify a novel and crucial role for IRF8 in this process.

Methods: Bone marrow derived macrophages (BMDM) were stimulated with IFN-γ and/or TGF-β. In selected experiments a ROCK inhibitor, Y-27632, was added. Cytokine production was evaluated by ELISA and/or by qPCR. ROCK activity was assessed by in vitro kinase assay. Chromatin immunoprecipitation (ChIP) assays were performed to determine the binding of IRF8 to the BAFF promoter.

Results: TGF-β augmented IFN-γ-induced BAFF production in BMDM (untreated: 24 ± 5 pg/ml, IFN-γ: 508 ± 181, TGF-β: 57 ± 13, IFN-γ + TGF-β: 990 ± 291, n=5, $p<0.01$). This amplification was specific for BAFF and was not seen when TNF-α or CTGF was examined. IFN-γ increased the expression of IRF8, which was not further increased by the addition of TGF-β. In the absence of IRF8, BAFF production by macrophages was markedly diminished (C57/B6 IFN-γ: 505 ± 207 pg/ml, IRF8 KO IFN-γ: 17 ± 10, n=4, $p<0.02$; C57/B6 IFN-γ + TGF-β: 867 ± 336, IRF8 KO IFN-γ + TGF-β: 14 ± 6, n=4,$p<0.02$). IRF8 KO BMDM exhibited normal differentiation and maintained the capacity to upregulate CTGF in response to TGF-β. In line with these results, we found that IRF8 directly binds to the BAFF promoter upon IFN-γ stimulation. Interestingly, the binding of IRF8 to the BAFF promoter was augmented by the concomitant addition of TGF-β. Given that TGF-β did not change the expression of IRF8, we explored the possibility that TGF-β could modulate IRF8 function by post-translational mechanisms. TGF-β, but not IFN-γ, activated the serine-threonine kinases ROCK1 and ROCK2 in BMDM. ROCK inhibitor Y-27632 decreased BAFF production by BMDM stimulated with IFN-γ and TGF-β and diminished the binding of IRF8 to the BAFF promoter.

Conclusion: We have shown that IRF8 is a critical regulator of BAFF production in BMDM. Our data indicate that while IFN-γ increases IRF8 expression, TGF-β may modulate its function via ROCK activation. We speculate that activated ROCK phosphorylates IRF8 and that increased binding of phosphorylated IRF8 to the BAFF promoter leads to the enhanced

BAFF production when macrophages are simultaneously exposed to IFN-γ and TGF-β. The pathways that mediate the cross talk between IFN-γ and TGF-β uncovered by this study identify novel processes that could lead to aberrant macrophage function in chronic inflammatory state and define new targets to ameliorate tissue damage in SLE.

Disclosure: **W. Yuan**, None; **S. Gupta**, None; **J. E. Salmon**, None; **A. B. Pernis**, None.

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Microrna-155 Regulates Chemokines and Chemokine Receptors in Rheumatoid Arthritis Monocyte.
Aziza Elmesmari, Derek S. Gilchrist, Alasdair R. Fraser, Diane Vaughan, Ross McQueenie, Gerard J. Graham, James Brewer, Iain B. McInnes and Mariola Kurowska-Stolarska. Institute of Infection,Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) is characterized by synovial tissue inflammation leading to joint destruction. Monocytes/macrophages are major effector cells in RA synovitis, principally by releasing TNF-α, IL-6 and other inflammatory cytokines and chemokines. MicroRNAs are a recently discovered class of post-transcriptional regulators –in particular miR-155 is upregulated in RA synovial macrophages where it regulates cytokine expression. We hypothesized that miR-155 regulates migration of monocytes by modulating the chemokine and chemokine receptor system.

Methods: Peripheral blood (PB) was obtained from healthy controls and RA patients who met the 2010 ACR/EULAR diagnostic criteria. Purified CD14+ PB monocytes obtained by magnetic bead isolation were transfected with miR-155 mimic or scrambled mimic using an N-TER nanoparticle system. Taqman Low Density Array and Luminex multiplex assay was used to evaluate chemokine receptor gene expression and chemokine production, respectively. Absolute copy numbers of miR-155 transcripts in PB and SF monocytes of RA and healthy controls were assessed by QPCR. The role of mir155 was investigated further using bone marrow monocytes (BMM) from miR-155$^{-/-}$and WT mice.

Results: RA PB and SF macrophages showed higher copy number of miR-155 compared with healthy controls. Overexpression of miR-155 induced the production of chemokines CCL4, CCL5, CCL8 and CCL22 in RA monocytes and CCL3 in both RA and healthy controls. However, overexpression of miR-155 in healthy control and RA monocytes did not affect the production of CCL2, CCL7, CCL21, CXCL5, CXCL8, CXCL7, CXCL10 and CX$_3$CL1. Analysis of chemokine receptors in BMM of miR-155$^{-/-}$ and WT mice revealed significantly higher levels of CCR1, CCR2, CCR5 and CXCR4 in miR-155 deficient cells suggesting that miR-155 can act as a negative regulator of these receptors in homeostatic state. TLR-4 ligand significantly suppressed expression of these receptors in both WT and miR-155$^{-/-}$cells. Analysis of 3'UTRs of chemokine and chemokine receptor (TargetScan) suggests that miR-155 likely interferes with signaling pathways implicated in chemokine and chemokine receptor system expression.

Conclusion: Deregulation of miR-155 in RA monocytes can contribute to the production of pro-inflammatory chemokines by these cells and to their accumulation at sites of inflammation.

Disclosure: **A. Elmesmari**, None; **D. S. Gilchrist**, None; **A. R. Fraser**, None; **D. Vaughan**, None; **R. McQueenie**, None; **G. J. Graham**, None; **J. Brewer**, None; **I. B. McInnes**, None; **M. Kurowska-Stolarska**, None.

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Anti-Inflammatory Effects of Phosphodiesterase 4 Inhibition Are Mediated by Mitogen-Activated Protein Kinase Phosphatase-1.
Riku Korhonen, Tuija Hömmö, Mirka Laavola, Tiina Keränen, Mari Hämäläinen and Eeva Moilanen. University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland

Background/Purpose: MAP kinase phosphatase-1 (MKP-1) is a nuclear tyrosine/threonine phosphatase that limits p38 MAP kinase activity. MKP-1 KO mice display excessive inflammatory response, and exhibit increased disease severity and more extensive bone destruction in experimental arthritis models. Anti-inflammatory effects of glucocorticoids are partly mediated by increased MKP-1 expression. Phosphodiesterase (PDE) 4 is expressed in several inflammatory and immune cells, and it hydrolyzes cAMP to 5'AMP down-regulating cAMP signalling in cells. PDE4 inhibitors are under investigation for treatment of arthritis, and they have already entered the clinics in the treatment of COPD as an anti-inflammatory remedy. In the present study,

we found that a PDE4 inhibitor rolipram enhanced MKP-1 expression which was involved in the anti-inflammatory effects of rolipram.

Methods: The effect of MKP-1 and a PDE4 inhibitor rolipram on inflammatory gene expression was investigated in mouse J774 and human THP-1 macrophage cell lines, and in primary mouse peritoneal macrophages (PM) from wild-type (WT) and MKP-1(–/–) mice. In cell lines, MKP-1 expression was silenced by siRNA. We also investigated the effect of rolipram on carrageenan-induced paw inflammation in WT and MKP-1(–/–) mice.

Results: TNF and IL-6 production was increased in macrophages with impaired MKP-1 (that is in cells transfected with MKP-1 siRNA or macrophages from MKP-1 KO mice), and it was related to increased p38 MAP kinase phosphorylation. p38 MAP kinase phosphorylation was inhibited by rolipram and by a cAMP analog 8-Br-cAMP. LPS-induced MKP-1 expression was enhanced by rolipram, by a non-selective PDE inhibitor IBMX and by 8-Br-cAMP in J774 and THP-1 cells and in PMs. Rolipram, IBMX and 8-Br-cAMP also inhibited TNF production in J774 and THP-1 cells. p38 MAP kinase inhibitor BIRB 796 inhibited TNF production in macrophages, as expected. Rolipram inhibited TNF production in PMs from WT mice (63% inhibition) but, interestingly, the inhibition of TNF production by rolipram was greatly attenuated (27% inhibition) in PMs from MKP-1(–/–) mice. Furthermore, rolipram attenuated carrageenan-induced paw inflammation in WT but not in MKP-1(–/–) mice.

Conclusion: The results showed that a PDE4 inhibitor rolipram suppressed p38 MAP kinase pathway, and inhibited TNF production and carrageenan-induced inflammation, and these effects were mediated by MKP-1. The results suggest that the anti-inflammatory effects of PDE4 inhibitors are, at least partly, mediated by MKP-1. The findings emphasize MKP-1 as a potential mediator of anti-inflammatory drug effects. Compounds that enhance MKP-1 expression and/or MKP-1 activity hold potential as novel anti-inflammatory drugs.

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Role of Phospholipase D1 (PLD1) in the Expression of Proinflammatory Genes in Rheumatoid Arthritis Synovial Fibroblasts (RASF). Sean C. Friday[1] and David A. Fox[2]. [1]The University of Michigan, Ann Arbor, MI, [2]Univ of Michigan Med Ctr, Ann Arbor, MI

Background/Purpose: Interleukin-17 (IL-17) and Tumor Necrosis Factor alpha ((TNFa), when co-applied to RASF, induce synergistic expression of proinflammatory genes such as IL-6 and IL-8.Work from our laboratory using co-cultures of cytokine-activated T cells and RASF has demonstrated that this synergy is largely contact-dependent (Tran et al., 2007).Recently, Hot et al (2011) showed that PLD1 mRNA was similarly upregulated by IL-17A and the less potent IL-17F in RASF.Another recent report (Sethu et al., 2010), used a mouse model of peritonitis to show that blocking PLD1 mitigates TNFa-driven inflammation *in vivo*. In light of these observations, we sought to examine the potential role of PLD1 in pro-inflammatory gene expression by RASF stimulated with IL-17A and/or TNFa.

Methods: We used quantitative real-time PCR to characterize the cytokine-mediated effects on mRNA levels for a cluster of genes encoding cytokines, chemokines, and tissue remodeling enzymes important in the pathogenesis of RA.Also, secretion of IL-6, IL-8, and CCL20 was measured by ELISA.To investigate the relevance of PLD1 activity, we added various concentrations of the PLD1 inhibitor 1-butanol, knocked down PLD1 expression with siRNA, and used the two approaches together.

Results: PLD1 mRNA was weakly induced by IL-17 and/or TNFa (<2-fold increase).1-butanol had complex effects on cytokine-induced target gene mRNA expression, in a manner that was dose-dependent and biphasic for all targets except ICAM1, IL-8, and MMP-14.Compared with the 10 other targets studied, including PLD1 itself, ICAM1 mRNA expression showed the least sensitivity to treatment with 1-butanol.When RASF were transfected with PLD1-specific siRNA, there was an effect on induction of mRNA and secreted protein, particularly for induction of IL-6, IL-8, and CCL20 when IL-17 was co-applied with TNFa.Effects on mRNA and secreted protein were not always positively correlated.For example, interference with PLD1 activity resulted in increased CCL20 mRNA, but inhibited CCL20 secretion. Effects of PLD1 knockdown were in part distinct from effects of 1-butanol.

Conclusion: PLD1 might be an important modulatory target for reducing cytokine-evoked expression of proinflammatory genes by RASF, because it exhibits gene-specific effects on mRNA levels and effects on efficacy of regulated secretion/exocytosis.Stability of mRNAs and modulation of tran-

scription efficiency are likely mechanisms by which PLD1 affects cytokine-induced expression of proinflammatory genes.The effects of 1-butanol may reflect inhibition of not only PLD1 but also PLD2 and possibly other enzymes.

Disclosure: **S. C. Friday**, Johnson & Johnson, 2; **D. A. Fox**, None.

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Receptor Activator of Nuclear Factor ÊB Ligand-Mediated Osteoclastogenesis Is Augmented by Interleukin-1â Via up-Regulation of Endoplasmic Reticulum Stress Signals. Myong-Joo Hong[1], Myung-Soon Sung[1], Eun-Gyeong Lee[1], Yoon Kyung Hong[1], Chang-Hoon Lee[2], Myeung Su Lee[3] and Wan-Hee Yoo[1]. [1]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [3]Reumatology, Iksan, Chonbuk, South Korea

Background/Purpose: Interleukin-1β (IL-1β) and thapsigargin (TG)-augmented endoplasmic reticulum (ER) stress modulate the receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated osteoclastogenesis. However, the mechanism by which IL-1β and TG affect osteoclastogenesis remains elusive. Thus, we investigated the relationships between RANKL-mediated osteoclast specific pathways and ER stress relevant signals in osteoclast differentiation of bone marrow-derived cells.

Methods: Bone marrow cells (BMCs) were obtained from 5-week-old male ICR mice. The cells were cultured to be differentiated into osteoclasts with macrophage-colony stimulating factor (M-CSF) and RANKL in the presence or absence of IL-1β, thapsigargin (TG, ER stress inducer), or 4-phenylbutyric acid (PBA, ER stress inhibitor). The formation of osteoclasts was evaluated by tartrate-resistant acid phosphatase (TRAP) staining and resorption pit assay with dentine slice. The molecular mechanisms of IL-1β and ER stress in osteoclastogenesis of BMCs were investigated using reverse transcription-polymerase chain reaction (RT-PCR) and immunoblotting. Osteoclast specific and ER stress relevant signaling molecules were analyzed. Transfections of small interfering RNA (siRNA) for glucose-regulated protein 78 (GRP78), protein kinase RNA-like ER kinase (PERK) and inositol-requiring enzyme 1 (IRE1) were performed to knockdown ER stress initiating signals to verify the relationships between osteoclast specific pathways and ER stress signals.

Results: The formation of osteoclasts was increased by IL-1β and TG augmented ER stress. PBA significantly inhibited IL-1β and TG induced osteoclats formation. The expressions of osteoclast specific pathways such as c-Fos and NFATc1, and ER stress associated signals such as PERK, IRE1, GRP78, and eIF2α were significantly increased by IL-1β and TG which was inhibited by PBA. Inhibition of ER stress initiating signals by siRNA inhibited the expression of above mentioned osteoclast specific signals, thus reduced IL-1β and/or TG-induced osteoclastogenesis.

Conclusion: IL-1β and/or TG-augmented ER stress significantly increased osteoclast formation which was inhibited by PBA. The mechanisms were mainly associated with up-regulation of ER stress signals such as GRP78, PERK, p-eIF2α and IRE1. Thus the modulation of ER stress signals affecting osteoclast formation might be a new therapeutic strategy to prevent inflammatory and destructive arthritis diseases such as rheumatoid arthritis (RA) and diverse osteoporotic diseases.

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Interferon α and Self-Organized Criticality Theory. Shunichi Shiozawa[1], Yumi Miyazaki[2] and Ken Tsumiyama[1]. [1]Kyushu University Beppu Hospital, Beppu, Japan, [2]Kyushu University Beppu Hospital/ Kobe University Graduate School of Health Sciences, Beppu/ Kobe, Japan

Background/Purpose: One of the biggest obstacle we face in elucidating the pathogenesis of autoimmunity today is the mechanism how autoreactive lymphocyte clones could survive or emerge beyond the firewall called 'forbidden clone' of Burnet. We have proposed that autoreactive clones emerge *via de novo* T cell receptor (TCR) revision from thymus-passed non-autoreactive clones at periphery, and we named this T cell as autoantibody-inducing CD4 (*ai*CD4) T cell (Tsumiyama K *et al*. PLoS ONE 4(12):e8382, 2009). Our novel 'self-organized criticality theory' explains that systemic autoimmunity or systemic lupus erytematosus (SLE) necessarily

takes place when host's immune system is overdriven by repeated exposure to antigen to levels that surpass the immune system's stability-limit, i.e., self-organized criticality. This *ai*CD4 T cells not only induced varieties of autoantibodies but also helped final maturation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce tissue injuries identical to SLE. We here examine the role of interferon α (IFNα) in relation to the *ai*CD4 T cell.

Methods: BALB/c mice were repeatedly immunized with ovalbumin (OVA), keyhole limpet hemocyanin (KLH) or staphylococcal enterotoxin B (SEB), and sera and tissues were examined using ELISA, immunohistopathogy, PCR, southern blotting and flow cytometry. Because IFNα transgenic (Tg) mice are basically infertile, we adopted a Tet-off expression system. Mouse IFNa1 (mIFNα)cDNA integrated under TetOp promoter (TetOp-mIFNα) was microinjected into fertilized eggs of C57BL/6 to obtain TetOp-mIFNα Tg mice. They were mated with EμSR-tTA Tg mice under the control of IgH chain enhancer/SRα promoter (EμSR-tTA) to obtain double Tg TetOp-mIFNα/EμSR-tTA mice. IFNα was inducible 12 weeks after doxycycline cessation.

Results: Repeated immunization with antigen caused lesions identical to SLE including anti-dsDNA and anti-Sm autoantibodies in the mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of CD4 T cells led to the development of *ai*CD4 T cell which had undergone TCR revision and was capable of inducing autoantibodies and overdriving CD8 T cell to become CTL *via* antigen cross-presentation leading to tissue injuries identical to SLE. However, in the IFNα Tg mice, the lesions identical to SLE just except for anti-Sm antibody were induced by solely increasing IFNα. Pathological lesions included IC-deposited glomerulonephritis, alopecia, epidermal liquefaction and positive skin lupus-band test and splenic onion-skin lesion. The IFNγ^+ activated CD4 and CD8 T cells with effector phenotype (CTL) and activated CD3$^+$CD4$^-$CD8$^-$ double negative (DN) T cell pathognomonic for SLE were increased. This DN T cell not only infiltrated to glomeruli, but also induced *de novo* glomerulonephritis and alopecia upon transfer to naïve mice.

Conclusion: IFNα causes SLE. However, IFNα does not represent the whole picture of SLE and thus, antigen induced mechanism, i.e., 'self-organized criticality theory', was discussed in relation to *ai*CD4 T cell and a classical DN T cell.

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Association Between Neutrophil Gene Signature and Disease Characteristics in Systemic Lupus Erythematosus Patients. Michelle Petri[1], Hong Fang[1], Jadwiga Bienkowska[2], Norm Allaire[2], Jeff Browning[2] and Susan Kalled[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA

Background/Purpose: Neutrophils and neutrophil death ("netosis") are now understood to play a role in the pathogenesis of SLE. A neutrophil gene signature exists in SLE, although its association with the clinical phenotype is unknown.

Methods: A total of 292 SLE patients were included in the analysis. Among these patients, 91.1% were female; 58.9% were Caucasian, 33.9% were African-American, and 7.2% were other ethnicities. Mean age (standard deviation) at baseline was 46.0 ($\pm$11.9) years. Neutrophil gene expression was high (>6) in 31.9% (N=93), medium (5–6) in 31.5% (N=92), and low (<5) in 36.6% (N=107) of patients.

Results: The neutrophil gene signature was more common in Caucasians (p=0.045). The neutrophil gene signature is strongly associated with same day disease activity, serologies (anti-dsDNA and low complements), and need for prednisone. It is also strongly associated with poor outcomes (myocardial infarction, deep venous thrombosis, diabetes, malignancy).

Table 1. Association between Same-day Visit Disease Activity and Neutrophil Gene Signature

Variable	Low Neutrophil (<5) (%, N=107)	Med Neutrophil (5–6) (%, N=92)	High Neutrophil (>6) (%, N=93)	Adjusted P-value for Ethnicity
Ethnicity African-American	36.5	42.4	22.6	0.045*
Caucasian	57.9	52.2	66.7	
Other	5.6	5.4	10.8	
Physician's global assessment >1	11.2	16.3	30.1	0.003
SELENA SLEDAI ≥2	47.7	60.9	65.6	0.012
Age at visit (years) ≤30	13.1	9.8	12.9	0.75
>30	86.9	90.2	87.1	

	Low Neutrophil (<5)	Med Neutrophil (5–6)	High Neutrophil (>6)	Adjusted P-value for Ethnicity
Use of Prednisone	25.2	32.6	49.5	0.0007
Use of Plaquenil	77.6	88.0	71.0	0.016
Use of Aspirin	30.8	41.3	51.6	0.011
Anti-dsDNA ≥10	10.3	26.1	31.2	0.0005
Lupus Anticoagulant	10.3	12.0	23.7	0.023
C3 <79 mg/dl	8.4	8.7	20.4	0.031
C4 <12 mg/dl	5.6	9.8	18.3	0.034
ESR >20	40.2	53.4	61.5	0.0018

* Unadjusted p-value.

Table 2. Association between SLICC/ACR Damage Index and Neutrophil Gene Expression in SLE

Variable	Low Neutrophil (<5) (%, N=107)	Med Neutrophil (5–6) (%, N=92)	High Neutrophil (>6) (%, N=93)	Adjusted P-value for Ethnicity
Myocardial Infarction	0.0	6.5	5.4	0.0056
Deep Venous Thrombosis	1.9	0.0	6.5	0.016
Diabetes	4.7	6.5	14.1	0.024
Malignancy	2.8	12.1	15.2	0.0043

Conclusion: This is the first gene signature to be associated with myocardial infarction, deep venous thrombosis and malignancy. Targeting the neutrophil gene signature appears to be promising for disease activity. Given that atherosclerosis disease is the major cause of death in late SLE, this gene signature may be the "missing link" in understanding how SLE accelerates atherosclerosis. A limitation of the technique is that the neutrophil gene signature will go up when there is lymphopenia.

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Microrna-155 Protects Against Pulmonary Fibrosis by Targeting the Transcription Regulator LXR Alpha. Mariola Kurowska-Stolarska[1], Manhl Hasoo[1], Derek G. Gilchrist[2], Eva Ruzicska[2], Darren Asquith[2], David Welsh[3], Lynn Crawford[2], Nik Hirani[4], Iain B. McInnes[2] and Charles McSharry[2], [1]Institute of Infection,Immunity and Inflammation, College of Medical, Veterinary and Life Sciences University of Glasgow, Glasgow, United Kingdom, [2]University of Glasgow, Glasgow, United Kingdom, [3]Western Infirmary, Glasgow, United Kingdom, [4]University of Edinburgh, Edinburgh, United Kingdom

Background/Purpose: MicroRNAs (miRs) are a novel class of post-transcriptional regulators. A single miR can have profound effects on cell activation due to its ability to modulate multiple pathways at once. We have previously shown that miR-155 is upregulated in rheumatoid arthritis (RA) synovial macrophages and promotes the development of autoimmunity and joint inflammation. Pre-clinical arthritis may be associated with lung changes e.g. bronchial wall thickening, thus the aim of this study was to investigate the contribution of miR-155 regulated pathways to lung homeostasis.

Methods: Normal human lung tissue was tested by *in situ* hybridisation with miR-155 and control probes. To model the fibrotic response, WT and miR-155$^{-/-}$ mice were given bleomycin (0.06 unit/mouse) intranasally. Intervention included intraperitoneal injections of the Liver X Receptor (LXR) agonist (GW3965 daily; 40 mg/kg). End-points included bronchial lavage (BAL) cytology, lung tissue histology, evaluation of the expression of inflammatory and fibrotic genes by qPCR and concentrations of soluble mediators in serum and BAL fluid by multiplex assays. The validation of miR-155 binding to LXR, and the LXR response element in collagen gene promoters were performed with reporter assays.

Results: *In situ* hybridisation showed an abundant expression of miR-155 in the normal human lung suggesting that this miR may contribute to normal lung homeostasis. miR-155$^{-/-}$ mice developed more severe bleomycin-induced lung fibrosis compared to WT mice, as seen by increased collagen 1a/3a mRNA expression and protein deposition in the lungs, as well as accumulation of macrophages and lymphocytes in BAL. Gene expression analysis of lung extracts revealed an increase in the M2 pro-fibrotic macrophage markers Arginase 2, IL-13R and Ym1. In addition, the levels of pro-fibrotic cytokines such as VEGF and bFGF were significantly higher in BAL and serum of miR-155$^{-/-}$ mice. Primary lung fibroblast lines derived from miR-155$^{-/-}$ mice showed higher proliferation rates and motility compared to WT cells in wound healing assays. Computational analysis followed by functional luciferase assays revealed that the transcription activator LXR alpha is a direct target of miR-155 in the lungs. Expression of

LXR alpha was significantly upregulated in the lungs of naïve miR-155$^{-/-}$ mice and was further increased in mice given bleomycin compared to similarly treated WT controls. Injection of the LXR agonist to WT mice increased LXR expression and mirrored the same phenotypic response to bleomycin as the miR-155 deficient mice; shown by increased collagen deposition and M2 macrophage and fibroblast activation. Promoter analysis revealed that LXRs could directly induce collagen production by binding to *col1a* and *col3a* promoters.

Conclusion: miR-155 appears important for lung homeostasis, likely by fine tuning levels of LXRα thereby protecting from excessive remodelling. Given this and the emerging contribution of miR-155 to development of autoimmunity, this miR may act as a master-switch determining the duration of inflammation and the initiation of remodelling, as well as the balance between the immune and auto-immune responses.

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Plasma Cells Express the Novel Cytokine Interleukin-36α in Psoriatic and Rheumatoid Arthritis Synovium. Anja Derer[1], Silke Frey[1], Maria-Elena Messbacher[1], Serena Bugatti[2], D. Baeten[3], Carlomaurizio Montecucco[4], Georg A. Schett[1] and Axel J. Hueber[1]. [1]University of Erlangen, Erlangen, Germany, [2]Division of Rheumatology, University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Background/Purpose: IL-36α is a recent described IL-1 cytokine family member with proinflammatory and clear pathogenic properties in psoriasis. Aim of this study was to determine IL-36α expression in psoriatic arthritis (PsA) compared to rheumatoid (RA) and osteoarthritis (OA).

Methods: Synovial tissue gathered from arthritis patients were stained for IL-36α, IL-36 receptor (IL-36R) and IL-36R antagonist (IL-36Ra) by immunohistochemistry and immunofluorescence. Lysates were tested for IL-36α by western blot analysis. Synovial fibroblasts (FLS) stimulated with IL-36α were assessed for cytokine expression.

Results: The IL-36R and its ligands IL-36α and IL-36Ra could be detected in inflammatory arthritis in the synovial lining layer as well as cellular infiltrates. IL-36α was significantly higher expressed in PsA and RA synovium compared to OA (p=0.0011 and p<0.0001, respectively). No differences were seen in IL-36R and IL-36Ra. The expression of IL-36α was confirmed by western blot analysis. IL-36α induced expression of IL-6 and IL-8 in FLS. CD138-positive plasma cells were determined as major cellular source for IL-36α.

Conclusion: We described that the novel cytokine IL-36α is upregulated in PsA and RA synovium mainly expressed by plasma cells. This insight needs further studies to determine if the IL-36 family can function as a potential target for arthritis therapy.

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Modeling Environmental and Genetic Determinants to Identify the Association of Risk Genes in Anti-Ro60-Mediated Injury: Relaxin Receptor I and Tumor Necrosis Factor. Joanne H. Reed[1], Paula S. Ramos[2], Jiri Zavadil[1], Jill P. Buyon[1] and Robert M. Clancy[1]. [1]New York University School of Medicine, New York, NY, [2]Medical University of South Carolina, Charleston, SC

Background/Purpose: Fetuses exposed to maternal anti-Ro60 antibodies can develop cardiac conduction abnormalities and life threatening cardiomyopathy; manifestations of neonatal lupus (NL). Recent data support an injury model in which immune complexes (IC) comprised of Ro60, ssRNA, and anti-Ro60 engage Toll-like receptors (TLR) and promote secretion of proinflammatory and profibrotic factors.To identify risk genes related to TLR-dependent fibrosis, a novel strategy was designed based on: 1) gene expression of macrophages stimulated by Ro60-related hY3 ssRNA as a proxy of the in utero environmental contribution and 2) the association of genetic variation with cardiac NL. This is the first approach to employ environmental

and genetic determinants to identify the association of risk genes in anti-Ro60-mediated injury.

Methods: Human macrophages obtained from PBMCs were transfected with hY3 or cultured with IC containing Ro60, anti-Ro60,and hY3 to ligate TLR7 with or without IRS661, a specific TLR7 inhibitor. Affymetrix HG-U133A 2.0 microarray analysis using RNA isolated from the test conditions (n=6) was employed.Selection was prioritized to expression of genes common to both hY3 and IC stimulation in which the copy number increased by 50%. Ingenuity Pathway Analysis was used to generate a list of genes with fibrotic functions.Variants from our previously published genome-wide association study (GWAS) were used to test for an enrichment of association in these genes. This list was then compared to the overexpressed transcripts, and shared genes were ranked using a weighted composite score with a focus on the TLR7 pathway (ratio of transcript copy number for IC/IC+IRS661, high to low, and by the P-value of the variant, most significant to least).

Results: In hY3 and IC stimulated conditions 1184 shared genes were upregulated of which 1110 and 891 were reduced by 50% with IRS661 co-treatment, respectively. Among these, there was an enrichment of genes known to be related to inflammation and fibrosis.Based on our previously published GWAS, 327 fibrotic genes showed a significant enrichment of associations with cardiac NL (P=2.27 $\times$ 10^{-9}).Of these genes, 20 were overexpressed in the macrophage array in a TLR7-dependent manner.To select candidates with a potential functional role in mediating cardiac injury, the candidate list was narrowed to three genes based on a ranking of a composite score. The risk gene with the highest score was the relaxin receptor 1 (*RXFP1*) (transcript copy number (IC/(IC+IRS661)) ratio=21.2 and rs10517692 P=0.035), a G-protein coupled receptor that binds relaxin and plays a role in collagen and connective tissue remodeling. Key inflammatory mediators included *C5* (ratio=6.4, rs2269066 P=0.008) and *TNF* (ratio=4.1, rs2844482 P=0.004). The latter was previously reported to have both genetic variation and biologic relevance associated with cardiac NL.

Conclusion: These data support the applicability of a novel model in which causal alleles can be identified by combining expression and association datasets to delineate the molecular mechanisms by which anti-Ro60 antibody mediates cardiac injury. The identification of *RXFP1* and the further confirmation of *TNF* provide important targets for consideration.

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The Role of Adipocytokines in Osteophyte Formation in Osteoarthritis. Susann Junker[1], Grit Krumbholz[1], Klaus Frommer[1], Angela Lehr[2], Stefan Rehart[2], Jürgen Steinmeyer[3], Markus Rickert[4], Georg A. Schett[5], Ulf Müller-Ladner[1] and Elena Neumann[6]. [1]Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Markus-Hospital, Frankfurt, Germany, [3]University Hospital Gießen and Marburg, Gießen, Germany, [4]University Hospital Giessen and Marburg, Giessen, Germany, [5]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [6]Justus-Liebig-University of Gießen, Kerckhoff-Klinik, Bad Nauheim, Germany

Background/Purpose: Obesity is an established risk factor in osteoarthritis (OA), but there is not much known about the interaction between bone formation and the so-called adipo(cyto)kines. Adipokines, such as adiponectin (Ad), visfatin (Vis) or resistin (Res), are adipose tissue-derived factors, which are associated with the pathogenesis of rheumatoid arthritis (RA) and OA. Adipokines can be produced by other cell types, *e.g.* fibroblasts, osteoblasts, osteoclasts and chondrocytes. However, in contrast to their joint-destructive effects in RA, their role in joint remodeling in OA, specifically in osteophyte formation, is still unclear. Therefore, the expression of adipokines in osteophyte development and cells of bone formation and their effect on these cells were analyzed.

Methods: Osteophytes, cartilage and osteoblasts were obtained from OA patients during joint replacement surgery. Serial sections of bone tissue were stained (Masson trichrome, TRAP) and scored from grade one (no ossification, mainly connective tissue and cartilage) to five (ossified, mineralized osteophyte, <10% connective tissue). For analysis of adipokine localization, immunohistochemistry was performed to detect alkaline phosphatase, collagen-type II, Ad, Vis, and Res. Immunoassays for Vis were performed on cartilage and isolated primary chondrocyte lysates. Osteoblast cultures were stimulated with Ad or Res and measurements of IL-6, IL-8, and MCP-1 were performed in cell culture supernatants.

Results: Ad, Res and Vis were detectable in all osteophyte grades. In osteophytes without ossification (grade 1), especially Ad and, to a lower extent, Res and Vis were localized in connective tissue fibroblasts. In ossified osteophytes (grade 2–5), Res and Vis protein expression was co-localized with osteoclasts and osteoblasts. Vis was detectable additionally in chondrocytes in osteophytes of all grades (50 % stained chondrocytes). Vis expression in human cartilage and cultured chondrocytes was confirmed on protein and mRNA level. Ad was detectable in co-localization with osteoblasts as well as around blood vessels.

Vis expression in osteoblasts was confirmed on mRNA level. Immunocytochemistry on cultured osteoblasts confirmed the expression of Ad, Res and Vis. Stimulation of osteoblasts with Ad and Res led to an increased IL-6, IL-8 and MCP-1 release when compared to unstimulated controls (Ad: 5,7-fold, 9,5-fold, 3,6-fold, respectively/Res: 1,7-fold, 1,6-fold, 1,3-fold, respectively). The immunomodulatory effect of Ad on osteoblasts was stronger than the effect of Res.

Conclusion: The expression of Ad and Vis in osteophyte connective tissue and cartilage suggests an involvement in early osteophyte formation. Res and Vis expression by osteoblasts and osteoclasts in ossified osteophytes suggests a role in bone remodeling of osteophytes at later stages. Osteoblasts respond to the stimulation with Ad and Res with an increased secretion of inflammatory mediators. Therefore, adipokines are most likely involved in osteophyte formation at different stages of OA and affect different cell types of cartilage and bone formation.

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Fatty Acids Promote Secretion of Proinflammatory and Prodestructive Factors by Synovial Fibroblasts. Klaus W. Frommer[1], Andreas Schäffler[2]. Stefan Rehart[3], Angela Lehr[3], Ulf Müller-Ladner[1] and Elena Neumann[1], [1]Justus-Liebig-University of Gießen, Bad Nauheim, Germany, [2]University of Regensburg, Regensburg, Germany, [3]Markus-Hospital, Frankfurt, Germany

Background/Purpose: Due to their role in inflammatory metabolic diseases, we hypothesized that free fatty acids (FFA) are also involved in primary inflammatory joint diseases including rheumatoid arthritis (RA) and psoriasis arthritis (PsA) as well as in degenerative joint diseases with secondary inflammatory properties, specifically osteoarthritis (OA). To test this hypothesis, we analyzed the effect of FFA on synovial fibroblasts (SF), a key cell type in the pathophysiology of arthritis. We also investigated whether FFA need to be internalized to have an effect and if the innate immune system is involved in the modulation of this effect.

Methods: RASF, OASF and PsASF were stimulated *in vitro* with different saturated and unsaturated FFA within their physiological range of concentrations. Immunoassays were used to quantify FFA-induced protein secretion. Sulfosuccinimidyl oleate sodium (SSO) was used to inhibit the fatty acid translocase (FAT), which is responsible for transporting long-chain fatty acids into the cell. In addition, TLR4 signaling, which can contribute to driving arthritis, was inhibited intracellularly and extracellularly.

Results: In RASF, FFA dose-dependently enhanced the secretion of the proinflammatory cytokine IL-6, the chemokines IL-8 and MCP-1, as well as the matrix-degrading enzymes MMP-1 and MMP-3. Cell population, cell source (RA, OA, or PsA) and the respective molecular parameters were factors that influenced the changes of protein secretion (e.g. for lauric acid [100 μM] with RASF/IL-6: 9.1-fold increase; IL-8: 14.9-fold increase; MCP-1: 2.4-fold increase; pro-MMP1: 5.1-fold increase; MMP-3: 83.6-fold increase). At equal concentrations, both saturated and unsaturated fatty acids showed similar effects, while responses to FFA were generally stronger for OASF and PsASF than for RASF (e.g. for palmitic acid [10 μM] with RASF/IL-6: 2.8-fold increase; with OASF: 15.2-fold increase; with PsA-SF: 39.3-fold increase). Pre-incubation of RASF with SSO almost completely abrogated the effect of palmitic acid on IL-8 secretion. However, both intracellular and extracellular TLR4 signaling inhibition blocked the palmitic acid-induced IL-6 secretion of RASF.

Conclusion: The data show that FFA are not only metabolic substrates but also directly contribute to articular inflammation and degradation in various joint diseases. Moreover, the data support the hypothesis that FFA-induced joint destruction is mediated through the innate immune system.

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The Epigenetically Repressed Long Noncoding RNA Hotair Influences the Expression of Matrix Metalloproteases in Synovial Fibroblasts. Michelle Trenkmann[1], Matthias Brock[2], Renate E. Gay[1], Beat A. Michel[3], Lars C. Huber[2] and Steffen Gay[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Long noncoding RNAs (lncRNA, >200nt) have recently emerged as regulators of gene expression functioning as signals, decoys, guides or scaffolds for transcription factors and/or the epigenetic machinery of the cell. The repressive epigenetic mark trimethylated histone 3 lysine 27 (H3K27me3) is transferred by the histone methyltransferase EZH2 which is up regulated in rheumatoid arthritis (RA) synovial fibroblasts (SF) and inducible by tumor necrosis factor (TNF)-α (Trenkmann M *et al.*, ARD, 2011). The lncRNA HOX transcript antisense RNA (HOTAIR) has been associated with cancer and metastasis; it was shown to interact with EZH2 and proposed to guide H3K27 trimethylation of target genes (Wang KC and Chang HY, Mol Cell, 2011). Here, we studied expression, regulation and function of HOTAIR in SF.

Methods: Gene expression in SF was measured by SYBR Green or TaqMan real-time PCR with normalization to GAPDH. SF were stimulated with TNFα (10ng/ml; n=11) and interleukin (IL)-1β (1ng/ml; n=5). Osteoarthritis (OA)SF were transfected with a vector encoding EZH2 (n=4) or siRNA targeting HOTAIR (n=11). Chromatin from SF was precipitated with antibodies for histone 3 (H3), H3 methylation H3K4me3 and H3K27me3, and H3 acetylation (Ac), and the HOTAIR promoter was analyzed for epigenetic regulation.

Results: The expression of HOTAIR was strongly decreased (12.7-fold) in RASF (n=9) compared to OASF (n=13) (ΔCt 14.3$\pm$3.3 vs. 10.6$\pm$1.7, p=0.005). EZH2 over expression in OASF reduced the expression of HOTAIR by 30$\pm$17% (p<0.05) suggesting that EZH2-mediated methylation of H3K27 may regulate HOTAIR expression. Indeed, HOTAIR levels in RASF and OASF inversely correlated with the repressive H3K27me3 epigenetic mark in the promoter of HOTAIR (Spearman R=$-$0.8725, p<0.0001). In detail, the H3K27me3 to H3 ratio in RASF was 0.51$\pm$0.35 whereas the HOTAIR promoter in OASF showed much less H3K27 trimethylation (ratio to H3 0.25$\pm$0.23; p=0.0309). Interestingly, neither in RASF nor in OASF H3K4me3 or H3-Ac could be detected at the HOTAIR promoter. Stimulation of OASF with TNFα for 24h and 48h decreased HOTAIR levels by 63$\pm$16% and 56$\pm$26% (p<0.0001). IL-1β-stimulation reduced HOTAIR expression by 54$\pm$10% and 63$\pm$6%, respectively (p<0.0005). To identify a functional role for HOTAIR repression in RASF, we silenced HOTAIR in OASF using RNA interference. The silencing of HOTAIR significantly increased mRNA levels of the matrix metalloproteases (MMP) 3, 13 and 14 (MMP3 by 1.8$\pm$0.7-fold, MMP13 by 4.3$\pm$3.1-fold and MMP14 by 2.1$\pm$0.7-fold, p<0.05); in contrast, results for MMP1 were inconsistent. The TNFα-induced expression of MMP3 (51.6$\pm$21.2-fold) and MMP13 (6.9$\pm$2.6-fold) was further increased by silencing of HOTAIR (71.5$\pm$28-fold and 18.8$\pm$8.6-fold, p<0.05) whereas the IL-1β-stimulated expression was not significantly changed (n=5 each).

Conclusion: This is the first report of a differential expression of a lncRNA in RA. The expression of HOTAIR is strongly reduced in RASF via the repressive epigenetic mark H3K27me3. We demonstrate that HOTAIR silencing may account for the up regulation of matrix-degrading enzymes indicating a potential role for HOTAIR repression in the activated, matrix-destructive phenotype of RASF.

Disclosure: M. Trenkmann, Masterswitch-FP7, IMI-BTCure, IAR, 2; M. Brock, ZIHP, IAR, 2; R. E. Gay, Masterswitch-FP7, 2; B. A. Michel, None; L. C. Huber, None; S. Gay, IAR, 2.

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Nuclear Factor-κB Activation by Type II Collagen Peptide in Osteoarthritic Chondrocytes: Its Inhibition by Hyaluronan Via CD44. Tadashi Yasuda. Tenri University, Tenri, Japan

Background/Purpose: Some proteolytic products of cartilage matrix may contribute to cartilage destruction through their catabolic activities. Recently, we have found that a 24-mer synthetic peptide of type II collagen named CB12-II stimulates type II collagen cleavage with induction of matrix metalloproteinase (MMP)-13 in cartilage explant culture. Although the intracellular signaling that leads to cartilage destruction is mediated by a

cluster of catabolic pathways including nuclear factor-κB (NF-κB), the effect of CB12-II on NF-κB remains unclear.

Hyaluronan (HA) of high molecular weight is widely used in the treatment of osteoarthritis (OA) by intra-articular injection. An increasing body of evidence indicates that HA suppresses catabolic actions by proinflammatory cytokines like interleukin-1 and matrikines such as fibronectin fragments. However, little is known of HA effect on actions of CB12-II through interaction with HA receptor such as CD44.

This study was aimed to examine activation of NF-κB in association with MMP-13 production by CB12-II and its inhibition by HA in chondrocytes.

Methods: Cartilage explants harvested from OA knee joints or isolated chondrocytes in monolayer were incubated with CB12-II or its scramble peptide with or without pretreatment with 2700 kDa HA. In another set of experiments, following preincubation with anti-CD44 antibody or non-specific IgG, cartilage explants were incubated with or without HA, followed by coincubation with CB12-II or the scramble peptide.

Enzyme-linked immunosorbent assays for phosphorylated p65 NF-κB and MMP13 were performed using total cell lysates and culture supernatants, respectively.

Results: When cartilage explants or chondrocytes in monolayer were incubated with CB12-II, the type II collagen peptide activated NF-κB in association with enhanced MMP-13 production. Inhibition studies with the specific inhibitor indicated the requirement of NF-κB for CB12-II-induced MMP-13 production. Pretreatment with HA resulted in significant suppression of CB12-II-stimulated MMP-13 production in cartilage as well as in chondrocyte monolayer cultures. HA suppressed NF-κB activation by CB12-II, leading to a decrease in MMP-13 production. Anti-CD44 antibody reversed HA effect on CB12-II action.

Conclusion: The present study clearly demonstrated that HA suppressed CB12-II-activated NF-κB via CD44 in OA articular chondrocytes, leading to decreased MMP-13 production. HA could down-regulate the catabolic action of type II collagen fragments in osteoarthritic joints through the mechanism demonstrated in this study.

Disclosure: T. Yasuda, None;

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Genetic Variants in the *IL-4* and *IL-4* Receptor Genes in Association with the Severity of Joint Damage in Rheumatoid Arthritis: A Study in Seven Cohorts.
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Background/Purpose: The severity of RA is reflected by the severity of radiological joint destruction. It is highly variable between patients and up to 58% of this variance is explained by genetic factors. In order to increase the understanding of the processes underlying joint damage progression, it is relevant to identify individual risk factors. In vitro studies and mice studies showed that *IL-4* has a role in suppressing arthritis severity. The effect of *IL-4* is mediated by a heterodimeric receptor composed of the IL-4R alpha chain. Several genetic variants in *IL-4* and *IL-4R* have been described to associate with RA severity, though these findings have not been replicated. Together these data prompted us to investigate the association between *IL-4* and *IL-4R* tagging SNPs and progression rate of joint damage in a multi-cohort candidate gene study.

Methods: *IL-4* and *IL-4R* tagging SNPs (8 and 39, respectively) were genotyped in 600 RA patients of whom 2,846 sets of hands and feet X-rays were collected during 7 years follow-up. Subsequently, significantly associated SNPs were genotyped and studied in relation to 3,523 X-rays of 2,064 RA patients of several European and North-American cohorts. These concerned data-sets from Lund (Sw) (781 X-rays in 147 patients), Sheffield (UK) (391 X-rays in 391 patients), Groningen (NL) (872 X-rays in 280 patients), NARAC (USA) (385 X-rays in 385 patients), Wichita (USA) (337 X-rays in 101 patients) and NDB (USA) (757 X-rays in 757 patients). Three SNPs of phase-2 were not available for the latter two cohorts. In all cohorts X-rays were scored with high reproducibility. The relative increase in progression rate per year in the presence of a genotype was determined, as this outcome measure is comparable between cohorts. Subsequently, since the individual replication cohorts had less number of X-rays than the discovery cohort, an inverse variance weighting meta-analysis was done on the cohorts that together formed the replication phase.

Results: In the discovery phase none of the *IL-4* SNPs and seven of the *IL-4R* SNPs were significantly associated with joint damage progression rate. In the replication phase, two SNPs in *IL-4R* gene were significantly associated with joint damage progression rate (rs1805011, p=0.017 and rs1119132, p=0.001). After Bonferroni correction for testing seven SNPs in phase-2 rs1119132 remained significantly associated with joint progression rate ($p_{corrected}$=0.007). Leiden RA-patients carrying both minor alleles of rs1119132 had a 1.09 fold rate of joint destruction compared to other patients, which corresponds to 81% higher rate of joint destruction over a period of 7 years.

Conclusion: rs1119132 in *IL-4R* was identified as well as independently replicated to associate with progression rate of joint damage in RA.

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Transcriptomics of Synovial Tissue of Early Human (CHECK) and Experimental OA Identify Pathways Associated with Cartilage Damage.
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Background/Purpose: Many osteoarthritis (OA) patients show synovial inflammation, even relatively early during the disease. Mechanisms through which synovial activation contributes to the joint pathology that characterizes OA, are not known. The objective of this study is to identify common pathways in the synovium that determine cartilage damage during OA.

Methods: From patients that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) and from controls (n=7) synovial biopsies were collected. CHECK is a prospective 10-year follow-up study on participants with early osteoarthritis-related complaints. Kellgrenn&Lawrence score (KL) was determined at inclusion (n=18). In addition, biopsies of 7 control synovia were collected. A longitudinal expression analysis was performed on murine synovial tissue at day 7, 21 and 42 after induction of collagenase induced OA (CIOA). CIOA was induced by intra-articular injection of collagenase and contra lateral knee joints served as controls. Microarray experiments were performed on all synovial tissues. Functional annotation clustering (FAC) and pathway analysis was done using DAVID.

Results: Gene expression profiles of control synovia were compared to CHECK synovia. Enrichment analysis revealed several annatations, including regulation of macrophage differentiation, innate immune responses, cell migration, TGFβ-, BMP- and wnt-signaling. This signifies clear activation of the synovium in CHECK patients compared to controls. Next we compared synovial tissue of patients with radiological damage (KL$\geq$1) with patients without damage (KL=0). Genes that showed the strongest association with cartilage damage were MMP-1, MMP-3, S100A8 and cartilage glycoprotein-39 (18, 10, 6 and 6-fold), all of which have been associated with cartilage damage. Response to wounding, chemotaxis, innate immune response and metalloproteases were strongly and significantly enriched and thus associated with joint damage. Pathway analysis demonstrated that in the synovium of patients with joint damage the complement-activation pathway, TGFβ- and BMP-signaling and TLR-activation were significantly upregulated. These results were underlined by analysis of synovium from CIOA. Among the genes that were strongly upregulated on all time points after induction were MMP-3, MMP-13, MMP-14 and COMP (6, 16, 6 an 13-fold). Again, wound healing, innate immune response and metalloproteases were significantly enriched, as were the complement pathway, the TLR-, TGFβ, BMP and wnt-signaling pathways. A recent publication demonstrated complement to be essential in experimental OA. We therefore determined expression of complement binding proteins, and found a strong upregulation of COMP, lumican, osteomodulin, biglycan, decorin and fibromodulin.

Conclusion: These data suggest an active role for the synovium in OA pathology, and identify pathways that are likely to be involved. In particular the association of cartilage damage with the complement pathway was strong.

In addition, TGFβ-, BMP- and wnt-signaling in the synovium, may contribute to further joint damage. The enhanced expression of cartilage damaging MMP-1, MMP-3 and MMP-13 suggests an active role of the synovium in OA pathology.

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Tyro3, Axl, MerTK-Receptor Activation by Gas6 or Pros1 Gene Delivery, ameliorates Collagen-induced arthritis. Fons A.J. van de Loo[1], Ben T. van Den Brand[1]. Shahla Abdollahi-Roodsaz[1], Eline A. Vermeij[2], Miranda B. Bennink[2], Onno J. Arntz[2] and Wim B. van den Berg[1], [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Nijmegen, Netherlands

Background/Purpose: Insufficient controlled activation of innate immunity by cytokines and pattern recognition receptors could develop into auto-immune diseases. Stimulation ofdendritic cells via the Axl receptor in conjunction with IFNAR leads to upregulation of suppressor of cytokine signaling (SOCS) proteins 1 and 3 and broadly inhibit both Toll-like Receptor (TLR) signaling and TLR-induced cytokine-receptor cascades (Rothlin et al. Cell 2007). This study evaluated whether Tyro3 Axl MerTK (TAM)- receptor stimulation by Growth arrest specific 6 (Gas6) and Protein S (Pros1) as natural negative feedback for Toll-Like Receptor and cytokine signaling can be used to treat collagen-induced arthritis.

Methods: Adenoviruses ($1 \times 10E7$ FFU) overexpressing Gas6 and Pros1 were injected intravenously (i.v.) or $3 \times 10E8$ FFU intra-articularly (i.a.) into mice before onset of collagen-induced arthritis. Splenic T-helper subsets of intravenously injected were studied by flow cytometry and knee joints of mice injected i.v. and i.a. were assessed histologically. Messenger RNA expression was analyzed in synovium of i.a. injected mice. Ciruclating cytokines were measured on a Luminex-100 System (Luminex corp.) using a magnetic bead-based multiplex immunoassay (Milliplex, Merck Millipore). Joint inflammation was imaged using the ProSense probe with the IVIS Lumina (Caliper Life Sciences), using the Cy5.5 filter.

Results: Gas6 or Pros1 did not affect arthritis incidence in either IV or IA injected animals. However, Pros1 did significantly reduce ankle joint swelling, and circulating levels of KC and IL-6. Histological analysis of knee joints revealed a moderate reduction of joint pathology and a significant reduction of splenic T-helper 1 cells when Pros1 was overexpressed systemically. Local overexpression of Gas6 decreased joint inflammation (as assessd histologically or imaged by ProSense) and joint pathology. Pros1 treatment showed a similar trend of protection. Consistently, Gas6 and Pros1 markedly reduced cytokine (IL-1β, IL-6, and TNFα) production in synovium. Moreover, IL-12 and IL-23 mRNA levels were reduced by Gas6 and Pros1, corresponding to a decrease in IFNγ and IL-17 production in synovium.

Conclusion: We provide the first evidence that TAM receptor stimulation by Gas6 and Pros1 can be used to ameliorate arthritis when applied systemically or locally. TAM receptor stimulation limits proinflammatory signaling and the adaptive immunity. This pathway provides a novel strategy to combat rheumatoid arthritis.

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IL-33 Promotes Mast Cell Survival Via Inhibition of Apoptosis Associated with Enhanced Expression of Bcl-X$_L$. Shinjiro Kaieda[1], Jun-Xia Wang[1] and Peter A. Nigrovic[2]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Mast cells (MCs) are potent innate immune cells that frequently accumulate in chronically inflamed tissues, including the arthritic synovium. The factors that regulate MC persistence and survival in such tissues are unknown. Recent studies have found that the mesenchymal-derived cytokine IL-33 exerts potent effects on MC phenotype and function. Knowing that IL-33 can inhibit apoptosis in cardiac myocytes and hepatocytes, we tested the hypothesis that IL-33 might also regulate MC proliferation and survival, including the development of synovial mastocytosis in the context of inflammatory arthritis.

Methods: Murine bone marrow derived MCs (mBMMCs) were generated from wild-type (WT) mice and animals lacking the IL-33 receptor IL1RL1. Cell viability, proliferation and apoptosis were examined after exposure to IL-33, and compared with exposure to IL-3, a known survival factor for MCs.Expression of the anti-apoptotic molecules Bcl-2 and Bcl-X$_L$ were determined both as mRNA and as protein. To examine the role of IL-33 in vivo, fluorescently-labeled mixed WT and IL1RL1$^{-/-}$ mBMMCs were transferred into the peritoneum of IL1RL1$^{-/-}$ mice. Following 6 days of treatment with IL-33 (100ng/d/mouse, i.p.), peritoneal MCs were harvested and analyzed using flow cytometry.WT and IL1RL1$^{-/-}$ mBMMCs were sorted and the levels of Bcl-2 and Bcl-X$_L$ mRNA were examined by qRT-PCR. Synovial tissue MCs were enumerated in WT and IL1RL1$^{-/-}$ animals at baseline and after induction of K/BxN serum transfer arthritis.

Results: While the viability of WT and IL1RL1$^{-/-}$ mBMMCs was similar in IL-3-supported culture, exogenous IL-33 was able to support the survival of WT but not IL1RL1$^{-/-}$ mBMMCs after IL-3 withdrawal. CFSE dilution studies confirmed that this effect did not reflect enhanced proliferation, but rather arose via inhibited apoptosis as evident by a reduction in the number of Annexin V positive cells. Exploring the mechanism of this effect, we found that IL-33 increased expression of Bcl-X$_L$ but not Bcl-2, unlike IL-3 which supported mBMMC survival via enhanced Bcl-2 but not Bcl-X$_L$. Correspondingly, WT mBMMC persisted better than IL1RL1$^{-/-}$ BMMC in IL-33-treated recipients, an effect again mediated not by proliferation but by impaired apoptosis and Bcl-X$_L$ expression. While WT and IL1RL1$^{-/-}$ demonstrated no difference in the number of synovial MC at baseline, after K/BxN serum transfer the number of MC in ankle synovium was significantly reduced in IL1RL1$^{-/-}$ compared with WT mice. However, since IL-1RL1$^{-/-}$ mice also exhibited less inflammation, the density of MC was similar in both strains, suggesting the IL-33 is not uniquely required for maintaining these cell populations in vivo.

Conclusion: These findings identify a novel role for IL-33 as a promoter of murine MC viability, an effect likely mediated by enhanced expression of the anti-apoptotic protein Bcl-X$_L$. This effect could represent a new mechanism by which IL-33-producing cells, such as fibroblasts, support the maintenance of tissue mastocytosis.However, at least in the short term K/BxN arthritis model, other pathways appear sufficient to enable and maintain tissue MCs even when this mechanism is interrupted by genetic deletion of the IL-33 receptor IL1RL1.

Disclosure: S. Kaieda, None; **J. X. Wang**, None; **P. A. Nigrovic**, None.

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Nuclear Receptor Related 1 Induces Synovial Hyperplasia Via Transcriptional Regulation of Novel Target Genes. Kimberlee S. Mix. Loyola University New Orleans, New Orleans, LA

Background/Purpose: Nuclear receptor related 1 (NURR1/NR4A2) is an orphan member of the nuclear receptor super-family that functions as a constitutively active transcription factor. This receptor has critical functions in the central nervous system, where it is required for the proper development of dopaminergic neurons. Furthermore, recent studies suggest that NURR1 promotes inflammatory diseases such as cancer, multiple sclerosis, and diabetes. We have documented over-expression of NURR1 in inflamed synovial tissues and cartilage from patients with rheumatoid arthritis and osteoarthritis. NURR1 is rapidly and potently induced by inflammatory cytokines, suggesting that this receptor may promote disease progression and tissue destruction.We have recently demonstrated that NURR1 induces a hyperplastic phenotype in fibroblast-like synoviocytes by increasing proliferation, anchorage-independent growth, and invasion. In the current study, we seek to elucidate the molecular mechanisms of NURR1 and identify downstream transcriptional targets of this receptor that may contribute to synovitis and cartilage degradation.

Methods: To achieve elevated levels of NURR1 similar to those observed in inflamed synovial tissues, NURR1 cDNA was transduced into normal human synoviocytes.Transcriptional activity was confirmed by the activation of a consensus NURR1 reporter construct. Quantitative RT-PCR arrays were used to identify genes that were differentially regulated by NURR1.

Results: Paralleling the effects of TNF-alpha, NURR1 regulates a subset of genes involved in angiogenesis, proliferation, and apoptosis. NURR1 potently induces expression of prolactin (300-fold), a peptide hormone that enhances synoviocyte activation and lymphocyte recruitment. Angiopoietin-1, a ligand for endothelium-specific tyrosine kinase receptors involved in synovial angiogenesis was induced by NURR1 (6-fold). Expression of the tyrosine kinase receptor TEK was also induced (30-fold), suggesting activation of an autocrine signaling pathway in synoviocytes.Raf kinase and the downstream mitogenic transcription factor c-Myc were both induced 3-fold by NURR1. Furthermore, the tumor suppressor gene p53 was

synergistically repressed by NURR1 and TNF-alpha, suggesting that NURR1 may block DNA repair mechanisms and prevent apoptosis of synoviocytes.

Conclusion: Taken together, we have identified a novel set of NURR1 target genes that converge on multiple pathways regulating synovial hyperplasia. We hypothesize that antagonizing NURR1 activity with a small molecule inhibitor may provide an innovative strategy to block pannus formation and tissue destruction.

Disclosure: **K. S. Mix**, None;

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A Role for Soluble Interleukin-6 Receptor As an Antagonist of Interleukin-27 Signaling. Misato Hashizume, Keiko Esaki and Yoshihiro Matsumoto. Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

Background/Purpose: Recently, it has been reported that interleukin (IL)-27 treatment reduces inflammation and ameliorates arthritis in collagen-induced arthritis mice. IL-27 is a heterodimeric cytokine composed of IL-27p28, which is similar to IL-6, and EBI3, which is similar to soluble IL-6 receptor (sIL-6R). Notably, each subunit is produced independently, allowing IL-27 to associate with other proteins. sIL-6R is highly concentrated in serum from patients with rheumatoid arthritis (RA). We elucidated the role of sIL-6R in regulating IL-27 signaling.

Methods: Surface Plasmon Resonance analysis was used to examine the binding of IL-27 to sIL-6R. Competitive ELISA was performed to evaluate the binding to IL-27p28 and the dissociation of EBI3 from IL-27p28 in the presence of sIL-6R. $CD14^+$ cells were isolated from peripheral blood mononuclear cells of healthy subjects. $CD14^+$ cells were incubated with IL-27 and sIL-6R for 20 minutes, and phosphorylation of STAT3 was measured by FACS. $CD14^+$ cells were incubated with M-CSF, TNF-α, IL-27 and sIL-6R for 48 hours, and MCP-1 production from $CD14^+$ cells was measured by ELISA. $CD14^+$ cells were cultured with RANKL and M-CSF in the presence of IL-27 and sIL-6R for 4 days, and the number of osteoclasts was counted after tartrate-resistant acid phosphatise (TRAP) staining. Concentrations of IL-27p28/sIL-6R complex and IL-27p28/EBI3 complex in serum from healthy subjects and those with RA were determined by ELISA.

Results: Surface Plasmon Resonance analysis showed that binding curves were generated from experiments in which IL-27 was exposed to a high-density of sIL-6R coated on a sensor chip. sIL-6R promoted the dissociation of EBI3 from IL-27p28 and the formation of IL-27p28/sIL-6R complex in a dose-dependent manner. Anti-IL-6 receptor antibody (tocilizumab) inhibited the formation of IL-27p28/sIL-6R complex. To examine the effect of sIL-6R on IL-27 signaling, we measured phosphorylation of STAT3, which is increased by IL-27, after stimulating sIL-6R and IL-27, and found that sIL-6R decreased phosphorylation of STAT3. Next, we examined whether sIL-6R inhibited the IL-27-mediated anti-arthritic effect. Whereas IL-27 reduced TNF-α-induced MCP-1 production from $CD14^+$ cells, IL-27 did not decrease TNF-α-induced MCP-1 production in the presence of sIL-6R. Similarly, RANKL-mediated osteoclast formation was inhibited by IL-27 but was not inhibited by IL-27 in the presence of sIL-6R. Finally, we examined whether IL-27p28/sIL-6R complex was formed in serum from healthy subjects and from those with RA. Surprisingly, IL-27p28/sIL-6R complex in RA serum was significantly higher than that in healthy serum.

Conclusion: We elucidated that sIL-6R binds to IL-27p28, antagonizes IL-27 signaling, and blocks IL-27-mediated anti-arthritic effect. In addition, we showed that IL-27p28/sIL-6R complex was more abundant in serum from RA patients than in that from healthy subjects. These data suggest that sIL-6R may be involved in regulating the IL-27 function in RA.

Disclosure: **M. Hashizume**, None; **K. Esaki**, None; **Y. Matsumoto**, None.

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Deletion of RBP-J in a Murine Model of Inflammatory Arthritis Reveals Differential Pro-Inflammatory Cytokine and FoxP3 Gene Expression. Soumya D. Chakravarty, Karmen Au, Xiaoyu Hu and Lionel B. Ivashkiv. Hospital for Special Surgery, New York, NY

Background/Purpose: The DNA-binding protein RBP-J serves as the central transcriptional regulator of the Notch signaling pathway. Prior work done using a knockdown approach of RBP-J in human macrophages and conditional deletion of RBP-J in mouse macrophages has demonstrated diminished LPS-induced expression of TNFa, IL-6 and IL-12p40, with IL-1 induction preserved. Elsewhere, it has been observed that host regulatory T cells in RBP-J deficient mice have an attenuated ability to suppress effector

T cell responses *in vitro*, with augmented proliferation and function of effector T cells noted *in vivo*, raising the possibility that dysregulation in the frequency or function of regulatory T cells may contribute to RBP-J's selective modulation of pro-inflammatory mediators. Here, we evaluated the *in vivo* effects of RBP-J's conditional deletion in the myeloid cell compartment on pro-inflammatory cytokine expression, as well as lymphoid tissue immunocyte composition, using a K/BxN serum transfer model of inflammatory arthritis.

Methods: RBP-J$^{flox/flox}$ LysM-Cre knock-out (KO) mice with littermate RBP-J$^{+/+}$LysM-Cre controls (n=5 for each group) were used. After treatment with K/BxN serum, the clinical course of arthritis was followed by measuring total joint thickness up to 14 days, at which point the mice were sacrificed. Total joint RNA from each mouse was obtained for gene expression analyses by qPCR. Splenic tissue was harvested from each mouse for gene expression analyses by qPCR, as well as pooled collectively for each group for immunophenotyping through flow cytometry. The latter was also done for superficial inguinal and draining popliteal lymph node (LN) tissue. Statistical analysis was done using the unpaired student's t-test with p < 0.05 considered significant.

Results: Preliminary findings showed no significant difference in clinical phenotype of K/BxN serum-induced arthritis between KO and control mice. Gene expression profiling of whole joint tissue showed decreases in TNFa, IL-6, IFN-g expression, as well as selective Notch target gene expression, while maintaining comparable IL-1, CXCL10, and IL-12p40 levels. Surprisingly, expression levels of FoxP3 in KO mice vs. controls were significantly decreased in both joint and splenic tissue (p=0.0244 and p=0.0286, respectively). Immunophenotyping of splenic and LN tissue showed increased proportions of total CD4+ T cells in KO mice vs. controls, but a markedly lower proportion of the CD4+CD25+FoxP3+ subset. Lower proportions of F4/80+ and Ly6G+ cell populations in splenic and draining LN tissue of KO mice vs controls, but higher populations of Ly6C+ cells, were also observed.

Conclusion: Deletion of RBP-J in the myeloid compartment does not lead to phenotypic differences in K/BxN serum-induced inflammatory arthritis, though selective modulation of pro-inflammatory cytokine gene expression *in vivo* does occur. Decreased gene expression of FoxP3 and fewer CD4+CD25+FoxP3+ cells in RBP-J deleted mice may contribute to this selective modulation. The functional significance of these findings, coupled with differences in myeloid cell composition and trafficking observed, remain undetermined and will be further studied.

Disclosure: **S. D. Chakravarty**, None; **K. Au**, None; **X. Hu**, None; **L. B. Ivashkiv**, None.

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Colony-Stimulating Factor (CSF) Receptor 1 Blockade Overcomes Overlapping Effects of M-CSF and Interleukin-34 On Myeloid Differentiation and Gene Expression to Reduce Inflammation in Human and Murine Models of Rheumatoid Arthritis. Samuel Garcia[1], Linda M. Hartkamp[1], Inge E. van Es[1], Haishan Lin[2], Li Long[2], Emma L. Masteller[2], Brian R. Wong[2], Paul P. Tak[3] and Kris A. Reedquist[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Five Prime Therapeutics, Inc., South San Francisco, CA, [3]Academic Medical Center, University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: Disease activity and response to therapy in RA correlates with changes in synovial macrophage numbers and their products. M-CSF or IL-34 stimulation of their receptor CSFR1 promotes macrophage differentiation, activation and osteoclastogenesis. Pharmacological inhibition of CSFR1 is beneficial in animal models of arthritis but the relative contributions of M-CSF, IL-34 and their receptor to inflammation in RA are unknown.

Methods: M-CSF, IL-34, and cellular markers were detected by immunohistochemistry and digital image analysis in synovial tissue from 18 biological-naïve RA patients, 14 PsA patients, and 4 controls without inflammatory disease (2 healthy donors and 2 OA patients). Gene expression in M-CSF and IL-34 –differentiated human macrophages was assessed by FACS analysis and q-PCR arrays. RA synovial explants were incubated with M-CSF, IL-34, control antibody (Ab), or a humanized CSFR1-blocking Ab. Prophylactic effects of control and CSFR1-blocking Ab were examined in murine collagen-induced arthritis (CIA).

Results: Expression of M-CSF and IL-34 was similar in RA and PsA synovial tissue, but lower in controls (p< 0.05). M-CSF expression was restricted to endothelial cells and IL-34 was observed in sublining mononuclear cells and intimal lining layer cells. *CXCL5, CXCL6, FN1, COL1A1, COL6A1–2, COL14A1, COL15A1, MMP7, MMP8* and *MMP9* mRNA

expression was significantly upregulated in macrophages differentiated in M-CSF compared to IL-34, while *CXCL7*, *CXCL9*, *CXCL10*, *CXCL11*, *CXCL12*, *LAMA1*, and *MMP2* were significantly downregulated. M-CSF or IL-34 had no effect on RA synovial explant IL-6 production, but anti-CSFR1 Ab dose-dependently reduced IL-6 production. Treatment with anti-CSFR1 Ab in CIA significantly reduced paw swelling and joint destruction.

Conclusion: M-CSF and IL-34 are expressed in topographically distinct regions of inflamed synovial tissue and differentially effect macrophage capacity to attract inflammatory cells and remodel tissue. Simultaneous inhibition of CSFR1 interactions with both M-CSF and IL-34 suppresses inflammatory activation of RA synovial tissue and pathology in CIA, suggesting a novel therapeutic strategy for the treatment of RA.

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Activation of NF-Kb Via Poly(I:C)-Induced Monocyte-Derived Microparticles Decreases TRAIL-Induced Apoptosis of Rheumatoid Arthritis Synovial Fibroblasts. Mojca Frank Bertoncelj[1], Blaz Rozman[2], Beat A. Michel[3], Renate E. Gay[1], David S. Pisetsky[4], Oliver Distler[5], Steffen Gay[6] and Astrid Juengel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Duke University Medical Center, Durham, NC, [5]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [6]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, CH-8091, Switzerland

Background/Purpose: Decreased sensitivity of rheumatoid arthritis (RA) synovial fibroblasts (SF) to apoptosis leads to synovial hyperplasia and destruction of joints in RA. Activation of NF-kB was shown to modulate apoptotic pathways in different target cells. Based on our recent finding that microparticles (MP) from monocytes, stimulated with Toll-like receptor 3 ligand Poly(I:C) (PIC), increase the resistance of RASF to TRAIL-induced apoptosis and enhance the production of NF-kB-dependent cytokines IL-6 and IL-8, the aim of the present study was to examine the role of NF-κB signaling in the resistance of RASF to TRAIL-induced apoptosis mediated via MP.

Methods: MP were isolated by differential centrifugation from supernatants of untreated or PIC-stimulated (16h) U937 cells or peripheral blood mononuclear cells (PBMC) and were analysed by nanoparticle tracking analysis, flow cytometry and BCA Protein Assay. RASF were treated with MP±TRAIL for 24h. To investigate direct effects of PIC on the apoptosis, RASF were stimulated with PIC±TRAIL for 24h. Apoptosis of RASF was measured by flow cytometry using Annexin V/propidium iodide staining. SC-514, a selective inhibitor of IκB kinase 2, was used to test the role of NF-kB signaling in MP actions in RASF. NF-κB activity was determined by luciferase reporter gene assay in RASF treated with MP for 6h.

Results: PIC-induced MP, but not MP from untreated U937 cells, significantly decreased TRAIL-induced apoptosis of RASF ($9\pm3\%$ vs TRAIL: $18\pm6\%$, p=0.003, n=8), and similar effects were observed with PIC-induced MP derived from PBMC ($18.\pm27\%$ vs $35\pm27\%$, n=3). In contrast, a direct stimulation with PIC alone significantly increased apoptosis of RASF ($11\pm4\%$ vs $6\pm2\%$ in untreated RASF, p=0.03, n=6), however it did not affect TRAIL-induced apoptosis of RASF. Number (MP from untreated cells: $3.0*10^{10}$/mL vs PIC-induced MP: $3.1*10^{10}$/mL; n=2 each), size (median diameter 207 vs 199nm, n=2 each), surface annexin V binding ($66\pm10\%$ vs $63 \pm 9\%$, n=3 each) and total protein content (330 ± 50 vs 325 ± 83 ng/mL, n=3 each) did not differ significantly between MP from untreated and PIC-stimulated U937 cells. SC-514 significantly increased TRAIL-induced apoptosis of RASF in the presence of PIC-induced MP ($20\pm3\%$ vs $9\pm3\%$ in the absence of SC-514, p=0.002, n=8). PIC-induced MP from U937 cells led to activation of NF-κB signaling in RASF (median x-fold change: 13 vs untreated RASF, n=4).

Conclusion: Most interestingly, we could show that the activation of NF-κB plays a major role in the resistance of RASF to TRAIL-induced apoptosis mediated via PIC-induced MP. This observed effect may reflect a specific composition of PIC-induced MP. Alternatively, the effects of MP could result from small amounts of PIC associated with MP although its activity would differ from that in the free state.

903

NR4A1 Mediates Anti-Inflammatory Effects of Apoptotic Cells. Natacha Ipseiz[1], Stefan Uderhardt[1], Georg A. Schett[2] and Gerhard Kronke[1]. [1]University of Erlangen, Erlangen, Germany, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: The nuclear receptor NR4A1 has been implicated as negative feedback regulator of NF kappa B signalling and as key regulator during the differentiation of Ly6C-low resident monocytes. Apoptotic cells are known to exert anti-inflammatory effects on macrophages but the underlying mechanisms are still poorly understood. Here we studied a potential role of NR4A1 as mediator of the macrophage response to apoptotic cells.

Methods: We analysed the effect of apoptotic thymocytes on wild type and NR4A1−/− peritoneal resident macrophages, and determined the consequences on intracellular signalling, gene expression and cytokine profile. Moreover, we examined the consequences of the lack of NR4A1 during maintenance of self tolerance by using the pristine-induced model of murine sytemic lupus erythematosus.

Results: Expresion of NR4A1 was rapidly and highly induced in resident macrophages after incubation with apoptotic thymocytes. NR4A1−/− resident macrophages showed an exacerbated pro-inflammatory profile as well as an increased activity of NF-κB. Moreover, the anti-inflammatory effects of apoptotic cells were reduced in NR4A1−/− macrophages. In the pristine model of murine lupus, NR4A1−/− mice displayed increased levels of autoantibodies such as ds-DNA antibodies.

Conclusion: Our data show for the first time that NR4A1 is an important mediator of the anti-inflammatory effects of apoptotic cells in tissue resident macrophages and thereby contributes to the maintenance of self-tolerance.

ACR/ARHP Poster Session B
Epidemiology and Health Services Research:
Epidemiology and Outcomes of Rheumatic Disease II
Monday, November 12, 2012, 9:00 AM–6:00 PM

904

Perinatal Characteristics, Maternal Reproductive History and Juvenile Idiopathic Arthritis: A Case-Control Study. Samantha W. Bell[1], Beth A. Mueller[1], J. Lee Nelson[2], Parveen Bhatti[1] and Susan Shenoi[3]. [1]University of Washington, Seattle, WA, [2]Fred Hutchinson Cancer Rsch, Seattle, WA, [3]Seattle Children's Hospital, University of Washington, Seattle, WA

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of chronic inflammatory arthritis conditions in children with onset before 16 years of age, and is the leading cause of acquired short and long-term disability in childhood. The etiology of JIA is largely unknown, however there is increasing evidence that autoimmune diseases, including JIA, may be associated with maternal reproductive or early childhood exposures.

Methods: We conducted a case-control study of JIA cases identified at a regional children's hospital in the Seattle-Puget Sound area, using linked birth certificate data from 1980 – 2009. Potential cases included all children <20 years with relevant ICD codes who had received inpatient or outpatient care. Their records were linked to Washington State birth records for 1980–2009 to identify those with a Washington State birth certificate (N=1,518). For comparison, control children were randomly selected in a ratio of 4:1 from the remaining birth records, frequency matched on year of birth (N=6,072). Review of medical records further refined case ascertainment based on

specific clinical criteria (N=1,254) and allowed categorization of cases into JIA subtypes. Multivariable logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations of JIA/JIA subtypes with maternal and early life exposures as measured in the birth certificates.

Results: Decreased ORs were observed for JIA in relation to greater maternal parity (2 prior live births, OR 0.70, 95% CI 0.58, 0.85; 4+ prior live births, OR 0.68, 95% CI 0.48, 0.97), a finding also observed for the persistent oligoarticular JIA subtype. Fewer cases (11.4%) than controls (13.3%) had a birth weight >4000 g (OR 0.81, 95% CI 0.67, 0.98). Mothers of cases (5.2%) were slightly more likely than those of controls (4.1%) to have had preeclampsia during their pregnancy (OR 1.29, 95% CI 0.96, 1.73).

Conclusion: To our knowledge, no studies to date in the United States have examined these exposures in relation to JIA. Greater maternal parity, specifically having 2 or more prior live births, was significantly associated with a decreased OR for JIA, a finding consistent with both the hygiene and microchimerism hypotheses.

Disclosure: S. W. Bell, None; B. A. Mueller, None; J. L. Nelson, None; P. Bhatti, None; S. Shenoi, None.

905

The Association Between Lower Body Mass Index and Increased Risk of Giant Cell Arteritis Is Not Explained by Differences in Physical Activity.
Karin Jakobsson[1], Lennart T.H. Jacobsson[1], Kenneth J. Warrington[2], Eric L. Matteson[2], Kimberly P. Liang[3], Olle Melander[1] and Carl Turesson[1]. [1]Lund University, Malmö, Sweden, [2]Mayo Clinic, Rochester, MN, [3]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: There is limited data on predictors of giant cell arteritis (GCA). Low body mass index (BMI), a history of smoking and several hormonal factors have been associated with GCA in a retrospective case-control study, and we have confirmed the association with low BMI in a prospective study. Potential explanations for the association between BMI and GCA, include a difference in the level of physical activity. To our knowledge, the impact of physical activity on the risk of GCA has not been studied previously.

Our purpose was to examine potential influence of physical activity as a risk factor of GCA in a nested case-control study based on a prospective health survey.

Methods: Incident cases of GCA among participants in a population based health survey, in which 30447 subject (12121 men and 18326 women) were included between 1991 and 1996, were used for the present study. As part of the health survey, information on medical history and life style factors was obtained using standard physical examinations and self-administered questionnaires. Information on physical activity were obtained by asking participants to estimate the number of minutes per week, for each of the four seasons, they spent performing 17 different physical activities. The answer was multiplied by an intensity factor depending on the activity creating a physical activity score. This method was adapted from the Minnesota physical activity questionnaire, and has been validated against accelerometer-monitoring, an objective measure of physical activity, in a subset of the present health survey population.

Individuals who developed GCA after inclusion was identified by linking the health survey database to the local patient administrative register and the national hospital discharge register. A structured review of the medical records of all identified cases was performed. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of GCA when the index person was diagnosed with GCA, were selected from the health survey. The impact of BMI and physical activity as predictors of GCA was examined in conditional logistic regression models.

Results: Fifty-five cases [mean age 73.6 years; standard deviation (SD) 5.21), 43 women (78 %), 31 temporal artery biopsy positive] had a confirmed diagnosis of GCA after inclusion. The median time from screening to GCA diagnosis was 9.4 years (range 0.4–16.6). BMI at screening was lower in GCA cases than in matched controls (mean 24.7 vs 26.1 kg/m^2). There was no association found between level of physical activity and development of GCA (mean score in cases and controls: 8349 vs 8134; p=0.95).The association between higher BMI and reduced risk of GCA was similar in bivariate analysis (OR 0.91 per kg/m^2; 95 % CI 0.84–0.99) and in multivariate analysis adjusted for physical activity (OR 0.92 per kg/m^2; 95 % CI 0.84–1.00).

Conclusion: GCA was predicted by a lower BMI, and this could not be explained by the level of physical activity at baseline. Physical activity did not

influence the risk of GCA. Other factors, such as diet, genetics or hormonal factors, may explain the association between low BMI and GCA.

Disclosure: K. Jakobsson, None; L. T. H. Jacobsson, None; K. J. Warrington, None; E. L. Matteson, None; K. P. Liang, None; O. Melander, None; C. Turesson, None.

906

Patient-Rheumatologist Communication Concerning Medication and Disease Risks.
Susan J. Blalock. University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: Medications play an important role in the management of rheumatoid arthritis.Principles of informed consent, informed and shared decision-making, and professional ethics highlight the importance of patients' understanding both the risks and benefits of different treatment options. Thus, the work described in this presentation is designed to increase current understanding of patient-rheumatologist communication about the risks associated with medications used to manage rheumatoid arthritis

Methods: We are content analyzing approximately 1000 audiotapes of rheumatoid arthritis patient-rheumatologist office visits that were collected in a previous study.The current study is guided by *fuzzy-trace theory*. This theory suggests that when an individual is exposed to information (e.g., a statement made by one's physician) two representations of the information are encoded in memory, a verbatim representation and a gist representation. Verbatim representations capture the precise information that was provided; whereas, gist representations reflect the essential meaning of the information to the person, including its emotional meaning. A central tenet of *fuzzy-trace theory* is that, when making judgments and decisions, people tend to rely on gist representations that are stored in memory and retrieve verbatim representations only when required by the task at hand. Thus, using *fuzzy-trace theory* as a guiding framework, we have developed a detailed 2-level coding scheme that captures the types of information concerning medication and disease risks that may be exchanged between patients and rheumatologists during office visits.

Results: A total of 3588 medication risks were identified in the transcripts. The most common medication risks were: methotrexate-GI problems (n=219); methotrexate-mouth/nose sores (n=190); methotrexate-need to monitor, but labs not specified (n=167); methotrexate-liver toxicity (n=141); methotrexate-pulmonary problems (n=109); and prednisone-implied risks by desire to minimize exposure to the medication (n=167).An average of 3.87 medication risks were discussed per office visit.Lower patient medication satisfaction was associated with: discussion of more medication risks (p < 0.03), patient and physician expression of medication safety concerns (p's < 0.05 and 0.0001, respectively) and lack of patient and physician endorsement of medication need/efficacy (p's < 0.0001 and.03, respectively).

Conclusion: By examining the manner in which medication and disease risks are discussed in combination, the findings from this study promise to provide a richer understanding of the risk communication that takes place during rheumatology office visits.

Disclosure: S. J. Blalock, None;

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Use of Patient Preferences to Inform the Development of Disease Modifying Drugs for Osteoarthritis.
Liana Fraenkel[1], Charles Cunningham[2], Gillian A. Hawker[3] and Lisa G. Suter[4]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [2]McMaster University, Hamilton, ON, [3]Women's College Research Institute, University of Toronto, Toronto, ON, [4]Yale University, New Haven, CT

Background/Purpose: Considerable efforts are currently being directed at developing robust and efficient trial designs to study the efficacy of disease modifying drugs (DMOADs) for osteoarthritis (OA). As part of this effort, an understanding of patients' preferences is needed.

Methods: We administered a conjoint analysis survey to a convenience sample of 304 patients attending outpatient clinics. The survey was composed of 4 attributes each having 3 levels: (1) administration (pill, injection (SC), infusion (IV)), (2) benefit (prevents progression in 40%, 60%, or 80%), (3) risk (mild: < 1 week and reversible, moderate: (1–2 weeks and requires treatment, serious: requires hospitalization), and (4) cost (easy, somewhat, hard to afford). All subjects were provided with a detailed description of each attribute before performing the survey. The survey included 12 choice tasks each with 3 medications and a "None" option (Figure). We performed Latent Class Segmentation analysis and simulations to estimate preferences for 4

options: Best Case (pill, prevents progression in 80%, mild side effects, easy to afford), Worst Case (IV, prevents progression in 40%, serious side effects, hard to afford), SC (SC, prevents progression in 40%, moderate risk, somewhat hard to afford), IV (same as previous except IV).

Results: 304 subjects participated; median (range) age=57 (34–89); 55% female; 69% Caucasian, 45% employed; 37% college graduates; 29% reported knee pain often or very often; 30% reported physician diagnosed knee arthritis. Segmentation analysis revealed 4 distinct groups of patients. The relative importances of the attributes are presented in Table 1. Treatment preferences are described in Table 2. Group 1 (5%) do not want to perform injections and only consider DMOADs under the Best Case scenario; Group 2 (19.4%) are most influenced by risk and fewer prefer DMOADs under more realistic scenarios; Group 3 (16.4%) consistently reject DMOADs, and Group 4 (59.2%) strongly prefer DMOADs regardless of risk or cost.

If these were your only options, which would you choose? Choose by marking one of the buttons below:

Injection given once a week. Prevents progression of arthritis in **80%** of people. Risk of **moderate** side effects. **Easily** affordable. **No** changes in budget needed.

Pill taken once a day. Prevents progression of arthritis in **60%** of people. Risk of **mild** side effects. **Hard** to afford. **Major** changes in budget needed.

Infusion given once a month. Prevents progression of arthritis in **40%** of people. Risk of **serious** side effects. **Somewhat** affordable. **Minor** changes in budget needed.

NONE: I wouldn't choose any of these.

Table 1. Relative Importances of Each Attribute

Attribute	Group 1 (N=15)	Group 2 (N=59)	Group 3 (N=50)	Group 4 (N=180)
1. Administration	58.5	11.5	11.8	2.9
2. Benefit	12.1	22.9	27.5	50.5
3. Risk	14.6	35.7	28.5	24.6
4. Cost	14.8	29.8	32.2	22.1

Table 2. Percent Preferring Each Hypothetical Treatment Option

Scenario	Group 1 (N=15)	Group 2 (N=59)	Group 3 (N=50)	Group 4 (N=180)
Best case	99.4	98.2	18.4	89.8
Worst case	0.7	4.4	7.6	85.4
SC	5.3	67.2	12.4	86.3
IV	20.2	54.9	11.1	86.1

Conclusion: Almost 60% of patients surveyed are willing to accept substantial risk in order to prevent progression of OA. These findings should help inform future drug development.

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Race, Gender and Total Knee Replacement Consideration: The Role of Social Support.
Ernest R. Vina[1], Yona Cloonan[2], Said Ibrahim[3], Michael J. Hannon[4], Robert M. Boudreau[2] and C. Kent Kwoh[1]. [1]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, [4]University of Pittsburgh School of Medicine, Pittsburgh, PA

Background/Purpose: There is marked variation in patient preference (i.e. willingness) regarding total knee replacement (TKR), an effective treatment option for end-stage osteoarthritis (OA).Studies have also shown that higher social support is associated with better patient decision-making.No study, though, has ever examined the importance of social support on patient preference.The purpose of this study is to determine whether there are racial differences in social support among patients with knee OA and whether the impact of social support on preference for TKR varies by race and gender.

Methods: Our sample consists of 514 white & 285 African-American (AA) patients with chronic, frequent knee pain and radiographic evidence of knee osteoarthritis (OA).Structured interviews were conducted to determine sociodemographic information, clinical characteristics, and extent of structural (marital status, # of close friends/relatives) and functional (Medical

Outcomes Study-Social Support Scale [MOS-SSS]) social support.A hypothetical, Likert-scaled question was also asked: "Would you be willing to have surgery to replace your knee if your doctor recommended it?". Hierarchical logistic regression models were performed to evaluate the relationship between willingness to undergo TKR and the interaction of patient race and sex, adjusted for recruitment site, age, income, WOMAC total score and measures of social support.

Results: Among AA participants, 22.8% were married, as compared with 53.5% of white participants (p<0.001).The mean numbers of close friends/relatives reported by AA and white patients were 7.52 ± 8.88 and 10.31 ± 13.13, respectively (p<0.001).Half of AA patients reported living alone, as compared with 33.5% of white patients (p<0.001).MOS-SSS scores were lower in AA (13.44 ± 5.26) as compared with white (15.17 ± 4.79) participants (p<0.001).Compared to white patients with knee OA, AA patients with knee OA were less willing to undergo TKR surgery (80.0% vs. 62.4%, p<0.001).

The odds of willingness to undergo TKR surgery was less in white females compared to white males when adjusted for recruitment site, age, income and WOMAC score (OR 0.57, 95% CI 0.34–0.96), but this difference was no longer significant when further adjusted for marital status, number of close friends/relatives and MOS-SSS score (OR 0.60, 95% CI 0.35–1.02).The odds of willingness to undergo TKR surgery was also less in AA females (OR 0.33, 95% CI 0.18–0.60) and AA males (OR 0.26, 95% CI 0.13–0.52) compared to white males when adjusted for sociodemographic and clinical factors.These differences in odds remained significant when further adjusted for all social support measures (OR 0.35, 95% CI 0.19–0.64, in AA females; OR 0.28, 95% CI 0.14–0.54, in AA males).

Conclusion: We found lower preference for TKR surgery in AA compared to white patients with knee OA.AA OA patients also reported less structural and functional social support than white patients.There was a race and gender interaction in patient preferences for TKR surgery.In white patients, social support accounted for the gender difference in willingness to consider TKR.Social support, though, did not seem to mediate the racial difference in patient preferences for TKR.

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Determinants of Patient Preferences for Total Knee Replacement: A Comparison of Whites and African-Americans.
C. Kent Kwoh[1], Robert M. Boudreau[2], Yona Cloonan[2], Michael J. Hannon[3], Ernest R. Vina[2] and Said Ibrahim[4]. [1]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background/Purpose: TKR is a cost-effective treatment option for end-stage knee osteoarthritis (OA). Although it is one of the fastest growing elective surgeries, there are marked racial disparities in the utilization of TKR. Patient's preferences have been found to be an important consideration in TKR disparities. However, determinants of patients' preference regarding TKR remain unclear. We sought to identify whether determinants of patients' preference for TKR differ by race.

Methods: Our sample consisted of 514 whites (59% female) and 285 AAs (73% female) with chronic, frequent knee pain and radiographic evidence of knee OA. Structured interviews were conducted to collect sociodemographic information, socio-cultural determinants, disease severity (i.e, WOMAC), and treatment preferences. We performed hierarchical logistic regression, stratified by race, to identify determinants of patients' preference for TKR. Clinical and socio-cultural factors were entered simultaneously into race stratified models. Stepwise selection identified factors for inclusion in the final models, using a criterion of p<0.20. All models were adjusted for age, sex, income level, disease severity (WOMAC), and study site.

Results: Compared to whites, AA patients were less willing to undergo TKR (80% vs. 62%, respectively, adjusted OR=0.45, 95%CI 0.29 to 0.70). The results of the multivariate modelare summarized in the table below. Among AA patients, knowledge (p=0.031) and expectations (p=0.084) regarding surgical outcomes, religiosity (p=0.045), and physician trust (p=0.104) were included in the final multivariate model. Among white patients, expectations regarding surgical outcomes (p<0.001), two items related to physician interaction and referral patterns (p=0.039), and trust in the healthcare system (0.068) were included in the final multivariate model.

OR for Willingness to Undergo TKR	AAs OR (95% CI)*	Whites OR (95% CI)*
Knowledge Regarding TKR		
Understands TKR	1.80 (0.97, 3.35)	
Prolonged Length of Stay After TKR	0.81 (0.58, 1.13)	
Residual Pain After TKR	0.73 (0.39, 1.35)	
Residual Difficulty Walking After TKR	0.66 (0.37, 1.16)	
Ever Discuss TKR with a physician		1.96 (1.05, 3.68)
Referred to Surgeon		0.56 (0.32, 0.99)
Expectations Regarding TKR** Second Quartile	1.85 (0.76, 4.51)	1.70 (0.86, 3.33)
Third Quartile	2.82 (1.30, 6.15)	2.73 (1.32, 5.65)
Highest Quartile	2.08 (0.91, 4.79)	5.11 (2.31, 11.30)
Religiosity** Second Quartile	2.52 (0.93, 6.84)	
Third Quartile	1.21 (0.43, 3.42)	
Highest Quartile	0.85 (0.32, 2.26)	
Physician Trust** Second Quartile	2.14 (0.89, 5.15)	
Third Quartile	1.01 (0.46, 2.25)	
Highest Quartile	2.17 (0.90, 5.23)	
Trust in Healthcare System** Second Quartile		2.69 (1.26, 5.76)
Third Quartile		1.94 (0.91, 4.13)
Highest Quartile		1.58 (0.75, 3.31)

* adjusted for sex, age, income level, WOMAC and site; ** Lowest Quartile is reference group.

Conclusion: Although expectations regarding surgical outcomes are associated with preference for TKR in both AA and white patients, they differed with regard to which other clinical and socio-cultural determinants impact the preference to undergo TKR. Interventions to reduce or eliminate racial disparities in the utilization of TKR should consider and target these factors.

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The Cost-Effectiveness of Total Joint Arthroplasty: A Systematic Review of Published Literature. Meghan E. Daigle, Alexander M. Weinstein. Jeffrey N. Katz and Elena Losina, Brigham and Women's Hospital, Boston, MA

Background/Purpose: Utilization of total hip arthroplasty (THA) and total knee arthroplasty (TKA) has nearly doubled in the last decade. These procedures are increasingly performed in younger, more active individuals. We sought to summarize the state of the literature evaluating the cost-effectiveness of these highly efficacious, costly procedures and identify areas where further work is needed.

Methods: We conducted a systematic review of cost-effectiveness analyses of elective THA and TKA that were published between January 1980 and February 2012. To limit our search to high-quality publications, we selected among papers included in the Cost-Effectiveness Analysis Registry (created by the Center for the Evaluation of Value and Risk in Health); we augmented our search with papers listed in PubMed. Only papers reporting incremental cost-effectiveness ratios (ICERs) as the change in cost over the change in quality-adjusted life expectancy between alternative treatment strategies were included. We abstracted the analysis perspective, time horizon, and ICERs (converted to 2011 USD) from the selected papers.

Results: Seven TKA and six THA studies met the criteria for our review. All economic evaluations of TKA were published between 2006 and 2012, whereas THA studies spanned 1996 to 2008. Out of the 13 included studies, four assumed the societal perspective, eight the payer perspective, and in one study the perspective was unclear. Seven studies spanned the lifetime horizon. Studies of both THA and TKA that have assumed a societal perspective and lifetime horizon have estimated ICERs below $50,000/QALY in cohorts with mean age 69 years or older. Hip resurfacing has been shown to be dominated by THA (more costly, less effective) in a cohort aged 65 years and younger. Unicondylar knee arthroplasty (UKA) has been shown to be cost effective or cost-saving among cohorts of mean age 65–75 years.

Comparison*	Paper		Perspective	ICER ($/QALY; 2011 USD)	Time Horizon
Total Hip Arthroplasty					
THA vs. No Surgery	Chang	1996	Societal	$10,402	Lifetime
Improved Implant (reduced revision rate, increased cost) vs. Standard Implant	Briggs	1998	Payer	$17,671	Lifetime
	Briggs	2004	Payer	cost saving	60 yrs
	Bozic	2006	Not clear	cost saving	Lifetime
THA vs. Hip Resurfacing	McKenzie	2003	Payer	THA dominates	20 yrs
Cementless vs. Cement	Marinelli	2008	Payer	Neither option clearly better	Lifetime
Total Knee Arthroplasty					
Computer Assisted Surgery vs. TKA	Dong	2006	Payer	cost saving	10 yrs
	Novak	2007	Payer	$54,234	15 yrs
UKA vs. TKA	Slover	2006	Payer	cost saving	Lifetime
	Soohoo	2006	Societal	$458	Lifetime
TKA vs. UKA	Xie	2010	Societal	$71,731	2 yrs
TKA vs. No Surgery	Losina	2009	Societal	$11,548	Lifetime
	Dakin	2012	Payer	$12,566	5 yrs

*The first strategy listed is the primary intervention studied, and the second strategy is the reference comparator; that is, ICERs refer to the cost-effectiveness of the first treatment option listed.

Conclusion: THA and TKA have been found to be highly cost-effective in a number of high-quality studies. Further analyses of the cost-effectiveness of alternative surgical options, including knee osteotomy, among young individuals are needed. Future economic evaluations should address the expanding indications of THA and TKA to younger, more physically active individuals.

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Race- and Sex-Specific Estimates of 10-, 20-, 30-Year, and Lifetime Risk of Diagnosed Symptomatic Knee Osteoarthritis and the Need for TKR in the US. Elena Losina, Meghan E. Daigle, Sara A. Burbine and Jeffrey N. Katz. Brigham and Women's Hospital, Boston, MA

Background/Purpose: A growing body of evidence suggests that females are more likely to be diagnosed with knee osteoarthritis (OA) and that obesity increases the risk of knee OA. Population-based studies suggest that Black and Hispanic females have a greater likelihood of being obese than White females. Sex- and race/ethnicity-specific risks of diagnosed symptomatic knee OA and the need for TKR have not been estimated.

Methods: We combined the OAPol Model – a validated state-transition, computer simulation model – with published data on the incidence of OA, stratified by sex and obesity. Obesity prevalence, stratified by sex and race/ethnicity, was derived from published literature and ranged from 19% for White males to 34% for Black females. The increased risk of symptomatic knee OA conferred by obesity was derived from published studies (RR = 1.7). Rates of progression of knee OA were derived from the Johnston County Osteoarthritis Project and calibrated to published data. The annual incidence of TKR among persons with advanced knee OA (Kellgren-Lawrence grade 3 or 4) was derived using data from two national longitudinal studies of persons with knee OA (Multicenter Osteoarthritis Study and Osteoarthritis Initiative). Input parameters related to mortality, obesity, comorbidities, non-surgical OA treatments, and implant failure were obtained from national survey data and published literature. Using the OAPol Model we estimated the 10-year, 20-year, 30-year and lifetime risks of diagnosed symptomatic knee OA and TKR from age 40, stratified by race and sex.

Results: In persons free of knee OA at age 40, the lifetime risk of diagnosed symptomatic knee OA ranged from 10% among White males to 17% among Black females (Figure). The 20-year risk of diagnosed symptomatic knee OA ranged from about 6% in males (race/ethnicity did not affect the rate meaningfully) to 8% in Black females. By age 65, 11.3%, 10.5%, and 10% of Black, Hispanic, and White females, free of knee OA at age 40, will be diagnosed with symptomatic knee OA (Figure). Lifetime need for TKR ranged from 3.8% for Hispanic males to 6.8% for Black females.

Risk of Diagnosed Symptomatic Knee Osteoarthritis
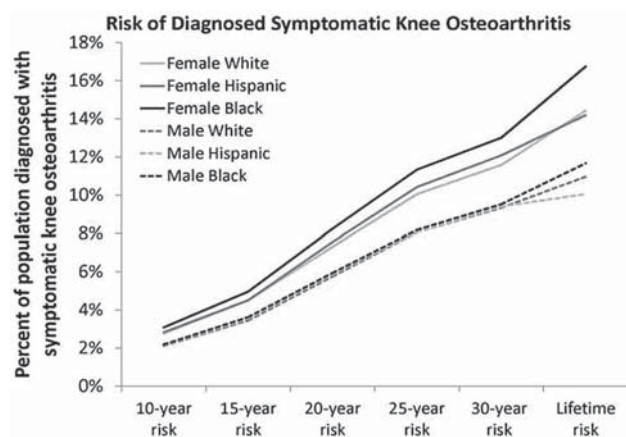
Conclusion: Lifetime risk of diagnosed symptomatic knee OA varies by age and race/ethnicity. Black females are more likely to be obese, which corresponds with their having the greatest lifetime risk of being diagnosed with knee OA and needing TKR. Race- and sex-tailored weight management programs may reduce the lifetime risk of knee OA.

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Clinical Features Associated with Progression of Knee Radiographic Osteoarthritis: Data From the Osteoarthritis Initiative. Michelle S. Yau[1], Laura Yerges-Armstrong[1], Braxton D. Mitchell[1] and Marc C. Hochberg[2]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: A better understanding of the factors associated with structural progression of knee osteoarthritis (OA) may help identify individuals not only at risk for more rapid OA progression who can benefit from early intervention, but also help classify high-risk OA patients for inclusion in clinical trials of new treatments. Using the complete 4-year follow-up data from the Osteoarthritis Initiative (OAI), we tested baseline measures from six domains [1) knee examination, 2) anthropometric characteristics, 3) sociodemographic characteristics, 4) medical and family history, 5) physical functioning, and 6) self-reported pain and symptoms] for their association with radiographic knee OA (RKOA) progression.

Methods: Subjects with evidence of RKOA in one or both knees at baseline and with at least 1 follow-up exam over the 4-year period (n = 3,204) were eligible for analysis; knees with end-stage disease were excluded from the analysis. We defined RKOA progression as an increase in Kellgren-Lawrence (KL) grade or osteophyte score or joint space narrowing score. We used Cox regression models to test the association of individual level measures with RKOA progression, adjusting for age, gender, and race. Within each of the six domains, we performed univariate and multivariable stepwise analyses. Significant predictors from all domain-level multivariable models were then included in an overall multivariable analysis with stepwise selection. We also conducted knee-specific analyses with the same approach, but included a robust sandwich estimate of the covariance matrix to account for non-independence of two knees within an individual.

Results: 51% of subjects with baseline RKOA (KL grade 1–3) experienced RKOA progression in one or both knees. Progressors were 58% female, 19% Black, and had mean (SD) age of 61 (9) years and mean body mass index of 29 (5) kg/m^{2}. Subjects with no RKOA progression had a similar profile. In the multivariable model for each domain, the following baseline factors were found to be significantly associated with RKOA progression: knee joint effusion, pain on flexion, patellofemoral crepitus, patellar grind, and flexion contracture; number of hand bony enlargements, history of knee injury, and use of analgesics; repeated chair stand pace, 400-meter walk pace, and pain during 400-meter walk; KOOS sports and recreational activities score and KOOS symptoms score. Similar results were obtained with the knee-specific analyses with the additional significant finding of KOOS pain score. Final, overall multivariable models for the individual and knee-specific analyses are presented in Table 1.

Table 1. Hazard Ratios for Associations with RKOA Progression

Domain	Parameter	Hazard Ratio (95% CI)	
		Individual-level	Knee-specific
Knee exam	Knee joint effusion, bulge sign positive	1.34 (1.14–1.58)	1.29 (1.09–1.52)
	Patello-femoral crepitus	1.58 (1.36–1.83)	1.39 (1.22–1.58)
	Knee flexion contracture	1.02 (1.00–1.04)	1.02 (1.00–1.04)
	Knee flexion pain/ tenderness	–	1.26 (1.06–1.49)
Medical and family history	Number of bony enlargements in hands	1.03 (1.00–1.05)	1.04 (1.01–1.06)
	History of knee injury	–	1.27 (1.11–1.46)
Physical functioning	Pain during 400-meter walk	1.33 (1.12–1.59)	–
Self-reported pain/ symptoms	KOOS sports/ recreational activities score	0.99 (0.99–0.99)	0.99 (0.99–1.00)
	KOOS Pain Score	–	0.99 (0.99–1.00)
Adjusted covariates	Black race	1.04 (0.86–1.26)	1.00 (0.84–1.18)
	Asian race	0.74 (0.27–2.00)	0.75 (0.28–2.00)
	Other race	0.63 (0.33–1.22)	0.72 (0.38–1.36)
	Male gender	0.94 (0.81–1.09)	0.93 (0.81–1.07)
	Age	1.00 (0.99–1.01)	1.00 (0.99–1.01)

Conclusion: Out of the six domains investigated, four domains yielded significant measures associated with RKOA progression. These measures may help identify individuals at increased risk of RKOA progression who may benefit from early intervention.

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Consultation Prevalence of Osteoarthritis in Southern Sweden. Aleksandra Turkiewicz[1], Ingemar F. Petersson[1], Jonas Björk[2], Leif E. Dahlberg[1] and Martin Englund[1], [1]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden, Lund, Sweden

Background/Purpose: To estimate the prevalence of subjects with osteoarthritis (OA) having led to doctor consultation.

Methods: The Skåne Health Care Register (SHCR) is a legislative, mandatory register based on physicians' International Classification of Diseases (ICD) 10 diagnostic codes. The register covers all in- and outpatient health care in southern Sweden (total population 1.3 million). We identified all adult (20 years of age or older) patients having received the diagnosis of knee OA (ICD-10: M17), hip OA (M16), hand OA (M15.1, M15.2, M18, M19.0D, M19.1D or M19.2D), spine OA (M47) and OA in other locations, i.e., elbow, foot, shoulder, or other joints (M19 different from M19.0D, M19.1D and M19.2D) or polyarthrosis (M15 different from M15.1 and M15.2) during the years 1999 until 2011. We obtained point estimates of consultation prevalence by Dec 31st 2011 by cross referencing with the population register to exclude subjects who had relocated from the county or were deceased. To obtain valid prevalence estimates and confidence intervals in presence of missing data on ICD-10 codes (mainly in private care and in primary care before the year 2004), we used the multiple imputation technique. The variables included in the imputation model were age, sex and clinic and their interactions, year, if consulted physiotherapist, if consulted psychiatrist, residential area, civil status, indicator for in- or outpatient care and the person as a random effect to account for the correlation between visits made by the same patient.

Results: The adult consultation prevalence of OA (any location) was 18.6% (95%CI: 18.4%; 18.7%), 15.8% (95%CI: 15.6%; 16.0%) for men and 21.3% (95%CI: 21.0%; 21.5%) for women. The most common location was knee OA with a prevalence of 9.0%, followed by OA of other joints –7.5%, OA of the hip –4.0%, hand OA – 2.7% and spine OA with the consultation prevalence of 1.6%. The consultation prevalence in population aged 65 or more was 45.5%, 40.5% for men and 49.6% for women. If we considered a diagnosis of joint pain (ICD-10: M25.5) and age 45 or older as OA, the consultation prevalence of OA in extremities increased from 29.6% to 38.5%. The age and sex-specific patterns are displayed in the graph (Figure).
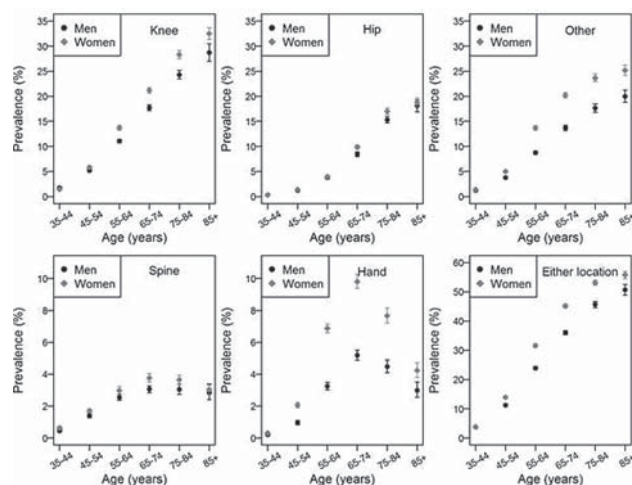
Figure. The prevalence of osteoarthritis by location, sex and age. Vertical bars represent the 95% confidence intervals.

Of subjects who consulted for OA 28% had OA diagnosed in more than one location, knee OA and other OA being the most common combination (12.5%).

Conclusion: The high doctor consultation prevalence of OA in extremities, 18.6% of all adults, 45.5% of all above 65 years of age, shed light on the burden on the health care system and concerns with a steadily ageing and increasingly obese population. It reinforces the need for improved OA patient care and preventive strategies as well as an increased need for join replacement operations.

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Prognosis for the Year 2030: The Consultation Prevalence of Osteoarthritis in Sweden May Increase by 50%. Aleksandra Turkiewicz[1]. Ingemar F. Petersson[1], Jonas Björk[2], Leif E. Dahlberg[1] and Martin Englund[1], [1]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden, Lund, Sweden

Background/Purpose: To project the future prevalence of knee and hip osteoarthritis (OA) leading to doctor consultation.

Methods: The Skåne Health Care Register is a legislative, mandatory register in Skåne County, Sweden (total population 1.3 million), based on physicians' International Classification of Diseases (ICD) 10 diagnostic codes. We used observational data on the consultation prevalence of the knee (M17) and hip OA (M16) by the 31st Dec 2011 based on the SHCR data from years 1999–2011. The age-specific (age 20–65 and >65 years) population structure prognosis and its confidence intervals for Skåne were provided by Statistics Sweden. We assumed two scenarios. In scenario 1 (conservative) we assumed that the age-specific prevalence would remain constant. In scenario 2 we assumed that the age-specific prevalence would increase relatively by 2.6% per year in the first 10 years and by 2% per year in the next 10 years for those aged ≤65 and by 1.6% per year in the first 10 years and by 1.2% per year in the next 10 years for the population >65. Initial values for that increase are based on the previously published changes in the prevalence of arthritis between 1994 and 2002 in Canada (Perrucio et al 2006). The reasons for this observed increase are not fully understood but the increase in obesity is the main plausible cause.

Results: In the conservative scenario which solely depends on changes in age distribution of the population, the consultation prevalence of knee OA in adults (aged 20+) will increase from 9.0% in 2011 to 9.9% in 2030. The hip OA consultation prevalence will increase from 4.0% in 2011 to 4.6% in 2030. Assuming the second scenario, i.e., an increase in age-specific prevalence, the consultation prevalence of knee and hip OA in adults will increase to 13.6% and 6.1% in 2030, respectively.
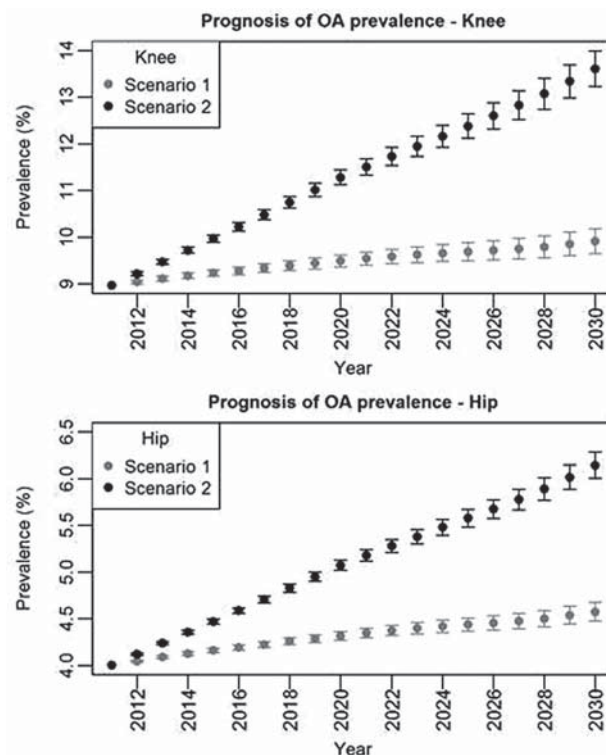
Figure. The prognosis of knee and hip OA consultation prevalence in Swedish adults (aged 20+). Vertical bars represent the confidence intervals of the prognosis due to uncertainty of the population prognosis.

Conclusion: There is a risk for a 50% increase in OA prevalence in 20 years from now. Results suggest that fighting the negative impact of obesity will be of primary importance to reduce the occurrence of the OA in the future.

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Incidence of Knee, Hip, and Hand Clinical Osteoarthritis: A Population-Based Cohort Study. Daniel Prieto-Alhambra[1], Aina Pagès-Castellà[2], M. Kassim Javaid[3], Andrew Judge[4]. Cyrus Cooper[5], Nigel K. Arden[3] and Adolfo Díez-Pérez[6], [1]URFOA-IMIM, Parc de Salut Mar; Idiap Jordi Gol; University of Oxford; University of Southampton, Barcelona, Spain, [2]IDIAP Jordi Gol; Institut Català de la Salut, Barcelona, Spain, [3]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Oxford, United Kingdom, [4]Oxford University, Oxford, United Kingdom, [5]University of Oxford; Southampton General Hospital, Southampton, United Kingdom, [6]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona, Barcelona; and RETICEF, ISCIII Madrid; Spain, Barcelona, Spain

Background/Purpose: Data on age-specific effects of gender, obesity and previous osteoarthritis (OA) on incident OA at other joints are scarce. We aimed to calculate age and gender-specific incidence of joint-specific clinical OA. Secondly, we studied the age-dependent effect of gender, and the excess risk related to obesity and previous OA on newly diagnosed OA at the knee, hip and hand.

Methods: We screened computerized medical records in the SIDIAP Database (www.sidiap.org) to identify those aged 40 years or older with an incident diagnosis of OA of the knee, hip and hand using ICD-10 codes in the period 2006–2010. SIDIAP contains the anonymised medical records of >3,100 GPs in Catalonia (North-East Spain) with information on an 80% of the total population. Age and gender-specific incidence rates (IR), Female: Male Rate Ratios (RR), and 95%Confidence Intervals (99%CI) were calculated assuming a Poisson distribution. Cox regression was used to compute adjusted (for age, gender, and body mass index(BMI)) hazard ratios (HR) for a new diagnosis of OA according to BMI (WHO categories) and to prevalent joint-specific OA status.

Results: We identified 26,381, 12,567 and 10,092 incident cases of knee, hip and hand OA respectively. Age-specific IRs for knee, hip, and hand OA are shown [Figure]. Female:Male RRs peaked at age 70–75 years for hip and knee, and at the age of 50–55 years for hand OA [Figure]. Adjusted HRs for BMI categories were highest for knee OA (overweight = HR 2.00 (99%CI 1.94–2.06), obesity 1 = HR 3.19 (3.09–2.30), obesity 2 = HR 4.72 (4.56–4.89)), followed by hip OA (HR 1.46 (1.39–1.52); 1.75 (1.66–1.83); 1.93 (1.82–2.05)), and lower for hand OA (HR 1.22 (1.17–1.27), 1.30 (1.25–1.36) and 1.31 (1.24–1.38)).
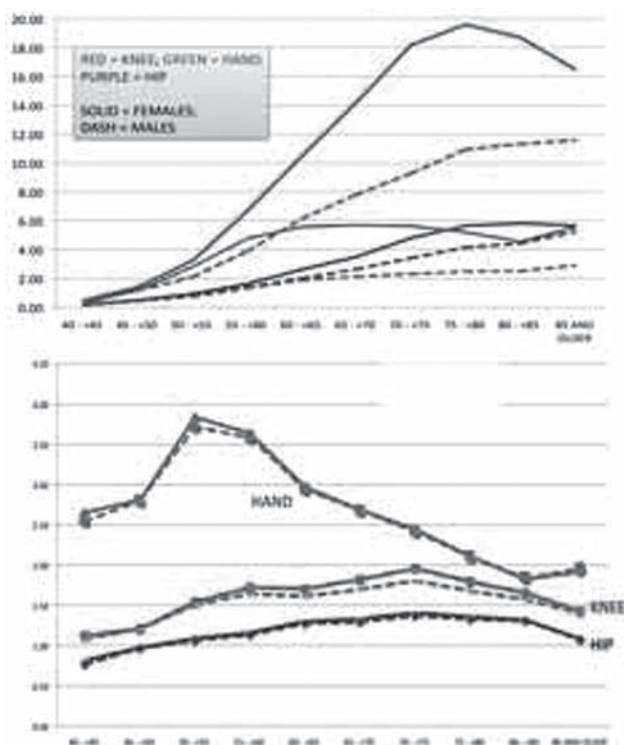
Figure. Age and gender-specific IR (/1,000 person-years) of knee, hip and hand OA [Top], and unadjusted (solid) and adjusted (dash) Female:Male RR [Below].

Adjusted HR for prevalent knee OA on hip OA was 1.35 (1.28–1.43); HR for previous hip OA on incident knee OA was 1.15 (1.08–1.23). Hand OA predicted both knee and hip OA (HR 1.20 (1.14–1.26) and 1.23 (1.13–1.34) respectively).

Conclusion: Age, gender, BMI and history of OA affecting other joints are related differently to incident knee, hip and hand OA: both the effect of age and gender are greatest in the elderly for knee and hip OA, but around menopause for hand OA. The effect of overweight and obesity is strongest on knee OA, and weakest but significant on hand OA. Finally, a history of knee or hip OA predict incidence of each other, and previous hand OA is related to increased risk of knee and hip OA, all independently of age, gender and BMI.

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Population Incidence of Soft Tissue Knee Injury: Estimates From a Swedish Health Care Register. Charlotte Bergknut[1], George Peat[2], Richard Frobell[1] and Martin Englund[3]. [1]Lund University, Lund, Sweden, [2]Arthritis Research UK Primary Care Centre, Keele University, United Kingdom, [3]Department of Orthopedics, Clinical Sciences Lund, Lund University, Sweden, Sweden

Background/Purpose: Soft tissue knee injury is a well-established and potent risk factor for development of knee osteoarthritis. However, there is a paucity of epidemiological data from the general population. Our aim was to address this gap using data from a large, regional health care register, i.e., to estimate the annual incidence of clinically diagnosed soft tissue knee-injured subjects in the entire population.

Methods: In Sweden, in- and outpatient health care is registered using each individuals' unique personal identifier. This register includes information on date of visit and the International Classification of Diseases (ICD) 10 diagnostic code(s) as determined by physicians' clinical examination. For the calendar years 2004–2011, we studied the population in southern Sweden, Skåne County (approx. 1.2 million individuals). We identified residents who had at least one visit to a physician with clinically diagnosed knee contusion (S80.0) or knee dislocation/distortion (S83 and all subdiagnoses). Consequently, knee fractures were not included. To calculate the annual cumulative incidence of clinically diagnosed soft tissue knee-injured subjects, stratified by age- and sex, the number of diagnosed patients during the calendar year formed the numerator of the rate and the population at risk at the start of the year, compensated for patients seeking private care (due to missing diagnostic codes), was the denominator. We then calculated the mean annual cumulative incidence over the 8-year period. In a second step, we investigated potential seasonal variations.

Results: The overall incidence of clinically diagnosed soft tissue knee-injured subjects was 718 per 100,000 per year (672 per 100,000 women and 766 per 100,000 men). The most frequently diagnosed injuries were contusion of knee (31.3% of subjects) followed by sprain and strain of knee (27.7%), injury to multiple structures of knee (22.3%), tear of meniscus (11.3%), collateral ligament injury (10.7%), and cruciate ligament injury (9.9%). The highest incidence of knee-injured subjects was found in those aged 15 to 19 years for both sexes (1424 per 100,000 women and 1658 per 100,000 men). After this age, there was a general decline but with an increase again in the incidence in the most elderly (figure). We found substantial seasonal variations in both genders with peaks in March-May and August-October.

Annual incidence of clinically diagnosed soft tissue knee-injured subjects (per 100,000 women and men, respectively. Data are means over the 8-year period (2004-2011).
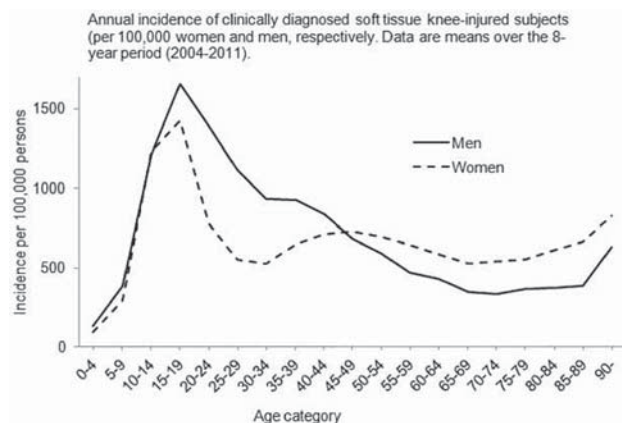
Conclusion: Clinically diagnosed soft tissue knee injury occurs with marked age and seasonal variations. The high incidence among young people warrants further attention as the potential induction point for many cases of post-traumatic knee osteoarthritis.

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Feasibility of Remote Activity and Functional Status Monitoring of Patients with Hip or Knee Pain. Pim Jetanalin[1], Hyeon Eui Kim[1], Zia Agha[2], Nathaniel Heintzman[1], Lucila Ohno-Macado[1] and Susan J. Lee[1]. [1]University of California, San Diego, La Jolla, CA, [2]San Diego Veterans Affairs Medical Center, San Diego, CA

Background/Purpose: The incidence of total hip and knee arthroplasties has risen over the past decade and by 2030, the demand of these arthroplasties is estimated to increase by 137% and 601%, respectively. Early ambulation is critical for timely recovery of functional independence. However, not all patients have access to rehabilitation due to lack of money, transportation, and/or time. Accelerometer has been validated in analyzing gait and physical activities among patients with arthritis. We assessed the feasibility of a wireless system that remotely monitors patient's physical activities, functional status, and pain among patients with hip or knee arthritis. This information can then provide feedback to patients to facilitate their post-operative rehabilitation regimen.

Methods: Patients with hip or knee arthritis who had internet access were asked to complete web-based patient-derived questionnaires and wear the SenseWear® armband (SWA) for 14 day except during sleep and shower. SWA collects heat flux, Galvanic Skin Response (GSR), 3-axis accelerometer, and skin temperature. Data on demographics (age, sex, highest level of education, marital status, and yearly household income) and baseline functional status using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were obtained. The web-based questionnaire comprised of WOMAC, visual analog scale (VAS) for pain, and self-reported duration of daily exercise. The web-based questionnaire was developed using a HIPAA compliant commercial survey tool called SurveyGizmo (www.surveygizmo.com).

Results: Convenient sample of 14 patients were recruited with 9 patients (64%) completing the study. The 2 most common reasons for incompletion were difficulty downloading the SWA software and inconvenience of wearing daily SWA. The majority of the completers were Caucasians (56%) and female (89%) with a mean age and body mass index (BMI) of 52.4 ± 12.3 years and 37.5 ± 9.2, respectively. Education level ranged from junior high to post-graduate levels with 77% having completed at least college. Majority (77%) had annual household income ≤ $40,000. Non-completers were older (70.0 ± 10.9 years) with lower BMI (29.5 ± 5.7). The majority of patients had significant arthritis with baseline VAS pain of 56.7 + 26.9 and WOMAC of 48.7 (out of 97). The paper- and web-based WOMAC score correlated well with intraclass coefficient (ICC) of 0.885 (p=0.0015). Patients wore SWA for mean 12hrs 25min daily with mean duration of exercise >3MET for 40min daily. The mean self-reported duration of exercise was higher than actual duration measured by SWA (94min vs 40min). There was no correlation between the level of pain and the duration of SWA-measured exercise.

Conclusion: As patients tend to overestimate their levels of physical activity, a wireless activity-monitoring tool such as SWA serves as a valuable tool to better assess the level of physical activity. This study demonstrated the feasibility of our activity and functional status monitoring system, which can be used to facilitate earlier return to independence after joint arthroplasties by providing a means to assist patients with home-based rehabilitation program.

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Impact of Comorbidities On Measuring Indirect Utility by the Medical Outcomes Study Short Form 6D in Lower-Limb Osteoarthritis. Kossar Hosseini[1], Cécile Gaujoux-Viala[2], Joel Coste[1], Jacques Pouchot[1], Bruno Fautrel[3], Anne-Christine Rat[1] and Francis Guillemin[1]. [1]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, France, Nancy, France, [2]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy; Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [3]Paris VI University, Paris, France

Background/Purpose: Comorbidities refer to chronic co-occuring disorders and are inversely and negatively correlated with HRQoL. Because indirect utility measurement involves HRQoL, comorbidities probably affect utility assessment. We investigated the impact of comorbidities to assess indirect utility measured by the Medical Outcomes Study Short Form 6D (SF-6D) in patients with osteoarthritis (OA).

Methods: The 878 patients of the KHOALA (Knee and Hip OsteoArthritis Long term assessment) cohort were included in the study. KHOALA cohort is a multiregional population based study of patients aged 45–75 years with symptomatic knee or/and hip OA. comorbidities were assessed by the Functional Comorbidity Index (FCI) and grouped in 9 categories. Limitation in activities and pain was measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Two separate linear regression models, using the number of comorbidities or the different categories of comorbidities of the FCI, were fitted to determine predictors of utility score.

Results: For the 878 patients included, the mean (SD) utility score was 0.66 (11; range 0.32–1.00) and mean number of comorbidities 2.05 (1.58). In the first multivariate model, for each additional comorbidity (range 0–9) the mean utility score decreased of 0.01 point (beta= −0.010, p<0.0001). In the second model, including comorbidities by categories, only psychiatric disease (beta=−0.043, p<0.0001) and degenerative disc disease (beta=−0.014, p=0.018) predicted low utility score. In both regression models a worsened function (increased WOMAC function score) significantly decreased the utility score. The number of comorbidities explained 2% of the variance in utility score (partial R-square=0.02) and psychiatric and degenerative disc diseases explained 2% (partial R-square=0.025) and 0.7% (partial R-square=0.007), respectively, of the variance in utility score, whereas the WOMAC function score explained 38% of the variance in both models (partial R-square = 0.38).

Conclusion: Compared to greater negative effect of functional impairment, comorbidities have a negative but relatively marginal impact on indirect utility score. This suggests that clinically, considering the functional severity of OA remains a first priority.

Disclosure: K. Hosseini, None; **C. Gaujoux-Viala**, None; **J. Coste**, None; **J. Pouchot**, None; **B. Fautrel**, None; **A. C. Rat**, None; **F. Guillemin**, None.

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Sedentary Time, Physical Activity, and Concurrent Blood Pressure in Osteoarthritis Initiative Participants. Min-Woong Sohn[1], Rowland W. Chang[1]. Grace Ahn[1], Linda S. Ehrlich-Jones[2], Marc C. Hochberg[3], Jungwha Lee[1], Michael C. Nevitt[4], Pamela A. Semanik[5], Jing Song[1], Kai Sun[6] and Dorothy D. Dunlop[1], [1]Northwestern University, Chicago, IL, [2]Rehabilitation Institute Chicago, Chicago, IL, [3]University of Maryland, Baltimore, MD, [4]University of California-San Francisco, San Francisco, CA, [5]Northwestern University, IL, [6]Northwestern University, Feinberg School of Medicine, Chicago, IL

Background/Purpose: The inactivity physiology hypothesis suggests that sedentarism is a cardiovascular risk factor independent of time spent in moderate-vigorous activity (MV). Previous research suggests that sedentary time may be associated with increased blood pressure. But research findings to date are mixed.

Methods: The Osteoarthritis Initiative accelerometer ancillary study includes 1760 with objective measures of physical activity, sedentary time, and blood pressure at the 48 month exam. Participants were classified into four quartile groups according to accelerometer measures of the percentage of wear time that was sedentary (<100 activity counts per minute).Systolic and diastolic blood pressures (SBP and DBP) were modeled as a function of sedentary quartiles, demographic factors (age, gender, race, income), health behaviors (average daily MV minutes, alcohol use) and general health (osteoarthritis status,Charlson comorbidity score, BMI, NSAID and antihypertensive medication use during the month preceding the 48⁻ month visit).

Results: Of 1,760 adults, 60% had knee OA, 42% used ≥1 antihypertensive medications within 30 days prior to the 48 month visit, and 24.4% had elevated BP (≥ 140/90 or 130/80 for diabetic or renal patients). BP values (see Table) show lowest SBP in the least sedentary group, while DBP is similar across all groups.Adjusted analyses found the least sedentary group on average had SBP 1.82 mm Hg lower (95% CI, 0.04 – 3.59) than the other combined groups. Also, SBP was significantly elevated in adults with OA (2.3 mm Hg), blacks (5.7 mm Hg), and obesity (3.3 mm Hg).But time spent in MV activity, NSAID use, and alcohol use were not associated with SBP.The effect of sedentary time on SBP was primarily observed among adults not taking antihypertensive medications. Sedentary and MV activity were not associated with DBP in adjusted analyses.

Relationship of Sedentary Behavior to Blood Pressure

Blood Pressure (mm Hg)	Quartile of Sedentary Behavior			
	Quartile 1 (Least Sedentary)	Quartile 2	Quartile 3	Quartile 4 (Most Sedentary)
Unadjusted Analysis				
Systolic, mean (SD)	122.0 (15.8)	124.9 (16.9)	124.2 (15.9)	126.4 (16.5)
Diastolic, mean (SD)	74.5 (10.1)	75.4 (9.8)	74.5 (9.8)	73.8 (10.7)
Multiple Regression Analysis				
Systolic, Adjusted* Mean Difference (95% CI)	Reference	2.44 (0.37–4.51)	1.03 (−1.12–3.17)	1.83 (−0.48–4.14) p = 0.045**
Diastolic, Adjusted* Mean Difference (95% CI)	Reference	1.23 (−0.05–2.50)	0.42 (−0.90–1.73)	0.29 (−1.12–1.71) p = 0.187**

* Adjusted for demographic factors (age, gender, race, income), health behaviors (average daily MV minutes, alcohol use) and general health (osteoarthritis status, Charlson comorbidity score, BMI, NSAID and antihypertensive medication use during the month preceding the 48⁻ month visit).
** Least sedentary Quartile 1 versus more sedentary Quartiles 2–4

Conclusion: Objectively measured sedentary time was significantly associated with increased SBP, while MV activity was not, in the model adjusted for all covariates. This finding supports the inactivity physiology hypothesis that, independent of MV physical activity, sedentary time is

associated with deleterious effect on cardiovascular risk. This is the first study to test this hypothesis using objectively measured sedentary time and simultaneously controlling for antihypertensive medication use.

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A Multimodal Intervention to Improve Osteoporosis Care in Home Health Settings: Results From a Cluster Randomized Trial. Meredith Kilgore[1], Kenneth G. Saag[2], Jeroan Allison[3], Elizabeth Kitchin[4], Julie L. Locher[1], Amy Mudano[4], Ryan C. Outman[1] and Jeffrey R. Curtis[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]University of Massachusetts Medical School, [4]Birmingham, AL

Background/Purpose: Although very effective osteoporosis treatments are available, the rates of use are low, even among individuals who have already experienced a fracture and are thus at very high risk for a subsequent fracture. Since many patients commonly receive home health services care post-fracture, the home health setting is a promising venue for improving osteoporosis care.To assess the utility of a home health care based strategy for osteoporosis care improvement, we developed a multimodal intervention for home health care patients with a fracture history. Our intervention targeted nurses, physicians, and patients involved in home health care.

Methods: We conducted a cluster randomized trial of a multimodal intervention targeted at patients receiving care in a state-wide home health care agency in Alabama. The intervention included an educational component and a computerized nursing care plan for nurses, prepared order sheets to facilitate osteoporosis prescription medications ordering for physicians, and patient education materials for patients.Offices throughout the state were randomized to receive the intervention or to continue usual care. Following the randomized controlled study, we delivered the intervention to the offices randomized to the usual care arm. At that time, we implemented an automatic prompt for nurses in each office that identified those patients at high risk for a subsequent fracture and required the nurse to decide to activate the care plan.This allowed us to evaluate the additional effect of the automatic prompt compared with nurse identification alone.The primary outcome was the proportion of patients with a fracture history prescribed osteoporosis medications.

Results: For the randomized trial, among the offices in the intervention arm the average proportion of eligible patients receiving osteoporosis medications post-intervention was 19.1%, compared with 15.7% in the usual care arm (difference in proportions 3.4%, 95% CI: $-2.6 - 9.5\%$). The difference was not statistically significant. Within the intervention arm, a secondary analysis among the patients who had the care plan activated (27.5%) found 37.7% received osteoporosis medications compared with 11.6% of those who did not have the care plan activated ($p < 0.0001$). The implementation of the automatic prompt improved overall rates of prescription of osteoporosis medications (14.8% prior to activation vs. 17.6% after activation), but the difference was not significant.

Table 1. Enrollment and Drug Treatment Rates in Usual Care & Intervention Arms of the Home Health Care Osteoporosis Trial

	Usual Care Offices		Intervention Offices	
	Fracture Cases*	Proportion Treated†	Fracture Cases*	Proportion Treated†
	48	17%	46	17%
	42	21%	39	18%
	37	11%	38	18%
	36	25%	37	16%
	36	11%	36	28%
	29	10%	31	16%
	28	11%	28	18%
	25	20%	25	12%
	22	23%	21	10%
	19	11%	16	19%
	15	13%	13	38%
Averages	31	16%	30	19%

*Number of patients with fracture diagnoses who were eligible for the intervention
†Proportion of fracture patients receiving prescription osteoporosis medications during follow up after the intervention

Conclusion: The cluster randomized controlled trial conducted in a state-wide home health care agency did not significantly improve rates of prescribed osteoporosis medications. This was also the case for the before and after comparison of rates with respect to the activation of the automated alert feature in the EMR. Treatment rates did significantly improve when the nursing care plan was activated.

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Association Between Metabolic Syndrome and Bone Mineral Density in a Community-Dwelling Older Women: The São Paulo Ageing & Health Study (SPAH). Luana G. Machado, Diogo S. Domiciano, Jaqueline B. Lopes, Camille P. Figueiredo, Valéria Caparbo, Liliam Takayama and Rosa M.R. Pereira. University of São Paulo, São Paulo, Brazil

Background/Purpose: Recent studies have shown a link between metabolic syndrome (MS) and bone mass. However, these results are uncertain about the positive/negative effect of the components of MS on bone mineral density (BMD) and risk of fragility fractures. Furthermore, the higher prevalence of MS among subjects with higher body mass index (BMI) is a confounding factor, since previous findings have demonstrated that obesity could be a protective factor against bone loss.In this way, the aim of this study was to evaluate the prevalence of MS in a community-dwelling older women with high frequency of overweight/obesity and its association with bone parameters.

Methods: 343 community-dwelling older women were evaluated by specific questionnaire (including history of clinical fractures and cardiovascular risk factors). Lumbar spine, femoral neck and total hip BMD were evaluated by DXA. Laboratory tests, including calcium, phosphorus, creatinine, lipid profile, insulin, glucose and uric acid were also performed. Thoracolumbar spine X-rays were assessed to identify vertebral fractures. National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) criteria were used to define MS. Logistic regression models were used to analyze the relationship between MS and bone parameters.

Results: The prevalence of MS was high (62.1%). Women with MS had higher BMI (30.7 ± 4.9 vs. 27.2 ± 4.9kg/m^2, $P<0.001$), body fat percentage(37.7 ± 5.0 vs. $34.9\pm6.5\%$, $P<0.001$), serum levels of creatinine (0.9 ± 0.2 vs. 0.8 ± 0.2mg/dl, $P=0.003$), insulin (12.7 ± 10.7vs. 8.7 ± 14.2U/mL, $P=0.004$), uric acid (5.6 ± 1.5 vs. 5.1 ± 1.3mg/dl, $P=0.001$), lumbar spine BMD (0.881 ± 0.171 vs. 0.837 ± 0.178g/cm^2, $P=0.025$), femoral neck BMD (0.684 ± 0.120 vs. 0.629 ± 0.121g/cm^2, $P<0.001$) and total hip BMD (0.814 ± 0.131 vs. 0.743 ± 0.140g/cm^2, $P<0.001$) compared to women without MS. After adjustments for BMI, logistic regression analyses demonstrated that hip BMD remained as an independent factor associated with MS (OR:10.73 95% CI:1.33–86.55, $P=0.026$).No significant difference concerning the prevalence of vertebral or nonvertebral fractures was observed between the women with and without MS.

Conclusion: A positive association between total hip BMD and MS was found in our community-dwelling older women, even after adjustment for BMI. Nevertheless, the frequency of vertebral and nonvertebral fractures was similar in women with and without MS. Taken together, these results suggest that higher BMI per se does not explain the positive association between higher BMD and MS and does not protect against osteoporotic fractures. Further studies are necessary to elucidate the effect of MS on bone mass and fracture risk, possibly related to bone quality.

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Risk of Fracture Among Treated and Untreated Men with Osteoporosis. Karen Tomic[1], Joanne Lafleur[2], Liisa Palmer[1], David M. Smith[1], Carly J. Paoli[3], Irene Agodoa[3] and Nicole Yurgin[3]. [1]Truven Health Analytics, Washington, DC, [2]University of Utah College of Pharmacy, Salt Lake City, UT, [3]Amgen Inc, Thousand Oaks, CA

Background/Purpose: Osteoporosis (OP) affects an estimated 2 million men in the United States. The relationship between treatment and fracture outcomes has been reported from clinical trial populations, but little is known

about the impact of treatment on fracture risk among men with OP in the real-world setting.

Methods: The *MarketScan® Medicare Supplemental and Coordination of Benefits Database* was used to identify treated (received an OP medication) and untreated (had an OP diagnosis or fragility fracture but no OP medication) men with OP between 1/1/04 and 4/30/10 and at least 12 months pre-period and 3 months post-period follow-up in the database.Patients were matched on pre-period fracture and age ($\pm$ 2 years).Follow-up time was variable and ended with fracture, inpatient death, end of health plan eligibility, or on 4/30/10, whichever came first.Fracture incidence rates and time to fracture were reported.A Cox proportional hazards model was used to assess whether treated men had a lower risk of fracture compared to untreated men after controlling for demographic and clinical characteristics.

Results: Of the 3,072,696 men $\geq$65 years in the database, a total of 31,696 men met the inclusion and match criteria (15,848 in each cohort).In both cohorts, the mean age was 78 years and 55% had a pre-period fracture.1,990 treated men had a follow-up fracture [incidence = 5.98/100 person-years (p-y)] over 33,274 p-y of follow-up, compared to 2,231 untreated men with a follow-up fracture (incidence = 8.03/100 p-y) over 27,785 p-y.Treated men also had longer mean time to fracture (588 days, SD 426) than untreated men (401 days, SD 372, p<0.001).The adjusted risk of fracture was lower among treated men compared to untreated men (adjusted hazards ratio = 0.83, 95% CI: 0.78 to 0.89).Other pre-period factors associated with an increased risk of fracture were urban residence, no bone mineral density test, use of benzodiazepines, and a higher number of comorbidities and concomitant medications.

Conclusion: The fracture incidence rate was lower and time to fracture was longer for men with OP who received treatment than for those without treatment. After controlling for prior fracture and other risk factors, treated men had a lower adjusted risk of fracture.To better characterize the benefit of OP treatment, more research is needed into the role of medication adherence and risk of fracture among men with OP.

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Low Bone Mineral Density and Higher Parathyroid Hormone Levels As Independent Factors to All-Cause Mortality in Community-Dwelling Older Adults: the São Paulo Ageing & Health Study (SPAH). Diogo S. Domiciano, Luana G. Machado, Jaqueline B. Lopes, Camille P. Figueiredo, Valéria Caparbo, Liliam Takayama, Eloisa Bonfa and Rosa M.R. Pereira. University of São Paulo, São Paulo, Brazil

Background/Purpose: Previous studies have shown a relationship between osteoporosis and increased risk of death. Moreover, secondary hyperparathyroidism has been linked to mortality amongst frail older hip fractures patients. However, none of these studies performed a concomitant evaluation of the parathormone(PTH)-calcium-vitamin D-axis and bone mass, and this is essential to determine more accurately the contribution of each of these parameters to survival in community-dwelling older subjects. The aim of this study was, therefore, to investigate the association between serum PTH status, calcium, vitamin D and bone mineral density (BMD) and all-cause mortality during a 5-year period in a community-dwelling older population.

Methods: 739 community-dwelling subjects (446 women and 293 men), aged over 65 years, were prospectively studied. Clinical data (including history of non-vertebral fractures and cardiovascular events as previous myocardial infarction, instable angina, stroke) were assessed by specific questionnaire. Serum 25(OH)D level, intact PTH, total calcium, phosphorus, creatinine, and alkaline phosphatase were also measured. BMD of the lumbar spine and hip were evaluated by DXA. Spine X-ray (T4-L4) was performed to identify vertebral fractures by the semiquantitative method. All analysis was done at baseline and after a 5-year period. Mortality was recorded during 5-year follow-up. Multivariate Cox regression analysis was used to compute hazard ratios for all-cause mortality.

Results: After 5-year follow-up, there were 104 (14.1%) deaths. Comparing with individuals who were alive at the end of follow-up, subjects who died were older (75.9±6.8 vs. 72.6±4.8 years, P<0.001), had lower weight (64.4±15 vs. 67.6±13.1 kg, P=0.03), lower glomerular filtration rate (GFR) (52.3±25.3 vs. 59.0 ±18.4 ml/min, P<0.001), higher PTH level (45.8±23.2 vs. 38.1±16.0 pg/dl, P=0.003) and lower 25(OH)D level (17.8±10.4 vs. 20.2±10.2 ng/ml, P=0.005). There was also difference between the groups (deceased vs. alive) related to frequency of *diabetes mellitus* (36.5 vs. 19.1%, P<0.001), prevalence of any cardiovascular event (26.0 vs. 13.1%, P=0.001) and low BMD (T-score $\leq$ −2: 74.0 vs. 61.3%, P=0.01). After adjustments for age, sex and GFR, low BMD (HR:1.8095% CI:1.1–2.9, P=0.02), PTH level (HR:1.1295% CI:1.01–1.23, P=0.003), *diabetes mellitus* (HR:2.77 95% CI:1.71–4.50, P<0.001) and any cardiovascular event (HR:1.97 95% CI:1.16–3.36, P=0.01) remained independently associated to all-cause mortality.

Conclusion: Low BMD and higher PTH level, but not vitamin D per se, were significantly associated with mortality in community-dwelling older adults. These findings support the notion that a careful screening of these bone parameters might improve the outcomes of elderly population.

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Methods to Link a U.S. Arthritis Cohort with Medicare Administrative Claims Data. Jeffrey R. Curtis[1], Lang Chen[2], Timothy Beukelman[1], Aseem Bharat[2], Fenglong Xie[2], Kenneth G. Saag[1] and Elizabeth S. Delzell[2]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Linkages between clinical and administrative data may provide a valuable resource for pharmacoepidemiologic and health services research.

Objective: To describe methods and validity of a linkage between a de-identified national arthritis registry and U.S. Medicare data.

Methods: Data from 2006-9 for rheumatoid arthritis (RA) patients participating in the Consortium of Rheumatology Researchers of North America (CORRONA) was linked to Medicare (100% sample selected using ICD-9 codes). Deterministic linkage was performed using age (in years), sex, provider identification number, and U.S. state of the CORRONA site. Medicare data were restricted to rheumatology claims or with an RA diagnosis occurring in CORRONA provider's state. Visit dates from CORRONA were matched to Medicare visit dates. At least 1 visit date was required to match exactly.

An 'all-visit match' was defined when a CORRONA participant had all CORRONA visits match to all Medicare visits. If a CORRONA participant had an all-visit match to >1 Medicare beneficiary, unique matches selected to be the beneficiary with the greatest number of matched CORRONA visits.In the event of ties, the participant was considered not matched. A fuzzy match was done for CORRONA participants without any all-visit match allowing date mismatches of +− 2 week, or +−1 digit in month, day or year.

Linkage accuracy was evaluated in a sub-cohort with more complete information (including full date of birth [DOB]); exact match on full DOB was used as a gold standard.

Results: CORRONA participants with self-reported Medicare coverage at any time (n=9326) were identified to be matched to 32,788 Medicare beneficiaries with arthritis treated by CORRONA physicians. A total of 7,441 CORRONA participants matched exactly on at least 1 visit, and 4413 (59%) had an all-visit match to 1 or more beneficiaries; 4013 (54%) were uniquely matched with a median (IQR) of 3 (2, 6) matched visits. For those without any all-visit matches (n=3028), only 346 (11.4%) were able to achieve at least 1 all-visit match after fuzzy matching.

For the 837 participants in the validation subcohort with an all-visit match to a single Medicare beneficiary, match accuracy was 95% for patients with > 2 matched visits, 87% for patients with exactly 2 matched visits, and 73% for those with exactly 1 matched visit. For additional patients who initially matched exactly on at least one but not all visit dates and achieved an all-visit match after fuzzy matching (n=162), linkage accuracy was < 15%. Ongoing work is refining the linkage strategy for resolution of ties and improvement of matching validity and to expand the validation sample

Conclusion: A novel linkage between a national, de-identified outpatient arthritis registry and U.S. Medicare claims data on multiple non-unique identifiers appears both feasible and valid.

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Use of Rheumatology Services for Arthritis: The Role of SES and Geographic Availability of Rheumatologists and Primary Care Physicians. E. M. Badley[1], Mayilee Canizares[2] and Aileen M. Davis[3]. [1]Division of Health Care and Outcomes Research,Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [2]Division of Health Care and Outcomes Research,Toronto Western Research Institute, Toronto, ON, Toronto, ON, [3]Division of Health Care and Outcomes Research, Toronto Western Research Institute, Departments of Rehabilitation Science and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON

Background/Purpose: Access to rheumatology is critical for timely treatment of new onset inflammatory arthritis (IA). Barriers to timely care include patient characteristics, the need for a referral from another physician (usually a primary care physician (PCP)), and the availability of a rheumatologist to be referred to.Treating patients with IA also needs to be balanced against the role of rheumatologists as the medical specialist with expertise in arthritis in general.There is a shortage of rheumatologist as well are large area variations in their availability. The objectives of this population-based study is to examine access to rheumatologists for IA and arthritis overall (AO) taking into account access to PCP, availability of rheumatologists, and population characteristics.

Methods: A population-based multilevel study of individuals aged 18+ living in 105 residential areas in Ontario, Canada (total population about 13 million) which has a publicly funded health care system covering all physician visits. The physician billing database was used to identify the number of patients seeing rheumatologists for IA and AO and to derive a measure of PCP availability by residential area.Census data were used to calculate indicators of socio-economic status (SES), population age and rurality. Data from a survey of rheumatologists gave postal code for practice locations and the number of clinic hours per week.Geographic Information System analysis was used to calculate a weighted measure of rheumatologist availability taking into account amount of clinic hours and distance to rheumatologist locations for each residential area. Multilevel Poisson regression was used to estimate rate ratios for visits to rheumatologists for IA and AO by rheumatologist availability, PCP access, and SES.

Results: 142,600 patients made at least one visit to rheumatologists (13.4 per 1000 population): only 47.7% of visits were for IA, with a seven-fold variation across residential areas.Comparing the highest to lowest quintile, rate of visits for IA were higher in areas of high SES (RR 1.3 95%CI:1.1–1.6) and areas with high PCP access (RR 1.2 95%CI:1.0–1.5).There was no association with rheumatologist availability.However higher rheumatologist availability was associated with visits for AO (RR 1.2: 95% CI 1.0:1.4), as were high SES (RR 1.4 95%CI:1.2–1.6) and high PCP access (RR 1.4 95%CI:1.2–1.7).

Conclusion: The lack of association with area-level rheumatologist availability for IA suggests that priority is given to these patients.The association of higher rheumatologist availability with patients seen with AO, raises questions of where these patients go for care when no rheumatologist is available. For both IA and AO, lack of PCP access may be a barrier to referral.This study also indicates that residents of high SES areas are more likely to see rheumatologists, suggesting inequalities in access to care. Models of care that incorporate the location and amount of rheumatologist and PCP resources are crucial to improve access to care for people with all types of arthritis particularly in areas of low SES.

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Accuracy of Canadian Health Administrative Databases in Identifying Patients with Rheumatoid Arthritis Using a Random Sample of 7500 Patients Seen in Primary Care. Jessica Widdifield[1], Claire Bombardier[1], Sasha Bernatsky[2], J. Michael Paterson[3], Jacqueline Young[3], Diane Green[3], J. Carter Thorne[4], Noah Ivers[1], Debra Butt[3], R. Liisa Jaakkimainen[1], Myra Wang[3], Vandana Ahluwalia[5]. George A. Tomlinson[6] and Karen Tu[3], [1]University of Toronto, Toronto, ON, [2]Research Institute of the McGill University Health Ctre, Montreal, QC, [3]Institute for Clinical Evaluative Sciences, Toronto, ON, [4]Southlake Regional Health Centre, Newmarket, ON, [5]William Osler Health Center, Mississauga, ON, [6]Toronto General Hospital, Toronto, ON

Background/Purpose: The use of population-based health administrative databases in rheumatology research is well established, but there are ongoing concerns about validity. To date, previous validation studies have sampled patients primarily from rheumatology clinics, which may limit the usefulness of the results. Our aim was to evaluate the accuracy of administrative data algorithms to identify RA patients drawn from family physician records.

Methods: We performed a retrospective chart abstraction study using a random sample of 7500 adult patients, age 20 years and over, from the primary care Electronic Medical Record Administrative data Linked Database (EMRALD) in Ontario, Canada. Our reference standard definition for classifying patients as RA included physician-reported RA diagnoses and supporting evidence. RA and non-RA patients were then linked to administrative data to validate different combinations of physician billing (P) and hospitalization (H) diagnostic codes for RA to estimate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results: Based on our reference standard definition, we identified 69 patients with physician-reported RA for an overall RA prevalence of 0.92%. Most RA cases were female (64%) and the mean (SD) age was 62 (14) years.Among RA cases, 86% had a documented diagnosis by a specialist and 80% had documentation of a disease-modifying anti-rheumatic drug exposure. Test characteristics of selected RA case definition algorithms tested are reported in Table 1. All algorithms tested had excellent specificity (97–100%), however sensitivity varied (75–90%) among physician billing diagnosis algorithms. Despite the low RA prevalence, algorithms for identifying RA patients had modest PPV, which improved substantially with the requirement of having musculoskeletal specialist billing codes for RA (51–83%). Varying the observation window had little impact on the accuracy of the algorithms tested.

Table 1. Test characteristics of selected algorithms

Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1 H ever	22	100	88	99
1 P ever	90	97	20	100
2 P in 1 year	84	99	46	100
2 P in 2 years	84	99	45	100
2 P in 3 years	84	100	42	100
3 P in 1 year	80	100	63	100
3 P in 2 years	80	100	60	100
3 P in 3 years	80	100	59	100
1 P ever by a specialist	81	99	51	100
2 P in 1 year at least 1 P by a specialist	78	100	65	100
2 P in 2 years at least 1 P by a specialist	78	100	65	100
2 P in 3 years at least 1 P by a specialist	78	100	62	100
3 P in 1 year at least 2 P by a specialist	75	100	83	100
3 P in 2 years at least 2 P by a specialist	75	100	81	100
3 P in 3 years at least 2 P by a specialist	75	100	81	100
1 H or 3 P in 1 year at least 1 P by a specialist	78	100	77	100
1 H or 3 P in 2 years at least 1 P by a specialist	78	100	76	100
1 H or 3 P in 3 years at least 1 P by a specialist	78	100	76	100

H: Hospitalization code; P=physician diagnostic code; Specialist = rheumatologist, internal medicine, orthopedic surgeon

Conclusion: The RA case definition algorithms that we tested had excellent specificity. To our knowledge, this is the first study to rigorously evaluate the accuracy of RA administrative data algorithms in a random sample from family physician records. We are independently validating these algorithms in a random sample of patients from rheumatology clinics to support the findings of this work.

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Shared Decision Making in Secondary Care: Rheumatologic Patient's Perspective. Raphael Battisti[1], Thiago D. Baumgratz[1], Mirella Cuziol[2], Ana Carolina Reiff Janini[2], Roger A. Levy Sr.[3] and Mirhelen M. Abreu[4]. [1]Medical Student, São Carlos, Brazil, [2]Medical Student at Universidade Federal de São Carlos, São Carlos, Brazil, [3]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [4]Universidade Federal de São Carlos, São Carlos, Brazil

Background/Purpose: This cross-sectional study aimed to analyze the willingness for shared decision making (SDM) of rheumatologic patients.

Methods: All rheumatic disease patients assisted at a specialty care unit were invited to participate in this study. A three parts questionnaire was applied (demographic, clinical data and 3 scenarios that simulate a clinical encounter). The scenarios presented the 3 typical steps of a consultation: 1) Diagnostic statement; 2) treatment options discussion; 3) decision-making. Each scenario was presented according to SDM process. For each step, interviewee was argued 3 questions: (a) To identify weather each part was similar to his/her clinical encounter or not; (b) to define whether SDM can be a feasible approach and (c) to answer if he/she wanted to be assisted in SDM process, justifying it. The outcomes were defined by the justification about the willingness for SDM. Descriptive and multiple correspondence analysis (MCA) techniques were performed to explore data.

Results: Demographic data (N=160): 89% female, 60% < 8 years of school, 76% < 3 folds the minimum wage (income), 24.3% employed and 10.6%, retired due to the disease; 75% of participants had a rheumatic diagnosis clearly defined, of which 48.8% had < 4 years of diagnosis and 30%, > 8 years of diagnosis. The first scenario showed that 97% would like to have SDM approach on their real clinical practice. They justified its desire according to 'communication empowerment' (75%) and 'patients' right relationship' (23%). For the scenario two, 98% would like to have this approach, although 65% declared that it never happen in his/her real life. They justified according to 'communication empowerment' (63%)'. Decision-making scenario showed that 65% of the participants never took part in the decision process. However, 98% would like to do it, justifying according to 'patients' right relationship' (30%), and 'communication empowerment' (28%). Despite these answers, 13% answered that the whole decision belongs to the physician because they have the technical knowledge. MCA plot illustrates that diagnostic statement correlates to 'communication empowerment', retired because of disease, and low literacy. To understand treatment option, communication empowerment and a practice of a patient's right was correlated with those who had < 4 years of diagnosis or > 8 years; > two rheumatic conditions, and low literacy. Finally, the desire for SDM was correlated among 'communication empowerment' and 'patient's right' with those with < 4 years of diagnosis, active working status, and age between 50– 59 years-old.

Conclusion: Communication empowerment and patient's right were the most common reasons for the willingness for SDM.

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Is There an Optimal Treatment Strategy for Disease-Modifying-Antirheumatic-Drug Naïve Patients with Rheumatoid Arthritis?
Roopa Akkineni[1] and Daniel A. Albert[2]. [1]Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]Dartmouth-Hitchcock Med Ctr, Lebanon, NH

Background/Purpose: There is a lack of head-to-head clinical trial data to determine the most effective treatment for rheumatoid arthritis (RA).However, these trials have had similar patient entry criteria and outcome measures allowing for meta-analysis.Patients with RA fall into three therapeutic groups: DMARD naïve (no prior exposure to conventional or biologic disease-modifying-anti rheumatic drugs [DMARD]), Biologic naïve (prior exposure to conventional DMARDs but not biologic DMARDs) and Biologic second-line (prior exposure to biologic DMARDs).

A decision analysis was designed to identify an optimal treatment strategy for DMARD naïve patients with RA.

Methods: A total of 270 studies were identified on ClinicalTrials.gov and Medline, of which 193 were eliminated in the abstract review phase.Seventy-seven studies were screened in full text and seventy were excluded for reasoning including lack of randomization, uncertain diagnoses, and non-standard treatment.Seven clinical trials were included for the DMARD naïve group corresponding to twelve treatment options.

The treatment options included placebo, methotrexate, biologic drugs alone and methotrexate plus biologic drugs.Drug effectiveness was measured by the ACR 20 and ACR 50 criteria and the rate of serious adverse events was modeled across different therapeutic options. Sensitivity analyses were conducted for probability of serious adverse drug reactions and the ACR 20 and ACR 50 effectiveness measures.

Results: In the biologic drugs group alone, treatment with etanercept 25mg bi-weekly resulted in the maximum quality-adjusted-life-year (QALY) gain of 23.24 years compared to placebo at 21.55 years (1 year and 8 months) and methotrexate at 22.12 years (1 year and 1 month).In the methotrexate plus biologic group, treatment with etanercept 50mg plus methotrexate resulted in 23.20 QALYs. Adalimumab 40mg (21.79 QALYs), Infliximab 3mg plus methotrexate (21.83 QALYs) and triple therapy (21.76 QALYs) resulted in the lowest QALY gain.

Sensitivity analysis showed at ACR 20 success criteria etanercept alone is preferred, while at ACR 50 criteria etanercept plus methotrexate is the preferred treatment option. At base case methotrexate was not a preferred treatment, however if methotrexate's ACR50 response rate exceeds 34% then it would become the optimal treatment strategy if all other factors were held constant. By contrast, treatment with etanercept 25mg on a bi-weekly basis and etanercept 50mg plus methotrexate are no longer the favored treatment options if their adverse drug reaction rates increase from 6% and 12% to 9% and 13% respectively.

Conclusion: Biologic therapy alone and biologic therapy plus methotrexate appear to be the favorable treatment strategies for the DMARD naïve group. The QALY gains for biologic therapy in rheumatoid arthritis are similar to that of biologic therapy in psoriasis and interferon therapy for multiple sclerosis (0.20–3.3 QALYs). The decision depends in part on the side effect profile and costs.Decision aids to elicit patient preferences and drug costs may override differences in drug effectiveness.

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Epidemiology of the US National Burden of Pediatric Lupus Hospitalization From 2000–2009.
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Background/Purpose: Studies indicate that of 11% of adult hospitalizations are related to systemic lupus erythematosus (SLE), with an average charge of $10,000 US per hospitalization and a 1 in 30 chance of death (1). There are few studies describing the hospitalization experience in pediatric SLE, and no national estimates for inpatient healthcare utilization. We aimed to characterize national US trends in inpatient healthcare utilization and mortality associated with pediatric SLE.

Methods: We performed a retrospective, serial, cross-sectional analysis of a nationally representative sample of pediatric SLE patients.Using the Kids' Inpatient Database (KID) for years 2000, 2003, 2006 and 2009, we identified patients with SLE by an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of 710.0 listed as a primary or secondary diagnosis. The main outcome measures were: SLE hospitalization rate, length of stay (LOS), total hospitalization charges and mortality. Patient-specific demographic variables included: age, race, sex and insurance status. Hospital-specific variables included: type (general or children's), teaching status, location (urban or rural) and region (Northeast, Midwest, South or West). We used KID reported sampling weights to calculate national estimates of the main outcome measures and multivariate regression to evaluate for trends over time.

Results: An estimated 27,076 (SE 1509) pediatric SLE discharges were identified in the KID for the years of study, with a hospitalization rate of 7.9 per 100,000 children (SE 0.5). The median LOS was constant across years at 2 days (IQR 2,3). The mean total charges per hospitalization (inflated to 2009 USD) were $29,304 for 2000, $36,987 for 2003, $41,664 for 2006 and $42269 for 2009. (p value for trend <0.001). Factors associated with increased total charges were: male sex (p=0.03); age>=18 years (p=0.03); Black race (p=0.02) and Hispanic ethnicity (p=0.003); urban location (p<0.001); and West region (p<0.001). The death rate during hospitalization was 1% for 2000, 1.1% for 2003, 1.2% for 2006 and 0.6% for 2009, which was statistically different across years (p=0.03). Risk factors associated with death were: male sex OR=1.6 (p=0.03), age>=18 years OR=3 (p=0.01); Black race OR=2.6 (p=0.002); other race OR=2.5 (p=0.01); South region OR=2.1 (p=0.006) and West region OR=1.8 (p=0.03).

Temporal Trend in Pediatric SLE Hospital Charges

— Pediatric SLE Discharges   - ○ - All Other KID discharges

*mean total charges per hospitalization adjusted to 2009 USD
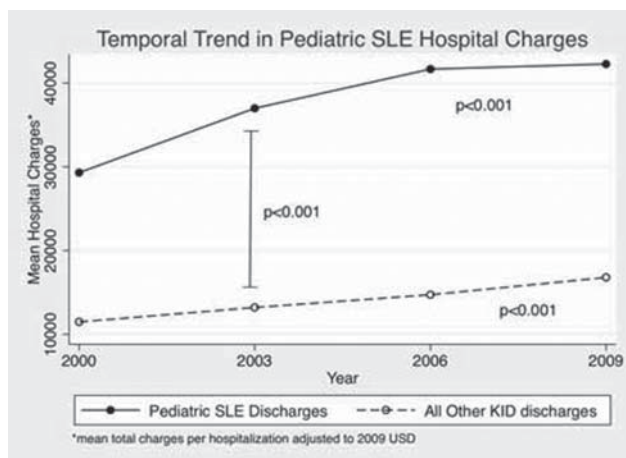
Conclusion: The length of stay for pediatric SLE has remained stable from 2000 to 2009. Total hospital charges have significantly increased, and mortality has decreased over time, with estimates differing by age, race, sex, hospital location and region. Further studies are needed to investigate the drivers of these differences in healthcare utilization and outcomes.

1. Krishnan E: **Hospitalization and mortality of patients with systemic lupus erythematosus**. *J Rheumatol* 2006, **33**(9):1770–1774.

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Disease Burden and Cost of Illness in SLE During 8 Years Follow up.
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Background/Purpose: To study the annual direct and indirect costs in SLE in a cohort, from a defined area in southern Sweden, and to find potential predictors of cost.

Methods: All 127 prevalent and incident cases of clinically confirmed SLE, all with at least 4 ACR classification criteria, being alive between January 1st 2003 and December 31st 2010 in a defined area with an adult population of 175.000, were included.Demographics, date of diagnosis, follow up period, phenotype, disease activity (SLEDAI), organ-damage (ACR/SLICC DI) and costs for SLE specific therapy was collected from the database of the rheumatology unit. From the population registry 508 individuals matched for age and sex constituted a reference group. For both cases and references the local Health Authorities database provided all costs for in-patient admissions, out-patient care with all types of health care personnel, and from the Swedish Social Security Agency data was obtained about sick leave and disability pensions. The data merge was done within the Epi-Centrum in Lund and the cost analysis at the Swedish Institute for Health Economics.

Results: Eighty-seven percent were females and the mean age in 2003 was 52 years with mean disease duration of 16 years and the total observed years were 869 for the patients and 4064 for the references.Annual median inpatient days for cases were 2.91, for subgroup with nephritis 5.68 and for references 0.70. Annual outpatient physician visits were for cases 6.25, for subgroup with nephritis 6.25 and for references 2.40. Annual net sick leave days for cases were 99.9, for subgroup with nephritis 111.6 and for references 35.6. The average total annual costs in SEK 2011, was per SLE patient 180 520 SEK (=$ 25 072) of which 72 percent were indirect costs, the corresponding costs for the subgroup with nephritis was 229 423 SEK(=$ 31 864) and for the references 59 985 SEK (=$ 8 331) of which 78 percent were indirect costs. Potential predictors of total costs were age at study year (p=0.001), disease activity measured by SLEDAI (p<0.001) and organ-damage measured by ACR/SLICC DI (p<0.001).

Conclusion: Disease burden for SLE was significantly increased compared with matched population references both for contacts with health care and loss of productivity, with indirect costs constituting 72 percent. Independent predictors of costs were age, disease activity and organ-damage.

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Health Care Utilization Among Medicaid Enrollees with Systemic Lupus Erythematosus Preceding the Development of End-Stage Renal Disease: Sociodemographic Variation. Candace H. Feldman[1], Linda T. Hiraki[2], Graciela S. Alarcon[3], Jinoos Yazdany[4], Jun Liu[5], Michael A. Fischer[1], Wolfgang C. Winkelmayer[6] and Karen H. Costenbader[7]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital/ Harvard School of Public Health, Boston, MA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of California San Francisco, San Francisco, CA, [5]Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [6]Stanford University School of Medicine, Stanford, CA, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Extreme sociodemographic disparities exist among systemic lupus erythematosus (SLE) patients in the development of end-stage renal disease (ESRD) from lupus nephritis. Better resource allocation and improved access to care may reduce the incidence of this adverse outcome. We aimed to understand sociodemographic variation in health care utilization prior to ESRD development among SLE patients enrolled in Medicaid, U.S. health insurance for low income individuals.

Methods: From the Medicaid Analytic eXtract (MAX) data containing all U.S. Medicaid billing claims from 2000–2004, we identified adults, ages 18 to 65 years, diagnosed with SLE ($\geq$3 visits, ICD-9 code 710.0, >30 days apart). To determine progression to ESRD we matched these individuals with SLE to the U.S. Renal Data System (USRDS), which contains information on nearly all ESRD patients from 2000–2004. We assessed duration of Medicaid enrollment prior to ESRD onset, and age, sex, race/ethnicity and U.S. region for each individual. We determined residence in a Health Professional Shortage Area, number of rheumatologists per state, and county-level socioeconomic status (SES) using a previously validated composite score of 7 U.S. Census variables. We examined 3 outcomes: emergency department (ED), outpatient and inpatient visits per year. We used multivariate-adjusted general linear models to understand the relationship between sociodemographic factors and these health care utilization outcomes.

Results: Of the 34,339 adults with SLE enrolled in Medicaid, 1,475 (4.3%) developed ESRD during the study period. 86% were female, the mean age of ESRD onset was 30.7 years (SD 11.6), and 58.9% were African American, 17.4% were White and 16.1% were Hispanic. The mean number of months in Medicaid prior to ESRD diagnosis was 23.4 (SD 16.4). There were an average of 2.2 (SD 3.2) ED visits, 10 (SD 9.5) outpatient visits and 2.3 (SD 3.0) inpatient visits per year. In multivariate models, men had significantly fewer annual outpatient visits than women (p<0.001). Asian patients had nearly 1 less ED visit per year (p=0.03) and 2.4 fewer outpatient visits per year (p=0.05), compared to Whites. There were more annual ED visits in the Midwest (p=0.01), and outpatient visits in the Midwest (p=0.001) and West (p<0.001), compared to the Northeast. Patients in the lowest county-level SES group had significantly more ED visits per year than the highest SES group (p=0.02). There were no significant differences in inpatient visits according to the sociodemographic groups examined by multivariate analysis.

Conclusion: In this nationwide cohort of Medicaid enrollees with SLE who developed ESRD, we observed significant variation in ED and outpatient visits by sex, race/ethnicity, region, and county-level SES.Increased ED visits in low SES areas may indicate a lack of sustained access to subspecialty care. Further studies are needed to determine whether differences in health care utilization, particularly in underserved areas, contribute to increased rates of progression to ESRD in this high-risk population.

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Medical Costs and Health Care Resource Use in Patients with Systemic Lupus Erythematosus in an Insured Population. Daniel E. Furst[1], Ann E. Clarke[2], Ancilla W. Fernandes[3]. Tim Bancroft[4], Kavita Gajria[3], Warren Greth[5] and Serban R. Iorga[4], [1]UCLA Medical School, Los Angeles, CA, [2]McGill University, Montreal, QC, [3]MedImmune LLC, Gaithersburg, MD, [4]OptumInsight, Eden Prairie, MN, [5]MedImmune, LLC, Gaithersburg, MD

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that may affect multiple organ systems. The clinical manifestations of SLE are heterogeneous, and subjects typically experience periods of disease flares and remission. The objective of this study was to investigate the economic burden and resource use associated with newly diagnosed and existing SLE patients in a large national US insurer.

Methods: Subjects at least 18 years of age and with claims-based evidence of SLE (ICD-9-CM 710.0x) were identified from a health plan database during 2003–2008. Subjects were divided into two cohorts; newly diagnosed and existing based on claims history of SLE. Subjects were matched based on demographic and clinical characteristics at a ratio of 1:3 to unaffected controls. Health care costs and resource use were captured during a 12 month post-index period. A generalized linear model (GLM) was used to predict costs, controlling for demographic and clinical characteristics.

Results: A total of 1,278 newly diagnosed SLE subjects were matched to 3,834 controls, and 10,152 subjects with existing SLE were matched to 30,456 controls. SLE subjects had significantly higher overall mean annual health care costs than matched controls (newly diagnosed: $19,178 vs. $4,909; existing: $15,487 vs. $5,156; both p<0.001).Inpatient costs were the largest component of medical costs for newly diagnosed subjects, while ambulatory costs were the largest component for existing SLE patients.When adjusting for clinical and demographic characteristics with a GLM model, the cost ratio of newly diagnosed SLE subjects to controls was 2.15 (95% CI: 1.90–2.42), and the cost ratio of subjects with existing SLE to controls was 2.05 (95% CI: 1.92–2.19).Presence of pharmacy claims for select medications (including corticosteroids, methotrexate, or cyclophosphamide), and evidence of specific organ involvement (including renal failure, CNS complications, and cardiovascular complications) were each associated with increased costs (all p<0.05). Health care resource use was significantly higher among SLE subjects than matched controls, including average annual numbers of primary care physician visits, specialist visits (nephrologist, rheumatologist, neurologist or dermatologist), emergency department visits, and inpatient hospital stays (all p<0.001).

Conclusion: Economic burden and resource use were high in both newly diagnosed and existing SLE patients compared to unaffected controls in this insured population. Serious complications and immunosuppressant use were associated with increased costs. These findings highlight the unmet need in SLE.

Economic Burden of Systemic Lupus Erythematosus by Flare Severity in a Commercially Insured Population in the United States. Siva Narayanan[1], Emily Durden[2], Alan Oglesby[3], Paul Juneau[4] and Kathleen L. Wilson[5]. [1]Human Genome Sciences, Inc., Rockville, MD, [2]Thomson Reuters, Austin, TX, [3]GlaxoSmithKline, Research Triangle Park, NC, [4]Truven Health Analytics, Washington, DC, [5]Thomson Reuters Healthcare, Cambridge, MA

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with an unpredictable disease course with sporadic periods of illness (flares). Little is known about how the severity of flares impacts the economic burden of SLE. The aim of the current study was to estimate the economic burden associated with SLE, stratified by flare severity among SLE patients in a commercially-insured population in the United States (U.S).

Methods: In this retrospective, observational study, commercially insured adults (employees or their dependents) ages 18–64 years with at least one SLE-related inpatient or emergency room (ER) claim or at least two SLE-related outpatient visits at least 30 days apart with a rheumatologist

between 7/1/2004 and 12/31/2008, and at least 6 months of pre-index and 12 months of post-index continuous medical/prescription coverage were identified in the MarketScan Commercial Claims database. Non-SLE controls were matched to SLE cases using propensity score matching. Mild, moderate, and severe flares were identified in the follow-up period for the SLE patients using a claims-based algorithm and patients were categorized according to their highest degree of flare. A log transformation was applied to the medical expenditures to accommodate specific observed data properties (e.g., skewness). A subsequent linear model was used to adjust for any remaining imbalances from matching and to estimate the incremental annual economic burden (all-cause direct medical cost, in 2010 U.S dollars) associated with SLE for different levels of flare severity for SLE patients in comparison to their matched non-SLE controls.

Results: 13,460 SLE cases (mean age: 45.6 years; 91.6% female; average length of follow-up: 2.9 years) were matched to 13,460 non-SLE controls (mean age: 47.1 years; 88.9% female; average length of follow-up: 2.0 years). During the follow-up period, SLE cases had a significantly higher overall comorbidity burden, (Charlson Comorbidity Index score 1.5, vs. 1.0; p<0.001) and a higher proportion had hospitalizations (49.7% vs. 27.7%; p<0.001) and ER visits (66.7% vs. 43.7%, p<0.001) compared to non-SLE controls. Among SLE cases with no flares, mild/moderate and severe flares as highest flare severity, annualized all-cause direct medical costs were $14,945, $21,606 and $64,578 respectively. In multivariate models comparing non-SLE controls, incremental adjusted annualized direct medical costs for SLE cases with no flares, mild/moderate and severe flares respectively were $441, $3,606 (p<0.05) and $18,953 (p<0.05).

Conclusion: Significantly greater proportions of patients with SLE had a hospitalization or ER visit over a 1-year follow-up than their matched non-SLE counterparts. The direct medical costs of patients with SLE were significantly higher than controls, with costs increasing substantially as the severity of flares increase.

Direct Medical Cost Associated with Organ System Involvement in a Commercially Insured Population with Systemic Lupus Erythematosus in the United States. Alan Oglesby[1], Emily Durden[2], Siva Narayanan[3], Paul Juneau[4] and Kathleen L. Wilson[5]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]Thomson Reuters, Austin, TX, [3]Human Genome Sciences, Inc., Rockville, MD, [4]Truven Health Analytics, Washington, DC, [5]Thomson Reuters Healthcare, Cambridge, MA

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs including the heart, lungs, kidneys, as well as the joints and the nervous system. While the economic burden has been explored for specific organ systems in SLE with high associated morbidity (e.g. renal), less is known about the economic impact of other organ systems associated with SLE, particularly those with less perceived serious morbidity (e.g. musculoskeletal, etc.)The objective of this analysis was to describe the annual direct medical costs associated with select organ system comorbidities among SLE patients in a commercially-insured population in the United States (U.S).

Methods: This study employed a retrospective, observational design. Adults ages 18–64 years with at least one SLE-related inpatient or emergency department (ED) claim or at least two SLE-related outpatient visits with a rheumatologist at least 30 days apart between 7/1/2004 and 12/31/2008, and continuous medical/prescription coverage for at least 6 months prior and 12 months following the index diagnosis of SLE were identified in the MarketScan Commercial Claims and Encounters database. Select comorbid conditions representing SLE-related major organ/system damage were identified using primary or secondary ICD-9-CM codes and included neuropsychiatric, renal, pulmonary, cardiovascular, musculoskeletal, and mucocutaneous manifestations.All-cause healthcare utilization and costs were assessed in the follow-up period and reported by type of service (e.g. inpatient, outpatient, pharmacy and total). Total, all-cause healthcare costs, adjusted to 2010 U.S dollars, are reported as annualized rates per patient to account for variable follow-up.Costs reflect the paid amounts of adjudicated claims and patient co-pays.

Results: 13,460 SLE cases (mean age: 45.6 years; female: 91.6% female) were identified.Mean length of follow-up was 1,054.6 days (SD: 522.9

days).During the follow-up period, cardiovascular (49.0%) and musculoskeletal (40.3%) comorbidities were observed most frequently, followed by neuropsychiatric (16.7%), renal (14.2%), mucocutaneous (5.4%) and pulmonary (3.4%) comorbidities. Total annual, mean all-cause costs were $30,369 $\pm$ $58,344 in the overall SLE population.Among patients with evidence of SLE-related organ damage, annual mean costs were highest for pulmonary ($74,433; SD=$97,787) and renal ($65,442; SD=$111,541) comorbidities (all p-values<0.001). Compared to the overall SLE population, costs were also higher among SLE patients with cardiovascular ($44,066; SD=$75,161), neuropsychiatric ($43,820; SD=$62,646), mucocutaneous ($41,841; SD=$104,766), and musculoskeletal ($38,986; SD=$66,986) comorbidities (all p-values<0.001).

Conclusion: As expected, organ system involvement associated with high morbidity were associated with highest annual costs on a per diem basis.However, other comorbidities such as cardiovascular and musculoskeletal manifestations, also represent a substantial impact to the health care system, particularly given their higher prevalence.

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Primary Care Preventive Services in Patients with Systemic Lupus Erythematosus Compared to Others in Their Community. Cristina Drenkard[1], Kimberley Rask[1], Gaobin Bao[1], Gnanesh Patel[1], Suparna Bagchi[2] and S. Sam Lim[1]. [1]Emory University, Atlanta, GA, [2]Georgia Department of Public Health, Atlanta, GA

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic illness frequently complicated by infections, cardiovascular disease (CVD) and cancer. Primary care preventive services (PCS) are recommended to prevent these complications among individuals at risk. Yet, the utilization of PCS in the US may be more challenging for SLE patients, especially given the worse SLE outcomes among ethnic minorities and those with low socioeconomic status. We compared the likelihood that a cohort of SLE patients from a large metropolitan area in Atlanta, GA, US received recommended PCS relative to the baseline rates of PCS in the same community from a national population-based survey.

Methods: The Georgians Organized Against Lupus (GOAL) is a cohort of validated SLE patients predominantly derived from the Georgia Lupus Registry, a population-based registry of lupus in the Atlanta metropolitan area. GOAL includes the full sociodemographic spectrum of SLE patients and collects self-reported measures on health care utilization and health conditions. Eleven self-reported PCS were assessed in 765 SLE GOAL participants (94% women, 78% blacks,18% uninsured) and 3 representative samples of individuals (9040 from the same community, 938 of them with diabetes, and 620 with CVD) derived from the Behavioral Risk Factor Surveillance System (BRFSS). We compared the proportion of eligible SLE and BRFSS individuals who received the recommended PCS on (1) immunizations, (2) cancer screening, (3) cholesterol monitoring, (4) counseling on medications and lifestyle modifications for high blood pressure (HBP), and (5) all 11 recommended PCS.

Results: Eligible SLE and BRFSS participants who received recommended PCS

PCS	SLE% (95% CI)	Community% (95% CI)	Diabetes% (95% CI)	CVD% (95% CI)
Immunizations (Influenza and/or Pneumococcal vaccine)	45 (41–49)	19 (18–21)	33 (29–37)	38 (33–43)
Cancer Screening (Pap smear and/or mammogram, and/or colonoscopy)	78 (74–81)	77 (76–79)	70 (65–75)	70 (64–76)
Cholesterol Monitoring	65 (62–69)	81 (79–83)	87 (81–92)	90 (84–93)
Counseling on HBP (Drugs and/or 4 lifestyle modifications)	48 (43–53)	38 (34–42)	50 (43–58)	42 (33–51)
All 11 recommended PCS	19 (17–22)	22 (21–23)	23 (20–27)	26 (22–31)

Conclusion: Although only 45% of eligible SLE participants received the recommended immunizations, the proportion was higher than in the community or those with diabetes, and similar to CVD. Over 78% of SLE received complete cancer screening services, which was comparable to the other BRFSS groups. However, only 65% of SLE participants were adequately screened for cholesterol, a lower proportion than in the BRFSS samples. Counseling on hypertension was reported by less than 50% of SLE, similar to the BRFSS groups. Less than 20% of SLE responders received all recommended PCS. Further research is needed to identify factors associated with gaps in the utilization of primary care among SLE patients.

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Autoimmune Diseases: Declining Mortality Between 1999 and 2008 However Continuing to be a Leading Cause of Death in Children— A 10-Year Retrospective Review. Eric Y. Yen and Deborah K. McCurdy. Mattel Children's Hospital, University of California at Los Angeles, Los Angeles, CA

Background/Purpose: Autoimmune diseases are chronic illnesses that cause significant and chronic disability in children and may lead to death. Using mortality data from 1995, Walsh and Rau showed that autoimmune disease deaths were the leading causes of death among young women. The objective of this study is to examine the trends in crude mortality rate in children for autoimmune diseases in the United States.

Methods: We selected 24 autoimmune diseases (Table 1) chosen by Jacobson et al using the criteria of Rose and Bona, who defined autoimmune diseases as having direct proof or indirect evidence of autoimmune pathogenesis. Every autoimmune disease was classified with ICD-10 diagnosis code(s). Using the information provided by the Center for Disease Control (CDC), we reviewed all mortality data from the period of 1999–2008 in 3 year intervals. CDC reports that >99% of all deaths in the United States are registered. Each death certificate that lists an autoimmune disease as the underlying cause of death was identified and counted. Age groups, crude mortality rates per 100,000 persons (=number of deaths/population*100,000), and total mortality changes (percent change) between 1998 and 2008 were defined and calculated. We also compared the number of autoimmune disease deaths to the top ten leading causes of death by age in 2008.

Table 1. Autoimmune Diseases (ICD-10 codes).

Addison's disease (E27.1, E27.2, E27.4)	Relapsing polychondritis (M94.1)
Autoimmune hemolytic anemia (D59.1)	Polymyositis/dermatomyositis (M33)
Chronic active hepatitis (K73)	Primary biliary cirrhosis (K74.3)
Glomerulonephritis (N00, N01, N03, N05, N18)	Rheumatic fever and Rheumatic heart disease
Goodpasture's syndrome (M31.0)	(I00, I01, I02, I05, I06, I07, I08, I09)
Graves' disease/hyperthyroidism (E05.0)	Rheumatoid arthritis (M05, M06, M08)
Idiopathic thrombocytopenia purpura (D69.3)	Scleroderma (M34, L94.0, L94.1)
Insulin dependent diabetes (E10)	Sjogren's (M35.0)
Multiple sclerosis (G35)	Systemic lupus erythematosus (M32)
Myasthenia gravis (G70.0)	Thyroiditis (E06.3)
Myocarditis (I40.1, I40.8, I40.9, I51.4, I51.8)	Uveitis (H20.0, H20.1, H20.8, H20.9, H30)
Pemphigus vulgaris (L10.0)	Vitiligo (L80)
Pernicious anemia (D51.0)	

Results: Table 2 presents the crude mortality rates of autoimmune diseases from 1999, 2002, 2005, and 2008 and the percent change between 1999 and 2008. Mortality rates decreased from 5% to 33% in all age groups except for children younger than 5 years old. The absolute numbers of autoimmune disease death did not increase over time. Likewise, mortality rates for all causes decreased for all age group under 20 years old. Despite a sharp decline in mortality rates, autoimmune diseases continue to be a leading cause of death among children (Table 3).

Table 2. Trends in crude mortality rates for autoimmune diseases and all causes of death. Crude mortality rates are expressed per 100,000 persons.

	Age	Crude Mortality Rate (=Deaths/Population*100,000)				% Change Between 1999 and 2008
		1999	2002	2005	2008	
Autoimmune Diseases	1–4	0.33	0.22	0.26	0.35	6.06%
	5–9	0.19	0.11	0.14	0.18	−5.26%
	10–14	0.26	0.21	0.21	0.19	−26.92%
	15–19	0.60	0.56	0.49	0.40	−33.33%
	20–24	1.05	0.97	1.01	0.93	−11.43%
All Causes of Death	1–4	34.22	31.19	29.36	28.37	−17.10%
	5–9	16.86	15.17	14.52	12.47	−26.04%
	10–14	20.39	19.55	18.05	15.7	−23.00%
	15–19	68.6	67.79	65.13	57.67	−15.93%
	20–24	90.78	95.15	97.59	93.98	3.53%

Table 3. Relative ranking of autoimmune disease deaths when compared to the official 10 leading causes of death in 2008.

Age	Relative Rank
1–4	#8
5–9	#10
10–14	#9
15–19	#6
20–24	#6

Conclusion: Although mortality rates from autoimmune diseases appear to be declining in children 5–20 years of age, autoimmune diseases continue to rank within the top ten leading causes of death.

Disclosure: E. Y. Yen, None; D. K. McCurdy, None.

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Changes in Ten Year Survival Among SLE Patients At an Academic Center in North America (1970–2011). Joseph F. Merola, Bonnie L. Bermas, Bing Lu, Peter Hsun Tsao, Tabatha Norton, Christina Iversen, Elizabeth W. Karlson, Peter H. Schur and Karen H. Costenbader. Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Data from other large SLE cohorts have suggested improving survival among SLE patients in recent years with protective effects from antimalarial use and less favorable prognoses among males. We investigated whether a change in survival has occurred among patients with SLE in our large academic lupus center over the past 41 years.

Methods: Our lupus registry contains data on 5,030 patients seen in our lupus center for potential SLE (ICD-9 billing code 710.0) since the 1960s.For this study, we included 1,099 patients who had validated SLE per both treating rheumatologist and an SLE expert, ≥ 4/11 of the 1997 ACR Criteria for Classification of SLE, date of diagnosis on or after January 1, 1970, and > 2 visits to our center.Data ascertained from the medical record included age at SLE diagnosis, validated history of lupus nephritis, clinical manifestations, serologies, hematology and renal laboratories, medication use and date of death. Individuals were followed for ten years, or until death or end of follow-up period (April 30, 2011). Kaplan Meier curves with log rank tests and multivariable Cox proportional hazards models, adjusted for age at diagnosis, race, sex, nephritis and hydroxychloroquine use, were used to estimate the risk of death over time, and to investigate potential predictors of mortality in our cohort.

Results: The 1,009 SLE patients were divided into two periods at a point where each group contributed equal person-time.Date ranges were January 1, 1970-August 31, 1993 (54,000 person-months) and September 1, 1993-April 30, 2011 (54,000 person-months). Clinical characteristics of the patients diagnosed in each period are compared in **Table 1A**. All patients were ANA positive and approximately 60% in both periods were anti-dsDNA positive. More SLE patients in the recent periods were non-White. They were also older at diagnosis and a higher proportion was prescribed hydroxychloroquine. Overall mean follow-up of all patients was 8.8 years (SD±2.4). There were 70 deaths in period 1; 28 deaths in period 2. Ten year survival was 84.5% in period 1 and 95.0% in period 2 (log rank test p=0.01). In multivariable Cox proportional hazards model, the hazard ratio (HR) for 10 year mortality was 0.47 (95% CI 0.29–0.75) for those diagnosed in the later period, compared to those in the earlier time period. Older age at diagnosis and male sex were associated with increased 10 year mortality (**Table 1B**). There was no significant association between hydroxychloroquine use, race or nephritis with survival over this time period among our subjects.

Table 1A. Comparison of Clinical Characteristics of SLE Patients Diagnosed in Early vs. Late Periods

Demographics	Period 1 (1970–1993), n=451	Period 2 (1993–2011), n=558	p value*
Mean Age at Diagnosis (SD)	29.4 (12.2)	36.0 (13.6)	**<0.001**
Male, (%)	30 (6.7)	53 (9.5)	0.11
White, (%)	283 (62.8)	226 (40.5)	**<0.001**
ANA Positive, (%)	451 (100)	558 (100)	0.50
Anti-dsDNA Positive, (%)	268 (59.4)	336 (60.2)	0.85
Lupus Nephritis, (%)	145 (32.2)	167 (29.9)	0.45
Hydroxychloroquine Use, (%)	338 (75.3)	483 (86.6)	**<0.001**

* t-tests and Fisher exact tests

Table 1B. Factors Associated with 10 Year Mortality**

	Hazard Ratio for Death (95% Confidence Interval)
SLE Diagnosis in Period 2 vs. Period 1	0.47 (0.29–0.75)
Increasing Age at Diagnosis, per year	1.05 (1.03–1.07)
Male Sex	2.36 (1.32–4.20)

**HR= Hazard Ratio
Cox proportional hazards models adjusted for age at diagnosis, race (White, Black, Hispanic, Asian, other), sex, hydroxychloroquine use, lupus nephritis.

Conclusion: Despite changes in patient demographics, survival of patients with immunologically-rich, validated SLE followed in our lupus center has improved over the past 41 years. This improved survival may be related to better management of comorbidities and new modalities of treatment.

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Hospitalizations in Systemic Lupus Erythematosus: A Longitudinal Study. Hong Fang, Jie Xu and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Hospitalizations are one of the major direct costs in SLE.A review of studies looking at the contributions of different medical components to the economic burden of SLE revealed that hospitalizations may count for 50% of the direct costs in SLE (Panopalis P, et al. Arthritis Rheum 2008; 59:1788–1795.).Lupus nephritis has been identified as one of the significant factors consistent with increased direct costs (Slawsky KA et al. Arthrit Care Res 2011; 63:1224–1232.).Identification of predictors of hospitalizations could lead to targeted interventions to reduce costs.

Methods: The medical resource use questionnaire was distributed to SLE patients in the Hopkins Lupus Cohort that covered the last 3 months before the baseline visit and then at the following two quarterly clinic visits. 359 patients (91% female, 55% Caucasian, 36% African-American, 9% other ethnicities, mean age at baseline 46±12 years) were included in the analysis.Exclusion criteria were diagnosis with lupus less than 6 months ago, age younger than 18 or older than 75, pregnant at baseline, and active HIV patients.

Results: Univariate analysis identified prednisone, disease activity (mean Physician's global assessment, SLEDAI), and renal lupus as predictors of hospitalization over the next 6 months (Table 1). In the multivariate model for number of hospitalizations, use of prednisone at baseline and mean SLEDAI were associated (Table 2).

Table 1. Predictors of hospitalizations (any vs none)—univariate analysis.

		Number (%) hospitalization during followup	P-value
Age at baseline (years)	≤ 40 (n=134)	11 (8.2)	0.21
	> 40 (n=225)	28 (12.4)	
Gender	Female (n=327)	35 (10.7)	0.77
	Male (n=32)	4 (14.3)	
Ethnicity	African-American (n=131)	19 (14.5)	0.096
	Caucasian (n=197)	17 (8.6)	
Family income ($)	≤ 50K (n=165)	21 (12.7)	0.30
	> 50K (n=194)	18 (9.3)	
Education (years)	< 12 (n=24)	2 (8.3)	>0.99
	≥ 12 (n=335)	37 (11.0)	
Use of prednisone at baseline	No (n=224)	17 (7.6)	0.010
	Yes (n=135)	22 (16.3)	
PGA[1] at baseline	≤1 (n=310)	32 (10.3)	0.41
	>1 (n=49)	7 (14.3)	
Mean PGA over year	≤1 (n=304)	28 (9.2)	0.018
	>1 (n=55)	11 (20.0)	
SLEDAI at baseline	≤2 (n=265)	23 (8.7)	0.026
	>2 (n=94)	16 (17.0)	
Mean SLEDAI over year	≤2 (n=242)	19 (7.9)	0.0083
	>2 (n=117)	20 (17.1)	
Anti-dsDNA at baseline	Negative (n=271)	28 (10.3)	0.39
	Positive (n=80)	11 (13.8)	
C3 or C4 at baseline	Low (n=67)	9 (13.4)	0.50
	Normal (n=284)	30 (10.6)	
Increased ESR at baseline	No (n=179)	15 (8.4)	0.11
	Yes (n=167)	23 (13.8)	
Urine Pr:Cr ratio at baseline	≤0.5 (n=314)	31 (9.9)	0.049
	>0.5 (n=26)	6 (23.1)	
Baseline history of hospitalizations	No (n=327)	34 (10.4)	0.37
	Yes (n=32)	5 (15.6)	

[1]PGA: Physician's global assessment (0–3 scale)

Table 2. Multivariate Linear Regression Model.

	Effect on number of hospitalizations	P-value
Age at baseline (per 10 years)	0.04 ± 0.02	0.061
Ethnicity (African-American)	0.06 ± 0.06	0.25
Education (<12 years)	−0.05 ± 0.10	0.61
Use of prednisone at baseline	0.14 ± 0.06	0.0091
Mean SLEDAI (per unit)	0.03 ± 0.01	0.0086
Urine Pr:Cr ratio at baseline (per unit)	0.01 ± 0.04	0.73

We next looked at hospitalizations due to lupus. In a multivariate linear regression model, baseline hospitalizations and mean SLEDAI were predictive.

Conclusion: Total hospitalizations are associated with prednisone use and disease activity. Hospitalizations due to SLE were also associated with disease activity captured by SLEDAI. Targeted therapies that reduce SLEDAI would thus be expected to reduce hospitalizations and direct costs.

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Shared High Risk of Intensive Care Unit Admission in Three Autoimmune Inflammatory Diseases. Christine Peschken, Carol A. Hitchon, Allan Garland. Charles N. Bernstein, Randy Fransoo and Ruth Ann Marrie, University of Manitoba, Winnipeg, MB

Background/Purpose: Little is known about the influence of autoimmune inflammatory diseases on the risk of critical illness, as defined by Intensive care unit admissions (ICU). Using a large, population-based dataset we determined the incidence of ICU admissions in rheumatoid arthritis (RA), multiple sclerosis (MS) and inflammatory bowel disease (IBD). These conditions are highly prevalent in Western countries and often managed with immunomodulatory therapies.

Methods: In a stable population of over 900,000 adults, hospital claims from an administrative database were linked to a population based ICU database to determine the incidence of ICU admissions from 2000–2010. RA, MS, and IBD patients were compared to cohorts from the general population, matched on sex, year of birth and region of residence, with up to 5 controls per case. Individuals with any diagnostic codes (ICD-9/10) for autoimmune inflammatory disease were excluded from the control cohorts. We used previously published and validated definitions for RA, MS, and IBD. Annual incidence rates were estimated by age group, sex, and geographic region (number of persons in each cohort with at ≥ 1ICU admission/ number of persons alive in that cohort at year-end). Results were age and sex standardized to the general Canadian population. The incidence of ICU admission between the disease specific cohorts and matched cohorts were compared using incidence rate ratios (IRR). The 10 year cumulative incidence of ICU admission for the period 2000–2010 was compared: (number of persons with disease who had ≥ 1 episode of critical illness/ person-years at risk).Hazard ratios for the 10 year period were calculated after adjustment for age, sex, socioeconomic status and comorbidity.

Results: The annual incidence rates of ICU admission over the 10 year period were:RA 0.82–1.18%; MS 0.51–1.07%; and IBD 0.55–1.12%, compared to the matched cohorts; 0.32–0.60%. The IRR for the 10 year cumulative incidence rate was 1.62 (95% CI 1.46–1.80) for RA; 1.54 (95% CI 1.30–1.77) for MS; 1.52 (95% CI 1.36–1.68) for IBD. Hazard ratios over the 10 year period for the 3 diseases were: RA HR=1.86 (95%CI 1.68–2.05); MS HR= 1.65 (95%CI 1.36–2.01); IBD HR= 2.02 (95%CI 1.78–2.28).
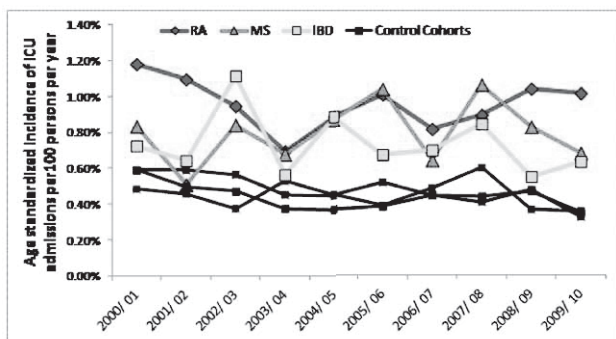
Conclusion: The risk of ICU admission is significantly increased in RA, MS and IBD patients compared to the general population. Close to 1% of adults with these diseases develop critical illness each year; representing a substantial cost to the healthcare system.The risks between the 3 diseases are remarkably similar, suggesting shared risks from chronic inflammation and/or immunomodulatory therapy.

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Incidence of Systemic Lupus Erythematosus in England, 1998–2010. Herve Caspard[1], Amy Steffey[2], Jie Li[2] and Trung N. Tran[2]. [1]MedImmune LLC, Gaithersburg, MD, [2]MedImmune, Gaithersburg, MD

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic auto-immune disease associated with a wide spectrum of clinical manifestations and increased mortality. The most recent data about incidence of SLE in England date back to 1999.

It has been suggested that the incidence of SLE and other auto-immune diseases has increased over time.

Our purpose was:

* To estimate the incidence of SLE in England from 1998 to 2010 and to describe the incidence rate distribution by demographic factors.

* To discuss the hypothesis that the incidence of SLE increased from 2001 to 2010.

Methods: We investigated the incidence of SLE among individuals documented in the Clinical Practice Research Datalink (CPRD) and linked with the Hospital Episode Statistics (HES) database. CPRD is a database of anonymized longitudinal medical records from primary care from over 600 practices in the United Kingdom. HES is a database documenting all admissions to the National Health System hospitals in England that can be linked with CPRD since 1997. All individuals documented in GPRD and HES prior to October 1st, 2010 and aged 18 years or older were retained in the analysis.

Patients with SLE were identified as individuals with at least one relevant diagnosis code in CPRD or HES (list of codes available upon request).

Incident cases were defined as patients with at least 12 months of registration in CPRD prior to the date of first diagnosis. Incidence rates were estimated each calendar year from January 1st 1998 to October 1st 2010.

Results: The incidence rate for the 2001–2010 time period is 5.5 per 100,000 patient*years (table 1): this estimate is very close to the 1998–2000 estimate (5.6 per 100,000 patient*years) and falls within the 95% confidence interval of each calendar year point estimate from 2001 to 2010.

Table 1. Incidence rate estimates per calendar year

Calendar year	Population exposed (patient*years)	Incident cases	Incidence rate (per 100,000 patient*years)
1998–2000	4,213,018	237	5.6 [4.9;6.3]
2001	1,504,620	83	5.1 [4.3;6.7]
2002	1,585,560	89	5.6 [4.4;6.8]
2003	1,639,386	87	5.3 [4.2;6.4]
2004	1,682,720	82	4.9 [3.8;5.9]
2005	1,720,965	88	5.1 [4.0;6.2]
2006	1,768,140	101	5.7 [4.6;6.8]
2007	1,812,779	109	6.0 [4.9;7.1]
2008	1,850,292	111	6.0 [4.9;7.1]
2009	1,859,559	93	5.0 [4.0;6.0]
2010 (through September 30)	1,359,960	79	5.8 [4.5;7.1]
2001-2010	16,784,884	922	5.5 [5.1;5.8]

Incidence rate is higher among women than men: 9.4 versus 1.5 per 100,000 patient*years. It reaches a maximum between 45 and 54 years of age in women (12.2 per 100,000 patient*years) while it keeps growing slightly with age in men; 25%(294) of the incident cases were documented in the HES database only.

Conclusion: These incidence rates of SLE in England from 1998 to 2010 are consistent with prior estimates and with estimates in other western countries.

We did not observe any significant change in the incidence of SLE in England from 2001 to 2010.

Disclosure: **H. Caspard**, None; **A. Steffey**, None; **J. Li**, None; **T. N. Tran**, None.

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Validity and Reliability of the Systemic Lupus Activity Questionnaire (SLAQ): A Prospective Study. Yuko Okamoto, Yasuhiro Katsumata, Yasushi Kawaguchi, Sayumi Baba, Kae Takagi, Hisae Ichida, Takahisa Gono, Masanori Hanaoka, Yuko Ota and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Traditional assessments of systemic lupus erythematosus (SLE) disease activity, such as the SLE Disease Activity Index 2000 (SLEDAI-2K) and the Systemic Lupus Activity Measure (SLAM), rely on a physician-obtained history, physical examination, and laboratory evaluation and thus may prove impractical and costly especially for large epidemiologic studies. The Systemic Lupus Activity Questionnaire (SLAQ) was developed based on the SLAM as a more economical way of following and tracking large groups of SLE patients who may be at a distance from a center in epidemiologic studies. The purpose of the present study was to translate and adapt the SLAQ to Japanese and further investigate its validity and reliability using a prospective observational cohort of SLE patients followed at a single university clinic while their physicians score the SLEDAI-2K.

Methods: The English version of the SLAQ was translated, back-translated and culturally adapted to Japanese using standard methodology. Japanese SLE patients who had 4 or more revised American College of Rheumatology (ACR) criteria for SLE were approached during their outpatient attendance in our university clinic. Some of the hospitalized patients during the study period were also eligible to the study. Patients were asked to complete the SLAQ and other related demographic questionnaires such as Medical Outcomes Study Short Form-36 (SF-36) and physicians were asked to complete the SLEDAI-2K and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI). Laboratory items were omitted from SLEDAI-2K scores in this study and the instrument will be called SLEDAI-2K-nolab. Patients were prospectively followed for repeat assessment next year.

Results: A total of 246 patients and 30 physicians (all rheumatologists) participated. The acceptability of the SLAQ was high, with most of items having 100% response rate. The distribution of the SLAQ, the SLEDAI-2K, and the SLEDAI-2K-nolab all skewed to the right. The median SLAQ score was 5 (range 0–32) and the median SLEDAI-2K score was 2 (range 0–18). The SLAQ had a weak correlation with the SLEDAI-2K-nolab (Spearman's $\rho = 0.18$, $p = 0.005$) but not with SLEDAI-2K ($p = 0.71$). The SLAQ demonstrated acceptable internal consistency, with a Cronbach's alpha of 0.78. The SLAQ showed weak correlation with the SDI, and moderate correlation with physical and mental component summary scores of the SF-36 (Spearman's $\rho = 0.17$, -0.53, and -0.54, respectively). Twenty-five patients with stable disease were asked to repeat the SLAQ after 2 weeks and the intraclass correlation coefficient was 0.85, which means good test–retest reliability. These figures come from the first year research and the second year gave similar results. The SLAQ did not demonstrate a good responsiveness by the longitudinal analyses.

Conclusion: We have successfully translated, adapted and validated the Japanese version of the SLAQ. There is evidence of acceptable reliability and validity of the Japanese version of the SLAQ among Japanese patients with SLE. Our study provides evidence of the cross-cultural validity of this tool and can be used to assess disease activities among Japanese patients with SLE.

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Validity and Reliability of the Lupus Damage Index Questionnaire (LDIQ): A Prospective Study. Yuko Okamoto, Yasuhiro Katsumata, Yasushi Kawaguchi, Sayumi Baba, Kae Takagi, Hisae Ichida, Takahisa Gono, Masanori Hanaoka, Yuko Ota and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SDI) is a validated instrument for assessing organ damage in systemic lupus erythematosus (SLE). Trained physicians must complete it, thus limiting utility where this is impossible. A self-administered questionnaire, modeled after the SDI, the Lupus Damage Index Questionnaire (LDIQ) has been previously developed and validated. It may allow the ascertainment of this construct in SLE patients followed in the community. The original English version of LDIQ

was subsequently translated into Spanish, Portuguese and French. The purpose of the present study was to translate and adapt the LDIQ to Japanese and further investigate its validity and reliability using a prospective observational cohort of SLE patients followed at a single university clinic.

Methods: The English version of the LDIQ was translated, back-translated and culturally adapted to Japanese using standard methodology. Japanese SLE patients who had 4 or more revised ACR criteria for SLE were approached during their outpatient attendance in our university clinic. Some of the hospitalized patients during the study period were also eligible to the study. Patients were asked to complete the LDIQ and other related demographic questionnaires such as Medical Outcomes Study Short Form-36 (SF-36) and physicians were asked to complete the SDI and the SLE Disease Activity Index 2000 (SLEDAI-2K). Patients were prospectively followed for repeat assessment next year.

Results: A total of 250 patients and 30 physicians (all rheumatologists) participated. The acceptability of the LDIQ was high, with most of items having 100% response rate. The distribution of the LDIQ and SDI both skewed to the right. The median LDIQ score was 2 (range 0–12) and the median SDI score was 1 (range 0–9). The LDIQ had a substantial correlation with the SDI (Spearman's $\rho = 0.71$, $p < 0.001$). Cohen's kappa coefficient, a statistical measure of agreement for qualitative items, between the individual SDI and LDIQ items varied between 0.07–1.00. The damage domains of the LDIQ were not associated with each other, which was reflected in low Cronbach's alpha (0.53). The LDIQ showed poor correlation with the SLEDAI-2K, and mental component summary scores of the SF-36, but had moderate correlation with physical component summary scores of the SF-36 (Spearman's $\rho = -0.08$, -0.11, and -0.41, respectively). Twenty-five patients with stable disease were asked to repeat the LDIQ after 2 weeks and the intraclass correlation coefficient was 0.85, which means good test–retest reliability. These figures come from the first year research and the second year gave similar results. The LDIQ demonstrated a good responsiveness: standardized response mean $= 0.40$ and effect size $= 0.32$ in patients with worsened SDI.

Conclusion: We have successfully translated, adapted and validated the Japanese version of the LDIQ. There is evidence of acceptable reliability and validity of the Japanese version of the LDIQ among Japanese patients with SLE. Our study provides evidence of the cross-cultural validity of this tool and can be used to assess SLE-related damage among Japanese patients with SLE.

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Impact of Systemic Lupus Erythematosus On Work Productivity and Income in the United States. Alan Oglesby[1], Ellen Sulcs[2], Siva Narayanan[3], Mechele Lee[2] and Cindy Garris[1]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]Harris Interactive Inc., Rochester, NY, [3]Human Genome Sciences, Inc., Rockville, MD

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disorder characterized by fluctuating periods of disease activity affecting multiple organ systems. This study was conducted to evaluate the impact of SLE on patients' employment and productivity.

Methods: A longitudinal cohort of employed SLE patients in the United States, recruited through a patient advocacy association and the Harris Chronic Illness Panel, was surveyed online (IRB approved) between Dec 2010 and Aug 2011. Inclusion criteria were 18 years old, self-reported SLE diagnosis, and ≥1 SLE flare in prior 3 months requiring medical attention (taking medications, calling or visiting a physician, or going to the ER or hospital). A control group of employed patients without SLE recruited from HarrisPollOnline (HPOL) were demographically matched (age, sex, race, income, and education) to the employed SLE cohort. Controls met the above inclusion criteria excluding the SLE related criteria and were also surveyed online. A group of unemployed SLE patients were also recruited for research, but not included in this analysis of employed cohorts. Both the employed SLE patients and controls completed baseline and follow-up surveys at the end of 6 months. Questions for the SLE cohort included perceived SLE disease activity over the past 3 months using a 10-point scale (mild: 0–3, moderate: 4–6, severe: 7–10), impact of SLE on work productivity and absenteeism. The control group answered similar questions about the impact of any health conditions on work. Employed and unemployed SLE patients were compared to controls by dependent sample t-tests.

Results: 281 employed SLE patients and 300 employed controls completed the survey; of the 300 control group respondents, 69% reported having ≥1 health condition(s). The mean age in the employed SLE group and control groups was 39.8 and 41.1 years, respectively (p<0.05). Of all surveyed respondents, 96%

were female and 79% were Caucasian (no significant differences across groups). The employed SLE cohort reported fewer overall hours worked per week (25.3 vs 32.8) and more lost work hours per week due to SLE (6.9 hours) than the employed control group due to any health condition (1.6 hours) (all p-values<0.05). While at work, patients reported significantly greater impact on productivity due to SLE (45%) compared to controls for any health reason (13%, p<0.05). In the SLE employed group, the number of work hours missed increased as self-reported disease severity worsened from mild, moderate, to severe (2.0, 4.2, and 7.9 hours, respectively (p<0.05). Hourly employees with SLE (52.3% of SLE cohort) reported losing an average of $346 per week due to their lupus. Similarly, lost income per week increased as SLE activity increased ($49 in mild to $522 in severe, p<0.05).

Conclusion: Patients with SLE reported significantly reduced ability to work compounded by worsening disease activity. For hourly employees with SLE, increased disease activity may have significant detrimental impacts to their earning potential.

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Job-Related Burden and Effort-Reward Imbalance in Patients with Systemic Lupus Erythematosus.

Jutta G. Richter, Thomas Muth, Ralph Brinks, Tobias Koch, Johannes Siegrist, Nicole Hoffmann, Peter Angerer and Matthias Schneider. Heinrich-Heine-University, Duesseldorf, Germany

Background/Purpose: Working life factors influence patients' (life) satisfaction and well being. Effort at work is part of a social contract that reciprocates effort by adequate reward. Components of work-related rewards matter for health. Research on effort-reward imbalance (ERI) might contribute to the understanding of factors related to the well-being of patients (pts) with systemic lupus erythematosus (SLE). We studied pts' job-tasks-related burdens and stress levels measured by the ERI model.

Methods: In a cross-sectional nationwide study a set of standardized self-administered questionnaires was applied to SLE pts. ERI was assessed by the corresponding questionnaire in pts capable for work. Effort reward ratio (ERR) scores > 1 and upper tertile scores of overcommitment (OCS) reflect relevant values. Based on pts' reported occupations, occupational physicians categorized tasks-related burden into a developed, standardized coding system that included 'working environment burden', 'physical burden', 'mental burden', and 'other burden'. Ethical approval was obtained.

Results: 252 pts (95.2% female) contributed data. Mean age was 40.1 ± 9.4 years, mean disease duration 10.5 ± 7.3 years, mean HAQ 0.8 ± 0.4. 86.0% self-reported at least one comorbidity (range 1–10). 77.4% took at least one immunosuppressive drug (DMARD, range 1–3), 40.5% steroids ≤ 7.5mg, 16.3% steroids >7.5mg, 34.0% NSAIDS.

For ERI results see table 1. 79.5% showed relevant effort-reward imbalance (ERR>1). ERR>1 pts scored significantly lower in the esteem, job security and the job promotion/salary scales (p-values<0.05). Above mentioned personal and disease related factors, pts' self-categorized occupation groups, working environment burden, physical burden, mental burden and other burden did not differ significantly in ERR>1 and ERR≤1 pts.

39.0% had relevant OCS, see table 1. Except HAQ above mentioned personal and disease related factors, working environment burden, physical burden, mental burden and other burden did not differ significantly in pts with OCS in the lower tertiles compared to pts with relevant OCS.

Table 1. ERI and overcommittment scores

Effort mean ± SD	Reward mean ± SD	ERR>1 %	Esteem mean ± SD	Job Security mean ± SD	Job Promotion/ Salary mean ± SD	Overcommittment mean ± SD
15.6 ± 4.9	21.6 ± 9.2	79.5	9.6 ± 4.9	3.9 ± 2.6	8.2 ± 3.7	14.3 ± 4.0

Conclusion: In this first study investigating the ERI in SLE pts a high proportion had effort reward imbalance (ERR>1). Analysis on mechanisms potentially involved in the relation between ERI and SLE showed that job-tasks-related burden scored by occupational physicians and most disease related factors did not differ in ERI and OCS subgroups. Further study data analysis will address pts' perceptions of their job-related burden to develop appropriate support strategies.

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Work Loss in Systemic Lupus Erythematosus, the General Public, and Other Chronic Conditions.

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Background/Purpose: Systemic lupus erythematosus (SLE) predominantly develops in young groups, when many are establishing themselves in the workforce and can have a devastating impact on employment. We studied the impact of sociodemographic factors on work loss in SLE, the general public, and other major chronic conditions.

Methods: The Georgians Organized Against Lupus (GOAL) cohort is derived predominantly from the population-based Georgia Lupus Registry and collects annually self-reported measures from validated patients with SLE. The Behavioral Risk Factor Surveillance System (BRFSS) survey samples representative individuals from the general population on self-reported health conditions and behaviors. We studied GOAL SLE participants who lived in the Atlanta metropolitan area surveyed between August 2011 and April 2012, and 4 BRFSS samples (general population and self-reported diabetes, asthma, and cardiovascular disease [CVD]) from the same geographic area, surveyed between 2005-10. The effect of sociodemographic factors on being unemployed/disabled at survey completion in SLE and BRFSS participants aged >18 and <65 was analyzed with logistic regression. We reported the adjusted odds ratios (OR) of being unemployed/disabled for each sociodemographic variable within SLE and 4 BRFSS samples.

Results:

	SLE n=630	General n=6339	Diabetes n=473	Asthma n=783	CVD n=244
Age, mean	45	41	49	38	51
Females %	94	52	51	57	49
Whites %	19	59	51	61	46
Blacks %	81	42	49	39	54
Education ≤high school %	35	23	30	28	34
Unemployed/disabled% (95% CI)	47 (43–50)	12 (11–13)	23 (18–28)	19 (14–23)	33 (25–42)
OR (95% CI) of unemployed/disabled[1]					
Age (Per 5 year increase)	1.1 (1.0–1.2)	1.1 (1.1–1.2)	1.1 (1.0–1.3)	1.2 (1.1–1.3)	0.9 (0.7–1.2)
Gender (Male vs Female)	1.2 (0.6–2.4)	1.2 (0.9–1.5)	0.9 (0.5–1.7)	2.0 (1.0–3.9)	1.0 (0.5–2.2)
Race (Black vs White)	2.7 (1.7–4.3)	1.9 (1.4–2.5)	1.0 (0.6–2.0)	1.7 (0.9–3.2)	1.5 (0.7–3.1)
Marital Status (Married vs other[2])	0.5 (0.4–0.7)	0.5 (0.4–0.6)	0.4 (0.2–0.7)	0.3 (0.2–0.7)	0.2 (0.1–0.4)
Education (≤High School vs >High School)	2.1 (1.5–3.0)	3.0 (2.3–3.9)	4.0 (2.2–7.3)	2.9 (1.5–5.7)	2.5 (1.1–5.8)

[1]Adjusted by the other sociodemographics
[2]never married, separated, divorced, widowed

Conclusion: The burden of unemployment/disability was significantly higher in SLE than in other chronic diseases, even when the mean age of SLE and the education level were similar across groups. Less than 1/3 of individuals with diabetes, asthma and CVD were unemployed, as compared to almost 50% of SLE. Black race was associated with unemployment/disability in SLE and the general population, but not in other chronic diseases. Lower education and not being married increased the risk of unemployment/disability in all groups. Important factors, such as disease severity, treatment response, or access to care in black patients with SLE must be further explored in order to reduce the burden of work loss in SLE.

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Self-Reported Disease Activity and Health-Related Quality of Life in a Longitudinal Cohort of Patients with Systemic Lupus Erythematosus.

Siva Narayanan[1], Ellen Sulcs[2], Alan Oglesby[3], Cindy Garris[4] and Mechele Lee[2]. [1]Human Genome Sciences, Inc., Rockville, MD, [2]Harris Interactive Inc., Rochester, NY, [3]GlaxoSmithKline, Research Triangle Park, NC, [4]GlaxoSmithKline R&D, Research Triangle Park, NC

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex, multisystem autoimmune disease with variable clinical manifestations and an unpredictable waxing and waning disease course impacting patient health-related quality of life (HRQoL). The objective of this analysis is to portray the self-perceived burden of illness by assessing patterns of self-reported disease activity and HRQoL over the course of 6 months.

Methods: A longitudinal cohort of employed SLE patients in the U.S meeting the following inclusion criteria were recruited between Dec 2010 and March 2011 through a patient advocacy association and the Harris Chronic Illness Panel: ≥18 years old, self-reported SLE diagnosis, and ≥1 SLE flare in prior 3 months requiring medical attention (physician/ER/ hospital encounter or taking SLE medications). SLE patients completed a baseline (BL) and six monthly follow-up (FU) surveys online. Monthly surveys included assessments of self-perceived SLE disease activity (scale: 0 (no activity) to 10 (most activity); mild: 0–3, moderate: 4–6 & severe: 7–10), Lupus Impact Tracker (LIT; scale: 0 (low) to 100 (high); a 10-item HRQoL tool assessing disease impact on pain, fatigue, ability to perform daily activities, etc), self-reported flares & symptoms and work/productivity (data not shown).

Results: 272 SLE patients (mean age: 40.9 yrs; female: 96%; Caucasian: 78%; had at least college education: 63%) who completed the BL and $\geq=1$ FU survey during the 6-month follow-up period were included in the analysis. Time since first onset of SLE symptoms and time since SLE diagnosis were 12.5yrs and 7.8yrs respectively. At BL, mean disease activity score was 5.9; patients reporting different levels of severity of lupus disease activity at BL and each of the monthly FUs were clustered consistently over time as follows - Mild: 15–16%, moderate: 40–42%, severe: 43–45%. For all patients, at BL, mean LIT score was 49.3, and monthly FUs ranged between 44.3 & 48.7. Fatigue, pain, and difficulty concentrating were identified by over 55%, 55%, and 30% of patients respectively as occurring at least 'most or all of the time' at every evaluation period. LIT scores for patients reporting mild, moderate and severe disease activity across the individual surveys were in the range of: 30.2–40.9, 49.7–59.7 and 56.8–75.2 respectively. Mean LIT scores statistically significantly ($p<.001$) correlated to disease activity scores at BL and monthly assessments (pearson correlation coefficients range: 0.57–0.67).

Conclusion: Overwhelming majority of SLE patients in the study consistently rated their disease activity to be moderate-to-severe over the course of 6-months, and it significantly correlated with HRQoL measured by LIT. While patient self-assessment of disease activity may differ from physician's clinical assessment, consistently high patient disease severity reported by the study cohort highlights the perceived disease burden. Incorporating patient perspective in clinical decision making may be important to consider in managing patients optimally and alleviate their burden of illness.

Disclosure: S. Narayanan, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **E. Sulcs**, Harris Interactive, 3; **A. Oglesby**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **C. Garris**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **M. Lee**, Harris Interactive, 3.

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The Impact of Dyspigmentation and Scarring in Cutaneous Lupus On Quality of Life. Saroj M. Verma[1], Joyce Okawa[2], Kathleen Propert[1] and Victoria P. Werth[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]Perelman School of Medicine at the University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA, [3]University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA

Background/Purpose: Patients with more severe cutaneous lupus activity have poorer quality of life. The main objective of the current study was to evaluate the impact that lupus-related disease damage had on skin-specific quality of life and the differences observed within a population of CLE patients from different racial backgrounds with respect to disease damage and its impact on quality of life.

Methods: Patients were enrolled into our prospective database and evaluated with a validated cutaneous lupus-scoring tool (CLASI). Data collected included sex, race, diagnosis, Cutaneous Lupus Area Activity and Severity Index (CLASI) scores, and Skindex-29 QoL scores. These parameters were analyzed at the initial and last visits. CLASI damage scores (dyspigmentation and scarring) and CLASI activity scores were collected, grouped by race, and correlated with Skindex-29 domains.

Results: 223 patients were analyzed at baseline, with 141 of these patients completing more than one study visit. The majority of patients were Caucasians (63.7%), followed by African Americans (29.1%) and Asian Americans (4.0%). African Americans accounted for a disproportionate percentage of both localized (50% of cases) and generalized (48.9% of cases) DLE. Median CLASI damage scores significantly differed between African Americans, Caucasians, and Asian Americans, at both first (8.5, 4.0, 7.0) (Kruskal-Wallis $p<0.0001$) and last visit (10.0, 6.0, 8.5) (Kruskal-Wallis $p<0.01$), (Dunn's Multiple Comparison $p<0.0001, p<0.01$). CLASI damage scores in African Americans correlated with CLASI activity scores (Spear-

man's r=0.45, $p=0.0003$). There was no significant correlation between CLASI damage scores and Skindex domains overall. Individually, dyspigmentation and scarring also did not have a significant effect on Quality of Life.

Conclusion: In conclusion, disease damage does not affect quality of life, as measured by the Skindex-29.Differences were found in CLE patients of different races: African American patients with CLE, do exhibit a high rate of DLE, experience damage early in their disease course, frequently in conjunction with disease activity

Disclosure: S. M. Verma, None; **J. Okawa**, None; **K. Propert**, None; **V. P. Werth**, None.

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Antibody-Based Prediction Rules for Connective Tissue Disease: Analysis of 12,555 Patients with Antinuclear Antibody Testing. Ryo Rokutanda[1]. Mitsumasa Kishimoto[1], Yasuharu Tokuda[2], Ken-ichi Yamaguchi[1], Hisanori Shimizu[1], Yasuhiro Suyama[1], Yuri Ohara[1], Yoichiro Haji[1], Chisun Min[1], Akira Takeda[1], Yukio Matsui[1] and Masato Okada[1], [1]St. Luke's International Hospital, Tokyo, Japan, [2]University of Tsukuba, Ibaraki, Japan

Background/Purpose: Antinuclear antibody (ANA) is widely used as a screening test for connective tissue diseases (CTDs). The sensitivity of this test is high in 3 CTDs--systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and mixed connective tissue disease (MCTD). ANA-associated specific autoantibodies are also identifiable in 3 additional CTDs including polymyositis and dermatomyositis (PM/DM), as well as primary Sjögren syndrome (SS).However, appropriate cutoff points for ANA titers or in combination with other CTD-specific antibodies remains unclear.

Methods: We reviewed records for all patients (n=12,555) with ANA immunofluorescence assay testing from January 2003 to June 2012. Among 3302 patients with positive ANA (≥a40), 94 were excluded due to lack of information about ANA titers. Data collection also included specific CTD diagnoses, ANA titers, and results of specific antibody tests for DNA, Sm, U1RNP, Ro, La, centromere, Scl-70, and RNA polymerase III. We calculated sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values for diagnosing each CTD at different ANA cutoffs. We then performed classification and regression tree (CART) analysis to develop prediction rules for each CTD. Potential predictors included ANA titers, ANA staining patterns, and specific antibody test results.

Results: Of 12,461 patients with ANA testing, 665 patients (5.3%) were diagnosed as having at least one of the 6 CTDs of interest. Area under the ROC curves of ANA testing were 0.943, 0.977, 0.926, 0.840, and 0.740 for SLE, MCTD, SSc, SS, and PM/DM, respectively. The sensitivities of ANA (≥a40) for SLE, SSC, MCTD, SS, PM/DM were 98.6%, 95.9%, 100%, 83.0%, and 69.6%, while PPV was 6.7%, 5.1%, 0.7%, 6.3, and 1.7%, respectively. Prediction rules developed by CART were as follows: (1) ANA (≥a40) with anti-DNA antibody (PPV: 70.3% for SLE), (2) ANA (≥a40) with anti-U1RNP antibody (PPV: 26.8% for MCTD), (3) ANA (≥a320) with anti-centromere antibody (PPV: 44.7% for SSc), and (4) ANA (≥a320) and anti-Ro without anti-DNA (PPV: 49% for SS).

Conclusion: ANA testing demonstrates substantial sensitivity, but has low PPV for CTDs. Nonetheless, in combination with other antibody testing, our prediction rules reveal a high specificity and PPV for diagnosing CTDs.

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The Inverse Association Between Obesity and Anti-Nuclear Antibodies Is Modified by Systemic Inflammation and Maybe Associated with Body Composition. Irene Blanco, Monalyn Labitigan and Matthew Abramowitz. Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Obesity and abdominal adiposity have been frequently associated with inflammation. However, an association of obesity with a decreased likelihood of anti-nuclear antibodies (ANAs) was recently reported in the general population. We used data from adult participants ≥20 years of age in the National Health and Nutrition and Examination Survey 1999–2004 to further explore this association.

Methods: To rule out a possible previous history of autoimmune disease, participants were excluded if they reported a history of arthritis other than osteoarthritis, thyroid or liver disease, or steroid use. ANAs were screened

using indirect immunofluorescence (IF). Titers were done on samples with IF≥ 3+. We subsequently strictly defined positive ANA as an ANA titer ' 1:160. Overweight and obesity were classified by traditional BMI criteria. High and low C-reactive protein (CRP) were defined using the 75th percentile cutpoint as ≥0.42 and <0.42 mg/dL, respectively. Dual-energy X-ray absorptiometry (DEXA) was used to determine body composition. Logistic regression models were created to examine associations with ANA status and were adjusted for demographics, comorbidities, smoking status, and total cholesterol.

Results: 2552 participants were included in our analyses. Obese participants were older (p<0.001), more likely to be men (p=0.004) and to have comorbidities, and had higher levels of CRP (<0.001).After multivariable adjustment, obesity was associated with a decreased odds of having ANAs (OR 0.78, 95%CI 0.62–0.99). However when adding log-transformed CRP into our model, this association was no longer significant (OR 0.85, 95%CI 0.62–1.15), and there was evidence of effect modification by CRP (p=0.12). To study the effect of systemic inflammation, as measured by CRP, we then stratified our models based on the CRP cutpoint.Among participants with low CRP (<0.42), obesity was again associated with a reduced likelihood of ANA positivity (OR 0.69, 95%CI 0.48–0.99), but a trend was seen in the opposite direction among those with high CRP (≥0.42) (OR 1.77, 95%CI 0.81–3.88).When looking specifically at the 1143 obese and overweight participants with low CRP, ANA positivity was associated with a higher prevalence of cardiovascular disease (p=0.02) and higher % total body fat (p=0.007), trunk fat (p=0.02), and non-trunk fat (p=0.004). This association, however, was not found in the high CRP group.

Conclusion: In the general population the association of obesity with ANA is modified by the presence of systemic inflammation as measured by CRP, where the inverse association previously found is eliminated when controlling for CRP. While this inverse relationship remains among obese participants with low CRP, when these obese and overweight participants are ANA positive, it is associated with greater total body and trunk fat. Therefore it is possible that body composition, particularly fat distribution, is driving autoimmunity in the general population even in the absence of systemic inflammation. Further studies are needed to determine if in fact this is the case.

Disclosure: **I. Blanco**, None; **M. Labitigan**, None; **M. Abramowitz**, None.

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Performance of Various Anti-Nuclear Antibody Methodologies in the Assessment of Autoimmune Connective Tissue Diseases. Xiaoli Deng, Cynthia S. Crowson, Helen Khun, Melissa R. Snyder and Kevin G. Moder. Mayo Clinic, Rochester, MN

Background/Purpose: The anti-nuclear antibody (ANA) is the classic biomarker associated with autoimmune connective tissue diseases (CTDs). ANA testing is often ordered as part of the evaluation of patients with suspected CTD. Different methods, including indirect immunofluorescence assays (IFAs), enzyme immunoassays (EIAs), and multiplex immunoassays (MIAs) are currently used by clinical labs for general ANA screening. However, because the methodologies are very different, discordance between results may be observed, leading to challenges in interpretation. The purpose of this study is to analyze the performance of these methods in a subset of patients referred for rheumatology consultation.

Methods: A cohort of patients who had an ANA ordered for clinical assessment and a rheumatology consultation at our institution in 2010– 2011 were enrolled. ANA testing was performed by IFA (Zeus Scientific), EIA (BioRad), and MIA (BioRad). A titer of ≥1:40 for the IFA and a value >1.0 for the EIA were identified as positive. Autoantibodies to dsDNA, chromatin, ribosome P, SS-A, SS-B, Sm, Sm/RNP, RNP, Scl-70, Jo-1 and centromere B were detected by MIA; positivity for at least 1 specific autoantibody identified the ANA as positive. Sensitivities and specificities were computed and were compared using McNemar's test.

Results: In the study cohort (n=327; 81% female; mean age 52 [sd: 16] years), a subset had no identifiable autoimmune disease (non-auto; n=87) and the remaining patients had a diagnosed autoimmune CTD (auto CTD; n=240), including systemic lupus erythematosus (SLE; n=51), Sjogren syndrome (SS; n=34), mixed CTD/undifferentiated CTD (MCTD/UCTD; n=51), rheumatoid arthritis (RA; n=33), and various other miscellaneous CTDs (n=71). Sensitivities and specificities of the IFA, EIA and MIA within these groups are shown in the table.

| | | Sensitivity | | | Specificity |
	Auto CTD (n=240)	SLE (n=51)	SS (n=34)	MCTD/UCTD (n=51)	Non-Auto (n=87)
IFA	92%	100%	100%	100%	25%
EIA	92%	98%	100%	100%	28%
MIA	75%	92%	100%	82%	62%

In the auto CTD group overall, IFA and EIA had similar sensitivities (p=0.83), both of which were significantly higher than MIA (p<0.001). However, in the non-auto group, the MIA demonstrated significantly improved specificity compared to both the IFA and EIA (p<0.001). In specific CTD groups, all SS patients were ANA positive by all 3 methods. In SLE patients, the EIA and IFA had similar sensitivities (p=0.32); the sensitivity of the MIA was significantly lower than the IFA (p=0.046) and marginally lower than the EIA (p=0.08). In the MCTD/UCTD group, the EIA and IFA were positive in all patients, and the MIA had significantly lower sensitivity (p=0.003).

Conclusion: The sensitivities of IFA, EIA, and MIA vary significantly depending on the specific diagnostic category. Although the sensitivities of IFA and EIA tend to be improved over the MIA, the specificities of these methods are a significant issue. Further comparisons of methods used for ANA screening can provide valuable information that could lead to improved interpretation and utilization of lab testing.

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A Systematic Review of Quality of Prognosis Studies in Systemic Lupus Erythematosus. Lily Siok Hoon Lim[1], Senq-J Lee[1], Brian M. Feldman[2], D. D. Gladman[3], Eleanor Pullenayegum[4] and Earl D. Silverman[5]. [1]Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON, [4]McMaster University, Hamilton, ON, [5]Pediatric Rheumatology Collaborative Study Group (PRSCG), Toronto, ON

Background/Purpose: Prognosis studies study future outcomes and/or seek to identify predictive or associative factors associated with outcomes. Strong and consistent prognostic factors can be used to individualize management and better outcomes of patients. Many prognostic factors have been identified in SLE but few have been consistent. We hypothesize that this is due to flawed study design. We aim to systematically assess methodological quality of prognosis studies in SLE.

Methods: A systematic search of prognosis studies in SLE was performed in MEDLINE and EMBASE, from January 1990 to June 2011. Non-English literature, non-original research, non- full length reports and animal studies were excluded. Of 5419 articles subjected to a title and abstract screen, 1039 articles were found. A representative sample of 150 articles was selected using a random number generator and assessed by 2 reviewers. Studies were classified according to design and the clarity of research question was assessed. Each study was assessed by a risk-of-bias tool "QUality In Prognosis Studies" (QUIPS) in 6 domains: study participation, study attrition, measurement of prognostic factors, measurement of outcomes, measurement/adjustment for confounders and appropriateness of statistical analysis. Information on missing data was also collected.

Results: Of 150 articles, 15 were pediatric studies, 3 made comparisons of pediatric and adult patients and the remainder were adult studies. The majority were published in rheumatology journals (69%). Cohort design was used in 67% of studies; the remainder used cross-sectional (21%), case-control (5%) and other designs (7%). The research question clearly included study population in 92%, prognostic factor in 54% and outcome in 61% of studies. High risk of bias (QUIPS) was noted in 57% of studies for study participation, 57% for attrition, 20% for prognostic factor, 18% for outcome, 65% for confounders and 36% for statistical analyses. Confounders were named in the methods section in only 12% of studies. Some consideration for confounding was built into the design of 21% of studies. The amount of missing data could not be assessed in 39% of studies.

Conclusion: Inadequate articulation of research questions for prognostic factors, poor design addressing confounding, study participation and attrition and inadequately reported information on missing data limited the quality of prognosis studies in SLE. Future prognosis studies should be designed with better consideration to the above factors to improve methodological rigor.

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Cognitive Behavioral Therapy and Milnacipran in Combination Appears to Be More Efficacious Than Either Therapy Alone. Dennis C. Ang[1], Mark P. Jensen[2], Jennifer L. Steiner[3], Janna Hilligoss[1], Richard Gracely[4] and Chandan Saha[5]. [1]Indiana University, Indianapolis, IN, [2]Seattle, WA, [3]Indianapolis, IN, [4]Chapel Hill, NC, [5]Indiana University

Background/Purpose: The two treatment options that have received the significant attention in fibromyalgia (FM) management are cognitive behavioral therapy (CBT) and medications. Given the fact that either therapy alone appears to only produce modest improvements in clinical symptoms, we completed a 3-arm randomized attention-controlled trial whose primary aim was to obtain preliminary estimates of the effects of combined CBT and milnacipran on primary clinical endpoints: changes in weekly average pain intensity (daily electronic recording of pain scores) and physical function (SF-36 physical component summary score).

Methods: Fifty eight patients with FM were randomized to one of the 3 treatment arms: (1) combination therapy (n=20), (2) drug + education attention (n=19), and (3) placebo + CBT (n=19). Throughout the 21-week study, subjects received either milnacipran (50 mg BID) or placebo (BID). Subjects also received 8 sessions of telephone-delivered CBT or educational instructions, but only from baseline to week 9. Assessments were conducted at baseline, week 9 and 21. Secondary clinical endpoints included changes in PHQ-8 depression severity (0–24), and evoked (thumb) pressure pain scores (0–20), a measure of pain sensitivity.

Results: Characteristics of the 58 FM subjects: mean age= 46.6 (10.4) years; female=93%; whites= 81%; high school graduates=71%; concomitant opioid analgesics=43%; PHQ-8 depression=10.55 (4.79); evoked pressure pain= 8.8 (0.59); weekly average pain intensity = 6.31 (1.27); and SF-36 physical function= 45.26 (22.4).

Compared to drug alone, combination therapy demonstrated a medium effect on reducing weekly average pain intensity (effect size/ES=0.67) and in improving SF-36 physical function (ES=0.60). The magnitude of change in the pain intensity score in the combination group was more than twice the magnitude of change in the drug monotherapy group.Compared to drug alone, CBT alone was marginally efficacious in improving SF-36 physical function. No significant between group differences were seen in improvement in depression severity and change in evoked pain scores. Interestingly, subjects in the drug groups (i.e., combination and drug alone) became less sensitive to pressure stimuli compared to subjects in the CBT monotherapy group, *albeit* this difference was not statistically significant.

Table 1.

	Combination therapy N=17	Drug monotherapy N=17	CBT monotherapy N=15	P values Combo vs. drug Combo vs. CBT Drug vs. CBT	Cohen's d (Effect sizes)
Primary Outcomes					
Δ Weekly average¶ pain intensity score	−2.15 (0.43)†	−0.97 (0.43)†	−1.67 (0.45)†	*0.067*	0.67
				0.441	0.27
				0.286	0.40
Δ SF-38 physical component summary score	13.47 (3.74)†	4.05 (3.84)	15.04 (4.01)†	*0.092*	0.60
				0.775	0.10
				0.058	0.70
Secondary Outcomes					
Δ PHQ-8 depression score	−2.65 (1.06)†	−2.93 (1.07)†	−3.19 (1.11)†	0.860	
				0.727	
				0.865	
Δ Evoked pain scores	−0.76 (1.20)	−0.41 (1.22)	0.78 (1.27)	0.838	
				0.379	
				0.504	

Δ: Baseline to week 21 change in the specified variable; Values represent means and standard error
†Significant <u>within</u> group difference (p<0.04)

Conclusion: Based on the observed effect sizes, our preliminary data justifies pursuing a larger definitive trial to test the superiority of combination therapy vs. monotherapy.Additionally, a direct comparison of CBT vs. drug monotherapy is warranted to inform future health care decisions.

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Comparative Symptom Severity of Patients Satisfying Chronic Widespread Pain and Fibromyalgia Criteria. Frederick Wolfe[1], Brian Wallitt[2], Robert S. Katz[3] and Winfried Häuser[4]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Washington Hospital Center, Baltimore, MD, [3]Rush University Medical Center, Chicago, IL, [4]Klinikum Saarbrücken, Saarbrücken, Germany

Background/Purpose: Chronic widespread pain (CWP) is often used as a surrogate for fibromyalgia in epidemiological research, particularly in Europe and in whiplash-related injuries. This CWP substitution occurred because it was operationally impossible to perform tender point examinations in epidemiological and survey research. CWP is a requirement for fibromyalgia diagnosis when the American College of Rheumatology (ACR) 1990 criteria are used. 20–35% of patients with CWP will also satisfy fibromyalgia criteria. Despite the common use of CWP, it is not clear how closely CWP positive patients resemble those with fibromyalgia, and whether CWP is a valid substitution for fibromyalgia. In this report we determined the relative severity of patients satisfying the CWP and fibromyalgia criteria.

Methods: We studied 6,583 rheumatic disease patients who completed a research questionnaire that contained assessments of criteria and severity variables. Fibromyalgia was diagnosed using the 2010 American College of Rheumatology (ACR) criteria for fibromyalgia, as modified for survey research. Widespread pain used the 1990 ACR definition: pain above and below the waist, on the left and right sides of the body, and involving the axial skeleton. Severity measures included the Polysymptomatic Distress Scale (PSD) and the Symptom Severity (SS) scale from the 2010 criteria. In addition, we employed other standard assessments of severity, including measures of pain, sleep, fatigue and quality of life. We categorized patients as a) without CWP, b) with fibromyalgia, c) with CWP assuming 20% of CWP cases had FM, and d) with CWP assuming 33% of CWP cases had fibromyalgia (Table 1).

Table 1. Severity status of patients with fibromyalgia or chronic widespread pain

Variable	Not Widespread pain Mean (95% C.I.)	FMS Mean (95% C.I.)	Widespread Pain At 20% FM Prevalence	Widespread Pain At 33% FM Prevalence
VAS Pain (0–10)	2.8 (2.7, 2.9)	6.1 (6.0, 6.3)	4.3 (4.2, 4.4)	4.6 (4.5, 4.7)
VAS Fatigue (0–10)	3.2 (3.1, 3.3)	7.0 (6.9, 7.1)	4.4 (4.3, 4.5)	4.8 (4.7, 5.0)
VAS Sleep problem (0–10)	3.1 (3.0, 3.2)	6.5 (6.3, 6.6)	4.3 (4.2, 4.5)	4.7 (4.6, 4.8)
Mood (0–10)	2.4 (2.3, 2.4)	4.1 (4.0, 4.2)	2.9 (2.8, 2.9)	3.1 (3.0, 3.2)
HAQ (0–3)	0.7 (0.6, 0.7)	1.5 (1.4, 1.5)	1.1 (1.0, 1.1)	1.1 (1.1, 1.2)
VAS Pt. Global (0–10)	2.8 (2.8, 2.9)	5.8 (5.7, 5.9)	4.1 (4.0, 4.2)	4.3 (4.2, 4.4)
SS Scale (0–12)	3.3 (3.2, 3.4)	7.7 (7.6, 7.8)	4.3 (4.2, 4.4)	4.9 (4.8, 5.0)
WS Pain Index (0–19)	2.1 (2.0, 2.3)	12.3 (12.1, 12.4)	8.2 (8.0, 8.4)	8.9 (8.7, 9.1)
PSD scale (0–31)	6.0 (5.8, 6.2)	20.6 (20.4, 20.9)	13.5 (13.2, 13.8)	14.7 (14.5, 15.0)
EQ-5D (0–1)	0.80 (0.79, 0.80)	0.56 (0.55, 0.57)	0.7 (0.7, 0.7)	0.7 (0.7, 0.7)
PCS	41.8 (41.4, 42.1)	29.3 (28.9, 29.8)	34.8 (34.3, 35.2)	33.9 (33.6, 34.3)
MCS	50.5 (50.1, 50.9)	39.5 (39.0, 40.0)	47.6 (47.1, 48.2)	46.3 (45.8, 46.8)
VAS QOL (0–100)	71.2 (70.5, 71.9)	52.6 (51.7, 53.5)	63.4 (62.5, 64.3)	61.8 (61.0, 62.7)

Results: Figure 1 shows the relation of both measures to PSD in the overall sample.X and y lines cross when probability of diagnosis is >= 0.5. This occurs at 9.3 and 13.3 on the PSD scale for CWP and FM, respectively. Table 1, adjusted for age and sex, demonstrates that patients with fibromyalgia have more severe symptoms than those with CWP at 20% and 33% prevalence levels. For the 3 clinical VAS scales, fibromyalgia patients are approximately 30% more severe than those with CWP.
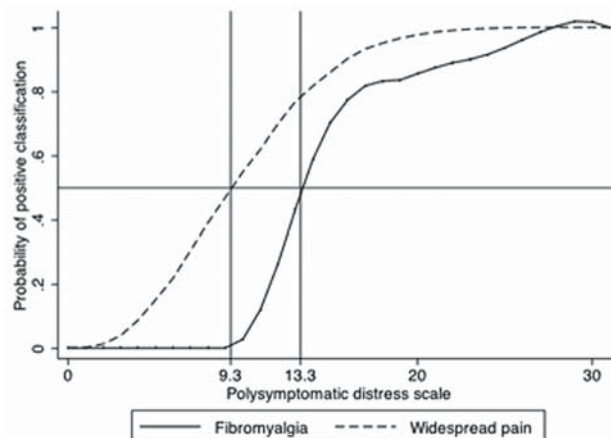
Conclusion: Patients satisfying fibromyalgia criteria have a more severe illness than those with CWP. The use of CWP as a surrogate measure of fibromyalgia substantially underestimates fibromyalgia severity, but still identifies a group of severe patients.

Disclosure: **F. Wolfe**, None; **B. Wallitt**, None; **R. S. Katz**, None; **W. Häuser**, None.

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Post–Surgical Outcome Is Correlated with Pre–Surgical Symptoms of Fibromyalgia in Patients Undergoing Spinal Surgery. Jacob N. Ablin[1], Mark Berman[1], Eyal Behrbalk[2], Dan Buskila[3], Gilad Regev[2] and Zvi Lidar[2]. [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Department of Neurosurgery and Orthopedic, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [3]Beer-Sheva, Israel

Background/Purpose: Chronic pain is a major symptom for which patients undergo spinal surgery. At the same time, chronic pain is considered an entity in and of itself, often constituting part of the clinical spectrum of central sensitization (e.g. fatigue, cognitive impairment etc) thus overlapping with the fibromyalgia syndrome (FMS).

The impact of surgical intervention on chronic pain is not well known. While such interventions may remove a local "pain generator" they may simultaneously constitute a form of physical trauma, as well as entailing prolonged immobilazion, both potentially detrimental for fibromyalgia patients.

The aim of this study was to evaluate patients who undergo spinal surgery for presence of central pain and central sensitization symptoms and evaluate the correlation between these symptoms and the surgical outcomes.

Methods: Participants were patients scheduled for spinal surgery. Pre-surgical evaluation included physical examination and manual dolorimetry, documenting the 1990 ACR FMS classification criteria. In addition, patients filled out the widespread pain index (WPI) and the Symptom Severity Scale (SSS) which are part of the suggested 2010 diagnostic criteria of fibromyalgia, as well as the fibromyalgia-Impact Questionnaire (FIQ) and SF-36.

Eight weeks after surgery, patients underwent follow-up evaluation. Statistics: Spearman correlations were calculated between the pre-surgery parameters (WPI and SSS) and the change in SF-36 items. P values under 0.05 were considered significant.

Results: Twenty eight patients (18 male, 10 female) were recruited. The average age was 56.3 (23–85). The average BMI was 26.7 kg. Three patients fulfilled ACR 1990 fibromyalgia criteria (10.7%), whereas 8 patients fulfilled the 2010 diagnostic criteria (28.6%).Thirteen patients were available for post–surgical evaluation.

Table 1 presents the correlations calculated between the pre–surgical WPI and SSS and the change in the SF-36 domains: Physical Functioning (PF), Role–Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), Mental Health (MH) as well as the Mental Component Score (MCS) and Physical Component Score (PCS). A significant negative correlation was observed between the WPI and the delta RP item; a significant negative correlation was also observed between the SSS and the delta of the GH and RE items.

	ΔTP	ΔPF	ΔRP	ΔBP	ΔGH	ΔVT	ΔSF	ΔRE	ΔMH	ΔPCS	ΔMCS
WPI-correlation	0.03	−0.04	**−0.72**	0.15	−0.33	0.09	0.15	−0.31	−0.01	−0.28	0.06
WPI-P value	0.95	0.88	**0.006**	0.63	0.27	0.77	0.62	0.30	0.96	0.34	0.84
SSS–correlation	0.25	0.20	−0.32	−0.41	**−0.69**	0.51	0.31	**−0.56**	0.04	−0.31	−0.18
SSS-P value	0.58	0.51	0.28	0.16	**0.008**	0.077	0.31	**0.047**	0.90	0.30	0.55

Conclusion: FMS symptoms were highly prevalent among patients scheduled for spinal surgery (28.6%). A negative correlation was observed between pre-surgical severity of FMS symptoms and components of the post-surgical SF-36. Patients with symptoms of FMS may have a poor outcome after spinal surgery. The clinical utility of surgical intervention in such patients should be carefully evaluated and treatment specific for FMS considered, before embarking on a surgical course.

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Learning Disability in Fibromyalgia Patients: FMS Patients Report More Language and Spatial Difficulties. Robert S. Katz[1], Alexandra Small[2]. Carlen Katz[3] and Susan Shott[1], [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois Medical School, [3]Rheumatology Associates, Chicago, IL

Background/Purpose: Fibromyalgia patients are reported to have central sensitization and abnormal central processing of sensory input. Fibromyalgia patients alsohave more neurocognitive complaints and abnormalities on certain types of neurocognitive testing, especially the Stroop test for naming speed and a distraction test, the Auditory Consonant Trigram.To evaluate other possible central nervous system dysfunction, we asked fibromyalgia patients and patients with other rheumatic diseases in a questionnaire whether or not they had symptoms and features of a learning disability.

Methods: Office patients and controls were asked to complete a questionnaire about difficulties in reading, writing, body awareness/spatial relationships, and oral expressive language. A score consisting of the percentage of items for which the respondent reported difficulty was obtained for each of these areas. Four diagnosis groups were compared with respect to questionnaire responses: 85 FMS patients, 39 RA patients, 21 SLE patients, and 14 controls without rheumatic diseases. The Kruskal-Wallis and Mann-Whitney tests were used to compare scores and the chi-square test of association was used to compare percentages, with a 0.05 significance level.

Results: Compared to controls, FMS patients had significantly worse reading and oral expressive language scores (p = 0.001). FMS patients had significantly worse scores for all four areas than the RA and SLE groups (p < 0.001–0.007). There were no statistically significant differences between the RA, SLE, and control groups with respect to any of the scores. FMS patients were significantly more likely to report the following difficulties: making mistakes when reading like skipping words or lines (FMS 43%, controls 0%, RA 3%, SLE 5%, p < 0.001); reading the same line twice (FMS 57%, controls 14%, RA 15%, SLE 19%, p < 0.001); problems remembering what was read (FMS 59%, controls 0%, RA 11%, SLE 24%, p < 0.001); difficulty understanding the main idea or identifying the important details from a story (FMS 27%, controls 0%, RA 5%, SLE 14%, p = 0.007); problems with grammar or punctuation (FMS 28%, controls 14%, RA 8%, SLE 0%, p = 0.004); tendency to be clumsy or uncoordinated (FMS 41%, controls 7%, RA 10%, SLE 10%, p < 0.001); difficulty with eye-hand coordination (FMS 27%, controls 7%, RA 5%, SLE 5%, p = 0.004); difficulty expressing self in words (FMS 42%, controls 7%, RA 8%, SLE 5%, p < 0.001); trouble finding the right words to say in a conversation (FMS 57%, controls 8%, RA 11%, SLE 24%, p < 0.001); and trouble talking about a subject or getting to the point of a conversation (FMS 43%, controls 7%, RA 5%, SLE 5%, p < 0.001).

Conclusion: Fibromyalgia patients, compared to rheumatic disease controls, are found to haveproblems in reading, writing, body awareness, and spatial relationships and problems in oral expressive language.Fibromyalgia patient responses suggested frequent symptoms of a learning disability.

Learning disability may be another part of central nervous system dysfunction in fibromyalgia patients.Patients, practitioners and educators should be made aware of the association between fibromyalgia and learning disabilities.

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Key Psychological Processes Associated with the Fibromyalgia Phenotype Exist On a Continuous Spectrum with Asymptomatic People. Katrina Malin[1] and Geoffrey O. Littlejohn[2]. [1]Monash University, Clayton, Australia, [2]Monash Medical Centre and Monash University, Clayton, Victoria, Australia

Background/Purpose: The core features of the fibromyalgia phenotype, the widespread pain and widespread tenderness, represent one extreme of a continuous spectrum with asymptomatic people at one end and those meeting criteria for fibromyalgia at the other. A number of key central processes associate with fibromyalgia, such as personality [neuroticism and Type A] and psychological characteristics, including attitude, control, coping, catastrophizing and stress-reactivity.We hypothesized that these psychologically linked processes also exist on a single continuous spectrum from normal in asymptomatic people to abnormal in fibromyalgia, and that increasing the "gain" of these processes will increase the features contributing to the fibromyalgia phenotype.

Methods: We identified 98 women with fibromyalgia diagnosed according to standard ACR criteria. Applied questionnaires included the Big 5 Personality Inventory, Type A scale, Fibromyalgia Impact Questionnaire, Perceived Control of Internal States, Mastery scale, the Coping Scale and Perceived Stress scale and the depression, anxiety, confusion and optimism scales of the Profile of Mood States questionnaire. Normallity assessment using Shapiro-Wilk test and correlations and regression modelling and comparisons between smallest and largest tertileswere used to explore the relationships between personality and psychological variables in both the healthy controls and in the patients with fibromyalgia.

Results: There was a significant relationship between lower and higher tertiles of neuroticism, internal and external control, attitude, coping and stress and the characteristic fibromyalgia phenotype features of fatigue, sleep and confusion, in both the healthy control and the fibromyalgia groups [p all <0.001]. Pain was also significantly different in the healthy controls [p<0.001] but showed a non-significant ceiling effect between lowest and highest tertiles in the fibromyalgia group. Personality and psychological variables also correlated significantly in both healthy controls and fibromyalgia with depression and anxiety [p<0.001]. The absolute levels of all characteristics in healthy controls and fibromyalgia patients differed significantly [p<0.001].Normality plots indicated that the psychological characteristics examined existed on a spectrum with healthy controls at one end and fibromyalgia patients at the other.

Conclusion: The personality and psychological variables that associate with fibromyalgia exist on a continuous spectrum, linking normal asymptomatic persons to the fibromyalgia phenotype.Increasing certain centrally important psychological variables will increase fibromyalgia clinical features. This is suggestive of a key role for central psychological factors in the pathogenesis of fibromyalgia.

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Prevelance of Spondyloarthropathy in Fibromyalgia Patients. A.Eftal Yucel, Derya Kaskari and Muhtesem Agýldere. Baskent University, Ankara, Turkey

Background/Purpose: Most of the tender points typical for fibromyalgia syndrome (FMS) are also entesis points. Besides, FMS and spondyloarthropathy (SpA) can co-exist. Both disease groups have negative effects on the life quality of patients. Our aim is to document the prevalence of SpA in patients diagnosed as FMS by physical therapy specialists and to emphasize evaluation of spondyloartropathy before diagnosing with FMS.

Methods: he patients diagnosed to have FMS in the department of Physical Therapy and Rehabilitation at our center between 2006 and 2011 were involved. Patients were called by phone and asked 3 questions about their inflammatory back pain. Questions were about the presence of 1.Nontraumatic pain, swelling and stiffness in any joint 2.Low back pain or back stiffness on awakening, which lasted over a period of at least 3 months and which improved with exercise 3.Heel pain more in the morning which lasted over a period of at least 3 months and improved with activity. The patients who answered positive to at least one of these three questions were invited for further evaluation and to be involved in this study. The study included 71 patients (70 female and 1 male).In all patients, comparative sacroiliac radiographies were taken for sacroiliitis and lateral radiographies of both feet were taken for enthesitis. Patients with stage 1 and stage 1–2 sacroiliitis on direct radiography, were examined with sacroiliac MR. In order to diagnose FMS, 1990 and 2010 ACR Classification were applied while ESSG Criteria were applied to diagnose SpA.

Results: According to 1990 ACR criteria, 23 patients out of 71(32.3%) were diagnosed as FMS however 33 patients (46.4%) were diagnosed as FMS according to 2010 ACR criteria.Fifteeen (21.1%) patients were diagnosed according to both 1990 and 2010 ACR criteria; however 41(57.7%) patients were diagnosed with either 1990 ACR criteria or 2010 ACR criteria.Of our 71 patients, 20 (28.1%) were diagnosed as SpA according to ESSG criteria.Ten (43.4%) FMS patients out of 23 who were diagnosed according to 1990 ACR criteria were rediagnosed as SpA according to ESSG criteria. Eleven (33.3%) patients out of 33 who were diagnosed as FMS with 2010 ACR criteriawere rediagnosed as SpA according to ESSG criteria. We determined 9(39.1%) patients out of 23 patients diagnosed with 1990 ACR criteria and 13 (39.3%) patients out of 33 diagnosed with 2010 ACR criteria were found to have stage 2 and higher sacroiliitis. According to sacroiliac MR examinations of 10 patients, 3 (30.0%) patients had sacroiliitis on MR who had stage 1 and stage 1–2 sacroiliitis on direct radiography who were diagnosed with SpA according to ESSG criteria Twelve (60.0%) out of 20 patients diagnosed as SpA

according to ESSG criteria were found to have 2nd stage and higher sacroiliitis. We determined that 14 (60.8%) out of 23 patients diagnosed with ACR's 1990 and 17 (51.5%) out of 33 patients diagnosed with ACR's 2010 found to have enthesopathy.

Conclusion: There is a meaningful percentage of patients who have clinically insidiously progressive SpA among the patients who were thought to be diagnosed as FMS or the patients who were diagnosed as FMS according to ACR's criteria

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Treatment of Lateral Epicondylitis with Injection of Platelet-Rich Plasma or Corticosteroid Versus Saline: A Randomized, Double-Blind, Placebo-Controlled Trial. Thoger Krogh[1], Ulrich Fredberg[1], Kristian Stengaard-Pedersen[2], Pia Jensen[1], Robin Christensen[3] and Torkell Ellingsen[1]. [1]Diagnostic Centre Region Hospital Silkeborg Denmark, Silkeborg, Denmark, [2]Arhus University Hospital, Aarhus, Denmark, [3]Copenhagen University Hospital at Frederiksberg, Copenhagen, Denmark

Background/Purpose: Lateral epicondylitis (LE) is a common musculoskeletal disorder for which an effective treatment strategy still remains absent. The objective is to examine whether one injection with Platelet-rich plasma (PRP) is more effective than saline and corticosteroid (CS) in reducing pain in adults with LE.

Methods: A block randomized, double-blind, placebo-controlled trial with primary outcome assessed at 3 months, and with a 12 months follow-up, conducted between January 2009, and June 2011. Patients who did not achieve a satisfying treatment response (assessment made by patient and doctor) at 3 month had the option to discontinue the study and receive other treatment. In total, 60 patients with chronic LE were randomized (1:1:1) to receive either a blinded injection of PRP, saline or CS. The primary outcome was change in pain compared to baseline using the Patient Rated Tennis Elbow Evaluation (PRTEE) questionnaire at 3 months. Secondary endpoints were all assessed at 1 month, plus ultrasonographic changes in tendon thickness and color Doppler activity at 3 months.

Results: The 60 enrolled patients in the intention to treat population had an average PRTEE pain score at baseline of 26.8 (SD 7.6). All randomized patients completed the study. At endpoint 3 months from baseline pain reduction was observed in all three groups, with no statistical significant difference between the groups. CS vs. saline −3.76 (95% CI −9.94 to 2.42), PRP vs. saline −2.64 (95% CI −8.80 to 3.52) and CS vs. PRP −1.12 (95% CI −7.23 to 4.99). However, at one month CS reduced pain more efficiently than both saline and PRP. The mean difference at one month between CS and saline was −8.11 (95% CI −14.29 to −1.93), between CS and PRP −9.27 (95% CI −15.38 to −3.16). CS was more efficient than PRP and saline in reducing both color Doppler activity and tendon thickness at three months. Only 16 of 60 patients completed the entire 12 months follow-up. The huge attrition rate was due to lack of treatment efficacy.
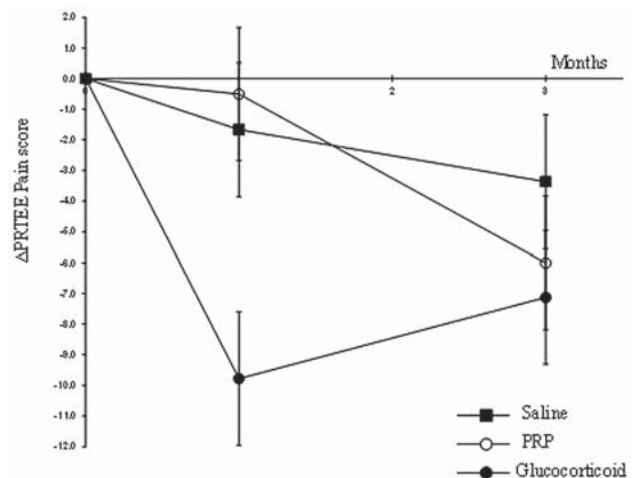
Figure. Changes in pain from baseline at 1 and 3 months using the PRTEE (Patient-Rated Tennis Elbow Evaluation) in patients treated with 1 injection of PRP (platelet-rich plasma), glucocorticoid, or saline. Values are Least Squares Means ± Standard Error.

Conclusion: This RCT showed no superiority of either PRP or CS compared to saline in pain reduction in LE at primary endpoint. However, anticipating immediate relief, CS had a short term pain reducing effect at one month in contrast to the other therapies. At 6 and 12 months the attrition rates in all treatment arms were too high for any meaningful conclusions to be made.

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Cyclobenzaprine (CBP) and Its Major Metabolite Norcyclobenzaprine (nCBP) Are Potent Antagonists of Human Serotonin Receptor 2a (5HT2a), Histamine Receptor H-1 and á-Adrenergic Receptors: Mechanistic and Safety Implications for Treating Fibromyalgia Syndrome by Improving Sleep Quality. Bruce Daugherty, Leland Gershell and Seth Lederman. Tonix Pharmaceuticals, Inc., New York, NY

Background/Purpose: Bedtime cyclobenzaprine (CBP) improves fibromyalgia symptoms (pain, fatigue, tenderness, and mood) and improves sleep quality (decreases Cyclic Alternating Pattern Type A2 + A3) (1).CBP is metabolized by the hepatic P450 isoforms CYP1A1/2 and CYP3A4 into desmethyl, or norcyclobenzaprine (nCBP)(2), but plasma nCBP has only been detected in cases of overdose (3–5). Although CBP has been shown to interact with both the serotonergic (6,7) and noradrenergic (8,9) receptor systems, the functional interactions of CBP with isolated receptors are not fully characterized and those of nCBP are unknown. Therefore, plasma nCBP was measured in healthy subjects after ingesting CBP and the binding and functional activity of CBP and nCBP was studied on a set of CNS targets with potential relevance to CBP actions.

Methods: Plasma CBP and nCBP were measured over 168 hr in ten healthy, fasting subjects who received 5 mg po immediate release CBP HCl.Equilibrium receptor binding assays were performed on cell lines expressing select recombinant human serotonin, adrenergic, histamine, and muscarinic receptors. Select receptors were analyzed in ligand-induced intracellular Ca^+ mobilization.

Results: The oral bioavailability of CBP was similar to published results (C_{max} = 4.12 ng mL^{-1}, t_{max} = 3.5 h, $T_{1/2}$ = 31.0 h, $AUC_{0-\infty}$ = 103.1 ng hr mL^{-1}), but plasma nCBP was unexpectedly high and persistent (C_{max} = 1.27ng mL^{-1}, t_{max} = 24.0 h, $T_{1/2}$ = 72.8 h, $AUC_{0-\infty}$ = 169.5 ng hr mL^{-1}).Unlike CBP, nCBP does not form a stable N^+-glucuronide, which may affect its clearance.In vitro, CBP and nCBP exhibited high affinity binding (K_i) to receptors: 5HT2a (5.2 and 13 nM, respectively) and 5HT2c (5.2 and 43 nM), adrenergic α-1A (5.6 and 34 nM), α-2B (K_i = 21 and 150 nM) and α-2C (K_i = 21 and 48 nM,); H1 (1.3 and 5.6 nM); and M1 (7.9 and 30 nM). Like CBP, nCBP is a functional antagonist at 5HT2a (IC_{50} = 92 nM) by Ca^+ mobilization.CBP is also an antagonist on 5HT2b (IC_{50} = 100 nM). CBP and nCBP are functional antagonists on 5HT2c (IC_{50} = 0.44 and 1.22 μM) and on α-2A (IC_{50} = 4.3 and 6.4 μM). In contrast, both CBP and nCBP are functional agonists on 5HT1a (EC_{50}= 5.3 and 3.2 μM).

Conclusion: CBP is metabolized to nCBP which persists in plasma at biologically relevant concentrations after oral CBP in healthy subjects.CPB and nCBP are potent antagonists of 5HT2a, 5HT2b, H-1, adrenergic α-1A, α-2B and α-2C receptors.CBP's antagonist activity on 5HT2b is consistent with the lack of any association with heart valve pathology.Antagonists of 5HT2a and H-1 are known to have effects on sleep and sleep maintenance.Adrenergic antagonists may have effects on autonomic dysfunction.The accumulation of biologically active nCBP without N^+-glucuronidation may affect responses to CBP therapy in a chronic bedtime dosing regimen.

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Disclosure: B. Daugherty, Tonix Pharmaceuticals Holding Corp., 3; **L. Gershell**, Tonix Pharmaceuticals Holding Corp., 3; **S. Lederman**, Tonix Pharmaceuticals Holding Corp., 1, Tonix Pharmaceuticals Holding Corp., 6.

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Cerebral Grey and White Matter Changes in Fibromyalgia Depend On Patients' Age. Marta Ceko, Mary-Ann Fitzcharles, M. Catherine Bushnell and Petra Schweinhardt. McGill University, Montreal, QC

Background/Purpose: Fibromyalgia (FM) patients show accelerated age-related decrease of grey matter (GM). Similarly, brain imaging studies in other chronic pain populations suggest interaction between age and GM changes. We investigated the relationship between age and GM alterations in FM patients categorized according to age.

Methods: This female study cohort comprised 29 FM patients and 29 controls matched for handedness, education, physical activity, and socioeconomic status. The sample was split at median age (50 yrs) into younger and older groups [mean age (SD)], FM vs. controls 42.4 (5.9), vs. 43.1 (5.3), p=0.7, and 54.9 (2.8) vs.55.7 (3.7), p=0.5. FM age groups were similar for disease duration, pain intensity, and medication use.All subjects underwent magnetic resonance imaging (MRI) in a 3T Siemens Trio scanner. T1-weighted images were obtained for GM analysis and diffusion-weighted images for interrogation of white matter.GM was analyzed using voxel-based morphometry (VBM)(SPM8, Wellcome Trust for Neuroimaging, London, UK), as well as cortical thickness analysis [CIVET 1.9.9. and Surfstat (MNI, Montreal, Canada)]. Diffusion data were analysed with FSL (FMRIB, Oxford, UK). For all analyses, voxel-wise differences between groups were examined using independent sample t-tests controling for age.

Results: The GM in the medial prefrontal cortex (MPFC), left superior frontal gyrus (SFG), and premotor cortex (PMC) was reduced in FM patients compared to controls.Total GM was negatively correlated with age in FM (p=0.009), but not in controls (p=0.6). Similar relationships with age were observed for the clusters in MPFC (FM p=0.02, controls p=0.9) and SFG (FM p=0.02, controls p=0.4). Older FM patients compared to controls showed pronounced GM decreases:patients had less GM in the MPFC/anterior cingulate cortex, right PMC, left inferior frontal gyrus (IFG), right posterior cingulate cortex, and right temporo-occipital gyrus. There were no regions where older FM patients had more grey matter. White matter adjacent to the posterior cingulate showed decreased fractional anisotropy (FA) in older FM patients. In contrast, younger FM patients showed exclusively grey matter increases compared to matched controls in the left putamen/insula, right putamen/globus pallidum, and IFG, with no region showing decreased GM. White matter adjacent to the left putamen showed increased FA.

Conclusion: FM-related brain changes depend on age with findings driven predominantly by older, postmenopausal patients. Younger, premenopausal patients showed regions of increased GM compared to age-matched controls, in line with previous findings in younger pain patients (Schweinhardt et al., 2008). Furthermore, GM alterations were partly paralleled by alterations of the adjacent white matter, with integrity compromised in older and increased in younger FM patients respectively.These findings highlight the interaction between age and cerebral changes in chronic pain states.

Schweinhardt P, Kuchinad A, Pukall CF, Bushnell MC (2008) Increased gray matter density in young women with chronic vulvar pain. Pain 140:411–419.

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Pain, Sleep Disturbance, and Depression Mediate the Association Between Body Mass Index and Fatigue in Fibromyalgia. Mary O. Whipple[1], Loren L. Toussaint[2], Daniel J. Clauw[3], David A. Williams[4], Terry H. Oh[1], Jeffrey M. Thompson[1], Connie A. Luedtke[1] and Ann Vincent[1]. [1]Mayo Clinic, Rochester, MN, [2]Luther College, Decorah, IA, [3]University of Michigan, Ann Arbor, MI, [4]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: Previous research and clinical observation suggest that patients with chronic disease who are obese report significant fatigue. Our objective was to explore similar relationships in patients with fibromyalgia and the extent to which pain, sleep disturbance, and depression mediated this relationship.

Methods: 3917 patients who consented to be part of a fibromyalgia registry were included in this analysis. Registry measures included demographics, body mass index (BMI), the modified 2010 American College of Rheumatology Fibromyalgia Survey Criteria, and selected items from the Multidimensional Assessment of Fatigue. Data were analyzed using the INDIRECT macro for SPSS which allows multiple mediator models to be specified. All analyses controlled for age and sex. INDIRECT provides unstandardized regression coefficients (reported below as "B") which are the preferred metric in mediation models.

Results: BMI was positively associated with fatigue (B =.03, p <.0001). BMI was also positively associated with pain (B =.06, p <.0001), sleep

disturbance (B =.004, p <.05), and depression (B =.003, p <.01). After controlling for pain, sleep disturbance, and depression, the relationship between BMI and fatigue (B = 02, p <.0001) was reduced by over 33% (.02/.03). In spite of this, pain, sleep disturbance, and depression remained statistically significant (all p's <.0001). Hence, we examined the partial mediating effects of these variables.Results indicated that pain, sleep disturbance, and depression combined mediate the association between BMI and fatigue (B =.01, p <.05). Additionally, pain (B =.01, p <.05), sleep disturbance (B =.01, p <.05), and depression (B =.002, p <.05) also had unique indirect effects on fatigue.

Conclusion: Statistically significant total and direct effects were present for the association between BMI and fatigue in patients with fibromyalgia.Hence, the association between BMI and fatigue was only partially explained by pain, sleep disturbance, and depression. While these data provide insight into a potential relationship between obesity and fatigue and possible mechanisms, these are cross-sectional results and do not offer insight into causality. These types of analyses should also be examined through longitudinal research.

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Efficacy of Long-Term Milnacipran Treatment in Patients Meeting Different Thresholds of Clinically Relevant Pain Relief: Subgroup Analysis of a Double-Blind, Placebo-Controlled Discontinuation Study. Daniel J. Clauw[1], Philip Mease[2], Robert H. Palmer[3], Joel M. Trugman[3] and Yimin Ma[3]. [1]University of Michigan, Ann Arbor, MI, [2]Swedish Medical Center and University of Washington, Seattle, WA, [3]Forest Research Institute, Jersey City, NJ

Background/Purpose: Patients with fibromyalgia (FM) who received up to 3.25 years of milnacipran (MLN) in a flexible-dose (≤200 mg/d) open-label (OL) study were eligible to continue into this randomized, double-blind (DB), placebo (PBO)-controlled discontinuation study, which demonstrated loss of therapeutic effect after withdrawal of long-term MLN treatment in patients who had achieved ≥50% pain improvement. The present analysis was conducted to determine whether patients from this study who met lower thresholds of pain improvement also experienced loss of therapeutic effect after discontinuing long-term MLN treatment.

Methods: After 4 weeks (OL) of continuing MLN treatment at the dose received in the prior long-term study, patients were evaluated for pain response and randomized (2:1) to continue MLN or discontinue treatment (ie, switch to PBO) for the 12-week DB withdrawal period. In patients who had received MLN ≥100 mg/d, 3 subgroups were identified based on percent of pain reduction from pre-MLN exposure: 1) ≥50%, n=150; 2) 30 to <50%, n=61; and 3) <30%, n=110. Efficacy assessments included visual analog scale pain (VAS, 0–100 mm), SF-36 Physical Component Summary (SF-36 PCS), Fibromyalgia Impact Questionnaire Revised (FIQR), and Beck Depression Inventory (BDI).

Results: In both subgroups of patients with clinically meaningful pain relief (≥50% and 30 to <50% subgroups), mean worsening of VAS pain scores from randomization to end of the DB withdrawal period was significantly greater (P<.05) in patients switched to PBO (≥50%, +17.7 mm; 30% to <50%, +8.5 mm) than in patients continuing MLN (≥50%, +8.3 mm; 30% to <50%, −0.5 mm). The absolute difference between treatment arms was similar in both subgroups (≥50%, −9.4 mm; 30 to <50%, −9.0 mm), as was the percentage of lost treatment effect after withdrawal (≥50%, 37.7%; 30 to <50%, 31.2%). Patients with ≥50% pain response also experienced notable worsening in SF-36 PCS and FIQR total scores after treatment withdrawal (P<.01, MLN vs PBO; both measures). In the subgroup with <30% pain improvement, no worsening in pain was observed in either treatment arm at endpoint (PBO, −1.1 mm; MLN, −5.3 mm; P=.14). However, patients in this subgroup experienced significant worsening in FIQR scores after withdrawal from MLN relative to those who continued treatment (P<.001). Additionally, patients in this subgroup who were withdrawn from MLN had worsened SF-36 PCS and BDI scores while patients continuing MLN experienced no worsening in these domains.

Conclusion: Significant worsening in pain after drug withdrawal was found in both subgroups of FM patients that had shown clinically meaningful responses to long-term MLN therapy (≥50%, 30 to <50% pain improvement), suggesting that the traditional ≥30% pain responder cutoff may be adequate to demonstrate efficacy in randomized withdrawal studies. Patients with <30% pain response did not experience worsening in pain following withdrawal, but did experience worsening in other symptoms, suggesting that these patients may have received long-term benefit from milnacipran treatment for some FM symptom domains despite only modest improvements in pain.

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High-Energy Extracorporeal Shock Wave Therapy Is Effective for Treating Chronic Calcific Tendonitis of the Shoulder: A Meta-Analysis. Nina E. Flavin, Raveendhara R. Bannuru, William F. Harvey and Timothy E. McAlindon. Tufts Medical Center, Boston, MA

Background/Purpose: Calcific tendonitis (CT) and noncalcific tendonitis (NCT) of the shoulder is a common cause of shoulder pain and can be unresponsive to conventional therapies. Based on several randomized controlled studies (RCTs), extracorporeal shock wave therapy (ESWT) has been considered an effective alternative treatment. We performed an updated meta-analysis using all available data to analyze the efficacy of ESWT on CT and NCT.

Methods: We searched Medline, Cochrane database, and Google Scholar from inception to May 2012 for human RCTs comparing ESWT versus placebo for shoulder pain due to CT or NCT. We hand searched review articles, manuscripts, and medical journal supplements for additional references. Inclusion criteria were outcome measures of pain (VAS score; low score = less pain), functional assessment (Constant score; high score = better function), and resolution of calcifications (for CT trials). Two reviewers independently determined eligibility, assessed the quality of each trial, and extracted means and variances for these outcome measures. We computed effect sizes for mean change from baseline to 6 months or 3 months if not reported, using Hedges' g statistic. Effect sizes were pooled using random effects model. We assessed heterogeneity and performed sensitivity analyses removing the outlier trials. Subgroup analyses for CT and NCT, and high energy (HE) and low energy (LE) trials were also performed.

Results: Fifteen trials met inclusion criteria; 11 for CT, 4 for NCT. Overall there were 1221 participants with mean age of 51 years (range 46–56). The proportion of women was 56% (range 39%–76%). Among all trials, the effect size (ES) for VAS pain favored HE (−2.17; 95%CI [−2.85, −1.49]; I² 51%, p=0.15) and LE showed no effect (−1.15; [−2.63, 0.32]; I² 96%, p=0.00) and the ES for Constant score favored HE (1.77; [1.41, 2.14]; I² 29%, p=0.24) and LE (0.53; [0.16, 0.89]; I² 28%, p=0.24). In CT trials, any level of ESWT improved VAS scores (−2.18; [−3.55, −0.8]; I² 95%, p=0.00) and Constant scores (1.39, [0.81, 1.97]; I² 84%, p=0.00). In NCT trials, any level of ESWT had no effect on VAS scores (−0.15; [−0.57, 0.27]; I² 0%, p=0.35) or Constant scores (0.65; [−0.51, 1.82], I² 75%, p=0.04). Among CT, effect sizes for VAS, Constant scores and resolution of calcifications favored HE over LE (VAS: −0.57; [−1.10, −0.03]; I² 74%, p=0.01; Constant: 0.57; [0.28, 0.87]; I² 56%, p=0.03; Resolution of calcifications: 3.95; [1.55, 10.03]; I² 70%, p <0.01). Sensitivity analysis removing outlier trials yielded comparable results. The overall trial quality was moderate.

Table 1. Characteristics of included studies

Study	Treatment 1	Treatment 2	N	Age (Mean, Years)	Female (%)
Calcific Tendonitis					
Rompe, 1998	0.28 mJ/mm2, 1500 pulses, 1 dose	0.06 mJ/mm2, 1500 pulses, 1 dose	100	48	56
Loew, 1999*	0.3 mJ/mm2, 2000 pulses, 1 dose	0.1 mJ/mm2, 2000 pulses, 1 dose	80	n/a	n/a
Cosentino, 2003	0.28 mJ/mm2, 1200 pulses, 4 doses weekly	0 mJ/mm2, 1200 pulses, 4 doses weekly	70	52	61
Gerdesmeyer, 2003*	0.32 mJ/mm2, 1500 pulses, 2 doses, 2 weeks apart	0.08 mJ/mm2, 6000 pulses, 2 doses, 2 weeks apart	144	50	60
Perlick, 2003	0.42 mJ/mm2, 2000 pulses, 2 doses, 3 weeks apart	0.23 mJ/mm2, 2000 pulses, 2 doses, 3 weeks apart	80	48	55
Peters, 2004*	0.44 mJ/mm2, 1500 pulses, up to 5 doses, 6 weeks apart	0.15 mJ/mm2, 1500 pulses, up to 5 doses, 6 weeks apart	90	52	61
Pleiner, 2004	0.28 mJ/mm2, 2000 pulses, 2 doses, 2 weeks apart	<0.07 mJ/mm2, 2000 pulses, 2 doses, 2 weeks apart	43	52	72
Cacchio, 2006 ‡	0.1 mJ/mm2, 2500 pulses, 4 doses weekly	0.1 mJ/mm2, 25 pulses, 4 doses weekly	90	56	39
Albert, 2007	0.45 mJ/mm2, 2500 pulses, 2 doses, 2 weeks apart	0.02–0.06 mJ/mm2, 2500 pulses, 2 doses, 2 weeks apart	80	47	76
Hsu, 2008	0.55 mJ/mm2, 1000 pulses, 2 doses, 2 weeks apart	0 mJ/mm2, 0 pulses, 2 doses 2 weeks apart	46	56	51
Farr, 2011	0.3 mJ/mm2, 3200 pulses, 1 dose	0.2 mJ/mm2, 1600 pulses, 2 doses, weekly	30	49	47
Noncalcific Tendonitis					
Schmitt, 2001‡	0.11 mJ/mm2, 2000 pulses, 3 doses weekly	0 mJ/mm2, 2000 pulses, 3 doses weekly	39	52	50
Speed, 2002‡	0.12 mJ/mm2, 1500 pulses, 3 doses, 4 weeks apart	0.04 mJ/mm2, 1500 pulses, 3 doses, 4 weeks apart	74	52	58
Schofer, 2009	0.35 mJ/mm2, 2000 pulses, 3 doses weekly	0.11 mJ/mm2, 2000 pulses, 3 doses weekly	40	53	53
Galasso, 2012‡	0.068 mJ/mm2, 3000 pulses, 2 doses weekly	0 mJ/mm2, 3000 pulses, 2 doses weekly	20	51	45

*Trial also included placebo group: Energy level 0 mJ/mm2, pulses and dosing equivalent to treatment 1 group.
‡Low Energy: ≤ 0.27 mJ/mm²

Conclusion: High energy shock wave therapy is effective for improving pain and shoulder function in patients with chronic calcific shoulder tendonitis, and can result in complete resolution of calcifications. Limitations include

the heterogeneous nature of the included studies. Despite this, ESWT may be an underutilized therapy for a condition that is difficult to manage otherwise.

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Increased Number of Painful Body Sites Is Associated with Worse Pain and Disability-Associated Outcomes Among Returning Operations Enduring Freedom/Operation Iraqi Freedom Service Members.

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Background/Purpose: Chronic pain is a critical health problem among Operations Enduring Freedom/Operation Iraqi Freedom service members. The deleterious impact of chronic pain on quality of life and function are well described in the literature. However, little is known about the relationship between the number of chronically painful body sites and pain severity and disability-associated outcomes. In this secondary data analysis of a randomized clinical trial of a stepped-care intervention for OEF/OIF veterans with chronic musculoskeletal pain, we evaluated the association between the number of chronically painful body sites with long term pain-related outcomes.

Methods: We analyzed 222 subjects (92% of the original cohort) with available data at baseline and at the last follow-up visit (i.e., month 9). Consistent with the 2010 ACR criteria for fibromyalgia*, we dichotomized the number of chronically painful body sites (primary independent variable) as ≥ 3 (yes or no).We measured baseline to month 9 changes on our two primary outcomes: 1) pain intensity (as measured by Graded Chronic Pain Scale/GCPS), and 2) pain-related disability (as measured by Brief Pain Interference (BPI). Secondary outcomes included changes in SF-36 Physical Component Summary (SF-36 PCS), depression (PHQ-9) and anxiety (GAD-7) measures. We used multiple linear regression analyses to determine the relationships of the number of painful body sites with the outcome measures.

Results: Characteristics of the 222 subjects at study entry: mean age (SD)=37.3 (10.2) years; male=88%; whites= 78%; married=57%; # comorbidity=1.0 (1.0); GCPS pain intensity=65.6 (13.7); BPI pain interference=5.3 (2.2); SF-36 PCS=37.6 (7.2); PHQ-9=10.8 (5.8); GAD-7=8.5 (5.2); # of pain-related medications=1.7 (1.2); # of physical symptoms=2.0 (1.8); and 69% (n=154) had $\geq$ 3 painful body sites.

Table 1.

Baseline Predictors	OUTCOMES Parameter estimate (standard error/SE), p values		
	Improvement in GCPS pain intensity	Improvement in BPI pain interference	Improvement in SF-36 PCS
Number of painful sites ≥ 3 (reference group: <3)	−4.9 (2.4), p=0.0396	−1.0 (0.3), p=0.0016	4.2 (1.0), p<0.0001
Treatment group Stepped care (vs. usual care)	6.9 (2.2), p=0.0017	0.9 (0.3), p=0.0034	−1.9 (0.9), p=0.0362
Number of comorbidity	−2.2 (1.2), p=0.0636	−0.3 (0.2), p=0.0911	−0.04 (0.5), p=0.9364
Response variable at study entry	0.2 (0.1), p=0.0172	0.4 (0.1), p<0.0001	0.3 (0.1), p<0.0001

Age, gender, race, and marital status were included on each of the multivariate models but were all non-significant (p>0.10)
Neither the number of painful sites nor the treatment group assignment was significantly associated with changes in PHQ-depression and GAD-7 anxiety. Only the number of comorbid medical conditions was associated with changes in depression (estimate (SE) =−0.9 (0.4), p=0.0184) and anxiety (estimate (SE) =−0.7 (0.3), p=0.0179).

Conclusion: Compared to veterans with <3 painful body sites, veterans with $\geq$3 painful body sites improved significantly less during the 9 months of the trial. Our findings suggest more aggressive treatment interventions are needed in this population of veterans with multiple pain sites.

Disclosure: D. C. Ang, None; J. Wu, None; S. Outcalt, None; Z. Yu, None; M. Bair, None.

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A Systematic Review of Evidence for the Effectiveness of Practitioner-Based Complementary and Alternative Therapies in the Management of Fibromyalgia.

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Background/Purpose: Approximately one-quarter of the UK population uses complementary or alternative treatments (CAM) each year, and this is higher among persons with pain, or musculoskeletal conditions such as arthritis.A recent review has summarised the evidence relating to the use of CAM medicines (anything taken orally or applied topically) in the treatment of fibromyalgia.The aim of the current study was to review the evidence relating to CAM therapies (treatments delivered by a practitioner).

Methods: Randomised controlled trials (RCTs), published in English up to May 2011, were identified using systematic searches of bibliographic databases and searching of reference lists.Data were extracted by a single reviewer, and checked by a second, and the Jadad (J) score was used to assess methodological quality of the RCTs (0=poor; 5=high quality).All outcomes were considered but with a focus on patient global assessment and pain reporting.

Results: From 525 articles, 25 RCTs were identified, examining 14 therapies.The effectiveness of biofeedback has been tested in five RCTs (median J = 3), ranging from 30 to 143 patients.One RCT that compared biofeedback against anti-depression medication reported positive findings in terms of pain and fatigue.However, four RCTs comparing biofeedback with sham biofeedback, usual care or fitness training found no significant difference in the same outcomes.Three RCTs examined progressive muscle relaxation (median J = 3) ranging from 24 to 45 patients.In two RCTs, no significant benefit was observed, compared to hydro-galvanic bath therapy or hypnotherapy, and one RCT demonstrated progressive muscle relaxation to be inferior to massage therapy in terms of pain, stiffness, fatigue and a number of other outcomes.

Aromatherapy, chiropractic, healing therapy, hypnotherapy, imagery and qigong were each examined in two RCTs (median J = 4.5; 2.5; 3.5; 1.5; 2.0 and 3.5 respectively).With the exception of hypnotherapy, there was generally no improvement in outcome in the intervention group, compared to various control treatments.In hypnotherapy, in one RCT patients receiving hypnotherapy reported significantly greater improvements in pain, fatigue, sleep and general health compared to those receiving in physical therapy; and in the second RCT, patients receiving hypnotherapy with analgesia suggestions reported improvements in pain intensity compared to those receiving hypnotherapy with relaxation suggestions, or relaxation alone.

Finally, one RCT each examined the effectiveness of autogenic training (J=3), craniosacral therapy (J=5), music therapy (J=3), static magnet therapy (J=4), meditation (J=5) and Tai-chi (J=4).Only in Tai chi was there evidence of positive effect of treatment: patients in this group reported significantly greater improvements in health, disease impact, mental health and sleep compared to a control group who received wellness education and stretching exercises.

Conclusion: The major limitation in reviewing the evidence for practitioner-based CAM therapies in the treatment of FM is the paucity of RCTs.The available studies provide no consistent evidence that these treatments are effective, but the lack of RCTs means that it is hard to reach firm conclusions.

Disclosure: G. T. Jones, None; P. Paudyal, None; G. J. Macfarlane, None;

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Haplotypes of GTP Cyclohydrolase Gene Polymorphisms Are Protective in the Susceptibility of Fibromyalgia Syndrome.

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Background/Purpose: Guanosine triphosphate cyclohydrolase 1 (GCH1) is the rate-limiting enzyme in the synthesis of tetrahydrobiopterin, which is an essential co-factor in nitric oxide (NO) production. Polymorphisms in the GCH1 gene have been implicated in protection against pain

sensitivity. Our study was to determine whether single nucleotide polymorphisms (SNPs) in the GCH1 gene affect susceptibility and/or pain sensitivity in fibromyalgia syndrome (FMS).

Methods: A total of 409 FMS patients and 422 controls were enrolled. The alleles and genotypes at four positions, rs3783641(T>A), rs841(C>T), rs752688(C>T), and rs4411417(T>C), in the GCH1 gene were analyzed. The associations of the GCH1 SNPs with susceptibility and clinical parameters in FMS patients were assessed.

Results: The frequencies of alleles and genotypes of the four SNPs did not differ between FMS patients and healthy controls. Among 13 constructed haplotypes, we further examined four (CCTT, TTCT, TTCA, and CCTA) with >1% frequency in both FMS and controls. No associations of GCH1 polymorphisms with FMS-related activity or severity indexes were found, although the number and total score of tender points in FMS patients differed among the four haplotypes (p = 0.03 and p = 0.01, respectively). The CCTA haplotype of GCH1 was associated with significantly lower pain sensitivity and occurred less frequently than the CCTT haplotype in FMS patients (OR = 0.45; 95% CI, 0.21–0.96).

Conclusion: This study provides evidence that certain GCH1 haplotypes may be protective against susceptibility and pain sensitivity in FMS. Our data also suggest that NO is responsible for pain sensitivity in the pathogenesis of FMS.

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Sympathetic Nervous System Dysfunction in Fibromyalgia and in Overlapping Central Sensitivity Syndromes. A Systematic Review of Controlled Studies. Laura Aline Martinez, Tania Mora, Angelica Vargas, Mario Fuentes and Manuel Martinez-Lavin. National Institute of Cardiology, Mexico City, Mexico

Background/Purpose: Fibromyalgia often coexists and overlaps with other common painful syndromes such as chronic fatigue, irritable bowel and interstitial cystitis. Yunus proposed the label "central sensitivity syndromes" as an umbrella term for these related maladies. Sympathetic nervous system dysfunction has been reported in these central sensitivity syndromes raising the possibility that such dysautonomia could be the common underlying pathogenesis that cluster fibromyalgia with these interrelated clinical entities.

Our objective: To carry out a systematic review of all published comparative case-control studies investigating sympathetic nervous system performance in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and interstitial cystitis.

Methods: PubMed and Embase were accessed using the following key words: autonomic (OR) sympathetic (AND) fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and interstitial cystitis. All entries up to April 30 2012 were reviewed by three investigators searching for case-control studies in humans. The Method for Evaluating Research and Guidelines Evidence (MERGE) adapted to the Scottish Intercollegiate Guidelines Network (SIGN 50) was used to rank the level of evidence contained in the selected articles. "Sympathetic predominance" was defined as statistically significant data suggesting higher sympathetic activity, decreased parasympathetic activity or both. Reverse definition applied for "parasympathetic predominance".

Results: See table. Heart rate variability analysis (36%) was the most often used method to assess sympathetic system performance. Other less frequently used methods were: Tilt table testing (9%), sympathetic skin response (9%) and genetic studies (5%).

Selected articles	Overall assessment MERGE - SIGN 50			Participants average age (years)
	Quality	n	%	
Fibromyalgia n = 58	High	18	31.03	43.6
34.9%	Medium	38	65.52	
	Low	2	3.45	
Chronic fatigue n = 49	High	22	44.90	33.4
29.5%	Medium	25	51.02	
	Low	2	4.08	
Irritable bowel n = 50	High	9	18.37	36.0
30.1%	Medium	33	67.35	
	Low	7	14.29	
Interstitial cystitis n = 9	High	3	33.33	49.3
5.4%	Medium	5	55.56	
	Low	1	11.11	

Total = 166

Source: PubMed only =24.09 %, Embase only = 21.08 %, both databases = 54.81%

The overwhelming majority of case-control studies described sympathetic predominance in these painful syndromes (figure). Heart rate variability analyses and tilt table testing disclosed a clear pattern of sympathetic dysfunction; basal sympathetic hyperactivity accompanied by sympathetic hypo-reactivity to stress.
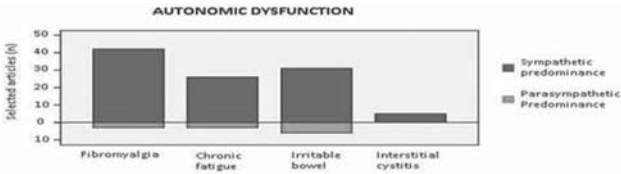
Conclusion: This systematic review suggests that sympathetic nervous system predominance is very common in these overlapping central sensitivity syndromes. This concordance raises the possibility that these syndromes may share similar clinical and pathogenic mechanisms.

Disclosure: L. A. Martinez, None; **T. Mora**, None; **A. Vargas**, None; **M. Fuentes**, None; **M. Martinez-Lavin**, None.

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Presence of Small Fiber Neuropathy in a Cohort of Patients with Fibromyalgia. Todd Levine[1], Victoria Lawson[2], Aidan Levine[1], Kevin V. Hackshaw[3] and David Saperstein[1]. [1]Phoenix Neurological Associates, Phoenix, AZ, [2]Ohio State University, Columbus, OH, [3]Ohio State Univ/Wm Davis Res, Columbus, OH

Background/Purpose: The pain associated with fibromyalgia is classically described as deep, muscular, aching and flu-like; however, a significant percentage of patients with fibromyalgia also describe neuropathic symptoms. The pain in these patients can be categorized and burning, tingling or stabbing.These clinical descriptors may raise the concern for a coexistent neuropathy. Yet, EMG/NCS in fibromyalgia patients are typically unrevealing. The constellation of neuropathic pain with normal nerve conduction studies, raises the possibility of a neuropathy confined purely to the small unmyelinated nerve fibers: a small fiber neuropathy. These small fiber neuropathies can be diagnosed through a 3-mm punch biopsy and may offer insight into the pathogenesis of some cases of fibromyalgia.

Methods: We retrospectively examined 56 patients referred for neurological evaluation who met diagnostic criteria for fibromyalgia. The patients were seen in neuromuscular consultation atthe Ohio State University or at Phoenix Neurological Associates. Patients were included if they met either the ACR criteria or the revised criteria of 2010 forfibromyalgia. Patients underwent 3 mm punch biopsies at a proximal and a distal site of one lower limb.PGP 9.5 immunolabelling was performed and the epidermal nerve fiber density was counted on 50 micron sections. The patients who were found to have reduced epidermal nerve fiber density underwent a standard serologic evaluation looking for identifiable causes for their neuropathy.

Results: 34/56 (61%) of the cases were diagnosed with small fiber neuropathy on the basis of reduced epidermal nerve fiber density. Of these 34 patients only 5 had evidence for neuropathy on EMG/Nerve conduction studies. Further, this evidence was subtle enough as to be inconclusive for diagnosis.24/34, 71%, of the patients with fibromyalgia and small fiber neuropathy had serologic evidence of an underlying etiology for their neuropathy that had not been detected prior to identification of the neuropathy: errors of glucose metabolism (n=11), vitamin D deficiency (n=5), elevated ESR (n=2), B6 deficiency (n=1), B12 deficiency (n=1), Sjogrens (n=2), elevated ANA (n=1), mutation in alpha galactosidase (Fabry's Disease) (n=1).

Conclusion: In this retrospective series, 61% of patients with fibromyalgia and neuropathic pain were found to have small fiber neuropathy based on

reduced epidermal nerve fiber density on a standard 3-mm punch biopsy. In 71% of these patients, a diagnosis was made based on serologic evaluation. These results suggest that testing for small fiber neuropathy in patients with fibromyalgiawill allow for earlier diagnosis of underlying conditions such as glucose dysmetabolism, toxicities, connective tissue disorders, and others. Further, identification of patients who have both fibromyalgia and small fiber neuropathy may suggest earlier therapeutic trials of neuropathic agents in treating the pain in these patients. It is unclear whether our patients had two separate disorders or whether patients had small fiber neuropathy and not fibromyalgia as the cause of their symptoms. A larger, prospective study is needed to answer this question.

ACR/ARHP Poster Session B
Genetics and Genomics of Rheumatic Diseases
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Genetic Interactions Between SNP Variants in C3 Receptor Subunits in Patients with SLE.

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Background/Purpose: Genome-wide and candidate gene studies have supported a role for genes involved in immune complex processing as being important contributors to development of SLE.The association of *ITGAM* variants and SLE highlights the importance of complement and complement receptors in the SLE diathesis.We hypothesized that there may also be statistical interactions between variants in genes that encode proteins in the complement system.We have developed a gene-based analysis strategy and present data that support a role for genetic interactions between variants in genes involved in the complement system.

Methods: A newly developed variation of the Rank Truncated Product (RTP) statistic was used to assess the combined genetic contribution of loci involved in complement component 3 (C3), C3 activation (*C2, C3, C4, CFH, CRP, MBL2*), and C3 recognition (*CR1, CR2, CR3 (ITGAM/ITGB2), CR4 (ITGAX/ITGB2)*)).The significance of the RTP statistic for each gene pair was assessed using a parametric bootstrap procedure.The study population included 16,105 unrelated SLE affecteds and controls from four different ancestry backgrounds (European (EA), African (AA), Hispanic (Hisp), Asian). All participants were of self-reported sex and race/ethnicity. Affecteds met 1997 American College of Rheumatology revised criteria for the classification of SLE.347 SNPs in these loci were genotyped on an Illumina iSelect custom array as part of the Large Lupus Association Study 2 (LLAS2).

Results: We identify new SNP associations across multiple race/ethnicities in the C2 locus with SLE ($p < 10^{-11}$/ $< 10^{-7}$, OR=1.8/1.7 in EA/AA) and confirm trans-racial associations of *ITGAM* and SLE ($P < 10^{-27}$/ 10^{-11}/10^{-12}OR=1.7/1.6/2.1 in EA/AA/Hisp respectively).

We hypothesized that there are genetic interactions between variants in genes encoding proteins in the C3 pathway that are known to functionally and/or physically interact.Indeed, significant gene-by-gene genetic interactions were identified between receptor-ligand, between C3 and complement regulators and between C3 receptor loci.Specific interactions included *C3-ITGAM* ($p < 0.001$ in AA), *C3-ITGB2* ($p=0.002$ in Hisp), *C3-CRP* ($p=0.003$ in AA), *C3-CFH* ($p=0.009$ in AA), *ITGAM-ITGB2* ($p < 0.001$ in Hisp) and *ITGAX-ITGB2* (with trans-racial association in both Hisp and EA, $p=0.02/0.045$).

Conclusion: We demonstrate significant and replicated genetic association of genes in the C3 pathway with SLE.These associations extend beyond the *ITGAM* locus to include other C3 receptor genes and regulators of C3 activation.The elucidation of genetic interactions between genes in this pathway demonstrates that the contribution of variants in the C3 pathway act both independently and jointly.

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Association of adam33 Polymorphisms with Systemic Lupus Erythematosus.

Seung Cheol Shim, Mi Kyoung Lim, Donghyuk Sheen and Hyo Park. Eulji University Hospital, Daejeon, South Korea

Background/Purpose: A Disintegrin and Metalloprotease 33 (ADAM33) is a member of a family of genes that encode membrane-anchored proteins with a disintegrin and a metalloprotease domain, and is located on chromosome 20p13. Recently, the polymorphisms in Adam33 have been found to be associated with asthma. Among the rheumatic diseases, systemic lupus erythematosus (SLE) is a prototypic Th2-mediated autoimmune disease like allergic disorders. To assess whether genetic functional variants of ADAM33 are associated with susceptibility to SLE or development of specific phenotypes in patients with SLE.

Methods: We have identified 48 SNPs, and nine SNPs were selected with regard to the LD pattern. Genotyping for g.10918G>C, g.12433T>C and g.13506C>G in the ADAM33 gene was conducted with PCR-RFLP methods, and genotyping for g.-330C>T, g.517 A>G, g.8227 G>A, g.9511 G>T, g.12462 C>T, g.12988 C>A polymorphisms was performed by single-base extension (SBE), using the ABI Prism[R] SNaPshot™ Multiplex kit (Applied Biosystems). We conducted an association study for ADAM33 polymorphisms in 190 SLE patients, 469 healthy controls, and 390 rheumatoid arthritis (RA) patients as a disease control. Haplotype analyses of related variants were performed as well.

Results: Significant associations of ADAM33 polymorphisms with susceptibility to SLE were found at g.8227 G>A, g.12988 C>A, and g.13506 C>G (P value were all below 0.001) (Table 1). Polymorphisms at g.8227 G>A was associated with the ANA titers among SLE patients ($P = 0.012$). In addition, we analysed the haplotype, and found a positive association of susceptibility to SLE with the major haplotype CGCG ($P = 3.5E-11$) (Table 2). There was no association between ADAM33 polymorphisms and RA as expected.

Table 1. Genotype and allele analyses of the polymorphisms of *Adam33* gene in SLE patients and healthy controls

Position[a]	Genotype/ Allele	Control n (%)	SLE n (%)	Odds ratio[b] (95% CI)	P
g.-330C>T	CC	426 (90.8)	168 (88.4)	1.00	0.347
	CT	43 (9.2)	22 (11.6)	1.30 (0.75–2.24)	
	TT	0 (0.0)	0 (0.0)	–	
	C	895 (95.4)	358 (94.2)	1.00	0.399
	T	43 (4.6)	22 (5.8)	1.28 (0.75–2.17)	
g.517 A>G	AA	165 (38.4)	62 (32.6)	1.00	0.392
	AG	201 (46.7)	97 (51.1)	1.29 (0.88–1.88)	
	GG	64 (14.9)	31 (16.3)	1.29 (0.77–2.17)	
	A	531 (61.7)	221 (58.2)	1.00	0.256
	G	329 (38.3)	159 (41.8)	1.16 (0.91–1.49)	
g.8227 G>A	GG	300 (64.1)	122 (65.2)	1.00	>0.0001
	GA	168 (35.9)	59 (31.6)	0.86 (0.60–1.24)	
	AA	0 (0.0)	6 (3.2)	-	
	G	768 (82.1)	303 (81.0)	1.00	0.692
	A	168 (17.9)	71 (19.0)	1.07 (0.79–1.46)	
g.9511 G>T	GG	390 (84.2)	156 (87.6)	1.00	0.093
	GT	71 (15.4)	19 (10.7)	0.67 (0.39–1.15)	
	TT	2 (0.4)	3 (1.7)	3.75 (0.62–22.66)	
	G	851 (91.9)	331 (93.0)	1.00	0.563
	T	75 (8.1)	25 (7.0)	0.86 (0.54–1.37)	
g.10918 G>C	GG	275 (59.4)	98 (61.3)	1.00	0.271
	GC	172 (37.1)	52 (2.5)	0.85 (0.58–1.25)	
	CC	17 (3.7)	10 (6.2)	1.65 (0.73–3.23)	
	G	722 (77.8)	248 (77.5)	1.00	0.938
	C	206 (22.2)	72 (22.5)	1.02 (0.75–1.38)	
g.12433 T>C	TT	391 (85.2)	178 (92.7)	1.00	0.025
	TC	66 (14.4)	13 (6.8)	0.43 (0.23–0.81)	
	CC	2 (0.4)	1 (0.5)	1.10 (0.10–12.19)	
	T	848 (92.4)	369 (96.1)	1.00	0.013
	C	70 (7.6)	15 (3.9)	0.49 (0.28–0.87)	
g.12462 C>T	CC	380 (84.5)	177 (93.2)	1.00	0.009
	CT	68 (15.1)	12 (6.3)	0.38 (0.20–0.72)	
	TT	2 (0.4)	1 (0.5)	1.07 (0.10–11.92)	
	C	828 (92.0)	366 (96.3)	1.00	0.005
	T	72 (8.0)	14 (3.7)	0.44 (0.25–0.79)	
g.12988 C>A	CC	327 (70.2)	170 (92.4)	1.00	>0.0001
	CA	134 (28.8)	14 (7.6)	0.20 (0.11–0.36)	
	AA	5 (1.0)	0 (0.0)	-	
	C	788 (84.5)	354 (96.2)	1.00	>0.0001
	A	144 (15.5)	14 (3.8)	0.22 (0.12–0.38)	
g.13506 C>G	CC	193 (43.3)	91 (49.5)	1.00	>0.0001
	CG	207 (46.4)	48 (26.1)	0.49 (0.33–0.73)	
	GG	46 (10.3)	45 (24.4)	2.08 (1.28–3.36)	
	C	593 (66.5)	230 (62.5)	1.00	0.193
	G	299 (33.5)	138 (37.5)	1.19 (0.92–1.53)	

[a] Calculated from the translation start site.
[b] Logistic regression analyses were used for calculating OR (95% CI; confidence interval)

Table 2. The haplotype frequencies by *Adam33* polymorphisms in both SLE patients and controls

Haplotype	g.-330 C>G	g.8227 G>A	g.12988 C>A	g.13506 C>G	Frequency[a] Control	SLE	Chi-square	P[b]
Ht 1	C	G	C	G	0.482	0.272	43.88	3.5E-11
Ht 2	C	G	C	C	0.259	0.484	56.53	5.5E-14
Ht 3	C	A	A	G	0.088	0.014	21.21	4.1E-6
Ht 4	C	A	C	G	0.057	0.043	0.915	0.339
Ht 5	G	G	C	C	0.030	0.022	0.517	0.472
Ht 6	C	G	A	G	0.027	0.003	6.655	0.010
others	-	-	-	-	0.057	-	-	-

Conclusion: ADAM33 polymorphisms were strongly associated with susceptibility to SLE and the development of specific clinical manifestations.

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Associations of Genetic Polymorphisms of Microrna-146a and Its Target Interleukin-1-Receptor-Associated Kinase 1 with Ankylosing Spondylitis.
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Background/Purpose: Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) were important mediators of inflammation response in the development of ankylosing spondylitis (AS). Especially, microRNA (miR)-146a targets TNF-receptor-associated-factor-6 (TRAF-6) and interleukin-1 receptor-associated kinase 1 (IRAK1) to suppress nuclear factor kB (NF-kB) activity and lipopolysaccharide (LPS)-induced inflammatory response. Here, we evaluated the effects of *miR-146a* rs2910164 G/C, *IRAK1* rs3027898 A/C, and *IRAK1* rs1059703 T/C genetic polymorphisms on the development of AS and clinical characteristics.

Methods: A total of 450 AS patients and 438 healthy controls were included, *miR-146a* genotypes were identified by polymerase chain reaction-restriction fragment length polymorphism, and *IRAK1* genetic polymorphisms were determined by the Taqman system.

Results: Our results showed that subjects possessing *miR-146a* rs2910164 GG genotype had 1.71-fold (95% confidence interval [C.I.] = 1.15–2.56) risk for AS development than those with GC/CC genotypes. Subjects with *IRAK1* rs3027898 A allele (odds ratio [OR] = 1.54, 95% C.I. = 1.20–1.99) also had a significantly increased risk of AS than those with C allele. Further, subjects carrying both of *miR-146a* rs2910164 GG genotype and *IRAK1* rs3027898 A allele had the highest risk (OR = 2.63, 95% C.I. = 1.25–5.55) for AS development than those with rs2910164 GC/CC genotypes and rs3027898 C allele, followed by subjects with rs2910164 GG genotype and rs3027898 C allele (OR = 1.75, 95% C.I. = 1.29–2.37) and subjects with rs2910164 GC/CC genotypes and rs3027898 A allele (OR = 1.57, 95% C.I. = 1.20–2.06). These results were also observed in males, but not in females. In addition, *IRAK1* rs3027898 A/C and *IRAK1* rs1059703 T/C polymorphisms were significantly associated with the abnormal erythrocyte sedimentation rate (ESR) level of AS patients, respectively. AS patients with both of *miR-146a* rs2910164 GG genotype and *IRAK1* rs3027898 A allele had a 6.68-fold (95% C.I. = 2.83–15.73) risk for uveitis development than patients without.

Conclusion: *MiR-146a* rs2910164 G/C and *IRAK1* rs3027898 A/C polymorphisms might be associated with the development of AS, as well as its clinical manifestations.

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New Genetic Risk Loci for the Radiographic Severity of Rheumatoid Arthritis.
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Background/Purpose: The severity of joint destruction is highly variable between Rheumatoid Arthritis (RA) patients; approximately 54% of this variance is explained by genetic factors. Many of the genetic factors responsible for the severity of joint destruction are unknown. We aimed to identify new genetic risk factors by studying genetic susceptibility loci of several auto-immune diseases.

Methods: In the first phase, 646 Dutch RA-patients with yearly X-rays of hands and feet over 7 years of follow-up were studied. These patients were genotyped for 148,880 SNPs by Immunochip which contains 186 loci previously associated with autoimmune diseases. Following quality control, association of SNPs with MAF >0.01 (130,841 SNPS) with joint destruction was analyzed using a marginal regression model. Correction for multiple testing was done using the Bonferroni correction for the number of uncorrelated SNPs (threshold p<1.1 $\times$ 10^{-6}). In the second phase, 686 North American RA-patients with repeated hands X-rays over 15 years of follow-up, for which Immunochip genotyping data were also available, were studied. SNPs that were significantly associated in phase 1 were selected and evaluated. All X-rays were scored by the Sharp van der Heijde score (ICC 0.91 and 0.98 for phase 1 and 2 respectively).

Results: In phase 1, 109 SNPs were significantly associated with joint destruction in Dutch RA-patients (threshold p<1.1 $\times$ 10^{-6}). Of these, 76 were located in the HLA-region in chromosome 6; since the association of this region with joint damage is already known, these SNPs were not analyzed in phase 2. The other 33 non-HLA genetic variants, though several were in high LD, were studied in the North-American RA-patients.

After correction for the number of number of uncorrelated SNPs (threshold $p<0.0036$), two variants were associated with the severity of joint destruction. These were rs451066 on chromosome 14 ($p_{uncorrected}=0.002$, MAF=0.20)) and rs11908352 on chromosome 20 ($p_{uncorrected}=0.002$, MAF=0.21). In the presence of a risk allele of rs451066 and rs11908352 respectively Dutch RA-patients had a 3.7% and 2.7% higher rate of joint destruction per year, which equals 29% and 20% more joint destruction over a seven years period.

Conclusion: Two new risk loci for progressive joint destruction in RA were identified. The region of rs451066 on chromosome 14 has previously been linked to susceptibility to type-1 diabetes. The other SNP is located at chromosome 20 and in low LD with rs4810485 (R^2 0.062), a variant that has previously been identified as RA risk locus. Altogether, the current data indicate that two loci that confer risk to other autoimmune disease may also affect the severity of RA.

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Identification of Susceptibility Loci for Inflammatory Arthritis.
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Background/Purpose: One of the principal findings of genome wide association studies in autoimmune diseases has been the substantial overlap of genetic susceptibility loci identified. This has underpinned fine mapping initiatives such as the Immunochip (IC) project in which custom chips were designed to fine-map regions of associations common to a number of autoimmune diseases. Samples from patients with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and psoriatic arthritis (PsA) have been genotyped using IC; given that all are types of inflammatory arthritis (IA) which exhibit common pathology and some overlap of associated loci, the data emerging from IC provides a unique opportunity to identify novel overlapping regions and determine whether the causal variants within overlapping loci are the same or different for each disease.

Methods: As part of the IC project, genotyping, quality control and association analysis was performed for RA (11475 cases and 15870 controls), JIA (2816 polygoarticular and oligoarticular JIA cases and 13056 controls) and PsA (929 cases and 4537 controls). Some controls were shared between cohorts. For this analysis all SNPs with a minor allele frequency $>1\%$ which reached $p<10^{-3}$ in any of the 3 diseases were first selected. IC regions were defined as including all SNPs from the 1000 Genomes Project CEU population (September 2009 release) that were in 0.1-cM (HapMap3 CEU) recombination blocks around each GWAS region lead marker. IC Regions which contained SNPs associated with more than one type of IA were considered overlapping.

Results: 49 regions showed association at $p<10^{-3}$ with more than one type of IA, of these, in RA and JIA 4 loci (*PTPN22 STAT4, ANKRD55* and *TYK2*) reached genome wide significance (5×10^{-8}), with a further 7 associated at $p<10^{-5}$ in both diseases. Interestingly 4 of these loci are also associated with PsA at $p<10^{-3}$ (*TNFAIP3, PTPN2. RUNX1* and *TYK2*). 6 of these loci have been previously associated with both RA and JIA (*PTPN22, STAT4, AFF3, TNFAIP3, PTPN2* and *IL2RA*) whilst 5 are novel overlapping regions *(DNASE1L3, ANKRD55, TYK2, RUNX1* and *IL2RB)*. For the *PTPN22, STAT4, DNASE1L3, ANKRD55, TYK2* and *RUNX1* regions the RA and JIA associated SNPs are either identical or highly correlated ($r^2>0.8$), the direction of effect is the same in both diseases and odds ratios similar. For *AFF3, TNFAIP3* and *PTPN2* the associated SNPs are different and weakly correlated ($r^2>0.4<0.8$) but the direction of effect is similar for each disease. An interesting finding is that for *IL2RA* and *IL2RB* the pattern of association in the region is completely different.

Conclusion: These findings add to the body of evidence that there are shared susceptibility genes for inflammatory arthritis. Further investigation is required to fully explore whether the regions contain the same or different causal effect, including functional studies to determine whether, in overlapping loci with the same causal variant, the variant predisposes to disease by the same mechanism.

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Dense Genotyping of Risk Loci in Black South Africans with Rheumatoid Arthritis: An Association Study.
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Background/Purpose: Genome wide association studies (GWAS) have identified numerous rheumatoid arthritis (RA) risk loci in patients of European and Asian ancestry but the causal variants have rarely been identified. These studies have also identified susceptibility loci that are common to various autoimmune diseases. The need to identify casual variants prompted the design of the Immunochip, a custom Illumina Infinium high density genotyping array, with 196 000 single nucleotide polymorphisms (SNPs) from 186 loci previously associated with 12 autoimmune diseases. Little is known about the genetics of RA in black South Africans. We aimed to test associations with known genetic loci and to identify novel risk loci in black South Africans with RA.

Methods: Consenting black RA patients fulfilling the 1987 ACR criteria for RA, >18 years at disease onset, and seen at a single centre in Johannesburg, South Africa were studied and compared to ethnically and geographically matched controls. Genotyping of 716 samples was performed using the Immunochip. Only samples with $\geq94\%$ call rate and individual SNPs with $\geq95\%$ call rate, were polymorphic, in Hardy-Weinberg equilibrium ($p\geq5 \times 10^{-7}$) and with a minor allele frequency of ≥0.02 were analyzed. The cohort was further pruned for relatedness and ancestral outliers. After quality control, 117 353 SNPs were tested for association in 263 cases and 365 controls. The statistical analysis was performed using PLINK vers1.07. A p value = $<5 \times 10^{-8}$ was considered significant based on previous genome wide association studies.

Results: The strongest associations were found in the MHC region with 64 SNPs reaching statistical significance. The most significant associations were in the intergenic region of the *HLA DRB1- HLA DQA1* alleles (rs3104413, OR=3.88, $p=5.49 \times 10^{-21}$; rs3129769, OR=3.91, $p=4.60 \times 10^{-21}$; rs6931277, OR=3.97, $p=1.03 \times 10^{-21}$). There were 2 non HLA SNPs that reached genome wide significance, rs9283487 (OR=3.25, $p=7.96 \times 10^{-18}$) in the *PRKRA* gene, and rs35198051 (OR=0.34, $p=2.94 \times 10^{-8}$) in the intergenic region of *C11orf76* and*LOC100133306*. In addition there were suggestive associations of 2 SNPs on chromosome 1, rs12739262 (OR=0.36, $p=1.36 \times 10^{-7}$) in the *PPP1R12B* gene and rs12738883 (OR=0.36, $p=1.69 \times 10^{-7}$) in the intergenic region of *PLD5* and *LOC400723*, both SNPs reached statistical significance in the rheumatoid factor (RF) positive subgroup (n=240/254) (rs12739262, OR=0.33, $p=9.10 \times 10^{-8}$ and rs12738883, OR= 0.33, $p=9.10 \times 10^{-8}$).

Conclusion: In keeping with previous studies the HLA class II region confers the strongest genetic risk for RA in black South Africans. We also found 2 novel SNPs in the overall cohort and a further 2 SNPs in the RF positive subgroup. The association of the *PRKRA* gene with RA is of interest

because of its recent association with Sjogren's Syndrome. Further studies in larger cohorts of African patients are required to validate these findings and to better understand the functional role of these novel loci in the pathogenesis of RA in black South Africans.

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Effect of Interactions Between Validated Rheumatoid Arthritis Genetic Factors and Environmental Factors On Rheumatoid Arthritis Risk.

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Background/Purpose: Studies have shown associations between environmental factors and rheumatoid arthritis (RA) risk. Also, genome-wide association studies (GWAS) have identified genetic markers associated with RA risk. We examined additive and multiplicative gene-environment interactions between 44 RA genetic markers and smoking, parity/breast-feeding, body mass index (BMI), and BMI at age 18 in determining RA risk.

Methods: We used a pooled nested case-control sample of 541 RA cases, including 303 seropositive (CCP+ and/or RF+) cases, and 549 matched controls from the Nurses' Health Study and Nurses' Health Study II. Controls were matched on age, menopausal status, and post-menopausal hormone use. All participants were Caucasian. We genotyped 36 single nucleotide polymorphisms identified in previous GWAS and meta-analysis, and 8 HLA-DBR1 shared epitope (SE) genotypes at 4 digit resolution. The information on cumulative pack-years of smoking, parity and months of breast-feeding prior and BMI variables determined prior to RA diagnosis, and BMI at age 18 was extracted from questionnaires. We examined the main effects of the genetic and environmental factors. We tested for additive interactions using the attributable proportion (AP) due to interaction and tested for multiplicative interactions using a 1 d.f. test. We used unconditional logistic regression models, adjusted for matching factors. Bonferroni correction was used to adjust for multiple comparisons. We further stratified the cases into seropositive RA and seronegative RA phenotypes and tested for interactions separately.

Results: We found significant main effects of HLA-DBR1*0401 (OR=1.77, 95% CI=1.32–2.38), any HLA-DBR1 SE (OR=1.80, 95% CI=1.41–2.29), and smoking (OR=1.55, 95% CI=1.21–1.99) on RA risk. For the interaction analyses, combined HLA-DRB1 SE and HLA-DBR1*0401 showed significant interaction with smoking in all RA and seropositive RA. Also, PTPN22 showed significant interaction with smoking in all RA (**Table**). The effect of interaction between BMI prior to RA diagnosis and PXK on RA risk was significant in all RA (AP=0.74, p<0.005) and seropositive RA (AP=0.80, p<0.005). We also found significant interaction effects on RA risk between BMI at age 18 and HLA-DBR1*0401 in all RA (AP=0.66, p=0.013) and seropositive RA (AP=0.67, p=0.031). However, we did not find any significant interaction between genetic factors and parity/breast-feeding. Also, there was no significant interaction found in the seronegative RA phenotype. Several multiplicative interactions were significant, but none remained significant after multiple comparisons correction.

Table 1. Summary of significant additive interactions for 44 RA risk alleles after multiple comparison adjustment and corresponding stratified analyses

Genetic factors	Environmental factors	All cases		Seropositive cases	
		OR (95% CI)	AP (corrected p-value[3])	OR (95% CI)	AP (corrected p-value[4])
HLA-DRB1*0401	Smoking prior to diagnosis[1]				
None	< 10 pack-years	Ref	0.49 (0.031)	Ref	0.56 (0.004)
None	≥ 10 pack-years	1.33 (1.01–1.75)		1.37 (0.99–1.90)	
Any	< 10 pack-years	1.32 (0.89–1.95)		1.16 (0.72–1.88)	
Any	≥ 10 pack-years	3.23 (2.03–5.15)		3.46 (2.07–5.81)	
Any HLA-DRB1 SE	Smoking prior to diagnosis[1]				
None	< 10 pack-years	Ref	0.48 (<0.005)	Ref	0.56 (<0.005)
None	≥ 10 pack-years	1.14 (0.82–1.59)		1.08 (0.71–1.65)	
Any	< 10 pack-years	1.35 (0.99–1.86)		1.62 (1.11–2.37)	
Any	≥ 10 pack-years	2.90 (2.03–4.16)		3.91 (2.59–5.90)	
PTPN22	Smoking prior to diagnosis[1]				
None	< 10 pack-years	Ref	0.53 (0.009)		
None	≥ 10 pack-years	1.31 (1.00–1.72)			
Any	< 10 pack-years	1.03 (0.68–1.54)			
Any	≥ 10 pack-years	2.84 (1.75–4.60)			
PXK	BMI prior to diagnosis[2]				
None	< 30 kg/m²	Ref	0.74 (<0.005)	Ref	0.80 (<0.005)
None	≥30 kg/m²	0.64 (0.45–0.91)		0.54 (0.35–0.83)	
Any	< 30 kg/m²	0.96 (0.65–1.43)		0.98 (0.62–1.57)	
Any	≥ 30 kg/m²	2.32 (1.00–5.42)		2.65 (1.05–6.68)	
HLA-DRB1*0401	BMI at age 18[2]				
None	< 25 kg/m²	Ref	0.66 (0.013)	Ref	0.67 (0.031)
None	≥ 25 kg/m²	0.97 (0.59–1.58)		0.96 (0.54–1.73)	
Any	< 25 kg/m²	1.60 (1.16–2.21)		0.55 (1.07–2.27)	
Any	≥ 25 kg/m²	4.66 (1.73–12.57)		4.60 (1.59–13.34)	

[1]cumulative pack-years of smoking none −10 vs. ≥10
[2]<30 vs. ≥30 kg/m² defined as obese by World Health Organization
[3]<25 vs. ≥25 kg/m² defined as overweight by World Health Organization
[4]P-values were corrected for multiple comparisons. We used unconditional logistic regression model with 3 indicator variables for genetic factor, environmental factor, and interaction, adjusting for age, menopausal status, and postmenopausal hormone use.
RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval; AP: attributable proportion due to interaction; SE: shared epitope; BMI: body mass index

Conclusion: We found significant gene-environment interaction effects on RA risk with stronger associations for the seropositive RA phenotype. We also found HLA-DBR1*0401 had different AP when interacting with different environmental factors, which suggests different mechanisms for these interactions. C:\data\abstract\acr\2012\Paper_28425_abstract_29444_0.jpg

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14-3-3 Eta Is a Novel Citrullination Target in Rheumatoid Arthritis That Enhances Diagnostic Utility in Anti-CCP Negative Patients.

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Background/Purpose: 14-3-3 eta is normally an intracellular protein and only in the disease state is it released into the extracellular space. We have previously presented data describing serum 14-3-3 eta's diagnostic utility as a marker that complements RF and anti-CCP in early and established RA and is associated with joint damage in RA and PsA. Circulating autoantibodies directed to citrullinated proteins are highly specific for RA, but a significant percentage of patients are or remain sero-negative for anti-CCP. Given that 14-3-3 eta is liberated into the synovial space where PAD enzymes are present, we investigated whether 14-3-3 eta represents a novel citrullination target that could identify anti-CCP negative RA patients.

Methods: Assays to measure the autoantibody levels to either non-citrullinated (non-cit) or citrullinated (cit) 14-3-3 eta were developed using full-length recombinant human 14-3-3 eta. Full-length cit-14-3-3 eta was generated by citrullinating the protein with purified PAD. Reactivity to non-cit and cit-14-3-3 eta was evaluated in 3 anti-CCP positive RA patients to confirm the presence of autoantibodies to cit-14-3-3 eta. To evaluate whether these novel autoantibodies are detectable in anti-CCP negative RA patients and differentially expressed compared to healthy controls, reactivity to both non-cit and cit-14-3-3 eta was measured in 30 anti-CCP negative RA patients and 30 confirmed anti-CCP negative healthy controls. Mean and median fluorescence intensity [1 MFI = 1 unit (U)] was evaluated and corresponding t-tests and Mann-Whitney U-tests were used to determine differences within and between groups. The area under the ROC curve (AUC) was generated for diagnostic utility estimates and to determine likelihood ratios (LR) for various anti-cit-14-3-3 eta cut-offs.

Results: Compared to non-cit 14-3-3 eta, up to 25X higher reactivity was observed to cit-14-3-3 eta in 2 of the 3 anti-CCP positive RA patients, revealing the novel expression of autoantibodies to the citrullinated form of 14-3-3 eta in RA. Within the anti-CCP negative RA group, significantly higher reactivity was observed to cit versus non-cit-14-3-3 eta at 1943U versus 395U, p=0.01. No significant differences in reactivity were observed within the healthy group. Anti-cit-14-3-3 eta expression was significantly higher in anti-CCP negative RA patients with means (SD) and medians (min-max) of 1943U (3045U) and 306U (68–8982U) compared to 155U (122U) and 100U (45–564U) for healthy controls, p<0.002.The corresponding ROC AUC for anti-cit-14-3-3 eta differential expression in anti-CCP negative RA patients compared to healthy controls was 0.79 (95% CI 0.68–0.91; p<0.0001). At a cut-off of 320U, the specificity and sensitivity were 90% and 50% delivering an LR positive of 5 increasing to 14 at 439U with a corresponding specificity of 97% and sensitivity of 47%.

Conclusion: Extracellular 14-3-3 eta protein has been described as an RA diagnostic biomarker with prognostic and therapy monitoring applications. 14-3-3 eta also represents a novel citrullination target that is differentially expressed in anti-CCP negative RA patients versus healthy controls, indicating that anti-cit-14-3-3 eta may improve RA diagnosis.

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A Genome-Wide Interaction Study with Smoking Suggests New Risk Loci for Two Different Subsets of Rheumatoid Arthritis; Results From Swedish Epidemiological Investigation of Rheumatoid Arthritis Study. Xia Jiang[1], Henrik Källberg[1], Leonid Padyukov[2], Lars Klareskog[2] and Lars Alfredsson[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Rheumatoid arthritis (RA) is believed to have a multifactorial etiology, involving both genetic and environmental components, and can be divided into two major subsets according to the presence/absence of anti-citrullinated protein/peptide antibodies (ACPA). Smoking is the most established environmental risk factor. Despite progress from genome-wide association studies (GWAS), identified genetic variants only explain a small proportion of RA occurrence. Hypothetically, gene-environment interaction could add etiologic understanding of the disease. The aim of current study was to investigate gene-environment interaction between smoking and SNPs from an Immunochip, with selected SNPs of interest from an inflammatory point of view, for each of the two major RA subsets.

Methods: Data from Swedish EIRA case-control study was analyzed by means of logistic regression models. Smoking history was collected through questionnaires. Heavy smoking was defined as more than 10 pack-years. Genetic information was obtained from an Immunochip scan. Interaction between smoking intensity and 133648 genetic markers that passed quality control were examined for the two RA subsets (1590 ACPA positive cases, 891 ACPA negative cases; compared with 1856 matched controls). Attributable proportion due to interaction together with 95% confidence interval was evaluated for each smoking-SNP pair.

Results: For ACPA positive RA, 390 SNPs were found to significantly interact with heavy smoking after Bonferroni correction, with a majority located in the HLA region (328 out of 390, 84.10%), all of which displayed high linkage disequilibrium (LD); for ACPA negative RA, 56 SNPs passed threshold for significance, most located outside the HLA region (51 out of 56, 91.07%). After adjusting for *HLA-DRB1* shared epitope (SE), 37 SNPs remained significant for ACPA positive RA, with 17 (45.95%) confined to HLA region and the rest spread across 9 other chromosomes; for ACPA negative RA, 19 SNPs stood out, all of them outside the HLA region. Through functional prediction and pathway annotation, 24 candidate genes/regions were identified for ACPA positive RA, several of them (*C6orf10, GRB10, HCG9, TAP2, PPT2, HLA-E, SMAD3*) together with *HLA-DR* presented a network of antigen presentation pathways; for ACPA negative RA, 13 genes were demonstrated, 6 of them (*GP1BA, AFF3, ICOSLG, NOTCH2, TGS1, LYN*) constitute T helper cell differentiation pathways. For ACPA positive RA, besides those SNPs in LD with known susceptibility variant at *HLA-DRB1*, none of the others have previously been identified.

Conclusion: Our study presents the most explicit picture to date, with regard to the patterns of gene-smoking interaction in ACPA positive/negative RA, suggesting fairly contrasting etiology of the two subsets. Our findings support the, by far, greatest influence from HLA-region on ACPA positive RA; while for ACPA negative RA, more genes outside HLA-region contribute to the etiology. Noticeably, for both RA subsets, new SNPs that are not significant in association analyses stand out in interaction analyses, indicating that genetic factors should be considered together with environmental factors in studies of RA etiology.

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Cell-Type Specific Type I Interferon Signatures in Systemic Lupus Erythematosus and Viral Infection: What Makes the Difference? Chieko Kyogoku[1], Joachim R. Grün[1], Tobias Alexander[2]. Robert Biesen[2], Falk Hiepe[2], Thomas Häupl[2], Andreas Radbruch[1] and Andreas Grützkau[1], [1]German Rheumatism Research Centre Berlin (DRFZ), an institute of the Leibniz Association, Berlin, Germany, [2]Charité University Hospital Berlin, Berlin, Germany

Background/Purpose: Gene expression profiling experiments using peripheral blood mononuclear cells (PBMCs) revealed a crucial role of type I interferon (IFN) in the pathogenesis of systemic lupus erythematosus (SLE). However, it is almost unknown how particular leukocyte subsets contribute to the overall type I IFN signature described for PBMCs. Furthermore, a detailed analysis of how IFN signatures differ in autoimmune disease from that observed after viral infection is missing so far. Therefore, we compared expression levels of 2442 IFN signature genes in peripheral CD4+ T helper cells, CD16-negative inflammatory and CD16-positive resident monocytes (Mo) isolated from patients with SLE, healthy donors (ND) and ND vaccinated against yellow fever by global gene expression profiling.

Methods: Peripheral blood from 6 patients with SLE and 4 ND for CD4+ T cells, 4 patients with SLE and 4 ND for CD16-negative Mo, and 4 patients with SLE and 3 ND for CD16-positive Mo were recruited. Same ND were examined before and after immunization by yellow fever vaccine. After sorting cells, isolated RNA were applied to Affymetrix Human Genome U133 Plus 2.0 Array. Data analysis was done using BioRetis database, Genesis Software and Ingenuity Pathway Analysis (IPA). A reference list of 2442 IFN-related genes was obtained from recent publications and used to estimate IFN imprints.

Results: When compared total significantly differentially expressed probe sets, 9/3/2 (CD4+ T cells/CD16-negative Mo/CD16-positive Mo, respectively) times more number of probes were detected in patients with SLE compared to immunized ND. The contribution of IFN signature to total gene signature was 20.7/23.3/23.3 % in patients with SLE, whereas 48.6/35.2/30.5 % in immunized ND. 98/165/173 probe sets (fold change>=2, <=−2) were detected as a "common" IFN signature observed both in autoimmunity and in immunized ND. 111/164/120 probe sets were detected as an "autoimmune-specific" IFN signature, whereas only 0/8/5 probe sets were detected to be specific for the "virus-induced" IFN signature. Expression pattern of these IFN signature genes clearly distinguished patients with SLE from immunized ND by hierarchical cluster analysis. Although major IFN signature genes were commonly expressed in CD4+ T cells and Mo of patients with SLE and immunized ND, expression magnitudes of them were higher in patients with SLE compared to immunized ND. In SLE, in addition to the typical "viral-induced" IFN signature, genes that are involved in apoptosis signaling, antiviral PKR signaling, Fcγ receptor-mediated phagocytosis and IL-10-/ IL-9-/ IL-15-mediated JAK/Stat signaling pathways were identified by IPA.

Conclusion: This study demonstrated that IFN signature in autoimmunity and that in viral infection are quite different in the number of IFN-related genes activated and their expression magnitudes. Autoimmunity is characterized by a much stronger expression of IFN signature genes and is obviously modulated by a separate set of co-regulated genes defining the "autoimmune-specific" IFN signature. "Common" and "autoimmune-specific" IFN signature genes can be applied as a clinical biomarker to diagnose SLE flare discriminating from viral infection.

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Genomewide Association Study in Systemic Lupus Erythematosus: Known Loci. Antonio Fernandez-Nebro[1]. Patricia E. Carreira[2], Ricardo Blanco[3], Victor M. Martinez-Taboada[4], Luis Carreño[5], Alejandro Olive[6], José Luis Andreu[7], Mª Angeles Aguirre[8], Paloma Vela[9], Jose Javier Pérez Venegas[10], Jose Luís Marenco[7], Joan Miquel Nolla[11], Antonio Zea[12], José M. Pego-Reigosa[13], Mercedes Freire González[14], Gabriela Ávila[15], María América López-Lasanta[15], Raül Tortosa[15], Antonio Julià[15] and Sara Marsal[15], [1]Hospital Regional Universitario Carlos Haya, Málaga, Spain, [2]Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain, [3]Hospital Universitario Marques De Valdecilla, Santander, Spain, [4]Hospital Universitario Marques de Valdecilla. IFIMAV, Santander, Spain, [5]Gregorio Marañón Hospital, Madrid, Spain, [6]Germans Trias Pujol Hospital, Barcelona, Spain, [7]HU Puerta de Hierro Majadahonda, Madrid, Spain, [8]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [9]Hospital General Universitario de Alicante, Alicante, Spain, [10]Hospital del SAS de Jerez de la Frontera, Jerez De La Frontera, Spain, [11]Hospital Universitari de Bellvitge, Barcelona, Spain, [12]Hospital Universitario Ramon y Cajal, Madrid, Spain, [13]Hospital do Meixoeiro, Vigo, Spain, [14]Complejo Hospitalario Universitario de La Coruña, La Coruña, Spain, [15]Vall d'Hebron Hospital Research Institute, Barcelona, Spain

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease with an estimated prevalence of 40:100,000 cases in European populations. SLE has a strong genetic risk component (sibling relative risk 30). Positional candidate studies have identified the association of *HLADRB1*, *STAT4* and *IRF5* loci with SLE risk. However, Genome-Wide Association Studies (GWAS) have allowed to expand the number of SLE risk loci to more than 20. In order to identify additional risk loci we have performed a GWAS in a Southern European population.

Methods: 510 SLE cases and 1,540 controls of Spanish origin were genotyped for more than 550,000 SNPs using Illumina Quad-610 platform. Only SNPs having >95% call rate and individuals having 95% of SNPs genotyped were included. Principal Component Analysis was used to identify the main axis of variation and discard any population outlier. After QC-filtering 489 SLE cases and 1490 Controls were included to test for association. In order to evaluate the association of all previously known SLE-risk loci all GWASs published from 2,008 to 2,012 where evaluated. Loci associated at a nominal *P*-value < 5e-5 were included. Within each SLE risk locus (n=43), the SNP having the highest statistical evidence was selected. For those SNPs not directly genotyped (n=3) genotype was imputed using MACH v1.0 software.

Results: From the 24 loci previously showing Genome-Wide level of association (*P*<5e-8) with SLE risk, loci *HLA-DRB1, ITGAM, STAT4* and *MSH5* were also replicated at Genome-Wide level. Four additional loci were also replicated at nominal (*P*<0.05) level of significance. From the remaining 19 loci still requiring additional evidence (5e-8 < P < 5 e-5) we were able to nominally replicate three loci. 20 SNPs within genomic regions previously not associated with SLE were also identified (*P*<5e-5).

Conclusion: The present study has validated previous SLE risk loci in an independent population and gives additional support to loci with suggestive association. The association of the new candidate risk loci for SLE identified in this GWAS is currently being tested for validation.

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Aggregated Genetic Information Explains Variations On Hand Radiographic Scores in Rheumatoid Arthritis Patient. Jing Cui[1], Nancy A. Shadick[2], Katherine P. Liao[1], Michael Weinblatt[3], Robert M. Plenge[1] and Elizabeth W. Karlson[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [3]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Rheumatoid arthritis (RA) has an estimated heritability of approximately 60%. Joint destruction as a severity measure of RA is influenced by genetic factors, however the heritability of this trait remains unclear. Our objective was to determine the genetic heritability of joint destruction,

quantified as Sharp/van der Heijde scores (SHS), and to conduct a genome wide association study (GWAS) to identify SNPs associated with quantitative joint damage in RA patients.

Methods: We studied 422 anti-CCP+ RA subjects in a prospective observational RA cohort at an academic hospital with baseline bilateral hand radiographs and blood samples. Using the SHS method, 4 radiologists assigned an erosion score (0–5) for 16 joints, and a joint space narrowing score (0–4) for 15 joints in each hand (total SHS range 0–280). The inter-rater reliability for the SHS in our study was 0.93. SHS measures were normalized by taking the inverse normal of the rank. Samples were genotyped on the Affymetrix 6.0 platform. We applied standard quality control procedures, followed by imputation to 2.5M SNPs using IMPUTE with HapMap2 CEU. Clinical predictors of SHS such as age. gender, disease duration were studied using general linear regression.We applied mixed linear model analysis to estimate the proportion of variance explained by genotyped SNPs from the whole genome to determine heritability. We studied the association between each SNP and SHS using linear regression assuming a genetic additive model adjusting for the first three principal component values from Eigenvector analysis and RA disease duration.

Results: The 422 RA cases had mean age of 59 yrs, mean disease duration of 17 yrs, and 81% were female. The SHS range was 0–270 with median of 40. Clinical predictors including age and disease duration were significant in univariate analyses, and only disease duration was significant (P <0.0001) in multivariate analyses. Heritability analysis adjusted for disease duration and 3 principal components estimated 22% (p=0.39) of SHS variation was attributable to genetic variants using all genotyped SNP information. From the GWAS, we found 2 SNPs that exceeded the genome-wide significance threshold of 5E-8 (rs16925520 p=4E-9, rs2832760 p=3E-8) for association with SHS. The independent top 10 findings are shown in the table. The MHC region was not significantly associated with SHS. No known RA risk alleles (50 loci) were associated with SHS.

Table. Top 10 SNPs associated with Sharp/van der Heijde Hand Score

chr	rs	gene	Base pair	Allele A	Minor allele frequency	beta	P value
9	rs16925520	*JMJD2C*	7162354	C	0.01	3.52	4.3E-09
21	rs2832760	CLDN8	30584023	G	0.30	0.31	3.3E-08
5	rs10079663	VDAC1	133384433	C	0.41	0.28	1.1E-07
8	rs13256240	-	83633555	A	0.01	-3.38	2.2E-07
9	rs10901313	FUBP3	132275229	C	0.02	-2.13	1.1E-06
4	rs1980037	GYPB	145136964	A	0.02	2.73	1.2E-06
19	rs4801371	ZNF71	61926872	A	0.04	-1.28	1.8E-06
4	rs10024454	IGFBP7	57942964	C	0.32	-0.27	2.2E-06
8	rs1471705	ZFHX4	77880207	A	0.01	-2.79	2.7E-06
1	rs6674099	DISC2	230033485	A	0.45	0.23	3.2E-06

Conclusion: Our study suggests that joint damage in RA (as measured by SHS) is a heritable trait where genetic factors explain 22% of the phenotypic variance.These findings corroborate with a previous study where heritability was estimated to be higher at 45%-58%. Although several SNPs were associated with SHS at genome-wide significance, none were known RA risk alleles.These findings require confirmation in an independent sample.

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Genetic Variants near Insulin-Like Growth Factor Binding Protein 3 (IGFBP3) Are Associated with Hip Osteoarthritis. Daniel S. Evans[1], Neeta Parimi[1], Ana M. Valdes[2], Hanneke J.M Kerkhof[3], Frederic Cailotto[4], Michael C. Nevitt[5], Steven R. Cummings[1], Rik J. Lories[4], Timothy D. Spector[2], Nigel K. Arden[6], Joyce B. van Meurs[3] and Nancy E. Lane[7]. [1]California Pacific Medical Center Research Institute, San Francisco, CA, [2]Dept of Twin Research and Genetic Epidemiology, St. Thomas' Hospital, King's College London, London, United Kingdom, [3]Department of Internal Medicine, Erasmus Medical Center and The Netherlands Genomics Initiative-Sponsored Netherlands Consortium for Healthy Aging, Rotterdam, Netherlands, [4]Laboratory for Skeletal Development and Joint Disorders, Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [5]University of California-San Francisco, San Francisco, CA, [6]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Oxford, United Kingdom, [7]UC Davis School of Medicine, Sacramento, CA

Background/Purpose: Hip osteoarthritis (HOA) is one of the most common joint disorders and can result in pain and disability.HOA is heritable,

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but the particular genes contributing to the development of HOA are not well defined.To identify genetic associations with HOA, we conducted a two-stage genome-wide association study (GWAS).

Methods: All analyses were restricted to individuals of European ancestry.The discovery phase was performed using radiographically determined HOA cases and controls selected from the Osteoporotic Fractures in Men (MrOS) Study and the Study of Osteoporotic Fractures (SOF) (combined cases = 662).HOA cases were defined as Croft grade $\geq$ 2 or total hip replacement (THR).HOA controls were defined as Croft grade $\leq$ 1, maximum joint space narrowing (JSN) $\leq$ 1, maximum osteophytes $\leq$ 1, and no THR.SNPs were genotyped using the Illumina Omni1-Quad array and approximately 2.5 million SNPs were imputed using the HapMap reference panel.Logistic regression was performed, and MrOS and SOF results were combined using inverse variance weighted fixed effect meta-analysis.SNP associations with P-values $\leq 5 \times 10^{-8}$ were examined for replication in the Rotterdam cohorts (RSI = original cohort, RSII = second recruitment cycle), Twins UK, and Chingford cohorts.Publicly available eQTL data from HapMap CEU lymphoblastoid cell lines were used.

Results: On average, MrOS participants (100% male) were older than SOF participants (100% female) at the clinic visits when HOA was assessed (MrOS: mean$\pm$SD = 77.5$\pm$5.4 years, range = 69–97; SOF: mean$\pm$SD = 70.9$\pm$5.0 years, range = 65–91).In the discovery meta-analysis, the rs788748 A allele and the rs879966 G allele were associated with decreased odds for HOA (Table 1).The two directly genotyped SNPs were 23 kb apart and were in moderate LD (HapMap CEU r^2 = 0.54).Neither SNP remained nominally significant in conditional analysis, indicating dependence.The SNP rs788748 replicated in the RSI cohort, but not the RSII cohort or the Chingford cohort.In the Twins UK cohort, the association between the rs788748 A allele and HOA was significant and in the opposite direction relative to the discovery samples (Table 1).The SNP rs879966 did not replicate (Table 1).

Table 1. SNP association results in discovery and replication cohorts.

SNP	Effect allele (Freq)	MrOS/SOF (discovery) cases/ controls	OR (P)	RSI cases/ controls	OR (P)	RSII cases/ controls	OR (P)	Twins UK cases/ controls	OR (P)	Chingford cases/ controls	OR (P)
rs788748	A (0.49)	662/4750	0.71 (3×10^{-8})	462/3428	0.86 (0.03)	149/1430	1.02 (0.86)	73/366	1.48(0.03)	83/492	1.11 (0.54)
rs879966	G (0.39)	662/4750	0.70 (2×10^{-8})	462/3428	0.92 (0.24)	149/1430	1.12 (0.38)	73/366	1.34(0.10)	83/492	1.00 (0.99)

From eQTL data, rs788748 and rs879966 were marginally associated with IGFBP3 expression (P-value = 0.07 and 0.06, respectively), but not IGFBP1 expression (P-value = 0.74 and 0.34, respectively).SNP associations with circulating IGFBP3 levels and results from IGFBP3 knockdown experiments in the ATDC5 chondrogenesis model system will be presented.

Conclusion: Our genetic association and eQTL results provide suggestive evidence for a link between IGFBP3 and HOA, but further replication is required for the association results to be considered robust.IGFBP3 is known to be expressed in human chondrocytes and might be an attractive candidate for follow-up studies.

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Genome-Wide Association Study and Gene Expression Analysis Identifies CD84 As a Predictor of Response to Etanercept Therapy in Rheumatoid Arthritis. Jing Cui[1] and International RA Consortium on Therapy (InteRACT)[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Boston, MA

Background/Purpose: There are no biomarkers that predict response to anti-TNF therapy in rheumatoid arthritis (RA).Here, we conduct a genome-wide association study (GWAS) to identify genetic variants that influence response to anti-TNF therapy.

Methods: GWAS data were aggregated on 2,743 RA patients as part of an international collaboration. Clinical data and Disease Activity Score (DAS28) were available for RA patients treated with three anti-TNF medications: etanercept (N=773), infliximab (N=894) or adalimumab (N=1,071). GWAS data were quality controlled by genotype batch, and all data were imputed to 2.5M SNPs using IMPUTE with HapMap2 CEU. Change in DAS28 (delta-DAS) was used as the primary phenotype in linear regression association tests of all samples combined and subset by anti-TNF drug.We adjusted for baseline DAS28 and three ancestry-derived principal component eigenvectors. Expression quantitative trait locus (eQTL) data for

the *CD84* locus were available for peripheral blood mononuclear cells (PBMCs, N=228). Replication samples from the Portuguese Reuma.pt registry (n=405), and the Japanese IORRA and Kyoto University Hospital registries (n=374), were genotyped using Sequenom and/or TaqMan and analyzed as in our GWAS.

Results: While no single SNP was genome-wide significant for association with delta-DAS in an analysis of all samples combined, a SNP at the *1q23/CD84* locus was highly significant in the etanercept subset of patients (rs6427528, $P=7 \times 10^{-8}$).This same SNP was not associated with delta-DAS in the infliximab or adalimumab subsets ($P>0.05$). The allele associated with a better response, which is in the 3' UTR of an immune-related gene *CD84*, is also associated with higher *CD84* gene expression in PBMCs ($P<10^{-12}$). In a subset of RA patients with gene expression data, *CD84* gene expression correlates with baseline DAS (n=210, $P=0.02$), and demonstrates a non-signficant trend toward predicting response to etanercept therapy.In a small replication study, the SNP was not associated with response to etanercept therapy among European (n=139, $P=0.4$) or Japanese (n=151, $P=0.8$) RA patients.

Conclusion: GWAS in etanercept-treated RA patients revealed a highly suggestive association with the *CD84* locus.Further, *CD84* gene expression is under genetic control and influenced by disease activity. These findings provide support that *CD84* genotypes and/or expression may serve as a useful biomarker for response to etanercept treatment in RA, although larger replication studies are required.

Disclosure: J. Cui, None;

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Association of Elevated C5a Levels, but Not the Presence of Anti-Cfh IgG Autoantibodies, with the Deletion of *CFHR3* and *CFHR1* in SLE. Jian Zhao, Seema Kamble, Yun Deng, Magdangal Erika, Daisuke Sakurai, Rongqun Li, Weiling Chen, Jennifer M. Grossman, Bevra H. Hahn and Betty P. Tsao. Division of Rheumatology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA

Background/Purpose: We previously reported association of the deletion of complement regulator factor H related *CFHR3* and *CFHR1* genes (*CFHR3-1Δ*), rather than *CFH* exonic SNPs, with SLE in 15,864 case-control subjects of multiple ancestries ($P=2.9\times10^{-7}$, OR=1.17). Both CFHR3 and CFHR1 suppress C5a generation, and *CFHR3-1Δ* has been associated with the presence of anti-CFH IgG autoantibodies that block CFH C-terminal binding in patients with atypical hemolytic uremic syndrome. To investigate possible functional consequences of *CFHR3-1Δ* in SLE, we tested its association with 1) the presence of anti-CFH IgG autoantibodies, and 2) elevated C5a levels.

Methods: *CFHR3-1Δ* was either directly genotyped by multiplex ligation-dependent probe amplification or deduced by its tag SNP rs6677604 (r^2=1).Levels of plasma C5a and anti-CFH IgG autoantibodies were measured by ELISA. The presence of anti-CFH IgG autoantibodies (anti-CFH+) was defined as higher levels than the mean + 3 SD of those from healthy controls carrying no deletion.

Results: Plasma anti-CFH IgG autoantibodies levels showed no difference between SLE cases and controls (Mean$\pm$SEM: 5.46$\pm$0.074 RU/ml in 75 cases vs. 5.47$\pm$0.063 RU/ml in 45 controls, $P=0.91$), no difference between men and women ($P=0.71$ in cases [9 men and 66 women]; $P=0.23$ in controls [22 men and 23 women]) and no correlation with age (r^2=0.00042 in cases [mean: 43 years old, range: 18–72], $P=0.91$; r^2=0.0010 in controls, $P=0.79$ [mean: 39, range: 20–77]). Anti-CFH+ was only identified in 4 of the 75 studied SLE cases (7%): two of them carried two copies of *CFHR3-1Δ* and the other two had zero copies, showing no association of anti-CFH+ with *CFHR3-1Δ* ($P=1.00$). Although none of the 45 controlswas classified as anti-CFH+, the presence of anti-CFH was not significantly associated with SLE ($P=0.30$) at the current sample size.

Preliminary results of plasma C5a levels were significantly higher in 15 SLE cases carrying two copies of *CFHR3-1Δ* than in 84 cases carrying one or zero copy (Mean$\pm$SEM: 5.23$\pm$0.13 ng/ml vs. 4.86$\pm$0.06 ng/ml, $P=0.018$). We observed no significant difference in plasma C5a levels between 5 controls carrying two copies of *CFHR3-1Δ* and 57 controls carrying one or zero copy (Mean$\pm$SEM: 4.57$\pm$0.29 ng/ml vs. 4.76$\pm$0.09 ng/ml, $P=0.55$), which might be due to the small sample size.

Conclusion: Our preliminary data showed that homozygous deletion of *CFHR3-1Δ*, which predisposes to SLE, was associated with elevated C5a levels in SLE cases, suggesting that this deletion might confer SLE risk by uninhibited production of C5a leading to neutrophil chemotaxis and inflammatory injuries. In contrast, the deletion was not associated with IgG

antibodies to CFH. Further investigation of these association in additional samples is ongoing.

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Inverse Relation Between the *tumor Necrosis Factor* Promoter Methylation and Trascript Levels in Leukocytes From Patients with Rheumatoid Arthritis. James R. Maxwell[1], Lyndsey H. Taylor[2], Richardo A. Pachecho[2], Neil Lawrence[2], Gordon W. Duff[3], M. Dawn. Teare[2] and Anthony G. Wilson[4]. [1]University of Sheffield, Sheffield, United Kingdom, [2]University of Sheffield, United Kingdom, [3]Royal Hallamshire Hospital, Sheffield, United Kingdom, [4]Section of Musculoskeletal Sciences, University of Sheffield, Sheffield, United Kingdom

Background/Purpose: The importance of the epigenetic signature in RA is unclear but levels of methylation of CpG motifs in the *TNF* promoter are known to be important determinants of transcriptional activity.In view of the central importance of this cytokine in RA we hypothesised that methylation of the TNF gene in peripheral blood cells might differ between RA patients and controls.The primary objectives were to determine if CpG motifs in the TNF gene promoter are differentially methylated in RA compared with controls and if TNF mRNA levels correlated with DNA methylation.We also determined whether methotrexate was associated with alterations in genomic or TNF promoter DNA methylation levels.

Methods: A cross-sectional RA population (n=218) and healthy controls (n=312) was used to investigate the primary objective.A second population of RA patients starting MTX were recruited (n=33) and DNA and DAS28 scores were obtained prior to treatment and at 3 months.Methylation of seven *TNF 5'* CpG motifs (-349 to -78) and LINE-1, an assay of genomic mehtylation, in peripheral blood leucocytes were assessed by pyrosequencing and levels of TNF mRNA were measured using quantitative PCR.

Results: Levels of methylation of 4 TNF CpGs (-170, -239, -245, -304) were higher in RA compared with controls (p=7.1×10^{-5} to 1.3×10^{-10}) and TNF mRNA was 58% lower in RA cases (p=1.5×10^{-10}).In both RA and controls negative correlations of *TNF*-245 methylation with TNF mRNA levels were detected (p=0.02 and 0.04 respectively). There was no difference in LINE-1 or TNF methylation in MTX treated patients and no correlation between change in methylation with DAS28 response after 3 months.

Conclusion: Higher levels of methylation of the *TNF* promoter are present in RA leukocytes compared with controls, and levels of TNF mRNA were lower in the patients.Methylation levels of *TNF*-245 were inversely correlated with TNF mRNA levels in both groups.Treatment with MTX was not associated with changes in genomic or *TNF* methylation levels.These results suggest that methylation of the *TNF* promoter is higher in RA compared with controls and that methylation of TNF-245 is an important regulatory mark for TNF expression.

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Genome Wide Association Studies of Knee Osteoarthritis in 2 Large North American Cohorts: A Meta-Analysis with 2667 Cases. Marc C. Hochberg[1], Laura Yerges-Armstrong[2], Changwan (Larry) Lu[2], Michelle S. Yau[1], Braxton D. Mitchell[2], Joanne M. Jordan[3], Youfang Liu[4], Jordan B. Renner[5], T. McSherry[6], D.M. Taverna[6], David Duggan[6], W.J. Mysiw[7] and Rebecca D. Jackson[8]. [1]University of Maryland, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD, [3]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC, [5]University of North Carolina at Chapel Hill Dept of Radiology, Chapel Hill, NC, [6]TGen, Pheonix, AZ, [7]Ohio State University, Columbus, [8]Ohio State University, Columbus, OH

Background/Purpose: A strong genetic contribution to knee osteoarthritis (OA) is widely recognized although few loci have been robustly associated with knee OA susceptibility. To identify genes associated with knee OA, we performed a meta-analysis of genome wide association (GWA) results from two large studies of knee OA: the Genetic Components of Knee OA (GeCKO) Study, an ancillary study from the Osteoarthritis Initiative (OAI), and the Johnston County (JoCo) Osteoarthritis Project.In addition, we attempted replication of 18 single nucleotide polymorphisms (SNPs) previously reported in the literature to be associated with hip or knee OA by the TREAT-OA Consortium, arcOGEN Study and others.

Methods: Cases with knee OA were Caucasians who had at least one knee with definite radiographic OA (Kellgren-Lawrence [KL] grade >=2) at any available visit.Controls were Caucasians who were free of definite radiographic OA in both knees (KL grade <=1) at all available study visits.In total, data from 2014 cases and 953 controls from the OAI and 653 cases and 823 controls from the JoCo Study were included in the analysis. The OAI and JoCo DNA samples were genotyped using the Illumina 2.5M and Illumina 1M genotyping chip, respectively.In both studies imputation was performed using the 1000 genomes reference panel (June 2011 release) and statistical analysis was performed assuming an additive genetic model and adjusting for participant age and sex. Fixed-effects meta-analysis was conducted using METAL.

Results: Over 5.8 million SNP variants present in both the OAI and JoCo datasets and having both high quality 1000 genomes imputation (r^2>0.3) and minor allele frequency of at least 5% were included in the meta-analysis.Ten variants had a meta-analysis P-value $< 1 \times 10^{-6}$ with Odds Ratios ranging from 1.27–1.54.The 10 variants were located in three loci: one on chromosome 11p15.4 upstream of the *TRIM21* gene (encodes for tripartite motif-containing protein 21, an intracellular antibody effector in the proteolysis pathway), and two in non-genic regions of chromosome 11p15.3and chromosome 2q35; the closest genes to the latter region being *MREG* and *FN1* (*FN1* encodes for fibronectin, a glycoprotein that binds to chondrocytes and is involved in cell adhesion and migration).Similar to previously reported findings (Osteoarthritis Cart 2012;20[Suppl 1]:S46), only the rs143383 SNP in *GDF5* (Growth and Differentiation Factor 5) was modestly associated with knee OA (P = 0.006) in the current analysis.

Conclusion: These data support the polygenic nature of the genetic contribution to knee OA. Further analyses will consist of both de novo and in silico replication in other datasets and populations.

Disclosure: **M. C. Hochberg**, Abbott Laboratories, Astra-Zeneca, Bioiberica S.A., Eli Lilly Inc., Genentech/Roche, Merck Inc., Novartis Pharma A.G., Pfizer Inc., Stryker LLC, Xoma., 5; **L. Yerges-Armstrong**, None; **C. Lu**, None; **M. S. Yau**, None; **B. D. Mitchell**, None; **J. M. Jordan**, Algynomics, Inc., 1, Johnson and Johnson, 5, Johnson & Johnson, 2, Interleukin Genetics, Inc., 5, Eli Lilly and Company, 5, Mutual Pharmaceutical Company, 5; **Y. Liu**, None; **J. B. Renner**, None; **T. McSherry**, TGen, 3; **D. M. Taverna**, TGen, 3; **D. Duggan**, TGen, 3; **W. J. Mysiw**, None; **R. D. Jackson**, None.

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Autoimmune Susceptibility Genes Are Regulators of Gene Expression Response to ER Stress. William E. Bernal[1], Michael P. Morley[2] and Vivian G. Cheung[3]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Howard Hughes Medical Institute, Chevy Chase, MD; University of Pennsylvania, Philadelphia, PA

Background/Purpose: Endoplasmic reticulum (ER) stress is caused by excessive demands on the protein-processing capacity of the ER; inefficiencies in response to ER stress lead to human diseases such as ankylosing spondylitis (AS). ER stress has been linked to inflammatory pathways. To study the role of ER stress in disease susceptibility, we identified the genes and pathways involved in ER stress response in human cells, assessed individual variation in these pathways, and mapped DNA sequence variants that influence ER stress response.

Methods: To study ER stress response in B-cells, we exposed the cells from 131 normal unrelated individuals to tunicamycin, a chemical inducer of ER stress, and measured changes in gene expression before and following ER stress. Then, to determine the genetic basis of variation in gene expression response to ER stress, we carried out genetic mapping using B-cells from members of 15 extended families.

Results: We identified 1,523 ER stress-responsive genes which showed at least 1.5 fold changes in gene expression following ER stress.The results showed extensive individual variation in gene expression response to ER stress.For instance, TNFSF13B (BAFF/Blys), a potent activator of B cells, has a mean induction of 1.6-fold but there is a 2.4-fold difference in its level between the individuals with the lowest and highest induction of this gene.XBP1 and DDIT3 (CHOP), which encode key ER stress transcription factors, vary by 5-fold and 9-fold. From our linkage and association studies, we focused our analysis on 778 ER stress-responsive genes and identified DNA sequence variants that regulate the response of 497 of the genes, including TNFSF13B.Regulators of gene expression response to ER stress include susceptibility genes for autoimmune diseases: BLK (systemic lupus erythematosus, rheumatoid arthritis, Kawasaki disease); SVIL (multiple

sclerosis); ANTXR2, RUNX3 and ERAP1 (AS). Genes associated with neurodegenerative diseases in which ER stress is known to play a role in disease pathology–amyotrophic lateral sclerosis, Alzheimer disease, Parkinson disease–are also represented among the regulators.

Conclusion: These results allowed us to identify genes and their regulators involved in ER stress response in human B-cells. The presence of susceptibility genes for autoimmune diseases among the regulators identified in our study implicates ER stress in disease pathology. Identification of TNFSF13B as an ER stress-responsive gene in human B-cells provides further evidence of a link between ER stress and inflammation.

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Zone-Specific Protein Profiles in Human Cartilage Unraveled by a Quantitative Proteomic Approach.
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Background/Purpose: Articular cartilage consists of a single type of cells called chondrocytes, which comprise 2–5% of total tissue mass and an extracellular matrix (ECM) mainly composed of water, proteoglycans and collagens. The tissue function is dependent on the molecular composition of this ECM. Articular cartilage is characterized by a zonal architecture with unique cell phenotypes and ECM properties in the superficial, middle and deep zone. In osteoarthritis (OA), cartilage is thinned, eventually completely degraded, resulting in joint dysfunction and pain. OA is also associated with hypertrophic bone changes with osteophyte formation, subchondral bone remodeling, and, chronic inflammation of the synovial membrane. The final common pathway of cartilage destruction results from a failure of chondrocytes to maintain a homeostatic balance between matrix synthesis and degradation. There is a considerable interest pointed in the characterization of new cartilage specific OA biomarkers for diagnosis and disease progression studies in OA. The aim of this work was to identify and localize proteins in normal cartilage, and compare them to the osteoarthritic tissue in a quantitative way.

Methods: Cartilage samples were obtained from OA patients undergoing joint replacement and normal donors without history of joint disease (n=3). For the localization studies, independent normal cartilage samples (n=3) were sectioned into three layers (superficial, middle and deep). Cartilage proteins were extracted, quantified, digested with trypsin and differentially labelled with iTRAQ isobaric tags. The peptide mixture was separated by two-dimensional LC coupled to MALDI-TOF/TOF mass spectrometry. Identification and relative quantification of the proteins were performed using ProteinPilot 3.0 software.

Results: We identified 220 different proteins in normal articular cartilage. An increased abundance of type VI collagen and small proteoglycans (mimecan, lumican or PRG4) was detected in the superficial layer of cartilage. Several proteins involved in cell adhesion processes were also increased in this layer (gelsolin, vitronectin, tenascins). The middle layer was characterized by a high presence of type II, V, IX and XXVIII collagens, cartilage intermediate layer proteins (CILPs), COMP, vitrin and decorin. Finally, the deep layer exhibited an increased abundance of type I and XI collagens, aggrecan and bone-related proteins (bone sialoprotein 2, osteomodulin, and bone morphogenetic protein 3). Comparison of this normal cartilage proteome with that from OA tissue led to the identification of 281 proteins: 23 were increased in the pathologic tissue (including aggrecan, COMP, complement factors or thrombospondin 1), whereas 36 were decreased in OA cartilage, such as type I, II and VI collagens, proteoglycans (biglycan, PRG4), tenascins or actin.

Conclusion: In summary, more than 300 different human articular cartilage proteins have been mapped according to their presence in the three different tissue layers. 59 of them were altered in OA cartilage when compared to normal tissue. This information would be of high relevance in the search of tissue-specific OA biomarkers.

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Genome-Wide Analysis Reveals a Recessive Association of *ERAP1* Variants with Behçet's Disease and Epistasis Between *ERAP1* and *HLA-B*51*.
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Background/Purpose: We recently performed a genome-wide association study in 1215 patients with Behçet's disease (BD) and 1278 controls from Turkey and found disease-associated variants within the class I region of the *MHC*, and in the *IL10* and *IL23R* loci. However, the combined effects of these loci account for less than 10% of the estimated disease heritability, suggesting other loci are yet to be identified.

Methods: To limit disease heterogeneity, we performed an analysis of the subset of patients with uveitis. In this subset we expanded the association analysis to include 3 genetic models, additive, dominant, and recessive, correcting the threshold for genome-wide significance for the 3 models examined. Confirmatory studies were conducted in our combined GWAS and replication sets of 2017 BD cases and 1875 controls, and in this sample an interaction between two loci was evaluated with a logistic likelihood ratio test comparing a full model (including a multiplicative interaction term) with a reduced model (without the interaction term).

Results: A genome-wide analysis, applying a recessive model, in 420 BD patients with uveitis and 1278 controls revealed one variant located 5′ of *ERAP1*, with near genome-wide significance (rs2927615, p = 1.02×10^{-7}). This effect was not observed with an additive or dominant model. *ERAP1* encodes an endoplasmic reticulum expressed aminopeptidase that plays an important role in trimming and loading intracellular peptides for class I MHC presentation. Fine-mapping with the same samples and replication in an independent collection of 370 Turkish BD cases with uveitis and 630 controls identified two disease-associated non-synonymous variants in *ERAP1*, with the most significant combined p value for rs17482078 (R725Q) = 4.73×10^{-11}, OR = 4.56, 95%CI: 2.88–7.22). Focusing solely on the recessive model, the effect of the variant was corroborated by meta-analysis of the combined 2017 BD cases (including those with and without uveitis) and 1875 controls (p = 4.35×10^{-8}). Furthermore, we identified a genetic interaction between the BD-associated MHC class I allele, *HLA-B*51*, and *ERAP1* (p < 0.0009) in the combined Turkish GWAS and replication samples. *ERAP1* R725Q homozygosity compared with non-homozygosity was associated with an OR for BD of 3.78 (95% CI = 1.94–7.35) in *HLA-B*51* positive individuals versus an OR of 1.48 (95% CI =0.78–2.80) in *HLA-B*51* negative individuals.

Conclusion: A coding variant of *ERAP1*, encoding endoplasmic reticulum expressed amino peptidase 1, recessively confers risk for BD preferentially to individuals carrying the disease-associated *HLA-B*51* allele. Genetic similarity with two other *MHC class I* associated diseases, ankylosing spondylitis and psoriasis (shared loci include *MHC class I*, *IL23R*, *ERAP1* and the *MHC-ERAP1* interaction), suggest shared pathogenic pathways among these diseases.

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Proteomic Shotgun Analysis of Mesenchymal Stem Cells Reveals an Altered Regulation of Proteosomal Proteins in Osteoarthritis Patients.
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Background/Purpose: To describe proteins with a potential role in OA pathogenesis, in this study we have followed a proteomic approach based on a shotgun comparative analysis of Mesenchymal Stem Cells (MSCs) isolated from OA patients and healthy donors.

Methods: MSCs were obtained from bone marrow aspirates at the time of joint replacement surgery of three OA patients (mean age 76.7 years) and three hip fracture subjects without OA (mean age 73.3). Cells were cultured and expanded. Confluent cells at the third passage (approximately 2×10^6) were used for the experiments. After Protein extraction, solubilization and digestion, samples were subjected to a LC-MS shotgun analysis. For protein identification the MS/MS spectra were extracted using the Proteome Discoverer 1.0 software and searched against the MSIPI human database (version 091510) using the Mascot 2.1 program. GeneCodis 2.0 software was used for functional classification of differential proteins.

Results: A total of 1748 proteins were identified. The statistical analysis revealed 123 differentially expressed proteins between OA-MSCs and control MSCs with foldchange values > 2 times at the p < 0.05 level of significance, of which 76 (62%) were upregulated and 47 (38%) were downregulated in OA-MSCs as compared with control cells. Interestingly, five proteosomal proteins, pertaining to the regulation of ubiquitin-protein ligase activity biological function: PSMD2 (2.52), PSMA1 (3.36), PSMB3 (4.56), PSMA3 (7.08) and PSMA4 (13.26) were clearly upregulated.

Conclusion: Given that proteasomal-dependent degradation has a critical role in regulating activities of key osteoblastogenic transcription factors (e.g., RUNX2, ATF4) and signaling pathways (e.g., Hedgehog, BMP, Wnt/β-catenin), upregulation of proteasome subunits and increased activity in MSCs from OA patients might be related to reduced bone mass and/or poor bone tissue quality in OA patients.

Disclosure: J. R. Lamas, None;

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MTHFR Polymorphisms in Systemic Lupus Erythematosus and Rheumatoid Arthritis: Associations with Intima Media Thickness Scores. Clio P. Mavragani[1], Maira Giannelou[2], Ioanna Papadaki[3], Eleni Antypa[4], Dimitrios Ioakeimidis[5], Haralampos M. Moutsopoulos[2] and Michael Koutsilieris[1]. [1]School of Medicine, University of Athens, Athens, Greece, Athens, Greece, [2]School of Medicine, University of Athens, Athens, Greece, [3]General Hospital of Athens "G. Gennimatas", Athens, Greece, [4]General Hospital of Athens, Greece, [5]General Hospital, Greece

Background/Purpose: Previous studies identified polymorphisms in the gene coding for the Methylenetetrahydrofolatereductase (MTHFR) enzyme as genetic contributors for cardiovascular disease in the general population. The purpose of the present study was to determine the prevalence of the MTHFR polymorphisms for either 677 or 1298 allele in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and to investigate whether they associate with carotid and femoral intima media thickness scores and plaque formation.

Methods: 77 consecutive SLE patients, according to the American/European classification criteria, 101 RA patientsand 137 healthy controls were enrolled. All study groups were assessed for MTHFR 677CT or 1298AC genotype. Furthermore, all patients underwent ultrasound determination of intima-media thickness score (IMT) and plaque formation in the carotid and femoral arteries.Data regarding clinical, hematological, serological, immunological information and therapeutic regimens were recorded in all patients. Classical risk factors for cardiovascular disease were also assessed.

Results: The prevalence of MTHFR TT and CC genotypes in the SLE group was 25% (19 of 77 patients) for the 677 allelle and 10.5% (8 of 77 patients) for the 1298 allele, respectively. The corresponding figures for the RA group were 9% (12 of 133) and 9.8% (13 of 133) and the healthy controls 13.13% (18 of 137) and 9.48% (13 of 137), respectively. A significantly higher prevalence for the MTHFR homozygous 677TT mutation was observed in patients with SLE compared to both RA patients and healthy controls (p-values 0.004 and 0.038, respectively). No differences were detected in the prevalence of the different MTHFR genotypes between RA and healthy controls.

Among the 77 SLE patients evaluated for subclinical atherosclerosis, 25 (32.46%) had increased IMT scores (defined as >0.90mm) and 44 (57.14%) had plaque. IMT score was found positively associated with the presence of either the MTHFR 677 or 1298 homozygous mutation (p=0.026). A trend of increased IMT scores was detected in RA patients

sharing the heterozygous MTHFR 1298 AC genotype compared to the other groups.No correlation was found between the development of plaque and the presence of any MTHFR mutation in SLE and RA populations.

Conclusion: The prevalence of MTHFR homozygous mutation for 677 allele was significantly higher in SLE compared to RA and controls. Furthermore, IMT score was found positively associated to homozygocity for either MTHFR 677TT or 1298CC, suggesting the effect of genetic risk factors in the accelerated atherosclerotic disease characterizing SLE patients.

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Functional Genomics of the Human ITGAM Locus. Yebin Zhou[1], Dan C. Bullard[1], Alexander Szalai[2]. Jianming Wu[3] and Jeffrey C. Edberg[4], [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of alabama at birmingham, Birmingham, AL, [3]University of minnesota, St. Paul, MN, [4]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: ITGAM encodes CD11b, the α_M subunit of the Mac-1-$\alpha_M\beta_2$ integrin. Mac-1 has many functions on leukocytes including its role as an adhesion molecule and complement receptor.Genome wide association studies (GWAS) have demonstrated that a non-synonymous SNP in the ITGAM locus, rs1143679 encoding an Arg/His in the extracellular domain, is associated with SLE susceptibility. This variant is in strong linkage disequilibrium with another common non-synonymous SNP (rs1143678 encoding a Ser/Lys in the cytoplasmic domain). We have explored possible functional changes due to these ITGAM variants through analysis of expression level, activation and cell function using ex vivo approach with neutrophils from genotyped healthy donors.

Methods: Neutrophils from healthy control donors genotyped at both rs1142679 and rs1143678 were isolated for ex-vivo functional studies.The phagocytic potential of CD11b variants was probed with complement coated erythrocytes (EAC) and serum treated zymosan (STZ).The adhesion potential of ITGAM variants was assessed in a flow chamber analyzing neutrophil adhesion to both ligand (ICAM-1) and endothelial cells.Total neutrophil CD11b expression and expression of the activation dependent I-domain was assessed by flow cytometry.

Results: In 2424 healthy control donors, we confirmed strong LD between SNP rs1134678 and rs1143679 (D'=0.97, r=0.82).We assessed the functional potential of neutrophils from donors heterozygous for each SNP alone using STZ to determine complement dependent binding and phagocytosis.Variation at either SNP results in a quantitative decrease in STZ phagocytosis and that donors heterozygous for both variants had even lower phagocytosis (repeated measures ANOVA, p<0.04, n=3).Quantitative complement dependent phagocytosis was also significantly decreased in donors homozygous for the variant alleles (39% decrease for STZ, n=3 pairs, p<0.02/38% decrease for EAC, n=3 pairs, p<0.02).In a flow chamber based assay of neutrophil adherence, cells from donors homozygous for the variant alleles of rs1134678 and rs1143679 adhered significantly less than neutrophils for donors homozygous for the common alleles (adherence to ICAM-1/endothelial cells:42% decrease, n=3 pairs, p<0.002/46% decrease, n=4 pairs, p<0.001).

These functional changes in neutrophil Mac-1 function were not attributable to differences in total CD11b expression nor to difference in expression of the activation induced I-domain in donors homozygous for the common vs. variant alleles of ITGAM.

Conclusion: We demonstrate that ITGAM variants rs1143678 and rs1143679 SNP each make separate contributions to alterations in Mac-1 function on human neutrophils.These functional alterations are not caused by differences in quantitative total receptor expression or expression of the I-domain.The study of the functional consequences of allelic variants associated with disease in primary human cells is necessary to fully understand the role of disease associated genetic variants.

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A Genome-Wide DNA Methylation Analysis Reveals Different Methylation Patterns in the OA Disease. Ignacio Rego-Pérez[1], Juan Fernandez-Tajes[1]. Mercedes Fernandez-Moreno[1], Maria Tamayo Novas[2], Alejandro Mosquera Rey[2], Natividad Oreiro[1], Carlos Fernandez-Lopez[1], Jose Luis Fernandez Garcia[2] and Francisco J. Blanco[1]. [1]INIBIC-Hospital Universitario A Coruña. Rheumatology Division. Genomic Group, A Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña. Genetic Deparment., A Coruña, Spain

Background/Purpose: DNA methylation is a basic mechanism involved in epigenetic regulation that affects gene transcription by the addition of a methyl group to the cytosine residue within a CpG dinucleotide to form methylated cytosine. The objective of this work is to identify and analyze the genome-wide DNA methylation profiles of human articular chondrocytes from a population-based case-control study of OA.

Methods: DNA methylation profiling was performed using the Infinium HumanMethylation27 beadchip (Illumina Inc.), which allows interrogation of 27,578 highly informative CpG loci. Previously, cartilage isolated DNA from 23 OA patients and 19 healthy controls was bisulfite-modified, using the EZ DNA methylation kit (Zymo Research) and hybridized according to the manufacturerxs instructions. DNA methylation b-values were normalized using GenomeStudio v3.0 (Illumina Inc.). Appropriate bioinformatics analyses were carried out using both R bioconductor software packages and Babelomics suite v4.2 (*babelomics.bioinfo.cipf.es*).

Results: A first approach based on an unsupervised clustering method for the most variable CpG loci (n=508) showed three distinct groups of samples called cluster 1, cluster 2 and cluster 3. Specifically, cluster 2 formed a particularly tight cluster with a characteristic DNA methylation profile (Figure 1). The analyses of the biological relevance of the differentially methylated genes in cluster 2 compared with non-cluster 2 by means of a gene set enrichment approach, showed that some of the biological processes significantly altered were those related to cellular adhesion, morphogenesis/angiogenesis and regulation of cell proliferation, all of them hypermethylated in cluster 2; on the contrary, those genes related to cytokine secretion/production as well as immune response and inflammation appeared significantly hypomethylated in cluster 2.
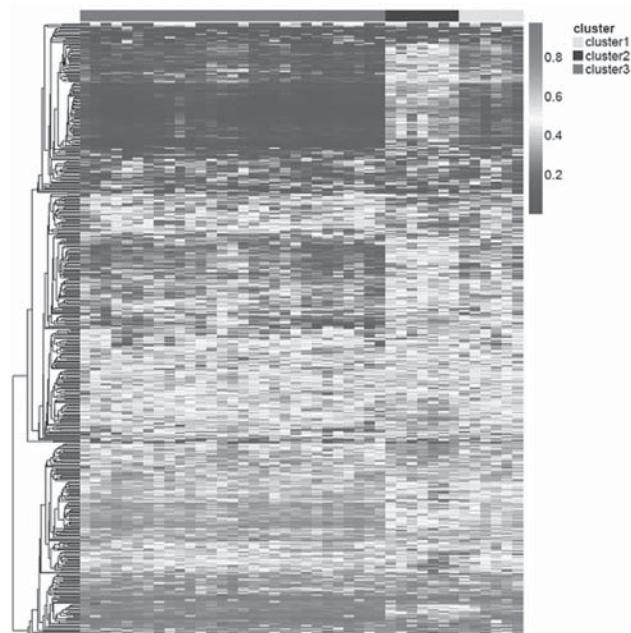
Figure 1. Heatmap showing the three distinct clusters. Cluster 2 shows a characteristic DNA methylation profile clearly different from the other two clusters.

Conclusion: The genome-wide methylation analysis shows a clearly distinct epigenetic profile for OA patients. The DNA methylation profile could be one of the reasons of the existence of different forms OA and could also be related to both the prevalence and progression of this disease.

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The Genome-Wide Expression of Human Osteoarthritic Cartilage Shows A Differential Pattern Between Two Subgroups of OA Patients. Ignacio Rego-Perez, Juan Fernandez-Tajes. Angel Soto-Hermida, Mercedes Fernandez Moreno, Maria Eugenia Vazquez Mosquera, Natividad Oreiro, Carlos Fernandez-Lopez, Estefania Cortes Pereira, Sara Relaño-Fernandez and Francisco J. Blanco, INIBIC-Hospital Universitario A Coruña. Genomic Group. Rheumatology Division., A Coruña, Spain

Background/Purpose: Many genes, many of them still unknown, are involved in the etiology and development of OA. Today, different tools are available to try to identify some of the key genes related to the OA process. Therefore, the objective of this work is to perform a genome-wide expression assay in order to identify different expression profiles in the OA disease

Methods: Total RNA from OA cartilage samples was isolated with RNeasy Kit (Qiagen, Madrin, Spain) following manufacturerxs instructions. RNA was checked for integrity and purity with the Agilent Bioanalyzer (Agilent Technologies) and NanoDrop spectrophotometer (Thermo Scientific). 150 nanograms of total RNA were used for cDNA synthesis using the Ambion WT Expression kit (Ambion). The fragmented cDNA was hybridized against the Human Gene 1.1 ST array strip (Affymetrix) and scanned using the GeneTitan system (Affymetrix). Quality controls, normalization, pre-processing, differential gene expression and functional analyses were carried out with Bioconductor packages using R software.

Results: Human Gene 1.1 ST Array, which interrogates more than 28,000 well-annotated genes of 33,297 probes, was used for studying the genome wide expression profile of 23 OA-patients cartilage samples. A non-specific filtering was previously applied for removing those probes with non-annotation information and with low intra-array variation. An unsupervised machine learning approach revealed a group of samples highly different (Figure 1). The differential expression analysis between this cluster, comprising a total of six OA-patients, and the rest of the samples allowed for the identification of 176 differentially expressed probes with an adjusted *p value* below 0.0001. The analysis of the biological processes related to these differentially expressed genes showed that inflammation and immune processes were the main pathways found to be altered when a gene set enrichment analysis was applied.
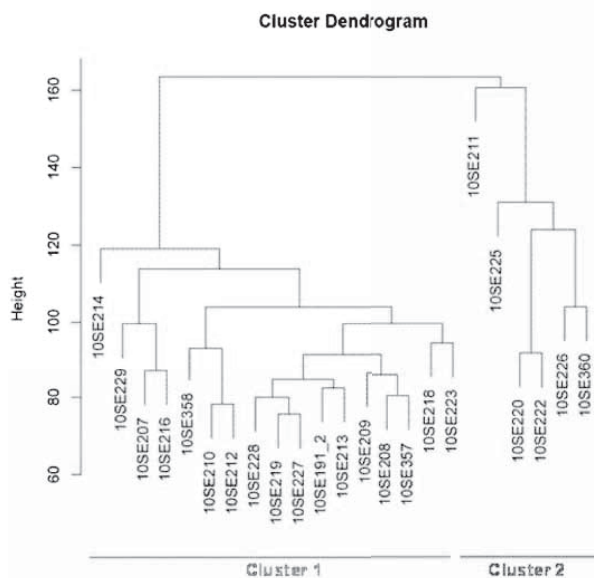
Figure 1. Dendrogram showing the two different groups of OA patients. Cluster 2 shows a characteristic expression profile among OA patients.

Conclusion: The genome-wide expression analysis shows a clearly distinct profile for a group of OA patients. Both inflammation and immune response processes appeared to be significantly altered and revealed as key factors in the development of the OA disease.

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Monday, November 12

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Genetic Effects of HLA-DRB1, IL4R, and FcγRIIb On Long-Term Treatment Responses in Patients with Early Rheumatoid Arthritis: 78-Week Results of a Phase 4 Study. Alla Skapenko[1], Josef S. Smolen[2], Arthur Kavanaugh[3], Vipin Arora[4], Hartmut Kupper[5] and Hendrik Schulze-Koops[1]. [1]University of Munich, Munich, Germany, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [3]UCSD School of Medicine, La Jolla, CA, [4]Abbott, Abbott Park, IL, [5]Abbott GmbH and Co. KG, Ludwigshafen, Germany

Background/Purpose: Previous analyses suggested that the HLA-DRB1 shared epitope (SE), and the IL4R V50I and the FcγRIIb I232T single nucleotide polymorphisms (SNPs) affected response to adalimumab (ADA) plus methotrexate (MTX) at 26 weeks.[1] Their effect on long-term responses is unclear. To examine 78-wk clinical responses according to 3 candidate loci: HLA-DRB1 SE, and IL4R I50V and FcγRIIb I232T SNPs.

Methods: MTX-naïve patients (pts) ≥18 yrs with RA <1 yr, active disease [DAS28(CRP)>3.2, ESR≥28 mm/hr or CRP≥1.5 mg/dL], and >1 erosion, RF+, or anti-CCP+ were randomized to ADA+MTX or placebo (PBO)+MTX for 26 wks (Period 1, P1). Pts who achieved a stable LDA target (DAS28<3.2 at wks 22 & 26) with ADA+MTX were re-randomized to continue ADA+MTX (ADA Continuation arm) or have ADA blindly withdrawn (ADA Withdrawal arm) for 52 wks (P2). Pts who achieved the stable LDA target with PBO+MTX continued blinded therapy (MTX Continuation arm). Pts who did not achieve the stable LDA target with initial combination therapy or MTX monotherapy were offered open-label (OL) ADA+MTX (OL ADA Carry On and Rescue ADA arms, respectively).

Results: Baseline demographics were similar across alleles. The **Table** shows the percentage of pts achieving DAS28<3.2 at wk 78. There were no consistent patterns for the IL4R alleles in any group. While limited by small sample sizes, pts with FcγRIIb-CC appeared to have higher responses at wk 78 among groups initially exposed to ADA+MTX during P1. The positive influence of SE was apparent at wk 78 in groups originally exposed to ADA+MTX, particularly in pts who did not achieve the stable LDA target at wks 22 & 26 but continued ADA+MTX. However, this pattern was not observed in pts who failed to achieve the target with MTX and were subsequently treated with ADA+MTX.

Table. Percentage of Pts with DAS28 <3.2 at Week 78, n/N (%), non-responder imputation

Treatment	HLA-DRB1 SE			IL4R			FcγRIIb		
	0x	1x	2x	AA	AG	GG	TT	TC	CC
ADA WITHDRAWAL	21/28 (75.0)	25/36 (69.4)	17/22 (77.3)	23/31 (74.2)	33/44 (75.0)	7/11 (63.6)	43/63 (68.3)	17/20 (85.0)	3/3 (100)
ADA CONTINUATION	16/22 (72.7)	36/45 (80.0)	18/20 (90.0)	23/31 (74.2)	33/39 (84.6)	14/17 (82.4)	54/67 (80.6)	14/18 (77.8)	2/2 (100)
OL ADA CARRY ON	29/81 (35.8)	49/113 (43.4)	18/36 (50.0)	28/68 (41.2)	49/109 (45.0)	19/53 (35.8)	87/200 (43.5)	8/29 (27.6)	1/1 (100)
MTX CONTINUATION	30/40 (75.0)	25/38 (65.8)	10/15 (66.7)	18/24 (75.0)	31/44 (70.5)	16/25 (64.0)	47/69 (68.1)	18/24 (75.0)	0/0 (0)
RESCUE ADA	59/115 (51.3)	80/148 (54.1)	19/42 (45.2)	49/93 (52.7)	83/164 (50.6)	26/48 (54.2)	117/225 (52.0)	40/76 (52.6)	1/4 (25.0)

Conclusion: Regardless of genetic background, wk 78 responses were generally higher for pts who achieved the stable LDA target at wks 22 & 26. The positive effects of HLA-DRB1 SE and FcγRIIb-CC in response to ADA+MTX previously noted at wk 26 were less apparent at wk 78, but noticeable in pts who failed to achieve the target. Further, while SE predicted clinical response to ADA+MTX, particularly when combined with IL4R alleles, it had no influence on the ability to withdraw ADA in pts who achieved LDA. These findings may indicate that genetic factors have a stronger influence on initial treatment response than on sustained disease control.

Reference

1. Skapenko A, et al. EULAR 2011 [THU0309].

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Genetic Predictors of Methotrexate Efficacy and Toxicity in Early Rheumatoid Arthritis: Results From the Treatment of Early Aggressive Rheumatoid Arthritis Trial. Stella Aslibekyan[1], Elizabeth Brown[2], Richard J. Reynolds[1], David T. Redden[1], Sarah L. Morgan[3], Joseph Baggott[1], Jin Sha[1], Larry W. Moreland[4]. James R. O'Dell[5], Jeffrey R. Curtis[6], S. Louis Bridges Jr.[7] and Donna K. Arnett[1], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama at Birmingham, Birmingham, AL, Birmingham, AL, [3]University of Alabama Birmingham, Birmingham, AL, [4]University of Pittsburgh, Pittsburgh, PA, [5]Univ of Nebraska Med Ctr, Omaha, NE, [6]Univ of Alabama-Birmingham, Birmingham, AL, [7]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Methotrexate (MTX) has emerged as first-line therapy for early moderate to severe rheumatoid arthritis (RA), but individual variation in treatment efficacy and toxicity remains unexplained. We test the hypothesis that genetic markers in genes involved in drug metabolism, excretion, and transport are associated with MTX response in early RA.

Methods: Treatment of Early Aggressive Rheumatoid Arthritis Trial participants (n=471) were analyzed for 863 markers spanning 224 genes from key pharmacogenetic pathways. Multiple regression models were fit with efficacy (Disease Activity Score on 28 joints at 24 weeks) and toxicity (self-report of any side effects or infections) as outcomes, adjusted for age, sex, race, and treatment, and single markers as predictors. Penalized regression models were used to test joint associations of markers and/or covariates with the outcomes.

Results: The strongest genetic associations with efficacy were in the CHST11 gene (five markers with P <0.0024), encoding carbohydrate (chondroitin 4) sulfotransferase 11. Top markers associated with MTX toxicity were in the cytochrome p450 superfamily genes CYP20A1 and CYP39A1, solute carrier genes SLC22A2 and SLC7A7, and the mitochondrial aldehyde dehydrogenase gene ALDH2 (P<0.004). Results from the penalized regression models included only genetic markers for the toxicity outcome, while clinical covariates were stronger predictors of MTX efficacy. The selected markers explained more variance in toxicity (9%) than efficacy (4%).

Conclusion: We identified several novel and biologically relevant genetic markers associated with MTX response in early RA. These preliminary findings could inform future development of personalized therapeutic approaches.

Disclosure: S. Aslibekyan, None; **E. Brown**, None; **R. J. Reynolds**, None; **D. T. Redden**, None; **S. L. Morgan**, None; **J. Baggott**, None; **J. Sha**, None; **L. W. Moreland**, None; **J. R. O'Dell**, None; **J. R. Curtis**, Roche/Genetech, UCB, Centocor, CORRONA, Amgen Pfizer, BMS, Crescendo, Abbott, 5, Roche/Genetech, UCB, Centocor, CORRONA, Amgen Pfizer, BMS, Crescendo, Abbott, 2; **S. L. Bridges Jr.**, None; **D. K. Arnett**, None.

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Evidence of Novel Genetic Predictors of Methotrexate Efficacy in Rheumatoid Arthritis. Stella Aslibekyan[1], Maria I. Danila[2], Jin Sha[1], David T. Redden[1], Richard J. Reynolds[1], Elizabeth Brown[3], Laura B. Hughes[1], Molly S. Bray[1], Sarah L. Morgan[4], Larry W. Moreland[5]. James R. O'Dell[6], Jeffrey R. Curtis[2], Robert P. Kimberly[1], Lindsey A. Criswell[7], Robert M. Plenge[8], S. Louis Bridges Jr.[9] and Donna K. Arnett[1], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Univ of Alabama at Birmingham, Birmingham, AL, Birmingham, AL, [4]University of Alabama Birmingham, Birmingham, AL, [5]University of Pittsburgh, Pittsburgh, PA, [6]Univ of Nebraska Med Ctr, Omaha, NE, [7]University of California San Francisco, San Francisco, CA, [8]Brigham and Women's Hospital, Boston, MA, [9]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Methotrexate (MTX), a disease-modifying anti-rheumatic drug used as first-line therapy in rheumatoid arthritis (RA), is characterized by considerable heterogeneity in individual treatment response. We tested the hypothesis that polymorphisms in RA susceptibility genes and MTX metabolism pathways are associated with MTX efficacy and toxicity.

Methods: Data from a combined population of three MTX trials (Treatment of Early Aggressive RA Trial; Immunex Early RA Trial; UAB Folic Acid Supplementation Trial, total subjects = 633) were analyzed for 3,127 genetic markers previously linked to RA risk or MTX metabolism pathways, with MTX efficacy (defined as the change joint count scores over 24 weeks of MTX therapy) and toxicity (defined as self-report of any adverse events) as outcomes. Gene-based tests were conducted to complement single marker analyses. All statistical models were adjusted for age, sex, race, and treatment as fixed effects, and for study as a random effect; the efficacy models were additionally adjusted for baseline disease activity.

Results: In the MTX efficacy models, the strongest signals were observed with variation in genes encoding efflux transporters (*ABCC1*; gene-based P= 1.4×10–4), B cell surface antigen (*CD40,* gene-based P=3.8×10–4), and immunoglobulin receptors (*FCGR2A*, *FCGR3A*; gene-based P= 1.5×10–5 and P= 1.6×10–5 respectively). Although no genetic variants reached statistical significance in the models of adverse effects associated with MTX therapy, the top hits included markers near *GFRA2* (rs12549890, P= 2.8×10–3), the *ABCA12* transporter (rs4673907, P= 4.6×10–3), and multiple SNPs in *ADK* included in the adenosine pathway.

Conclusion: This study provides preliminary identification of several novel targets relevant to MTX metabolism in RA. These findings will inform future studies aimed at developing pharmacogenetic tools to predict response to MTX therapy.

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Association Study of Genetic Risk Variants for Psoriasis in a Large Cohort of Psoriatic Arthritis, Psoriasis and Controls of the Spanish Population and Association with Relevant Clinical Subphenotypes. J. D. Cañete[1], Jose Luis Fernandez-Sueiro[2]. Raimon Sanmarti[3], Jesus Rodriguez[4], Jordi Gratacós[5], Rubén Queiro[6], Juan Carlos Torre-Alonso[7], Jose Perez Venegas[8], Santiago Muñoz-Fernandez[9], Carlos Gonzalez[10], Carlos Montilla[11], Daniel Roig[12], Alba Erra[13], Isabel Acosta[14], Antonio Fernández-Nebro[15], Pedro Zarco[16], Arnald Alonso[17], María América López-Lasanta[17], Antonio Julià[17], Raül Tortosa[17] and Sara Marsal[18], [1]Hospital Clínic de Barcelona, Barcelona, Spain, [2]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Hospital Universitari de Bellvitge, Barcelona, Spain, [5]Hospital Parc Taulí, Sabadell (Barcelona), [6]Hospital Universitario Central de Asturias, Oviedo, Spain, [7]Hospital Monte Naranco, Oviedo, Spain, [8]Hospital del SAS de Jerez de la Frontera, Jerez De La Frontera, Spain, [9]Hospital Infanta Sofía, Madrid, Spain, [10]Hospital Gregorio Marañon, Madrid, Spain, [11]Hospital Universitario de Salamanca, Salamanca, Spain, [12]Hospital Universitari de Bellvitge, Hospitalet de Llobregat- Barcelona, Spain, [13]Hospital San Rafael, Barcelona, Spain, [14]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [15]Hospital Regional Universitario Carlos Haya, Málaga, Spain, [16]Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain, [17]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [18]University Hospital Vall d'Hebron, Barcelona, Spain

Background/Purpose: Psoriatic Arthritis (PsA) is a complex disease with a substantial genetic risk component (first-degree relative risk 55). Recently, Genomewide Association Studies (GWAS) have expanded the number of risk loci for Psoriasis (Ps) in >20 new loci.We have studied the association of Ps risk loci in PsA and purely cutaneous Ps (PsC). We have also analyzed the genetic association with several subphenotypes of clinical relevance.

Methods: Loci showing the strongest statistical evidence of association to Ps were selected (n=32). For each locus, the SNP having the highest statistical evidence was genotyped using Taqman technology in a cohort of n = 955 PsA, 1,050 PsC and 1,497 hypernormal controls of the Spanish population. According to each subphenotype variable, the genetic association was performed using the chi-square test, logistic regression or linear regression.

Results: We have replicated the association to *COG6* and *SERPINB8* loci with Ps for the first time in a Caucasian population. We have identified, for the first time, an association of PsA with variation at *IFIH1*, *DPP6* and *COG6*. Analyzing the association with other clinically relevant subphenotypes we have identified a strong association of *LCE3D* locus with the severity of cutaneous affection ($P<$ 2e-5). We have also found a significant association of *IL1RN* gene with nail disease ($P < $3e-4).

Conclusion: Our findings show that common genetic variants associated to a complex phenotype like PsV influence PsA as well as different subphenotypes of high clinical relevance.

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Identification of New Epistatic Interactions with the *HLA* Region in the Genetic Etiology of Psoriasis and Psoriatic Arthritis. Sara Marsal[1], Juan D. Cañete[2], Jose Luis Fernandez-Sueiro[3]. Raimon Sanmarti[2], Jesus Rodriguez Moreno[4], Jordi Gratacós[5], Rubén Queiro[6], Carlos Montilla[7], Juan Carlos Torre-Alonso[8], Jose Perez Venegas[9], Santiago Muñoz-Fernández[10], Carlos M. Gonzalez[11], Daniel Roig[12], Alba Erra[13], Isabel Acosta[14], Antonio Fernández-Nebro[14], Pedro Zarco[15], Arnald Alonso[16], María América López-Lasanta[16], Raül Tortosa[16] and Antonio Julià[16], [1]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [2]Hospital Clínic of Barcelona, Barcelona, Spain, [3]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [4]Hospital Universitario de Bellvitge., Barcelona, Spain, [5]Hospital Parc Taulí, Sabadell (Barcelona), [6]Hospital Universitario Central de Asturias, Oviedo, Spain, [7]Hospital Universitario de Salamanca, Salamanca, Spain, [8]Hospital Monte Naranco, Oviedo, Spain, [9]Hospital del SAS de Jerez de La Frontera, Jerez De La Frontera, Spain, [10]Hospital Universitario Infanta Sofía, San Sebastián de los Reyes (Madrid), Spain, [11]Hospital Gregorio Maranon, Madrid, Spain, [12]Hospital Universitari de Bellvitge, Hospitalet de Llobregat-Barcelona, Spain, [13]Hospital San Rafael, Barcelona, Spain, [14]Hospital Regional Universitario Carlos Haya, Málaga, Spain, [15]Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain, [16]Vall d'Hebron Hospital Research Institute, Barcelona, Spain

Background/Purpose: Psoriatic Arthritis (PsA) is a complex disease and is present in 11% in patients with Psoriasis (Ps). Recently, Genomewide Association Studies (GWAS) have expanded the number of risk loci for Ps in >20 new loci. Two of these genes, *ERAP-1* and *HLA-C*, have been shown to interact epistatically in the risk to develop Ps. We have studied the presence of new genetic interactions between Ps risk lci with the *HLA* region in Purely cutaneous Psoriasis (PsC) and PsA.

Methods: Within each Ps risk locus (n=31), the SNP having the highest statistical evidence was selected. The 31 SNPs were genotyped using Taqman technology in a cohort of n = 955 PsA, 1,050 PsC and 1,497 hypernormal controls of the Spanish population. The presence of statistically significant gene-gene interactions was performed using a logistic regression model with three parameters to determine the presence of interaction at the allelic level.

Results:: We replicated the previously described interaction of *HLA-C* and *ERAP1* in the PsC cohort but not in the PsA cohort. We identified, for the first time, a significative epistatic association between *HLA-C* and *SERPINB8*. Microarray gene expression studies on cutaneous biopsies corroborate the presence of this interaction at a functional level. In PsA, no statistically significant interactions where identified with variation at *HLA-C*. However, 6 of the studied genes showed a significant ($P<0.05$) association with *HLA-B27* positivity.

Conclusion: The present study has identified new genetic interactions associated with the risk to develop PsC and PsA. The functional study of these interactions will improve our knowledge of the biological basis of these complex diseases.

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Epistatic Interaction Between *BANK1* and *BLK* in Rheumatoid Arthritis: Results From a Large Trans-Ethnic Meta-Analysis. Emmanuelle Genin[1], Baptiste Coustet[2], Yannick Allanore[3], Maria Teruel[4], Arnaud L. Constantin[5], Shigeto Tohma[6], O. Vittecoq[7], Hiroshi Furukawa[8], Alejandro Balsa[9]. Thierry Schaeverbeke[10], Miguel Angel González-Gay[11], Gilles Chiocchia[12], Naoyuki Tsuchiya[13], Javier Martin[14] and Philippe Dieude[15], [1]INSERM UMR-S946, Paris, France, [2]Université Paris Descartes, Hopital Cochin, Paris, France, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [4]Instituto de Parasitologia y Biomedicina Lopez-Neyra, CSIC, Granada, Spain, [5]Purpan University Hospital, Toulouse Cedex 9, France, [6]Sagamihara National Hospital, Sagamihara City, Japan, [7]University Hospital, Rouen, France, [8]Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan, [9]La Paz Hospital. IdiPaz, Madrid, Spain, [10]Groupe Hospitalier Pellegrin, Bordeaux, France, [11]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [12]Institut Cochin - INSERM U1016 - CNRS (UMR 8104), Paris, France, [13]Molecular and Genetic Epidemiology Laboratory, University of Tsukuba, Tsukuba, Japan, [14]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [15]APHP, Hopital Bichat, Paris, France

Background/Purpose: *BANK1* and *BLK* belong to pleiotropic genes and recently a genetic and physical interaction between *BANK1* and *BLK* has been detected in systemic lupus erythematosus. Although *BLK* has been reproducibly identified as a RA risk factor, conflicting results have been reported regarding the contribution of *BANK1* in RA susceptibility. To ascertain the real impact of *BANK1* on RA genetic susceptibility we performed a large meta-analysis. In addition, we tested for an epistatic interaction between *BLK* and *BANK1* in RA susceptibility.

Methods: We performed a large trans-ethnic meta-analysis including data from 8,898 RA patients and 15,479 controls genotyped for *BANK1* rs10516487 and data from 3,641 RA cases and 3,710 controls genotyped for *BANK1* rs3733197. *BLK* rs13277113 and *BANK1* genotypes available from 1,901 RA patients and 1,898 ethnically matched controls coming from France, Spain and Japan were used to test for epistasis by logistic regression analysis.

Results: The meta-analysis provided evidence for an association between RA and *BANK1* rs3733197 G risk allele (OR=1.11 95% CI[1.02–1.21], P=0.012). An epistatic interaction between *BLK* rs13277113 and *BANK1* rs3733197 was detected (P_{ep}=0.037). The association between the *BANK1* rs3733197 G risk allele and RA was restricted to individuals carrying the *BLK* rs13277113 GG genotype:OR=1.21 95%CI[1.04–1.41], P=0.015

Conclusion: This study confirms *BANK1* as a RA susceptibility gene and provides for the first time, evidence for epistasis between *BLK* and *BANK1*. Our results illustrate the concept of pleiotropic epistatic interaction suggesting that BLK and BANK1 might play a role in RA pathogenesis.

ACR/ARHP Poster Session B
Biology and Pathology of Bone and Joint
Monday, November 12, 2012, 9:00 AM–6:00 PM

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CNstream2: Improved SNP and CNV Genotyping Reveals New Loci Associated with Rheumatic Diseases. Arnald Alonso, Antonio Julià, Raül Tortosa and Sara Marsal. Vall d'Hebron Hospital Research Institute, Barcelona, Spain

Background/Purpose: In Genome-Wide Association Studies (GWAS), the performance of the genotyping algorithm is crucial to identify new SNPs associated to disease risk. Recently, new methods have been developed to exploit SNP-oriented microarrays in order to genotype Copy Number Variations (CNVs), albeit with a reduced performance compared to SNPs. In this study we present CNstream2, a method for both SNP and CNV genotyping that achieves a superior accuracy compared to other established methods. In addition, we have identified several new CNV loci that are in high linkage disequilibrium (LD) with SNPs previously associated to rheumatic diseases.

Methods: CNstream2 is a substantially improved version of our previous CNstream software which achieves a superior accuracy in both SNP and CNV genotyping compared to other well-established methods (i.e. GenoSNP/GenCall for SNP genotyping and PennCNV/QuantiSNP for CNV genotyping). All these improvements have been assessed in different Illumina platforms using public microarray data from HapMap samples. SNP genotypes from the 1000 Genomes Project (1KGP) and CNV genotypes from recent studies using CNV-oriented technologies have been used as golden standards for performance comparisons. In order to show the power of CNstream2, we performed a correlation analysis between SNPs associated with rheumatic diseases reported by the GWAS catalog and the CNVs identified by CNstream2 over the same HapMap samples using HumanOmni1 data. All the CNV loci that obtained an r2>0.7 (N=16) were reported in this study.

Results: CNstream2 obtained a high performance both on SNP and CNV genotyping. When assessing SNP genotyping accuracy, CNstream2 obtained an average gain of 0.20% with respect to GenoSNP and GenCall (representing a gain of 1,000–2000 genotyped SNPs per GWAS). On the other hand, when comparing CNV calls obtained by CNstream2, PennCNV and QuantiSNP within previously characterized CNV loci, CNstream2 exceeded by an average of 20% the number of correctly captured loci compared to its competitors. The LD analysis between SNPs associated to rheumatic diseases and CNVs detected by CNstream2 revealed 16 highly correlated SNP-CNV pairs. From these, 11 pairs were located in the HLA region and were associated to several rheumatic diseases. Given the strong correlation of the CNV with the disease risk SNP, additional functional studies exploring its relevance are warranted. Outside the *HLA* region, 5 new CNVs from loci associated with rheumatological diseases were identified. From these, a previously unidentified intronic deletion in Rheumatoid Arthritis risk gene *PADI4*, showed a strong association.

Conclusion: After an exhaustive evaluation of CNstream2 performance we can conclude that this new software tool provides an unprecedented accuracy both in SNP and CNV genotyping. Using CNStream2 on publicly available data, we have identified new CNVs on loci previously associated to rheumatological diseases which could likely explain the observed disease risk association.

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Microrna Expression Profiles in Peripheral Blood Mononuclear Cells of Early Onset Psoriatic Arthritis. G. Ciancio[1], Manuela Ferracin[2], Barbara Zagatti[2], Elena Saccenti[2], Valentina Bagnari[1], Ilaria Farina[1], Matteo Colina[3], Marco Seri[4], Francesco Trotta[1], Massimo Negrini[2] and Marcello Govoni[1]. [1]Rheumatology Unit-Azienda Ospedaliera-Universitaria Sant'Anna, Ferrara, Italy, [2]Laboratory for Technologies of Advanced Therapies (LTTA), University of Ferrara, Ferrara, Italy, [3]Section of Internal Medicine A.Ospedale Maggiore, Bologna, Italy, [4]Medical Genetics Unit, Bologna, Italy

Background/Purpose: Micro-RNAs (miRNAs) are small non-coding RNAs that negatively regulate gene expression. It is known that an altered miRNA expression plays an important role in cancer. A new emerging role for miRNAs has been evidenced in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA), in which miR-146a has gained increasing relevance, psoriasis and systemic lupus erithematosus. No data about the miRNA expression profile in psoriatic arthritis (PsA) are available to date. In a preliminary study, we identified 16 miRNAs (9 up- and 7 down-regulated) differentially expressed in a sample of 13 early PsA *vs* 7 healthy controls (submitted data). Now, our main purpose is to validate the identified miRNA signature in a larger series of patients and controls.

Methods: Blood samples from 21 consecutive patients with early, active and naïve from treatment PsA (disease duration < 6 months; M:9; W:12; mean age:39,3±8,1; DAS 44: 4,12 ± 0,29; SPARCC Enthesitis Index score: 2 ± 0.5) were collected. As controls, 12 random healthy volunteers (M:4; W:8; mean age 34 ± 11) were recruited. The expression levels of 723 mature miRNAs in peripheral blood mononuclear cells (PMBC) were investigated in all patients and controls by using an Agilent miRNA microarray. Differentially expressed genes were identified by applying a two-tailed unpaired t-test (Graph-Pad).

Results: We identified 3 microRNAs (miR-21,miR-34a and miR-21*),

previously described as upregulated in PsA as significantly upregulated also in this new cohort of patients (p 0.01-0.001) compared to controls.

Conclusion: A 3-miRNA signature was identified in patients with early active PsA. The upregulated miR-21, miR-34a and miR-21* appear of great interest to understand the underlying pathogenic processes of PsA. Moreover, their expression in patients with active disease makes them attractive as potential biomarkers.

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Role of Particular Class I MHC Haplotypes in Determining Different Traits within the Psoriatic Arthritis Phenotypes. Muhammad Haroon[1], Jon T. Giles[2], Robert Winchester[3] and Oliver M. FitzGerald[1]. [1]Dublin Academic Medical Center, St. Vincent's University Hospital, Dublin, Ireland, [2]Columbia University Medical Center, New York, NY, [3]Columbia University, New York, NY

Background/Purpose: A rigorously ascertained psoriatic arthritis (PsA) cohort demonstrated considerable genetic heterogeneity and provided preliminary evidence that MHC genes determine quantitative traits within the PsA phenotype with different patterns of MHC effect.

Methods: We now extend these findings by performing detailed clinical phenotyping of PsA cases to better characterize the clinical features associated with particular HLA class I alleles and their haplotypes.

Results: A total of 150 PsA patients [mean age 52 ± 12 years; 46% male; mean PsA duration$=25 \pm 12$ years; 45% with axial involvement; 25% with sacroiliitis; 41% with radiographic erosions; median PASI$=1.2$] were studied. In univariate analysis, the inheritance of B*27:05 was apparently associated with a more severe joint disease phenotype including: joint erosions, the requirement for TNF therapy and axial disease manifestations such as spine involvement and sacroiliitis that were temporally preceded by or coincident with skin disease. In striking contrast, the presence of HLA-C*06, whether on a B*57-C*06 or B*37-C*06 haplotype, was associated with a considerable delay in the development of arthritis, and conferred a reciprocal phenotype of significant negative associations with arthritis severity, including the presence of erosions, the requirement for TNF inhibitor therapy, and axial disease. B*08 and B*08-C*07 (EH8.1) were correlated with joint deformities, erosions, TNF inhibitor requirement, osteolysis, and dactylitis, developing after the appearance of psoriasis, suggesting this haplotype denotes a more severe but delayed arthritic phenotype.

Surprisingly, in contrast to the uniform association of disease susceptibility with B*27, the association with phenotypic features was not uniform across all B*27 alleles, and was mainly accounted for by the B*27-C*01 (EH27.1) haplotype and not B*27-C*02 (EH27.2), suggesting the influence of additional genetic effects on EH27.1. The predictive value of these haplotypes was confirmed by logistic regression, which after adjustment for confounders showed, for example, the probability of developing sacroiliitis was almost completely determined by the inheritance of EH27.1, EH8.1 or C*05, figure A. Similarly, the probability of developing peripheral joint erosions was strongly associated with the presence of EH27.1, EH8.1 or C*03, figure B.
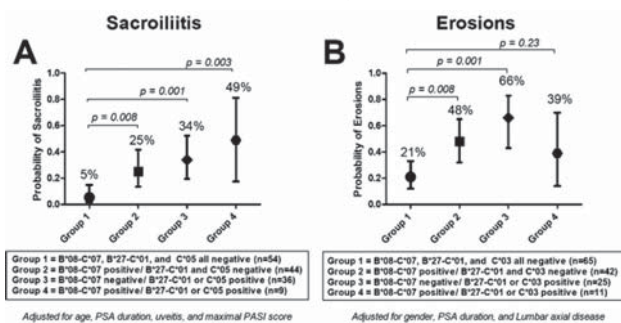
Conclusion: Certain HLA alleles, and, most strikingly particular haplotypes, contribute importantly to the magnitude of traits comprising the diverse phenotypes of PsA, but this contribution does not completely parallel the role of these alleles or haplotypes in determining susceptibility.

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A Unique Single Nucleotide Polymorphism in the 3' UTR of the MED29 Gene On Chromosome 19 Is Associated with the Clinical Outcome of Different Biologic Response Modifiers. Susanne Drynda, David Leesch, Marietta Gloetzner and Joern Kekow. Univ of Magdeburg, Vogelsang-Gommern, Germany

Background/Purpose: Due to the wide range of highly specific and effective biologic response modifiers that are available today for the treatment of RA it has become of great importance to identify biomarkers for the prediction of therapy outcome, supporting an individualized therapy. Most studies in this field analysed potential markers for a single biological or substance group, respectively. In this study we analysed the association of genotypes of the single nucleotide polymorphism (SNP) rs10414216 in the 3' UTR of the MED29 gene with the outcome of two biologic response modifiers, targeting different pathways.

Methods: We studied 275 RA patients treated first with the TNF-blocker etanercept (ETN) and a subgroup of 62 patients treated later in the course of the disease with a B-cell directed therapy, with rituximab (RTX). The frequency of the SNP rs10414216 MED29 C/T was analysed using a validated TaqMan™ genotyping assay containing sequence-specific primers and fluorescence-labelled allele-specific probes. Disease activity and therapy response were assessed according to the EULAR improvement criteria (http://www.das-score.nl). The primary response of the ETN therapy was assessed 3–4 months after initiation of therapy, the outcome of rituximab after 4–6 months after the first infusion of RTX.

Results: The genotype distribution of the SNP rs10414216 MED29 C/T in 275 RA patients was comparable with a cohort of non-affected controls. There were no differences in the genotype frequencies in subgroups of ACPA- positive and -negative RA patients. There was no association of genotypes with disease activity observed. The DAS28 at baseline before start of ETN or RTX treatment was comparable for all genotypes. After 3–4 months of ETN treatment the DAS28 decreased by 1.670 ± 1.377, 2.083 ± 1.348 and 2.382 ± 1.286 (mean$\pm$SD) for the C/C, C/T and T/T genotypes, respectively. The improvement of the DAS28 was significantly better for the T/T genotype compared to C/C (p$=0.003$). 58% of T/T carriers but only 27.2 % of the C/C carriers were identified as good responders to ETN. However, in RTX treated patients the carriers of the C/C genotype were identified as better responders, after 4–6 months the DAS28 decreased by 2.277 ± 1.558 for the C/C genotype compared to 1.310 ± 1.347 for the C/T genotype (p$=0,025$). 46.2% of C/C and only 27.3% of C/T carriers were good responders to RTX. The T/T carriers were underrepresented in the RTX subgroup, probably as a result of a better outcome of the TNF-blocker therapy in these patients.

Conclusion: Our data clearly indicate that a single SNP has the potential to predict the outcome to different therapeutic approaches. The functional importance of this genetic variation has not yet been characterized. However, this SNP is located in the gene region of MED29, a subunit of the mediator complex which plays a substantial role in the regulation of gene expression. Further analysis of this SNP and the respective gene locus could provide further insight into the mechanisms which determine the outcome of different targeted therapies.

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The Identification of Pathway Markers in Behcet's Disease Using Genomewide Association Data From Two Different Populations. Burcu Bakir-Gungor[1], Elaine Remmers[2], Daniel L. Kastner[3], Akira Meguro[4], Nobuhisa Mizuki[4], Ahmet Gul[5] and Osman Ugur Sezerman[6]. [1]Bahcesehir University, Istanbul, Turkey, [2]National Institutes of Health, National Human Genome Research Institute, Bethesda, MD, [3]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [4]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [5]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [6]Sabancı University, Istanbul, Turkey

Background/Purpose: Behcet's disease (BD) is a multi-system inflammatory disease, characterized by recurrent exacerbations affecting several organs including orogenital mucosa, eyes and skin. Two recent genome-wide association study (GWAS) of BD in Turkish and Japanese populations both confirmed the strong association of MHC Class I region and identified two non-HLA common genetic variations with a mild effect on BD. In complex

diseases such as BD, multiple factors [e.g. single nucleotide polymorphisms (SNPs), miRNAs, metabolic and epigenetic factors] may target different sets of genes in the same pathway crippling its function and thus causing the disease development. In this regard, we hypothesized that the pathways critical to the mechanisms underlying BD will be conserved within and across populations.

Methods: To identify these disease-associated pathways, we previously developed a novel methodology that combines nominally significant evidence of genetic association with current knowledge of biochemical pathways, protein-protein interaction networks, and functional information of selected SNPs. Using this methodology, we herein searched for the disease related pathways on two BD GWAS in Turkish and Japanese case-control cohorts by using the list of SNPs providing a P value <0,05.

Results: Even though there were a few significantly conserved SNPs/genes within and between populations, five of the top ten affected pathways were found to be significant in both populations. The probability of random occurrence of such an event is 5.13E-36. These shared pathways were Notch signaling pathway, focal adhesion, Jak-STAT signaling pathway, long-term potentiation and pathways in cancer. Considering some differences in the clinical manifestations such as more frequent involvement of major vessels in Turkish patients, we observed some correlating rankings in the pathways. The complement and coagulation cascades pathway was identified in 5th and 33rd rankings with P=2.47E-20, P=2.6E-12 in Turkish and Japanese populations, respectively.

Conclusion: By applying our method on two BD GWAS dataset, here we have shown that while the total number of genome-wide significant genetic associations is limited, identification of the shared pathways between the Turkish and the Japanese populations may help further explaining the general mechanisms of BD pathogenesis. Even though each individual has a unique combination of factors involved in disease development mechanism, most of the targeted pathways that need to be altered by these factors are expected to be conserved. The pathways that are identified by population specific GWAS need to be examined to gain a more comprehensive understanding of BD pathogenesis and their potential to be used as biomarkers and/or drug targets.

Disclosure: **B. Bakir-Gungor**, None; **E. Remmers**, None; **D. L. Kastner**, None; **A. Meguro**, None; **N. Mizuki**, None; **A. Gul**, None; **O. U. Sezerman**, None.

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Dynamic Gene Expression of Wnt Signaling Pathway During Osteogenic Stimulation *in Vitro* of Osteoarthritis Mesenchymal Stem Cells. A. Peralta-Sastre[1], M. Hernandez-Molinero[2], P. Tornero-Esteban[2], E. Villa-fuertes[2], B. Fernandez-Gutierrez[3] and Jose Ramon Lamas[4]. [1]UGC de Reumatología, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain., [2]Hospital Clinico San Carlos, Madrid, Spain, [3]Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain, [4]Hospital clinico San Carlos, Madrid, Spain

Background/Purpose: The role of Wnt signalling in Mesenchymal Stem Cell (MSC) fate is still unclarified. Both, canonical and non-canonical pathways have been implicated in differentiation and proliferation resulting from specific Wnt ligands, receptors, inhibitors and downstream molecules responsible for the signalling and/or the developmental commitment. Although osteogenesis is a well-studied process, molecular details remain unknown. Te aim of the study was to delineate the changes in gene expression of Wnt related occurring during osteogenesis in OA and control patients.

Methods: MSCs were obtained from bone marrow aspirates at the time of joint replacement surgery of five OA patients (mean 76 years) and three control subjects without OA signs (mean 80 years). Cells were cultured and expanded under osteogenic stimuli. Confluent cells in passage 6 were collected at days 1, 10 and 21. RNA was purified and retrotranscribed prior quantitative PCR analysis. Simultaneous gene expression of 84 Wnt related genes was analysed using the Human Wnt PCR Array PAHS-043A, from SABiosciences according. The resulting expression raw data was analyzed using the SABiosciences web-based PCR Array Data Analysis tool. ΔΔCt values relative to the *RPL13A* housekeeping gene were used to calculate the expression changes. Two-fold changes with p<0.05 were considered significative.

Results: MSCs from OA patients undergoing osteogenesis progressively increases the number of downregulated genes related to the Wnt signaling. While at basal conditions only two genes were downregulated, at days 10 and 21, twelve and sixteen genes were downregulated respectively. Among downregulated genes, some encode for essential proteins participating both in canonical and non-canonical Wnt pathway and including several ligands, co-rreceptors, inhibitors, kinases and transcription factors.

Conclusion: Our data demosnstrate a clear alteration during osteogenesis of MSCs biology from OA patients. We hypothesized that a possible cause of OA may lie in these intrinsic alterations of MSCs preventing proper differentiation into fully functional adult tissues.

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ACR/ARHP Poster Session B
Imaging of Rheumatic Diseases:
Magnetic Resonance Imaging, Computed Tomography and X-ray
Monday, November 12, 2012, 9:00 AM–6:00 PM

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High Resolution Peripheral Quantitative CT Detects Marked Differences in Metacarpal Head and Shaft and Ultra-Ultra-Distal Radius Bone Volumetric Density and Microstructure in Early Rheumatoid Arthritis. Lynne M. Feehan[1], Helen R. Buie[2], Linda C. Li[1], Kamran Shojania[3], Cheryl Barnabe[2] and Heather A. McKay[3]. [1]Arthritis Research Centre of Canada and University of British Columbia, Vancouver, BC, [2]University of Calgary, Calgary, AB, [3]University of British Columbia, Vancouver, BC

Background/Purpose: Despite improvements in clinical management of rheumatoid arthritis (RA), many with early disease are still at high risk for developing periarticular erosions and osteopenia, as well as, generalized systemic bone loss. It is essential to develop new approaches to assess changes in bone microstructure in people with early RA **before** permanent macro structural bone damage occurs. High Resolution Peripheral Quantitative CT (HR-pQCT) [XtremeCT, Scanco Medical AG] provides a solution; it is a novel imaging system that images bone microstructure at the thickness of a human hair. The purpose of this study was to determine if HR-pQCT could identify and characterize early volumetric density or microstructural differences in people with early RA relative to controls.

Methods: Thirty individuals with early RA and 30 age and gender matched controls consented to participate. Five regions of interest (ROI) of the dominant side were imaged with HR-pQCT (82 μm, 60 kVp, 900 μA, 100 ms): ultra-ultra-distal radius (UUDr) [9 mm, starting 3 mm proximal to the medial tip distal radius]; metacarpal heads (MH) of the 2nd and 3rd digits [18 mm, starting 2 mm distal to tip of most distal 2nd or 3rd MH]; and metacarpal shafts (MS) of the 2nd and 3rd digits [9 mm, starting 4.5 mm distal to 3rd MS mid-shaft].

Standard manufacturer protocols were used for segmentation of the bone from the soft tissue. Cortical and trabecular regions were extracted using direct transformation methods with modified boundary conditions for the MH. Primary outcome variables included: 1) whole, trabecular and cortical region apparent volumetric bone density (vBMD) and bone volume fraction (BV/TV), 2) trabecular region structural model index (SMI), 3) cortical region thickness (CtTh) and material vBMD, and 4) MS marrow space diameter (MSd). Paired Student T-test statistical analyses were used to compare all variables.

Results: *Participants:* Both groups = Sex (Females 24, Males 6); age (mean 53 years, range 21 to 73). RA group = 73% Rheumatoid Factor &/or anti-CCP positive; mean 8 (SD 5) months since diagnosis and 13 (SD8) months since symptom onset and a Health Assessment Questionairre - Disability Index mean of 0.6 (SD 0.6). *Imaging:* HR-pQCT identified marked differences in whole, trabecular and cortical bone volumetric density and microstructure in the periarticular UUDr and MH regions, as well as, the extra-articular MS regions between RA subjects and controls. All density and microstructural outcome variables were lower in early RA participants with the exception of UUDr and MH trabecular bone SMI and MSd, which were higher (Table 1).

Table 1. Comparison of Volumetric Density and Microstructural Outcomes for UUD, MH3 and MS2 ROIs

Ultra-Ultra-Distal Radius ROI (n=54, 27 Pairs)		RA [Mean (SD)]	Non-RA [Mean (SD)]	Difference (%)
Whole Bone	Apparent vBMD (mgHA/cm^3)	262.26 (53.27)	281.52 (44.41)	-7%
Trabecular Region	* Apparent vBMD (mgHA/cm^3)	167.30 (34.74)	187.70 (36.26)	**-11%**
Cortical Region	Apparent vBMD (mgHA/cm^3)	760.25 (93.2)	785.52 (74.9)	-3%
	aterial vBMD (mgHA/cm^3)	942.28 (41.83)	949.81 (35.29)	-0.8%
Whole Bone	Bone Volume Fraction - BV/TV (%)	36.70 (4.9)	38.33 (4.5)	-6%
Trabecular Region	* Bone Volume Fraction - BV/TV (%)	26.88 (0.9)	29.39 (0.9)	**-9%**
	* Structural Model Index -SMI	1.87 (0.38)	1.60 (0.37)	17%
Cortical Region	Bone Volume Fraction - BV/TV (%)	90.49 (5.3)	91.47 (5.3)	-1%
	Thickness - CtTh (mm)	0.56 (0.14)	0.58 (0.11)	-1%
3rd Metacarpal Head ROI (n=54, 27 Pairs)		RA [Mean (SD)]	Non-RA [Mean (SD)]	Difference (%)
Whole Bone	* Apparent vBMD (mgHA/cm^3)	290.28 (47.16)	316.96 (40.72)	**-9%**
Trabecular Region	* Apparent vBMD (mgHA/cm^3)	241.78 (31.32)	262.56 (33.02)	**-8%**
Cortical Region	* Apparent vBMD (mgHA/cm^3)	542.42 (73.31)	592.91 (72.49)	**-8%**
	* Material vBMD (mgHA/cm^3)	817.34 (72.49)	843.87 (45.04)	**-3%**
Whole Bone	* Bone Volume Fraction - BV/TV (%)	42.32 (4.6)	44.91 (3.7)	**-7%**
Trabecular Region	* Bone Volume Fraction - BV/TV (%)	35.74 (4.4)	37.99 (3.2)	**-6%**
	* Structural Model Index -SMI	0.88 (0.45)	0.60 (0.42)	47%
Cortical Bone	* Bone Volume Fraction - BV/TV (%)	42.32 (4.6)	44.91 (3.7)	**-7%**
	* Thickness - CtTh (mm)	0.35 (0.09)	0.39 (0.07)	**-13%**
2nd Metacarpal Shaft ROI (n=52, 26 Pairs)		RA [Mean (SD)]	Non-RA [Mean (SD)]	Difference (%)
Cortical Bone	* Apparent vBMD (mgHA/cm^3)	1033.79 (34.57)	1050.48 (21.78)	**-2%**
	* Material vBMD (mgHA/cm^3)	1079.82 (27.78)	1091.87 (18.30)	**-1%**
Whole Bone	* Apparent vBMD (mgHA/cm^3)	796.84 (112.32)	843.17 (79.35)	**-5%**
Cortical Region	* Bone Volume Fraction - BV/TV (%)	97.96 (1.2)	98.48 (0.61)	**-1%**
	* Thickness - CtTh (mm)	1.93 (0.36)	2.08 (0.29)	**-7%**
Whole Bone	* Bone Volume Fraction - BV/TV (%)	72.68 (9.7)	76.63 (6.9)	**-5%**
	Marrow Space Diameter = MSd (mm)	2.79 (0.61)	2.67 (0.51)	4%

Bold Difference (%) & * = p < 0.05 (Paired T-Test, no adjustment for multiple comparisons). NOTE: MH2 and MS3 similar results, not shown

Conclusion: HR-pQCT is a promising new imaging technology that can identify and quantify very early changes in hand and distal forearm bone volumetric density and microstructure in people with early RA. Participants in this study will be evaluated again at 1 year.

Disclosure: **L. M. Feehan**, None; **H. R. Buie**, None; **L. C. Li**, None; **K. Shojania**, None; **C. Barnabe**, None; **H. A. McKay**, None.

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Segmentation and Quantification of Bone Erosions in the Hands of Patients with Rheumatoid Arthritis Using High Resolution Computed Tomography. Dominique Toepfer[1], Stephanie Finzel[1], Oleg Museyko[1], Klaus Engelke[1] and Georg A. Schett[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Bone erosions are important for diagnosis and monitoring of disease activity in RA. However, semi-quantitative scoring schemes may be inadequate for a true 3D quantification of size and shape. Recently high-resolution peripheral quantitative CT (HR-pQCT) with an isotropic spatial resolution of about 120μm has been used for a semiquantitative assessment of erosion volume in the metacarpophalangeal (MCP) joints. Here we developed a highly automated 3D analysis technique to more accurately quantify volume, shape and surface of erosions and to increase precision.

Methods: In the MCP joints of the second to forth digit of 18 patients 80 slices distally and 242 slices proximally to the surface of the third metacarpal head were scanned (XtremeCT, Scanco Switzerland; isotropic voxel size 82μm). Erosions were quantified as follows: After segmenting the periosteal surface the user identified each erosion by manually placing a seed point. The erosions were then automatically segmented by a 3D level-set algorithm (Fig. 1a) with the option of operator corrections. Erosion volume (Vol), surface area (SA), and sphericity (SP), a parameter describing the shape deviation from a perfect sphere, were determined. In addition manual measurements were carried out. Here the erosion volume was approximated by a half-ellipsoid constructed from the surface area of the cortical break and the maximum erosion depth perpendicular to it (Fig. 1b). In order to compare both methods the lengths measurements obtained from the manual technique were also determined during the automated 3D analysis.
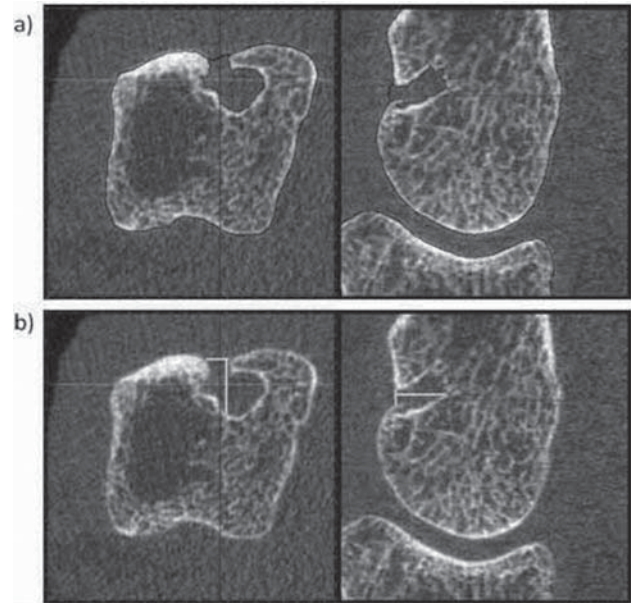
Figure 1. a) Metacarpal bone with periosteal segmentation and segmented erosion. b) Manual measurement of cortical break and maximum depth.

Results: 32 erosions were assessed in the 18 datasets with a mean/min/max Vol of 9.66mm$\geq$/0.37mm$\geq$/54.7mm$\geq$ (automated 3D analysis). Inter-operator precision errors (3 operators, root mean squares coefficients of variation (RMSCV)/RMS standard deviation (RMSSD)) were 7.8%/0.8 mm$\geq$, 10.4%/3.8 mm^2 and 4.9%/0.02 for Vol, SA and SP, respectively. Excluding 18 erosions, in which operator interactions were performed, decreased the errors by about a factor of 3. Correlation between the manual analysis and the length measurements obtained from the automated 3D analysis was r = 0.87, however, correlation with the Vol obtained from the full 3D analysis was r = 0.39, indicating that a simplistic approximation of erosion volume may not capture the full shape information.

Conclusion: We developed a new precise full 3D characterization of bone erosions that may help improving the assessment of disease activity and treatment efficacy. Precision errors depend on the degree of user interaction that may be necessary to correct the automated segmentation, which is more frequent in erosions with large cortical breaks. Manual measurements are less impacted by image quality, such as motion artifacts; however, the approximation of erosion volume by a half-ellipsoid underestimates the true erosion volume. The clinical evaluation of this method is currently being performed.

Disclosure: **D. Toepfer**, None; **S. Finzel**, None; **O. Museyko**, None; **K. Engelke**, None; **G. A. Schett**, None.

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A New Approach for Detecting Progressive Joint Damage Using 3D Imaging From High-Resolution Peripheral Quantitative Computed Tomography: Measuring Reproducibility. Cheryl Barnabe, Helen R. Buie, Michelle Kan, Susan G. Barr, Liam Martin and Steven K. Boyd. University of Calgary, Calgary, AB

Background/Purpose: Joint space narrowing is an important feature of progressive joint damage and functional impairment in rheumatoid arthritis (RA). Methodology to provide longitudinal and sensitive 3D measurements of joint space width have not yet been developed for research or clinical applications. High-resolution peripheral quantitative computed tomography (HR-pQCT) (Scanco Medical AG, Switzerland) has recently become available to accurately and reproducibly measure bone microstructure at a nominal isotropic voxel dimension of 82 μm. Given the ability of HR-pQCT to detect bone margins with high precision, we developed a methodology to measure the 3D metacarpophalangeal (MCP) joint space width. This work determines the reproducibility of the scan protocol with hand repositioning for application for early detection and longitudinal monitoring of RA.

Methods: Two repeated HR-pQCT scans of the 2nd and 3rd MCP joints of ten subjects with early RA (70% female, mean age 45 years) withrepositioning between scans were obtained. The periosteal edges of the metacarpal head

and proximal phalanx base were detected and segmented, and from these images the joint space width and distribution of joint space thickness were measured using a custom analysis implemented for the HR-pQCT based on direct measurements from the high resolution image data.

Results: In this population, the mean joint space width of the 2nd MCP was 1.82 mm (SD 0.20) and of the 3rd MCP 1.84 mm (SD 0.23). Reproducibility with repositioning was excellent, with overlapping filtered histograms and a root square mean coefficient of variance of 4.8%.
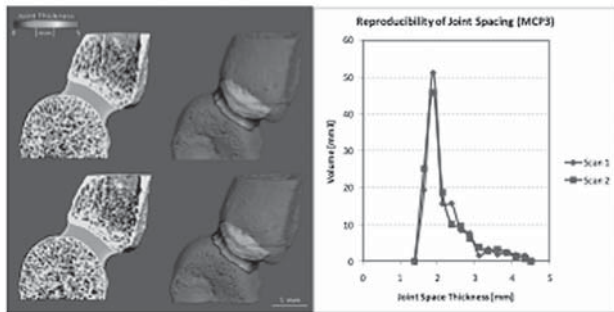
Figure 1. Cross-sectional views (left) and three-dimensional views (middle) of the third metacarpal joint for repeat scans showing consistent repositioning and highly reproducible joint space distribution measurements (right).

Conclusion: We have established a highly reproducible methodology for evaluating the joint space width, applied here to the MCP joints. Currently, we combine this assessment with measures of joint erosions and periarticular bone density. Together, these measures from HR-pQCT show great promise for a new approach for early RA detection, and monitoring of disease activity and/or treatment.

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Bone Loss Before Clinical Onset of Rheumatoid Arthritis o Subjects with Anti-Citrullinated Protein Antibodies. Stephanie Finzel[1], Veronika Lang[2], Arnd Kleyer[1], Juergen Rech[1], Bernhard Manger[1], Elizabeth Araujo[1], Axel J. Hueber[1], Ulrike Harre[3] and Georg Schett[3]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Germany, [3]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are a major risk factor for rapid disease progression in rheumatoid arthritis (RA). We have recently shown that ACPA directly induce bone loss by stimulating osteoclast differentiation (Harre et al, J Clin Invest 2012;122:1791). As ACPA precede the clinical onset of RA we hypothesized that ACPA positive healthy individuals may shows skeletal changes.

Methods: performed a comparative micro computed tomography analysis of the bone microstructure in the metacarpophalangeal joints (MCPJ) of ACPA positive and -negative healthy individuals without signs of arthritis.

Results: ACPA positive (N= 10) and -negative (N= 10) healthy individuals were not different in age (48.2 ± 4.1 vs. 51.4 ± 3.8 years, p = 0.57) and gender (each 8 females and 2 males). Bone minaral density was significantly reduced in ACPA-positive individuals (mean ± SEM: 280 ± 11 mg/ccm) as compared to controls (327 ± 6 mg/ccm). Bone loss was based on cortical bone changes with significant (p = 0.044) reduction in cortical thickness in the ACPA-positive group (mean ± SEM: 0.22 ± 0.03 mm) as compared to controls (0.32 ± 0.03 mm).

Conclusion: Structural bone damage starts before the clinical onset of arthritis in subjects with ACPA. These findings revise the concept of bone damage as an exclusive consequence of synovitis in ACPA positive individuals.

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Structural Damage Is Reduced by Early Achievement of Clinical Remission. Paul Emery[1], Vibeke Strand[2], Andrew S. Koenig[3], Ronald Pedersen[3] and Eustratios Bananis[3]. [1]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [2]Stanford University, Portola Valley, CA, [3]Pfizer Inc., Collegeville, PA

Background/Purpose: The importance of early, intensive treatment of rheumatoid arthritis (RA) to decrease disease activity and prevent structural damage is established.[1] The objective of this analysis was to examine the relationship between disease activity measured by CDAI and DAS28 at week 24, and inhibition of radiographic progression by mean mTSS change from baseline at year 2 in patients treated with etanercept (ETN) + methotrexate (MTX) or MTX monotherapy.

Methods: Randomized subjects from TEMPO (moderate-severe RA, 6.6 years mean disease duration) and COMET (moderate-severe RA, 9 months mean disease duration) who received ETN 50 mg weekly + MTX or MTX alone for 2 years with available X-rays were included in this analysis. Stratified and multivariate regression analyses (observed data) were performed to determine the relationship between variables.

Results: There were a total of 182 patients in COMET and 296 in TEMPO included in this analysis. Patients receiving ETN + MTX had less radiographic progression after 2 years of treatment than MTX monotherapy, independent of disease activity at week 24. In COMET, the percentage of patients achieving CDAI and DAS28 remission in the ETN + MTX group were 17.0% and 46.5% vs 8.8% and 27.7% in the MTX group, respectively. Results were similar in TEMPO with 18.6% and 35.5% of patients in ETN + MTX group and 6.4% and 20.2% in the MTX group achieving remission. Mean change (SD) in annualized mTSS were lower in patients who achieved remission at week 24 compared with those with low disease activity or non-responders, which were significant (P<0.05) in the ETN + MTX group (Table). In the ETN + MTX groups, the majority of patients who achieved CDAI or DAS28 remission were non-progressors by mTSS change scores ≤0.5 (TEMPO 100% and 86.9%; COMET 87.5% and 87.0%) with similar observations in the MTX group (TEMPO 100% and 72.0%; COMET 71.4% and 78.3%).

Table 1. Descriptive Statistics for mTSS by Week 36 Clinical Disease Response Category

Week 36 Response	n	ETN + MTX mTSS Baseline, Units Mean (Median)	Final Time Point,† Units Mean (Median)	Progression Rate, Units/Yr Mean (95% CI)
CDAI Remission (≤2.8)	195	36.5 (14.5)*	36.6 (14.5)*	0.1 (−0.1, 0.4)*
CDAI LDA (>2.8 ≤10)	415	39.3 (17.5)	39.7 (19.5)	0.4 (0.2, 0.6)
CDAI NR (>10)	94	44.4 (22.3)	45.0 (22.3)	0.6 (−0.3, 1.4)
DAS28 Remission (≤2.6)	487	37.9 (16.5)	38.2 (18.0)	0.3 (0.2, 0.5)*
DAS28 LDA (>2.6≤3.2)	135	41.9 (19.4)	42.1 (19.5)	0.2 (−0.1, 0.6)
DAS28 NR (>3.2)	82	42.6 (16.0)	43.3 (17.0)	0.7 (−0.2, 1.6)

*P < 0.05, Kruskal Walis test for differences in distributions. †Final time point defined as the sum of baseline and progression rate. DAS28 = 28-joint Disease Activity Score; CDAI = Clinical Disease Activity Index; LDA = low disease activity; NR = no response.

Conclusion: Inhibition of radiographic progression was more robust with ETN + MTX therapy compared with MTX, regardless of week 24 disease activity. Overall, patients who achieved remission at week 24 had less radiographic progression at year 2 than those with LDA or NR, and less progression with remission defined by CDAI than DAS28. These results may be the first to indicate that achievement of clinical remission within 6 months may predict longer term inhibition of structural damage.

Reference
1. Combe B. *Best Pract Res Clin Rheumatol.* 2007;21:1;27-42.

1012

Radiographic Deformity of the Foot Is Starting From the Early Stage of Rheumatoid Arthritis. Kenji Mamoto, Tatsuya Koike, Tadashi Okano, Atsuko Kamiyama, Yuko Sugioka, Masahiro Tada and Hiroaki Nakamura. Osaka City University Graduate School of Medicine, Osaka, Japan

Background/Purpose: Foot deformities frequently arise in patients with rheumatoid arthritis (RA). It might cause gait dysfunction and lead to disability. However, the precise mechanism of progression of foot deformity is still unclear.

The aim of this study is to clarify the relationship between disease progression and the deformity of feet in patients with RA.

Methods: The prospective cohort TOMORROW (TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOWer morbidity and mortality; clinical trial registration number, UMIN000003876) study was started in 2010. We examined antero-posterior and lateral radiographs obtained from 416 weight-bearing feet of 208 patients with RA from this cohort. The stage of articular destruction was classified from the hand radiographs based on Steinbrocker's classification. We measured the hallux valgus angle (HVA), the intermetatarsal angle between the first and second metatarsals (M1M2) and the first and fifth metatarsals (M1M5) on antero-posterior radiographs, and calcaneal pitch (CP) on lateral radiographs. Each deformity was defined as hallux valgus: HVA>15 degree, spread foot: M1M5>30 degree and flat foot:CP<20 degree.

Results: We finally analyzed 387 feet of 196 patients excluding those that had been surgically treated. The mean age and mean disease duration were 58.2 years old and 12.7 years, respectively. Steinbrocker's stages 1, 2, 3 and 4 were identified 39, 48, 44 and 65 patients, respectively (Table 1). We identified any of hallux valgus, spread foot and flat foot in Steinbrocker's stage 1. Moreover HVA and CP had progressed according to the progression of stage and disease duration. However, M1M2 and M1M5 had been progressed from the early stage. These findings indicate that foot deformities started from the early stage of RA and progressed with advancing stages.

Table 1. Development of foot deformities in patients with rheumatoid arthritis according to Steinbrocker's stage.

Steinbrocker's stage	1 (n = 39)	2 (n = 48)	3 (n = 44)	4 (n = 65)
Disease duration (y)	6.9	7.6	14.5	21.8
DAS28-ESR	2.8	3.2	3.8	3.9
HVA (°)	15.6	18.9	17.4	24.9
M1/M2 angle (°)	9.5	10.5	9.7	9.4
M1/M5 angle (°)	29.5	29.4	30.3	29.2
Calcaneal pitch (°)	19.3	18.2	16.9	15.5
Hallux valgus (%)	47.4	59.4	50.6	63.5
Spread foot (%)	41.6	40.6	44.8	42.1
Flat foot (%)	52.6	58.3	67.8	73.8

Conclusion: Foot deformities started from an early stage of RA, and correlated with disease stage and duration in patients with RA. This result suggests that the disease activity may be underestimated without the assessment of feet in routine clinical care. It is necessary to consider joint destruction and deformity of the foot from the early stage of RA.

Disclosure: K. Mamoto, None; **T. Koike**, Chugai Pharmaceutical, 2, Eli Lilly Japan, 8, Novartis Pharmaceutical Corporation, 2, Teijin Pharma, 8, Bristol-Myers Squibb, 5, Ono Pharmaceutical, 8, Santen Pharmaceutical, 8, Eisai, 8, Abbott Japan, 8, Mitsubishi Tanabe Pharma Corporation, 2, Takeda Pharmaceutical, 8, Astellas Pharma Inc., 8, Pfizer Japan Inc., 8, Janssen Pharmaceutical, 2, Asahi Kasei Pharma Corporation, 8, Daiichi Sankyo Company, 2; **T. Okano**, None; **A. Kamiyama**, None; **Y. Sugioka**, None; **M. Tada**, None; **H. Nakamura**, None.

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The Influence of Vertebral Fractures On the Functional Disability of Patients with Rheumatoid Arthritis. Soo-Kyung Cho[1], Joo-Hyun Lee[2], Min-Kyung Han[3], Seunghun Lee[4], Ji Young Kim[4], Jeong Ah Ryu[4], Yun Young Choi[4], Sang-Cheol Bae[5] and Yoon-Kyoung Sung[5]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Ilsan Paik Hospital, Inje University, Goyang, South Korea, [3]Hanyang University Hospital for Rheumatic Disease, Seoul, South Korea, [4]Hanyang University College of Medicine, Seoul, South Korea, [5]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, painful, and disabling disease associated with reduced health-related quality of life (HRQOL) compared to the general population. Higher levels of comorbidity can make the physical disability of RA patients even worse. Osteoporosis leading to bone fracture is one of the main co-morbidities of RA, and approximately one-third of women with RA report a fracture within 5 years of follow-up. Few studies have examined the influence of vertebral fracture (VF) on the outcome of patients with RA. The aim of the present study was to compare functional disability between RA patients with and without VF.

Methods: All female RA patients aged 50 years or older who visited our hospital for periodic examination between April 2011 and August 2011 were asked to participate in this study. Of these 169 patients, 100 were consecutively enrolled after excluding 69 patients who either did not wish to participate or recently had a routine examination for osteoporosis. Participants completed questionnaires via interview regarding demographic and lifestyle characteristics. Functional disability as a primary outcome was evaluated with the Health Assessment Questionnaire Disability Index (HAQ-DI). Each participant underwent thoracolumbar radiography, and the results were evaluated by two radiologists. We used multivariable-adjusted logistic regression analysis to test for associations between functional disability and the presence of VF, the severity of VF, and the number of VFs.

Results: Among the 100 RA patients, 47 had at least one VF, but 34 of these patients were unaware that they had experienced a fracture. The presence of two or more VFs (OR 3.0, CI 1.18.1) and moderate or severe VF (OR 3.4, CI 1.39.0) were related to disability in univariate analyses, but these effects were no longer significant after adjusting for age, disease duration, current steroid use, disease activity, and no previous history of VF. Among those RA patients with higher disease activity (n=51), the presence of VF (OR 5.1, CI 1.221.7) and moderate or severe VF (OR 7.1, CI 1.339.4) were associated with disability.

Table 1. Factors influencing functional disability in patients with RA (n=100)

	Unadjusted analysis	Adjusted analysis
Age 50-60	1	
61-70	2.3 (0.9~5.8)	
71 ≤	2.0 (0.7~6.1)	
Disease duration (years) 10 ≤	1.8 (0.7~4.3)	
BMI Normal or low (≤22.9)	1	
Over weight (23.0~24.9)	1.3 (0.5~3.2)	
Obesity (25.0<)	0.9 (0.3~2.4)	
Current steroid use	1.3 (0.6~2.8)	
DAS28 Remission and low (<3.2)	1	1
Moderate and high (≥3.2)	4.7 (2.0~10.9)	5.4 (2.2~13.2)
No previous history of VF	0.7 (0.2~1.8)	0.4 (0.1~1.3)
Presence of VF	2.2 (1.0~4.9)	
Number of VFs 0	1	
1	1.6 (0.6~4.4)	
≥ 2	**3.0 (1.1~8.1)**	
Severity of VF None	1	
Mild	1.3 (0.5~3.8)	
Moderate or severe	**3.4 (1.3~9.0)**	

Table 2. Influence of vertebral fracture on disability in RA patients with moderate or high disease activity

Regression model	Details of VF	OR (95% CI) Moderate or high disease activity (n=51)
Model 1	Presence of VF	5.1 (1.2~21.7)
Model 2	Number of VFs 0	1
	1	3.2 (0.5~23.2)
	2≤	4.8 (0.9~24.7)
Model 3	Severity of VF Normal	1
	Mild	3.3 (0.6~18.6)
	Moderate or sever	7.1 (1.3~39.4)

Conclusion: Many patients with RA have occult VF. Among RA patients with higher disease activity, the presence and severity of VF may affect functional disability.

Disclosure: S. K. Cho, None; **J. H. Lee**, None; **M. K. Han**, None; **S. Lee**, None; **J. Y. Kim**, None; **J. A. Ryu**, None; **Y. Y. Choi**, None; **S. C. Bae**, None; **Y. K. Sung**, None.

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Trimmed Analyses, a New Approach to the Analysis of Sharp Score Data in the Assessment of Progression in Patients with Rheumatoid Arthritis. Robert B. M. Landewé[1] Désirée van der Heijde[2], Carol Connell[3], John Bradley[3], David Gruben[3] and Michael Brown[3]. [1]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Pfizer Inc., Groton, CT

Background/Purpose: Tofacitinib is a novel oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. In the Phase 3 ORAL Scan study [NCT00847613], progression in radiographic scores (mean change from baseline [BL] in modified Total Sharp Scores [mTSS] at Month 6) was a primary analysis using an Analysis of Covariance (ANCOVA). ANCOVA demonstrated statistically significant inhibition in structural damage progression for tofacitinib 10 mg but not 5 mg twice daily (BID) doses, compared with placebo (PBO).[1] There has been a general trend towards less PBO progression in recent radiographic studies;[2] the PBO period is generally shorter (≤3 months) and most patients receiving PBO are rescued. It is therefore important to confirm that efficacy detected in a primary analysis is robust. Rank analysis of ORAL Scan data demonstrated borderline evidence of inhibition by both doses. Rank analyses are used to show results are not driven primarily through extreme values, as ranking down weights extreme values

relative to ANCOVA, but analyses of ranks do not yield intuitively interpretable values representing the magnitude of damage inhibition. A conceptual bridge between rank analyses and ANCOVA is the trimmed-analysis approach, where extreme values are systematically removed from the data set.

Methods: In this analysis, mTSS data were trimmed in 1% increments up to 10%, eg 2% trimming deletes observations <1st percentile and >99th percentile. In the ORAL Scan study this resulted in approximately 2–3 observations symmetrically removed per group per 1% trimming. ANCOVA was then applied to each resulting trimmed set (0% was the primary analysis).

Results: At 1% trimming, nominal statistical significance was achieved for both tofacitinib doses (CI less than 0) and was maintained with further trimming (Figure). As expected, the mean difference from PBO diminished slightly with trimming, but was more than compensated for by reductions in variability.
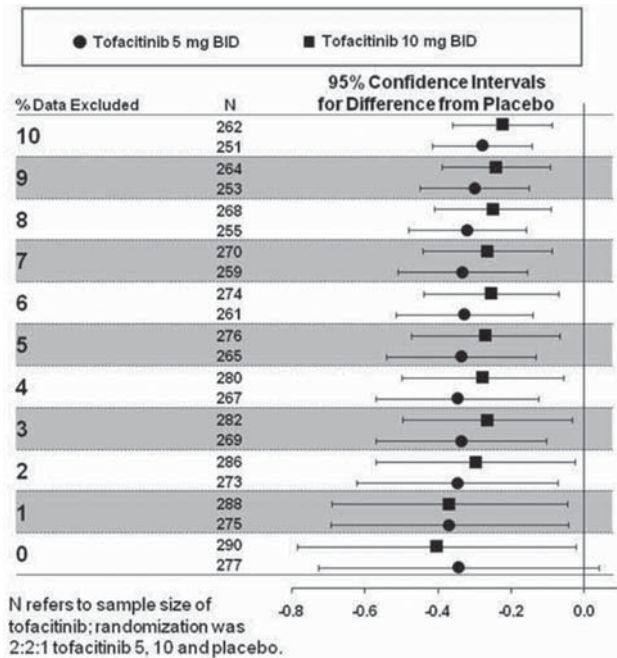
Figure.

Trimmed data = % Data Excluded

Conclusion: In ORAL Scan, significance of inhibition of structural damage was demonstrated for both tofacitinib doses after just 1% trimming, indicating that significance in the primary analysis was not dependent on extreme data. Trimmed analyses give improved insight into the influence of extreme values and should be considered as one of the sensitivity analyses of choice for structural data.

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Analysis of Integrated Radiographic Data for Two Long-Term, Open-Label Extension Studies of Adalimumab. Désirée van der Heijde[1], Robert Landewé[2], Edward C. Keystone[3], Ferdinand C. Breedveld[1], Shufang Liu[4] and Neelufar Mozaffarian[4] [1]Leiden University Medical Center, Leiden, Netherlands, [2]Academic Medical Center, Amsterdam, Netherlands, [3]University of Toronto, Toronto, ON, [4]Abbott, Abbott Park, IL

Background/Purpose: The assessment of radiographic data from long-term studies in patients (pts) with rheumatoid arthritis (RA) poses a significant challenge, given the potential involvement of multiple readers who typically evaluate films from only a subset of the available time points, often re-scoring previously read images. This analysis describes an integration approach to evaluate the complete set of radiographic scores assessed over several years (yrs) from long-term studies of adalimumab (ADA).

Methods: Data from 2 large, multicenter, phase 3, randomized, placebo (PBO)-controlled trials of ADA were analyzed: PREMIER (MTX-naïve pts, early RA[1]), had a 2-yr double-blind (DB) period followed by an ongoing 8-yr open-label extension (OLE); DE019 (MTX-inadequate responders, longstanding RA[2]), had a 1-yr DB period followed by a completed 9-yr OLE. Pts received OL ADA±MTX in both OLEs. This post hoc analysis evaluated radiographic data based on randomization to the original PBO+MTX and standard dose ADA+MTX arms through 8 yrs of treatment in PREMIER and 10 yrs in DE019. Radiographic progression was assessed using the change in modified total Sharp score (ΔmTSS) from baseline (BL). Radiographs were assessed at Yrs 2, 3, 5, and 8 (PREMIER) and Yrs 1, 2, 3, 5, 6, 8, and 10 (DE019). At each assessment yr, radiographs from BL and selected prior yrs were re-read. A mixed effect model was used to evaluate the repeated measurements at different time points within different assessment yrs in the integrated analysis. ΔmTSS at each time point was estimated by least square mean and summarized alongside the most recent assessment yr of PREMIER (Yr 8, which included repeat reads for BL, and Yrs 2 and 6) and DE019 (Yr 10, which included repeat reads for BL, and Yrs 1 and 8).

Results: Radiographic data from 452 pts in PREMIER (215, PBO+MTX; 237, ADA+MTX) and 327 pts in DE019 (162, PBO+MTX; 165, ADA+MTX) with BL and ≥1 post-BL radiograph were identified. Radiographic progression was most pronounced in pts receiving PBO+MTX during the DB periods, but progression slowed dramatically upon switch to OL ADA±MTX therapy in both trials (**Figure**). Following up to 8 yrs of treatment, pts in PREMIER experienced ΔmTSS estimates of 11.1 (PBO+MTX) and 3.9 (ADA+MTX) units; pts in DE019 experienced estimates of 6.6 (PBO+MTX) and 0.9 (ADA+MTX) units through up to 10 yrs of treatment. The estimated curves in each of the studies revealed subtle changes in progression rates not seen in their respective most recent assessment yr.
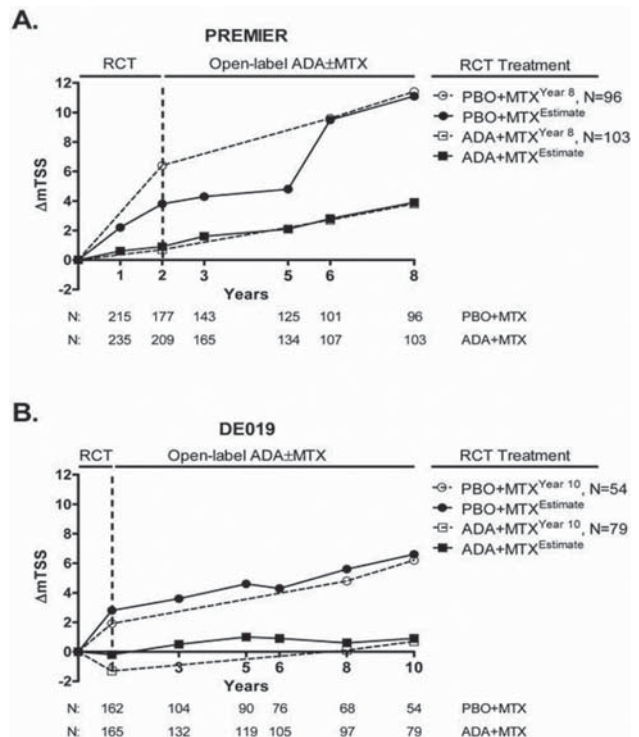
Conclusion: Longitudinal, data integration analyses factoring in mTSS from all available assessments enabled a robust estimate of total radiographic progression in 2 long-term studies of ADA±MTX. Moreover, the present analysis confirmed the radiographic efficacy of long-term therapy with ADA±MTX.

Reference

1 *Arthritis Rheum* 2006;54:26–37; [2]*Arthritis Rheum* 2004;50:1400-11.

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The Effect of Evaluation Variability At the Unit of Measurement On the Reliability of Omeract Ramris and Van Der Heijde-Modified Sharp Score. Ruben Tavares[1], Naveen Parasu[2], Karen Finlay[2], Erik Jurriaans[2], Hao Wu[1], Karen A. Beattie[1], Maggie Larche[1], Lawrence E. Hart[3], William G. Bensen[4], Raja S. Bobba[1], Alfred A. Cividino[1], Colin E. Webber[5], Jean-Eric Tarride[6] and Jonathan D. Adachi[7]. [1]McMaster University, Hamilton, ON, [2]Hamilton Health Sciences, Hamilton, [3]St. Joseph's Health Care, Hamilton, ON, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON, Hamilton, ON, [5]Hamilton Health Sciences, Hamilton, ON, [6]Programs for Assessment of Technology in Health (PATH) Research Institute, Hamilton, ON, [7]Charlton Medical Centre, Hamilton, ON

Background/Purpose: The Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) and van der Heijde-modified Sharp score (vdHSS) are recognized semi-quantitative measures for the evaluation of rheumatoid arthritis (RA) disease progression on magnetic resonance imaging (MRI) and radiography (X-ray), respectively. The smallest detectable difference (SDD) is used to quantify the reliability between ratings of status scores in scale units. To date, the SDD has been evaluated at the overall or component feature score levels of analysis thereby ignoring variability at the unit of measurement. The objective of this study was to determine the reliability of RAMRIS and vdHSS at the unit of measurement across four radiologists and to compare it to the conventional approach.

Methods: A paired, cross-sectional study of RA patients with varying symptom duration (mean 6.8 years (SD 6.4) for MRI, 7.6 years (SD 7.3) for X-ray) was conducted. 19 MR image sets of metacarpophalangeal joints (MCP) 2–5 and 9 X-ray image sets of both hands, wrists, and forefeet were each independently evaluated by 4 radiologists using RAMRIS and vdHSS, respectively. Shrout and Fleiss fixed and random effects intra-class correlation coefficients (fICC and rICC, respectively), and SDD were calculated for overall and component feature scores, as well as at the unit of measurement.

Results: At the unit of measurement, the RAMRIS erosion, edema, and synovitis fICC were 0.71, 0.56, and 0.41, respectively. The corresponding SDD values (rounded to scale unit) for erosion, edema, and synovitis were 2, 1 and 2. Overall and component feature score reliability measures were dependent on the anatomy compared. For single MCP 2–5 joint sets (i.e. per hands), the fICC for the overall RAMRIS and component feature subscore for erosion, edema, and synovitis were 0.66, 0.55, 0.60, and 0.39. The corresponding SDD values were 11, 7, 4, and 5. For X-ray, erosion and joint space narrowing (JSN) fICC at the unit of measurement were 0.61 and 0.69, and the associated SDD values were both 2. For the hands, wrists and feet, the overall and component feature scores for erosion and JSN were 0.69, 0.60, and 0.85. The corresponding SDD values were 39, 34, and 11.

Conclusion: The conventional approach to the calculation of reliability for overall or component feature scores fails to account for variability at the unit of measurement. In order for reliability of composite measure scores to be valid, the assumption is made that the SDD at the unit of measurement is less than the scale unit. The study findings suggest that this prerequisite assumption may be false. The validity of literature evidence for the reliability of diagnostic imaging and composite measures in general is therefore questionable.

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Bye Bye Biopsy: Diffusion Tensor and Dynamic Contrast Enhance Magnetic Resonance Imaging Parameters Reflect Molecular Events of Inflammation in the Synovium. Vikas Agarwal[1], Rishi Awasthi[2], Deepak Tripathi[3], Vinita Agrawal[3], Ram Kishore Singh Rathore[4], Kusum Sharma[5], CM Pandey[3] and Rakesh K. Gupta[3]. [1]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India, [2]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India, Lucknow, India, [3]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Lucknow, India, [4]Indian Institute of Technology, Kanpur, India, [5]Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background/Purpose: Chronic synovial inflammation is characterized by accumulation of inflammatory cells and increased vascularity. Synovial histology remains the most definitive way to delineate the severity of inflammation. Herein we hypothesize that Diffusion tensor imaging (DTI) derived metrics may delineate the aggregation of the inflammatory cells. Dynamic contrast enhanced (DCE) imaging may provide information regarding vascularity in the inflamed synovium. Combination of these may provide information about the ongoing inflammation.

Methods: Patients with chronic knee arthritis underwent conventional, DTI and DCE MRI (3T) followed by arthroscopic synovial biopsy. Masks of synovial regions that enhanced on post contrast T1-weighted imaging were created using an automated segmentation algorithm. Created masks were used to segment the inflamed synovium to extract various DCE and DTI metrics. Synovium was subjected to histopathology, immunohistochemistry (IHC), culture and PCR.

Results: There were 65 patients (45 male) with mean age 39 years [range 18–76] and mean disease duration 29 months [range 4–192]. Fifteen patients had tuberculosis and rest had; undifferentiated spondyloarthropathy (n=14), chronic monoarthritis (n=11), chronic undifferentiated monoarthritis (n=10), rheumatoid arthritis (n=6), osteoarthritis (n=3), ankylosing spondylitis (n=2), reactive arthritis (n=2) and juvenile idiopathic arthritis and leprosy one each.

The mean values of various DTI and DCE and IHC parameters are presented in (Table-1). Amongst the DTI parameters, FA significantly correlated with all the inflammatory cells infiltrating into the synovium (Table-2) and various proinflammatory cytokines. FA was the best predictor of infiltrating T cells, B cells, plasma cells, macrophages, adhesion molecule and proinflammatory cytokines. DCE parameters significantly correlated with CD34 and blood volume was the best predictor of CD34.

Table 1. Mean values of DTI, DCE, IHC markers

DTI indices	Mean ±SD
FA	0.22 ± 0.031
MD ($\times 10^{-3}$ mm^{2}sec^{-1})	1.63 ± 0.51
CL	0.06 ± 0.027
CP	0.15 ± 0.054
CS	0.75 ± 0.023
DCE indices	
BF(ml/100gm/min)	109.9 ± 42.8
BV(ml/100gm)	9.5 ± 4.2
k $_{ep}$(min^{-1})	2.5 ± 1.0
PCI	1820.4 ± 211.6
Immune cells in synovium	
CD3	154.94 ± 48.65
CD4	63.42 ± 32.85
CD8	53.58 ± 17.63
CD20	39.34 ± 13.96
CD34	52.94 ± 17.28
CD54	36.35 ± 13.14
CD68	163.2 ± 34.62
CD138	36.06 ± 14.49
TOTAL CELLS	489.66 ± 106.39
IL-1β	31.09 ± 18.15
TNF-α	24.71 ± 11.52

FA: Fractional Anisotropy, MD: Mean Diffusivity, CL:Linear anisotropy, CP:Planar anisotropy, CS:Spherical isotropy, BV: Blood Volume, BF: Blood Flow, ktrans: Volume transfer constant, PCI: post-contrast signal intensity.

Table 2. Correlation between the values of DTI & DCE -MRI indices with various inflammatory cells, adhesion molecule and proinflammatory cytokines and angiogenesis marker in the synovium (n=65)

| DTI-MRI Indices | Infiltrating Immune cells in synovium | | | | | | | | | Total Inflammatory cells | DCE-MRI Indices | Angiogenesis Marker in the synovium |
	CD3	CD 4	CD 8	CD 20	CD 68	CD 138	CD 54	TNF-α	IL-1β			CD 34
FA	0.800#	0.773#	0.859#	0.276*	0.681#	0.308*	0.513#	0.418*	0.604#	0.913#	BF	0.814#
ADC	-0.396#	-0.391#	-0.468#	-0.087	-0.283*	-0.079	-0.203	-0.019	0.305*	0.431#	BV	0.848#
CL	0.452#	0.325#	0.410#	0.258*	0.141	0.257*	0.172	0.237	0.510#	0.464#		
CP	0.044	0.054	0.127	0.025	0.106	0.019	0.083	0.087	0.067	0.072	k_{ep}	0.308*
CS	-0.307*	-0.376*	-0.354#	0.069	-0.351#	0.078	-0.159	-0.151	-0.346#	-0.322#		
PCI	-0.070	0.111	0.102	0.067	-0.036	0.177	-0.156	0.15	0.107	0.069	PCI	0.156

\# $p < 0.01$ level
* $P < 0.05$

Conclusion: DTI and DCE metrics capture cellular and molecular events and correlated with the degree of synovial inflammation. They may replace synovial histology in future.

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Reliability of the Early Erosions in Rheumatoid Arthritis Software When Quantifying Bone Loss. Melissa XP. Koh[1], Joshua WJ. Barbosa[1], Ruben Tavares[1], Stephen Tytus[1], Patrick Emond[1], Chris Gordon[1], George Ioannidis[1], Karen A. Beattie[1], William G. Bensen[2], Raja S. Bobba[1], Alfred A. Cividino[1], Lawrence E. Hart[3], Maggie Larche[1], Arthur N. Lau[1] and Jonathan D. Adachi[4]. [1]McMaster University, Hamilton, ON, [2]St. Joseph's Hospital and McMaster University, Hamilton, ON, [3]St. Joseph's Health Care, Hamilton, ON, [4]St. Joseph's Health Care and McMaster University, Hamilton, ON

Background/Purpose: Instruments designed to determine the clinical relevance of bone erosions captured by magnetic resonance imaging (MRI) in rheumatoid arthritis (RA) patients have been set-back by inconsistency in both intra and inter-rater reliability. The developed *Early Erosions in Rheumatoid Arthritis* (EERA) software holds promise for increasing reliability across readers by quantifying RA patient erosions in a semi-automated fashion using an amalgamation of conventional Region Growing and Level-Set Segmentation algorithms. The principle aim of this study was to determine intra and inter-rater reliability when applying EERA software to the quantification of erosions in the metacarpal phalanges (MCPs) of RA patients.

Methods: Two readers, R1 and R2, trained to use EERA software, but otherwise inexperienced with conventional quantification techniques, evaluated erosions captured by MRI in the second through fifth MCPs of 50 patients diagnosed with RA under the American College of Rheumatology 1987 revised definition. A 1T magnet, 100mm diameter cylindrical transmit and receive coil, and a 3D spoiled gradient echo sequence were used in acquiring the images. Images were evaluated by each reader twice with a 72 hour wait period between runs. Intra and inter-rater reliabilities for the total volume measures between the two readers and two runs was assessed via intra-class correlations, ICC(2,1), with 95% confidence intervals. For each run, volume differences between readers were graphed against R2's volume measures in Bland-Altman difference plots so as to visually capture the degree to which scores varied.

Results: Of the 50 participants recruited for the study, 16 were male and 34 were female. Study subjects had a mean age of 57 (SD=11.5)yr, a mean weight of 78 (SD=15.6)kg, and a mean height of 169 (SD=13.9)cm. Readers identified 64 ± 1 erosions in the patients: 15 of these occurred in second MCP, 33 ± 1 in the third MCP, 12 ± 1 in the fourth MCP, and 4 in the fifth MCP. Mean erosion size, as determined by R1 during the first and second runs, were 87.1 (SD=118.9)mm³ and 88.1 (SD=121.2)mm³ respectively. R2's measures had a mean erosion volume of 90.7 (SD=130.1)mm³ for the first run and 103.2 (SD=151.0)mm³ for the second run. For both runs, agreement between readers was better for smaller sized erosions decreasing appreciably beyond 100mm³ (See Figure 1. Run 2 results are not shown but are available upon request). The intra-rater reliability had an ICC value of 0.956 with the 95% confidence interval ranging from 0.935 to 0.970. Between R1 and R2, the inter-rater reliability had an ICC value of 0.921 with a 95% confidence interval from 0.886 to 0.946.
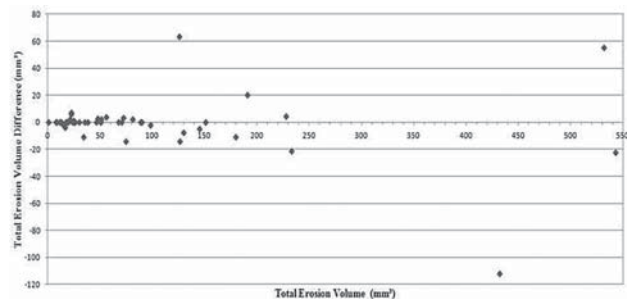
Figure 1. Run 1 Reader Measured Erosion Volume Differences Plotted against R2's Measures

Conclusion: Results obtained suggest that EERA software can be applied to acquire MCP erosion volume measures in a reliable manner.

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Visualization of Cartilage in High-Resolution Magnetic Resonance Imaging Is a New Imaging Biomarker for the Quantification of Joint Damage in Rheumatoid Arthritis. Barbara Herz[1], Stephanie Finzel[1], Andreas Albrecht[1], Juergen Rech[1], Matthias Englbrecht[1], Goetz Welsch[2] and Georg Schett[3]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Traumatic Surgery, University Clinic of Erlangen-Nuremberg, Erlangen, Germany, Erlangen, Germany, [3]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Recent achievements in Magnetic Resonance Imaging (MRI) have been the gradient-echo-based T1-delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) focussing on the detection of proteoglycan content in cartilage; moreover, the multi-echo and spin-echo T2-mapping has been developed for the assessment of cartilage hydration and collagen microstructure. Current MRI-studies suggest a link between dGEMRIC and T2-mapping and early changes of cartilage in inflammatory diseases. However, their diagnostic value in inflammatory diseases has not yet been fully clarified..To investigate the relation between morphological and biochemical alterations in the cartilage of patients with Rheumatoid Arthritis (RA) by high-resolution 3Tesla-MRI.

Methods: 29 RA-patients received a 3Tesla-MRI scan of the 2nd and 3rd metacarpophalangeal (MCP) joint of the dominant hand. T2-mapping and dGEMRIC were performed with 2 small-diameter surface coils designed for high-resolution imaging of cartilage (0.26×0.26×105mm voxel size; Verio Siemens Healthcare, Erlangen, Germany). T2 and T1 relaxation times were obtained via a region-of-interest (ROI) evaluation. MCP heads and bases were scored semiquantitatively for synovitis, bone marrow edema (BME) and bone erosion (BE) using the RA MRI scoring (RAMRIS) system; joint space and cartilage thickness were measured perpendicular to the joint plane in all 3 joint regions (fig. 1a).

Results: Inter- and intraobserver agreement was good (details see fig. 1b). For correlation analysis mean values of real and total joint spaces (RJS, TJS), RAMRIS-subscores, and ROIs of dGEMRIC- and T2-evaluations were used; image 1a shows details of source data acquisition, image 1c data of correlation analysis. Interestingly, early changes of cartilage such as BME and synovitis in RAMRIS as compared to dGEMRIC were correlated negative (p=0.029; p=0.003); likewise, BME and synovitis showed positive correlation (p=0.013; p=0.015) in T2. In contrast, periarticular changes occurring later in the course of the disease such as BE did not correlate with dGEMRIC (p=0.704) and weakly with T2 (p=0.026). All joint space subanalyses of MCP3 despite RJS correlated with dGEMRIC and T2 mainly in medial region (TJS p=0.017; TCT p=0.020; CT p=0.018). Additionally, in dGEMRIC MCP2 and RJS correlated in ulnar side (p=0.001).
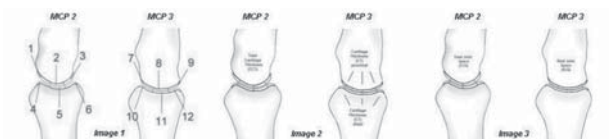
Figure 1a: Details of cartilage and joint space analysis. Image 1 shows details of ROI-evaluation in MCP2 and 3, image 2 Total Cartilage Thickness (TCT, left), Cartilage Thickness (CT, right) proximally and distally, image 3 shows Total Joint Space (TJS, left) and Real Joint Space (RJS, right).

Figure 1b: Details of Intra- and Interobserver Reliability; ranges of r-values are shown.

Figure 1c: Details of Correlation analysis; P-values are shown. nd = not done; ns = not significant

	Dorsal Medial	Dorsal Lateral	Plantar Medial	Plantar Lateral
1st Proximal Phalanx	7	3	5	7
1st Metatarsal	6	4	13	19
2nd Proximal Phalanx	0	1	5	8
2nd Metatarsal	6	5	9	6
3rd Proximal Phalanx	1	1	6	6
3rd Metatarsal	3	4	10	8
4th Proximal Phalanx	1	1	6	6
4th Metatarsal	6	3	12	6
5th Proximal Phalanx	2	4	9	5
5th Metatarsal	10	11	14	14
Total	42	37	89	75

Conclusion: High-resolution MRI using dGEMRIC and T2-mapping enables meticulous detection of very early inflammatory changes in cartilage which are known to precede RA-typical periarticular bone damage. This is important both for early discovery of those damages, adequate therapy decisions and therapy monitoring; moreover, it may also have an impact on the development of anti-inflammatory drugs in the future. Additional studies on mechanical influences on cartilage are needed to further evaluate the mechanisms of joint space alterations.

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1020

Location of Erosions At the Metatarsophalangeal Joints in Patients with Rheumatoid Arthritis. Heidi J. Siddle[1], Richard J. Hodgson[2], Andrew J. Grainger[3], Anthony C. Redmond[4], Richard J. Wakefield[4] and Philip S. Helliwell[5]. [1]University of Leeds, Leeds, United Kingdom, [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]Leeds Teaching Hospitals NHS Trust and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [4]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [5]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Background/Purpose: The forefoot is described as the most common site of symptoms in the foot and ankle of patients with rheumatoid arthritis (RA). Pressure under the forefoot area is significantly increased in patients with RA compared to normal subjects and forefoot peak pressures have been reported to correlate with pain, damage and higher erosion scores at the MTP joints. Damage to plantar structures such as the capsule and plantar plate of the MTP joints in patients with RA is associated with bone erosion, suggesting altered biomechanics or mechanical effects due to capsule or plantar plate abnormalities may cause bone changes. While a tendency towards a lateral distribution has been noted in the hands, the location of erosions at the MTP joints has not been previously reported in patients with RA. This exploratory study hypothesised that the majority of erosions at the MTP joints in patients with RA are on the plantar aspect, contributing to pain, damage and increased pressure.

Methods: In 24 patients with RA the more symptomatic forefoot was imaged using 3Tesla MRI. T1 weighted sagittal and short axis post gadolinium sequences were acquired through the MTP joints. Images were scored for bone erosion in the distal and proximal part of the MTP joints using the RAMRIS system. The base of the proximal phalanx and the head of the metatarsal were divided into quadrants to determine the location of erosions in dorsal-medial, dorsal lateral, plantar medial and plantar lateral regions.

Results: Seventeen females and seven males with a mean age of 55.5 years, disease duration 10.6 years (range 0.6 – 36) and self reported foot pain measured by 100mm visual analogue scale (VAS) of 43.4 (SD 27.9) took part in the study. Eighteen patients were rheumatoid factor positive, the mean (SD) DAS44 (CRP) and DAS44 (ESR) were 2.5 (0.8) and 2.6 (0.9) respectively. The location of erosions at the MTP joints in patients with RA is shown in the table below. The majority of erosions are reported on the plantar aspect of the MTP joints.

Conclusion: This is the first study to report the location of erosions at the MTP joints in patients with RA and forefoot pain. The results confirm the hypothesis of this exploratory study; erosions were more commonly reported on the plantar aspect of the distal and proximal parts of the MTP joints, often in sites not readily imaged using standard ultrasound protocols. Further work is required to determine the relationship between forefoot pain, deformity and raised plantar pressures with the location of erosions at the MTP joints in patients with RA. Furthermore, these study findings highlight the need to image the dorsal and plantar aspect of the MTP joint when using ultrasound alone to detect erosions in RA.

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1021

Magnetic Resonance Imaging in Follow-up of Clinical Remission in Juvenile Idiopathic Arthritis. Mira van Veenendaal[1], Robert Hemke[2], Marjolein I. Bos[1], Mario Maas[2], Marion A. J. Van Rossum[1] and Taco W. Kuijpers[1]. [1]Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, Netherlands, [2]Academic Medical Center (AMC), Amsterdam, Netherlands

Background/Purpose: Despite clinical remission, a substantial proportion of Juvenile Idiopathic Arthritis (JIA) patients will flare after a period of inactive disease. MRI has proven to depict subclinical inflammation as reflected by synovial hypertrophy, and may therefore be useful to identify patients at risk for flaring during follow-up.

The purpose of this study, focussing on the main target joint, was to use MRI in JIA patients in clinical remission, and to identify inflammatory changes as compared to clinical status over time.

Methods: In this prospective study, 16 patients with JIA (median age 11.8 years [IQR, 10.5–14.5], median disease duration 3.2 years [IQR, 1.8–5.6]) in clinical remission (fulfilling the Pediatric Rheumatology International Trials Organization (PRINTO) preliminary criteria for clinical remission) werestudied with MRI at 2 consecutive time points (median interval 16.1 months [IQR 14.4–17.1]) and assessed for clinical relapse. Initial clinical remission was achieved in 14 patients on medication (CRM) (median duration inactive disease 11.0 months [IQR 7.2–13.7]) and in 2 patients off medication (CR) (median duration inactive disease 28.7 months [IQR 15.7–28.7]). Contrast-enhanced MRI of the formerly most involved knee was performed to evaluate the degree of synovial hypertrophy, using the validated Juvenile Arthritis MRI Scoring (JAMRIS) (synovial hypertrophy score; <2 mm=0, 2–4 mm=1 and >4 mm=2, at 8 knee regions).

Results: The first MRI showed signs of subclinical synovitis in 8 patients (50 %) and no synovitis in 8 patients. The second MRI in follow-up demonstrated an increased score of synovial hypertrophy as compared to the first MRI in the 6 patients with relapse of arthritis. In contrast, all patients with sustained clinical remission showed either stable (6 patients) or improved (4 patients) scores of synovial hypertrophy. CRP and erythrocyte sedimentation rate were not increased at both MRI time points.

Conclusion: A large degree of JIA patients who satisfy the PRINTO remission criteria with normal findings on clinical and laboratory assessment had MRI based synovitis in this study, suggestive of ongoing disease activity. Increase of synovial hypertrophy over time was related to disease flaring, whereas stable or further reduction of synovial hypertrophy was associated with sustained clinical remission. Serial MRI allows for adequate follow-up of underlying disease even when clinically silent.

Disclosure: **M. van Veenendaal**, None; **R. Hemke**, None; **M. I. Bos**, None; **M. Maas**, None; **M. A. J. Van Rossum**, None; **T. W. Kuijpers**, None.

Monday, November 12

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1022

Imaging of Ankle Joints by MRI in Murine Models of Inflammatory Arthritis. Shawn M. Rose[1], Harris R. Perlman[1], Emily Alex Waters[2] and Thomas Meade[2]. [1]Northwestern University, Chicago, IL, [2]Northwestern University, Evanston, IL

Background/Purpose: One of the fundamental shortcomings in the field of experimental rheumatology is the inability to non-invasively monitor the development of inflammatory arthritis longitudinally. Magnetic resonance imaging (MRI) overcomes this limitation, by allowing for detailed examination of anatomical structures as well as the assessment of joint and soft tissue inflammation. Here, we have utilized cutting-edge MRI technologies to image ankle joints in control (C57BL/6) and arthritic (K/BxN serum transfer-induced arthritis (STIA) and K/BxA^{g7}) mice over time. Further, the MRI data was validated against both clinical, histological, and in vivo imaging system (IVIS) assessments of inflammatory arthritis.

Methods: C57BL/6 mice were injected with PBS (controls) or 100 mL of K/BxN serum at day 0. Mice were scored clinically and imaged via IVIS and MRI at days 0, 3, 7, 15, and 21 after arthritis induction. MRI imaging was also performed on ankle joints from 10- and 21-week-old K/BxA^{g7} mice. Arthritis severity was assessed by measurement of ankle width and clinical score. Decalcified ankle joint specimens were sectioned and stained with hematoxylin and eosin for histological analysis. Luminescence acquisition was performed using an IVIS Spectrum System 10 minutes after intraperitoneal injection of 100 mL (200 mg/kg) of XenoLight Rediject Inflammation Probe. Radiance signal intensity from normalized gated analyses of forepaw and hindpaw joints was quantified utilizing Living Image software. Ankle joint MRI was performed on a 9.4T Bruker Biospec MRI system. Two high-resolution 3D images were acquired; a gradient echo pulse sequence (FLASH) to evaluate bone and a spin echo sequence (MSME) to evaluate inflammation (long T2 signal volume). Amira software was used to perform MRI long T2 signal analyses and bone reconstructions. Graphpad Prism software was used for ANOVA and linear regression analyses with statistical significance established at $p < 0.05$.

Results: Arthritic STIA animals demonstrated increased clinical, histological, IVIS, and MRI measures of disease severity compared to controls. Peak arthritis intensity occurred at day 7 and complete resolution of inflammation was observed by day 21. Following induction of arthritis, the majority of increased long T2 signal and volume expansion of ankle joints occurred in a juxtaarticular rather than intrarticular fashion. Ankle joint bone destruction in K/BxA^{g7} mice was readily detectible via MRI as early as age 10 weeks. Linear regression analyses demonstrated a strong correlation between clinical score and paw joint radiance intensity by IVIS ($R^2 = 0.54$, $p < 0.0001$). There was also a statistically significant relationship between ankle joint width and volume of long T2 signal by MRI ($R^2 = 0.57$, $p < 0.0001$).

Conclusion: MRI is an optimal technology for anatomic localization of articular and soft tissue changes during the development and resolution of inflammatory arthritis. Future studies may combine MRI imaging with various in vivo labeling agents to investigate joint disease in a cell-type specific fashion.

1023

Scoring Radiographic Progression in Axial Spa: Should We Use the Modified Stoke in Ankylosing Spondylitis Spine Score or the Radiographic Ankylosing Spondylitis Spinal Score? Sofia Ramiro[1], A.M. Van Tubergen[2], Carmen Stolwijk[2], Robert Landewé[3] and Désirée van der Heijde[4]. [1]Academic Medical Center, University of Amsterdam, The Netherlands and Hospital Garcia de Orta, Almada, Portugal, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Academic Medical Center, University of Amsterdam and Atrium Medical Center, Heerlen, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Radiographic damage is one of the core outcomes in axial SpA and it is usually assessed with the modified Stoke Ankylosing Spondylitis (AS) Spine Score (mSASSS). The recently proposed Radiographic AS Spinal Score (RASSS)[1] includes an assessment of the lower thoracic vertebrae, under the hypothesis that most progression occurred in these segments. We aimed to compare the mSASSS and RASSS with regard to efficiency and added value.

Methods: Two-yearly spinal radiographs from patients followed in the Outcome in AS International Study (OASIS) were used. Two readers independently scored the x-rays, and averaged scores per vertebral corner (VC) were used. Only radiographs with ≤3 missing VCs per segment (cervical and lumbar, the latter with 4 thoracic VCs included as described for the RASSS) were included, so that both scores could be calculated. Status- and 2-year progression scores of both scoring methods were compared, first in terms of their availability. To assess the potential additional value of including the thoracic segment in the score, the relative contribution (in %) to the 2-year total RASSS progression of each spinal segment (cervical, thoracic and lumbar) was determined, and compared to the expected contribution, assuming a balanced segmental progression and proportional to the number of sites (12 cervical VCs, 4 thoracic VCs and 12 lumbar VCs).

Results: The mSASSS could be scored in a total of 809 radiographs. The RASSS could be calculated in 78% of these radiographs. In 58% of those, the RASSS was calculated based on 1 or 2 present thoracic VC scores (of the 4 possible thoracic VC scores), and the remaining 2–3 had to be imputed because they were missing (these imputed VCs were therefore uninformative). There were 520 two-year mSASSS interval progression scores available, and in 63% of them a 2-year RASSS interval progression score could be determined.

Of all the radiographs in which both scores could be determined (n=629), the mean (SD) status- score was 15.5 (17.9) units for the mSASSS and 18.0 (20.9) units for the RASSS. The mean (SD) 2-year interval progression scores (in 330 two-year intervals) were 2.0 (3.6) for the mSASSS and 2.4 (4.4) for the RASSS. Exclusive progression of the thoracic segment occurred in only 5% of the cases. There were no significant differences between the observed and expected contributions of the thoracic segment to progression (Table), whilst progression was more frequently than expected observed in the cervical spine, and less frequently in the lumbar spine.

Table. MRI scores at baseline, week 6 and week 28/end of study

	Relative contribution to total RASSS progression (in %)		
	Expected	Observed	*P*-value for the difference
Cervical segment (12 VCs)	43	55	0.09
Lumbar segment (12 VCs)	43	29	0.04
Thoracic segment (4 VCs)	14	16	0.70
Total (28 VCs)	100	100	

Conclusion: The determination of a RASSS for status or progression of radiographic abnormalities in the spine is frequently impossible or strongly influenced by non-contributory imputation. In comparison to the conventional mSASSS method, the contribution of thoracic VCs in the RASSS-method is negligible, and does not justify the additional scoring efforts.

Reference
A&R:61,764-71

1024

What Constitutes the Characteristic Fat Lesion On MRI of the Sacroiliac Joints in Early Spondyloarthritis? Ulrich Weber[1], Susanne Juhl Pedersen[2], Veronika Zubler[1], Kaspar Rufibach[3], Stanley Chan[4], Robert GW Lambert[4], Mikkel Ostergaard[5] and Walter P. Maksymowych[4]. [1]Balgrist University Hospital, Zurich, Switzerland, [2]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [3]University of Zurich, Zurich, Switzerland, [4]University of Alberta, Edmonton, AB, [5]Copenhagen University Hospital at Glostrup, Glostrup, Denmark

Background/Purpose: It is well known that fat infiltration (FI) of bone marrow may be observed on T1-weighted MRI in the sacroiliac joints (SIJ) of healthy individuals and patients with mechanical back pain and with spondyloarthritis (SpA). But it is unclear whether the MRI features of FI allow characterization of FI as pathological rather than physiological. Moreover, it is unclear if this might have diagnostic utility in early SpA. We aimed to assess which MRI features of fat contribute to diagnostic utility of SIJ MRI in 2 inception cohorts of early SpA.

Methods: Cohort A comprised 69 consecutive patients ≤50 years referred from rheumatology and primary care practices for assessment of clinically suspected SpA, cohort B comprised 88 consecutive patients ≤50 years with acute anterior uveitis and back pain. They were classified according to clinical examination and pelvic X-ray as having non-radiographic axial SpA (nr-axSpA) (n=20 and 31 for cohorts A and B, respectively), ankylosing spondylitis (AS) (n=10 and 24), or mechanical back pain (MBP) (n=39 and 33). Cohort A also comprised 20 healthy volunteers (HV). SIJ MRI were assessed independently in random order by 4 blinded readers for the following morphological features of FI: distinct border around the region of FI, homogeneity of the T1-weighted signal, proximity to subchondral bone, and association with other SIJ lesions (bone marrow edema (BME), erosion (ER)).

Results: In cohort A and B, FI in ≥2 SIJ quadrants was recorded by any 2 readers in AS in 90% and 100%, in nr-axSpA in 45% and 48%, in MBP in 36% and 24%, respectively, and in HV in 10%. Inter-reader agreement for FI expressed as intraclass correlation coefficient over all 4 readers was 0.59 and 0.75 for cohort A and B.

Diagnostic utility (mean of 4 readers for cohort A/B) of SIJ FI in nr-axSpA vs MBP patients

Feature	Sensitivity	Specificity	Positive LR	Negative LR
FI per se	0.44/0.42	0.73/0.78	1.62/1.91	0.77/0.74
FI with distinct border	0.21/0.21	0.97/0.90	8.29/2.13	0.81/0.88
Homogeneous FI	0.20/0.26	0.97/0.93	6.24/3.78	0.83/0.80
Subchondral FI	0.36/0.35	0.85/0.83	2.36/2.04	0.75/0.78
FI with any 2 features	0.24/0.30	0.97/0.92	9.26/3.58	0.78/0.77
FI+BME	0.19/0.18	0.99/0.92	14.63/2.13	0.82/0.90
FI+ER	0.21/0.24	0.99/0.93	33.15/3.55	0.79/0.81

BME: Bone marrow edema. ER: Erosion. FI: Fat infiltration. LR: Likelihood ratio. FI with any 2 features: ≥2 features out of FI with distinct border/ Homogeneous FI/Subchondral FI

Conclusion: SIJ FI characterized by a distinct border or homogeneity on MRI had substantial diagnostic utility in early SpA. FI in combination with BME or ER also showed high diagnostic utility.

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Spinal Inflammation in the Absence of SI Joint Inflammation On MRI in Patients with Active Non-Radiographic Axial Spondyloarthritis. Désirée van der Heijde[1], Joachim Sieper[2], Walter P. Maksymowych[3], Matthew A. Brown[4], Suchitrita S. Rathmann[5] and Aileen L. Pangan[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Charité Universitätesmedizin Berlin, Berlin, Germany, [3]University of Alberta, Edmonton, AB, [4]University of Queensland Diamantina Insititute, Brisbane, Australia, [5]Abbott Laboratories, Abbott Park, IL

Background/Purpose: The imaging arm of the ASAS axial spondyloarthritis (SpA) criteria requires the presence of sacroiliitis on MRI or radiographs. In patients (pts) with non-radiographic axial SpA (nr-axSpA), there may be inflammation along the spine in the absence of sacroiliac joint (SIJ) inflammation on MRI. This analysis evaluated the existence of spinal inflammation on MRI at baseline (BL) in nr-axSpA pts with and without inflammation in the SIJs on MRI.

Methods: ABILITY-1 is an ongoing multicenter, randomized, controlled trial of adalimumab vs. placebo in pts with nr-axSpA classified using the ASAS axial SpA criteria, who had an inadequate response, intolerance to, or contraindication for NSAIDs. MRI of the SIJ and spine performed at BL were centrally scored using the SPARCC method (6-DVU method for the spine) by 2 independent readers blinded to the treatment codes. Mean scores of the readers were used. SPARCC score ≥2 for either the SIJ or spine was used as the operational definition of positive MRI evidence of inflammation. For these analyses, all pts were combined, independent of randomization.

Results: Mean symptom duration of the study population (N=185) was 10 yrs. At BL, 48% of pts were reported by the local investigator to have past or present MRI evidence of sacroiliitis as required by the ASAS axial SpA criteria. Of pts with available BL SPARCC scores, 40% had a BL SIJ score ≥2 and 52% had a BL spine score ≥2. Of the pts with BL SPARCC SIJ score <2, 49% had evidence of spinal inflammation (BL SPARCC spine score

≥2). Comparison of BL disease characteristics based on BL spine and SIJ scores <2 vs. ≥2 were generally comparable except for a greater proportion of males among those with spine and SIJ scores ≥2, and younger age and shorter symptom duration among those with spine and SIJ scores <2. The cumulative probability plot (figure) shows a similar distribution of SPARCC spine scores regardless of presence or absence of SIJ inflammation on MRI. The most frequently involved DVUs with bone marrow edema were in the lower thoracic and lumbar spine.
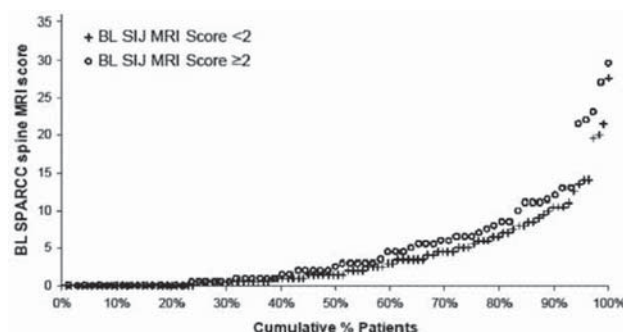
Figure.

Conclusion: Assessment by experienced readers shows that spinal inflammation on MRI may be observed in half of nr-axSpA pts without SIJ inflammation on MRI. MRI of both sites might be of value when evaluating pts with nr-axSpA. These data in pts with long-standing disease need to be confirmed in pts with shorter disease duration.

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Psoriatic Arthritis and Spondyloarthritis: Inflammation Assessed by "Head to Toe" Wholebody Magnetic Resonance Imaging—A Comparison with Clinical Joint Examination. René Panduro Poggenborg[1], Susanne Juhl Pedersen[2], Iris Eshed[3], Inge Juul Sørensen[2], Ole Rintek Madsen[4], J.M. Møller[5] and Mikkel Østergaard[6]. [1]Copenhagen University Hospital in Glostrup, Copenhagen, Denmark, [2]Glostrup Hospital, Copenhagen, Denmark, [3]Sheba Medical Center, Tel Hashomer, Israel, [4]Copenhagen University Hospital in Gentofte, Copenhagen, Denmark, [5]Copenhagen University Hospital in Herlev, Copenhagen, Denmark, [6]Copenhagen University Hospital Glostrup, Glostrup, Denmark

Background/Purpose: Psoriatic arthritis (PsA) and spondyloarthritis (SpA) is associated with a varied pattern of axial and peripheral inflammation. Wholebody magnetic resonance imaging (WBMRI) is a new imaging modality where patients are scanned from head to toe in one single examination. The purpose was to explore the potential of WBMRI for detecting peripheral and axial inflammation.

Methods: Patients with clinically active peripheral PsA (Moll and Wright, n=19) or axial SpA (ESSG, n=19) and healthy subjects (HS, n=12) were included. T_1-weighted pre/post-contrast and STIR sequences were performed on a 3 tesla MRI unit. Synovitis and bone marrow oedema (BME) were evaluated at sites included in the 78-tender joint count (TJC). Axially, BME was evaluated dichotomously in each discovertebral unit (DVU) of the spine, and in each quadrant of the sacroiliac joints (SIJ).

Results: Characteristics median (range): PsA/SpA/HS age 49(23–79)/ 42(26–61)/32(20–61) yrs. PsA/SpA disease duration: 4 (0–34)/17 (5–48) yrs; 78-TJC: 11(3–65)/3(0–17), 76-swollen joint count (SJC): 5 (0–20)/ 1(0–5), and BASDAI score 45(9–85)/55(2–93) mm.

WBMRI assessment was done in 3800 joints included in the TJC, and

synovitis/BME were detected in 593 (16%)/207 (5%) joints, synovitis/BME was absent in 1929 (51%)/1860 (49%) joints, and 1278 (34%)/1733 (54%) joints were not possible to evaluate. Evaluation was most frequently possible in the hip joints (188 joints (94%)), knees (186 (93%)), and the spine (in overall 94% of DVUs). In contrast, no temperomandibular joints, and only 17 (8%) of elbows could be evaluated.

In PsA, synovitis was found most frequently in carpometacarpal (CMC) (19 joints (61%)) and shoulder (18 (53%)) joints. In SpA, synovitis was found most frequently in 1st metatarsophalangeal joints (21 (67%)), and shoulders (17 (50%)).

In patients, the best agreement between WBMRI synovitis and clinical swelling was found at the right hand proximal interphalangeal (PIP) (kappa: 0.65), left hand 3rd distal interphalangeal joint (0.63), and the right hand 3rd PIP joints (0.62). The best agreement between WBMRI synovitis and tenderness was found at left foot 2nd and 3rd PIP (0.78; 0.47), and right hand 2nd PIP (0.70) joints.

In PsA, we found a significant correlation between SJC-28 and BME assessed in 28 and 78 joints (Spearman's rho: 0.54, P<0.05; 0.69, P<0.005). WBMRI synovitis did not correlate significantly with clinical joint examination. Scores of BME assessed in 78 joints were significantly higher in PsA/SpA compared to HS (Mann-Whitney, P<0.05).

BME in the spine was detected in PsA/SpA in median 2 (0–6)/1 (0–11) DVU, respectively, and BME in the SIJ was detected in 0 (0–2)/0 (0–8) quadrants, respectively. Sum scores of BME detected in spine and SIJ were for PsA: 2 (0–7) and SpA: 4 (0–11), which were significantly higher than in HS (1 (0–4)) (P<0.05).

Conclusion: Wholebody MRI scores of axial and peripheral bone marrow oedema are significantly higher in clinically active PsA and SpA patients than in healthy subjects. In PsA, we found a significant correlation between number of joints with BME and SJC, whereas TJC did not correlate. WBMRI is a promising imaging modality, as it allows simultaneous visualisation of inflammation in peripheral and axial joints.

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Frequency of MRI-Detected Hip Osteoarthritis Features in Persons with Chronic Hip Pain and the Diagnostic Performance of Radiography Using MRI As the Reference. Li Xu[1], Daichi Hayashi[1], Ali Guermazi[1], David J. Hunter[2], Anton Winterstein[3], Ling Li[4], Klaus Bohndorf[3] and Frank Roemer[3]. [1]Boston University School of Medicine, Boston, MA, [2]University of Sydney, Sydney, Australia, [3]Klinikum Augsburg, Augsburg, Germany, [4]New England Baptist Hospital, Boston, MA

Background/Purpose: Conventional radiography has been the standard imaging tool to diagnose and grade the severity of hip OA. However, radiography cannot visualize the bone marrow, cartilage and articular soft tissues that are relevant for clinical manifestation and structural progression of disease. The Hip Osteoarthritis MRI Scoring System (HOAMS) was recently developed to enable MRI-based whole-organ semiquantitative assessment of the hip. Frequency distribution of OA-associated features in the various anatomical subregions of the hip has not been described before. Further, the diagnostic performance of radiography to detect these abnormalities is unknown. Our aim was to describe the frequency of MRI-detected features of hip OA (cartilage damage, subchondral cysts, osteophytes and attrition) in various subregions of the hip joint and to evaluate the diagnostic performance of radiography for detection of these features using MRI as the reference.

Methods: 52 consecutive patients with chronic hip pain (mean age ±SD 63.5±9.5 years; 54% women) without inflammatory arthritis or recent trauma were imaged by 1.5T MRI. Of these, 44 subjects (85%) underwent weight-bearing antero-posterior pelvic radiography. For MRI assessment, the hip joint was subdivided into the following subregions (modified HOAMS system): latero-superior, centro-medial, anterior and posterior. According to HOAMS, cartilage was graded 0 to 4 based on extent (depth and area) of surface damage. Subchondral cysts and osteophytes were graded 0–3 and 0–4, respectively based on size. Bone attrition was noted as absent or present in the latero-superior subregion only. Presence of radiographic joint space narrowing (JSN) was compared to MRI-assessed cartilage damage. Sensitivity and specificity of radiography for diagnosing each feature (presence or

absence) were calculated using MRI as the reference standard, and the AUC was calculated from the ROC curve for each feature.

Results: 21 of 44 subjects had radiographic OA. Frequency of diffuse cartilage damage (for n=44) (HOAMS grade 3–4) in the latero-superior, centro-medial, anterior and posterior subregions was 58%, 58%, 35% and 33%, respectively. Frequency of subchondral cysts (grade≥1) and osteophytes (grade≥1) was 31% and 64% in the latero-superior, 12% and 77% in the centro-medial, 27% and 15% in the anterior, 8% and 35% in the posterior subregions, respectively. Frequency of bone attrition in the latero-superior subregion was 17%. Sensitivity, specificity and AUC of radiography to detect MRI assessed cartilage damage were 64%, 88% and 0.76 for JSN, 84%, 71% and 0.78 for osteophytes, 44%, 89% and 0.67 for subchondral cyst, and 78%, 86% and 0.82 for attrition.

Conclusion: In this cohort of subjects with hip pain diffuse cartilage damage and osteophytes were more frequent in the latero-superior and centro-medial subregions, while subchondral cysts were more frequent in the latero-superior and anterior subregions. Radiography offers acceptable diagnostic performance for attrition, diffuse cartilage damage (in the form of joint space narrowing) and osteophytes, but shows low sensitivity in detecting acetabular subchondral cysts a finding explained by the projectional drawbacks of radiography.

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Semi-Quantitative Assessment of Bone Marrow Edema and Synovitis-Effusion in Osteoarthritis with the Knee Inflammation MRI Scoring System: A Target Lesion Based Methodology. Walter P. Maksymowych[1], Ulrich Weber[2], Marcus Pianta[3] and Robert GW Lambert[1]. [1]University of Alberta, Edmonton, AB, [2]Balgrist University Hospital, Zurich, Switzerland, [3]University of Alberta, AB

Background/Purpose: Current MRI scoring methods for assessment of bone marrow lesions (BML) in the knee of patients with osteoarthritis rely on a complex subdivision of the knee into 15 subregions and then a further estimation of the proportion of subregion with BML[1]. Scoring of synovitis-effusion (S-E) is based on a restricted grading scheme assessing the whole joint (0= none, 3 = large) which limits responsiveness. We aimed to develop and conduct preliminary validation of an MRI method for direct semi-quantitative assessment of BML and S-E, that focuses on detection of change (Knee Inflammation MRI Scoring System (KIMRISS)).

Methods: Assessment of BML is based on assessment of coronal and sagittal images for medial/lateral knee compartments and axial/sagittal images for patella-femoral compartment using a fluid-sensitive MRI sequence (STIR, T2 FatSat). Size of a BML lesion is defined according to the largest continuous increase in signal assessed in all dimensions and number of slices in which the increased signal can be detected (small = <1cm in all dimensions on 2 slices; moderate = >1cm but NOT >2 cm in ≥2 dimensions; large = >2cm in ≥ 2 dimensions). A weighting is applied to change in BML size (1.5× and 2× for moderate and large lesions, respectively). Size of S-E is assessed in each of 4 compartments (medial and lateral patellar recess, suprapatellar, semimembranosus bursa) according to a 0–4 grading scheme and a weighting is applied for change in S-E size (1.5× and 2× for grade 3 and 4 lesions, respectively). MRI scans were performed on the knee joints of 15 patients enrolled into an open label trial of an anti-TNF agent in subjects with persistent pain due to knee osteoarthritis and clinical evidence of effusion who had failed conventional therapy. Scans were performed at baseline and 12 weeks and independently reviewed by 3 readers blinded to timepoint. Reliability of change scores was assessed by intraclass correlation coefficient (ICC) and responsiveness by standardized response mean (SRM). We assessed correlations with WOMAC pain, patient global, and target joint clinical effusion score.

Results: Reliability of detection of change in KIMRISS BML (ICC for 3 reader pairs = 0.71. 0.73. 0.75), KIMRISS S-E (ICC for 3 reader pairs = 0.78, 0.82, 0.86), and Total KIMRISS (ICC for 3 reader pairs = 0.77, 0.81, 0.89) was very good with substantial responsiveness after 12 weeks of treatment (Table). Improvement in Total KIMRISS score was observed in 12 patients although change in either the Total KIMRISS or KIMRISS BML did not significantly correlate with change in WOMAC pain or patient global. KIMRISS S-E did not correlate with target joint effusion score.

	ICC (3 readers)	SRM
KIMRISS BML	0.73	0.82
KIMRISS Synovitis-Effusion	0.82	0.70
KIMRISS Total	0.81	0.88

Conclusion: The KIMRISS methodology for MRI-based semi-quantitative assessment of acute lesions in knee joints is responsive and is capable of reliably detecting change. It merits further validation in inflammatory knee joint disorders.

1. Hunter et al. Osteoarthritis Cartilage 2011; 19: 990

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Frequency of Mediopatellar Plica in Persons with Chronic Knee Pain and Its Cross-Sectional Association with Patellofemoral Cartilage Damage and Bone Marrow Lesions: Data From the Joints On Glucosamine Study.

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Background/Purpose: Osteoarthritis (OA) commonly occurs in the patellofemoral joint (PFJ) and knee pain in subjects with knee OA often emanates from the PFJ rather than the tibiofemoral joint (TFJ). Despite this, research into risk factors and mechanisms for PFJ OA is limited compared to that of the TFJ. Mediopatellar plica (MPP) is often observed in conjunction with patello-femoral structural damage and plica syndrome is a common cause of knee pain. However, it is unclear if MPP is an independent risk factor for structural PFJ damage or if MPP is an incidental finding of questionable relevance. Our aim was to describe the frequency of different types of MPP in a cohort of subjects with knee pain and to assess the cross-sectional association of MPP with cartilage damage and bone marrow lesions (BMLs) in the PFJ.

Methods: 177 subjects aged 35–65 with chronic, frequent knee pain were included. 3T MRI of both knees was performed and a total of 342 knees were included. MPP was scored as Types A, B, and C according to a grading system modified from the Sakakibara arthroscopic classification, which takes into account the relative size of the plica in relation to the osteochondral junction of the anterior medial trochlea. Using the Whole Organ Magnetic Resonance Imaging Score (WORMS) system, cartilage (graded 0 to 6) and BMLs (graded 0 to 3) were semiquantitatively assessed for the medial patella, medial trochlea, lateral patella, and lateral trochlea. In addition Hoffa-synovitis and effusion-synovitis were scored from 0 to 3. Anatomical measurements of the PFJ that are potential risk factors for cartilage loss included the patellar length ratio (PLR), lateral patellar tilt angle (LPTA), bisect offset (BO), and sulcus angle (SA) on MR images. The frequencies of each type of MPP were recorded. Further, presence of MPP (any type) and its cross-sectional association with cartilage damage (defined as WORMS score ≥ 2) and BMLs (defined as WORMS score ≥ 1) in the PFJ was assessed using logistic regression. Adjustment was made for age, gender, body mass index (BMI), PLR, LPTA, BO, SA, and Hoffa- and effusion-synovitis.

Results: The mean age of subjects was 52 (SD±6) years, 95 (53.7%) were men, 160 (90.4%) were white and 144 (81.4%) had a BMI ≥ 25. Altogether 163 (47.7%) knees exhibited MPP (76 knees (22.2%) were Type A, 69 knees (20.2%) were Type B, and 18 knees (5.3%) were Type C). Significant cross-sectional associations between MPP and cartilage damage were observed for the medial patella (adjusted odds ratio (aOR) 2.12, 95% CI 1.23–3.64), but not for the medial trochlea or the lateral PFJ. No associations were found for MPP and presence of BMLs in the medial and lateral patellofemoral compartments.

Conclusion: Type A and B plicae were common while type C plicae were less common. The presence of MPP is cross-sectionally associated with medial patellar cartilage damage. No increased risk was observed for presence of MPP and cartilage damage at the medial trochlea or the lateral compartment. No associations were found between MPP and BMLs in any of the PF subregions. The latter finding might be explained by different loading conditions in the PFJ in comparison to the TFJ.

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Frequency and Fluctuation of Susceptibility Artifacts in the Tibio-Femoral Joint Space in Painful Knees On 3T MRI and Association with Meniscal Tears, Radiographic Joint Space Narrowing and Calcifications.

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Background/Purpose: Linear or punctate hypointensities are commonly seen on gradient echo (GRE) sequences in the tibiofemoral joint (TFJ) space of osteoarthritic joints. These magnetic susceptibility artifacts (SAs) are thought to represent vacuum phenomenon, a common radiologic finding in OA joints and vertebral disks. They appear adjacent to the cartilage or menisci and cartilage assessment may be impaired due to signal loss or be misinterpreted as a lesion. Aim was to assess the frequency of SAs in the TFJ space on dual-echo steady state (DESS, a GRE sequence very sensitive to magnetic susceptibility) and on intermediate-weighted (IW) fat-suppressed (fs) sequence, and assess associations with intraarticular calcifications and joint space narrowing (JSN) on X-ray (XR), and with MRI-detected meniscal damage in the TFJ.

Methods: 346 knees of 177 subjects aged 35–65 with knee pain were included. 3T MRI was performed at baseline and at 6-month follow-up (f/u). Baseline anteroposterior knee XR were read for JSN according to the OARSI atlas and linear/punctate calcifications within the TFJ were recorded as present or absent. The WORMS system was used to assess meniscal damage on MRI, and the presence of any damage (grade ≥ 1) was recorded at baseline. Linear/punctate hypointensities representing SAs in the TFJ space were assessed on coronal DESS and IW fs sequences. Readings were done blinded and in a random order. XR, DESS and IW images were each read on separate reading sessions >2 weeks apart. κ statistics were applied to assess concordance between findings on the baseline DESS and IW fs or XR.

Results: Subjects had a mean age of 52 (SD±6) years, BMI of 29±4, and 95 (54%) were men. Baseline Kellgren-Lawrence (KL) grades (for worst knee) were: KL 0– 37 (21%) knees; KL 1– 14 (8%) knees; KL 2– 26 (15%) knees; KL 3– 81 (46%) knees; KL 4– 19 (11%). On XR, 44 (13%) and 9 (3%) knees had medial and lateral JSN, respectively; and 7 (2%) and 14 (4%) knees had calcifications in the medial and lateral TFJ space, respectively. On MRI, 126 (36%) knees had medial and 31 (9%) knees had lateral meniscal damage. In the medial TFJ, 13 and 4 knees showed SAs at baseline on DESS and IW fs, respectively. On DESS, 6 of 13 knees had persistent SA at f/u and 6 knees had incident SA at f/u. In the lateral TFJ, 5 and 1 knees showed SAs at baseline on DESS and IW fs, respectively. On DESS, 2 of 5 knees had persistent SAs at f/u and 1 new SA was noted at f/u. In the medial TFJ, compared to knees without SAs on DESS, knees with SAs on DESS were more likely to have medial meniscal damage (9/13, 69% vs. 117/333, 35%, p=0.017) and medial JSN (5/13, 38%, vs. 39/333, 60%, p=0.016). Agreement on presence/absence of SAs between DESS and IW was κ=0.46 (95%CI 0.17–0.75) and that between SAs on DESS and calcifications on XR was κ=0.18 (-0.06 – 0.42) in the medial TFJ. We could not calculate p-values or κ in the lateral TFJ due to a very small number of SAs.

Conclusion: SAs on GRE sequence in the TFJ were seen in <5% of knees in this cohort. SAs are more frequently seen in knees with medial meniscal tears and medial JSN, which suggests an association with more advanced OA-related joint damage. SAs on MRI rarely correspond to XR-detected calcifications and commonly show longitudinal changes, which support the theory that these represent vacuum phenomenon.

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High Degree of Symmetricity of MRI-Detected Articular Tissue Damage in Subjects with Knee Pain: A within-Person Analysis From the JOG Study. Frank Roemer[1], C. Kent Kwoh[2], Michael J. Hannon[3], Robert M. Boudreau[4], Stephanie M. Green[4], John M. Jakicic[5], Carolyn E. Moore[6] and Ali Guermazi[7]. [1]Klinikum Augsburg, Augsburg, Germany, [2]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA, [5]University of Pittsburgh, PA, [6]Texas Women's University, Houston, TX, [7]Boston University School of Medicine, Boston, MA

Background/Purpose: Several risk factors for osteoarthritis (OA) have been described to be associated with an increased risk for incident radiographic OA, on a local (joint) or systemic (person) level. While radiography depicts articular changes only late in the disease process, magnetic resonance imaging (MRI) is capable of visualizing tissue pathology at a much earlier stage. Most MRI-based studies have used a one knee per person approach and thus data on bilaterality of OA features is sparse. Study aim was to describe symmetricity of MRI-detected OA features in a cohort with knee pain.

Methods: 169 subjects aged 35–65 with chronic, frequent knee pain were included in the Joint in Glucosamine (JOG) study. 3T MRI of both knees was performed using the same pulse sequence protocol as in the Osteoarthritis Initiative (OAI). Knees were semiquantitatively assessed according to the WORMS system by one expert MSK radiologist. Cartilage damage and bone marrow lesions (BMLs) were read in five plates (medial/lateral femur, medial lateral tibia, patella, femoral trochlea) while meniscal damage was read in three medial and three lateral subregions. Chi[2] tests were used to compare the proportion of people with unilateral tissue pathology to the proportion what would be expected if the two knees were independent. For this analysis, all MRI features were divided into present (score≥1) and absent (score=0). We further used linear weighted (w) kappa statistics to describe agreement between knees for cartilage damage and BMLs in the same articular plates using the full WORMS scores (0–4 for cartilage and 0–3 for BML).

Results: 52.1 % of participants were men, mean age was 51.2 (±6.2) years old, mean BMI was 29.0 (± 4.1). The worst Kellgren/Lawrence (KL) grades in either knee were: K/L 0: 37 (21.9%) knees, K/L 1: 14 (8.3%) knees, K/L 2: 26 (15.4%) knees, K/L 3: 78 (46.2%) knees K/L 4: 14 (8.3). All plates showed a significant lower degree of unilaterality for any cartilage damage (ranging between 15.5% and 32.0%) than expected (ranging between 27.1% and 50.2%). For any BMLs the degree of unilaterality was lower for the patella, trochlea, medial tibia, and medial femur; for any meniscal damage the degree of unilaterality was lower for all medial meniscal subregions but not lateral. All plates showed higher overall % agreement (range 82.6–94.7%) than expected (range 73.0–93.1%) for cartilage damage and BMLs. Moderate agreement (defined as w-kappa 0.4–0.6) was observed for patellar and trochlear cartilage damage (0.59 and 0.54) and patellar (0.41) BMLs.

Table 1. Expected and exact overall % agreement and w kappa for different articular plates

Plate (Worst grade in plate)	Exact % agreement	Expected % agreement	Weighted kappa	Standard Error
Cartilage				
Patella	88.99%	73.00%	0.59	0.054
Femoral Trochlea	91.12%	80.73%	0.54	0.058
Medial Femur	86.09%	79.55%	0.32	0.055
Lateral Femur	89.94%	85.28%	0.32	0.069
Medial tibia	86.39%	79.27%	0.34	0.057
Lateral Tibia	90.53%	85.25%	0.36	0.059
BMLs				
Patella	82.64%	70.64%	0.41	0.058
Femoral Trochlea	83.63%	75.11%	0.34	0.059
Medial Femur	86.39%	81.54%	0.27	0.060
Lateral Femur	94.67%	93.08%	0.23	0.060
Medial tibia	87.50%	83.55%	0.24	0.061
Lateral Tibia	90.53%	89.80%	0.07	0.061

Table 2. Expected and exact overall % agreement and kappa for different articular subregions in descending order by kappa

Subregions ranked by descending order of w kappa value (4 highest shown)	Exact % agreement	Expected % agreement	Non-weighted kappa	Standard Error
Cartilage				
1. Lateral patella	84.52%	51.70%	0.68	0.077
2. Lateral fem. ant.	84.02%	61.63%	0.58	0.076
3. Medial tib. central	82.25%	62.05%	0.53	0.077
4. Medial patella	77.38%	52.56%	0.52	0.077
BMLs				
1. Lat. femur post.	96.45%	92.05%	0.55	0.076
2. Lateral patella	74.56%	58.99%	0.38	0.077
3. Medial fem central	79.29%	70.21%	0.30	0.075
4. Lateral fem. ant.	78.11%	68.89%	0.30	0.077

Conclusion: A higher degree of symmetricity of articular tissue damage than expected by chance was observed in this cohort of subjects with knee pain. These findings support the hypothesis that OA is a multifactorial disease triggered by risk factors on an individual joint level but also by person-based risk factors that predispose joints not only to radiographic OA but also to articular tissue damage commonly associated with OA.

Medial Meniscal Root Tears and the Association with Meniscal Extrusion, Prevalent Cartilage Damage and Longitudinal Cartilage Loss: The MOST Study. Mohamed Jarraya[1], David T. Feslon[1], Daichi Hayashi[1], Frank Roemer[2], Yuqing Zhang[1], Jingbo Niu[1], Michel Crema[1], Martin Englund[3], John A. Lynch[4], Michael C. Nevitt[5], James Torner[6], C.E. Lewis[7] and Ali Guermazi[1]. [1]Boston University, Boston, MA, [2]Klinikum Augsburg, Augsburg, Germany, [3]Lund University, Lund, Sweden, [4]University of California at San Francisco, San Francisco, CA, [5]University of California-San Francisco, San Francisco, CA, [6]University of Iowa, Iowa City, IA, [7]University of Alabama at Birmingham, Birmingham City, AL

Background/Purpose: The meniscal root is a ligamentous structure that anchors the posterior horn of the meniscus to the tibial plateau. The association of isolated meniscal root tears with progression of osteoarthritis or cartilage loss has not been examined. Aim of the study was to assess the cross-sectional association of medial meniscal root tears with prevalent medial tibiofemoral cartilage damage and medial meniscal extrusion in subjects with radiographic osteoarthritis. We further wished to assess if isolated medial meniscal root tears increase the risk of incident and progressive cartilage damage in the medial tibiofemoral compartment at 30-month follow up.

Methods: The Multicenter Osteoarthritis (MOST) Study is a longitudinal observational study of subjects with or at risk for knee osteoarthritis. Knees were randomly selected from subjects with radiographic OA at baseline and read for presence of absence of root tear ($\kappa=1$ for intrareader agreement). Cartilage damage was graded from 0 to 6 in each of the 5 medial tibiofemoral subregions according to WORMS scoring system. Prevalent cartilage damage was defined as any score ≥2 in at least one subregion. Longitudinal progression of cartilage damage was studied for 548 patients who had follow up MRIs read, and was defined as at least within grade or more increase in at least one subregion including incident cartilage damage. Meniscal extrusion was recorded as present or absent. Isolated meniscal root tear was defined as the presence of a root tear without any additional meniscal damage (WORMS1–4). Knees were divided into 3 groups: knees with an isolated medial meniscal root tear (i.e., exposed group), those without root tears but with other meniscal damage (i.e., referent group A); and knees without root tear or meniscal damage (i.e., referent group B). In the longitudinal analysis, we calculated relative risk (RR) of cartilage worsening comparing the exposed group and the group A with the group B.

Results: Of 594 knees included in the cross-sectional analysis (64.1% women, mean age 62.8 +/− 7.9, mean BMI 30.9 +/−5.2), 37 knees were in the exposed group, 293 in referent group A and 264 in referent group B. Exposed knees showed higher prevalence of meniscal extrusion than referent group B (91.9% vs. 60.7%, p<0.0001). Prevalence of cartilage damage was

also higher in the exposed group than in group B (97.3% vs 63.7%, p<0.0001) but not group A (97.3% vs 95.2%, p=0.057). Of 548 knees included in the longitudinal analysis, 33 knees were in the exposed group, 270 in group A, and 245 in group B. The adjusted RRs of cartilage loss in the exposed group and the group A were 2.04 (95%CI 1.19 – 3.49) and 1.84 (95% CI 1.32 - 2.58), respectively, when compared with group B.

Conclusion: Knees with isolated medial meniscal root tears exhibit a higher prevalence of ipsicompartimental extrusion when compared to knees without meniscal damage. Isolated meniscal root tears increase the risk of ipsicompartmental cartilage loss longitudinally.

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Reliability and Responsiveness of Two Methods for Assessment of Magnetic Resonance Imaging Abnormalities in Hip Osteoarthritis in a Placebo-Controlled Trial of Intra-Articular Steroid Injection. Walter P. Maksymowych[1], Jolanda Cibere[2], Ulrich Weber[3], Jacob Jaremko[1], Damien Loeuille[4], Veronika Zubler[3], Frank Roemer[5], Eric C. Sayre[6] and Robert GW Lambert[1]. [1]University of Alberta, Edmonton, AB, [2]Arthritis Research Ctr of CA, Vancouver, BC, [3]Balgrist University Hospital, Zurich, Switzerland, [4]CHU Brabois, Vandoeuvre les Nancy, France, [5]Klinikum Augsburg, Augsburg, Germany, [6]Arthritis Research Centre of Canada, Vancouver, BC

Background/Purpose: Inflammation in osteoarthritis (OA) is the basis for the use of steroid injection therapy which has demonstrated efficacy for symptoms of hip OA in a randomized placebo-controlled trial[1]. Both synovitis and bone marrow lesions (BML) have been associated with pain in OA and can be detected on MRI. Two scoring methods have been developed which assess synovitis-effusion but score BML using different approaches: 1) the Hip Inflammation MRI Scoring System (HIMRISS) assesses BML using consecutive images in the coronal plane and a dichotomous (yes/no) scoring method; 2) the Hip Osteoarthritis MRI Scoring System (HOAMS) is a whole joint scoring system which assesses BML according to volume of region affected on both coronal and sagittal scans. We aimed to determine the reliability and responsiveness of both methods for detecting change in these MRI lesions and associations with clinical changes in patients receiving steroid injection therapy.

Methods: Six readers (3 radiologists, 3 rheumatologists) assessed MRI scans of hip joints from 18 patients enrolled into a randomized double-blinded placebo-controlled trial of intra-articular steroid treatment for hip OA. Scans were performed at baseline and the primary endpoint at 8 weeks. Coronal STIR sequences of the hip joints were evaluated. For HIMRISS, the sum of femoral BML scores (0–65), acetabular BML scores (0–35), effusion score (0–30) and total score was calculated based on femoral and acetabular subregion readings. In HOAMS, BML (0–3) and synovitis (0–2), were assessed in femoral and acetabular subregions and summed scores for all subregions were calculated for BML (0–45) and synovitis (0–8). Reliability of change scores was assessed using intra-class correlation coefficient (ICC), responsiveness by standardized response mean (SRM) and Guyatt's effect size (ES). We assessed associations with WOMAC pain subscale in the same patients and a second cohort of 27 patients with early OA by regression analysis.

Results: Inter-observer reliability of change scores was very good to excellent for femoral BML, and good to very good for synovitis-effusion and acetabular BML despite limited training. Reliability was comparable between radiologists and rheumatologists. Responsiveness and discrimination was moderate to high for synovitis-effusion. Significant associations were noted between BML or synovitis scores and pain scores for baseline values (p ≤ 0.001 in combined N=45) but not change values (N=18). The association with pain was particularly evident in patients with early OA (N=27) with the HIMRISS synovitis-effusion (p = 0.001) and HOAMS synovitis (p = 0.005) scores.

	ICC (change)	ICC (Rheumatologist)	ICC (Radiologist)	SRM	Guyatt's ES
Total HIMRISS	0.77	0.76	0.82	0.16	0.33
Femoral BML HIMRISS	0.81	0.80	0.82	0.03	0.08
Acetabular BML HIMRISS	0.49	0.52	0.54	0.14	0.19
Synovitis-effusion HIMRISS	0.35	0.48	0.36	0.55	0.69
HOAMS BML	0.71	0.73	0.71	0.18	0.29
HOAMS Synovitis	0.58	0.58	0.69	0.44	0.95

Conclusion: Change in BML and synovitis on MRI is reliably detected using both HOAMS and HIMRISS but only synovitis scores are responsive to treatment. Association with pain is primarily evident in early OA and with scores for synovitis-effusion.

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Changing Osteoarthritis Treatment Assessment Paradigms: Subchondral Bone Is a More Responsive Measure of Progression Than the Current Radiographic Standard. Michael A. Bowes[1], Christopher B. Wolstenholme[1], Devan Hopkinson[1], Graham R. Vincent[1] and Philip G. Conaghan[2]. [1]Imorphics Ltd, Manchester, United Kingdom, [2]University of Leeds, Leeds, United Kingdom

Background/Purpose: Radiographic joint space width (JSW) assessment, a surrogate for cartilage assessment, is the standard for structure modification trials of osteoarthritis (OA). However the subchondral bone is integral to OA progression and modern image analysis techniques allow accurate, automated identification of bone in MR images. The objective of this study was a comparison of the sensitivity of 3D bone area measures in MR images with minimum medial JSW in radiographs in all subjects in the Osteoarthritis Initiative dataset with definite medial OA over a 2 year period, representative of a typical OA clinical trial.

Methods: 828 subjects with medial OA and MR images at baseline, 12 and 24 months, and available radiograph scoring were selected from the Osteoarthritis Initiative dataset; medial OA was defined as KL≥2 and presence of medial osteophytes. Femur, tibia and patella bones were automatically segmented from MRIs using active appearance models[1]. Anatomical areas were automatically identified within the model[2] and were measured at each time-point. All regions of the articulating surface of the femur, tibia and patella were included in the analysis. Minimum medial joint space width (minMJSW) was provided by the OAI, using a semi-automated software method[3]. Sensitivity of both methods to change was assessed using the standardised response mean (mean/SD of change).

Results: Mean age (SD) of the case group was 62 years (8.8); BMI 29.7(4.8); KL 2.55(0.65); 35% females. MinMJSW showed significant change at 12 and 24 months with SRM values of −0.16 and −0.33. Change in bone area was significant in all regions for all time-points, except the lateral femur at 12 months (see Figure 1). Medial femur compartments provided the greatest sensitivity to change, with SRM values typically twice those of minMJSW. Tibial compartments and the notch of the femur also showed higher SRM figures than minMJSW, while patellar compartments had comparable SRMs to the radiographic measure. Only the lateral femoral compartments had lower SRMs than the minMJSW method.

Figure 1. Sensitivity of bone area to change, compared with minMJSW measures on 828 subjects.

	Mean Change		SRM	
	Year 1	Year 2	Year 1	Year 2
Minimum median JSW	−0.1 (0.04)	−0.23 (0.05)	−0.16	−0.33
MF	0.52 (0.09)	1 (0.12)	0.39	0.57
TrFMed	0.55 (0.1)	1.1 (0.12)	0.39	0.63
LF	0.1 (0.12)*	0.17 (0.16)	0.05	0.07
TrFLat	0.1 (0.09)	0.35 (0.1)	0.07	0.23
Notch	0.44 (0.1)	0.73 (0.11)	0.31	0.45
MT	0.45 (0.1)	0.87 (0.12)	0.31	0.48
LT	0.34 (0.1)	0.69 (0.12)	0.23	0.38
MP	0.34 (0.16)	0.91 (0.2)	0.15	0.31
LP	0.33 (0.16)	0.95 (0.19)	0.14	0.34

JSW values are in mm, bone area change in % change in bone area from baseline (95% confidence limits). All changes were highly significant except* which was not significant

Conclusion: Change in bone area was more sensitive than the minMJSW method in a number of knee compartments, particularly in the medial femur

and tibia. Measurement of bone change provided a more responsive tool for monitoring OA progression in a cohort selected for typical OA trial characteristics.

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Disclosure: **M. A. Bowes**, Imorphics Ltd, 1, Imorphics Ltd, 3; **C. B. Wolstenholme**, Imorphics Ltd, 3, Imorphics Ltd, 1; **D. Hopkinson**, None; **G. R. Vincent**, Imorphics Ltd, 3, Imorphics Ltd, 1; **P. G. Conaghan**, None.

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Characterisation of New Bone Formation in Gout: A Quantitative Site-by-Site Analysis Using Plain Radiography and Computed Tomography. Nicola Dalbeth[1], Aaron Milligan[2], Barnaby Clark[2], Fiona M. McQueen[1] and Anthony Doyle[1]. [1]University of Auckland, Auckland, New Zealand, [2]Department of Radiology, Auckland District Health Board, Auckland, New Zealand

Background/Purpose: Radiographic descriptions of gout have noted the tendency to hypertrophic bone changes. The aim of this study was to characterise the features of new bone formation (NBF) in gout, and to determine the relationship between NBF and other radiographic features of disease, particularly erosion and tophus.

Methods: Paired plain radiographs (XR) and computed tomography (CT) scans of 798 individual hand and wrist joints from 20 patients with gout were analyzed. Following a structured review of a separate set of images, films were scored for the presence of the following features of NBF: spur, osteophyte, periosteal NBF, ankylosis and sclerosis (Figure). Sites for NBF scoring were those included in the gout-modified Sharp-van der Heijde method for erosion scoring. The relationship between NBF and other imaging features of gout (erosion and tophus) was analysed.
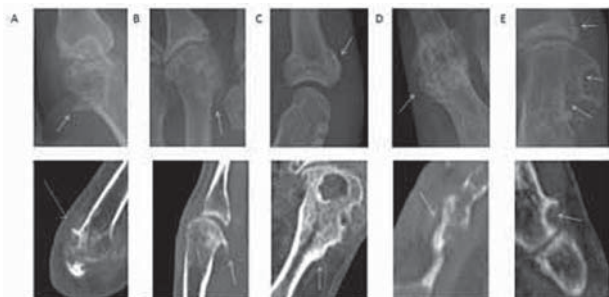
Figure. Examples of the features of new bone formation (NBF) observed by plain radiography and computed tomography in patients with gout. A. Spur. B. Osteophyte. C. Periosteal NBF. D. Ankylosis. E. Sclerosis. Top panel shows plain radiographic images and lower panel shows CT images.

Results: The most frequent forms of NBF were bone sclerosis (28.6% of all assessed joints using CT) and osteophyte (30.5%). Spur and periosteal NBF were less common (17.8% and 6.0% respectively), and ankylosis was rare (0.6%). On both XR and CT, joints with bone erosion were more likely to have NBF; for XR, odds ratios (OR) 64.9 for spur, 64.9 for osteophyte, 119.8 for periosteal NBF, 30.1 for ankylosis and 101.1 for sclerosis (p for all <0.0001); and for CT, OR 45.1 for spur, 3.3 for osteophyte, 16.6 for periosteal NBF, 26.6 for ankylosis and 32.3 for sclerosis (p for all <0.01). Similarly, on CT, joints with intraosseous tophus were more likely to have NBF; OR 48.4 for spur, 3.3 for osteophyte, 14.5 for periosteal NBF, 35.1 for ankylosis and 39.1 for sclerosis (p for all <0.001).

Conclusion: This detailed quantitative analysis has demonstrated that NBF occurs more frequently in joints affected by other features of gout. This work suggests a connection between bone loss, tophus, and formation of new bone during the process of joint remodelling in gout.

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The Prevalence of Chondrocalcinosis of the Acromioclavicular Joint On Chest Radiographs and correlation with Calcium Pyrophosphate Dihydrate Crystal Deposition Disease. Konstantinos M. Parperis, Guillermo F. Carrera, Keith E. Baynes, Alan P. Mautz, Melissa S. DuBois, Ross M. Cerniglia and Lawrence M. Ryan. Medical College of Wisconsin, Milwaukee, WI

Background/Purpose: Digital imaging combined with picture archiving and communication system (PACS) access allows detailed image retrieval and magnification. Calcium pyrophosphate dihydrate (CPPD) crystals preferentially deposit in fibrocartilages, the cartilage of the acromioclavicular (AC) joint being one such structure. We sought to determine if careful examination of the AC joints on magnified PACS imaging of routine chest films would be useful in identifying chondrocalcinosis (CC).

Methods: Retrospective radiographic readings and chart reviews involving all 1920 patients aged 50 or more who had routine outpatient chest radiographs over a 4 month period were performed. CC was identified as linear or punctate cartilage calcifications. Knee radiographs were available for comparison in 489 patients. Medical records were reviewed to abstract demographics, chest film reports, and diagnoses.

Results: AC joint CC was identified in 1.1% (21/1920) of consecutive chest films. Patients with AC joint CC were 75 ($\pm$ 11.6 S.D.) years of age versus 65 ($\pm$10.5 S.D.) in those without CC (p<0.0002, Wilcoxon rank sum). There was no significant gender difference in the prevalence of AC CC. 489 patients had knee films. 6 of these patients had AC joint CC and of these 5 also had knee CC (83%). Of the 483 without AC joint CC 62 (12%) had knee CC (p=0.002 Fischer's exact). Of the patients with AC joint CC only 14% had a diagnosis of CPPD recorded on the chart and none had AC joint calcification noted on the official radiology report. Patients with AC joint CC were more likely to have a recorded history of CPPD crystal disease than those without AC joint CC (14% versus 1%, p=0.0017 Fischer's exact).

Conclusion: By using digital imaging and PACS software magnification, AC joint CC is discernible on routine chest films. The prevalence of AC joint CC increases with age and is usually an indicator of associated knee CC. AC joint CC is most often overlooked by radiologists reading routine chest images. Rheumatologists (and radiologists) should consider scrutiny of available chest films for AC joint CC. A finding of AC joint CC should heighten suspicion of pseudogout or secondary osteoarthritis in appropriate clinical settings. And AC joint CC in a young patient should alert the clinician to the possibility of an associated metabolic condition. Moreover, such scrutiny is without cost other than less than a minute of time.

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Magnetic Resonance Imaging (MRI) Assessment of Inflammatory Myopathy: Quantitative Fat-Corrected Muscle T2 and Conventional T2 Measurement Versus Standard MRI and Clinical Metrics. Lawrence Yao[1], Adrienne L. Yip[2], Sepehr Mesdaghinia[3], Ashkan Shademan[3], Joseph A. Shrader[1], Anna V. Jansen[2], Frederick W. Miller[2] and Lisa G. Rider[2]. [1]Clinical Center, NIH, Bethesda, MD, [2]NIEHS, NIH, Bethesda, MD, [3]NIEHS, NIH, Bethesda

Background/Purpose: Active muscle disease in patients with idiopathic inflammatory myopathies (IIM) is characterized by prolonged muscle T2 relaxation on MRI. We examined the utility of MR T2 maps, and a method of correcting these maps for varying fat content, as quantitative, semi-automated alternatives to conventional MRI in the evaluation of IIM. MRI measures were also validated against other myositis metrics.

Methods: Forty-four IIM patients (8 dermatomyositis [DM], 13 polymyositis [PM], 22 juvenile DM, 1 juvenile PM) underwent MRI of the thighs at 1.5 Tesla and extensive clinical testing, including assessment of Physician Global Activity (PGA), muscle strength by isometric dynamometry (QMT), functional assessment by Childhood Myositis Assessment Scale (CMAS) and Childhood Health Assessment Questionnaire (CHAQ), and the Myositis Damage Index (MDI). Follow-up imaging was also performed 11 months later in 20 patients after therapy. MRI included a Carr-Purcell-Meiboom-Gill sequence and a Dixon-based

fat water separation sequence, for generation of T2, fat fraction (FF), and fat-corrected T2 (fc-T2) maps, and Short Tau Inversion Recovery (STIR) and T1 spin echo (SE) sequences for standard visual assessment. Muscle edema and damage were visually scored on STIR and T1 SE images, respectively, using a semi-quantitative rating system that incorporates anatomic extent and severity of findings. T2, fc-T2, and fat fraction (FF) values were tabulated for the thigh muscles of each patient with an automated segmentation algorithm.

Results: STIR scores correlated significantly with mean T2 and mean fc-T2 values (Spearman $r_s = 0.65$ and 0.61, $p< 0.001$), while T1 damage scores correlated with mean FF ($r_s = 0.67$, $p< 0.001$). Baseline mean T2, mean fc-T2, and visual STIR scores correlated significantly with the CMAS ($r_s = -0.50$, -0.36, -0.55, respectively, $p<0.05$) and CHAQ ($r_s = 0.46$, 0.35, 0.43 respectively, $p< 0.05$), and with QMT ($r_s = -0.49$, -0.52, -0.48, respectively, $p<0.05$). MDI muscle damage scores correlated significantly with visual T1 damage scores ($r_s = 0.72$, $p<0.001$) and mean FF measurements ($r_s = 0.67$, $p<0.001$). For 20 patients evaluated after a change in therapy, standardized response means for visual STIR, mean fc-T2, and mean T2 scores were -0.52, -0.31, -0.12, respectively. The change in PGA assessment correlated with changes in STIR ($r_s = 0.74$, $p<0.01$) and mean fc-T2 scores ($r_s = 0.46$, $p<0.05$). However, changes in STIR scores and mean fc-T2 values were discordant with outcomes, based on 20% improvement in PGA, in 5 and 6 of 20 patients, respectively.

Conclusion: Semi-automated survey of quantitative thigh muscle T2, FF, and fc-T2 MRI maps have good content validity with visual scoring of clinical MRI. These quantitative MRI measures have good construct validity with other measures of myositis disease activity and damage, particularly muscle measures. While fc-T2 appears to be more responsive than conventional T2, fc-T2 and T2 are less responsive than visual STIR scores. Additionally, both visual and quantitative MR analysis of thigh muscles exhibited limited agreement with global disease improvement after therapy, as reflected by the PGA assessment.

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Assessment of Aortic Stiffness by Cardiac Magnetic Resonance Imaging in Systemic Autoimmune Rheumatic Diseases. Galia Karp[1], Arik Wolak[2], Nina Baram[3], Victor Novack[4], Philip Rosen[3], Yael Perl[5], Talia Wolak[6], Ilan Shelef[3] and Mahmoud Abu-Shakra[7]. [1]Department of Medicine, Soroka Medical Centre and Ben Gurion University, Beer-Sheva, Israel, [2]Dept. of Cardiology, Cardiac MRI unit, Soroka University Medical Center, and Ben Gurion University, Beer-Sheva, Israel, [3]Radiology division, Soroka University Medical Center and Ben Gurion University, [4]Department of Medicine, Clinical Research center, Soroka University Medical Center and Ben Gurion University, [5]Clinical Research center, Soroka University Medical Center and Ben Gurion University, [6]Department of Medicine and Hypertension unit, Soroka University Medical Center and Ben-Gurion University, [7]Department of Medicine and Rheumatology, Soroka Medical Centre and Ben Gurion University, Beer-Sheva, Israel

Background/Purpose: Systemic Lupus Erythematosus (SLE) and rheumatoid arthritis (RA) are known to cause premature arterial aging and early atherosclerosis hence leading to increased stiffness of the large arteries. Recently, Cardiac MRI (CMRI) was introduced as a new technique for assessment of aortic stiffness by measuring the Pulse Wave Velocity (PWV). Therefore, we aimed to assess aortic stiffness by CMRI in RA and SLE patients.

Methods: We prospectively recruited 25 RA female patients, 26 SLE female patients and adjusted controls that matched each patient for age, comorbidities (hypertension, diabetes mellitus, dyslipidemia) and smoking status. Clinical and laboratory data were gathered. CMRI was performed using a 1.5T scanner and included phase contrast images of the ascending and descending aorta. Dedicated cardiovascular analysis software was used to measure the flow at the level of the ascending and the descending aorta. The distance between these 2 levels was obtained and PWV was calculated accordingly

Results: The mean age of RA patients and their healthy control group was 51.83 ± 15.14 and 51.33 ± 14.47 respectively. Systolic Blood pressure was higher amongst RA patients, 132.61 ± 15.16 mmHg versus 121.72 ± 20.55 mmHg for controls ($p=0.02$). PWV was higher among the RA group;

9.11 ± 3.96 for RA and 7.79 ± 2.98 for the control group ($p=0.13$). SLE patients were younger than RA patients, averaging 41.31 ± 13.51. SLE patients were heavier and had larger waist circumference than their controls. Their Framingham score was slightly lower than their paired controls. PWV was higher than their paired controls, 6.67 ± 2.39 vs. 6.03 ± 2.23 ($p=0.02$), thus reaching statistical significance. We further found positive correlation between SLE disease activity and PWV ($p=0.02$). This correlation was not found among RA patients.

Conclusion: PWV is higher amongst SLE patients, as opposed to healthy controls ($p=0.02$). In addition PWV is positively correlated with SLE disease activity ($p=0.02$). Amongst RA patients, PWV was higher as opposed to paired controls, but this failed to achieve statistical significance. Our data raise the hypothesis that amongst SLE patients, who are known to have significantly higher levels of atherosclerosis, PWV may serve a marker for cardiovascular morbidity.

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Cardiac Involvement in Systemic Sclerosis: The Added Value of Magnetic Resonance Imaging. Luna Gargani[1], Alessandro Pingitore[2], Daniele De Marchi[2], Serena Guiducci[3], Giancarlo Todiere[2], Silvia Bellando Randone[3], Cosimo Bruni[3], Marica Doveri[4], Laura Bazzichi[4], Stefano Bombardieri[4], Massimo Lombardi[2], Eugenio Picano[1] and Marco Matucci Cerinic[3]. [1]Institute of Clinical Physiology, National Research Council, Pisa, Italy, [2]Gabriele Monasterio Foundation, CNR-Regione Toscana, Pisa, Italy, [3]Department of Biomedicine, Division of Rheumatology AOUC, Excellence Centre for Research, Florence, Italy, [4]Rheumatology Unit, University of Pisa, Pisa, Italy

Background/Purpose: Cardiac involvement in systemic sclerosis (SSc) affects the prognosis of the disease. Myocardial fibrosis is the pathological hallmark of this complication and has been reported in 50-80% of cases in necropsy. Echocardiography is the routine imaging tool to easily detect cardiac involvement, but it is not accurate to detect myocardial fibrosis. Delayed gadolinium enhancement (DE) cardiovascular magnetic resonance (CMR) is the gold-standard for myocardial fibrosis assessment. The aim of the present study was to evaluate the added value of DE-CMR to echocolorDoppler in SSc patients.

Methods: After a thorough clinical characterization, 171 SSc patients (age=52 ± 14, 91% females, 22% diffuse form) underwent, on the same day, a comprehensive echocardiogram, including tissue Doppler imaging (TDI), and a DE-CMR.

Results: Echocardiography showed normal systolic function (ejection fraction>50%) and wall motion score index (=1) in 100% of patients, whereas DE-CMR showed a pattern of non-ischaemic myocardial fibrosis in 12/53 (23%) patients. In 2/53 patients (4%), T2-weighted CMR showed myocardial oedema, that resolved after steroid therapy. No clinical parameter (age, duration of disease, limited or cutaneous form, Scl-70 positivity, Rodnan skin score, activity score) was an independent predictor of the presence of myocardial fibrosis.

Conclusion: Subclinical cardiac involvement is relatively frequent in SSc and is not necessarily related to duration of disease or other clinical characteristics. CMR can detect different patterns of reversible (by T2-weighted) and irreversible (by DE) cardiac involvement (see figure), not detectable by echocardiography.

Normal   Myocardial fibrosis   Myocardial oedema

irreversible   reversible
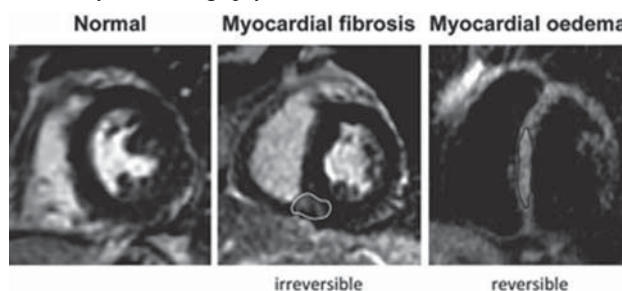
Disclosure: L. Gargani, None; **A. Pingitore**, None; **D. De Marchi**, None; **S. Guiducci**, None; **G. Todiere**, None; **S. Bellando Randone**, None; **C. Bruni**, None; **M. Doveri**, None; **L. Bazzichi**, None; **S. Bombardieri**, None; **M. Lombardi**, None; **E. Picano**, None; **M. Matucci Cerinic**, None.

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Combined High-Resolution Single Photon Emission Computed Tomography and Magnetic Resonance Imaging for Therapy Monitoring in Rheumatoid Arthritis. Philipp Sewerin[1], Christian Buchbender[1], Katalin Mattes-György[1], Falk Miese[1], Hans-Jörg Wittsack[1], Christof Specker[2], Gerald Antoch[1], Matthias Schneider[3], Axel Scherer[1] and Ben Ostendorf[1]. [1]Heinrich-Heine-University, Düsseldorf, Germany, [2]Hospital Essen Sued, Essem, Germany, [3]Heinrich-Heine-University, Duesseldorf, Germany

Background/Purpose: To evaluate whether combined multi-pinhole single photon emission computed tomography (MPH-SPECT) with technetium-99m-labelled disphosphonates (Tc99m-DPD) and magnetic resonance imaging (MRI) detect changes in inflammation in early rheumatoid arthritis (ERA) patients under methotrexat (MTX) therapy and to investigate the relation between Tc99m-DPD uptake and the development of erosion.

Methods: MPH-SPECT and MRI of metacarpophalangeal joints (MCP) have been prospectively performed in 10 consecutive ERA patients (8 female, 2 male; 49 ± 13 years [mean $\pm$ SD]), range: 24–68) prior to and 6 months after initiation of MTX. The Tc99m-DPD uptake was measured using a region of analysis. The course of synovitis, bone marrow edema (BME) and erosions were scored according to the Rheumatoid Arthritis MRI Score (RAMRIS) criteria.

Results: The frequency of increased Tc99m-DPD uptake, synovitis and BME decreased under MTX therapy; but the number of bone erosions increased. Joints with progressive and newly developed erosions on follow-up had a higher baseline Tc99m-DPD uptake (2.64 ± 1.23 vs. 1.43 ± 0.91) ($p < 0.001$). Joints with persistent synovitis did not show higher Tc99m-DPD uptake values (1.56 ± 1.27 vs. 1.47 ± 0.75) ($p=0.74$). There was no correlation between persistence of synovitis and the development of erosions ($Fc= 0.3$, $p= 0.12$).

Conclusion: Persistence of synovitis seems to be independent from Tc99m-DPD uptake and the development of erosions, while early increased bone metabolism is found in MCP joints which show erosive progression under MTX therapy. Hybrid MPH-SPECT and MRI might thus provide valuable additional information for individual risk-stratified therapeutic decisions.

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Whole-Body Magnetic Resonance Imaging - A New Diagnostic Tool in the Assessment of Activity in Juvenile Dermatomyositis Patients? Tania Monteiro de Castro[1], Henrique Lederman[1], Maria Teresa Terreri[1], Wanda I. Caldana[1], Edmar Zanoteli[2] and Maria Odete Hilario[1]. [1]Federal University of São Paulo, São Paulo, Brazil, [2]University of São Paulo, São Paulo, Brazil

Background/Purpose: Juvenile dermatomyositis (JDM) is a rare autoimmune disorder, but remains the most commonly chronic inflammatory myopathy among children. A redefinition of the diagnostic criteria is currently underway and is likely to lead to non-invasive exams such as magnetic resonance (MR) imaging, in place of electromyography and muscle biopsy in the diagnosis of the disease. Our goal was to demonstrate the benefit of whole-body MR imaging as a diagnostic tool in the detection of muscle inflammatory activity in JDM and to correlate these findings with clinical evaluation including muscle strength, laboratorial exams, nailfold capillaroscopy and muscle biopsy.

Methods: Thirty-three patients aged 6–19 years (median age, 12.1 years), 22 girls with a diagnose of JDM according to Bohan & Peter criteria were evaluated at any point during their illness course using clinical examination, muscle enzymes determination, muscle strength tests such as Childhood Myositis Assessment Scale (CMAS) and Manual Muscle Testing (MMT), nailfold capillaroscopy and short tau inversion recovery (STIR) whole-body MR imaging. JDM activity was evaluated by Disease Activity Score (DAS). An open muscle biopsy was performed in deltoids or biceps braquialis if muscle disease activity was detected on MR exam.

Results: Whole-body scanning gave a complete assessment of all muscles groups and disease activity was detected in STIR MR imaging in four (12.1%) patients confirmed by muscle biopsy. All four patients had elevation of at least one muscle enzyme and the nailfold capillaroscopy showed scleroderma (SD) pattern in these patients. CMAS, MMT and DAS means were 25.7, 32.3 and 9 respectively in patients with altered MR, and 48.1, 77 and 2.35 respectively in patients whose MR were normal. Twenty-nine patients had inactive disease (24 with medication and five without medication). Nailfold capillaroscopy was normal in 16 patients and with SD pattern in nine patients (not done in four patients). Muscle strength tests (CMAS and MMT) were normal in 16 out of 29 patients (MMT not done in four patients).

Conclusion: Whole-body MR allows us to evaluate the extent and symmetry of muscle disease and inflammatory activity in a single exam by revealing muscles groups not seen with standard protocols. Nailfold capillaroscopy is an important additional exam to assess disease activity. Muscle strength tests are important to evaluate not only the disease in the acute phase, but the accumulated effect over the same time.

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Psoriatic Arthritis Patients Assessed by Dynamic Contrast-Enhanced MRI in High Disease Versus Minimal Disease Activity State - a Cross-Sectional Study Correlating Conventional MRI and Clinical Composite Measures. René Panduro Poggenborg[1], Pernille Bøyesen[2], Charlotte Wiell[3], Susanne Juhl Pedersen[4], Inge Juul Sørensen[5], Ole Rintek Madsen[6], Ole Slot[1], Jakob M. Møller[7], Mikael Boesen[8], Henning Bliddal[9], Olga Kubassova[10] and Mikkel Østergaard[11]. [1]Copenhagen University Hospital in Glostrup, Copenhagen, Denmark, [2]Diakonhjemmet Hospital, Olso, Norway, [3]Copenhagen University Hospital in Gentofte, Copenhagen, Denmark, [4]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [5]Glostrup Hospital, Copenhagen, Denmark, [6]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Copenhagen, Denmark, [7]Copenhagen University Hospital in Herlev, Copenhagen, Denmark, [8]Copenhagen University Hospital at Frederiksberg, Copenhagen, Denmark, [9]Copenhagen University Hospital at Frederiksberg, Frederiksberg, Denmark, [10]Image Analysis Ltd., Leeds, United Kingdom, [11]Glostrup Hospital, Glostrup, Denmark

Background/Purpose: Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) has been validated in rheumatoid arthritis for measuring inflammation, but has rarely been studied in psoriatic arthritis (PsA).

The purpose was to investigate whether DCE-MRI can discriminate PsA patients with high disease activity from minimal disease activity (MDA)(1), and to correlate DCE-MRI findings with conventional MRI and clinical measures.

Methods: PsA patients fulfilling CASPAR criteria were eligible in this investigator-initiated study of patients with either high disease activity (group 1) or MDA (group 2). Inclusion criteria were for group 1: swollen joint count (SJC)$\geq$6, tender joints count (TJC)$\geq$6, hand involvement and clinical indication for initiation of anti-TNF therapy, and for group 2: hand involvement within 1 year, long-term treatment with adalimumab 40 mg eow, and fulfilling criteria for MDA (at least 5 out of 7: TJC$\leq$1; SJC'1; body surface area$\leq$3%; PtGA$\leq$20; pain$\leq$15; HAQ$\leq$0.5; 13-enthesitis$\leq$1). DAS28 and the new Disease Activity index for PSoriatic Arthritis (DAPSA)(2) score (sum of SCJ, TJC, PtGA, pain and CRP) was calculated. The validated PsAMRIS scoring system (3) was used for analyzing conventional MRI (0.6 tesla). PsAMRIS total inflammation was calculated by adding synovitis, flexor tenosynovitis, periarticular inflammation and bone marrow oedema scores. DCE-MRI were analysed by Dynamika software (Image Analysis Ltd., Leeds, UK). Regions of interest (ROIs) were drawn around 2.-5. metacarpophalalangeal joints, excluding large blood vessels. The ROIs were used for automatic computing of the number of pixels with plateau and washout pattern (N_{p+w}), the initial rate of enhancement (IRE), and maximum enhancement (ME).

Results: Patient characteristics were: 9 males/8 females, median age 45 (25–63) years, joint/skin disease duration 8 (2–59)/15(2–59) years (no difference between groups). Clinical and imaging data are shown in the table.

	Group 1: High disease activity (n=9)	Group 2: Minimal Disease Activity (n=8)	P value
N_{p+w}	712 (13–1587)	362 (25–1316)	0.25
IRE $\times 10^3$	8 (5–33)	10 (6–14)	0.29
ME	1.20 (1.17–1.33)	1.21 (1.16–1.33)	0.92
N_{p+w}* IRE	5.4 (0.4–15.9)	2.8 (0.2–13.2)	0.44
N_{p+w}* ME	946 (16–1903)	434 (29–1608)	0.29
PsAMRIS synovitis	3 (0–5)	2 (0–5)	0.59
PsAMRIS total inflammation	16 (1–24)	7.5 (3–18)	0.19
DAS28 score	5.5 (3.9–6.4)	1.4 (1.1–2.4)	0.01
DAPSA score	64.9 (30.9–103.3)	2.4 (0.1–5.6)	0.01

Median (range). Groups compared using Krustal-Wallis test.

We found a significant correlation between the DCE-MRI parameters (N_{p+w}*IRE, N_{p+w}*ME and N_{p+w}) and PsAMRIS total inflammation (Spearman's rho: 0.53, 0.51 and 0.51; all $P<0.05$). DCE-MRI parameters were not statistically significant correlated with clinical measures, but N_{p+w}*IRE, N_{p+w}*ME and N_{p+w} were numerically lower in the MDA group.

Conclusion: DCE-MRI parameters correlated significantly with PsAMRIS total inflammation score, and showed a trend toward higher values in the high disease activity versus the MDA group. DCE-MRI is a promising method for assessing joint inflammation in PsA. However, a larger longitudinal study is needed to clarify, if DCE-MRI is superior to conventional MRI for discriminating between disease activity levels.

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Assessment of Rheumatoid Arthritis Disease Activity by Power Doppler Ultrasonography: Association with Routine Clinical Indices and Its Usefulness in Detecting Remission. Hiroaki Taguchi, Kazuo Nishi, Takeo Kudo and Yutaka Okano. Kawasaki Municipal Kawasaki Hospital, Kawasaki, Japan

Background/Purpose: Power Doppler ultrasonography (PDUS) is sensitive for detecting synovitis in patients with rheumatoid arthritis (RA). We aimed to clarify the association of PDUS findings with routine clinical indices and its usefulness in detecting disease remission.

Methods: We studied 72 RA patients with mean age 62.5 years, mean disease duration 5.6 years, and 61% women. We examined 22 joints including bilateral wrists, metacarpo-phalangeal, and proximal interphalangeal joints using PDUS to evaluate the presence of inflammation with scoring from 0 to 3 according to the signal intensity of each joint, and the sum score (ranging from 0 to 66) was defined as "PDUS score". Clinical disease activity score/indices including DAS28CRP, SDAI, and CDAI were also recorded. Clinical remission was defined according to the following criteria: DAS28CRP < 2.3, SDAI ≤ 3.3, CDAI ≤ 2.8, and Boolean-based definition. Sonographic remission was defined by absence of PDUS signals.

Results: Mean values ± SD of DAS28CRP, SDAI, and CDAI were 3.3±1.5, 18.8 ±15.0, and 17.3±13.5, respectively. Mean values ± SD of PDUS score was 6.2 ± 6.3 and significantly correlated with all three clinical disease activity score/indices; among them the correlation with SDAI was strongest (r=0.77, p<0.001). PDUS score was more significantly correlated with swollen joint counts (r=0.73), patient global assessment (GA) (r=0.77), or evaluator GA (r=0.85), than with tender joint counts (r=0.50) or serum CRP (r=0.61). Remission was observed in 17 (24%) patients by DAS28CRP, in 11 (15%) by SDAI, in 12 (17%) by CDAI, and in 14 (19%) by Boolean-based definition, respectively. Sonographic remission was observed in 9 (13%) patients. In 36-59% of the patients satisfying clinical remission criteria, the PDUS signals were detected indicating the presence of synovitis (Table 1). Values of DAS28CRP, SDAI, and CDAI of patients with sonographic remission were 1.3, 1.7, and 1.9, respectively.

Table 1. Distribution of patients with absence and presence of PDUS signals for patients with clinical disease remission defined by DAS28CRP, SDAI, CDAI, and Boolean-based criteria.

	n	sonographic signals absence	sonographic signals presence
DAS28CRP <2.3	17	7 (41%)	10 (59%)
SDAI ≤3.3	11	7 (64%)	4 (36%)
CDAI ≤2.8	12	7 (58%)	5 (42%)
Boolean-based criteria	14	8 (57%)	6 (43%)

Conclusion: PDUS is useful for evaluating RA disease activity, is exceedingly sensitive, and is a useful method for detecting "pure" RA disease remission.

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Ultrasound Scores of Enthesitis and Dactylitis Do Not Correlate with Corresponding Clinical Findings in Psoriasis Arthritis. Rusmir Husic[1], Josef Hermann[1], Judith Gretler[2], Winfried B. Graninger[1] and Christian Dejaco[1]. [1]Medical University Graz, Graz, Austria, [2]Auenbruggerplatz 15, Graz, Austria

Background/Purpose: To compare sonography verified inflammation of entheses, tendons and joints with corresponding clinical findings in psoriasis arthritis (PsA) patients.

Methods: Prospective study of 70 consecutive PsA patients [mean age 51.1 (±SD 11.6) years, 30% female, median disease duration 7.0 (range 0–44.7) years]. Clinical and ultrasound examination was performed at 68 joints and 14 entheses (lateral epicondyle, triceps insertion, quadrizeps insertion, proximal and distal insertion of patellar ligament, Achilles tendon, plantar fascia), and clinical scores including the Disease Activity index for PSoriatic Arthritis (DAPSA), composite psoriatic disease activity index (CPDAI), dactylitis score, Leeds enthesitis index (LEI), HAQ and PASI were calculated. Sonography was performed by two rheumatologists blinded to clinical data using an ESAOTE Twice ultrasound device. Synovial hypertrophy and/or joint effusion (SH/E) as well as Power Doppler (PD) were graded at each joint from 0 to 3 in accordance with prior publications. At hands and feet we also recorded the presence of perisynovitis and tenosynovitis. For grading of enthesitis by ultrasound the MASEI and GUESS scores were used. Ultrasound signs of dactylitis were defined by the presence of synovitis plus tenosynovitis at MCP/MTP, PIP and DIP joints.

Results: The median DAPSA was 12.1 (0.1–70.2), mean CPDAI 4.8 (±2.5), median clinical Dactylitis score 0 (0–10), median LEI 0 (0–4), mean HAQ 0.73 (±0.81) and median PASI 1.0 (0–23.2). Using sonography, we found SH/E and/or PD at 12 (range 3–35) [median SH/E score 16.0 (range 3.0–56.0)] and/or 2 (0–19) [PD-score 3.0 (0–31.0)] joints, respectively. Eighteen patients (25.7%) had evidence of perisynovitis in at least one MCP joint and 20 (28.6%) patients demonstrated flexor tenosynovitis affecting at least one whole finger or toe. Median MASEI and GUESS scores were 32.5 (7.0–73.0) and 13.0 (4.0–27.0), respectively. Ultrasound signs of dactylitis were found in 5 (7.1%) patients.

DAPSA showed a moderate correlation with total SH/E (corrcoeff 0.35, p=0.003) and PD-scores (corrcoeff 0.36, p=0.002), as well as with the number of joints affected by SH/E (corrcoeff 0.24, p=0.045) and/or PD (corrcoeff 0.32, p=0.006). Total CPDAI did not correlate with SH/E, PD, enthesitis or dactilytis scores; however, within the CPDAI-joint domain we found differences concerning SH/E- and PD-scores between patients with no [n=17, median SH/E 12.0 (3.0–32.0); PD-score 1.0 (0–11.0)] and moderate [n=17, SH/E 25.0 (6.0–43.0), p=0.009; PD 5.0 (0–31.0), p=0.005] or high clinical activity [n=26, SH/E 18.5 (6.0–56.0), p=0.025; PD 5.5 (0–30.0), p=0.005). In the CPDAI enthesitis and dactilytis domains no differences were found, comparing the MASES/GUESS and ultrasound defined dactylitis, respectively between the groups. No correlation was found between clinical and sonographic dactylitis scores; or LEI (clinical) and MASEI/GUESS (sonography).

Conclusion: No association was found between sonographic and clinical assessment of enthesitis and dactylitis in PsA patients. Ultrasound verified joint inflammation moderately correlated with DAPSA and CPAI joint components.

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Dynamic Contrast-Enhanced Magnetic Resonance Imaging of the Wrist in Rheumatoid Arthritis Patients Treated with Methotrexate, Intra-Articular Glucocorticoid and Adalimumab/Placebo. Mette Bjørndal Axelsen[1], Merete L. Hetland[2], Kim Hørslev-Petersen[3], Kristian Stengaard-Pedersen[4], Peter Junker[5], Jan Pødenphant[6], Jakob M. Møller[7], Henning Bliddal[8], Olga Kubassova[9], Mikael Boesen[10] and Mikkel Østergaard[1]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [3]University of Southern Denmark, Graasten, Denmark, [4]Arhus University Hospital, Aarhus, Denmark, [5]Odense University Hospital, Odense C, Denmark, [6]Copenhagen University at Gentofte, Hellerup, Denmark, [7]Copenhagen University Hospital in Herlev, Copenhagen, Denmark, [8]The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen, Denmark, [9]Image Analysis Ltd., Leeds, United Kingdom, [10]Copenhagen University Hospital at Frederiksberg, Copenhagen, Denmark

Background/Purpose: To validate parameters of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in an early rheumatoid arthritis (RA)

clinical trial by comparison with clinical parameters of disease activity, and by investigating the sensitivity to change during a 2-year-follow-up.

Methods: 14 early RA patients diagnosed according to the ACR1987 criteria within 6 months of inclusion and with a DAS28 ≥3.2 (9/5 women/men, median aged 37 [range 27-69] years, disease duration 82 [42-129] days) were randomized 1:1 to treatment with methotrexate (MTX) and adalimumab or MTX and placebo. Any swollen joints were injected with triamcinolone (max 4 joints/4 ml per visit) in a 2-year-follow-up. If continuous disease activity was present, treatment was intensified. Conventional MRI and DCE-MRI of the right wrist were performed at baseline, and after 6, 12 and 24 months using a 0.6 Tesla MRI-unit. A 3-slice dynamic sequence was obtained at the time of injection of the contrast agent (Gadoteric acid 0.2 mL/kg). DCE-MRI parameters: TR 33ms, TE 4.2ms, flip angle 25°, FOV 200 mm^2, matrix 108×192, slice thickness 3 mm.

On DCE-MR images, the wrist were manually delineated using the image software Dynamika version 4.6.0 (Image analysis Ltd., Leeds, UK, www.image analysis.org) and for these regions of interest (ROI) the number of enhancing voxels (Nvoxel), the initial rate of enhancement (IRE), the maximum enhancement (ME), the IRE×Nvoxel and ME×Nvoxel were extracted by the software and compared to clinical parameters of disease activity.

Results:

Table 1. Clinical and MRI data at baseline and at follow-up visits.

	Baseline	6 months	12 months	24 months
DAS28(CRP)	4.75 (3.5–6.1)	2.2 (1.8–2.8)***	2.0 (1.7–3.9)***	2.1 (1.7–3.3)***
CRP (mg/mL)	14 (7–116)	7 (7–11)**	7 (7–47)*	7 (7–31)*
Patient's VAS pain	48 (12–82)	11 (2–37)***	22 (1–72)*	15 (0–72)***
Patient's VAS global	54 (19–98)	22 (3–45)***	24 (0–75)*	21 (0–67)***
Patient's VAS fatique	46 (9–90)	18 (2–83)^{NS}	30 (0–85)^{NS}	24.5 (0–68)*
Health Assessment Questionnaire	1.0 (0.0–1.875)	0.130 (0–1)***	0.125 (0.0–1.00)**	0.13 (0.0–1.0)**
VAS doctor	51 (15–76)	5 (0–16)***	2 (0–26)***	3 (0–33)***
Swollen Joint Count 28	3 (1–7)	0 (0–1)***	0 (0–1)	0 (0–0)
Tender Joint Count 28	5 (2–17)	0 (0–2)***	0 (0–2)	0 (0–3)
Number of Enhancing voxels (Nvoxel)	548 (0–3786)	73 (0–1763)^{NS}	181 (0–1694)^{NS}	74 (0–617)^{NS}
Maximum Enhancement (ME)	1.21 (0–1.39)	1.17 (0.00–1.32)^{NS}	1.19 (0–1.39)^{NS}	1.23 (0–1.51)^{NS}
Initial Rate of Enhancement (IRE) (%/s)	0.45 (0.0–1.20)	0.35 (0–0.9)^{NS}	0.40 (0.0–1.0)^{NS}	0.6 (0.0–1.7)^{NS}
ME×Nvoxel	666 (0–5251)	85 (0–2329)^{NS}	215 (0–2350)^{NS}	90 (0–929)^{NS}
IRE×Nvoxel (%/s)	246 (0–4543)	26 (0–1587)^{NS}	63 (0–1694)^{NS}	44 (0–1049)^{NS}

Values are presented as medians (minimum–maximum). VAS: visual analog scale. Change from baseline: Wilcoxon Signed Ranks Test, *: p<0.05, **: p<0.01, ***: p<0.005, ^{NS}: not significant.

All clinical parameters decreased during follow-up, while there were no statistically significant changes for the DCE-MRI parameters, which may reflect lack of power. Furthermore, it should be emphasized that only 3 of the examined wrist joints were clinically affected at baseline.

Conclusion: DCE-MRI is a promising outcome measure in clinical trials, but MRI at baseline must include clinically involved joints.

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Automated Breast Volume Scanner (ABVS), a New Automated Ultrasonic Device, Is Useful to Examine Joint Injury in Patients with Rheumatoid Arthritis. Shin-ya Kawashiri[1], Takahisa Suzuki[1], Yoshikazu Nakashima[1], Akitomo Okada[1], Naoki Iwamoto[1], Kunihiro Ichinose[1], Mami Tamai[1], Kazuhiko Arima[2], Hideki Nakamura[2], Tomoki Origuchi[1], Masataka Uetani[1], Kiyoshi Aoyagi[1] and Atsushi Kawakami[1]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Nagasaki University, Nagasaki, Japan

Background/Purpose: Automated Breast Volume Scanner (ABVS) is an ultrasonic device to be developed for the automated scanning for mammary glands. We have tried to explore the clinical application of ABVS toward the synovial lesion in patients with rheumatoid arthritis (RA).

Methods: Ten active RA patients of mean 54 y.o., whose mean disease duration 15 months and DAS28-ESR 5.69, were recruited. Patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. We have examined in total 100 metacarpophalangeal (MCP) joints as well as 20 wrist joints at dorsal sites by both ABVS (ACUSON S2000) and conventional ultrasonography (US) at the same day consecutively. ABVS was scanned in a water tank. Presence of synovial hypertrophy and bone erosion by gray-scale were examined by both methods, and the association of both methods was calculated by kappa coefficient.

Results: The scanning time of ABVS was 2 min per patient and that of conventional US was 15 min per patient, respectively. ABVS detected synovial hypertrophy in 10 MCP joints and 13 wrist joints whereas conventional US detected synovial hypertrophy in 11 MCP joints and 13 wrist joints. Kappa coefficient of synovial hypertrophy was 0.84 in MCP joints and 0.78 in wrist joints, respectively. ABVS detected bone erosion in 2 MCP joints and 5 wrist joints whereas conventional US detected bone erosion in 5 MCP joints and 6 wrist joints. Kappa coefficient of bone erosion was 0.56 in MCP joints and 0.90 in wrist joints, respectively.

Conclusion: Present data have shown a substantial agreement of ABVS with conventional US to find the synovial hypertrophy and bone erosion of wrist and finger joints in patients with RA. Since ABVS is able to scan the wrist and finger joints automatically in a short time, ABVS is a helpful new ultrasonic method to examine joint injury in patients with RA.

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Evaluation of Ankle Swelling Due to Löfgren's Syndrome: A Pilot Study Using B -mode and Power Doppler Ultrasonography. Emmanuelle LeBras[1], Sandra Balser[1], Valentin S. Schäfer[1], Boris P. Ehrenstein[1], Patrick Hoffstetter[1], Martina Müller[2], Martin Fleck[1] and Wolfgang Hartung[1]. [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [2]University Clinic Regensburg, Regensburg

Background/Purpose: Patients suffering from acute sarcoidosis frequently present with bilateral painfull swelling of the ankles, establishing ankle arthritis as a hallmark of Löfgren's syndrome. Standardized high resolution musculoskeletal ultrasound (MUS) including power Doppler has been utilized to further characterize the nature of the ankle swelling in patients presenting with Löfgren's syndrome.

Methods: Ankle joints of 36 consecutive patients suffering from Löfgren's syndrom were investigated by high resolution MUS using B- and power Doppler mode. Presence of effusion/synovitis and tenosynovitis has been determined, and hyperperfusion was scored in a semiquantitative fashion (grade 0–3).

Results: The majority of patients (26/36; 72,2%) did not present characteristic arthrosonographic findings of an acute arthritis (distension of the capsule and hyperperfusion). Ankle joint effusion was only observed in 9 of the 36 patients (25%). Remarkably, 88,8% of these patients had an ankle effusion grade I and only 11,1% presented an effusion grade II. Instead, an extensive subcutaneous edema indicating periarthritis was detected in 23 of 26 patients (88,4%). In addition, tenosynovitis could be visualized in 14 patients (38,8%).

Conclusion: Utilizing MUS including power Doppler, the present results clearly demonstrate that ankle swelling in patients suffering from Löfgren's syndrome is predominantely due to periarticular soft tissue swelling and tenosynovitis. In contrast, distinct articular synovitis is rare and if present only of mild degree without relevant power Doppler activity.

Tenosynovitis in Carpal Tunnel Syndrome - Prevalence and Comparison Between Ultrasonography, Surgery and Histology. David F. Ten Cate[1], Nick Glaser[1], Jolanda J. Luime[2], K.H. Lam[3], Johannes W.G. Jacobs[4], Ruud W. Selles[2], Johanna Hazes[5] and M. Bertleff[6]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus MC - University Medical Center, Rotterdam, Netherlands, [3]Erasmus University Medical Center, Netherlands, [4]University Medical Center Utrecht, Utrecht, Netherlands, [5]Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands, [6]Xpert Clinic, Rotterdam, Netherlands

Background/Purpose: Carpal tunnel syndrome (CTS) is a common neuropathy affecting the median nerve. CTS occurs more frequently in inflammatory arthropathies, such as rheumatoid arthritis (RA). This may relate to the presence of tenosynovitis in the wrist. Patients with tenosynovitis might be better treated conservatively with a diagnostic rheumatological consultation and other non-surgical methods, such as a glucocorticoid injection. However, flexor tenosynovitis at carpal tunnel level is not always easy to detect at clinical examination, but may be detected reliably by ultrasonography (US). Our aim was to determine the presence of tensynovitis detected at US in idiopathic CTS patients referred for surgery and to compare this with the peroperative evaluation and histological findings.

Methods: The wrists of 34 consecutive idiopathic CTS patients, with an indication for carpal tunnel release, were assessed before surgery with greyscale US (GSUS) and power Doppler US (PDUS) at the volar aspect of the wrist. Flexor tenosynovitis was scored according OMERACT US definitions. During surgery, tenosynovitis was evaluated by the surgeon according to a three-grade tenosynovitis classification system. Biopsy specimens were obtained in 28 patients; tenosynovitis was scored histologically by a pathologist according to a three-grade scoring system.

Results: US Tenosynovitis was detected in 59% of the patients. Peroperative, surgical tenosynovitis was detected in 88% of the patients. The pathologist found minor tenosynovitis in 17% of the patients, while 79% showed reactive changes (Table 1). The agreement between the respective modalities is presented in tables 2 and 3.

Table 1. Prevalence of tenosynovitis

	US	Surgery	Histology
TS +	59%	46%	17%
TS +/−	N.A.	42%	79%
TS−	41%	12%	4%

- TS: Tenosynovitis
- For surgery and histology TS +/− is grade 1

Table 2. Comparison US-Surgery

US	Surgery	TS+	TS−
TS+	17	3	20
TS−	13	1	14
	30	4	34

Surgical TS: Grade 1 + grade 2. Histological TS: Grade 2 (expert opinion)

Table 3. Comparison US-Histology

US	Histology	TS+	TS−
TS+	4	12	16
TS−	1	11	15
	5	23	28

Surgical TS: Grade 1 + grade 2. Histological TS: Grade 2 (expert opinion)

Conclusion: In idiopathic CTS patients undergoing surgery, frequently tenosynovial changes are found at US and surgical evaluation, but histology did not confirm this entirely. Tenosynovitis was seen, histologically, in only a minority of all cases. However, reactive changes can be observed in a large number of cases and this could also be the basis of the surgical and ultrasonographic findings. The exact definition of tenosynovitis in these three modalities needs further investigation.

The Prevalence of the Ultrasonographic Positive Power Doppler Synovitis Is High and Predicts the Risk of Relapse and Structural Progression in Rheumatoid Arthritis in Clinical Remission: A Systematic Literature Review and Meta Analysis. Huong Nguyen[1], Adeline Ruyssen-Witrand[1], Arnaud L. Constantin[1], Violaine Foltz[2], Frédérique Gandjbakhch[2] and Alain G. Cantagrel[1]. [1]Purpan University Hospital, Toulouse, France, [2]Pitié Salpétrière Hospital, Paris, France

Background/Purpose: Ultrasonography (US) can detect synovitis in patients with rheumatoid arthritis (RA) more sensitively than clinical examination either in active disease or in remission.[1,2] There are many definitions of clinical remission, no consensus on US assessment of RA activity and the clinical implication of residual US synovitis is hotly debated.[3,4] This study is to assess the prevalence of residual US synovial hypertrophy (USGS+) and US power Doppler (PD) activity in patients in clinical remission and evaluate the predictive value of this residual synovitis in terms of relapse and structural progression.

Methods: A systematic literature search was performed in the Medline, Embase and Rheumatology meeting databases up to 28 May 2012. The prevalence of USGS+, cold synovitis (USGS+/PD-), active synovitis (USGS+/PD+) and complete remission (USGS-/PD-) were collected taking into account the definition of clinical remission, the stage of RA (early or established disease) and the US examination method. A meta-analysis assessing the risk of relapse or structural progression in patients with USGS+/PD+ compared to other patients was performed calculating the odds ratio (OR[MH]) and 95% confidence interval [95%CI] with the Mantel-Haenszel method.

Results: 18 studies including 1528 patients were included in this systematic literature review. All of the studies used the OMERACT method for US scoring. The prevalence of US GS+, USGS+/PD-, USGS+/PD+ and USGS-/PD- were 81.8 %, 40%, 43% and 15.7%, respectively. USGS+ or USGS+/PD+ prevalence was comparable between the different definitions of clinical remission (DAS44, DAS28, SDAI, ACR 1981 or ACR/EULAR 2011) and between the different US examination methods (from 5 to 44 joints assessed). The prevalence of USGS+ and USGS+/PD+ was higher in the patients with established RA in comparison to patients with early RA (respectively 87% of USGS+ compared to 64%, p<0.001 and 45% of USGS+/PD+ compared to 34%, p<0.001). According to the results of the meta-analysis performed on 4 studies[5–8] (including 178 patients) and 3 studies[5, 9, 10] (including 173 patients), the presence of USGS+/PD+ was associated with an increased risk of relapse (OR[MH][95%CI]=2.9, [1.5,5.9], p=0.002) and an increased risk of structural progression (OR[95%CI]= 12.8, [1.3, 126.8], p=0.03), respectively, over 1 to 2 years.

Conclusion: The prevalence of residual US synovitis is high in patients in clinical remission. Residual USGS+/PD+ increase the risk of relapse and structural progression in these patients.

Assessment of Validity of Magnetic Resonance Imaging Measures of Joint Inflammation and Damage in Rheumatoid Arthritis Wrist/Hand - a Systematic Literature Review. TG Woodworth[1], O. Morgacheva[2], OM Troum[3], OL Pimienta[3], P. Maranian[2], V.K. Ranganath[2] and D.E. Furst[2]. [1]Visiting Clinical Researcher, David Geffen School of Medicine, UCLA, Los Angeles, CA, [2]David Geffen School of Medicine, UCLA, Los Angeles, CA, [3]USC Keck School of Medicine, Santa Monica, CA

Background/Purpose: Limitation of x-ray joint damage is a key indicator of therapeutic efficacy in rheumatoid arthritis (RA). Although magnetic resonance imaging (MRI) is increasingly used due to its greater sensitivity vs radiographs, summary evidence validating MRI features of RA joint inflammation and damage is lacking. By systematic literature review (SLR), we examined the validity of MRI for assessment of RA wrist/hand features according to Outcome Measures in Rheumatology Clinical Trials (OMERACT) criteria.

Methods: An SLR in PubMed with Cochrane hedge was conducted using search terms: RA, AND MRI, AND specific terms i.e., synovitis, joint space narrowing (JSN), erosions or bone marrow edema (BME) AND humans AND randomized controlled trials [RCTs], clinical studies; 1970 to Aug 2011; English. Pairs of authors evaluated titles/abstracts, selecting articles for extraction according to these criteria: adults with RA, MRI of hands and/or

wrists assessing at least one of the following: synovitis, BME/osteitis, tenosynovitis, erosions, JSN; RCT, observational study, or case series ≥10 patients. To achieve ≥ 95% consistent data extraction, authors evaluated the same 5 articles, ensuring consensus on data extraction methods. Each author then extracted a proportion of the articles. Data extracted included MRI, field strength, measurement methods, and validity criteria: criterion, content, construct, reliability, responsiveness, and discrimination. Level of evidence was assessed using Cochrane Handbook criteria, adapted for imaging research.

Results: Of 575 MRI titles/abstracts, 180 met criteria with 81 having at least 1 type of validation. Although MRI measurement methods were developed using several approaches, OMERACT RA MRI scoring (RAMRIS) was determined to be the dominant method. As 43 articles utilized 1.5T, and 7 used other field strengths; only 1.5T articles were analyzed. (Table) 19 articles including 6 RCTs using 1.5T and RAMRIS were extracted seeking validation of MRI measures. The table summarizes the number of articles with data for validation. Histologic or radiographic evidence for criterion validity was extracted from 5 other articles.

Table. Validation status for measurement with 1.5T MRI images of synovitis, tenosynovitis, osteitis, erosions, joint space narrowing (JSN)—**number of articles providing data**

Type of validity	Criterion	Content	Construct (Discriminant)	Construct (Convergent)	Responsiveness to change	Intra-rater reliability	Inter-rater reliability	Summary
Definition	Extent to which measure agrees with "gold standard"	Describes joint features regardless of age, gender, RA duration, treatment	Correlation with clinical assessment of joint status	Compares correlation coefficients between scores on the same health component, as measured by two different instruments	Sensitivity to change	Same reader scores similarly (ICCs)	Two or more readers score similarly (ICCs)	# validated of 7 required validity criteria
Synovitis (RAMRIS) 1	2	12	4	1	7	6	5	7
0	1	3			1			
Tenosynovitis 1		5	1	*(a)	3	2	1	5
0	1				1			
Erosions (RAMRIS) 1	1	13		2	3	7	7	6
0	1	5	1		7			
BME/Osteitis (RAMRIS) 1	3	9	2	*(b)	5	6	5	6
0		4			2			
JSN 1		1						1

1=statistically significant validation; 0=non-significant data; ICC = intra/inter-class correlation coefficient

Conclusion: Using a rigorous PRISMA-compliant method for quality assurance and uniform article extraction in a SLR, we found that synovitis, osteitis/BME, and erosions are the best-validated features of joint inflammation and damage for RA wrist and hand. Assessment of other measurement methods, field strengths and joints requires further work.

* Requires histology: a) Jain A, et al. Arthritis Rheum 2001;44:1754ΠI60; b) Jimenez-Boj E, et al. Arthritis Rheum 2007;56:1118ΠI24.

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Magnetic Resonance Imaging in Inflammatory Bowel Disease Patients with Arthralgia.

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Background/Purpose: Joint manifestations frequently occur in chronic inflammatory bowel diseases (IBD). Arthralgia, non-inflammatory joint pain without objective evidence of swelling or effusion, is present in 8–30% of all patients.(1–3) An underlying cause of arthralgia in IBD patients is not known and might be autoimmune related, which might express on MR as bone marrow edema. The purpose of this study is to assess whether inflammatory changes, including bone marrow edema can be detected on MRI in IBD patients with joint pain without clinical synovitis.

Methods: The most painful peripheral joint, without clinical signs of inflammation based on examination by a rheumatologist, at most 2 weeks prior to MR, was scanned in 14 IBD patients (11 Crohn's disease/3 ulcerative colitis) on a 1.5T extremity MRI. In addition the same joints were scanned in a control group of 14 IBD patients who were matched for form of IBD, disease duration, sex and age without joint complaints. MR imaging was performed according to a standard arthritis protocol including T1 and fat-suppressed T2 weighted images and T1 weigthed fat-suppressed post gadolinium sequences. MRI images were evaluated by two musculoskeletal radiologists in consensus for the presence of synovitis, tenosynovitis, bone marrow edema and erosions. The readers were blinded for all patient information.

Results: MR imaging of the MCP, PIP and/or DIP 2–5 joints of the hand was performed in 10 patients and 10 matched controls, MRI of the knee in 4 patients and 4 matched controls. A total amount of 62 painful joints were evaluated and 62 corresponding joints in the control group. Minimal synovitis was seen in one of the MCP joints in two of the arthralgia patients (3.2% of all painful joints) and in none of the control group (p=0.50). Bone marrow edema was not appreciated in the arthralgia patients, but a small amount of bone-marrow edema was seen in a MCP joint of a control (1.6% of total joints, p=1.00). Tenosynovitis and erosions were absent in both groups.

Conclusion: Subclinical inflammation on MRI was not seen more often in painful joints in arthralgia patients than in joints of controls. No anatomical substrate was found for arthralgia in IBD patients.

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Systematic Review of the Association Between Magnetic Resonance Imaging and Radiographic Detection of Erosions in Rheumatoid Arthritis.

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Background/Purpose: In rheumatoid arthritis (RA), disparities between erosive bone lesion detection on magnetic resonance imaging (MRI) and X-ray require reconciliation. It is hypothesized that early erosions detectable on MRI increase in size with disease progression to become detectable on radiography (X-ray). The study's objectives were 1) to compare the relative diagnostic test accuracy of X-ray for MRI-detected erosions; and 2) to determine if MRI erosions develop into X-ray erosions over time.

Methods: A systematic review was conducted. Medline (Jan 1996-Apr 2011) and EMBASE (Jan 1998-Apr 2011) citation indexes were searched using the PICO strategy. RA studies with paired comparisons of erosion detection on X-ray and MRI at the joint or more precise level of analysis were included. Two reviewers independently screened the titles, abstracts and full articles to determine eligibility. Disagreements on eligibility between reviewers were mutually resolved by discussion or arbitrated by a third, independent reviewer if mutual resolution was not achieved. Cross-sectional comparisons were examined overall and then sorted by study sample symptom duration. Temporal explorations sorted data by time between initial MRI and subsequent X-ray. Study quality was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and reported. Cochrane Collaboration Review Manager software was used to manage and analyze the data collected.

Results: Sixteen eligible studies reporting 34 unique datasets comprising 10,953 paired observations were included. The relative diagnostic test accuracy results were heterogeneous across studies. Sensitivity results ranged from 0.00 (95% CI: 0.00–0.04) to 0.87 (95% CI: 0.60–0.98). Average sensitivity weighted by study sample size was 0.28 (95% CI: 0.28–0.29). Specificity ranged from 0.38 (95% CI: 0.14–0.68) to 1.00 (95% CI: 0.99–1.00). The weighted mean specificity was 0.97 (95%CI: 0.97-0.97). The sensitivity of X-ray for MRI erosions appeared to increase with increasing symptom duration. Sensitivity ranged from 0.07 (95% CI: 0.01–0.24) for patients with a mean symptom duration of 0.25 years, to 0.34 (95% CI: 0.20–0.51) for patients with 14 years symptom duration. Specificity decreased slightly with increasing symptom duration. Specificity ranged from approximately 0.99 (95% CI: 0.97–1.00) to 0.92 (95% CI: 0.88–0.95) for

symptom durations ranging from 0.25 to 9.5 years, respectively. Studies varied by sample symptom duration, anatomy investigated, MRI magnetic strength, definition of erosion, number of X-ray projections, use of prescribed scoring systems, number of raters, unit of analysis, and QUADAS parameters.

Conclusion: X-ray has low sensitivity and high specificity for MRI erosions. The relationship between X-ray and MRI erosion detection is dependent on symptom duration and the time interval between imaging interventions. As the time between initial MRI and follow-up X-ray increases, there is decreasing specificity of X-ray for MRI erosions. This suggests that erosive progression is not limited to joints initially detected on MRI. Sources of study heterogeneity and potential bias warrant attention in future comparative investigations.

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Severe Joint Injury Assessed by Musculoskeletal Ultrasonography (MSKUS) Predicts the Presence of MRI-Proven Osteitis in Patients with Rheumatoid Arthritis. Shin-ya Kawashiri[1], Takahisa Suzuki[1], Yoshikazu Nakashima[1], Yoshiro Horai[1], Naoki Iwamoto[2], Kunihiro Ichinose[1], Kazuhiko Arima[2], Mami Tamai[2], Hideki Nakamura[2], Tomoki Origuchi[1], Kiyoshi Aoyagi[1] and Atsushi Kawakami[1]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Nagasaki University, Nagasaki, Japan

Background/Purpose: MRI-proven osteitis is known as the prognostic factor toward radiographic progression in patients with rheumatoid arthritis (RA). Musculoskeletal ultrasonography (MSKUS) is another high sensitive imaging modality to find joint injury of RA patients. We have tried to explore whether MSKUS assessment of synovial joint injury predict the presence of MRI-proven osteitis in patients with RA.

Methods: Thirty RA patients, who fulfilled 2010 RA classification criteria and are naïve to disease-modifying antirheumatic drugs (DMARDs) including biologics or glucocorticoids, are consecutively enrolled in this study from May 2010 through December 2011. Twenty-two joints from each patient including bilateral wrists and finger joints of the 1st - 5th metacarpophalangeal (MCP) joints, the 1st interpharangeal (IP) joint and the 2nd–5th proximal interpharangeal (PIP) joints were examined by both MSKUS and plain MRI. Therefore, a total of 660 joints were investigated by both methods in the present study. Power Doppler (PD) and gray scale (GS) assessment of articular synovitis by a semi-quantitative manner as well as the presence of bone erosion were examined by MSKUS. Plain MRI-proven osteitis was evaluated by RAMRI scoring (RAMRIS) technique. The Cochran-Armitage test was used to investigate a correlation of each MSKUS finding with MRI-proven osteitis.

Results: The mean disease duration, age, DAS28-ESR, prevalence of RF and anti-cyclic citrullinated peptide antibodies (ACPA) at examination were 4 months, 62 years-old, 5.06, 83.3% and 73.3%, respectively. MSKUS-proven bone erosion was found in 40 sites and MRI-proven osteitis 64 sites, respectively. A remarkable correlation of the PD grade (p < 0.0001), GS grade (p < 0.0001) and the presence of MSKUS-proven bone erosion (p < 0.0001) with the presence of osteitis was demonstrated by the Cochran-Armitage test.

Conclusion: Our present data suggest that severe joint injury assessed by MSKUS predicts the presence of MRI-proven osteitis in patients with rheumatoid arthritis.

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Diffusion Tensor and Dynamic Contrast Enhanced Perfusion Imaging Metrics Discriminate Chronic Tubercular Synovitis From Chronic Inflammatory Synovitis of the Knee. Vikas Agarwal[1], Rakesh K. Gupta[2], Rishi Awasthi[2], Deepak Tripathi[2], Prativa Sahoo[3], Vinita Agrawal[2], Kusum Sharma[4], Rungmei Marak[5], Ram Kishore Singh Rathore[3] and CM Pandey[2]. [1]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India, [2]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Lucknow, India, [3]Indian Institute of Technology, Kanpur, India, [4]Postgraduate Institute of Medical Education and Research, Chandigarh, India, [5]Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Lucknow, India

Background/Purpose: The study was performed to quantify dynamic contrast enhanced (DCE) and diffusion tensor imaging (DTI) metrics in synovium of patients with tubercular synovitis (TS) and chronic inflammatory synovitis (CIS) with an aim to discriminate between TS and CIS.

Methods: Seventy-three patients with knee synovitis (18–75 years, 51 Male) underwent conventional, DTI and DCE-MRI. DTI and DCE data were quantified from the segmented contrast enhanced synovium. Descriptive statistics, Box-plot with Tukey's hinges were produced for all DTI (fractional anisotropy, FA and mean diffusivity, MD) and perfusion metrics (blood volume, BV; blood flow, BF and volume transfer constant, k^{trans}). The mean difference between the two groups was compared using Student's t-test for independent samples. To classify subjects into TS and CIS, two-group discriminant function analysis with stepwise inclusion of variables was performed.

Results: Out of 73 patients, 15 were detected to have TS, while rests were found to have CIS. DCE (BV, BF) and DTI metrics (FA, MD) were significantly (p<0.001) different between the two groups (TS: BV=14.35±4.21 ml/100gm, CIS:BV=4.57±2.77 ml/100gm, TS BF=155.7±29.5 ml/100gm/min, CIS BF=94.9±34.5 ml/100gm/min, TS FA=0.26±0.02, MD=1.23±0.39×10^{-3} mm^{2}sec^{-1}; CIS FA=0.20±0.02, MD=1.7±0.5×10^{-3} mm^{2}sec^{-1}). Discriminant analysis revealed BV and FA as discriminators of TS and CIS. It classified 93.3% of TS and 100% of CIS correctly. The overall model classified 98.6% cases correctly.

Conclusion: DTI and DCE-MRI metrics are able to discriminate TS from CIS. FA and BV may be used as non-invasive image biomarkers for its differentiation.

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ACR/ARHP Poster Session B
Innate Immunity and Rheumatic Disease
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Sec61 Is Indispensable for Antigen Cross-Presentation and the Development of Lupus Nephritis: A Novel 'Self-Organized Criticality Theory' Explaining the Cause of Systemic Lupus Erythematosus (SLE). Ken Tsumiyama and Shunichi Shiozawa. Kyushu University Beppu Hospital, Beppu, Japan

Background/Purpose: We found that systemic lupus erythematosus (SLE) was induced experimentally by repeatedly immunizing the mice normally not prone to autoimmune diseases by any exogenous antigen so far examined (Tsumiyama K *et al.* PLoS One 4(12):e8382, 2009). We have then proposed a novel 'self-organized criticality theory' that explains the cause of SLE. Systemic autoimmunity, or SLE, necessarily takes place when host's immune system is overstimulated by repeated exposure to antigen to levels that surpass the immune system's stability limit, i.e., self-organized criticality. The autoreactive lymphocyte clones, which we name autoantibody-inducing CD4$^+$ T cells (aiCD4$^+$ T cells) are newly generated *via de novo* T cell receptor (TCR) revision from thymus-passed non-autoreactive clones at peripheral lymphoid organs. They not only stimulated B cells to generate varieties of autoantibodies but also helped final differentiation of CD8$^+$ T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce tissue injuries identical to SLE. Here we show the essential role of a translocon Sec61 for antigen cross-presentstion and lupus tissue injuries with regard to self-organized criticality theory.

Methods: Bone marrow-derived dendritic cell (BMDC) of BALB/c mice was cultured with fluorescent-labeled ovalbumin (OVA). Early endosome antigen 1 (EEA1) and calnexin were detected by using immunofluorescent staining to identify endosome and endoplasmic reticulum (ER), respectively. A translocon Sec61 was also detected to examine whether or not engulfed antigen is exported from endosome to cytoplasm through Sec61. For *in vivo* study, BALB/c mice were repeatedly immunized with OVA to induce SLE. The CD11c$^+$ DC isolated form spleen (spDC) of the mice immunized 12× with OVA was cultured with fluorescent-labeled OVA to examine localization of engulfed antigen. Localization of OVA, EEA1, calnexin and Sec61 in BMDC and spDC was examined under confocal laser microscopy. Further, exotoxin A was co-immunized with OVA to inhibit Sec61 *in vivo* in BALB/c mice. Renal lesion and the generation of CTL were assessed by proteinuria and the number of IFNγ-producing CD8$^+$ T cell.

Results: In BMDC, OVA was co-localized with an endosomal marker EEA1 until 15 min of culture, and subsequently separated from EEA1. OVA did not co-localize with an ER marker calnexin. Instead, OVA was co-localized with a translocon Sec61. The same result was obtained using spDC, suggesting that OVA could be exported from endosome directly to cytoplasm *via* Sec61. After repeated immunization with OVA, we found that the amount of Sec61 localized in endosome was gradually and significantly increased compared with control. While we showed previously that antigen cross-presentation is a pre-requisite for lupus tissue injury inducing nephritis, we did found that treatment of BALB/c mice with a Sec61 inhibitor exotoxin A inhibited both the generation of CTL and lupus nephritis.

Conclusion: Direct export of antigen from endosome to cytoplasm *via* Sec61 is essential not only for antigen cross-presentation but also development of lupus nephritis.

Disclosure: **K. Tsumiyama**, None; **S. Shiozawa**, None.

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Fc Receptor Gamma-Dependent Autoimmune Endocarditis in K/BxN Mice. Patricia M. Hobday[1], Jennifer L. Auger[1], J. Sjef Verbeek[2], Jeffrey V. Ravetch[3] and Bryce A. Binstadt[1]. [1]University of Minnesota, Minneapolis, MN, [2]Leiden University Medical Center, Leiden, Netherlands, [3]The Rockefeller University, New York, NY

Background/Purpose: Arthritis and endocarditis co-exist in several human rheumatic diseases, including systemic lupus erythematosus, rheumatic fever, and rheumatoid arthritis. K/BxN TCR transgenic mice, well known for their inflammatory arthritis, also develop spontaneous endocarditis. FcRγ, the cytoplasmic signaling molecule shared by the three activating Fcγ receptors in the mouse (FcγRI, III, and IV), is required for endocarditis in K/BxN mice. Here we addressed two main questions: first, which of the three activating Fcγ receptors is required for endocarditis in this model and second, what FcRγ-expressing cell type drives endocarditis.

Methods: Knockout alleles of each of the activating Fcγ receptors (FcγRI−/−, FcγRIII−/−, and FcγRIV−/−) were bred into the K/BxN system. In addition, we utilized a reciprocal bone marrow transplantation approach to determine if endocarditis depended on FcRγ expression by bone marrow-derived cells or by radio-resistant host cells. We assessed hearts for the presence of endocarditis via standard hematoxylin and eosin staining. Additionally, we used immunohistochemistry to examine the expression of the three activating Fcγ receptors in the cardiac valves as well as the isotypes of antibodies bound to the inflamed cardiac valves.

Results: Although IgG1 is the predominant autoantibody isotype in K/BxN mice, we found that IgG1, IgG2b, and IgG2c were all bound to their inflamed cardiac valves. We also detected expression of each of the activating Fcγ receptors in the cardiac valves. K/BxN mice lacking expression of FcγRI, FcγRIII, or FcγRIV developed endocarditis with equivalent severity to control mice. The bone marrow transplant experiments revealed that recipient mice lacking FcRγ were protected from endocarditis. Surprisingly, the presence or absence of FcRγ on bone marrow-derived donor cells did not influence the severity of endocarditis.

Conclusion: Our results indicate that no single activating Fcγ receptor is solely required for the development of endocarditis in K/BxN mice. The simplest explanation for these findings is that there is redundancy among the activating Fcγ receptors in driving endocarditis. This interpretation is consistent with our data showing that multiple immunoglobulin isotypes are bound to the inflamed valves and that that each of the activating Fcγ receptors can be detected in the valves. A less likely explanation is that an FcRγ-utilizing receptor type other than the activating Fcγ receptors is at play. We also conclude that FcRγ chain expression by radio-resistant host cells rather than by radiosensitive, bone-marrow derived cells is required for the development of endocarditis. Candidate cell types include cardiac stromal cells and/or radio-resistant dendritic cells. Our findings provide new insight into the pathogenesis of cardiovascular inflammation in the setting of autoantibody-associated diseases.

Disclosure: **P. M. Hobday**, None; **J. L. Auger**, None; **J. S. Verbeek**, None; **J. V. Ravetch**, None; **B. A. Binstadt**, None.

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A Specific Inhibitor of Spleen Tyrosine Kinase, PRT062607, Is a Potent Modulator of Innate Immune Cell Function. Lynn A. Kamen, Gillian Stephens, Anjali Pandey and Uma Sinha. Portola Pharmaceuticals, South San Francisco, CA

Background/Purpose: Tumor Necrosis Factor-α (TNF-α) is an essential component of the inflammatory stimuli leading to rheumatoid arthritis (RA). Therapeutics targeting TNF-α are the standard of care but are not always capable of inhibiting disease progression. Thus, there is an unmet need for novel targets for treatment of RA. Spleen tyrosine kinase (Syk) is a non-receptor tyrosine kinase that plays an important role in phagocyte (macrophage and neutrophil) activation. Phagocytes are known to be important in the pathology of RA; the purpose of this study was to evaluate the impact of Syk inhibition in modulating phagocyte activation.

Methods: Macrophages were generated by culturing peripheral blood monocytes from healthy human volunteers with M-CSF (5ng/mL) for five days. Neutrophils were isolated from human peripheral blood on a Ficoll gradient and separated from erythrocytes via dextran sedimentation. As a surrogate for pathogenic autoantibodies in the arthritic synovial joint, immune complex was used for activation of macrophages and neutrophils. Immune complex was prepared by preincubating chicken egg ovalbumin with goat anti-chicken egg ovalbumin IgG at 37°C. To mimic integrin-mediated activation, plate-bound poly-RGD (20 μg/mL) was used as a stimulus. TNF-α release from macrophages was measured via ELISA (R and D Systems). The SOD-inhibitable oxidative burst response in neutrophils was measured through cytochrome c reduction in a plate-based absorbance assay. Specific Syk inhibitor, PRT062607 (P505-15) was added *in vitro* to the experimental system containing human macrophages or neutrophils.

Results: Syk inhibition by PRT062607 suppressed inflammatory cytokine release. Cytokine levels, as measured by TNF-α release from macrophages stimulated with immune complex, was potently inhibited by PRT062607 (IC$_{50}$=0.070μM). Furthermore, PRT062607 treatment was a potent inhibitor of neutrophil-mediated superoxide production in response to various physiologically relevant stimuli (integrin ligation IC$_{50}$=0.037μM and immune complex stimulation IC$_{50}$=0.195μM). Interestingly TNF-α alone was able to facilitate neutrophil-mediated superoxide production, and this activity was potently suppressed by PRT062607 (IC$_{50}$=0.065μM).

Conclusion: Together these data indicate a novel role for Syk inhibition in controlling TNF-α-mediated inflammation. These results suggest that in addition to decreasing immune cell activation and inflammation in the joint, Syk inhibition could also partly mimic the effects of an anti- TNF-α therapy. Thus, Syk inhibition by a small molecule kinase inhibitor has the potential to be a novel mode of therapy in RA.

Disclosure: **L. A. Kamen**, Portola Pharmaceuticals Inc, 1; **G. Stephens**, Portola Pharmaceuticals, 3; **A. Pandey**, Portola Pharmaceuticals, 1; **U. Sinha**, Portola Pharmaceuticals, 1.

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Fulminant Toll-Like Receptor 9-Induced Macrophage Activation Syndrome and Hemophagocytosis Occur Independently of Interferon Gamma. Scott W. Canna[1], Julia Wrobel[2], Portia A. Kreiger[3], Michele E. Paessler[1] and Edward M. Behrens[1]. [1]Childrens Hospital of Philadelphia, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, [3]Nemours/A.I. DuPont Hospital for Children, Wilmington, DE

Background/Purpose: Macrophage Activation Syndrome (MAS) is a potentially lethal cytokine storm syndrome that complicates various rheumatic diseases. We have previously shown that Toll-like Receptor (TLR9) mediated MAS is Interferon gamma (IFNg) dependent, and others have demonstrated IFNg-dependence in models of Hemophagocytic Lymphohistiocytosis. We have also shown the critical role of IL-10 in regulating TLR9-induced MAS, and mice co-treated with TLR9-agonism and IL-10 receptor blockade (IL10RB) develop "fulminant MAS." This study seeks to determine the role of IFNg in the fulminant MAS model.

Methods: We gave CpG1826 repeatedly to WT and transgenic mice as described. Antibodies inhibiting the action of the IL-10 receptor (IL10RB, 1B1.3A) and IL-12p40 (C17.8) were given as described. All injections were intraperitoneal. We then evaluated for signs of MAS.

Results: Fulminant MAS resulted in greatly enhanced serum IL-10, IL-12, and IFNg. While dendritic cell populations were dominant producers of IFNg in IL-10 sufficiency, in fulminant MAS IFNg was also produced by hepatic NK and CD8 T cells. When IL-12 was blocked in fulminant MAS mice, disease progression was unaltered, despite much lower serum IFNg. Strikingly, we also observed the continued presence of hemophagocytes (HPCs) despite IL-12 blockade. This observation caused us to question whether fulminant MAS was due to enhanced IFNg activity or whether, distinct from the IL-10 sufficient scenario, other proinflammatory forces were at work. Administration of CpG and IL10RB to IFNg−/− mice resulted in fulminant MAS nearly comparable to that seen in WT mice. Notably,

IFNg$-/-$ mice were spared from severe anemia and severe hepatitis but developed all other aspects of fulminant MAS including HPCs. Thus, while certain aspects of disease (anemia and hepatitis) are IFNg-dependent, fulminant MAS, including hemophagocytosis, occurs independent of IFNg. Interestingly, blockade of type I interferon signaling (using IFNAR$-/-$ mice) did not prevent disease in the IL-10 sufficient situation, but partially abrogated fulminant MAS. HPCs also persisted despite Type I IFN receptor blockade.

Conclusion: In the TLR9-mediated model, IL-12 functions to induce IFNg. However, fulminant MAS is largely IFNg-independent. This suggests that therapeutic targeting of IFNg may not be sufficient in all cases of hemophagocytic syndrome. Furthermore, our results dissociate the development of IFNg-induced "consumptive" anemia and hepatitis, and the presence of HPCs. Thus, the goal of chemotherapeutic elimination of HPCs may not be of benefit for many aspects of the disease, since their presence does not correlate with either anemia or hepatitis.

Disclosure: S. W. Canna, None; **J. Wrobel**, None; **P. A. Kreiger**, None; **M. E. Paessler**, None; **E. M. Behrens**, None.

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Endogenous Complement Factor H Plays an Important Role in Controlling Immune Complex-Induced Inflammatory Arthritis. Nirmal K. Banda[1], Gaurav Mehta[1], Viviana P. Ferreira[2], Claudio Cortes[2], Michael K. Pangburn[3], William P. Arend[1] and V. Michael Holers[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]University of Toledo Health Science Campus, Toledo, OH, [3]University of Texas Health Sciences Center, Tyler, TX

Background/Purpose: The complement system, a major component of innate immunity, likely plays an important role in the pathogenesis of rheumatoid arthritis (RA). Factor H (fH) is an endogenous regulator of the alternative pathway (AP) that binds surface polyanions in combination with the C3-derived fragments C3b and C3d initially through its carboxy-terminal domain containing short consensus repeats (SCR) 19–20, thereby inhibiting both AP activation and engagement of the AP amplification loop. We have shown that the AP is uniquely both necessary and sufficient for the development of collagen antibody-induced arthritis (CAIA) in mice. However, the mechanisms whereby normal control of the AP is overcome and injury develops are unknown. The hypothesis pursued in the current studies is that fH plays a critical role in regulating the AP in immune complex-initiated injury in CAIA. We have examined the role of fH in CAIA by inhibiting its binding to tissues through administration of a recombinant dominant negative inhibitor containing murine SCR19–20 (rfH19–20), which impairs fH surface AP regulation, and the use of gene-targeted fH deficient mice.

Methods: CAIA was induced in C57BL/6 WT, $fH^{-/-}$ and $fH^{+/-}$ mice by injecting four anti-type II collagen (CII) mAbs i.p. on day 0 and lipopolysaccharide (LPS) i.p. on day 3. Intraperitoneal injections of 100 and 300 μg/mouse of rfH19–20 were carried out 15 min after the injection of mAb to CII on day 0 and again 15 min after LPS on day 3. Blood was drawn intraorbitally from all mice at day 0 prior to injection of mAb to CII, at day 3 prior to LPS injection, and at day 10 prior to sacrifice. All mice were sacrificed on day 10 for histopathologic scoring of injury and immunohistochemical analysis of C3 deposition. Control experiments were performed using rfH3–5 which does not inhibit fH binding to tissues. The absolute levels of C3, fH and C5a in serum of mice were measured by ELISA.

Results: Both doses of rfH19–20 significantly increased the clinical disease activity score (DAS) using a sub-maximal dose (0.5 mg/mouse) of anti-CII mAbs. Scores for histopathologic injury and C3 deposition on the surface of the cartilage and in the synovium increased with treatment in an identical fashion. No significant differences in the DAS were observed when WT mice were treated with 300 μg/mouse of control rfH3–5. $fH^{-/-}$ mice, compared with WT mice, were resistant to CAIA due to the significantly reduced serum levels of C3. WT and $fH^{+/-}$ mice have identical serum levels of C3, but $fH^{+/-}$ mice have 30% reduced levels of fH. WT and $fH^{+/-}$ mice developed indistinguishable DAS using a sub-maximal dose as well as a maximum dose (8 mg) of anti-CII mAb. In addition, though, the DAS at day 10 in $fH^{+/-}$ mice treated with 300 μg/mouse of rfH19–20 increased to 5.5 $\pm$ 0.65 compared with untreated $fH^{+/-}$ mice which was 1.75 $\pm$ 0.25 (p < 0.05).

Conclusion: We show for the first time that endogenous fH makes a significant contribution to regulating immune complex-induced injury in CAIA through binding to target surfaces via SCR19–20 and blocking AP activation and amplification.

Disclosure: N. K. Banda, None; **G. Mehta**, None; **V. P. Ferreira**, None; **C. Cortes**, None; **M. K. Pangburn**, Complement Technology Inc, 4; **W. P. Arend**, None; **V. M. Holers**, None.

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Protein Kinase C Inhibitor Generates Human Tolerogenic Dendritic Cells That Induce Tr1 and Foxp3$^+$ Regulatory T Cells. Takuya Matsumoto, Hitoshi Hasegawa, Jun Ishizaki, Koichiro Suemori, Sachiko Onishi and Masaki Yasukawa. Ehime University Graduate School of Medicine, Toon, Japan

Background/Purpose: Tolerogenic dendritic cells (tDCs) play a critical role in immune tolerance and are involved in the pathogenesis of autoimmune diseases such as rheumatoid arthritis. Suppression by tDCs is primarily mediated via the induction of regulatory T cells (Treg). tDCs are induced in the presence of specific biological agents. Therefore, we screened the molecules that enhanced induction of tDCs from the libraries of lipids, nuclear receptor ligands, and kinase inhibitors. Of these, protein kinase C inhibitors (PKCIs) such as bisindolylmaleimide I, Go6983, and Ro32–0243, suppressed the expression of CD80, CD83, and CD86 on DCs and suppressed allogenic T cell responses. In this study, we showed the characterization of PKCI-treated human tDCs and application to the therapy for autoimmune diseases.

Methods: Mature DCs (mDCs) were prepared from human monocytes by treating with GM-CSF and IL-4 for 5 days, and then induced maturation wtih TNF-alpha for 48h. PKCI-treated tDCs were generated by adding bisindolylmaleimide I, Go6983, or Ro32–0243 during this process. We analyzed the cell surface expression on DCs, cytokine production, and phagocytic ability. Furthermore, we examined the effects of these molecules on stability and plasticity of DCs, antigen presenting, allogenic T cell responses, and induction of Tr1 and Treg cells.

Results: DCs treated with PKC inhibitors such as bisindolylmaleimide I, Go6983, and Ro32–0243 decreased the expression levels of CD40, CD80, CD83, CD86, and HLA class I significantly but not those of CD1a, CD11c, and HLA classII compared with mDCs. Moreover, PKCI-treated tDCs produced 15–20-fold and 2–4-fold higher concentration of IL-10 and TGF-beta than mDCs, respectively, resulting in a strong reduction of allogenic T cell responses. From the co-culture of DCs and naïve T cells, PKCI-treated tDCs induced IL-10-producing Tr1 cells and Foxp3$^+$ regulatory T cells. PKCI-treated tDCs retained phagocytic ability as well as immature DCs (iDCs). PKC I-treated tDCs kept the low expression levels of CD80, CD83, and CD86 and suppressive properties at least one week after stimulated with a cocktail of proinflammatory cytokines or LPS, whereas iDCs recovered the similar expression levels to mDCs and did not have suppressive properties.

Conclusion: We showed that PKCI-treated human DCs acted as a strong and stable tDCs. PKCI-treated tDCs may be useful method to the therapy for autoimmune diseases.

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Generation of Myeloid-Derived Suppressor Cells in Vitro From Murine Bone Marrow Precursors. Julia Kurko, Beata Tryniszewska, Tibor A. Rauch, Colt Egelston, Tibor T. Glant and Katalin Mikecz. Rush University Medical Center, Chicago, IL

Background/Purpose: Myeloid-derived suppressor cells (MDSCs) are innate immune cells that expand under pathological conditions (such as cancer and autoimmune diseases) in response to local growth factors or cytokines. MDSCs are a heterogeneous population of immature myeloid lineage (monocyte-like and granulocyte-like) cells with immunosuppressive ability. These cells have the potential to down-regulate autoreactive T cell responses in autoimmune diseases such as rheumatoid arthritis (RA). Using proteoglycan (PG)-induced arthritis (PGIA), a mouse model of RA, we previously reported that MDSCs are present in synovial fluid (SF) of the arthritic joints of mice and suppress antigen-specific T cell proliferation. As the number of cells that can be collected from murine SF is limited and SF MDSCs do not expand in culture, we sought an alternative source for generating greater quantities of MDSCs for potential therapeutic intervention (via cell transfer) in PGIA.

Methods: Bone marrow (BM) cells were isolated from naïve BALB/c mice and cultured in the presence of recombinant murine granulocyte macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) and interleukin-6 (IL-6) for up to 7 days. After

harvest, the phenotype of cells was evaluated by flow cytometry. Their suppressive function towards PG-specific T cells was tested by co-culture with PG-loaded BM-derived dendritic cells (DCs) and T cells from naïve PG-specific T cell receptor transgenic (PG-TCR-Tg) mice. The mechanisms of MDSC-mediated suppression were investigated using inhibitors of MDSC-produced effector molecules including arginase-1, inducible nitric oxide (NO) synthase (iNOS), and reactive oxygen species. Expression of MDSC effector molecules was analyzed by RT-PCR and Western blot.

Results: Similar to SF MDSCs, BM-derived MDSCs expressed the common myeloid marker CD11b. However, unlike SF MDSCs, BM MDSCs contained a smaller population of Ly6G positive (granulocyte-like) cells, and the majority of them expressed both Ly6G and the monocytoid cell surface marker Ly6C. Upon co-culture with PG-TCR-Tg T cells in the presence of PG-loaded DCs, BM MDSCs profoundly inhibited the proliferation of T cells, thereby confirming their suppressor activity. BM cells grown with GM-CSF, G-CSF, and IL-6 for only 3 days already showed potent suppressive effect on T cell proliferation. Despite expression of Ly6C by most BM MDSCs, these cells retained their suppressor activity after depletion of the Ly6C positive population. Experiments with inhibitors of MDSC effector molecules revealed that the primary mechanism of suppression of T cell proliferation was via NO release. Indeed, iNOS expression in BM MDSCs was found elevated at both mRNA and protein levels.

Conclusion: We developed an in vitro culture method of generating large quantities of immunosupressive murine MDSCs. Characterization of the phenotype, gene expression, suppressor activity of BM-derived MDSCs revealed that these cells are similar to SF MDSCs, but are dominated by a less mature (double Ly6C/Ly6G positive) population. BM-derived MDSCs appear to be suitable for in vivo cell transfer experiments.

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Identification of Highly Potent and Selective Interleukin-1 Receptor-Associated Kinase 4 Inhibitors for the Treatment of Rheumatic Diseases. Divya Chaudhary[1], Shaughnessy Robinson[2], Craig E. Masse[1], Matthew D. Wessel[2], Shawn Watts[2], Jeremy Greenwood[2], Mee Shelley[2], Mark Brewer[2], Geraldine Harriman[1], Leah L. Frye[2], Ronald T. Wester[1], Rosana Kapeller[1] and Donna Romero[1]. [1]Nimbus Discovery, Inc., Cambridge, MA, [2]Schrödinger, Inc., New York, NY

Background/Purpose: Interleukin-1 receptor-associated kinase 4 (IRAK4) is a key mediator of the innate immune response orchestrated by interleukin-1 receptor (IL-1R), interleukin-18 receptor (IL-18R), IL-33 receptor (IL-33R), and Toll-like receptors (TLRs). IRAK4 activation is mediated by MYD88, a common signaling adaptor protein downstream of these receptors. Mutations leading to inactivation or activation of MYD88 have been reported in patients with immune deficiencies and cancer, respectively. In addition, IRAK4-deficient humans are protected from chronic inflammatory diseases. Thus, IRAK4 is an attractive therapeutic target for the treatment of autoimmune diseases such as lupus. Historically, identification of potent and selective IRAK4 inhibitors has been challenging due to structural features in the catalytic binding site that block access to the hydrophobic back pocket. We have developed new structure-activity relationship (SAR) insights, including the identification of unstable (high-energy) hydration sites, which guide the design of potent and selective small molecule ligands.

Methods: Using this innovative structure-based approach, we designed, synthesized and tested small molecule inhibitors based on hits originated from a virtual screen. These novel compounds were profiled for IRAK4 kinase inhibition, selectivity, and drug-like properties. Furthermore, selected compounds were tested in THP1 cells, human peripheral blood mononuclear cells (hPBMCs) and whole blood for impact on LPS-, IL-1-, R848-, and/or CpG-mediated signaling. The inhibitors were also tested *in vivo* in acute LPS challenge and chronic collagen induced arthritis (CIA) models.

Results: Here, we feature three highly potent, selective IRAK4 inhibitors, ND-346, ND-2110 and ND-2158. The K_is of ND-346, ND-2110, and ND-2158 for IRAK4 are 50, 7.5 and 1 nM, respectively. These compounds are highly selective against 334 kinases, and are potent inhibitors of IL-1-induced IRAK1 degradation in MRC5 cells, LPS-, IL-1-, R848 (TLR-7 agonist)- and CpG (TLR-9 agonist)-induced cytokine production in hPBMCs and whole blood. Furthermore, these compounds are efficacious in the acute LPS challenge model *in vivo*, and ND-346 shows efficacy in rat CIA at 10 mg/kg (PO, QD).

Conclusion: Utilizing unique and innovative structure-based drug design, we have rapidly discovered potent and selective IRAK4 inhibitors as potential drug candidates for the treatment of chronic rheumatic diseases.

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Dysfunction of Natural Killer and Natural Killer T Cells in Patients with Adult Onset Still's Disease. Young-Nan Cho[1], Sung-Ji Lee[1], Tae-Jong Kim[2], Hye-Mi Jin[1], Dong-Jin Park[2], Seung-Jung Kee[1] and Yong-Wook Park[1]. [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Chonnam National University Medical School, Gwangju, South Korea

Background/Purpose: Adult onset Still's disease (AOSD) is an uncommon systemic inflammatory disorder of unknown etiology. Natural killer (NK) cell dysfunction is frequently observed in some human autoimmune disease, such as systemic lupus erythematosus and rheumatoid arthritis. However, NK cell function has not previously been investigated in AOSD. Furthermore, the relation between NK and NKT cells has not been determined. Purpose of this study is to examine the levels and functions of NK and NKT cells, to investigate relationships between NK and NKT cells, and to determine the clinical relevance of NKT cell levels in patients with AOSD.

Methods: Patients with active untreated AOSD (n = 25) and age- and sex-matched healthy controls (n = 25) were enrolled in the study. NK and NKT cell levels were measured by flow cytometry. Peripheral blood mononuclear cells were cultured in vitro with α-galactosylceramide (α-GalCer). NK cytotoxicities against K562 cells and proliferation indices of NKT cells were estimated by flow cytometry.

Results: Percentages and absolute numbers of NKT cells were significantly lower in the peripheral blood of patients than in healthy controls. Proliferative responses of NKT cells to α-GalCer were also lower in patients, and this was found to be due to proinflammatory cytokines and NKT cell apoptosis. In addition, NK cytotoxicities were found to be significantly lower in patients than in healthy controls, but NK cell levels were comparable in the two groups. Notably, this NKT cell deficiency was found to be correlated with NK cell dysfunction and to reflect an active disease status. Furthermore, α-GalCer-mediated NK cytotoxicity, showing the interaction between NK and NKT cells, was significantly lower in patients than in healthy controls.

Conclusion: Our findings show that NKT cells are numerically and functionally deficient in AOSD. In addition, we report a novel observation that NK cell dysfunction is related to NKT cell deficiency. These findings provide important information concerning the pathogenesis of AOSD.

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CD1c-Expressing Myeloid Dendritic Cells From Joints of Rheumatoid Arthritis Patients Produce Increased Levels of T Cell-Attracting Chemokines and Strongly Activate Autologous T Cells. F.M. Moret, C.E. Hack, F.P.J.G. Lafeber, T.R.D.J. Radstake and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: Myeloid dendritic cells (mDCs) are potent T cell-activating antigen-presenting cells that have been implicated to play a crucial role in the regulation of tolerance and pro-inflammatory immune responses in many disease states, including rheumatoid arthritis (RA). Despite this, studies that have reported on the role of naturally occurring circulating mDCs in RA are scarce. Recently, CD1c mDCs from RA patients were suggested to migrate from the circulation to the joint where they exhibit a semi-mature phenotype. However, data on the capacity of these CD1c mDCs to regulate T cell activation in RA are lacking. The present study investigated the expression profiles of co-stimulatory molecules and pro-inflammatory mediators secreted by CD1c mDCs from synovial fluid (SF) versus peripheral blood (PB) of RA patients and studied their capacity to stimulate autologous CD4 T cell proliferation and cytokine production.

Methods: CD1c mDC numbers and their expression of surface molecules involved in T cell activation were assessed by FACS analysis in SF and PB from RA patients (n=9). Production of inflammatory mediators by CD1c mDCs from SF and PB of RA patients (n=6) was determined after 20h of

culture by multiplex immunoassay (measuring 51 cytokines). The capacity of CD1c mDCs from SF (n=5) and PB (n=11) to activate autologous CD4 T cell proliferation in the absence of additional stimuli was measured after 6 days of culture by ^{3}H-thymidine incorporation assay. Additionally, T-cell cytokine production was measured upon ionomycin/PMA restimulation.

Results: The number of CD1c mDCs was significantly increased in SF versus PB of RA patients (mean 5.0% vs. 0.6%, resp., p<0.01). mDCs from SF showed increased expression of CD80 and CD86 (CD80: MFI 131 vs. 68, p<0.04; CD86: 157 vs. 89, p<0.02, resp.). Furthermore, the number of positive mDCs for HLA-II, CD80 and CD40 was significantly increased in SF versus PB (all p<0.05). Numerous cytokines were abundantly and equally produced by mDCs both from PB and SF (incl. IL-12, IL-23, IL-13, IL-21). mDCs from SF produced higher IP10, MIG, TARC, and OPG concentrations as compared to mDCs from PB (IP10: 247 vs. 54, p<0.05; MIG: 90 vs. 24, p<0.01; TARC: 26 vs. 1, p<0.01; OPG: 354 vs. 156, p<0.05, resp., all pg/ml). By contrast, MDC secretion by mDCs from SF was significantly lower than mDCs from PB (2456 vs. 4397 pg/ml, p<0.05, resp.). mDCs from SF had a strongly increased capacity to induce proliferation of CD4 T cells as compared to mDCs from PB (ratio DC:T cell 1:5, 26935 vs. 1503 CPM, p<0.01, resp.). The augmented T cell proliferation was associated with a strongly increased IFNγ, IL-17, and IL-4 cytokine production (ratio DC:T cell 1:5, SF vs. PB, IFNγ: 3428 vs. 179 pg/ml; IL-17: 363 vs. 39 pg/ml; IL-4: 193 vs. 17 pg/ml, resp.).

Conclusion: The present study indicates that increased numbers of CD1c mDCs in SF play an essential role in the inflammation cascade by the secretion of specific T cell-attracting chemokines and the activation of self-reactive T cells to induce Th1, Th17, and Th2 activity. Targeting of CD1c mDCs or the specific triggers of these cells could represent a novel therapeutic approach to prevent immunopathology of RA.

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Hypoxia-Inducible Factor-1α: Trigger of Toll-Like Receptor Signalling-Engaged Inflammation in Rheumatoid Arthritis. Fanlei Hu[1], Rong Mu[1], Jiaxin Zhu[1], Wenwei Shao[2], Lianjie Shi[1], Philip L. Cohen[3], Xiaoyan Qiu[2] and Zhanguo Li[1]. [1]Peking University People's Hospital, Beijing, China, [2]School of Basic Medical Science, Peking University, Beijing, China, [3]Temple University, Philadelphia, PA

Background/Purpose: Hyperplasia of synovial fibroblasts, infiltration with lymphocytes, and tissue hypoxia are the major characteristics of rheumatoid arthritis (RA). Data has confirmed the central role of toll-like receptors (TLRs) in RA. However, much remains unknown regarding the impact of hypoxia on TLR signalling-induced inflammatory response in RA. The aim of this study was to reveal the effect of hypoxia and its regulator hypoxia-inducible factor-1α (HIF-1α) on the inflammatory response in rheumatoid arthritis synovial fibroblast (RASF) upon the recognition of pathogen molecules.

Methods: Hypoxia was induced in RASF by incubation with $Na_2S_2O_4$. TLR3 ligand polyIC, TLR2 ligand PGN, TLR4 ligand LPS, and TLR9 ligand CpG were used to stimulate the cells. Effects of hypoxia on these ligands-induced inflammatory cytokines and matrix metalloproteinases (MMPs) were determined by RT-PCR, realtime PCR, and ELISA. Overexpressing HIF-1α as well as knocking-down its expression by siRNA were used to reveal its fundamental role. RASF-induced inflammatory T cell expansion was determined by flow cytometry, realtime PCR, and ELISA analyses after RASF/T cell coculture.

Results: Hypoxia potentiated the expression of inflammatory cytokines, MMPs, and VEGF in RASF stimulated by different TLR ligands, especially polyIC, a synthetic mimic of dsRNA from virus or apoptotic cells. HIF-1α played a fundamental role in this synergy. Moreover, overexpression of HIF-1α enhanced RASF-mediated inflammatory T cell expansion, inducing more proinflammatory IFN-γ and IL-17 production.

Conclusion: Our findings suggest that hypoxia and HIF-1α may function collaboratively with TLR-engaged inflammatory response to excerbrate the pathogenesis of RA, and HIF-1α might serve as a therapeutic target for this disease.

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Extrathymic Autoimmune Regulator (AIRE) Expression in Rheumatoid Arthritis. A.R. Noort[1], K.P.M. van Zoest[1], M.C. Lebre[1], P. P. Tak[2] and S.W. Tas[1]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: The Autoimmune Regulator (AIRE) is a transcription factor that is involved in the negative selection of self-reactive thymocytes in the thymus and therefore is pivotal in the establishment of central tolerance. It has been suggested that non-canonical NF-kappaB signaling is required for thymic AIRE expression. Recently, AIRE protein has also been detected in peripheral lymphoid organs, predominantly in dendritic cells (DC). In these peripheral sites, AIRE was found to regulate the expression of a group of tissue-specific antigens that is distinct from those expressed in the thymus, suggesting that peripheral AIRE may play a complementary role in tolerance induction. It is currently unknown whether AIRE may play a role in inflamed tissues associated with ectopic lymphoid neogenesis, such as rheumatoid arthritis (RA) synovial tissue (ST).

Objective: To document and further characterize extrathymic AIRE expressing cells in ST and paired peripheral blood (PB) mononuclear cells (MCs) as well synovial fluid (SF) MCs of RA patients.

Methods: ST was obtained via mini-arthroscopy from inflamed joints of RA or undifferentiated arthritis (UA) patients. Expression of AIRE was evaluated using immunohistochemistry and immunofluorescence (IF) microscopy. AIRE expression was also investigated in PB and SF DC using flow cytometry.

Results: AIRE expressing cells were detected in 80% of analyzed RA ST and in contrast only in 25% of UA ST. Further characterization using double-immunofluorescence microscopy revealed that these cells were predominantly CD1c (BDCA1)[+] myeloid (m)DC. Interestingly, a significantly higher percentage of CD1c+ mDC in RA SF expressed AIRE (55 + 5 %; n=12) compared to RA PB (20 + 3 %; n=12; p<0.05) and healthy PB (19.7 + 2 %; n=5; p<0.05).

Conclusion: Extrathymic AIRE expressing cells are present in RA ST and RA SF, suggesting a role in synovial inflammation. These AIRE expressing cells appear to be mainly CD1c+ mDCs. Extrathymic AIRE expression in RA synovial inflammation may be an attempt to control inflammation through the induction of peripheral tolerance to antigens involved in the perpetuation of the chronic inflammatory response. This mechanism may be exploited to develop new treatments for RA patients.

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Spontaneous Aggregation of the Anti-Viral Mavs Protein in Certain Systemic Lupus Erythematosus Patients May Explain Excessive Type I Interferon Production. Philip L. Cohen[1] and Wen-Hai Shao[2]. [1]Temple University, Philadelphia, PA, [2]Temple University School of Medicine, Philadelphia, PA

Background/Purpose: Patients with systemic lupus (SLE) often have increased type I interferon levels (IFN-I) and activation of IFN-inducible genes (IFN signature). The mitochondrial adaptor protein MAVS (also known as IPS1, VISA or CARDIF) is a key intermediary in the RIG-I pathway, where viral RNA triggers a conformational change in RIG-I, leading to MAVS activation and then downstream activation of IKK and TBK1, with subsequent IFN production driven by IRF-3/7 (IRF3 for IFN-beta; IRF7 for IFN-alpha) and NFkB activation and translocation. Using *in vitro* methods, it has been observed that MAVS may form large prion-like aggregates that might stimulate IFN-I activation in a potent and prolonged fashion (Hou et. al., *Cell* 146:448, 2011). We wondered if such aggregates might be detectable *ex vivo* in SLE patients, and whether they might play a role in the sustained increased production of IFN-I.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 17 patients fulfilling ACR criteria for SLE, and from 9 controls. Thirty million PBMCs were lysed and supernatants loaded onto semi-denaturing 1.5% vertical agarose gels. After electrophoresis, the proteins were transferred to membranes for immunoblotting with anti-MAVS antibody or anti-beta-actin.

Results: Four of 17 SLE patients showed clear MAVS aggregation, with essentially all of their MAVS protein in a high molecular weight aggregated form. None of 9 controls had abnormal MAVS. Three of the four

aggregation-positive SLE patients had nephritis and the fourth had lung involvement. SLEDAI scores of MAVS-aggregate positive SLE patients did not differ from patients with normal molecular weight MAVS. Patient 4 (P-4) shows the aggregated MAVS phenotype in the western blot below (Panel B, P-4). Denatured MAVS immunoblotting is shown in panel A and actin immunoblotting in panel C. N-1 and N-2 are normal controls. P-1 has less protein loaded and no MAVS band is discernible.
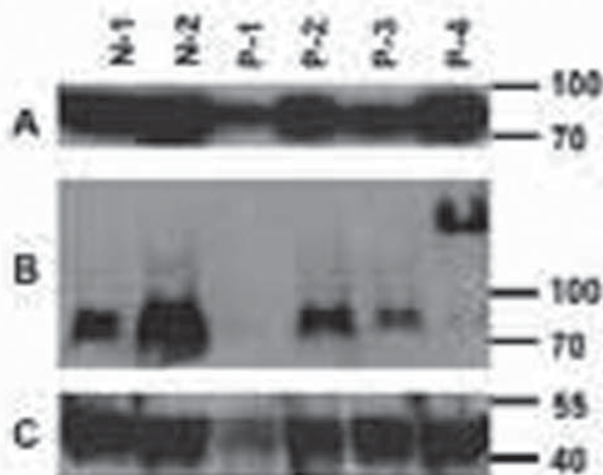
Conclusion: This is the first report of aggregated MAVS in human cells. The significance of this abnormality needs further investigation, it is possible that prolonged and increased IFN-I production could result from such MAVS aggregation, and that the poorly degradable prion-like protein could signal IFN-I production for prolonged periods.

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A Selective Inhibitor of Endosomal Toll-Like Receptors, IMO-8400, Suppresses Activation of Multiple Cytokines, Th17 Response and Inflammasome Activation. Weiven Jiang, Fugang Zhu, Dong Yu, Ekambar R. Kandimalla. Nicola La Monica and Sudhir Agrawal, Idera Pharmaceuticals, Cambridge, MA

Background/Purpose: In autoimmune diseases, activation of Th1 and Th17 pathways has been associated with disease maintenance and progression. Engagement of endosomal Toll-like receptors (TLRs) 7, 8 and 9 through interaction with immune complexes containing nucleic acids induces production of proinflammatory cytokines leading to the activation of Th1 and Th17 responses. Blocking the engagement of these receptors through an antagonist may inhibit this pathway, thus providing a novel approach to the treatment of autoimmune diseases.

Methods: In C57BL/6 mice, psoriasis-like skin lesions were induced by intradermal injection of IL-23. Skin lesions were examined histopathologically and gene expression was monitored. IL-23 injection stimulated upregulation in the skin of genes of multiple cytokines (including IL-12, IL-21, IL-23 and IL-17) keratinocyte peptides (including LL-37) and inflammasome protein NLRP3. Treatment of mice with IMO-8400 was carried out by subcutaneous administration.

Results: IMO-8400 was well tolerated at the dose level used in this study. IMO-8400 treatment showed reduction in epidermal hyperplasia and infiltration of leukocytes. In addition, mice treated with IMO-8400 showed suppression of multiple cytokines including IL-12, IL-21, IL-23 and IL-17 compared to untreated mice. Expression of inflammasome protein NLRP3 and of keratinocyte genes Defensin B4, S100a4 and LL-37 was also suppressed in IMO-8400 treated mice compared to untreated mice.

Conclusion: Treatment with IMO-8400 exerts a therapeutic effect on the IL-23 mediated induction of psoriatic lesions by blocking Th1 and Th17 pathways and NLRP3. IMO-8400 is in development for the treatment of lupus and other autoimmune diseases.

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The Effects of TNF Stimulation On Control of Apoptosis in Neutrophils. Direkrit Chiewchengchol, Connie Lam, Kate Roberts, Helen Wright, Huw Thomas, Robert Moots and Steven Edwards. University of Liverpool, Liverpool, United Kingdom

Background/Purpose: TNF is a key regulator of immune function and plays a pivotal role in inflammatory conditions such as rheumatoid arthritis. Human neutrophils express and release TNF, and are activated by it. Neutrophil responses to TNF are bimodal: low concentrations of TNF (10 ng/mL) delay apoptosis but higher concentrations (>20 ng/mL) accelerate apoptosis. When neutrophils are activated to express TNF, complex regulatory mechanisms must control their response to both autocrine and paracrine signalling. This study investigated the mechanisms by which neutrophils respond to anti-apoptotic concentrations of TNF and control apoptosis delay.

Methods: Human neutrophils were exposed to 10 ng/mL of TNF: apoptosis was determined by flow cytometry (annexin V/PI binding); gene expression was determined by analysis of mRNA levels, flow cytometery and western blotting.

Results: Transcriptome analysis revealed that TNF signalling significantly increased mRNA levels for TNF, ICAM1, TNFAIP3, CD40, BFL1 plus several genes associated with NF-kB signalling. In contrast, mRNA levels of TNF receptor 1, TNF receptor 2, FADD, Bax and Caspase 8 were all significantly down-regulated. Many of these changes in mRNA levels were paralleled by changes in protein levels. These data indicate that neutrophils contribute to TNF-mediated signalling pathways via activated secretion of this cytokine. In parallel, they up-regulate genes that delay apoptosis (e.g. BFL1) but down-regulate expression of pro-apoptotic genes such as Bax and FADD.

Conclusion: These data shed important new insights into understanding the function of neutrophils in inflammation and inflammatory diseases; neutrophils contribute to TNF-mediated inflammation and in doing so become more resistant to apoptosis.

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CD11c+ Dendritic Cells Play an Important Proinflammatory Role in Inflammatory Arthritis. Antonia Puchner[1], Stephan Blüml[2], Harald Leiss[2], Victoria Saferding[2] and Kurt Redlich[2]. [1]Medical University Vienna, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria

Background/Purpose: Dendritic cells (DCs) play an important role in bridging innate and adaptive immune responses by serving as antigen presenting cells. Therefore DCs are implicated in the initiation of chronic autoimmune diseases, including rheumatoid arthritis. Using the K/BxN serum transfer arthritis, a model of human rheumatoid arthritis, which depends only on the innate immune system, allowed us to investigate the innate role of dendritic cells in inflammatory arthritis.

Methods: KBxN serum transfer arthritis was induced in CD11c-diphteria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter. This allows for specific depletion of CD11c+ cells by administration of diphtheria toxin (DT). DT or PBS was given on day −1, 3, 6 and 9 and the severity of arthritis was determined clinically and histologically. In addition, serum transfer arthritis was induced in wild type animals who also received DT.

Results: Efficient depletion of DCs after injection of DT was confirmed by flow cytometry and histological analysis of spleens of CD11c-DTR transgenic mice. Clinical scores of arthritis showed that CD11c-DTR transgenic mice had significantly reduced paw swelling and loss of grip strength after administration of DT when compared to PBS treated animals. Moreover, histological analysis showed decreased synovial inflammation and a trend towards reduced local bone destruction in these animals. In contrast, in wild type mice receiving DT we detected identical clinical signs of arthritis as in PBS treated animals, indicating that DT has no unspecific effects on the development of arthritis.

Conclusion: These data show that DCs are involved in innate reactions leading to inflammatory arthritis and therefore could be an important target for treating rheumatoid arthritis.

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TLR3 As a Therapeutic Target for OA? Ashwini Maratha and Sinead M. Miggin. Immune Signalling Laboratory, Maynooth, Ireland

Background/Purpose: Osteoarthritis (OA) is a multifactorial and most disabling disease that affects millions of people globally, with a largely unknown aetiology. OA is now considered a whole-joint inflammatory disease, associated with synovitis of the fibroblast-like synoviocytes (FLS). FLS are sentinel cells that contribute to OA pathogenesis, possibly through activation of the innate immune Toll-Like Receptors (TLRs) aiding in induction of inflammatory mediators and cellular infiltration, however, the exact role of TLRs in OA is poorly understood. The aim of the research work was to characterise the role and functionality of TLRs in OA and to identify the key TLR/s that modulate OA pathology.

Methods: TLR3 neutralisation assays, ELISA, Proteomics, Confocal analysis, Immunoblot analysis, Luciferase reporter gene assays.

Results: Interestingly, we found that TLR3, activated by Poly(I:C)/ dsRNA, RNA from necrotic cells or OA synovial fluid, plays a key role in OA and this was confirmed by neutralisation of TLR3 expression which shifted the balance from pro-inflammatory to an anti-inflammatory cytokine milieu. Next, using a proteomic approach, we found that prohibitin 1 (PHB1), an anti-proliferative and anti-inflammatory molecule, was drastically down-regulated in FLS upon poly(I:C) stimulation and in whole synovial tissue biopsies from early and late stage OA. Interestingly, neutralisation of surface bound TLR3 in FLS restored the PHB1 levels and showed an immuno-modulatory/signal transduction modulatory role by employing anti-TLR3 antibody. These findings were supported by confocal and immunoblot analysis in FLS and through luciferase reporter gene assays in HEK293-TLR3, MAVS-wild type and deficient MEFs.

Conclusion: Thus, our data suggests that TLR3 hyper-activation plays a key role in perpetuating synovial inflammation in OA and suggests that therapeutic intervention of OA may be achieved through TLR3 blockade. *Kindly supported by the Health Research Board of Ireland.*

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Enzymatic Lipid Oxidation Contributes to the Maintenance of Self-Tolerance by Regulating Antigen Clearance and Dendritic Cell Function. Stefan Uderhardt[1], Tobias Rothe[1], Elisabeth Zinser[1], Olga Oskolkova[2], Martin Herrmann[3], Alexander Steinkasserer[4], Valery Bochkov[2], Georg Schett[5] and Gerhard Kronke[1]. [1]University of Erlangen, Erlangen, Germany, [2]Department of Vascular Biology and Thrombosis Research, Center for Physiology and Pharmacology, Medical University of Vienna, Vienna, Austria, Vienna, Austria, [3]PhD, Erlangen, Germany, [4]Department of Immune Modulation at the Department of Dermatology, University Hospital Erlangen, Erlangen, Germany, [5]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: During inflammation and tissue damage, pathogens as well as dying cells are ingested by different phagocytes such as macrophages and dendritic cells. The uptake of particles and subsequent presentation of derived antigens by antigen presenting cells (APC) are key events in the initiation of an adaptive immune response. Thus, both the nature and the activation state of the respective phagocyte determine the resulting immune response ranging from specific immunity to tolerance. However, defects and alterations of these processes are associated with chronic inflammation and autoimmunity. Specific lipid oxidation products, generated by the enzyme 12/15-lipoxygenase (12/15-LO) were implicated in the active resolution of inflammation and limitation of inflammation-associated tissue damage. In this study, we investigated the potential role of enzymatic lipid oxidation by 12/15-LO during initiation of an adaptive immune response and the maintenance of self-tolerance.

Methods: We studied both the clearance of AC and pathogens, as well as the maturation and function of monocyte-derived, antigen-presenting phagocytes in wildtype and 12/15-LO $-/-$ animals *in vitro* and *in vivo*, respectively.

Results: We observed a pivotal role of 12/15-LO in the maintenance of self-tolerance as aged 12/15-LO-deficient mice spontaneously developed autoimmune features indicating a break of self-tolerance. Moreover, a loss of 12/15-LO resulted in an exacerbation of a murine disease model of experimental autoimmune encephalomyelitis (EAE), which resembles clinical and pathological hallmarks of human multiple sclerosis.

Consistently, 12/15-LO $-/-$ mice showed a disturbed clearance of AC under inflammatory conditions, with a clear shift of phagocytosis towards pro-inflammatory antigen-presenting cells. In addition, we could detect a marked expression of 12/15-LO in *in vitro*-generated bone marrow-derived dendritic cells (BMDC). Interestingly, BMDC isolated from 12/15-LO $-/-$ mice presented an increased expression of co-stimulatory molecules on their surface, accompanied by an altered pro-inflammatory cytokine profile. Under inflammatory conditions, the uptake of AC-derived model-antigens by APC from 12/15-LO $-/-$ mice resulted in an increased antigen presentation and subsequent T cell activation, both *in vitro* and *in vivo*. By adding 12/15-LO-generated phospholipid oxidation products, we were, in turn, able to restore an anti-inflammatory clearance of AC *in vitro* and *in vivo*, down-regulate co-stimulatory markers expressed by APC and, thereby, limit T cell activation *in vitro*.

Conclusion: Together, these data indicate a potential regulatory role of enzymatic lipid oxidation by 12/15-LO during the initiation of an adaptive immune response by both orchestrating a cell- and context-specific clearance of antigens by different phagocyte subsets and regulating the maturation and activation status of the respective APC.

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Increased Oxidative Burst in Neutrophils but Not Monocytes in Systemic Lupus Erythematosus. Sandro F. Perazzio[1], Reinaldo Salomao[1], Neusa P. Silva[2] and Luis Eduardo C. Andrade[3]. [1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo, Sao Paulo, Brazil

Background/Purpose: The role of innate immunity in the pathogenesis of Systemic Lupus Erythematosus (SLE) has acquired increasing importance lately. Chronic Granulomatosus Disease (CGD), a hereditary inability of phagocytes in producing Reactive Oxygen Species (ROS), has been associated with increased frequency of discoid lupus erythematosus (2.7%) and with SLE (0.5%). This study aimed to evaluate the oxidative response in monocytes and neutrophils from SLE patients and healthy controls (HC) at basal state and after bacterial stimulus.

Methods: 300 SLE patients and 301 age- and gender-paired HC (blood donors) were clinically examined and evaluated for quantification of the oxidative burst in phagocytes by flow cytometry based on the oxidation of 2,7-dichlorofluorescein-diacetate before and after stimuli with *Staphilococcus aureus* and *Pseudomonas aeruginosa*. There was a 7-day wash-out period for immunosuppressant drugs before sample collection.

Results: No patient or HC presented oxidative burst profile compatible with CGD, however one patient was classified as carrier of defective gene (0.33%). SLE neutrophils had higher basal oxidative activity than HC [mean fluorescence intensity (MFI)$=53.77\pm11.38$ versus 15.08 ± 2.63, respectively; $p<0.001$]. ROS production was also significantly higher in SLE as compared with HC after stimulation with *S. aureus* (MFI$=355.46\pm58.55$ versus 151.92 ± 28.25, respectively; $p<0.001$) or *P. aeruginosa* (MFI$=82.53\pm10.1$ versus 48.99 ± 6.74, respectively; $p<0.001$). Furthermore, the neutrophilic response after bacterial stimuli (DMFI = post-stimulus MFI minus basal MFI) was more intense in SLE than in HC (*S aureus*: 301.69 ± 54.42 versus 118.38 ± 26.03, respectively; $p<0.001$; *P aeruginosa*: 28.76 ± 12.3 versus 15.45 ± 5.15, respectively; $p<0.001$). Oxidative burst profile was not associated with disease activity (SLEDAI≥6) or severity (SLICC-DI≥2). Neutrophil basal ROS production was higher in patients with lupus nephritis (median MFI$=39.43$; ranging from 1.0 to 167.4) than in patients without nephritis (median MFI$=27.29$; ranging from 1.2 to 143.9; $p=0.014$). In addition neutrophils from patients with lupus nephritis (n$=166$) presented higher increment in ROS production after stimulus with *S. aureus* (median DMFI$=320.1$; ranging from 194.9 to 826.1) than neutrophils from patients without nephritis (n$=133$; median ΔMFI$=278.5$; ranging from 149.9 to 649.9; $p=0.03$). These differences in ROS production were not observed in monocytes from patients with lupus nephritis. There was no association of PMN oxidative burst profile and the therapeutic regimen.

Conclusion: Neutrophils from SLE patients presented increased basal ROS production and increased oxidative response to bacterial stimuli. These findings were particularly evident in patients with kidney involvement. The present findings corroborate the important role of innate

immunity in SLE and implicate neutrophils in the pathophysiology of the disease.

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TLR2 Deletion Promotes Arthritis and Joint Destruction Through Reduction of IL-10. Qi Quan Huang[1], Renee E. Koessler[1], Robert Birkett[2], Harris R. Perlman[1], Lianping Xing[3] and Richard M. Pope[4]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]University of Rochester, Rochester, NY, [4]Northwestern Univ Med School, Chicago, IL

Background/Purpose: TLR2 signaling pathway has been suggested as a potential therapeutic target in RA. However, studies with mice deficient in TLR2 (TLR2−/−) and IL-1Ra suggest that TLR2 may suppress arthritis mediated through increased interferon-γ, and reduced TGFβ and T regulatory cell function. In order to determine the role of TLR2 deletion on the effector phase of arthritis, studies were performed with the K/BxN serum transfer model of RA, mediated by antibodies to glucose-6-phosphate isomerase (GPI) which results in an immune complex-mediated arthritis.

Methods: Wild type and homozygous $Tlr2^{\text{tm1Kir}}$ mutation ($Tlr2$−/−) mice on the C57Bl/6 background were injected intraperitoneally with 100 ml anti-GPI serum and evaluated between days 0 to 9 post-induction by ankle swelling and clinical score. Ankles were harvested and sections analyzed by hematoxylin and eosin, and TRAP activity staining for osteoclasts. IL-1b, IL-10, RANKL and osteoprotegerin (OPG) in ankle homogenates were quantified by ELISA. Bone marrow-derived macrophages (BMM) were generated from wild type and $Tlr2$−/− mice by *in vitro* differentiation in GM-CSF for 7 days. BMM activation was induced by incubation with model immune complexes employing mouse IgG coated on plastic plates for 4 hours. Supernatants were assessed for TNFα and IL-10 expression by ELISA. The macrophage Fc receptor mediated macrophage signaling was assessed by immunoblot analysis employing phospho-antibodies to Akt, p38, and ERK. Fc receptor expression on cell membranes was determined employing antibodies to CD16/CD32, analyzed by flow cytometry. Macrophage Fc receptor isoform expression at mRNA level was determined by quantitative real-time RT-PCR.

Results: The transfer of anti-GPI serum resulted in significantly worse arthritis in TLR2−/− mice compared to wild type controls. Histological exam demonstrated more inflammation and joint destruction. Examination of the joints homogenates collected at the peak of inflammation (day7 post-induction) revealed increased IL-1b and decreased IL-10 in TLR2−/− mice. TLR2 deficiency also resulted in increased osteoclasts, identified by TRAP staining. There was a trend toward reduction of OPG (p = 0.056) in the ankles of TLR2−/− mice, and a strong negative correlation (p < 0.001) between OPG and joint swelling. There was no difference in the expression of inhibitory or activating Fc receptors in TLR2−/− mice. However, activation of TLR2−/− macrophages with immune complexes resulted in significantly reduced IL-10, while there was no difference in TNFa, compared to the controls. Macrophages from the TLR2−/− demonstrated decreased activation of Akt, but not ERK or p38, following activation with immune complexes.

Conclusion: These observations demonstrate that deletion of TLR2 exacerbates serum transfer-induced arthritis. In the absence of TLR2, there was a reduction of IL-10 in the joints, and this may be due to the reduced activation of Akt by immune complexes. These observations demonstrate cross-talk between TLR2 and Fc receptor signaling modulates the effector phase of inflammatory arthritis.

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Effects of siRNA Depletion of Interferon Regulatory Factor 5 On Pro-Inflammatory Cytokine Production and IgG Secretion by Primary Human Immune Cells in Response to TLR7/8 Stimulation. Dinesh Srinivasan[1], Sandip Panicker[2], Gang Lu[1], Yajuan Gu[1], Rothschild Soto[2], Seng-Lai Tan[1] and Julie Demartino[1] [1]Hoffmann-La Roche, Nutley, NJ, [2]Hoffmann La Roche, Nutley, NJ

Background/Purpose: Interferon regulatory factor 5 (IRF5) has been identified as a genetic risk factor for multiple human autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis and systemic sclerosis. Knockout animal studies suggest IRF5 plays an important role in the regulation of pro-inflammatory cytokine production, type I interferon production as well as IgG secretion. The aim of this study was to examine the contribution of IRF5 to pro-inflammatory cytokine production and IgG secretion by primary human immune cells in response to TLR7/8 agonist, R848,. For comparison purpose, the role of NFkB and interferon regulatory factor 7 was also evaluated.

Methods: Monocytes and total B cells were isolated from healthy volunteers. Monocytes were further differentiated into monocyte derived dendritic cells (MDDC) using IL-4 and GM-CSF or into monocyte derived macrophages (MDMC) using GM-CSF. Expression of IRF5 was confirmed by Western Blot analysis and mRNA expression analysis. siRNA to IRF5 were introduced using Amaxa Nucleofector. Knockdown of IRF5 in the MDDC, MDMC and B cells was confirmed by Western Blot. Cells were then stimulated with R848 o/n and cytokine levels in the supernatant were measured. Cytokines measured included IL-6, TNF-a, IL-12 and IL-23 and were detected using Alphalisa or ELISA based methods. IgG levels in supernatant from B cells were measured after 7 days. Data were normalized to cell number as determined by *CellTiter-Glo®* viability assay (Promega).

Results: Western blot data and mRNA expression analysis confirmed the expression of IRF5 in the cell types tested. As expected, expression of IRF5 in MDDC and MDMC increased during differentiation. Using nucleofection, we typically obtained about 40–60% depletion of IRF5 proteinby the siRNA, which persisted up to 48h. We found that the knockdown of IRF5 in MDDC, MDMC and B cells significantly attenuated IL-6 and TNF-a produced by R848 stimulated cells. The level of attenuation was similar to that obtained using siRelA. No additional attenuation was observed when the siRNA to both IRF5 and RelA were combined. siIRF7 did not significantly attenuate IL-6 or TNF-a levels in MDDC. IL-12 and IL-23 production from MDDC stimulated with R848 were both attenuated by siIRF5. Interestingly, siRelA blocked IL-12 but did not affect IL-23 production from MDDC. In B cells, the siIRF5, but not siRelA, completely blocked R848 and CpGB-mediated IgG secretion.

Conclusion: In this report, we extend the known literature surrounding the role of IRF5 as a critical regulator of both pro-inflammatory cytokine production and IgG secretion downstream of TLR7/8. Furthermore, IRF5, but not NFkB, regulates R848-mediated IL-23production from MDDC and plays a critical role in IgG secretion by B cells.

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FLIP in Dendritic Cells May Regulate Hematopoietic Homeostasis and Modulating Inflammation and Immunity. Qi Quan Huang[1], Robert Birkett[2], Harris R. Perlman[1] and Richard M. Pope[3]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern Univ Med School, Chicago, IL

Background/Purpose: We previously demonstrated that FLIP in myeloid linage cells is necessary for neutrophil homeostasis and macrophage differentiation. Therefore studies were performed to determine the in vivo role of FLIP in CD11c positive dendritic cells.

Methods: Mice with Flip deficient in dendritic cells ($Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$) were generated by crossing $Flip^{\text{f/f}}$ mice with a $CD11c^{\text{cre}}$ transgenic line. Cell types and differential in peripheral blood were determined by complete blood count. Cell types from different organs were determined by immunophenotyping employing multi-color fluorochrome-conjugated cell marker antibodies, analyzed by Flow cytometry. Age and gender matched mice were used as controls.

Results: Many phenotypic disorders developed in $Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$ mice, including growth retardation (significantly reduced body size and weight) with increased severity in females, and approximately 15% died prematurely. Almost 40% of the mice that reached 4 months of age or older spontaneously experienced an arthropathy characterized by joint swelling and/or deformity. Proteinuria was not detected. All $Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$ mice developed lymphadenopathy, but the spleens were normal both in size and in cell numbers. Immunophenotype analysis demonstrated a significant reduction CD11c,CD8 dendritic cells in the spleens of the $Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$ mice. In $Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$ mice granulocytes were significantly increased in peripheral blood, spleens, lymph nodes and peritoneal cavities and they infiltrated in all organs examined. Although circulating monocytes were significantly increased in $Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$ mice, there is no difference in macrophage numbers in the organs examined. Although B cell numbers were increased in the lymph nodes of $Flip^{\text{f/f}}$, $CD11c^{\text{cre/+}}$ mice, which may contribute to lymphadenopathy, neither B cells nor T cells were increased in the peripheral blood or other organs.

Conclusion: The survival of CD11c+ dendritic cells in the spleen requires FLIP. The deletion of FLIP in CD11c dendritic cells also results in increased circulating neutrophils and a multiorgan neutrophil infiltration. A substantial proportion of these mice develop an arthropathy but proteinuria was not observed. FLIP expression in CD11c+ dendritic cells is necessary for survival in the spleen and for neutrophil homeostasis.

Disclosure: Q. Q. Huang, None; **R. Birkett**, None; **H. R. Perlman**, None; **R. M. Pope**, None.

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p21 Promotes Inflammatory Arthritis Resolution by Facilitating Alternative Activation of Macrophages. Angelica K. Gierut[1], Carla M. Cuda[2], Alexander V. Misharin[3], Rana Saber[3] and Harris R. Perlman[3]. [1]Northwestern Med Faculty Found, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern University, Chicago, IL

Background/Purpose: Current understanding of pathogenesis suggests that RA is mainly a Th1 mediated process that promotes robust inflammatory cytokine production by "classically" activated macrophages. This is in contrast to Th2 diseases such as parasitic infection or allergy that balance potential catastrophic tissue destruction from large worm invasion, or chronic inflammatory response to ubiquitous proteins, by skewing macrophages to an alternatively activated state. Alternatively activated cells appear to be generated from local macrophage proliferation in pure Th2 environments. However, in conditions with concomitant Th1 stimuli, recruited monocytes can be skewed toward alternative activation as well. It is unknown what role alternative macrophages may play in RA. It seems reasonable to assume that their presence would be favorable given their "anti-inflammatory" properties. However, they theoretically have the potential to hinder response to, and clearance of, a yet unknown foreign antigen. Given that alternative macrophages display distinct proliferating capabilities, it seems reasonable to suspect that proteins controlling the cell cycle may be involved in their regulation. One such protein, a cyclin dependent kinase inhibitor, p21, is decreased in RA patient synovium, and is associated with worse serum transfer-induced arthritis (STIA) compared to wild type (WT) controls.

Methods: *In vitro* studies were done with bone marrow derived macrophages (BMDMs) and thioglycollate induced peritoneal macrophages (PMs). Cells were treated with stimuli for classical, alternative, and regulatory macrophage differentiation. Supernatants were analyzed for production of cytokines by ELISA, and for nitric oxide (NO) by colorimetry. Quantigene assays were performed for various genetic markers of macrophage phenotype. Mice were also injected IP with thioglycollate and IL-4, with or without BRDU added 3 hours prior to harvest. Peritoneal cells were assessed by flow cytometry. Finally, mice were treated with IV IL-4 + KBxN serum and observed for arthritis.

Results: *In vitro* analysis of skewed BMDMs and PMs revealed increased production of nitric oxide in p21−/− cells stimulated with interferon gamma + lipopolysaccharide compared to B6 control cells. Conversely, p21−/− BMDMs and PMs stimulated by IL-4 had less relm alpha mRNA, a marker of alternative activation. *In vivo* studies were concordant in that p21−/− mice treated with thioglycollate + IL-4 had less relm alpha protein expression by flow cytometry. Intriguingly, there was increased local proliferation of p21−/− PMs as measured by 3 hr BRDU incorporation. However, recently recruited p21−/− monocytes showed significantly less proliferation compared to B6. Finally, IV IL-4 significantly dampened STIA in B6 mice whereas arthritis in p21−/− mice was not attenuated.

Conclusion: p21 may promote homeostasis during inflammatory conditions by potentiating recruited monocytes and possibly local macrophage differentiation into alternatively activated states. This appears to be independent of its role as a cell-cycle inhibitor because monocytes recruited to inflammatory sites have *less* proliferation in the absence of p21.

Disclosure: A. K. Gierut, None; **C. M. Cuda**, None; **A. V. Misharin**, None; **R. Saber**, None; **H. R. Perlman**, None.

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Prolactin Is Increased in Responders to Anti-TNFα Treatment and the Role of the Prolactin Receptor in Rheumatoid Arthritis. Man Wai Tang[1], Danielle Marie Gerlag[2], Veronica Codullo[3], Elsa Vieira-Sousa[4], Anne Q. Reuwer[5], Marcel T. Twickler[5], Robert B. M. Landewé[6] and Paul Peter Tak[7]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center, Amsterdam, Netherlands, [3]Academic Medical Center/University of Amsterdam/University of Pavia, IRCCS Policlinico San Matteo Foundation, Amsterdam/Pavia, Netherlands, [4]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [5]Academic Medical Center/University of Amsterdam, Amsterddam, Netherlands, [6]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [7]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is the most common rheumatic disease which mainly affects women. In the last decade, it is known that prolactin (PRL) is a sex hormone with immunomodulatory properties. It has been shown that high prolactin levels are associated with an increase of the disease activity postpartum and that the PRL inhibitor, bromocriptine, improves disease activity of patients with RA. Furthermore, the serum PRL levels correlated positively with the Larsen score.

Recently, the prolactin receptor (PRLR), belonging to the family of cytokine receptors, has been described in atherosclerotic plaques, mainly on macrophages.

The objective of the study is to determine 1) the level of PRL in RA patients related to rheumatoid factor (RF), anti-cylic citrullinated peptide antibodies (ACPA), erosive disease and response to anti-TNF treatment 2) PRLR expression in synovial tissue of RA, psoriatic arthritis (PsA) and osteoarthritis (OA) patients 3) the phenotype of the PRLR expressing cell.

Methods: Serum prolactin levels were measured using immunofluorescent metric assay in patients with RA before TNF-α blockade (n=101). The expression of PRLR was determined in synovial tissue (ST) of RA (n=91), PsA (n=15) and OA (n=9) patients using digital image analysis. Immunofluorescence (IF) was used to detect the PRLR expressing cell type.

Results: A trend towards higher PRL levels were found in patients who are rheumatoid factor positive compared to rheumatoid factor negative RA patients (5.0 (2–24) and 7.3 (2.5–36) μg/L; P=0.06). When the PRL levels were divided into 3 categories, the percentage of the RF positive patients had significantly higher PRL levels (P=0.021). A trend towards higher PRL levels were also seen in patients who are ACPA positive (P=0.063) and similar results with erosive disease (P=0.057). Baseline PRL levels were significantly lower in non-responders (median (range): 5.3 (2.0–22) ug/L) than in moderate (7.0 (2.5–36)) and responders (8.5 (4.0–19)) on anti-TNF treatment (P=0.025). Overall, the prolactin levels were similar between females and males.

PRLR expression was higher in RA (median (range): 0.055 (0.000–5.673) IOD/nuclei/mm^2) and PsA (0.182 (0.000–5.336)) compared to OA (0.000 (0.000–0.908); P=0.024; Fig 1). Using IF, co-localisation was observed with macrophages and endothelial cells. The expression of the PRLR was also confirmed by RT-PCR in macrophages.
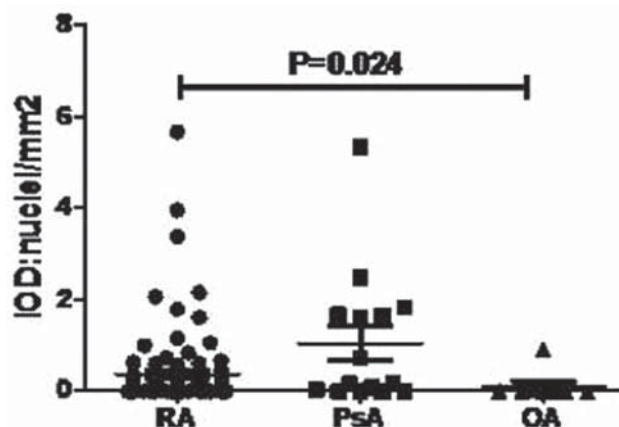
Fig. 1 PRLR expression is higher in RA and PsA compared to OA.

Conclusion: Higher levels of PRL are found in patients who respond to anti-TNF treatment. The expression of the PRLR in synovial tissue, mainly by macrophages, is higher in the inflammatory diseases (RA and PsA) than in OA. Our combined data suggest an important role of prolactin and its receptor in RA.

Disclosure: M. W. Tang, None; **D. M. Gerlag**, None; **V. Codullo**, None; **E. Vieira-Sousa**, None; **A. Q. Reuwer**, None; **M. T. Twickler**, None; **R. B. M. Landewé**, None; **P. P. Tak**, GlaxoSmithKline, 3.

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Polyclonal CD4$^+$Foxp3$^+$ treg Cells Induce TGFb-Dependent Tolerogenic Dendritic Cells That Suppress Murine Lupus-Like Syndrome. Qin Lan[1] and Song G. Zheng[2]. [1]University of Southern California, Los Angeles, CA, [2]Keck School of Medicine of USC, Los Angeles, CA

Background/Purpose: Interplay between Foxp3$^+$ regulatory T cells (Treg) and dendritic cells (DCs) maintains immunologic tolerance, but the effects of each cell on the other are not well understood.

Methods: Naive CD4+Foxp3- cells isolated from DBA/2 mice were stimulated with anti-CD3/CD28 antibodies with IL-2 and TGF-β to develop polyclonal CD4+ iTregs. These cells were adoptively transferred to D2B6F1 mice that also received D2 spleen cells. Anti-IL-10R, Anti-TGFβ or ALK5 (TGFβRI) inhibitor was administrated in some groups of mice. To determine molecular mechanism, TGFβRII DC conditional KO mice were developed and colitis model was used. DC numbers and phenotypes were determined in chronic lupus mice before and after iTreg or Tcon cell treatment. DC were sorted in iTreg or Tcon treated groups and were adoptively transferred to another lupus mice to determine the therpeutic role of DC subsets.

Results: We report that polyclonal CD4$^+$Foxp3$^+$ Treg cells induced *ex-vivo* with TGFβ (iTreg) suppress a lupus-like chronic graft-versus-host disease by preventing the expansion of immunogenic DCs and inducing protective DCs that generate additional recipient CD4$^+$Foxp3$^+$ cells. The protective effects of the transferred iTreg cells required both IL-10 and TGFβ, but the tolerogenic effects of the iTreg on DCs, and the immunosuppressive effects of these DCs, was exclusively TGFβ-dependent. The iTreg were unable to tolerize *Tgfbr2*-deficient DCs.

Conclusion: These results support the essential role of DCs in "infectious tolerance" and emphasize the central role of TGFβ in protective iTreg/DCs interactions *in vivo*.

Disclosure: Q. Lan, None; **S. G. Zheng**, None.

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Effect of Anti-NKG2A Antibody Treatment On NK Cell Receptor Expression in Rheumatoid Arthritis Patients. Joseph Wahle, John Bui and Kristen Bontadelli. Novo Nordisk, Seattle, WA

Background/Purpose: This study explored the effect of *in vitro* blockade of the NKG2A HLA-E interaction on peripheral NK cells from rheumatoid arthritis patients. To block this interaction we have utilized an anti-NKG2A monoclonal antibody, NNC141-0100, a novel therapeutic mAb designed for the treatment of rheumatoid arthritis.

Natural killer cells are potent members of the innate immune system with both cytotoxic and cytokine producing ability. NK cells express a myriad of germ line encoded receptors on their surface that provide multiple pathways via which NK cells activity can be regulated. These receptors include both activating receptors, that recognize stress inducible ligands, and inhibitory receptors that provide protection to self via the recognition of HLA molecules. One such inhibitory receptor is NKG2A, which functions as a heterodimeric receptor with CD94, in order to recognize HLA-E and thereby block NK cell activation. Additionally, NK cells express a number of chemokine receptors and other homing related molecules. The expression of these molecules is crucial for the NK cell to maintain proper lymphoid and non-lymphoid tissue distribution as well as for NK cells to home to and remain at the site of inflammation.

Methods: A whole blood culture system that allows for up to 48 hours of whole blood culturing was utilized for all experiments. This technique allowed for exploring the effect of NKG2A blockade in the context of the complex interactions that exist in the periphery with minimal manipulation.

Results: The addition of the anti-NKG2A mAb to the whole blood cultures led to alteration of the surface phenotype of NK cells from rheumatoid arthritis patients. These alterations included the up-regulation of chemokine receptors as well as the modulation of CD27. This appeared to be a specific pattern of up-regulation as a wide panel of NK related receptors were explored and were not found to be altered. This up-regulation was also found to be rapid occurring within 24 hours of culture. Finally the effect was specific to RA patients as similar changes were not seen in normal donors.

Conclusion: These results indicate that treatment with an anti-NKG2A mAb may alter the homing potential of an NK cell to the site of inflammation. Once at the site of inflammation the presence of the anti-NKG2A mAb may skew the inhibitory balance and thus enable the elimination of stressed and/or inflamed cells. These two activities provide a novel mechanism of action, via the anti-NKG2A mAb, for the treatment of RA.

Disclosure: J. Wahle, Novo Nordisk, 3; **J. Bui**, Novo Nordisk, 3; **K. Bontadelli**, Novo Nordisk, 3.

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Toll-Like Receptor 7, 8 and 9 Activation of Primary Human Cells by Lupus Immune Complexes Is Dependent On Interleukin 1 Receptor Associated Kinase 4 Activity. Aaron Winkler, Weiyong Sun, Ken Dower, Elizabeth A. Murphy, Julia Shin, Michael Luong, Michael J. Primiano, Varenka A. Rodriguez, Tatyana Souza, Lih-Ling Lin, J. Perry Hall, Katherine Lee, Vikram R. Rao and Margaret Fleming. Pfizer, Cambridge, MA

Background/Purpose: Genetic, *in vitro* and *in vivo* evidence strongly implicate the activation of nucleic acid sensing toll like receptors (TLR) 7, 8, and 9 in the pathophysiology of systemic lupus erythematosus (SLE). IRAK4 is a serine/threonine kinase activated by TLRs that utilizes the MyD88 adaptor protein for signaling. The relative importance of IRAK4 scaffolding and kinase functions in signaling is not clear. Indeed, at least one recent report indicates profound differences between species, stimuli, and cell types with regard to the requirement of IRAK4 kinase activity for cell activation[1]. Utilizing a potent, selective and cell-permeable small molecule inhibitor of IRAK4, we queried the importance of IRAK4 kinase activity in primary human cell based assays utilizing SLE disease relevant stimuli.

Methods: Sera from SLE patients was screened for the ability to induce interferon-alpha (IFN-α) protein release from primary human plasmacytoid dendritic cells (pDC). Immunoglobulin-G (IgG) was purified from SLE sera that could induce IFN from pDCs, and then combined with debris from apoptotic U937 cells as a source of TLR 7, 8 and 9 ligands, to form SLE immune complexes (SLE-IC). Human peripheral blood mononuclear cells (PBMC) were stimulated with SLE-IC, and type I interferon (i.e., IFN-α) release in cell culture supernatant was assayed by ELISA. Type I IFN exposure can be monitored in whole blood from SLE patients using an IFN-responsive gene signature, so the expression of IFN-induced genes was assayed in RNA from SLE-IC stimulated PBMC using quantitative real-time polymerase chain reaction (qRT-PCR). As auto-antibody production by B cells is also a key component of pathophysiology in SLE, B cell activation and differentiation induced by TLR ligands was measured by flow cytometry, and cytokine release by B cells was measured by ELISA.

Results: The IRAK4 inhibitor potently blocked SLE-IC induced type I IFN release and IFN gene signature in PBMC. This compound also blocked B cell activation- B cell surface activation marker expression in response to R848 in whole blood, 7 day plasma cell differentiation in PBMC, and cytokine expression by purified B cells exposed to IFN-α and R848.

Conclusion: Using a potent and selective inhibitor of IRAK4 kinase activity in primary human cells, we can demonstrate that IRAK4 kinase activity is essential to inflammatory cytokine release, type I IFN production, and B cell activation, all of which are components of SLE pathophysiology *in vivo*.

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Disclosure: A. Winkler, Pfizer Inc, 3; **W. Sun**, Pfizer Inc, 3; **K. Dower**, Pfizer Inc, 3; **E. A. Murphy**, Pfizer Inc, 3; **J. Shin**, Pfizer Inc, 3; **M. Luong**, Pfizer Inc, 3; **M. J. Primiano**, Pfizer Inc, 3; **V. A. Rodriguez**, Pfizer Inc, 3; **T. Souza**, Pfizer Inc, 3; **L. L. Lin**, Pfizer Inc, 3; **J. P. Hall**, Pfizer Inc, 3; **K. Lee**, None; **V. R. Rao**, Pfizer Inc, 3; **M. Fleming**, Pfizer Inc, 3.

ACR/ARHP Poster Session B
Orthopedics, Low Back Pain, and Rehabilitation Poster
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Predictors of Persistence in People with Subacute Low Back Pain. Souraya Torbey, Ali Mansour, Kristina Herrmann, Marwan Baliki, Thomas J. Schnitzer and A. Vania Apkarian. Northwestern University, Chicago, IL

Background/Purpose: Acute pain is a vital adaptive and protective mechanism. Conversely, chronic pain is a persistent, maladaptive response that outlasts the normal healing period of an injury or insult, and may result in drastic deterioration of quality of life, sometimes for the rest of life. In a

longitudinal brain imaging study of people with subacute back pain, we recently identified brain markers by fMRI that predict transition to chronic pain. Here we investigate, in the same study, behavioral biomarkers that may be predictive of pain chronification.

Methods: 62 patients with new onset subacute back pain (less than 3 mo duration, no back pain for at least a year prior to symptom onset) were seen 6 times over one year. At each visit, pain intensity was determined using a 100mm visual analog scale, behavioral questionnaires completed and fMRI brain scans obtained. For this analysis, the subacute group was divided into persisting (SBPp) and recovering (SBPr) groups using a greater than 20 % change criterion, from the baseline visit to the one year visit. Multivariate logistic regression was utilized to evaluate individual behavioral parameters and their association with pain persistence.

Results: There were 32 males and 30 females, with mean age at study onset of 43 ± 11 yrs, mean pain duration 10 weeks, and mean initial VAS pain intensity was 64 ± 16. By the end of one year, there were 36 SBPr and 26 SBPp. No significant group differences in VAS pain intensity were evident at baseline. However, when evaluated over time, SBPp and SBPr segregated as early as their second visit (within 2 weeks) and the divergence persisted until the final visit at one year. The Neuropathic Pain Scale (NPS), the McGill Pain Questionnaire affective (MPQa), Pain detect (pDetect) and smoking status were significantly different between SBPr and SBPp groups at baseline (t-test). Smoking status at time of entry into the study was the strongest predictor of SBPr and SBPp groups at one year from symptom onset, odds ratio = 5, CI 1.6–16, $p < 0.007$, accuracy = 0.67. NPS, MPQa and pDetect were correlated with each other, and their logistic multiple regression was not significant. Thus, all three parameters reflect interrelated properties of back pain. In a multiple regression logistic model when we include all four parameters, only smoking status remains significant with a stronger odds ratio = 13.5, CI = 2.5–75, p=0.003, accuracy =0.84; thus after correcting for pain characteristics the effects of smoking on pain chronification are even stronger.

Conclusion: There is a strong association between smoking at the time of the onset of back pain symptoms and longer term pain chronification. As this observation was not a prespecified hypothesis of the study, we label the observed result as an association that needs to be validated in a systematic study.

Disclosure: S. Torbey, None; **A. Mansour**, None; **K. Herrmann**, None; **M. Baliki**, None; **T. J. Schnitzer**, None; **A. V. Apkarian**, None.

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Physicians' Recommendations for Total Knee Arthroplasty in Younger Persons with Moderate Osteoarthritis. Liana Fraenkel[1], Lawrence Weis[2] and Lisa G. Suter[2]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [2]Yale University, New Haven, CT

Background/Purpose: Rates of total knee arthroplasty (TKA) are increasing among all age groups. The most rapidly growing population of patients undergoing TKA are those under the age of 65. This reason for this increasing prevalence is unclear. While physicians' recommendations regarding use of TKA are likely to be fairly uniform for patients with severe OA, little is known regarding physicians' decision-making for younger patients with less severe arthritis. The objective of this study was to gain insight into the factors influencing physicians' recommendations for younger persons with OA using an experimental $2 \times 2 \times 2$ design.

Methods: A convenience sample of rheumatologists and orthopedic surgeons, recruited at their respective national meetings, completed a survey including a standardized scenario of a 62 year old person with knee OA who has moderate knee pain limiting strenuous activity despite medical management. The scenarios varied on patient gender, employment status (business manager vs retired), and x-ray (mild vs moderate OA). Each subject rated their recommendation for a single scenario (distributed randomly) on a 7-point scale. Recommendation was treated as a dichotomous variable: For vs Against TKA.

Results: 406 surgeons [mean age (SD) = 49 (10), 18% female] and 494 rheumatologists; [mean age (SD) = 48 (10), 44% female] participated. Overall, 51% of both surgeons and rheumatologists recommended TKA. As expected, both groups recommended TKA more frequently for scenarios including more severe radiographic OA (Table 1). However, this feature had a greater influence among rheumatologists than orthopedic surgeons. Orthopedic surgeons were more likely to recommend TKA for male vs female patients. Whereas, rheumatologists were less likely to recommend referral for TKA for business managers compared to housewives or retired men. The

influence of physicians' demographic characteristics on TKA recommendation is presented in Table 2. Younger physicians, regardless of specialty, were more likely to recommend TKA ($p < 0.05$). Rheumatologist' recommendations for TKA did not vary by geographic location; however, American and Asian surgeons were more likely to recommend TKA compared to their European counterparts.

Table 1. Influence of Patient Characteristics on Physicians' Recommendations for TKA

Patient Characteristics	Percent of Rheumatologists Recommending TKA	Percent of Orthopedic Surgeons Recommending TKA
Moderate vs Mild radiographic changes	60 vs 41, p<0.0001	56 vs 47, p=0.05
Male vs Female	49 vs 52, p=0.5	59 vs 44, p=0.002
Working outside of the home vs Retired/Housewife	42 vs 56, p=0.002	49 vs 53, p=0.4

Table 2. Influence of Physician Characteristics on their Recommendations for TKA

Physician Characteristics	Percent of Rheumatologists Recommending TKA	Percent of Orthopedic Surgeons Recommending TKA
Age (<50 vs ≥ 50)	55 vs 46, p=0.03	57 vs 47, p=0.04
Male vs Female	50 vs 53, p=0.5	51 vs 56, p=0.7
Location (Asia vs Europe vs US)	54 vs 49 vs 52, p=0.8	67 vs 34 vs 52, p=0.006

Conclusion: Physicians recommendations for TKA vary significantly for younger patients with moderate OA. Recommendations are influenced by both physician and patient characteristics.

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1084

In Vivo Kinematics of Three-Component Mobile-Bearing Total Ankle Replacement for Rheumatoid Arthritis. Keiji Iwamoto[1], Tetsuya Tomita[1], Takaharu Yamazaki[2], Kenrin Shi[1], Norimasa Shimizu[1], Masahiro Kurita[1], Kazuma Futai[1], Yasuo Kunugiza[1], Hideki Yoshikawa[1] and Kazuomi Sugamoto[1]. [1]Osaka University Graduate School of Medicine, Osaka, Japan, [2]Osaka University, Osaka, Japan

Background/Purpose: The standard treatment for end-stage arthritis of the ankle joint due to rheumatoid arthritis (RA) has been an ankle arthrodesis. Patients with RA who require surgery usually already have degeneration of the subtalar and midtarsal joints. Fusion of the ankle and hindfoot will result in functional problems with gait. Thus, total ankle replacement (TAR) that can relieve pain while retaining ankle movement is important for patients with RA. However, high complication rates and low survivorship are still problematic in TAR, as compared to total knee and hip replacements. This could primarily be due to implant loosening and subsidence induced by excessive articular contact stress during ankle motion. A better understanding of ankle kinematics after TAR may be important to explain the failures in TAR, especially those attributed to loosening and subsidence. The purpose of this paper was to study in vivo kinematics of a three-component mobile-bearing TAR by 3D-evaluation of fluoroscopic imaging of ankle motion.

Methods: We investigated ten ankles in 7 patients with RA implanted with a three-component mobile-bearing TAR (FINE Total Ankle System, Nakashima Medical, Okayama, Japan), which allows not only internal/external rotation but also anteroposterior translation. Fluoroscopic images were obtained while each patient was asked to perform normal gait with full weight-bearing on the implanted ankle. Thereafter tibio-talar motion was analyzed by 2D/3D registration technique; a reproduction method of the spatial position of each component in TAR, from single-view fluoroscopic images by use of computer-assisted design models. We evaluated the dorsi-/plantarflexion angle, internal/external rotation angle and anteroposterior translation between the components.

Results: The average range of tibio-talar motion during the stance phase of gait with full weight-bearing on the implanted ankle was $11.2 \pm 2.7°$. The average range of internal/external rotation was $3.9 \pm 1.4°$. However, large intersubject variability resulted in the lack of a uniform pattern of rotational movement. The average absolute amount of anteroposterior translation was 1.6 ± 0.7mm.

Conclusion: The range of motion, with regard to plantar/dorsi flexion, was not so wide as expected, and was almost the same with other non-mobile

TAR. As intended by mobile bearing design, however, the tibial and talar components rotated internally/externally with respect to each other. Antero-posterior translation was also observed but was within small amount. These results suggest that mobile bearing TAR should be advantageous in durability with expectation that it could compensate rotational malposition of the components as well as malalignment of the subtalar joint.

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Differences in Baseline Characteristics Between TKR and THR Patients: Results From a National Research Consortium. Patricia D. Franklin[1], Benjamin Snyder[1], Jeroan Allison[2], Wenjun Li[1], Milagros Rosal[1], Leslie R. Harrold[3], Bruce Barton[2] and David Ayers[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]University of Massachusetts Medical School, [3]UMass Medical School, Worcester, MA

Background/Purpose: Both total knee replacement (TKR) and total hip replacement (THR) reliably relieve pain, restore function, and ensure mobility in patients with advanced joint arthritis; however these results are not uniform across all patient populations. Previous studies have shown baseline differences between patients undergoing TKR and THR. We compared baseline demographic and symptom profiles in a national research consortium of advanced OA patients undergoing primary TKR and THR to evaluate these differences.

Methods: Patients undergoing primary TKR and THR between 7/1/2011 and 3/30/2012 were identified from the national research consortium which collects comprehensive data on enrolled patients from 89 surgeons across 27 states. Gathered data includes patient demographics, comorbidity (Charlson Comorbidity Index), operative joint pain severity, physical function (SF-36; Physical Component Score (PCS)), emotional health (SF-36 Mental Component Score (MCS)), and musculoskeletal burden of illness (Hip and Knee Disability and Osteoarthritis Outcome Scores;Oswestry Disability Index. Descriptive statistics compared baseline demographic and symptom profiles.

Results: Our analysis compared 1362 primary TKR patients and 1013 primary THR patients. TKR patients were significantly older (66.5 vs. 64.3 years), more obese (BMI 31.7 vs. 29.3), and less educated ($p < 0.005$). TKR patients had higher rates of comorbidities, specifically diabetes, gastrointestinal ulcers, and cerebrovascular disease ($p \leq 0.006$). THR patients had significantly worse physical function (PCS 31.6 vs. 33.3), lower back pain (35.6% vs. 30.5% moderate-severe), and operative joint pain, stiffness, and function ($p < 0.005$).

Conclusion: Patients undergoing primary TKR are older with more comorbidities, however THR patient baseline functional and musculoskeletal disability are significantly greater than primary TKR patients, which may help explain the variability in results shown after primary TKR as compared to primary THR.

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1086

Has the Level of Disability At Time of TKR Changed Over the Past 10 Years?: Results From Two National Cohorts. Patricia D. Franklin[1], Wenjun Li[1], Benjamin Snyder[1], Courtland Lewis[2], Philip Noble[3] and David Ayers[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]CT Joint Replacement Institute, St. Francis Hospital, Hartford, CT, [3]Baylor College of Medicine, Houston, TX

Background/Purpose: A growing numbers of younger adults report knee pain consistent with OA, although parallel analyses of knee x-rays show no increase in classic radiographic signs of OA. To evaluate whether surgeons are performing TKR at an earlier stage in the condition, we compared pre-operative demographic and symptom profiles from 2 national cohorts of TKR patients, one from 2011–2012 and another from 2000–2004.

Methods: Following informed consent, we collected comprehensive demographic, comorbidity, and patient-reported pain and physical function from a national sample of 2011-12 TKR patients, across 27 states with 89 surgeons. Comparable data collected by one implant manufacturer between 2000–2004 from 136 surgeons in 31 states were analyzed. Descriptive statistics compared the demographic and symptom profiles of the two cohorts.

Results: There were minimal differences between the two cohorts in terms of age (2011-12: 66.5 years, vs. 2000/4: 67.6 years; p0.05). The more recent patient cohort consisted of fewer females (57%) compared to the earlier group (66%). Pre-operative physical function scores (SF36/PCS) were 3 points higher in 2011-12 than 2000-04 (33.6 ± 0.3 vs. 30.3 ± 0.1; $p < 0.0000$). The 2000–2004 cohort (n=7686) had a mean BMI of 32 vs 31.7 for the 2011-12 cohort (n=1362). When compared to the national PCS norm of 50 (SD=10), TKR patients from both time periods reported pre-operative function levels almost 2 standard deviations below the national norm.

Conclusion: The profile of primary TKR patients changed between 2000-04, and 2011-12. Today, patients are younger and have a higher pre-operative physical function scores. They continue to report significant levels of disability with mean pre-TKR PCS significantly lower than average OA patients.

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Do Younger TKR Patients Have Similar Disability At Time of Surgery As Older Adults? Patricia D. Franklin[1], Wenjun Li[1], Leslie R. Harrold[2], Benjamin Snyder[1], Courtland Lewis[3], Philip Noble[4] and David Ayers[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]UMass Medical School, Worcester, MA, [3]CT Joint Replacement Institute, St. Francis Hospital, Hartford, CT, [4]Baylor College of Medicine, Houston, TX

Background/Purpose: The trend toward greater numbers of working-aged patients choosing TKR has raised concerns that younger patients may receive surgery prematurely. We compared the severity of operative knee pain and functional status in younger versus older TKR patients.

Methods: Patients undergoing primary TKR from 7/1/11 through 3/30/12 were identified from a national research consortium which enrolls patients from 89 surgeons in 27 US states. Patients, surgeons and hospitals submit data including the SF 36 Physical Component Score (PCS), the Knee injury and Osteoarthritis Outcome Score (KOOS) and the Oswestry Low Back Pain Disability Questionnaire. The KOOS data were used to estimate the Western Ontario and McMaster Universities Arthritis Index (WOMAC). We compared those <65 to those who were ≥65 years of age using descriptive statistics.

Results: Primary TKR was performed in 570 younger (<65) and 769 older (≥65) patients. Younger patients were less likely to be white (89% vs. 92%, p=0.02), and had a greater body mass index (mean BMI 33.0 vs. 30.7, $p < 0.0001$). Younger patients reported greater pain (48.9 vs. 53.8, $p < 0.001$) and stiffness (38.5 vs. 46.7, $p < 0.001$) in the operative knee joint. Overall function as measured by the WOMAC and SF36 PCS were similar in the two age groups (WOMAC 51.9 vs. 53.8; PCS 32.8 vs. 33.8). Function levels in both groups reflect significant impairment at time of surgery.

Conclusion: At the time of TKR, younger and older patients have similar levels of functional impairment suggesting surgeons use comparable standards for selecting TKR in younger and older adults.

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Factors Influencing Long-Term Recovery of Total Knee Arthroplasty. C. Allyson Jones[1], Gian S. Jhangri[2] and Maria E. Suarez-Almazor[3]. [1]Departments of Physical Therapy and School of Public Health, University of Alberta, Edmonton, AB, [2]School of Public Health, University of Alberta, Edmonton, AB, [3]University of Texas MD Anderson Cancer Center, Houston, TX

Background/Purpose: Although a number of studies have examined short term outcomes after total knee arthroplasty (TKA), few have prospectively examined the long term trajectory of recovery of health-related quality of life. The aim of this study was to identify patient-related outcomes that explained the pattern of pain and functional recovery over 10 years for TKA.

Methods: This is a prospective observational study that followed a community-based cohort of patients receiving elective primary TKA within a month before surgery, 6 months, 3 years and 10 years after surgery. Data were collected from patient interviews, chart reviews and regional administrative databases. Joint pain and function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Health status

was evaluated over time using the SF-36. Effect sizes were calculated to measure change over time. Pre-operative and operative factors were inspected as possible variables that predicted the pattern of recovery. Linear mixed models for pain and functional recovery were used to evaluate changes over time while adjusting for covariates.

Results: Of the 289 patients followed, the mean age was 69.4 (SD 9.2) yrs;170 (59%) were female. At 10 years 145 patients responded. The mean number of comorbid conditions was 3.5 (SD 2.0) at baseline and 4.7 (SD 2.3) at 10 years. WOMAC pain score mean difference from baseline to 6 months was 33.0 (95% 30.5, 35.5) with the largest effect size (ES) of 1.89. Long-term change was much smaller from 6 months to 3 years (ES 0.18) and from 3 to10 years (ES 0.03). Smaller changes were seen with function; baseline to 6 months (ES 1.65), 6 months to 3 years (ES 0.07) and 3 to 10 years (ES −0.13). The ES of the SF-36 physical summary score at 6 months was 1.17 and over the 10 years was 1.87. After adjusting for age and gender, the 10 year trajectory for pain was explained by baseline health status (SF-36 summary scores), and baseline WOMAC pain (p< 0.05). The 10 year trajectory for function had similar covariates which explained the trajectory, in that baseline WOMAC function and health status were significant factors. In-hospital complications, prosthesis-type, and obesity did not impact long-term recovery pattern.

Conclusion: Pain and functional recovery after TKA occurs primarily within 6 months after surgery with negligible change from 3 to 10 years. Greater pain, dysfunction and lower overall health at baseline explained slower long-term recovery patterns for TKA.

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The Number of Ruptured Tendons As a Prognostic Factor for Reconstructing Extensor Tendon Rupture in Patients with Rheumatoid Arthritis. Yu Sakuma, Kensuke Ochi, Takuji Iwamoto, Shinji Yoshida, Asami Saitou, Katsunori Ikari and Shigeki Momohara. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Extensor tendon rupture seen in patients with rheumatoid arthritis (RA) is usually surgically treated in combination with extensor tendon reconstruction and wrist arthroplasty. However, limited data exist in literature concerning factors significantly correlating with poor prognosis of the extensor tendon reconstruction. The purpose of this study is to investigate factors significantly correlating with poor prognosis of the extensor tendon reconstruction.

Methods: Total of 68 RA patients (mean age of 52 years old; 57 females) who underwent combined surgical procedures of tendon reconstruction and wrist arthroplasty because of spontaneous extensor tendon ruptures were investigated. The result of extensor tendon reconstruction was evaluated as "good", "fair" and "poor". This evaluation was defined based on active flexion and extension lag of metacarophalangeal (MP) joint of the affected fingers at 3 months after the surgery. The cases in which active flexion arc was greater than 45 degrees and extension lag was less than 15 degrees were defined as "good". The cases, in which active flexion arc was greater than 45 degrees and extension lag ranged from 15 to 45 degrees, or active flexion arc was less than 45 degrees and extension lag was less than 15 degrees, were defined as "fair". All other cases were defined as "poor". We investigated the relation among clinical factors such as age at surgery, the number of ruptured extensor tendons, duration between onset of rupture and surgery, methods for reconstructing ruptured tendons, surgical procedures for wrist arthroplasty, the time interval between surgery and beginning of postoperative rehabilitation, and the frequency of ambulatory visit for rehabilitation, and the postoperative results by using multiple regression analysis. The correlation between factors relating to the postoperative result and duration between onset of rupture and surgery were additionally analyzed using single regression analysis.

Results: Forty-two (61.8%) patients were evaluated as "good", while 19(28.0%) and 7(10.3%) patients were evaluated as "fair" and "poor", respectively. Number of ruptured tendons was the only independent variable which significantly related to poor postoperative results (p=0.0002). The longer duration between onset of rupture and surgery had significant correlation between increased number of ruptured tendons (p=0.03).

Conclusion: Increased number of ruptured extensor tendons significantly correlated with poor postoperative result of extensor tendon reconstruction in patients with RA. The number of increased ruptured extensor tendons also significantly correlated with duration between onset of rupture and surgery. We therefore recommend surgical intervention at early stage of extensor

tendon rupture, in which only few tendons are suspected to be involved, to result in better prognosis.

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A Comparison of Patient-Reported and Measured Range of Motion in a Cohort of Total Knee Replacement Patients. Jamie E. Collins, Benjamin N. Rome, Vladislav Lerner, Jeffrey N. Katz and Elena Losina. Brigham and Women's Hospital, Boston, MA

Background/Purpose: Range of motion (ROM) is an important component of the assessment of total knee replacement (TKR) outcome. Traditionally, ROM is measured by a clinician or trained researcher, making ROM less practical than self-report measures that can be obtained by phone or mail. Recently, Gioe et al. developed a method that presents patients a set of lateral knee photographs depicting varying levels of flexion and extension and asks the patients to select the photographs that most closely resemble their motion. We aimed to compare this self-reported method of assessing flexion and extension with clinical measurement before and after TKR.

Methods: As part of a prospective cohort study of consecutive patients undergoing TKR, patients were asked to self report flexion and extension on their operated knee using the method of Gioe et al. In addition, flexion and extension were measured using a goniometer by a trained research assistant. These measures were obtained preoperatively and at three and six months postoperatively. We compared self-reported ROM category with measured ROM for both flexion and extension using ANOVA. We dichotomized flexion at 90 degrees and determined the sensitivity and specificity of the self-report flexion categories for identifying patients with poor ROM.

Results: One hundred and one patients provided both self-report and RA-measured ROM at baseline. There was a significant association between self-report ROM category and ROM measurement for both flexion and extension (P<0.001). The Spearman correlation coefficient was 0.51 for extension and 0.45 for flexion, indicating moderate correlation. We combined all 3 visits to assess sensitivity and specificity of self-report flexion categories. Overall 15 of 25 patients with poor measured flexion (≤90°) also self-reported poor flexion (to 90° or lower) for a sensitivity of 60% and 177 of 190 patients without poor flexion (>90°) did not self-report poor flexion (to 100° or higher) for a specificity of 93%. The negative predictive value for self-report was 95%, indicating that the vast majority of patients self-reporting adequate flexion do not have poor flexion.

Table 1. Performance of self-report flexion categories for identifying patients with poor ROM

		Measured Flexion	
		≤90°	>90°
Self Report – How well can you bend your knee?	To 90° or lower	15	13
	To 100° or higher	10	177
	Total	**25**	**190**
	Sensitivity	60.0%	
	Specificity	93.2%	
	Predictive Value+	53.6%	
	Predictive Value-	94.7%	

Conclusion: Patient self-reported ROM may be a useful outcome measurement for TKR when clinical ROM measurement is not possible. These findings are based on a small sample in one center and should be confirmed. Self-report is particularly effective (>90% specificity) in confirming adequate ROM.

Disclosure: **J. E. Collins**, None; **B. N. Rome**, None; **V. Lerner**, None; **J. N. Katz**, None; **E. Losina**, None.

1091

Trends in Patient Physical Activity Before and After Primary Total Hip Arthroplasty. Anne Lübbeke, Dorith Zimmermann, Constantinos Roussos, Alexis Bonvin, Robin Peter and Pierre Hoffmeyer. Geneva University Hospitals, Geneva, Switzerland

Background/Purpose: Total hip arthroplasties (THA) are performed to reduce pain and enhance patients' function and physical activity (PA) level. PA is also recognized as the most important patient-related factor determining

implant survival. Furthermore, unrealistic patient expectations regarding PA after surgery have been identified as one of the reasons for increased dissatisfaction. Detailed assessement of PA before and after THA is lacking. Our objective was to evaluate (1) how patient's PA level evolves: prior to disease onset, prior to THA, and at 5 and 10 years postoperative, and (2) whether PA level before and after THA has changed over the last decade across birth cohorts of identical age.

Methods: Patients included are part of a prospective hospital-based cohort of all THAs of a University hospital and followed longitudinally since 1996. We included all primary THAs between 1/2000 and 4/2012. PA was assessed by the physician and self-reported, preoperatively and at 5 and 10 years postoperative. Moreover, PA was evaluated with the UCLA activity scale. To determine PA evolution over the course of OA and THA, cross-sectional analyses were performed to assess mean UCLA scores over four periods: prior to disease, prior to surgery, 5- and 10-years postoperative independently of the year of surgery. Separate analyses were performed for men and women and by age categories (<55, 55–64, 65–74, ≥75 yrs. at operation). To analyze secular trends in PA, cross-sectional analyses were performed at three time periods within identical ages categories (2000–2003, 2004–2007, 2008–2011).

Results: Overall, lifestyle was assessed preoperatively for 2916 THAs and postoperatively for 1565 THAs. The UCLA score was assessed at follow-up for 1345 THAs. Mean age at operation was 68.4 years, 56% were women.

Prior to surgery 61% of patients reported a sedentary lifestyle compared to 45% at 5 years postoperative (RD 16%, 95% CI 12; 20). The proportion of patients with sedentary lifestyle prior to surgery decreased from 68% in 2000–2003 to 54% in 2007–2011 (RD 14%, 95% CI 9; 18) despite a similar mean age (p=0.1). Sedentary lifestyle 5 years after surgery was reported by 53% of those operated 2000–2003 compared to 39% of those operated 2004–2007 (RD 14%, 95% CI 9; 20).

Mean UCLA scores prior to OA onset, prior to THA and 5 and 10 years postoperative were respectively in men 8.4, 3.7, 6.2 and 6.2 and in women 6.1, 3.4, 5.1 and 4.8.

Prior to surgery UCLA scores were similar across age categories ranging form 3.7 in the youngest to 3.2 in the eldest group (p=0.8). Five years postoperative UCLA scores declined as age increased. Across the four age categories the mean UCLA scores were respectively 6.7, 6.4, 5.6 and 4.2 (p<0.0001). Ten years postoperative mean UCLA scores were 6.4, 6.4, 5.2 and 3.8, respectively (p<0.0001).

Conclusion: Primary THA substantially and durably improved PA levels in men and women and in all age categories. Activity levels were lower in women than in men at all times. In the last decade the proportion of patients with an active lifestyle before and after THA increased by 14%.

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Effect of FULL Contact FOOT Orthosis On Plantar Fasciitis. Hilda A. Oliveira[1], Anamaria Jones[1], Emilia Moreira[1], Fabio Jennings[1] and Jamil Natour[2]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Plantar fasciitis (PF) is an inflammation of the foot *plantar fascia*, characterized by stiffness in the medial arch and ankle, especially during first steps, and can have a significant effect on activities of daily living. Insoles are one of the most often employed methods for the treatment of PF. The full contact foot orthosis is the most recommended, as it redistributes the load uniformly throughout the sole of the foot. However, few studies have demonstrated the effectiveness of this device and there is no consensus on which type of insole is the most adequate. The aim of the present study was to assess the effectiveness of a full contact foot orthosis regarding pain, foot function and quality of life in patients with PF.

Methods: Seventy-four patients were randomly allocated to an experimental group (n=37) using a full contact foot orthosis or a control group (n=37) using a sham insole. Evaluations were performed of pain (VAS), quality of life (SF-36), foot function (FFI and FSHQ), six-minute walk test and static/dynamic baropodometry (AM Cube FootWalk Pro program). The groups were evaluated at baseline and after 45, 90 and 180 days after randomization by a blinded evaluator.

Results: The groups were homogeneous at baseline regarding clinical and demographic characteristics. In the comparisons over time, we found better results for the experimental group for pain during walking on the right feet (p=0.008 - Figure 1). In the intragroup analysis we found in both groups

improvement regarding pain during walking on the left feet, the six-minute walk test, foot function and some quality of life parameters, with no statistically significant differences between groups. No changes in foot pressure were found with the use of the insole.

Figure 1 - Walking pain - right feet
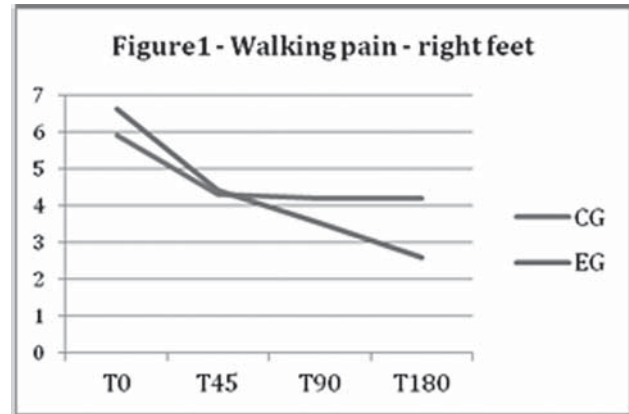
Conclusion: The benefit of the use of full contact foot orthosis for the treatment of PF was restricted to the improvement in pain during walking in right feet.

Disclosure: H. A. Oliveira, None; **A. Jones**, None; **E. Moreira**, None; **F. Jennings**, None; **J. Natour**, None.

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Obesity Is Not a Risk Factor for Poor Pain and Function Two Years After Total Knee Replacement. Lisa A. Mandl. Mark P. Figgie, Alejandro Gonzalez Della Valle, Michael Alexiades and Susan M. Goodman, Hospital for Special Surgery, New York, NY

Background/Purpose: Almost 90% of referring physicians think obesity increases the likelihood of poor outcomes after total knee replacement (TKR). However, current data are conflicting. The purpose of this study is to assess of the association of body mass index (BMI) with pain, function and satisfaction 2 years after primary TKR.

Methods: Institutional TKR Registry patients who had a primary TKR between July 2007 and June 2009 and BMI>18.5 were enrolled. Poor pain and function were defined as WOMAC score <= 60. Data were collected prior to surgery and 2 years post-op. Multivariate regressions were performed to evaluate the association between BMI at baseline and poor pain and function at 2 years, controlling for gender, age, race, Deyo Comorbidity score and educational attainment. Expectations were measured with a validated TKR Expectations Survey.

Results: 2524 patients were included in the analysis. BMI > 40 were more likely to be non-Caucasian, female, have less education and more co-morbidities. Pre-operatively, both pain and function were least severe in <25 BMI category, increasing as BMI increased. At 2 years, change in WOMAC pain and function showed a step wise, dose dependant improvement across BMI categories, with BMI > 40 showing the most improvement. At 2 years, there was a statistically significant trend towards lower BMI categories having the least pain (p-value=0.0003) and best function, (p-value<0.0001), but the differences between groups were not clinically significant. In the multivariate regressions, there were no statistically significant associations between any BMI category or number of co-morbidities and poor pain or function at 2 years. Being female significantly increased the risk of having poor pain (OR 1.6; 95% CI 1.2–2.2) or poor function (OR 1.5; 95% CI 1.1–2.1) at 2 years. Being Caucasian decreased the risk of poor pain (OR 0.6; 95% CI 0.4–0.9) or poor function (OR 0.5; 95% CI 0.3–0.7). Having only high school education also increased the risk of poor pain (OR 1.5; 95% CI 1.1– 2.1) and poor function (OR 1.9; 95% CI 1.4–2.6) at 2 years. Age group 61–70 showed a decreased risk of poor pain compared to age <=60, (OR 0.5; 95% CI 0.4– 0.8). At 2 years, 20.4% of patients lost weight, (mean weight loss 0.6 lbs +/− 2.7), with the greatest loss in BMI >40 (2.7 lbs, +/− 5). There were no significant differences in expectations or satisfaction between BMI categories.

Conclusion: Although obese patients have worse pain and function at the time they elect TKR, their outcomes at 2 years are not clinically significantly different than other patients. However, race and educational

attainment were significantly associated with poor outcomes. Obese patients have similar expectations and are as satisfied as patients with lower BMI. More research should be done on the effect of race and education on TKR outcomes. Obesity should not be regarded as a risk factor for poor outcomes after primary TKR.

Patient Characteristics	Average Weight (18.5 ≤ BMI <25) N=523	Overweight (25 ≤ BMI <30) N=902	Obese class I (30 ≤ BMI <35) N=633	Obese class II (35 ≤ BMI <40) N=289	Obese class III (40 ≤ BMI) N=177	P-value
Age	71.0 ± 10.0	69.1 ± 9.7	66.7 ± 9.2	64.8 ± 8.9	64.3 ± 7.9	<0.0001
Female	365 (70.3%)	476 (53.0%)	359 (57.2%)	200 (69.4%)	132 (75.4%)	<0.0001
Caucasian	491 (93.9%)	824 (91.4%)	560 (88.5%)	251 (86.9%)	156 (88.1%)	0.0027
High school or less	56 (17.9%)	153 (24.1%)	140 (29.4%)	72 (29.4%)	51 (30.3%)	<0.0001*
Some college or college graduate	254 (81.2%)	416 (65.5%)	286 (60.0%)	130 (53.2%)	82 (48.8%)	
Masters professional or doctorate degrees	207 (66.1%)	323 (50.9%)	203 (42.6%)	86 (35.2%)	42 (25.0%)	
0 Deyo comorbidities	409 (79.4%)	664 (75.5%)	435 (70.7%)	195 (68.8%)	100 (59.0%)	<0.0001*
1-2 Deyo comorbidities	103 (20.0%)	214 (24.3%)	178 (28.9%)	86 (30.3%)	67 (39.5%)	
>= 3 Deyo comorbidities	7 (1.4%)	20 (2.3%)	15 (2.4%)	7 (2.5%)	8 (4.7%)	
Pre-Operative WOMAC Pain	59.4 ± 17.1	57.0 ± 17.5	53.6 ± 17.1	51.0 ± 18.3	46.5 ± 16.3	<0.0001
2-Year Post-Operative WOMAC Pain	89.2 ± 15.1	88.9 ± 14.5	86.9 ± 16.2	84.8 ± 17.2	86.0 ± 16.5	0.0001
Change in WOMAC Pain	29.9 ± 20.0	31.9 ± 19.6	33.3 ± 20.2	34.0 ± 21.6	39.3 ± 21.9	<0.0001
Pre-Operative WOMAC Function	58.7 ± 17.5	57.6 ± 17.2	52.6 ± 17.0	49.7 ± 17.7	43.5 ± 15.9	<0.0001
2-Year Post-Operative WOMAC Function	87.9 ± 15.5	87.3 ± 15.0	84.7 ± 17.0	82.8 ± 18.2	82.2 ± 16.6	<0.0001
Change in WOMAC Function	29.0 ± 20.1	30.5 ± 18.8	32.4 ± 19.1	34.1 ± 18.6	38.0 ± 20.5	<0.0001
Change in Weight (lbs)	0.2 ± 1.7	−0.3 ± 1.9	−0.8 ± 2.7	−1.3 ± 3.2	−2.7 ± 5.5	<0.0001
Somewhat/Very Satisfied with Relieving Pain	453 (90.2%)	797 (93.1%)	547 (91.0%)	253 (90.7%)	152 (92.7%)	0.333
Somewhat/Very Satisfied with Improving ability to do recreational activities	413 (83.4%)	695 (82.1%)	495 (83.2%)	230 (82.4%)	123 (76.9%)	0.401
Overall Somewhat/ Very Satisfied with TKR	445 (88.3%)	786 (91.5%)	537 (89.2%)	252 (89.7%)	148 (91.4%)	0.333

*= test for trend

1094

The Relationship Between Lumbar Spine Individual Radiographic Features and Low Back Symptoms with and without Associated Leg Symptoms: The Johnston County Osteoarthritis Project. Adam P. Goode[1], Janet K. Freburger[2], Timothy S. Carey[3], Chad E. Cook[4], Jordan Renner[5], Sean D. Rundell[6] and Joanne M. Jordan[7]. [1]Duke University, Durham, NC, [2]University of NC CB 7590, Chapel Hill, NC, [3]Cecil G. Sheps Center for Health Services Research University of North Carolina, Chapel Hill, NC, [4]Walsh University, OH, [5]University of North Carolina, Chapel Hill, NC, [6]University of Washington, Seatle, WA, [7]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC

Background/Purpose: Little is known of the relationships between low back symptoms (LBS) and associated leg symptoms and lumbar spine individual radiographic features (IRF). We examined the associations between LBS, with and without associated leg symptoms, and lumbar spine IRF of disc space narrowing (DSN), vertebral osteophytes (OST) and facet joint osteoarthritis (FOA) and determined if these associations differed by race or gender.

Methods: 840 newly enrolled participants in the Johnston County Osteoarthritis Project from 2003-04 having data on lumbar spine IRF (DSN, OST and FOA) were the subjects (mean age 60.1 (SD 10.3), 62.3% female, 37.6% African American, mean body mass index (BMI) 31.3 (SD 7.4)). Lateral lumbar spine films were graded for each lumbar level in a semi-quantitative fashion (0–3) for DSN and OST according to the Burnett Atlas, while FOA was graded present or absent. Low back symptoms with and without associated leg symptoms were determined with the following questions "On most days have you had symptoms of pain, aching or stiffness in your low back? "and" On most days do you have pain (sciatica) radiating down your right or left leg?" Two outcome groups were created: LBS and LBS with associated leg symptoms. Each group was compared separately to those with no symptoms. Logistic regression models were used for all analyses while adjusting for BMI, race, gender and age. Interactions between lumbar spine IRF and race or gender were tested with likelihood ratios tests (p<0.10 for significance).

Results: Low back symptoms and LBS with associated leg symptoms

were present in 51.8% and 24.9% of participants, respectfully. Disc space narrowing was present in 57.6%, OST present in 88.1% and FOA present in 57.9% of participants. Those with LBS were 32% as likely than those without LBS to have DSN (adjusted odds ratio [aOR] 1.32 ((95% CI 1.09, 1.52)). No association was found with FOA and either LBS or LBS with associated leg symptoms. No significant association was found between OST and LBS with associated leg symptoms.

A significant interaction (p<0.001) was observed between race and OST with LBS. African Americans (AAs) with OST were more likely (aOR 1.78 ((95% CI 1.25, 2.55)) to report LBS than AAs without OST. There was no effect among Caucasians.

Conclusion: Modest associations were found between DSN and LBS but no significant associations were found with LBS and associated leg symptoms. LBS with associated leg symptoms may have an etiology other than disc degeneration; suggesting that plain film radiographs may have limited clinical utility for this subgroup.

1095

Metal Concentrations in Patients with Failed Metal-On-Metal Hip Prostheses Determine the Inflammatory Phenotype in Peri-Implant Tissue. Erja-Leena Paukkeri[1], Riku Korhonen[1], Antti Eskelinen[2], Marko Pesu[3], Kaija Vasama[4], Teemu Moilanen[2] and Eeva Moilanen[1]. [1]The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland, [2]Coxa Hospital for Joint Replacement, Tampere, Finland, [3]Immunoregulation, Institute of Biomedical Technology, University of Tampere, Tampere, Finland, [4]Fimlab Laboratories, Tampere, Finland

Background/Purpose: Hip arthroplasty is the standard treatment of a painful hip destruction in rheumatoid arthritis and osteoarthritis. The use of metal-on-metal (MoM) bearing surfaces in total hip arthroplasty gained popularity especially in young and active patients during the last decade. Recently, worrisome failures due to inflammatory soft tissue reactions related to wear particles have been widely reported. The pathogenesis of this reaction is unknown. The aim of the present study was to clarify the inflammatory responses in peri-implant tissue in patients with a failure of MoM articulation.

Methods: Sixteen patients with a failed Articular Surface Replacement (ASR) implant were included in the study. Blood metal ion levels were analysed with coupled plasma mass spectrometry before revision surgery. Samples of peri-implant tissues collected during revision surgery were degraded by enzyme digestion and the distributions of cell populations were analysed by flow cytometry.

Results: In macroscopic observation, peri-implant reactions had variable amounts of necrotic and granulomatous tissue and cystic pseudotumour formation. All patients expressed elevated levels of blood chromium and cobalt, but the patient-to-patient variation was significant. In histological examination, intensive inflammatory cell infiltration was a characteristic feature, but only few metal containing cells were observed. An analysis by flow cytometry showed that the distributions of the inflammatory cells were mainly polarized either to macrophage-rich ($CD45^+/CD14^+$) or T-lymphocyte-rich ($CD45^+/CD3^+$) phenotypes with the average portions being 54 % (macrophages) and 20 % (T-lymphocytes) in macrophage-dominated inflammation and 25 % (macrophages) and 54 % (T-lymphocytes) in T-lymphocyte-dominated conditions. The portions of B-lymphocytes ($CD45^+/CD19^+$) and granulocytes ($CD45^+/CD15^+$) were small. Interestingly, the levels of blood chromium and cobalt were significantly higher in patients with macrophage-dominated inflammation than in patients with T-lymphocyte-dominated inflammation.

Conclusion: The results suggest that the adverse reactions induced by MoM wear particles contain heterogeneous pathogeneses and the metal levels seem to be an important factor in the determination of inflammatory phenotype. The present results support the hypothesis that higher levels of metal particles cause tissue necrosis and macrophages are recruited to clear the necrotic debris. The lymphocyte-dominated inflammation may, on the other hand, reflect a delayed hypersensitivity reaction induced by lower metal concentrations.

1096

Lower Income Paradoxically Associated with Better Patient-Reported Outcomes After Knee Arthroplasty in the U.S. Jasvinder A. Singh[1] and David Lewallen[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Mayo Clinic college of medicine, Rochester

Background/Purpose: To assess whether income is associated with patient-reported outcomes (PROs) after primary total knee arthroplasty (TKA).

Methods: We used the prospectively collected data from the Mayo Clinic Total Joint Registry to assess the association of income with index knee functional improvement, and moderate-severe pain at 2- and 5-year follow-up after primary TKA using multivariable-adjusted logistic regression analyses. Analyses were adjusted for various characteristics previously shown to be associated with PROs after TKA, namely demographics (age, gender, body mass index (BMI), comorbidity as measured by Deyo-Charlson index, American Society of Anesthesiologist (ASA) score as a measure of perioperative mortality, implant fixation (cemented/hybrid versus not cemented), underlying diagnosis (osteoarthritis, rheumatoid/inflammatory arthritis or other) and distance from medical center (categorized <100, 100–500 and >500 miles/overseas). ASA score was not collinear with Deyo-Charlson index (correlation coefficient <0.40).

Results: There were 7,139 primary TKAs at 2-years and 4,234 at 5-years. In multivariable-adjusted analyses, at 2-year follow-up, both lower income groups (<=\$35K and >\$35–45K) were significantly associated with lower odds ratio (OR) [95% confidence interval (CI) of moderate-severe pain, OR 0.6 [95% CI, 0.4, 0.9] (p=0.02) and 0.7 [95% CI, 0.5, 0.9] (p=0.02). The overall improvement in knee function was rated as 'better' more often at 2-years by patients with income in the <=\$35K compared to patients with income >\$45K, with OR of 1.9 [95% CI, 1.0, 3.6] (p=0.06), respectively. At 5-years, numerically similar but non-significant odds were noted.

Conclusion: We found that lower income was associated with better pain outcome and more improvement in knee function postoperatively. Insights into mediators of these relationships need to be investigated to understand how income influences outcomes after TKA.

ACR/ARHP Poster Session B
Osteoarthritis - Clinical Aspects
Monday, November 12, 2012, 9:00 AM–6:00 PM

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The Association of Fat Distribution and Clinically Defined Hand Osteoarthritis: The Netherlands Epidemiology of Obesity Study. A. Willemien Visser, Marieke Loef, Andreea Ioan-Fascinay, Martin den Heijer, Frits R. Rosendaal and Margreet Kloppenburg. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Obesity, assessed as body mass index (BMI) ≥ 30 kg/m^2, is an important risk factor for osteoarthritis (OA). BMI depends only upon height and weight and therefore gives no insight in underlying causal pathways. The aim of this study was to investigate whether the association of BMI and OA in the hands, being non-weight bearing joints, can be explained by the amount of fat mass (FM) and the abdominal fat distribution.

Methods: Data from participants of the NEO (Netherlands Epidemiology of Obesity) study, a population-based cohort of men and women aged 45–65 years with a BMI ≥ 27 kg/m^2 and a control group with a BMI < 27 kg/m^2, were used. BMI was assessed by measured weight in kg and length in cm. Waist-to-hip ratio (WHR) was calculated from waist and hip circumference measured in cm. FM was assessed in kg using bioelectrical impedance analysis. In 30% of participants MR imaging of the abdomen, at the level of the 5th lumbar vertebra, was used to assess the relative amounts of visceral adipose tissue and subcutaneous adipose tissue in cm^3. Hand OA was defined using the criteria of the American College of Rheumatology; pain was measured using a standardized questionnaire and physical examination of the hands was performed by trained research nurses. Pearson correlations were calculated between BMI and WHR and FM, visceral fat and subcutaneous fat. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to associate BMI, WHR, FM, visceral fat and subcutaneous fat with hand OA using logistic regression analyses, stratified for sex and adjusted for age.

Results: Data from 4562 participants (mean age 56 years, 48% male) were analyzed, including 425 controls with a BMI < 27 kg/m^2. Median BMI of the total study population was 30.3 kg/m^2 (IQR 28.4–33.1), median FM was 33.5 kg (IQR 27.5–40.8) and median WHR was 0.94 (IQR 0.88–0.99). Abdominal fat was measured in a subset of 1524 participants: median visceral fat was 122.8 cm^3 (IQR 86.4–167.0) and median subcutaneous fat 306.7 cm^3 (IQR 239.7–388.8). Hand OA was present in 8% of men and 21% of women. BMI was strongly correlated to FM (men r=0.89, women r=0.90) and subcutaneous fat (men r=0.72, women r=0.82), and moderately to visceral fat (men r=0.54, women r=0.57). WHR was moderately correlated to visceral fat (men r=0.59, women r=0.46), and only weakly to very weakly correlated to subcutaneous fat (men r=0.36, women, r=0.17). BMI was associated with hand OA in women (OR 1.02; 95% CI 1.00–1.04), but not in men. WHR was strongly associated with hand OA in men (OR 132.2; 95% CI 9.2–1901.9) and in women (OR 10.1; 95% CI 2.0–50.0). In both sexes, FM and subcutaneous fat were not significantly associated with hand OA. Visceral fat was associated with hand OA only in men (OR 1.005; 95% CI 1.001–1.009).

Conclusion: BMI was associated with clinical hand OA only in women. FM and subcutaneous fat, which were strongly correlated with BMI, were not associated with hand OA in both men and women. In men, the WHR and visceral fat were associated with hand OA, suggesting involvement of visceral fat in the development of hand OA. In women, other underlying processes might play a role.

1098

Knee Osteoarthritis and Frailty in Older Adults: Findings From the Multicenter Osteoarthritis Study and Osteoarthritis Initiative. Devyani Misra[1], Michael C. Nevitt[2], Cora E. Lewis[3], James Torner[4], David T. Felson[1] and Tuhina Neogi[1]. [1]Boston University School of Medicine, Boston, MA, [2]University of California-San Francisco, San Francisco, CA, [3]University of Alabama, Birmingham City, Birmingham, AL, [4]University of Iowa, Iowa City, Iowa City, IA

Background/Purpose: Both knee osteoarthritis (OA) and the frailty syndrome affect older adults and both are associated with functional limitation and disability. Frailty in elders is a state of increased vulnerability to adverse outcomes, such as falls, fractures, hospitalization and even death. While frailty is perceived to occur in thin older adults, it has been shown to be present in those who are obese, a common feature of those with knee OA. If knee OA and frailty are associated, then by extension those with knee OA might be at risk for not only the known OA outcomes of pain, functional limitation, and disability, but also the adverse outcomes related to frailty. We therefore examined the cross-sectional association of knee OA and frailty in community-dwelling older adults using data from two large cohorts.

Methods: The Multicenter Osteoarthritis (MOST) Study and the Osteoarthritis Initiative (OAI) are two NIH-funded longitudinal observational studies of individuals with or at high risk for knee OA. We included subjects from these two studies who had knee x-rays read and information on frailty parameters available at baseline and at the 30-mo (MOST) or 24-mo (OAI) follow-up visits. Prevalent knee OA was defined at the follow-up visit described above as: 1) **Radiographic knee OA (ROA):** Kellgren and Lawrence (KL) grade ≥2; 2) **Symptomatic knee ROA**: presence of ROA plus frequent knee pain; 3) **Severity of ROA**: highest KL grade of either knee, with replaced knees considered to be KL grade 4; 4) **Number of knees with ROA**: subjects categorized as having no knee ROA, unilateral knee ROA, or bilateral knee ROA. Frailty was defined using the Study of Osteoporotic Fractures (Ensrud) index as presence of 2 of 3 of the following criteria: 1) Weight loss >5% between baseline and the follow-up visit; 2) Inability to rise from chair 4 times without using support at the follow-up visit; 3) Poor energy from the SF12 questionnaire at the follow-up visit. We evaluated the cross-sectional association of knee OA (4 definitions) with prevalent frailty at the follow-up visit using Poisson regression to calculate prevalence ratios (PR), adjusting for age, sex, BMI, physical activity, education, smoking, co-morbidities (modified Charlson score), race and study site.

Results: Among 7822 participants (3026 MOST, 4796 OAI; mean age 62±8.81, 59% women, mean BMI 29±5.44), there were 213 (186 poor energy, 116 inability to rise from chair and 145 weight loss) prevalent frail subjects. Prevalence of frailty was higher in those with radiographic knee OA and symptomatic knee OA, and increased in prevalence with

increasing x-ray severity and with number of knees involved with OA (**Table**).

Table 1. Cross-sectional Association of Knee OA with Prevalent Frailty

		Presence of Frailty	
Knee OA Status	Crude PR	Adjusted* PR (95% CI)	
Radiographic Knee OA (yes vs. no)	1.67	1.41 (1.02, 1.94)	
Symptomatic Knee OA (yes vs. no)	2.36	1.86 (1.38, 2.50)	
Severity of Radiographic Knee OA:	1.0	1.0 (Ref)	
KL=0 (reference)	1.41	1.27 (0.75, 2.15)	
KL=1	1.64	1.49 (0.96, 2.31)	
KL=2	1.71	1.42 (0.90, 2.26)	
KL=3	2.52	1.78 ((1.12, 2.83)	
KL=4			
Number of Knees with OA:	1.0	1.0 (Ref)	
None (reference)	1.04	1.02 (0.67, 1.55)	
Unilateral	2.10	1.68 (1.19, 2.38)	
Bilateral			

*Adjusted for age, sex, BMI, physical activity, smoking, education, knee injury, co-morbidities, study site

Conclusion: Frailty is present more frequently in persons with knee OA than those without. Further research is needed to explore whether knee OA predisposes to frailty, and whether early management of knee OA might prevent frailty and its related adverse outcomes.

1099

Whole Blood Lead Is Associated with Symptoms, but Not Radiographic Osteoarthritis, in Multiple Joint Sites: The Johnston County Osteoarthritis Project. Amanda E. Nelson[1], Xiaoyan A. Shi[2], Todd A. Schwartz[3], Jordan B. Renner[4], Kathleen L. Caldwell[5], Charles G. Helmick[5] and Joanne M. Jordan[1]. [1]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [2]SAS Institute, Inc, Cary, NC, [3]University of North Carolina Gillings School of Global Public Health, Dept of Biostatistics, Chapel Hill, NC, [4]University of North Carolina School of Medicine, Dept of Radiology, Chapel Hill, NC, [5]Centers for Disease Control and Prevention, Atlanta, GA

Background/Purpose: We have previously identified associations between whole blood lead (Pb) and knee osteoarthritis (OA) and with biomarkers of joint metabolism. We hypothesized that Pb may be associated with burden of OA as assessed by multiple joint radiographs and symptoms.

Methods: Whole blood Pb concentrations, representing recent exposure and Pb mobilized from bone, were determined at the Centers for Disease Control and Prevention using inductively coupled plasma-dynamic reaction cell-mass spectrometer analysis; levels were categorized into quartiles for analysis. We used composite scores obtained from previously described factor analysis (1) of radiographic OA (rOA) scores from the hands, knees, and spine, and symptoms scores of the low back, hands, knees, and hips, to reflect body burden of OA as outcome measures (categorized due to non-normal distributions). Generalized logit and proportional odds models were used for these multi-level outcomes, and were adjusted first for age, body mass index (BMI), race, and sex, and then additionally for the other joint site scores.

Results: This cross-sectional analysis includes data (collected at a single visit during 2003-8) for 1659 individuals, 33% male and 35% African American with a mean age of 65 years and BMI 30 kg/m^{2}. At individual sites, rOA with symptoms was present in 13% for hand, 12% for hip, 24% for knee, and 28% for spine. Whole blood Pb was associated with spine rOA scores (30% increased odds of having higher spine rOA scores in the highest Pb quartile compared to the lowest, adjusted OR 1.34 [95% CI 1.01–1.77]), although this was no longer significant after adjustment for the composite scores of other joint sites (Table). The composite score of symptoms, however, was associated with Pb in models adjusted for covariates (OR 1.84 [95% CI 1.41, 2.40]) and after adjustment for rOA scores (Table), such that those in the highest quartile of Pb had 70–85% higher odds of reporting more symptoms compared to those in the lowest Pb quartile.

Composite Factor Score	Joints Included	Score calculation*	Adjusted† OR (95% CI) for highest quartile of Pb‡
IP/CMC	20 (DIP-8, PIP-8, thumb IP-2 & CMC-2)	Mean of summed KLG	0.89(0.64–1.23)
MCP	8 (all MCPs except thumb)	Mean of summed KLG	1.10(0.80–1.54)
Knee	4 (bilateral TFJ and PFJ)	Mean of summed KLG and OST scores	0.77(0.55–1.08)
Spine	5 (L1/2 to L5/S1) OST & DN at each level	Mean of summed OST & DN scores	1.16(0.84–1.61)
Symptoms	7 (hands-2, knees-2, hips-2, low back-1)	Mean of summed 0–3 score	**1.71(1.24–2.36)**

*Scores were calculated as the mean score, then standardized by dividing by the standard deviation
†Adjusted for age, sex, race, BMI, and all other factor scores
‡Mean Pb level (SD) in μg/dL: Q1 (referent); 0.9 (0.2); Q2: 1.5 (0.2); Q3: 2.1 (0.2); Q4: 4.9 (3.9)
IP: interpholongeol; CMC; c●; D●P: Distol IP; PIP: Pr● IP; MCP: metocarpopholongeol; KLG: Kellgren Lawrence Grade; OR: odds ratio; CI: confidence interval; TFJ: ●femoral; PFJ: pa●; OST: Osteophyte grade; DN: Disc narrowing grade; ●b: Whole blood lead level

Conclusion: There was a statistically significant positive association between blood Pb levels and the composite symptoms score, reflecting symptoms at multiple joint sites. No associations were seen for multiple joint rOA in this cross-sectional study.

1. Nelson AE et al, Arthritis Res Ther 2011;13:R76.

1100

A Functional Growth Hormone Receptor Polymorphism, Exon 3 Deleted Ghr, Is Associated with Radiographic Knee Osteoarthritis in Females with Familial Osteoarthritis At Multiple Sites: The Garp Study. Kim M.J.A. Claessen[1], Margreet Kloppenburg[2], H.M. Kroon[1], Jessica Bijsterbosch[1], Alberto M. Pereira[1], Hans A. Romijn[1], Tahar Straaten van der[1], Marian Beekman[1], P.E. Slagboom[1], Nienke R. Biermasz[1] and Ingrid Meulenbelt[3]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Department Rheumatology and Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands, Leiden, Netherlands, [3]The Netherlands Genomics Initiative-Sponsored Netherlands Consortium for Healthy Aging, Rotterdam, Netherlands

Background/Purpose: Genetic influences contribute considerably to the development of osteoarthritis (OA), and are most likely of a polygenic nature. Until now, genetic studies have identified several genetic variants associated with primary OA, providing strong clue for the involvement of endochondral ossification in OA onset. Endochondral ossification is the main process in longitudinal skeletal growth, and is tightly regulated by a complex network of hormones, growth factors and extracellular matrix components. One of the main players in this process is growth hormone (GH), exerting its effects predominantly through stimulation of insulin-like growth factor-1 (IGF-1) secretion. This qualifies genetic variations within genes involved in the GH/IGF-1 axis as obvious candidates for association studies in primary OA.

Recently, presence of a common growth hormone receptor (GHR) polymorphism, exon 3 deletion (d3-GHR), associated with increased GH sensitivity of the GHR, was demonstrated to have functional consequences in various clinical conditions. The aim of the present study was to investigate the effects of the d3-GHR polymorphism on the extent and characteristics of radiographic in patients with primary OA at multiple joint sites.

Methods: In a case-control study, we compared frequency of GHR$_{fl-d3}$ genotype between patients with familial primary OA from the GARP (Genetics, ARthrosis and Progression) Study, and controls. Kellgren-Lawrence scores were used to assess ROA in the knee, hip and hand; the Osteoarthritis Research Society atlas for the assessment of individual ROA features. Patients and controls were genotyped for 7 single nucleotide polymorphisms (SNPs) encompassing the d3-GHR gene to allow high throughput genotyping. One tagSNP was used as proxy for d3-GHR (full LD, pairwise r^2=1). Binary logistic regression analyses with robust standard errors were performed, to assess the relationship between d3-GHR and ROA.

Results: We studied 373 patients (mean age 60.1, 82% female) and 752 controls. GHR$_{fl-d3}$ genotype was significantly associated with ROA, especially in females (adjusted odds ratio (OR) (95%CI) 1.5(1.1–2.1), p=0.017). Strongest association was found with knee OA (adjusted OR 2.0(1.3–3.0), p=0.002), followed by hand OA (adjusted OR 1.5(1.1–2.1), p=0.024). No

such a relationship was found in males. GHR_{fl-d3} genotype was related to both osteophytes and joint space narrowing.

Conclusion: GHR_{d3-fl} genotype was associated with knee and hand ROA in females with a severe primary OA phenotype, indicating a role for the GH/IGF1 axis in the pathophysiology of primary OA.

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Condroitin Sulfate Decreases Chemokine Levels and Synovitis in knee osteoarthritis Patients.

Jordi Monfort[1], Paula Escudero[2], Cristobal Orellana[3], Laura Piqueras[4], Laura Tio[5], Francisco Montañés[1], Natalia García[5], Chantal Company[2], Pere Benito[1] and Maria Jesús Sanz[2]. [1]Hospital del Mar, Barcelona, Spain, [2]Universitary Clinic Hospital Research Foundation-INCLIVA, University of Valencia, Valencia, Spain, [3]Corporació Sanitaria Parc Taulí, Sabadell, Spain, [4]University Clinic Hospital Research Foundation-INCLIVA, University of Valencia, Valencia, Spain, [5]GRICIC. FIMIM, Barcelona, Spain

Background/Purpose: Synovitis is one of the major signs of structure damage in osteoarthritis (OA) progression. Chondroitin sulfate (CS) is an effective drug in the treatment of OA since it can reduce joint swelling and effusion in OA patients as described in the NIH-funded GAIT study. Therefore, the aim of this study was to compare the effect of CS vs. acetaminophen on synovitis in OA patients and to evaluate their impact on chemokine concentrations.

Methods: Synovitis (synovial hypertrophy+effusion≥4mm) assessed by sonography and synovial effusion quantified by artrhocentesis were evaluated in 45 patients treated with CS (800mg/day) or acetaminophen (4g/day) for 6 months. Patients were followed-up until month 9 to evaluate the carry-over effect. Symptomatic effect of both treatments was also evaluated by Lequesne Algo-functional Index (baseline,1.5, 3, 6 and 9 months). The levels of CXCL16, fractalkine/CX_3CL1, MCP-1/CCL-2, RANTES/CCL5 and GRO-α/CXCL1 were determined by ELISA in the plasma and synovial samples collected in each visit. Analysis of continuous variables was based on analyses of covariance (ANCOVA) model. Study of the chemokine variations between each time and the baselines was performed by a Wilcoxon two-related samples test Comparison between the two groups was obtained using an independent sample t-test for quantitative variables or a chi-squared test for qualitative variables. P values ≤0.05 were considered statistically significant for each variable.

Results: Eligible patients had clinical and radiographic evidence of OA (K&L grade 2 and 3) with synovitis. Mean age of patients was 70.4 years being women 72.1% of them. Mean BMI was 28.97. At the end of the study, CS significantly reduced synovitis compared to acetaminophen ($p<0.01$).This significant reduction was also detected in MCP-1 and fracktalkine synovial levels. Compared to baseline, CS treated patients showed significant reductions in synovitis (25.5%) and significant impairment of synovial hypertrophy (61.9% reduction). These effects were accompanied by significant decreases in synovial and serum MCP-1 content. In contrast, in the acetaminophen-treated group no effect on synovitis was observed and increased synovial RANTES levels were even detected. Additionally, CS but not acetaminophen effectively reduced functional incapacity after 6 months of treatment (CS-treated group: 11.5±2.5 vs. 7.9±3.0; $p<0.01$; acetaminophen-treated group: 9.9±4.1 vs. 8.3±4.9; n.s.). CS functional improvement remained after 3 months treatment cessation (month 9) thus confirming CS carry-over effect.

Conclusion: These results indicates that CS but not acetaminophen effectively reduces synovitis and clinical symptoms in OA patients. Evidence of an anti-inflammatory effect for CS has been also provided since it can decrease synovial and plasma levels of relevant chemokines. This study also adds further support and extends the finings described in the NIH-funded GAIT study and suggests that CS seems to be a more effective therapeutic tool for OA and synovial inflammation than analgesics.

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Immunoreactive Collagen Type II Cleavage Products and Their Nitrated Forms in Rheumatoid Arthritis and Osteoarthritis: An Outpatient Cross-Sectional Study.

Ruediger Mueller[1], Axel Finckh[2], Guy Heynen[3] and Johannes von Kempis[4]. [1]Cantonal Hospital, St. Gallen, Switzerland, [2]Geneva University Hospitals, Geneva 14, Switzerland, [3]Consulting, CH-6300 Zug, Switzerland, [4]MD, St. Gallen, Switzerland

Background/Purpose: Catabolism of type II collagen (COLII) involves multiple metalloproteinases, aggrecanases and cathepsin, releasing heterogeneous triple helix cleavage products. The complex regulation of these enzymes and of inducible NOS (iNOS)includes inflammatory cytokines. Col2-1 peptide (Col), located towards the N-telopeptide region of COLII contains a tyrosine residue susceptible to endogenous nitration by reactive nitrogen species, forming Col-2-1-NO2 (NCol). Specific immunoassays allow for estimation of nitration index (NI). Using these assays in OA and RA should show differences since RA, unlike OA, is treated with DMARDs known to inhibit structural damage progression.

Methods: Serum (S) and Urine (U) Col and NCol were measured by ELISA in a cross-sectional study (49 RA and 118 outpatients with active hand OA). The ratio of NCol (nmol)/Col (nmol) provided NI. Clinical variables were age, sex, DAS and VAS. Urinary fractional excretions (UFE) of biomarkers was calculated in RA patients.Statistical analysis used STATA® Version 12.1

Results: OA patients were older (64 years vs 58 in RA). Mean DAS28 was 2.64 with 60% receiving corticoids or synthetic and biological DMARD treatment in RA. VAS pain was higher in OA than RA patients (46 vs. 34;$p<0.0001$). Mean SCol concentrations (nmol/l) and SNCol (pmol/l) were higher in RA (308±17 and 687 ±90) than OA (241 ± 13 and 465±39; $p<0.0001$). Mean UCol (nmol/mmol creatinine) was higher in RA than in OA (16.3 vs. 8.1; $p<0.0001$) whereas UNCol (pmol/mmol creatinine) values were similar between the 2 groups (22.4 ±4.3 in RA and 26.2 ±2.1 in OA; $p>0.1$). Col and NCol UFE were 2.87% (2.25–3.48; 95%CI) in RA and 2.63 % (1.81–3.46; 95%CI) and highly correlated (r-square=0.53; $p<0.0001$).The SCol2-1NI was similar in RA (0.238 %, 95% CI: 0.214–0.262) and in OA (0.217, 95% CI: 0.19–0.24; $p>0.05$) but the UCol2-1NI was markedly lower in RA (0.164, 95%CI: 0.141–0.187) than OA (0.37, 95%CI: 0.33–0.42; $p<0.0001$). In both RA and OA, pairwise comparisons of serum and urine NI indicated highly significant differences ($p<0.0001$). None of the disease activity indices were associated with any of the two biomarkers or their ratios in serum or urine.

Conclusion: Data indicate excess nitrated forms of Col2-1 in the urine of patients suffering from active OA in comparison to DMARD treated RA patients, indicating that a greater proportion of OA SNCol immunoreactive forms pass through the renal glomerular membrane than in RA. In RA, fractional excretion of both Col and NCol was low and similar for Col and NCol, excluding a differential renal handling of the detected epitopes. The excess of urinary nitrated forms in OA vs RA may result from the OA disease process itself or from DMARD interference with the iNOS activity in RA. Within patients' differences between serum and urine NI values indicate biological heterogeneity of immunoreactive species containing the Col2-1 epitope. The clinical relevance of this heterogeneity is unknown since the half-life of measured components have not been studied. Additional investigations with specific enzyme inhibitors in OA and biological DMARDs in early RA are warranted to quantify the dynamics of serum and urine components of Col2-1 and its nitrated forms.

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Cumulative Occupational Physical Load As Risk Factor for Knee Osteoarthritis.

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Background/Purpose: Knee osteoarthritis (OA) results from the interaction of multiple risk factors, one of which may be physically demanding occupations. The purpose of this study was to determine the association between cumulative occupational physical load (COPL) and the presence of knee OA, defined as Symptomatic Radiographic Osteoarthritis (SOA) or Magnetic Resonance Imaging Osteoarthritis (MRI-OA).

Methods: This was a cross-sectional analysis of symptomatic (n=255) and asymptomatic (n=72) knee cohorts recruited as a random sample from the same population. Participants were 40 to 79 years old. Inclusion criteria

for the symptomatic cohort, Model for the Development of Early Knee Osteoarthritis (MoDEKO), were: 1) pain, aching, or discomfort in/around the knee on most days of the month at any time in the past; 2) pain, aching or discomfort in/around the knee in the past 12 months. In the asymptomatic cohort, participants responded no to both knee pain questions. All participants received a standardized knee exam, fixed flexion knee radiographs and MRI, and completed a comprehensive questionnaire, which included a detailed lifetime occupational history of activity level (5 levels) and knee bending/kneeling activities (3 levels) for each occupation held. Self-reported COPL was calculated by multiplying the number of years in each occupation by the activity level and by the knee bending within that occupation, then summing all occupations. COPL was then grouped into quartiles (QCOPL). SOA was defined by the Kellgren Lawrence x-ray grade > 2, plus the presence of knee pain. MRI-OA was defined using a novel definition by Hunter et al[1] which required either both group A features: osteophyte formation and full thickness cartilage loss; or one group A and two group B features: bone marrow lesion or cyst, meniscal subluxation or tear, partial cartilage loss, or bone attrition. Weighted analysis was done using logistic regression to examine the association between QCOPL and the presence of SOA and MRI-OA, respectively, after adjusting for age, sex, body mass index, and two-way interactions.

Results: Participants (women=167, men=160) were on average 58.5 (SD=11.0) years old with a BMI of 26.3 (SD=4.7). Of those, 102 (31.2%) participants had SOA. A monotonic statistically significant relationship was found between QCOPL and SOA with adjusted odds ratio (OR) of 8.16 (95% CI = 1.89, 35.27) for QCOPL 4 (highest) vs. QCOPL 1 (lowest), and 5.73 (95% CI= 1.36, 24.12) for QCOPL 3 vs. 1. A total of 131(40.1%) participants had MRI-OA. Adjusted OR were also monotonic and statistically significant: QCOPL 4 vs. 1 (OR= 9.54; 95% CI = 2.65, 34.27); QCOPL 3 vs. 1 (OR= 9.04; 95% CI = 2.65, 30.88); QCOPL 2 vs. 1 (OR = 7.18; 95% CI = 2.17, 23.70).

Conclusion: COPL is a significant risk factor for knee OA. A dose response relationship between COPL and both SOA and MRI-OA was found. MRI-OA is a new definition, which has potential to capture early structural disease in a way not previously quantified. Due to the nature of the cross-sectional study design, these results should be interpreted cautiously but provide evidence for further prospective, longitudinal studies.

(1) Hunter et al. *Osteoarthritis and Cartilage* 2011; 19(8):963–969.

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The Association of Demographic, Modifiable, Structural and Biomechanical Risk Factors with Medial and Lateral Patellofemoral Joint Structural Damage On MRI: The Multicenter Osteoarthritis Study. Joshua J. Stefanik[1], Ke Wang[1], K. Douglas Gross[2], Frank Roemer[3], John A. Lynch[4], Neil Segal[5], Cora E. Lewis[6], Michael C. Nevitt[4], Ali Guermazi[1] and David T. Felson[1]. [1]Boston University, Boston, MA, [2]MGH Institute of Health Professions, Boston, MA, [3]Klinikum Augsburg, Augsburg, Germany, [4]University of California-San Francisco, San Francisco, CA, [5]University of Iowa, Iowa City, [6]University of Alabama, Birmingham City, Birmingham, AL

Background/Purpose: Past investigations into risk factors for patellofemoral joint (PFJ) osteoarthritis (OA) have been limited by the use of radiography, which is insensitive to identify PFJ OA and have focused on only a few risk factors. MRI offers a unique opportunity to directly visualize tissue damage in the PFJ, and risk factors related to medial PFJ damage, which was recently reported as common (Gross, ARD, 2012), can be distinguished from those related to lateral damage. The purpose of this study is to evaluate the association between PFJ structural damage on MRI with a wide spectrum of risk factors including: demographic, modifiable, structural, and biomechanical factors.

Methods: We analyzed data from the baseline exam of MOST, a NIH-funded cohort study of persons aged 50–79 years with or at risk for knee OA. Knees for this study came from persons with x-ray OA in tibiofemoral joint and/or PFJ. *Demographic* risk factors included age, sex, and race. *Modifiable* risk factors included BMI, occupational history, quadriceps strength, and hamstring-quadriceps strength ratio. *Structural* risk factors included Insall-Salvati ratio (measure of patella alta), lateral trochlear inclination (measure of trochlear morphology), and femur length. *Biomechanical* risk factors included varus and valgus alignment (from long limb x-rays). Cartilage damage and bone marrow lesions (BMLs) were assessed on MRI using the WORMS scale in 4 regions (medial and lateral patella and trochlea). PFJ structural damage was defined in two ways: 1) full-thickness cartilage loss (WORMS 2.5; ≥5 on a 0–6 scale) and 2) full-thickness cartilage loss in addition to a BML (≥1 on a 0–3 scale). We examined the cross-sectional

association between risk factors and PFJ structural damage using logistic regression with GEE to account for the correlation between regions from the same knee. We performed analyses in the PFJ overall (damage in any of the four regions) and for the medial and lateral PFJ separately.

Results: 1268 regions from 317 knees were studied (mean age 63.5 years, mean BMI 30.5 kg/m², 67% female). Full-thickness cartilage damage was present in any PFJ region, medial, and lateral in 20%, 16%, and 25% of regions, respectively. The hamstring-quadriceps ratio, Insall-Salvati ratio, and lateral trochlear inclination demonstrated the strongest associations with overall and lateral PFJ damage (see table). Females and older subjects were more likely to have medial but not lateral PFJ damage. Femur length was strongly associated with lateral PFJ damage. Similar results were seen for the PFJ damage definition including a BML.

Association between demographic, modifiable, structural, and biomechanical risk factors and full-thickness cartilage damage (WORMS 2.5; ≥5) in the PFJ

	Any PFJ	Medial PFJ	Lateral PFJ
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Demographic risk factors			
Age (per 10 years)	**1.3 (1.1, 1.7)**	1.7 (1.2, 2.4)	1.2 (0.8, 1.8)
Sex (Reference=Male)	1.4 (0.9, 2.1)	**2.9 (1.5, 5.6)**	0.9 (0.5, 1.7)
Race			
Other (Reference)	1.0	1.0	1.0
African American	0.9 (0.4, 1.7)	0.6 (0.2, 1.4)	1.1 (0.4,2.9)
Modifiable risk factors			
BMI (per 5 units)	1.1 (0.9, 1.3)	1.2 (0.9, 1.5)	1.0 (0.7, 1.3)
Occupational history			
No labor (Reference)	1.0	1.0	1.0
Labor	1.0 (0.6, 1.5)	1.2 (0.7, 2.2)	0.8 (0.4, 1.7)
Other	1.0 (0.6, 1.5)	0.7 (0.4, 1.4)	1.3 (0.7, 2.4)
History of knee injury (Reference=none)	**0.4 (0.3, 0.7)**	0.4 (0.2, 0.7)	0.4 (0.2, 0.9)
History of knee surgery (Reference=none)	0.8 (0.5, 1.5)	1.0 (0.5, 2.2)	0.6 (0.3, 1.5)
Quadriceps strength			
Tertile 1 (Weak)	**1.5 (1.0, 2.4)**	1.4 (0.7, 2.9)	1.9 (0.9, 3.7)
Tertile 2	**1.6 (1.0, 2.4)**	1.8 (1.0, 3.4)	1.6 (0.8, 3.2)
Tertile 3 (Reference)	1.0	1.0	1.0
Hamstring-quadriceps strength ratio			
Tertile 1 (Reference; Low)	1.0	1.0	1.0
Tertile 2	0.8 (0.5, 1.3)	0.8 (0.5, 1.5)	0.8 (0.4, 1.6)
Tertile 3 (High)	**1.8 (1.2, 2.6)**	1.1 (0.6, 1.9)	**2.9 (1.5, 5.6)**
Structural risk factors			
Insall-Salvati Ratio			
Tertile 1 (Reference)	1.0	1.0	1.0
Tertile 2	1.2 (0.8, 1.8)	1.2 (0.7, 2.1)	1.3 (0.7, 2.6)
Tertile 3 (Patella alta)	**1.5 (1.0, 2.4)**	1.1 (0.6, 2.0)	**2.2 (1.1, 4.1)**
Lateral trochlear inclination			
Tertile 1 (Flat trochlea)	1.0 (0.6, 1.5)	0.7 (0.4, 1.4)	**4.4 (2.1, 9.4)**
Tertile 2	**1.8 (1.1, 2.7)**	0.9 (0.5, 1.7)	1.1 (0.5, 2.2)
Tertile 3 (Reference)	1.0	1.0	1.0
Femur length			
Tertile 1 (Reference; Short)	1.0	1.0	1.0
Tertile 2	1.3 (0.9, 2.1)	0.8 (0.5, 1.4)	**2.5 (1.2, 5.3)**
Tertile 3 (Long)	1.3 (0.8, 2.0)	0.6 (0.3, 1.2)	**2.8 (1.3, 6.0)**
Biomechanical risk factors			
Frontal plane knee alignment			
Neutral (Reference)	1.0	1.0	1.0
Valgus	1.5 (0.97, 2.4)	1.1 (0.5, 2.4)	**2.2 (1.1, 4.3)**
Varus	0.9 (0.6, 1.3)	1.3 (0.7, 2.4)	0.6 (0.3, 1.1)

Conclusion: PFJ structural damage is more strongly related to structural and demographic factors than to modifiable ones. Risk factors may be different for medial and lateral PFJ structural damage. Future studies should evaluate risk factors separately for medial and lateral PFJ damage.

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Lateral Tibio-Femoral Shift Related to Medial Knee Osteoarthritis. Roy H. Lidtke[1], Berna Goker[2], Abdurrahman Tufan[2], Laura E. Thorp[1] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Gazi University Medical School, Ankara, Turkey

Background/Purpose: Medial knee osteoarthritis (MKOA) has been shown to be related to malalignment of the knee joint with several radiographs used to quantify the abnormality. Radiographic observations of a lateral tibial shift in subjects with MKOA has led the authors to hypothesize that this finding is more prevalent in MKOA than normal controls and is associated with MKOA measurable gait parameters.

Methods: 90 subjects (69F 21M, Age 60±8, BMI 28.3±4.0) with radiographic and symptomatic medial knee OA (K-L grade 2–3, ambulatory pain >30 mm on a 100 mm VAS) were compared to 24 (18F 6M) age (59±10) and BMI (28.8±8.3) matched controls with no knee pain (K-L grade 0–1). Full limb mechanical axis and AP X-rays of the ankles were obtained. The tibial lateral shift (*figure 1*), defined as the distance between the center of the intercondylar notch of the femur and midpoint of the tibial plateau, was measured using Image J software (US NIH, Bethesda, MD, http://rsbweb.nih.gov/ij/). Subjects underwent gait analyses using an optoelectronic camera system and multi-component force plate. Comparisons were performed after matching for speed. The peak external knee Adduction Moment (%body weight * height, %BW*Ht) and knee adduction angular impulse was calculated and used as the primary endpoint. Paired t-tests were used to compare group differences. Pearson's correlations were calculated to analyze the relationship between knee moments and the other radiographic parameters with significance set at $p<0.05$.

Results: The mean ± S.D. lateral tibio-femoral shift was 5.18±2.45 mm in the MKOA group compared to 1.5±1.22 mm in the control group ($p<0.01$). Interestingly there was no relationship between the lateral shift and mechanical axis ($r=0.11$, $p=0.23$). There was an apparent relationship between the external knee adduction moment and lateral tibial shift in the MKOA group with greater lateral tibial shift related to greater knee moments ($r=0.46$, $p<0.01$). There was no relationship between knee adduction moments and lateral tibial shift in the control group ($r=0.13$, $p=0.09$). There was a relationship between knee angular impulse to the lateral shift in the MKOA group ($r=0.48$, $p<0.01$).

Conclusion: Lateral tibio-femoral shift is greater in MKOA than in normal controls and is related to increased medial knee loads. These findings suggest that the lateral tibio-femoral shift may be a new radiographic marker for MKOA. Further studies are needed to determine the clinical validity of assessing the tibio-femoral shift.

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1106

Evaluation of Foot Posture and Plantar Pressure Changes in Knee Osteoarthritis: Preliminary Report. Necati Balci and Lale Cerrahoglu. Celal Bayar University Medical School, Manisa, Turkey

Background/Purpose: Disturbances of weight bearing and walking pattern occur in patients with knee osteoarthritis (OA) due to impairments in knee joint. These impairments may lead to changes in the mechanical alignment of lower limb and dynamic function of the foot. Therefore, it has been given special attention to foot orthoses and footwear modifications as a non-operative treatment of knee OA. However, in order to fully understand the effect of these interventions on the knee and other lower limb joints, greater knowledge of foot structure is required. We aimed to study the plantar pressure and foot posture characteristics of knee OA and their relationship with disease characteristics.

Methods: A total of 78 feet of 39 patients with bilateral knee OA (ACR criteria) were evaluated regarding clinical and biometrics data. Demographic and disease characteristics were obtained. The radiographical evaluation was done based on anterior-posterior tibio-femoral radiographs using the Kellgren-Lawrence (KL) grading scale (0-4). Barefoot dynamic plantar pressure and the Arch index (AI) were measured by the 3D footscan system. The Foot posture index (FPI-6) was obtained. Correlation (Pearson's correlation coefficient) and regression analyses were performed between various plantar pressure analysis, clinical parameters and disease-related parameters.

Results: Thirty nine patients (11 male) with mean age 51,53 (standard deviation (SD):11,89) and mean BMI 30,5 (SD:4,9) were recruited. For dynamic plantar pressures; grade in right knee according to KL radiologic criteria correlates with left foot medial heel, left midfoot and left middle forefoot pressures ($r=0,40$, $p=0,010$; $r=0,33$, $p=0,040$; $r=0,36$, $p=0,022$ respectively). Grade in left knee according to KL radiologic criteria correlates with left heel, left midfoot and inversely correlates with right foot toe pressure ($r=0,33$, $p=0,036$; $r=0,41$, $p=0,010$; $r=-0,41$, $p=0,009$ respectively). For foot posture; grade in right knee according to KL radiologic criteria correlates with right FPI-6, grade in left knee according to KL radiologic criteria correlates with left FPI-6, right FPI-6 and left AI ($r=0,38$, $p=0,015$; $r=0,41$, $p=0,008$; $r=0,41$, $p=0,009$; $r=0,33$, $p=0,036$ respectively). In multivariate regression analysis it is found that left KL grade was most affected from left AI ($p=0,045$).

Conclusion: The dynamic variables of plantar pressure and foot posture are sensitive to the OA grading. These results suggest that people with the higher OA grade exhibit a more pronated foot type and shifted pressure distribution. We can

maintain a superior biomechanical correction by advanced evaluation of foot structure in non-operative treatment of knee OA such as orthoses and footwear modifications. As a result, the assessment of patients with knee OA in clinical practice should include simple foot measures and evaluation.

Disclosure: N. Balci, None; **L. Cerrahoglu**, None.

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Baseline Knee Flexion Pain, Age and Joint Line Tenderness Predict the Progression of Asymptomatic, Radiographic Knee Osteoarthritis to Symptomatic Knee Osteoarthritis Over 5 Years. Abhiram Gande[1] and James J. Irrgang[2]. [1]University of Pittsburgh School of Medicine, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Knee Osteoarthritis (OA) is the most prevalent form of OA. Historically, not all people who have tell-tale signs of radiographic knee osteoarthritis progress to symptomatic knee osteoarthritis, and vice versa. According to a meta-analysis by Bedson et. al, the prevalence of radiographic knee OA (Rad OA) in symptomatic patients can range between 15–76%. However, Duncan et. al observed a strong correlation between increased symptoms and radiographic OA findings. Such inconsistencies may be resolved with a better understanding of the risk factors for symptomatic knee OA. To date, there has been no survey of risk factors involved in the progression of baseline asymptomatic Rad OA to symptomatic Rad OA (Symp OA). Therefore, we evaluated the abilities of various physical exam measures and demographical variables in predicting such progression over five years.

Methods: Data from the Knee Osteoarthritis Initiative (OAI), a prospective longitudinal study of biomarkers involved in the onset and progression of OA in nearly 5000 subjects, were used for this study. Inclusion criteria were individuals who had Rad OA—score ≥ 2 on the Kellgren/Lawrence (K-L)—at baseline. The cases progressed to develop Symp OA—knee pain on most days of the month over the last 12 months—at 3 years, and remained symptomatic at 4 and 5 years, while the controls remained asymptomatic at all three time points from baseline. Cases and controls were matched for baseline knee K-L score, presence of unilateral or bilateral index knees and consistency of symptoms at all three time points (3, 4, and 5 years). The predictor variables were age, gender, BMI, abdominal circumference, walking ability (20m and 400m walk times), chair stands time, presence of Hand OA, varus/valgus malalignment, medial and lateral joint line tenderness, knee flexion pain, flexion contracture or hyperextension sign, bulge sign, patellar tap sign and isometric quadriceps strength corrected for body weight. Univariate conditional logistic regression was performed and p-values, odds ratios and 95 %confidence intervals were calculated.

Results: The baseline sample included 2093 individuals with Rad OA (K-L ≥ 2). The matching process yielded 94 cases and controls, with similar demographic data (Table 1). Logistic regression analysis revealed that age ($p=0.04$), medial joint line tenderness ($p=0.008$), lateral joint line tenderness ($p=0.01$) and knee flexion pain ($p=0.047$) were significant predictor variables. 95% confidence intervals were >1 and odds ratios were >1 for the four significant variables.

Conclusion: Age, knee flexion pain, medial and lateral joint line tenderness are measures with significant ($p<0.05$) predictive ability of progression from baseline Rad OA to Symp OA. As such, these commonly used demographic and physical exam measures can help physicians identify individuals with asymptomatic radiographic OA who may be at risk for developing chronic knee pain. Ultimately, older age and positive signs on these physical exam measures can serve as markers to initiate aggressive management to help prevent the onset of symptomatic knee OA.

Disclosure: A. Gande, None; **J. J. Irrgang**, None.

1108

A Randomized Controlled Trial of Hylan G-F 20 for the Treatment of Carpometacarpal Osteoarthritis. Lisa A. Mandl[1], Scott Wolfe[2], Aaron Daluiski[2], Robert N. Hotchkiss[1], Stephen L. Lyman[3] and Jeffrey N. Katz[4]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital For Special Surgery, New York, NY, [3]Hospital Special Surgery, New York, NY, [4]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Painful carpometacarpal osteoarthritis (CMC OA) is associated with substantial impairment, and is often unresponsive to medical treatment. Hylan G-F 20 has been shown to improve pain and function in patients with knee OA; however, its effectiveness in CMC OA is unknown.

Methods: 200 patients with radiologic evidence of CMC OA and no inflammatory arthritis were randomized to receive one of the following three

regimens: 1cc of Hylan G-F 20 weekly for 2 weeks; 1cc triamcinolone acetonide (40mg) followed 1 week later by 1cc 0.5% bupivacaine; or 0.5% 1cc bupivacaine weekly for 2 weeks. Randomization was double blind and stratified on previous intra-articular steroid treatment. An experienced hand surgeon performed all injections without radiologic guidance. Patients were assessed 26 weeks after the first injection. An intention to treat, last-value carried forward analysis was performed on all patients who had at least one post-injection visit.

Results: 188 patients were eligible for this analysis. Average age was 66.5 years (range 45–89), 67.7% female and 90.4% Caucasian. 33%, 31% and 38 % had previously received a corticosteroid injection in the Hylan G-F 20, triamcinolone and bupivacaine groups respectively. 100 (53%) had Kellegren and Lawrence (K+L) Grade <=3 in the CMC joint and 88 (47%) had K+L Grade 4. At 26 weeks, pain as measured by the Visual Analogue Scale (VAS) showed statistically and clinically significant improvement in all treatment groups. However, there was no statistically or clinically significant difference in VAS between treatment arms at 26 weeks. No treatment arm resulted in clinically meaningful improvements in function, as measured by the Disabilities of the Arm, Shoulder and Hand Questionnaire (DASH). In a multivariate regression analysis, controlling for age, sex, K+L grade, baseline pain and treatment assignment, neither K+L Grade nor treatment assignment was associated with a difference in pain at 26 weeks. Among those with severe K+L Grade 4 CMC OA, all three treatments led to clinically and statistically significant improvements in pain at 26 weeks, with no differences between groups.

Table 1.

	Hylan G-F 20 Mean ± s.d.	Triamcinolone Mean ± s.d.	Bupivacaine Mean ± s.d
All Patients (188)			
VAS Baseline (100=severe)	60.7 ± 19.3	63.2 ± 20.2	57.1 ± 20.1
VAS 26 weeks	49.8 ± 26.3	50.1 ± 29.4	42.9 ± 26.5
Delta VAS	-10.9 ± 26.7	-13.1 ± 29.9	-14.2 ± 20.8
p-value within group change	**0.002**	**0.003**	**<0.0001**
DASH Baseline	28.8 ± 17.3	28.9 ± 17.9	25.7 ± 17.1
DASH 26 Weeks	26.1 ± 19.0	27.0 ± 18.0	24.2 ± 17.4
Delta DASH (N=175*)	-3.53 ± 11.4	-2.88 ± 14.9	-1.39 ± 12.3
p-value within group change	**0.02**	0.14	0.07
K+L <3 (N=100)			
VAS for Pain	61.7 ± 19.5	64.8 ± 18.8	51.1 ± 23.4
VAS at 26 weeks	51.6 ± 28.8	56.8 ± 31.6	40.6 ± 28.9
Delta VAS	-10.1 ± 23.7	-7.96 ± 29.1	-10.5 ± 21.3
p-value within group change	**0.02**	0.22	**0.02**
K+L 4 (N=88)			
VAS for Pain	59.3 ± 19.3	61.1 ± 22.1	61.9 ± 16.0
VAS at 26 weeks	47.3 ± 22.6	41.3 ± 23.9	44.8 ± 24.8
Delta VAS	-12.0 ± 30.9	-19.8 ± 30.0	-17.1 ± 20.2
P-value within group change	**0.009**	**0.003**	**<0.0001**

* N=175 due to missing data

Conclusion: In patients with CMC OA, intra-articular Hylan G-F 20 was not superior to corticosteroids or bupivacaine in reducing pain and improving function at 26 weeks. All three treatments resulted in significant improvements in pain, even among patients with severe CMC OA. A variety of injectable therapies appear to be effective treatments for this condition, even in those with severe arthritis.

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1109

Effects of Strontium Ranelate On Hand Osteoarthritis - Analysis of Data From the Sekoia Trial. E. Maheu[1], C. Cadet[2] and F. Berenbaum[1]. [1]AP-HP St Antoine Hospital, Paris, France, [2]Paris, France

Background/Purpose: Strontium ranelate (SrRan) has shown the ability to reduce radiological progression of knee osteoarthritis (OA) over 3 years. Patients with knee OA are also frequently affected by hand OA. In this secondary analysis, we assessed the effects of SrRan on radiological and symptom progression of hand OA.

Methods: This international 3-year, randomized, placebo-controlled phase III trial was designed to assess the effect of SrRan 1g and 2g/day compared to placebo on the radiographic progression of knee OA. Main inclusion criteria were symptomatic primary knee osteoarthritis (ACR criteria), a Kellgren-Lawrence (KL) grade II or III, and a joint space width (JSW) between 2.5-5 mm. There were no specific inclusion criteria regarding hand

OA. Hand OA radiographic and clinical assessments were secondary outcomes. During the study, baseline and final postero-anterior radiographs of each hand were performed and scored by 2 independent readers, blinded to treatment and time sequence, using KL (range 0–128), Kallman (0–204) and Verbruggen (0–218) scoring methods. Clinical symptoms were assessed at each visit by the Auscan (0–300) and Functional Index for Hand OA (FIHOA) (0–30). Between-group analyses were performed using a general linear model with baseline, center and gender as covariates.

Results: Of the 1669 patients included in the SEKOIA trial, 999 had radiologic hand OA at baseline (73%). 71% were female. Mean age was 64±7 years, body mass index 29.6±4.7 kg/m^2, and initial knee JSW 3.4±0.8 mm. Hand OA was mild in radiologic severity: KL score 21±13, Kallman score 25±22 and Verbruggen score 14±15. Mean Auscan global score was 96+80 mm and mean FIHOA score was: 4±5.

The radiographic progression of hand OA observed over 3 years was modest in the placebo group with a mean change of 2.4±3.3 for KL score, 3.7±5.3 for Kallman score and 2.0±3.9 for Verbruggen score. There was no difference between the treatment groups for any radiological score. A significantly higher rate of patients reported an improvement of 20% or more in the Auscan pain subscale in the SrRan 2 g group (95% CI [0.1; 16.3]; p=0.047) compared to placebo.

In erosive patients (≥2 erosive joints, N=71), a significant improvement of KL score (p=0.031) in the SrRan 2 g compared to placebo was observed. In symptomatic patients (FIHOA >5 and pain within the 48 hours prior to the visit, N=126), a trend toward a higher improvement of KL score was noted in the SrRan 2 g group compared to placebo (p=0.079)

Conclusion: Overall, mild hand OA patients showed a very slow radiological progression, with no between-group difference over 3 years. However, in subgroup analyses, a slight beneficial effect of strontium ranelate 2g could be observed on pain and a positive effect on the change in KL score was suggested in the more severe hand OA patients. These results encourage conducting a specific trial in hand OA in the next future.

Disclosure: E. Maheu, Expanscience, Genévrier, Genzyme, Pierre Fabre, Rottapharm, Servier, 9, Expanscience, Ibsa-Genévrier, Rottapharm, TRB-Chemedica, 9; **C. Cadet**, Expanscience, Servier, 9, Expanscience, Rottapharm, 9; **F. Berenbaum**, Expanscience, Pierre Fabre, Servier, TRB-Chemedica, Rottapharm, Génévrier, 9.

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Radiologic Progression in Hand Osteoarthritis (OA) Over 2.6 Years - Data From the Sekoia Trial. Emmanuel Maheu[1], Christian Cadet[2] and Francis Berenbaum[1]. [1]AP-HP, St Antoine Hospital, Paris, France, [2]Rheumatology, Paris, France

Background/Purpose: Hand OA is a frequent polyarticular disease. Few is known with respect to its radiological progression over time, which in addition is difficult to assess, considering that no radiographic scoring method has, today, proved being superior to another. The goal of this study was to assess hand OA radiological progression over 3 years using three validated scoring methods.

Methods: Data came from an international 3-year, randomized, placebo-controlled phase III trial designed to assess the effect of strontium ranelate compared to placebo on the radiographic progression of knee OA which included symptomatic primary knee OA patients (ACR criteria) at a Kellgren-Lawrence (KL) grade II or III, with a minimal joint space width (JSW) between 2.5–5 mm. During this trial, baseline and final postero-anterior radiographs of each hand were performed. Symptoms were assessed using the functional index for Hand OA (FIHOA; range 0–30) and the AUSCAN (0–300). Two independent readers scored half of the pairs of radiographs obtained each, blinded to treatment and time sequence, using the KL (range 0–128), Kallman (0–204) and Verbruggen anatomical phase (0–218) scoring methods with a good inter-rater reproducibility. Hand OA radiographic progression was studied in the placebo group by looking at 1/baseline-end changes in global scores, 2/the numbers of progressors (progression was defined for each global score by a change over each reader's smallest detectable difference (SDD)), and 3/the number of patients in whom at least 1 joint showed a deterioration (from KL0–1 to KL≥2; progression of ≥1 phase for Verbruggen score).

Results: Of 1669 patients included in the SEKOIA trial, 999 had radiologic hand OA: 73%. 297 patients in the placebo group had baseline and post-baseline radiographs. 72% were female, mean age 64±7 years, body mass index 29.5±5 kg/m^2, and initial knee JSW 3.5±0.8 mm. Baseline hand OA radiologic severity was mild: KL score 21±13, Kallman score 24±21 and Verbruggen score 13±14. FIHOA score was 4±5, Auscan global score was 96+80. Mean time interval between baseline and final radiographs was 31.5 months.

Hand OA radiographic progression over 2.6 years was modest with a mean change of 2.4±3.3 for KL score, 3.7±5.3 for Kallman score and 2.0±4.0 for Verbruggen score.

The numbers (%) of progressors (change≥SDD) were 7 (2%), 17 (6%), and 21 (7%) respectively.

The numbers (%) of patients with at least 1 worsened joint were 169 (57%) for KL and 139 (47%) for Verbruggen score, with respective means of 2.0±1.3 and 1.7±1.1 worsening joint.

Conclusion: Whatever the radiological scoring method used, and the kind of analysis performed, mild radiographic hand OA patients showed a very weak global radiological progression over 2.6 years. In future structure-modification trials in hand OA, analysing the number of patients with at least one joint worsening could be the most sensitive method.

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Erosive Evolution in Hand Osteoarthritis Is Associated with Incident Joint Tenderness Independent of MRI-Defined Bone Marrow Lesions and Synovitis.

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Background/Purpose: Previous studies have shown no association between increased amount of radiographic hand osteoarthritis (OA) resulting in more hand pain/disabilities. In this longitudinal study, our aim was to study whether radiographic hand OA was related to joint tenderness in cross-sectional and longitudinal settings focusing on joint-specific analyses, and whether presence of MRI-defined synovitis and bone marrow lesions (BMLs) at follow-up had an effect on the observed longitudinal associations.

Methods: We included 190 patients (173 women, mean (SD) age 61.5 (5.7) years) from the Oslo hand OA cohort with hand radiographs at baseline, of which 112 (102 women) had 7-years follow-up data. Of those, 89 had pre-/post-Gd T1w fs MRIs of the distal (DIP) and proximal interphalangeal (PIP) joints in the right hand, whereas 101 had STIR images. The bilateral DIP, PIP and carpometacarpal joints were scored for radiographic OA according to Kellgren-Lawrence scale and OARSI atlas, whereas the right hand's DIP and PIP joints were scored for synovitis and BMLs according to Oslo hand OA MRI score. Joint tenderness on palpation (absent/present) was assessed by a rheumatologist. To explore the associations between radiographic hand OA and tenderness in the same joint, we performed uni-/multivariate logistic regression analyses with Generalized Estimating Equations. In the longitudinal analyses only joints with potential for radiographic progression and without tenderness at baseline were included. Features that were associated with tenderness in univariate analyses (p<0.20) were included in a multivariate model and excluded by backward selection. All analyses were adjusted for age and sex. Using the final multivariate model from the longitudinal analyses, we did additional adjustment for presence of MRI-defined synovitis (grade 2–3) and BMLs (grade 1–3) at follow-up (only DIP and PIP joints in right hand included in these analyses).

Results: Incident erosions seemed to be the most important predictor for incident tenderness, but also progression of osteophytes and JSN remained in the final model. Sclerosis and cysts were not associated with tenderness in the multivariate models, and malalignment remained in the final multivariate model for cross-sectional data only (table). Associations between radiographic progression of osteophytes, JSN and erosions and incident joint tenderness were similar after adjustment for BMLs and synovitis at follow-up (data not shown).

Table. Associations between OA severity and joint tenderness in cross-sectional analyses and between radiographic progression and incident tenderness in longitudinal analyses (no progression as reference).

		Cross-sectional analyses (OR, 95% CI)*	Longitudinal analyses (OR, 95% CI)*
Model 1: Global score:			
Kellgren/Lawrence	Grade0	1.0 (ref.)	1.0 (ref.)
	Grade1	1.4 (1.2-1.7)	1.2 (0.7-2.0)
	Grade2	3.0 (2.4-3.7)	1.5 (0.9-2.5)
	Grade3	6.8 (4.5-10)	5.7 (3.0-11)
	Grade4	5.3 (3.3-8.6)	11 (4.0-33)

Model 2: Individual radiographic features (one multivariate model):			
Osteophyte	Grade0	1.0 (ref.)	1.0 (ref.)
	Grade1	2.4 (1.9-3.0)	1.6 (1.0-2.4)
	Grade2	2.7 (1.9-4.0)	
	Grade3	2.8 (1.7-4.5)	
Joint space narrowing	Grade0	1.0 (ref.)	1.0 (ref.)
	Grade1	0.9 (0.7-1.1)	2.1 (1.2-3.7)
	Grade2	1.4 (1.0-1.8)	
	Grade3	1.1 (0.7-1.6)	
Erosions	Grade0	1.0 (ref.)	1.0 (ref.)
	Grade1	1.6 (1.0-2.4)	1.0 (ref.)
Malalignment	Grade0	1.0 (ref.)	-
	Grade1	1.6 (1.1-2.2)	

Conclusion: Erosive development can strongly predict future joint tenderness, and the association to tenderness seemed to be independent of MRI-defined BMLs and synovitis. However, future longitudinal MRI studies are warranted.

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Patients with Erosive Osteoarthritis Have Less Extensive Synovitis Than Patients with Rheumatoid Arthritis On Histopathology.

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Background/Purpose: Patients with erosive osteoarthritis (EOA) often develop disfiguring deformities and associated decline in hand function. We have previously demonstrated that synovitis was a common finding on MRI and histology in patients with EOA and along with BME were associated with the presence of erosions, on MRI. Treatment of EOA with anti-rheuamtic disease modifying drugs and anti-tumor necrosis factor therapies however has not been successful. We therefore sought to identify the difference on histopathology between EOA and rheumatoid arthritis (RA).

Objective: To compare the extent of synovial inflammation, inflammatory cell infiltration, vascularity and lymphoid follicles on histopathology specimens from EOA and RA patients

Methods: This was a single center, retrospective, observational study. The records of all EOA patients from a cohort of 112 patients were reviewed for pathology or biopsy of any joint. Patients with a diagnosis of EOA had to meet the following criteria: (1) OA of hands based on the ACR criteria (2) erosions in at least 2 interphalangeal joints (IP) of which one must be a distal IP joint (3) be negative for rheumatoid factor and anti-CCP antibody (4) negative personal and family history of psoriasis and psoriatic arthritis and (5) absence of history of gout or pseudogout in hands. These were compared with synovial specimens from 15 RA patients who had elective orthopedic surgeries. The synovial tissue was graded on a scale of 0–4 (none, minimal, mild, moderate and marked) for the presence and degree of synovial lining hyperplasia, the cellularity of the synovial stroma, extent of inflammatory infiltrate, degree of vasculairy and the number of lymphoid follicles on routine hematoxylin and eosin stained slides.

Results: A total of 8 synovial specimens (6 proximal interphalangeal joints and 2 knees) were obtained from 5 patients for the EOA group and 15 specimens (5 knees, 5 wrists, 2 hips, 1 elbow, 1 shoulder and I proximal interphalangeal joint) from 14 patients was obtained for the RA group. The EOA group comprised 4 females and 1 male with a mean age of 60.4 while the RA group was comprised of 12 females and 2 males with an average age of 59.5. All RA patients were on therapy: 3 on biologic therapies, 1 on biologic and methotrexate, 7 on methotrexate monotherapy and 3 on methotrexate and hydroxychloroquine. One of the EOA patients was on hydroxychloroquine and one on methotrexate. Synovial hyperplasia and inflammatory infiltrate were noted in all RA specimens and in most EOA specimens (7 and 6) but the grading of extent revealed mean scores for hyperplasia and inflammatory infiltrate of 2.6 and 3.1 respectively for RA and 1.4 and 1.1 respectively for EOA. Synovial stroma cellularity and vascularity were also common in both conditions (14 of 15 RA and 7 of 8 EOA) but again differed on the grading from 2.5 and 2.4 for RA and 1.4 and 1 for EOA. The presence of lymphoid follicles was seen in only 1 EOA patients but noted in 7 RA subjects.

Conclusion: Synovial hypertrophy, synovial stroma cellularity, vasculiary and inflammatory cell infiltrate are commonly seen in both EOA and RA but the extent of involvement is less in EOA than in RA. The difference in

pathology may the lack of response in EOA to traditional DMARDs and anti-TNF therapies.

1113

Characterization of Lumbar Spine Individual Radiographic Features in African American and White Women and Men: The Johnston County Osteoarthritis Project. Adam P. Goode[1], Amanda E. Nelson[2], Kelli D. Allen[3], Jordan Renner[4], Timothy S. Carey[5] and Joanne M. Jordan[2]. [1]Duke University, Durham, NC, [2]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [3]Duke and Durham VA Medical Center, Durham, NC, [4]University of North Carolina, Chapel Hill, NC, [5]Cecil G. Sheps Center for Health Services Research University of North Carolina, Chapel Hill, NC

Background/Purpose: Race and gender differences have been found to exist in hip and knee osteoarthritis (OA). Whether such differences occur with lumbar spine individual radiographic features (IRF) of disc space narrowing (DSN) and vertebral osteophytes (OST) are unknown. The purposes of these analyses are to describe differences in the severity of DSN and OST among African American and Caucasian men and women.

Methods: Lumbar spine radiographs (DSN and OST) were available for 1,633 participants returning for second follow-up in the Johnston County Osteoarthritis Project from 2008-11. Participants had a mean age 68.1 (SD 9.2), and were 68.0% female and 31.7% African American (AA), with mean body mass index (BMI) 31.4 (SD 7.2). Seventy-eight percent had $>=12$ years education. Lateral lumbar spine films were graded for each level in a semi-quantitative fashion (0–3) for DSN and (0–3) for both anterior superior and inferior OST according to the Burnett Atlas. Lumbar spine IRF were coded (individually for DSN and superior and inferior OST) based upon a participant's most severely affected lumbar level. For all analyses, AAs were the referent group and results were stratified by gender. Multivariable associations were determined with proportional odds models while adjusting for age, BMI, and education.

Results: After adjustment, White women had a significantly greater odds of DSN (adjusted Odds Ratio [aOR]= 1.56 ((95% CI 1.23, 1.98)) whereas no significant association was found across race for men (aOR= 1.24 ((95% CI 0.86, 1.79)). No association was found across race for either women (aOR=1.00 ((95% CI 0.78, 1.28)) or men (aOR= 1.13 ((95% CI 0.78, 1.65)) for superior anterior OST. White women (aOR= 1.50 ((95% CI 1.16, 1.95)) and White men (aOR= 1.88 ((95% CI 1.27, 2.77)) both had a greater odds of inferior anterior vertebral OST.

Conclusion: Severity of some lumbar spine IRFs differs by race, suggesting the possibility of anatomic or developmental variation in the spine. The greater severity of DSN in White women compared to AA women is important because this IRF has been consistently associated with low back symptoms. The fact that both White women and White men had greater severity of inferior vertebral OST, compared with their AA counterparts, suggests anatomic racial differences in this region.

1114

Prevalence of Radiographic and Symptomatic Hip Osteoarthritis in an Urban US Population: The Framingham Osteoarthritis Study. Katherine D. Linsenmeyer[1], Ali Guermazi[1], Kyu-Chan Kim[1], David T. Felson[2], Mary M. Clancy[2] and Steven C. Vlad[2]. [1]Boston Medical Center, Boston, MA, [2]Boston University, Boston, MA

Background/Purpose: There are few studies of hip osteoarthritis (OA) in the United States and none in the last 35 years that have addressed the prevalence of hip OA in an urban population. Recent estimates from Europe suggest that 2–5% of the population age 50 and over has symptomatic hip OA. Our goal was to assess the prevalence of radiographic and symptomatic hip OA within the Framingham Osteoarthritis cohort.

Methods: We studied the Community sample of the Framingham Osteoarthritis study which was recruited among those 50–79 years using random digit dialing from the town of Framingham in 2002–2005. As part of this examination standing long-limb radiographs of the lower extremities including the pelvis were obtained using a near horizontal beam. In addition, subjects answered questions regarding the presence and frequency of joint symptoms and indicated on a homunculus whether they had hip joint pain on most days of the previous month. Two reviewers who received training from an expert musculoskeletal radiologist read all films and verified abnormal ones with the radiologist. Films where both hips were unreadable were excluded. Films were also assessed for Kellgren-Lawrence grade: radiographic OA (ROA) was defined as K/L $\geq$ 2 (probable joint space narrowing plus an osteophyte ' 2). Interobserver kappas were 0.72 between the readers. Persons with a hip replacement were defined as having hip OA in that joint (n=22 subjects). Symptomatic hip OA (SxOA) was defined as radiographic OA with ipsilateral hip pain.

Results: Of 1025 subjects with radiographs, 949 films could be evaluated in both hips. Mean age was 63.5 years (sd 9.0), 56% were women, mean BMI was 27.9 (sd 4.6), 98.1% were white. 16.9% had radiographic hip OA (20.8% of men, 13.8% of women). Of those with ROA, 73.1% were unilateral and 26.9% bilateral. 11.7% of subjects under 65 had ROA (67/571) as compared to 24.7% of subjects 65 and over (93/376). In subjects with BMI < 25, 19.3% (53/276) had ROA; for BMI 25–29.9, 16.3% (66/404) had ROA; for BMI $\geq$ 30, 15.2% (41/269) had ROA. Both whites and non-whites had similar rates of ROA (16.9%). Of those with ROA, 21.9% had hip joint pain, yielding a SxOA prevalence of 3.7% of the total population (4.3% of men, 3.2% of women).

Conclusion: Around 1/6 of the subjects in this population-based cohort had radiographic evidence of hip OA; 3.7% of men and women had symptomatic OA, an estimate similar to studies from Europe.

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Relation Between Hip Dysplasia, Pain, and Osteoarthritis in a Cohort of Patients with Hip Symptoms. Johanne Morvan[1], Ronan Bouttier[2], Bernard Mazieres[3], Evelyne Verrouil[3], Jacques Pouchot[4], Anne-Christine Rat[5], Joel Coste[6] and Alain Saraux[7]. [1]CH Quimper, Quimper, France, [2]CHU Brest, Brest, [3]Hopital de Rangueil, Toulouse, FRANCE, France, [4]Hopital Louis Mourier, Colombes, FRANCE, France, [5]Nancy Teaching Hospital, Nancy, France, [6]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, France, Nancy, France, [7]Université Brest Occidentale, Brest, France

Background/Purpose: The relationship between acetabular dysplasia (HD) and hip osteoarthritis remains unclear, especially for mild forms of dysplasia. Our objectives were to estimate the prevalence of HD in a population-based sample with hip symptoms and to evaluate potential associations linking HD, hip osteoarthritis, and hip pain.

Methods: Individuals 40 to 75 years of age with symptoms in one or both hips were recruited during a multiregional prevalence survey. All study participants underwent a physical examination and radiographs. Radiographs were evaluated using Kellgren and Lawrence (KL) staging (with stages $\geq$2 indicating hip osteoarthritis) and HD parameters (center-edge [CE] angle, acetabular inclination angle [HTE], acetabular depth [AD], and vertical-center-anterior margin [VCA] angle).

Results: We studied both hips of 842 individuals (1684 hips) among whom 203 had hip osteoarthritis. Compared to left hips, right hips had significantly smaller CE angles and significantly greater AD and HTE values ($P \leq 0.001$). Overall, the prevalence of HD ranged from 7.6% to 22.2% of the hips depending on the parameter used. The prevalence of HD was higher in individuals with hip osteoarthritis, with significant differences for abnormal HTE (19.1% vs. 11.4%; $P < 0.0001$) and abnormal CE (11.3% vs. 7.5%; $P = 0.04$). By logistic regression, only abnormal HTE remained associated with OA ($P = 0.05$). Hip pain was more common in individuals with HD ($P < 0.0001$) but the association was not statistically significant after stratification on osteoarthritis status ($P = 0.25$).

Conclusion: Our study confirms the relationship between osteoarthritis and HD, particularly defined based on the HTE angle. HD was not associated with hip pain.

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Diagnostic Value of Internal Rotation Measurement in Patients with Cam- and Pincer-Type Deformities of the Hip. Stephan Reichenbach[1], Michael Leunig[2], Stefan Werlen[3], Andreas Limacher[1], Christian W. Pfirrmann[4], Reinhold Ganz[1] and Peter Jüni[1]. [1]University of Bern, Bern, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland, [3]Hospital Sonnenhof, Bern, Switzerland, [4]Balgrist University Hospital, Zurich, Switzerland

Background/Purpose: It has been proposed that femoroacetabular impingement (FAI) causes early osteoarthritis (OA) in non-dysplastic hips. FAI occurs predominantly in two different types, "cam" or "pincer". Cam impingement is due to a cam-type deformity with a non-spherical femoral head and/or a decreased anterior head-neck offset. Pincer impingement results from increased acetabular depth with over-coverage of the femoral head, while the head-neck configuration may be normal. FAI is often seen in young male athletes referred to rheumatologists or orthopaedic surgeons because of groin pain, and internal rotation in flexion is usually diminished. The aim of this study was to determine whether diminished internal rotation can be used to detect FAI in young asymptomatic males.

Methods: Study subjects were young males aged 18 to 21 undergoing compulsory conscription for the Swiss army. Participants completed questionnaires pertaining to pain, stiffness, and physical function, and internal rotation was measured on a validated examination chair. A random sample of the examined participants was invited for magnetic resonance imaging (MRI) of the hip. Cam-type deformities were graded from 0 to 3: 0=normal, 1=mild, 2=moderate, 3=severe. Pincer impingement was defined by increased acetabular depth, which was specified as the distance (in mm) between the center of the femoral neck and the line connecting the anterior and posterior acetabular rims. Values were positive if the center of the femoral neck was lateral to the acetabular rim, with ≤3 mm representing increased acetabular depth. Based on a fitted receiver operating characteristics (ROC) curve, we estimated sensitivity, specificity, positive and negative likelihood ratios (LR) for different internal rotation cutoffs for cam impingement, pincer impingement, and the combination of both, as compared with the reference group without deformity on MRI.

Results: 244 asymptomatic males underwent imaging, with a mean age of 19.9 years. Fifty-nine subjects showed definite cam-type deformity, eight increased acetabular depth, and eight a combination of both. Area under ROC-curves were 0.725 for detection of the first group, 0.549 for detection of the second, and 0.895 for detection of the third group as compared with the reference group. A cut-off value of 30° of internal rotation yielded a sensitivity of 0.63 and a specificity of 0.69 for the first group, 0.13 and 0.69 for the second, and 1.00 and 0.69 for the third. An internal rotation of ≥30° had sufficient power to rule out the combination of both types of impingement: the crude negative likelihood ratio (LR) was below 0.10. Conversely, an internal rotation of ≤20° had the required power to rule in the combination of both types of impingement, with a positive LR of 12.7.

Conclusion: Different cut-offs for internal rotation may be used to accurately rule in or rule out the combination of cam- and pincer-type impingement. Internal rotation is not useful for detecting pincer-type impingement.

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Association Between Hip Bone Marrow Lesions (BMLs) and Bone Mineral Density: A Cross-Sectional and Longitudinal Population-Based Study. Harbeer Ahedi[1], Dawn Dore[1], Leigh Blizzard[1], Flavia Cicuttini[2] and Graeme Jones[1]. [1]Menzies Research institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: Bone marrow lesions (BMLs) have been identified one of the key pathologic features in knee osteoarthritis (OA)[1]. However, there is limited data on hip BMLs and their relation to bone mass. The aim of this study was to examine the cross-sectional and longitudinal association between hip BMLs and BMD at three different sites.

Methods: 198 subjects in the Tasmanian Older Adult Cohort (TASOAC) study (average age 64 yrs) with a right hip MRI and dual-energy x-ray absorptiometry (DXA) scans conducted at two time points, approx. 2.6 years apart, were included in this study. MR images were used to assess femoral and acetabular hip BML presence and size (cm²) by manually drawing contours around the outer edges of the BML using Osiris X (Geneva) software. DEXA scans were used to determine total hip, femoral neck and spine BMD.

Results: Fifty-five subjects (28 %) had either femoral and/or acetabular BMLs. In cross-sectional analysis, femoral BMLs were not associated with either hip or femoral neck BMD whereas acetabular BMLs were associated with lower hip BMD and femoral neck BMD *(mean diff: −0.05 g/cm², p=0.009 & mean diff: −0.06 g/cm², p<0.001 resp.)*. Neither was associated with spine BMD. Longitudinally, resolving acetabular BMLs were associated with an increase in BMD at both hip *(mean diff: +0.02 g/cm², p=0.05)* and femoral neck *(mean diff: +0.01 g/cm², p=0.02)* sites while incident femoral BMLs were associated with an increase *(mean diff: +0.03 g/cm², p<0.001)* and resolving femoral BMLs with a decrease in femoral neck BMD *(mean diff: −0.04 g/cm², p=0.04)*. Finally, change in femoral BML size was associated with change in femoral neck BMD (*βeta: +0.03, p<0.001)* and change in acetabular BML size was associated with change in femoral neck BMD (*βeta: −0.01, p=0.004)*.

Conclusion: Hip BMLs are associated with site-specific changes but not distant changes in bone mass. These results, especially in the longitudinal data, suggest this is a combination of changes related directly to the underlying BML pathology as well as changes adjacent to the disease process perhaps due to pain, disuse or paracrine effects.

References
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Association Between Hip and Knee Cartilage Measured Using Radiographs and Magnetic Resonance Imaging: The Tasmanian Older Adult Cohort Study. Hussain Ijaz Khan[1], Dawn Dore[1], Guangju Zhai[2], Changhai Ding[3], Jean Pierre Pelletier[4], Johanne Martel-Pelletier[4], Flavia Cicuttini[5] and Graeme Jones[1]. [1]Menzies Research institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St John's, NL, [3]Menzies research institute & Monash University, Hobart, Australia, [4]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [5]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, 3004, Australia

Background/Purpose: Cartilage loss is the key pathological feature of osteoarthritis (OA) and can be assessed indirectly using radiography or directly through magnetic resonance imaging (MRI). A number of cross-sectional studies have examined the association of hand OA with hip or knee OA, suggesting that primary generalised OA (PGOA) may be a distinct disease in which systemic predisposition is more important than local (mechanical) factors. However, despite the high frequency of involvement of the hip and the knee joints in OA, only a few studies have looked at the radiographic association of joint space narrowing (JSN) in these two joints with inconsistent results. None has done so using MRI. The aim of this study was to examine the association of hip and knee cartilage measured by both radiography and MRI.

Methods: We studied 151 participants from a cohort study of older adults. MRI was used to assess hip and knee cartilage volume and radiography was used to asses JSN at both sites. Correlation analyses were used to compare cartilage volume measurements and JSN.

Results: In adjusted analysis, there was a consistent, positive association between knee cartilage volume and hip cartilage volume which was best for total knee cartilage volume (R= 0.23–0.50, all P= <0.05). In contrast, there was no or at best a weak correlation between hip and knee JSN (R= −0.01–0.24).
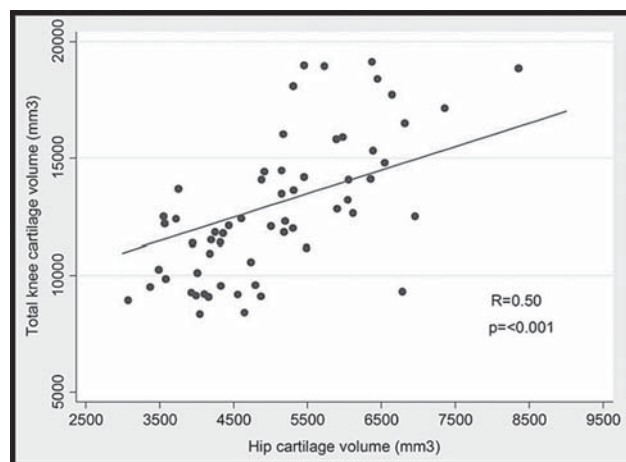
Figure 1. Correlation between hip cartilage volume and total knee cartilage volume. Line of best fit, R-value and p-value were adjusted for age and sex.

Conclusion: Hip and knee cartilage volume are more strongly associated than hip and knee radiographic JSN suggesting commonality of cartilage volume at different anatomic sites. The weaker radiographic association may reflect less measurement error with MRI or the contribution of multiple structures to JSN in the knee.

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Prediction of MRI-Detected Cartilage Loss Over 30 Months Using Simplified Radiographic and Clinical Stratification: The MOST Study.

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Background/Purpose: MRI-detected cartilage loss is the main structural outcome measure in large studies of knee OA. Definition of subjects at high risk for cartilage loss is important as this subgroup is likely to benefit most from interventional efforts and will potentially reduce subject numbers and duration of clinical trials. A simple stratification strategy is needed for pre-selecting subjects at high risk. We assessed a set of potential factors in regard to their predictive capability of cartilage loss over 30 months.

Methods: The Multicenter Osteoarthritis (MOST) Study is a longitudinal study of subjects with knee OA or at risk of OA. 1.0 T MRI was performed at baseline and 30 months follow-up in subjects with radiographic knee OA at baseline. MRIs were assessed according to the WORMS scoring system including within-grade assessment. Altogether 10 tibiofemoral subregions were scored. Cartilage loss was defined as at least within-grade increase in cartilage score in ≥1, ≥2, or ≥3 subregions. Analyses were repeated with cartilage loss defined as full grade increase. Six predictors that are commonly acquired in screening efforts, i.e., gender, age, BMI, Kellgren Lawrence (K-L) grade (0–1, 2, 3–4), joint effusion (0–1, 2–3) and knee pain (pain on most days during the past 30 days or maximal WOMAC pain score as 0, 1–2, 3–4) were assessed using a 10-fold cross-validation method. The cross-validation was repeated 10 times, and averaged receiver operating characteristics (ROC) curve, i.e., C-statistic, was calculated as a measure of the overall performance. Age and sex were forced in all models. We plotted the ROC curves for each variable selected in the final model according to cross-validation method.

Results: Of 544 knees randomly selected from the progression cohort, risk of at least within-grade cartilage loss occurring in ≥1, or ≥2, or ≥3 subregions was 53.6%, 31.6%, and 18.1%, respectively. The model contain-

ing age, sex, K-L grade, effusion, and knee pain provided the highest prediction accuracy (C-statistic 0.533) for any cartilage loss occurring in at least one subregion. The best models for prediction of at least within-grade cartilage loss of ≥2 or ≥3 included the same variables, i.e., age, sex, K-L grade and knee pain (C-statistics=0.561 for ≥2, and 0.571 for ≥3 subregions). Risk of full-grade cartilage loss in ≥1, ≥2, or ≥3 subregions was 38.8%, 18.8% and 9.7%, respectively. The same variables were included for predicting cartilage loss of a full grade in ≥1, or ≥2, or ≥3 subregions as those for at least within-grade loss. The corresponding C-statistics were 0.559, 0.599, and 0.615 (Figure 1), respectively.
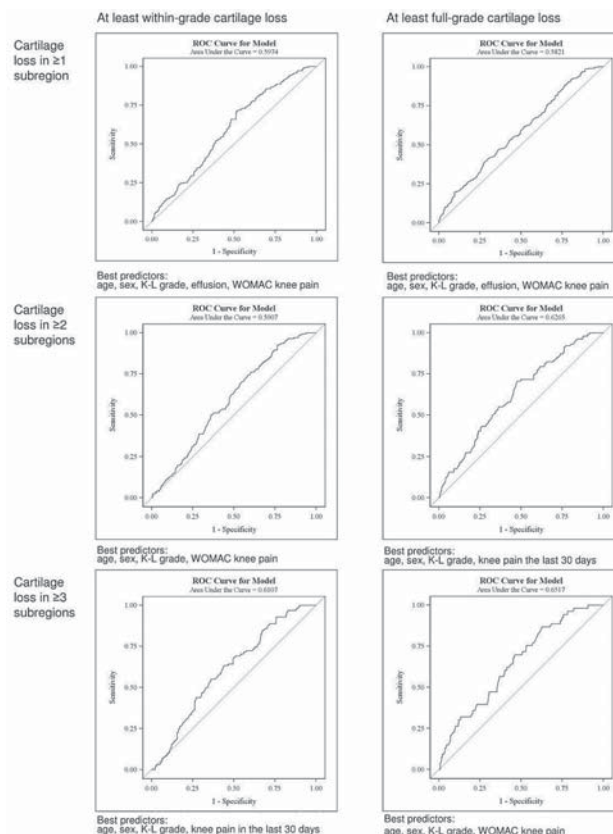
Conclusion: Among knees with radiographic OA, age, sex, K-L grade and knee pain only had the moderate capability of predicting cartilage loss. Of them the strongest predictors were baseline K-L grade, followed by knee pain. The prediction accuracy of this model needs to be further validated using large databases from other populations.

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Cartilage Volume Loss Occurs in Most Older Adults and the Rate of Loss Increases with Age.

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Background/Purpose: Radiographic data suggests knee osteoarthritis is a relatively static disease even over the long term. It is uncertain how much this is influenced by measurement error and whether it accurately reflects what is happening to the cartilage. Initial cross-sectional studies suggest little

change in cartilage volume with age but a decrease in thickness. However, longitudinal studies in younger age groups suggest the rate of cartilage volume loss increases with age. There are no longitudinal studies in older age groups.

The aim of this study was to describe cartilage loss over time and the association between age and knee cartilage volume loss in older adults.

Methods: A total of 407 randomly selected community-dwelling older adults (mean age 63.2 years, range 51–79 years; 50% female) were measured at baseline and approximately 2.7 years later. T1-weighted fat-suppressed magnetic resonance imaging (MRI) was used to measure knee cartilage volume at the tibial and femoral sites. Body mass index (BMI) and radiographic osteoarthritis (ROA) were measured by standard protocol. A real change in volume loss was assessed using the least significant criterion which takes into account measurement error and the correlation between measurements at baseline and follow up.

Results: On average, participants had 1.5% per annum tibiofemoral cartilage volume loss. Of the 407, 74% had a decrease larger than measurement error while, 14% which had a genuine increase in volume and only 12% were unchanged. After adjustment for sex, BMI and ROA, age was significantly associated with annual decrease in medial and total tibial (β −0.08 to −0.13%/yr, all P< 0.008) but not lateral tibial cartilage volume (β −0.03%/yr, P>0.05). In addition, age was associated with a decrease in medial and lateral femoral cartilage volume in males (β −0.05 to −0.06%/yr, all P <0.01) but not females (β −0.001 to 0.005%/yr, P >0.05).

Conclusion: Knee cartilage volume is rarely static even over a three year time frame. The majority of subjects lose cartilage and this rate of loss increases with age. These findings suggest radiographs are not sensitive measures of changes in cartilage volume and challenge the view that osteoarthritis is largely static over time.

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Degenerative Medial Meniscal Pathology May Initiate in the Posterior Horn: Data From the Osteoarthritis Initiative. Robert J. Ward[1], Jeffrey B. Driban[1], Eric E. Wong[1], Jonathan W. Pack[1], Kunal K. Kothari[2], Grace H. Lo[3] and Timothy E. McAlindon[1]. [1]Tufts Medical Center, Boston, MA, [2]Tufts University School of Medicine, Boston, MA, [3]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

Background/Purpose: Meniscal pathology is highly prevalent in knee Osteoarthritis (OA). However, details regarding the distribution of pathology within the meniscus has yet to be described in patients with and without radiographic signs of OA. Cross-sectional distribution of medial meniscal pathology as it relates to the anterior horn, body, and posterior horn may be informative of the role of the meniscus in the natural history of OA.

Methods: We studied participants in the Osteoarthritis Initiative (OAI) progression subcohort who had the OAI core set of magnetic resonance (MR) images at the 24-month OAI visit and consented to participate in the Bone ancillary project. By definition, members of the progression subcohort had at least one symptomatic knee with radiographic evidence of OA.. The right knee was selected as the index knee for investigation among these participants unless there was a contraindication for MR imaging; therefore, the index knee did not have OA as a pre-requisite. A single experienced fellowship trained musculoskeletal radiologist reviewed the MR images for meniscal pathology by location (e.g. anterior, body, and posterior horn) within the medial menisci using a modified International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine (ISAKOS) meniscal tear classification system. We presented the prevalence of meniscal pathology within the medial meniscus among this sample both with and without knee OA. PA standing radiographs were obtained of the same knees and read for Kellgren-Lawrence grade.

Results: 464 knees were included in the analysis; 454 were right knees; 244 (53%) men, with a mean age of 63 years (SD). 135 (29.4%) knees had no radiographic evidence of knee OA (Kellgren-Lawrence Grade = 0 or 1). 114 (24.6%) had normal medial menisci, leaving 350 (75.4%) with some pathology in at least one region of the medial meniscus. 117 (25.2%) knees had pathologic anterior medial menisci and among those 98.3% had concurrent findings in the body or posterior horn. 272 (58.6%) medial menisci have pathologic findings in the meniscal body and among those 97.4% had concurrent findings in the anterior or posterior

meniscal horn. 336 (72.4%) medial menisci had pathologic findings in the posterior meniscus and among those 263 (78.3%) had concurrent findings in the body or anterior regions. Finally, 107 (23.1%) had pathologic findings in all three regions (regardless of type of finding).

Conclusion: Medial meniscal pathology is highly prevalent. In our sample, of those with medial menisci pathology some damage was also almost universally found in the posterior horn. Those with posterior horn damage also very commonly had concurrent pathology in the body and anterior horn. Isolated involvement of the anterior horn and body of the medial meniscus are rare. Though this is a cross-sectional study, these findings suggest that medial meniscal pathology may initiate in the posterior horn. Longitudinal studies are needed to confirm this possibility.

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Identifying Radiographic Phenotypes of Early Knee Osteoarthritis Using Separate Quantitative Features Might Improve Patient Selection for More Targeted Treatment. Margot B. Kinds[1], Anne C. A. Marijnissen[1], Max A. Viergever[1], P.J. Emans[2], J.W.J. Bijlsma[1], F.P.J.G. Lafeber[1] and P.M.J. Welsing[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands

Background/Purpose: Osteoarthritis (OA) is a degenerative joint disease characterized by pain and functional disability. The expression of OA varies significantly between individuals and over time, implying the existence of different phenotypes. This study aims at identifying phenotypes of progression of radiographic knee OA and to describe their radiographic and clinical characteristics.

Methods: In individuals with early knee OA from the Cohort Hip & Cohort Knee (CHECK), baseline, two-year, and five-year follow-up radiographs were evaluated. Separate radiographic OA parameters were quantitatively measured by Knee Images Digital Analysis (KIDA). To identify phenotypes of radiographic knee OA progression, hierarchical clustering was performed using the KIDA measurements of participants with complete data at T0, T2y, and T5y (n=417 of 1002). The phenotypes were compared for development of joint space width (JSW), varus angle, osteophyte area, eminence height, bone density, and for clinical characteristics at T0. Additionally, logistic regression analysis evaluated whether baseline radiographic features predicted to which phenotype an individual belonged.

Results: Overall, the radiographic features showed OA progression during follow-up. Based on the development, five clusters were identified that were interpreted as 'severe' (n=17; most progression of all radiographic features) or 'no' (n=108) progression, 'early' (n=110; progression of all features specifically between T0 and T2y) or 'late' (n=69; progression of all features specifically between T2y and T5y) progression, or specific involvement of 'bone density' (n=113). Clinical characteristics at T0 were not evidently different between the clusters, and WOMAC scores were only slightly lower in the 'no' cluster than in the other clusters. In the evaluation of predictors for the different clusters, the area under the curve (AUC) improved when radiographic features were added to basic demographic and clinical variables. Kellgren & Lawrence grading was not a significant predictor for any of the phenotypes. The predictors for 'early', 'late', and 'no' progression phenotypes generally had an opposite effect than the predictors for the 'severe' and 'bone density' phenotypes. Larger medial JSW, varus angle, osteophyte area, eminence height, and bone density at T0 were associated with 'severe' and 'bone density' progression. The 'bone density' model had AUC=0.91. Smaller eminence height and bone density were associated with 'early' and 'late' progression (AUC= 0.79, and 0.76 respectively). Larger varus angle and smaller osteophyte area were associated with 'no' progression (AUC=0.72).

Conclusion: This is the first study to identify specific phenotypes of radiographic knee OA progression in individuals with early OA complaints. Phenotypes represented the level (severe vs. no) and phase of progression (early vs. late), and the involvement of a specific feature (bone density). Baseline radiographic features could predict the phenotypes. The phenotypes might represent relevant subgroups for the evaluation of treatment strategies in clinical trials, and with that drive the discovery of more targeted treatment.

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Comparison of Anatomic Knee Alignment On Physical Examination and Radiographs. Iman Hemmati[1], Eric C. Sayre[2], Ali Guermazi[3], Savvakis Nicolaou[1], Anona Thorne[4], Joel Singer[1] and Jolanda Cibere[2]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Vancouver, BC, [3]Boston University, Boston, MA, [4]Canadian Institutes of Health Research HIV Trials Network, Vancouver, BC

Background/Purpose: Severity of knee malalignment is a risk factor for osteoarthritis (OA) progression. Currently the hip-knee-angle (mechanical axis), assessed on a full-limb radiograph, is the gold standard. Direct measurement of the anatomic axis using standard knee radiographs has been validated as an alternative method. In clinical practice, examining knee alignment with a goniometer may be more practical. The aim of the current study was to 1) evaluate the correlation of knee alignment angle measured by goniometer on physical examination with the anatomic angle measured on knee radiographs and 2) to evaluate whether the relationship is confounded by clinical variables that may affect goniometric measurements.

Methods: A simple random sample (n=120) was selected from the MoDEKO (Model for the Diagnosis of Early Knee Osteoarthritis) cohort, a population-based cohort of people with knee pain, age 40–79. Knee alignment was measured to the nearest degree by two methods: 1) anatomic-axis on fixed-flexion PA knee radiographs and 2) standardized goniometer assessment on physical examination, previously shown to be reliable. In this study varus was defined as angle < 0, valgus > 0 and $0°$ as neutral. On PA radiographs anatomic axis was defined by the intersection of two lines originating from points bisecting the femur and tibia and converging at the centre of tibial spine tips. Inter- and intra-rater reliability of anatomic angle measurements from radiographs were determined by intraclass correlation coefficient (ICC) of two independent assessors. The correlation of radiographic anatomic angle with goniometer measurements was analyzed by linear regression. Western Ontario and McMaster Universities (WOMAC) pain score, body mass index (BMI) and flexion contracture were assessed as potential confounders. Analysis was weighted by stratum sampling weights.

Results: Of 120 subjects, 52% were male, with mean (SD) age of 58 (11) years and BMI of 27 (5). The mean (SD) angle measured on PA radiographs and goniometer were 2 (3.6) and 3 (2.3) degrees respectively. Intra-rater ICC for radiographic measurements was 0.93, while inter-rater ICC was 0.83. A significant correlation was found between radiographic and goniometer measurements ($r = 0.48$; $P < 0.0001$). A model was developed to predict anatomic angle based on goniometer angle: anatomic angle on PA radiographs = $0.410 + 0.749$*goniometer angle. WOMAC pain score, BMI and flexion contracture were not significantly associated with PA radiographic angle and did not significantly change the correlation of radiographic and goniometric measurements, and so these variables were dropped from the model.

Conclusion: In this study, knee alignment assessed by goniometer was significantly correlated with the anatomic axis angle on fixed-flexion PA knee radiographs. Moreover, factors such as pain, BMI and flexion contracture did not confound the relationship of goniometric with radiographic angle measurements. Given the ease of application, goniometric measurements may be preferable to x-ray, although the predictive utility of goniometric alignment measurement will require further assessment in longitudinal studies of knee OA.

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Total Knee Replacement As an Osteoarthritis Study Outcome: Predictors Derived From Long-Term Observation Following a Randomized Clinical Trial. Jean-Pierre Raynauld[1], Johanne Martel-Pelletier[1], Marc Dorais[2], Boulos Haraoui[1], Denis Choquette[1], François Abram[3], André Beaulieu[4], Louis Bessette[5], Frédéric Morin[6], Lukas M. Wildi[1] and Jean Pierre Pelletier[7]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]StatSciences Inc., Notre-Dame de l'Île Perrot, QC, [3]Imaging Research & Development, ArthroLab Inc., Montreal, QC, [4]Faculty of Medicine, Laval University, Quebec, QC, [5]Centre Hospitalier Universitaire de Québec, pavillon CHUL, Sainte-Foy, QC, [6]Centre de Recherche Musculo-squelettique, Trois-Rivières, QC, [7]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC

Background/Purpose: Using data from a 4-year follow-up of knee OA patients who formerly received treatment with chondroitin sulfate (CS) within a 6-month clinical trial, we wanted to find predictors of the incidence of total knee replacement (TKR).

Methods: Knee OA patients participating in a randomized, double-blind controlled trial evaluating the impact of CS (Bioibérica S.A., Barcelona, Spain) (400 mg BID) vs. placebo who had serial MRI acquisitions (qMRI) and clinical evaluations of the symptomatic knee[1] were contacted to evaluate retrospectively the incidence of TKR of the study knee. A sub-group of patients (n=57) who received the study medication and had all the MRI evaluations (intent to treat (ITT)) were selected for this post hoc retrospective analysis. The TKR incidence was assessed blindly to the treatment allocation with a standardized phone interview.

Results: The patients' mean age was 63.2 years, 63% were female and the average body mass index (BMI) was 30.7 kg¨ Mm[2]. A total of 13 TKRs (22.8%) were performed on this sub-population in the time frame of 4 years after completion of the original study. Interestingly, there were more TKRs performed within the placebo group (n=9) than the CS group (n=4) (69% vs. 31%, p=0.15, logistic regression). We further investigated the predictors of long-term TKRs for the target knee by comparing, within the ITT cohort, the patients who had TKR (n=13) for the target knee to those who did not (n=44), using data at baseline or the change at 1 year. Baseline values of WOMAC pain (p=0.01, logistic regression) and function (p=0.04), bone marrow lesions (BMLs) in the medial tibial plateau (p=0.0008) and global knee (0.02), and C-reactive protein (CRP) level (p=0.05) were strong predictors of TKR. Changes at 1 year in the medial cartilage volume higher than 7% (p=0.03) and the change in WOMAC pain (p=0.02) and function (p=0.02) also predicted the occurrence of TKR. Multivariate analyses controlling for age, sex, and BMI revealed that baseline presence of BML (p=0.003) and WOMAC pain (p=0.006) were independent strong predictors of TKR. Time to occurrence of the TKR from the study inception also favored the CS group vs. placebo (Log-Rank, p=0.14). Cox regressions that included age, sex, and BMI in the model indicated that baseline values of WOMAC pain (p=0.0006), presence of BML in the medial compartment (p=0.0007) and CRP (p=0.02) were the strongest independent predictors of TKR over time.

Conclusion: Treatment with CS appeared to reduce the need for TKR. There are very few OA RCTs that use qMRI to probe knee structural outcomes. According to this study, predictors of long-term occurrence of a TKR were greater levels of knee pain, lower level of function and presence of BML at baseline, and greater loss of cartilage over time. This study links MRI findings to long-term clinical outcomes.

Reference

[1] Wildi LM, et al. Ann Rheum Dis 2011;70(6):982-9

Disclosure: J. P. Raynauld, ArthroLab Inc., 4; **J. Martel-Pelletier**, ArthroLab Inc., 4, Bioibérica S.A., 5; **M. Dorais**, ArthroLab Inc., 5; **B. Haraoui**, ArthroLab Inc., 9; **D. Choquette**, ArthroLab Inc., 9; **F. Abram**, ArthroLab Inc., 3; **A. Beaulieu**, ArthroLab Inc., 9; **L. Bessette**, ArthroLab Inc., 9; **F. Morin**, ArthroLab Inc., 9; **L. M. Wildi**, None; **J. P. Pelletier**, ArthroLab Inc., 4, Bioibérica S.A., 5.

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Three Trajectories of Activity Limitations in Early Symptomatic Knee Osteoarthritis: A 5-Year Follow-up Study. Jasmijn F. M. Holla[1], Marike van der Leeden[1], Leo D. Roorda[1], Martijn W. Heymans[2], Sita M.A. Bierma-Zeinstra[3], Maarten Boers[2], Willem F. Lems[2], Martijn P.M. Steultjens[4] and Joost Dekker[2]. [1]Reade, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Erasmus MC - University Medical Center, Rotterdam, Netherlands, [4]Glasgow Caledonian University, Glasgow, Scotland

Background/Purpose: Knee osteoarthritis (OA) is one of the leading causes of activity limitations among older adults. The course of activity limitations is highly variable; some patients seem to be stable or even improve, whereas others deteriorate. The aim of the present study was to identify subgroups of knee OA patients with different trajectories of activity limitations, and to describe patient characteristics for each subgroup.

Methods: Five-year follow-up data from a sample of 713 participants with early symptomatic knee OA from the Cohort Hip and Cohort Knee (CHECK) were used. Activity limitations were measured yearly with the physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Latent class growth analyses (LCGA) were used to identify trajectory classes of activity limitations. Multivariable logistic regression analyses were used to examine differences in demographic, clinical and psychological characteristics between the trajectory classes.

Results: The LCGA yielded 3 trajectory classes for activity limitations. Participants in class 1 ('slight limitations'; n = 336) reported permanent low levels of activity limitations, or moved from moderate or high levels at baseline to low levels of activity limitations over 5 years. Participants in class 2 ('moderate limitations'; n = 261) reported permanent moderate levels of activity limitations, or moved from fairly high or fairly low levels to moderate levels of activity limitations over 5 years. Participants in class 3 ('severe limitations'; n = 116) reported permanent high levels of activity limitations, or moved from low or moderate levels of activity limitations to high levels of activity limitations over 5 years. Participants in class 1 ('slight limitations') were more likely to have a lower BMI, to have less than 3 comorbidities, to report a lower level of knee pain, no to have hip pain, not to have joint space narrowing, and to feel more vital, compared with participants in class 2 ('moderate limitations') (AUC: 0.75). Participants in class 3 ('severe limitations') were more likely to report a higher level of knee pain, to have bilateral knee pain, to have osteophytosis, to feel less vital, and to avoid physical activities (AUC: 0.76).

Conclusion: Three trajectory classes of activity limitations were identified using 5-year follow-up data of 713 participants with early symptomatic knee OA: 'slight limitations'; 'moderate limitations'; and 'severe limitations'. The 'slight limitations' group was characterized by a lower BMI, a lower comorbidity count, lower levels of knee pain, not having hip pain, not having joint space narrowing, and high vitality. The 'severe limitations' group was characterized by higher levels of knee pain, bilateral knee pain, osteophytosis, low vitality, and avoidance of physical activities.

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Comparison between Osteoartritis Initiative and CHECK study (Cohort Hip & Cohort Knee); Development of pain and function during 4 years follow-up. Janet Wesseling[1], Sita M.A. Bierma-Zeinstra[2], Margreet Kloppenburg[3], Johannes WJ Bijlsma[1] and CHECK steering group[4]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Erasmus MC - University Medical Center, Rotterdam, Netherlands, [3]Department Rheumatology and Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands, Leiden, Netherlands, [4]Utrecht

Background/Purpose: Pain and disability related to osteoarthritis (OA) may generally be considered to be chronic, but it is known that its course can be very different between patients. In this study, it is investigated whether there is a difference in course of pain, physical function and radiographic damage during follow-up between two OA cohorts: Osteoarthritis Initiative (OAI) and Cohort Hip & Cohort Knee study (CHECK).

Methods: For the current study, longitudinal data of four years follow-up of the CHECK study and OA Initiative were used. The CHECK study is a Dutch prospective 10-year follow-up study, initiated by the Dutch Arthritis Association, to study progression of OA in participants with early symptomatic OA of knee or hip. Individuals were eligible if they had pain of knee or hip, were aged 45–65 years, and had not yet consulted their physician for these symptoms. In the same time in the U.S. an observational 4-year follow-up study was started to create a public archive of data, biological samples and joint images to study the natural history of, and risk factors for, the onset and progression of knee OA. The WOMAC was utilized to measure pain during activities (range 0–20) and physical functioning (range 0–68). For comparison with CHECK a subgroup of the OAI Incidence cohort was selected which was comparable with the CHECK cohort. Generalized estimating equations (GEE) were used to account for correlations within individuals and all models were adjusted for gender, BMI, age, amount of working hours and baseline radiographic joint damage. Interaction terms were investigated to measure the effect of time and the effect of progression in course of pain and function.

Results: Data of 688 CHECK participants with knee pain at baseline were analyzed, mean age 56 years, BMI 25 kg/m^2 and 79% female. The subgroup of OAI Incidence cohort with infrequent or frequent knee pain consisted of 1417 participants, with a mean age of 56, BMI of 28 kg/m^2 and 64% female. At baseline CHECK had less radiographic OA (K&L $\geq$ 2) compared to OAI Incidence subgroup, but at follow-up CHECK had more radiographic progression (42% vs 15% of at least 1 K&L point increase; p< 0.001). A final longitudinal regression model with pain as outcome showed slight decrease of course of pain in both cohorts, but a consistent lower level of course of pain in OAI Incidence subgroup of 2 points (better health). In a final model with function as outcome, in both cohorts there is a slight decrease of physical function, but a consistent higher level of function of 10.2 points (worse health) in CHECK. There is no different effect of time in course of pain (p= 0.7) and function (p=0.06) for CHECK or OAI. There is also no different effect of progression of joint damage on course of pain and function (both p=0.07) for CHECK or OAI.

Conclusion: In the total group, participants of the OAI Incidence subgroup and the CHECK participants with knee pain, there is a slight decrease over time in pain and physical functioning. In CHECK participants more progression of joint damage over time was observed and these participants recorded a higher level of pain and function problems. Difference between the 2 cohorts in course of pain and function could not be explained by the effect of time or of progression of joint damage on pain and function.

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Dynamic Stereo X-Ray Evaluation of Knee Joint Mechanics During Downhill Walking in Subject with Knee Osteoarthritis. Shawn Farrokhi, Carrie A. Rainis, G. Kelley Fitzgerald and Scott Tashman. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Altered tibiofemoral (TF) joint kinematics and joint surface interactions have been linked with development and progression of knee osteoarthritis (OA). However, accurate in-vivo investigations of the TF joint mechanics in patients with knee OA have been difficult to perform due to limitations of conventional techniques. This study sought to accurately characterize TF joint kinematics and the interactions of the articulating joint surfaces using high-speed dynamic stereo x-ray (DSX) technology during the loading phase of downhill walking in older adults with and without knee OA.

Methods: Eleven subjects with knee OA and 10 subjects without OA participated in this study. Subjects with knee OA were included if they demonstrated a Kellgren and Lawrence radiographic OA severity of at least grade II or higher. High speed DSX images were acquired during the loading phase of a moderately declined walking condition (7% grade, 0.75 m/s) on an instrumented treadmill. Computerized tomography images were also taken to create subject-specific 3D bone models of the distal femur and proximal tibia. A previously validated model-based tracking algorithm was employed to determine 3D joint motion by matching the radiographic images with projections through the volumetric bone models. The anterior/posterior (AP) and medial/lateral (ML) positions of the TF joint contact points were estimated using the distance-weighted centroids of the region of closest bony proximity in both the medial and lateral TF compartments. ML and AP contact path lengths were determined by subtracting the minimum from the maximum AP and ML contact positions. In addition, the total contact path was determined as the algebraic summation of the ML and AP translations of the contact points in each compartment.

Results: Compared to the control group, subjects with knee OA contacted the ground with more knee flexion but moved through less flexion range of motion. Conversely, subjects with knee OA moved through more knee adduction range of motion despite contacting the ground with a near neutral frontal plane knee alignment. Additionally, the OA group demonstrated longer ML and total contact path lengths for the medial TF compartment and a longer ML contact path for the lateral TF compartment. rate of OA progression. Intervention strategies to improve knee flexion during loading while limiting excessive frontal plane motion and joint translations should be considered.

Table 1. Means and standard deviations for subject demographics, knee joint kinematics and tibiofemoral compartment contact path translations during the loading phase of downhill gait.

	Control (n = 10)	OA (n = 11)
Age (years)	67.8 ± 5.1	69.6 ± 8.0
Sex (% female)	60%	72%
BMI (Kg/m²)	25.0 ± 2.2	30.4 ± 5.3*
Knee Flexion		
Position @ Heel Contact (degrees)	0.01 ± 3.8	7.7 ± 8.7*
Total Joint Excursion (degrees)	10.2 ± 5.1	7.0 ± 4.5*
Knee Adduction(−)/Abduction(+)		
Position @ Heel Contact (degrees)	0.5 ± 3.6	−0.6 ± 8.3
Total Joint Excursion (degrees)	0.9 ± 0.4	2.0 ± 1.6*
Knee External Rotation (−)/Internal Rotation (+)		
Position @ Heel Contact (degrees)	−2.2 ± 5.9	−1.4 ± 9.3
Total Joint Excursion (degrees)	4.3 ± 2.0	4.1 ± 2.6
Medial Compartment Contact Path		
Anterior/Posterior Distance (mm)	3.0 ± 1.9	4.2 ± 2.6
Medial/Lateral Distance (mm)	0.4 ± 0.3	1.3 ± 1.4*
Total Distance (mm)	4.0 ± 1.9	6.2 ± 2.9*
Lateral Compartment Contact Path		
Anterior/Posterior Distance (mm)	3.5 ± 2.4	2.9 ± 1.6
Medial/Lateral Distance (mm)	0.6 ± 0.3	1.2 ± 0.9*
Total Distance (mm)	4.2 ± 2.6	4.6 ± 2.0

*Statistically significant differences ($p < 0.05$)

Conclusion: Consistent with previous reports, subjects with knee OA contacted the ground with more knee flexion. However, findings from this study further suggest that individuals with knee OA also move through less knee flexion range of motion which can adversely affect shock absorption. Additionally, individuals with knee OA demonstrated signs of frontal plane TF joint instability (excessive adduction motion and ML translation) and a longer medial TF compartment translation which can negatively impact the

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Different of Patterns Knee Pain Trajectories: Longitudinal Data From the Osteoarthritis Initiative (OAI). Joseph Devich Jr.[1], Michael J. Hannon[2], Zhijie Wang[2], Robert M. Boudreau[3] and C. Kent Kwoh[4]. [1]UPMC Shadyside, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA

Background/Purpose: Knee osteoarthritis (KOA) is one of the most common forms of arthritis and the most common cause of disability among the elderly. Knee pain is the presenting symptom of KOA, and symptomatic knee KOA is defined as "frequent knee pain" (pain on most days of at least one month in the past 12 months) and radiographic KOA. There is little data, however, on changes in knee pain over time. The purpose of this study was to identify whether there were different patterns of knee pain trajectories over four years of follow-up using data from the Osteoarthritis Initiative (OAI).

Methods: We studied 7,543 knees from OAI from baseline to 48 months (OAI public use data sets 2.1 and 2.2). Knee pain trajectories were based on the following knee pain reports at each visit: "No Pain" (no pain or aching in the past 12 months)=0, "Some Pain" (pain but not frequent pain)=1, or "Frequent Pain" (as above)=2. Unchanging subgroups had knees with same pain report at each visit: Group 1a, always 0; Group 1b, always 1; and Group 1c, always 2. Worsening subgroups had knees with consistent progression to worse pain: Group 2a for knees going 0-->(1)-->2; Group 2b 1-->2; and Group 2c 0-->1. Improving subgroups had knees with consistent progression to less pain: Group 3a for knees going from 2-->(1)-->0; Group 3b 2-->1; and Group 3c 1-->0. Fluctuating knee pain patterns (i.e., alternating between 0, 1 or 2 from visit to visit) were excluded from this analysis. To reduce the chances that a fluctuating knee was misclassified, for the worsening and improving subgroups, knees had to have two time points at the initial level of lower/higher pain or two time points at the final lower/higher level, respectively. Knee-specific WOMAC pain scores across the five visits were compared within each knee pain group using GEE (STATA 11.2) with each model adjusted for age, sex, race, educational level, depression, hand OA, and BMI. Subgroups within a group that were not distinct from each were combined. Comparison of differences between the larger subgroups was then performed.

Results: Group 1a and Group 1b, Group 2a and Group 2b, Group 3a and Group 3b were no different from each other (p-values > 0.1). Each of these pairs was then collapsed into three respective subgroups. The results between remaining subgroups are summarized in Table 1 below. There were significant differences in the adjusted mean WOMAC pain scores at each OAI visit between the referent group (i.e., unchanging no/some pain) and the unchanging frequent pain subgroup, the worsening pain subgroups and the improving pain subgroups.

Table 1. Comparisons of Adjusted Mean WOMAC Pain Scores of the Knee Pain Trajectories

Knee Pain Frequency	Baseline	M12	M24	M36	M48	P for change over time between groups
Unchanging Pattern						
Always 0 (n = 717) or Always 1 (n = 434)	3.2055*	2.2147	2.4398	2.4167	2.2598	reference
Always 2 (n = 606)	28.5385*	28.1584*	29.8006*	29.7471*	29.1578*	0.332, 0.004, 0.001, 0.031
Worsening Pain						
0→(1)→2 (n = 200) or 1→2 (n = 231)	9.2034*	10.374*	12.1654	14.7872*	17.5806*	< 0.001 all time points
0→1 (n = 316)	2.3465*	1.788	2.3214	3.2002	4.1065*	0.247, 0.146, < .001, < .001
Improving Pain						
2→(1)→0 (n = 171) or 2→1 (n = 291)	15.8499*	12.7436*	11.5562	9.2976*	7.3585*	< 0.001 all time points
1→0 (n = 220)	4.4188*	2.3249	2.1787	1.3796	0.7486	0.005, < .001, < .001, < .001

*Different at $p < .05$ from all other groups, Tukey pairwise adjustment.
Where:
0 = "No Pain"
1 = "Sometimes Pain"
2 = "Frequent Pain"

Conclusion: We have been able to define distinct knee pain trajectories of unchanging, worsening and improving knee pain. Further work is underway to better characterize these groups. Better understanding of these knee pain trajectories may help to identify subgroups to target for specific interventions.

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Prevalence of Symptomatic Basilar Thumb Joint Osteoarthritis in the General Population. Jennifer Moriatis Wolf[1], Aleksandra Turkiewicz[2], Isam Atroshi[3] and Martin Englund[2]. [1]University of Connecticut Health Center, Farmington, CT, [2]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [3]Lund University, Hässleholm, Sweden

Background/Purpose: While the radiographic prevalence of basilar thumb osteoarthritis (OA) is well described, little is known about whether this translates to clinically symptomatic arthritis. The purpose of this study is to determine the prevalence of physician-diagnosed thumb carpometacarpal (CMC) arthritis.

Methods: Using healthcare register data from Skåne County, in southern Sweden (predominantly Caucasian population 1.3 million), we identified all adults aged 20 years or older who consulted a physician at least once and were given a diagnosis code for OA of the first CMC joint (ICD-10 code M18). Data were analyzed over the 13-year period between 1999 and 2011. Using cross-referencing with the Swedish population register to exclude subjects who were deceased or had relocated out of the county by end of year 2011, we obtained frequencies and point prevalence estimates by age and gender. The population was reduced with 20% to compensate for the loss of patients seen by the private care practitioners exclusively (ICD-10 codes partially forwarded to the register).

Results: The point prevalence of physician-diagnosed symptomatic OA of the basilar thumb joint in adults was estimated to 1.3% overall (2.0% in women and 0.57% in men). The prevalence peaked in women aged 65–74 with prevalence of 5.3%. The corresponding peak in men was in men aged 75–84 with a prevalence of 1.7%.

Conclusion: In a well-defined population, the clinically important prevalence of basilar thumb OA is substantially higher in women than men, with peak prevalence in women between 60–79 years of age. Thumb base OA can have a large impact on function and activities of daily living, and the high prevalence in elderly women and men is a health and economic concern in an aging population.

Women / Men — Prevalence (%) by Age group (35-44, 45-54, 55-64, 65-74, 75-84, 85+)
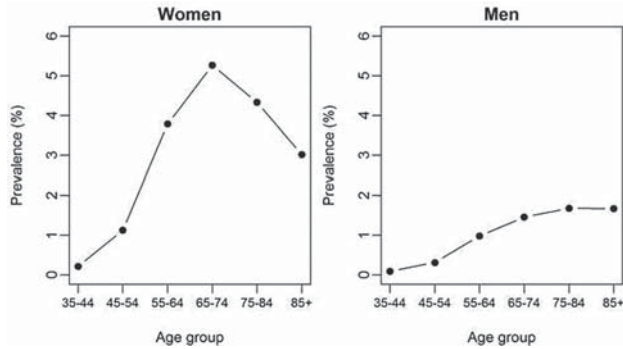
Disclosure: J. M. Wolf, None; **A. Turkiewicz**, None; **I. Atroshi**, None; **M. Englund**, None.

1130

The Effect of Age On the Number of Osteoarthritis Flares with Continuous Versus Intermittent Celecoxib Treatment. George H. Sands. Pritha Bhadra and Margaret Noyes Essex, Pfizer, Inc, New York, NY

Background/Purpose: Continuous nonsteroidal anti-inflammatory drug (NSAID) treatment is significantly more efficacious than intermittent dosing[1] during 22-weeks in preventing flares in patients with osteoarthritis (OA) of the knee or hip who have successfully treated an initial flare. The objective was to characterize the effect of age on efficacy, as measured by the number of flares, of continuous daily celecoxib treatment versus intermittent celecoxib treatment.

Methods: An exploratory analysis of a multinational, randomized clinical trial[1]was conducted to determine if the number of OA flares during the blinded postrandomization period was different for patients aged $<$ or $\geq$ 60 years. In the trial, 858 patients aged 18 to 80 years with OA of the knee or hip, meeting American College of Rheumatology criteria, were randomized to receive celecoxib 200 mg qd either as "continuous" (daily) or "intermittent" (celecoxib 200 mg qd when needed to treat OA flare meeting predefined criteria) treatment. Analyses were performed on the intention-to-treat (ITT) population ($\geq$ 1 dose of study medication post-randomization) and flare-modified ITT population (all patients meeting criteria for ITT population plus having flare durations $\leq$ 14 $+$ 2 days), using a 2-sided type I error rate of 0.05.

Results: Mean ages were 51.3 and 67.2 years in the 2 continuous treatment groups (n = 236 and n = 195, respectively) and 51.2 and 66.7 years in the 2 intermittent treatment groups (n = 220 and n = 207, respectively). For patients aged $<$ 60 years, 0.50 flares/month (SD 0.60) were reported in the group receiving continuous treatment, while 0.89 flares/month (SD 0.98) were observed in those receiving intermittent treatment ($P < 0.0001$). For patients aged $\geq$ 60 years, the continuous treatment group had 0.59 flares/month (SD 0.87) compared with 0.97 flares/month (SD 1.04) in the intermittent group ($P < 0.0001$). These results are consistent with the primary results.[1]

In the flare-modified ITT population, patients aged $<$ 60 years receiving continuous treatment had 0.45 flares/month (SD 0.61) vs 0.87 flares/month (SD 1.15) for the intermittent group ($P < 0.0001$). The older flare-modified ITT population ($\geq$ 60 years) had similar results: 0.55 flares/month (SD 1.02) vs 1.02 flares/month (SD 1.22) for the continuous and intermittent groups, respectively ($P = 0.001$). The mean number of flares was significantly lower in the continuous group than in the intermittent group irrespective of whether the patients were aged $<$ or $\geq$ 60 years.

Conclusion: Daily celecoxib treatment was significantly more efficacious, as assessed by the number of flares/month, than intermittent use, irrespective of whether the patients were aged $<$ or $\geq$ 60 years. These data may be useful in considering the treatment of OA patients aged $\geq$ 60 years.

Reference
1. Strand V, et al. *J Rheumatol.* 2011;38:2625-34.

Disclosure: G. H. Sands, Pfizer Inc, 3; **P. Bhadra**, Pfizer Inc, 3; **M. Noyes Essex**, Pfizer Inc, 3.

1131

Intraarticular Infliximab for Knee Osteoarthritis: High Baseline Levels of Synovial Cellularity and High MRI Cartilage Injury At the Lateral Tibial Plateau Predict Improvement in Total WOMAC Score.
Jeremy R. Schue[1], Ossama Tawfik[1], Rebecca Bolce[2], Donald D. Smith[1], Gary Hinson[1], Jo A. Wick[1] and Herbert B. Lindsley[1]. [1]Kansas University Med Ctr, Kansas City, KS, [2]Crescendo Bioscience Inc., South San Francisco, CA

Background/Purpose: Synovial tissue from patients with OA often demonstrates inflammation. We hypothesized that a single intraarticular (IA) injection of an anti-TNF drug would decrease inflammatory cell infiltration (primary outcome) and ultimately reduce articular injury. These data were drawn from the infliximab (IFX) group, part of a larger study presented previously (ACR Ann Mtg, Chicago 2011; EULAR Ann Mtg, Berlin 2012). The results noted below represent new findings.

Methods: The original pilot study was a single center, 2:1:1 (IFX: MP:P) randomization, double-blind, placebo-controlled IA treatment of knee OA: infliximab (IFX) 100 mg, methylprednisolone (MP) 80 mg or saline (P) on Day 0. Subjects (n=16) had to have knee pain and show minimal to moderate OA on knee radiographs. Demographics for IFX group: Age 54 (IQR 44–62) Race AA/C=3/5; Gender F/M=5/3; BMI 28.9 (IQR 23.1–31.4). Closed needle synovial biopsies and PBMCs for flow cytometry were obtained on Days 0 and 28. Total WOMAC scores and blood samples were obtained on Days 0, 14, 28 and 56. MRI of the target knee was obtained before Day 0. Statistics: nonparametric Wilcoxon test and Spearman correlation coefficient.

Results: Total WOMAC score improved significantly only for Group IFX, comparing baseline (BL) to Day 56 (p<0.05). The BL total WOMAC scores were greater in the high vs low cellularity subgroups. When comparing subjects with high vs low cellularity (4 each), significant improvement (p<0.05) occurred only in the high cellularity subgroup (See Fig). The high cellularity subgroup had higher scores (p<0.02) for inflammatory intensity, mononuclear cells (CD68+ cells, CD3+ cells), blood vessels, Cox-2 expression and IL-1β expression. No significant baseline differences between the high and low subgroups were noted for synovial TNFα, IL-6, IL-17, or CD54+ cells, or serum levels of CRP, SAA, IL-6, TNFα, MMP-3 or COMP. BL PBMC biomarkers were compared for differences between high and low cellularity subgroups; two cell subsets trended higher (p=0.097) in the high cellularity subgroup: B cells and low-MFI CD14 CXCR3 monocytes. Higher BL Total WOMAC scores correlated with lower CD14 MFI (p=0.067, R=-0.67); no such correlation was noted with TNFα, MMP-3 or COMP. Circulating levels of IFX peaked at Day 4 with a Cmax of 6.1 ug/ml in 6 subjects; two subjects with detectable anti-IFX Ab had a lower Cmax of 1.6 ug/ml; Cmax did not differ between the two subgroups (5.5 vs 4.3 ug/ml).

WOMAC Total vs Study Day (0, 14, 28, 42, 56) for High and Low Baseline Cellularity; $P < 0.05$.
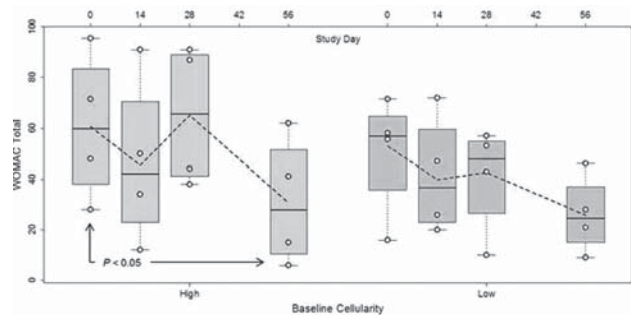
Conclusion: BL characteristics of the subjects responsive to IA anti-TNF therapy included those with higher WOMAC scores, more abnormal cartilage MRI scores at the lateral compartment, and higher levels of inflammatory cells, including T lymphocytes and macrophages, as well as more blood vessels, Cox 2 and IL-1β expression. In subjects with higher WOMAC scores and higher levels of synovial inflammation IA IFX offers promise as a symptomatic intervention.

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Prevalence of Knee Pain in Ultramarathon Runners. Victoria M. Kelly[1], Martin Hoffman[2], Bharathi Lingala[1], Mihoko Bennett[1] and Eswar Krishnan[1]. [1]Stanford University, Palo Alto, CA, [2]Department of Veteran's Affairs, Northern California Health Care System and University of California Davis Medical Center, Sacramento, CA

Background/Purpose: Approximately one in four Americans suffer from frequent knee pain. While some studies have linked long-distance running with the risk for knee pain, others have not observed such associations. Since the proposed mechanism of such a link involves mechanical stress to the joints, greater lifetime running miles should be associated with a greater risk for knee pain and an earlier age of onset. We tested these expectations by cross sectional analysis of data from the baseline questionnaire of a new cohort of ultramarathon runners.

Methods: The ULTRA study is a cohort of runners who have participated in at least one ultramarathon race (≥ 50 kilometers) in their lifetime. This study has been enrolling participants since November 2011. For the purposes of this analysis, "knee pain" was defined as "any knee pain in the past 6 months", as there were almost no individuals with chronic-frequent knee pain in this cohort of high functioning individuals. To assess the impact of mileage on knee pain, we performed a logistic regression model, where the dependent variable was knee pain and independent variables were quartiles of lifetime running distance, age, body mass index (BMI) and current running status. Ex-runners were defined as those who have not run regularly in the preceding 12 months.

Results: Of the 1,083 runners included in the present analysis, 68% were men and 6% were classified as ex-runners. The mean age, and BMI were 44 years and 27 kg/square meters respectively. After adjusting for age, gender and BMI, the prevalence of knee pain was higher in those with lower lifetime mileage, both in runners and ex-runners. Overall rates of knee pain did not differ between runners and ex-runners (47% vs. 48%), and confidence intervals overlapped significantly for knee pain within each mileage group (see Figure). In the logistic regression model, runners in the highest distance quartile (>25,000 miles) were the least likely to report knee pain, OR 0.5 (CI 0.4–0.8), suggesting that lifetime running distance is inversely correlated with knee pain.
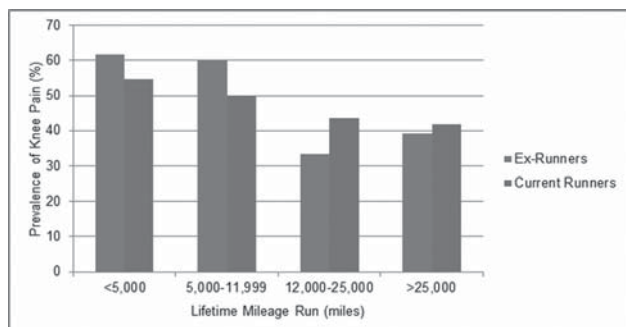
Conclusion: Knee pain was more common among low mileage runners; the causal direction of this association can be ascertained in prospective studies. There was no difference in overall knee pain between current and ex-runners.

Disclosure: V. M. Kelly, None; **M. Hoffman**, None; **B. Lingala**, None; **M. Bennett**, None; **E. Krishnan**, None.

Gait Differences Are Present in Subjects with Symptomatic Vs. Asymptomatic Mild Radiographic Hip Osteoarthritis. Samir S. Chabra[1], Najia Shakoor[2] and Kharma C. Foucher[2]. [1]University of Illinois at Chicago, Chicago, IL, [2]Rush University Medical Center, Chicago, IL

Background/Purpose: It is known that joint mechanics are involved in the hip osteoarthritis (OA) disease process. In a previous study[1], several gait variables were lower in subjects with symptomatic hip OA compared to asymptomatic controls. In the OA subjects gait variables were significantly correlated with radiographic OA severity but not pain. It remains unclear, however, whether structural changes or clinical symptoms initiate the gait changes associated with hip OA. In this study we tested the hypothesis that gait variables are different in people with symptomatic radiographic hip OA compared to those with radiographic changes but no symptoms.

Methods: 25 subjects with mild radiographic hip OA (Kellgren-Lawrence grade 2) were identified from an IRB approved repository of gait and radiographic data. 12 had been enrolled in a study of subjects with symptomatic unilateral hip OA and 13 came from a database of asymptomatic subjects. Demographics and BMI were similar between the two groups (Table). Gait analysis was performed with standard published methods: participants completed 3 trials per limb walking at a self-selected normal speed. Kinematics and kinetics were calculated from marker positions and ground reaction forces. Standard inverse dynamics methods were used. The variables of interest were speed, dynamic hip range of motion, and peak 3D external moments normalized to body weight times height (%BWxHt). Data were averaged for the 3 trials. T-tests were used to compare gait variables between the two groups.

Results: Walking speeds were not significantly different between the two groups (Table). The peak adduction and internal rotation moments were 17% and 29% lower in the symptomatic OA group compared to the asymptomatic group (p=0.017 and p=0.044, Table). The external rotation moment was 26% lower in the symptomatic group (*trend* p=0.059). No other comparisons were statistically significant.

Table. Comparisons between subjects with mild radiographic hip OA who are symptomatic vs. asymptomatic

Variable	Symptomatic	Asymptomatic	p Value
Age (years)	53 ± 6	58 ± 10	0.166
BMI (kg/m²)	26 ± 3	28 ± 5	0.198
Sex	9 Female/3 Male	11 Female/2 Male	0.548
'Normal' walking speed (m/s)	1.16 ± 0.20	1.20 ± 0.11	0.615
Dynamic sagittal plane hip range of motion (degrees)	29.2 ± 7.4	30.8 ± 6.3	0.568
Peak Flexion Moment (%BW × Ht)	5.15 ± 1.48	5.85 ± 1.30	0.221
Peak Extension Moment (%BWxHt)	2.37 ± 0.61	2.64 ± 0.99	0.427
*Peak Adduction Moment (%BWxHt)	**3.53 ± 0.84**	**4.27 ± 0.60**	**0.017**
Peak Abduction Moment (%BWxHt)	1.84 ± 0.81	2.05 ± 1.02	0.587
*Peak Internal Rotation Moment (%BWxHt)	**0.53 ± 0.19**	**0.75 ± 0.29**	**0.044**
Peak External Rotation Moment (%BWxHt)	0.44 ± 0.13	0.60 ± 0.26	0.059

* bold text indicates p<0.05.

Conclusion: Subjects with mild *symptomatic* radiographic hip OA had different gait than subjects with mild radiographic OA alone. Notably, walking speeds were similar between groups. Thus gait differences observed were not attributable to slower speeds in the symptomatic group. The adduction, internal rotation, and external rotation moments, which each reflect aspects of hip abductor function, were reduced in the symptomatic group. This suggests that this muscle group plays an important role in early symptomatic OA. Further, these results support previous speculations that pain may be an initial stimulus that initiates joint loading alterations in hip and knee OA[1,2].

References
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Disclosure: S. S. Chabra, None; **N. Shakoor**, None; **K. C. Foucher**, None.

What Are the Levels of Physical Activities and Their Associations with Quality of Life in Patients with Symptomatic Hip and/or Knee Osteoarthritis? Irawati Lemonnier[1], Anne Vuillemin[2] and Anne-Christine Rat[3]. [1]Lorraine Université Paris Descartes University, EA 4360 Apemac, Nancy, France, Nancy, France, [2]Universite de Lorraine, Paris Descartes University, EA 4360 Apemac, Nancy, France, Nancy, France, [3]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F- 54 000, Nancy, France

Background/Purpose: Physical activities (PA) practice is recommended by numerous public health organizations. According to international recommendations, patients with hip and knee osteoarthritis (OA) should be encouraged to undertake more specific activities: regular aerobic, muscle

strengthening and range of motion exercises. However, the level of PA practice in patients with symptomatic hip and/or knee OA in a real setting is not well known and associations between PA practice and quality of life (QoL) should be clarified. The aim of the study was to study 1.the level of PA practice in patients with symptomatic hip and/or knee OA in a real setting 2. the associations between PA practice and QoL in patients with symptomatic hip and/or knee OA.

Methods: The 878 patients of the KHOALA (Knee and Hip Osteo-Arthritis Long term assessment) cohort were included in the study. KHOALA cohort is a multiregional population based study of patients aged 45–75 years with symptomatic knee or/and hip OA. The MAQ (modifiable activity questionnaire) was used to measure the PA during the past year. It includes 2 scores: the numbers of hours spend weekly for physical activities in leisure activities (PAL) and in professional activities (PAP). QoL was measured by a generic questionnaire, the SF-36; pain, function, and clinical data by the Index of Severity for Knee (ISK) and the Harris hip score. All measures were completed at baseline. Multivariate linear-regression models were constructed to identify the associations between PA and QoL. The models were adjusted on OA functional and pain scores, age, sex, BMI, current smoking status, current employment status and occupation during their life.

Results: Among the 878 patients, 222 had hip OA, 607 knee OA and 49 both. Patients with hip and knee OA were slightly older (64.7+8) than those with knee (62+8.5) or hip OA only (61.2+8.8). The average body mass index was 26.9+4.4 and 30.3+6.2 for patients with hip and knee OA respectively. 67 and 71% of the patients were women in hip and knee OA respectively. The level of PAP was of 25 hours a week in patients with hip or knee OA only and was lower (20 hours a week) in patients with both hip and knee OA. The level PAL was of 5.6, 6.2, 6.5 hours a week for hip OA, knee OA and both respectively. No relation was observed between physical activities level and QoL in patients with hip OA. For patients followed for knee OA, more hours spend on leisure activities were associated with better mental health (p=0.001), role emotional (p=0.02), social functioning (p=0.04) and vitality (p<0.001) scores in multivariate analyses. The number of hours spent on professional activities by patients who suffered from both hip and knee OA were associated with lower role emotional (p=0.03) and social functioning (p=0.04) scores.

Conclusion: These results suggest that more hours spend weekly on leisure activities may positively affect patients with symptomatic knee and/or hip OA independently of pain, function and sociodemographic variables. The associations are found for mental state and social functioning. On the other hand, physical activities for professional reasons seemed to be associated with more difficulties in social functioning of patients with both hip and knee OA.

Disclosure: I. Lemonnier, None; **A. Vuillemin**, None; **A. C. Rat**, None.

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Combined Glucosamine and Chondroitin Sulfate, Once of Three Times Daily, Provide Clinically Relevant Analgesia in Knee Osteoarthritis. Jose R. Provenza[1], Samuel K. Shinjo[2], Joyce M. Silva[3], Carla RGS. Peron[4] and Francisco AC Rocha[5]. [1]Pontifícia Universidade Católica de Campinas, Campinas, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Sao Paulo, Brazil, [4]Laboratórios Aché Ltda, Sao Paulo, Brazil, [5]Federal University of Ceara, Fortaleza, Brazil

Background/Purpose: The analgesic efficacy of combined glucosamine and chondroitin sulfate (CS) in knee osteoarthritis (OA) remains controversial. Criticism to previous studies includes small sample size, short term evaluation and lack of intent-to-treat (ITT) analysis. Glucosamine sulfate (GS) or hydrochloride (GH) formulations and dosing schedule relevance are also not clearly defined.

Methods: 1,120 subjects with radiographic knee OA (Kellgren/Lawrence grades 2–3) and moderate-severe knee pain flare after analgesic washout were randomized (1:1:1) at 16 centers in Brazil to receive GS 500mg/CS 400mg three times daily capsules (GI) or once daily sachet (GII), or GH 500mg/CS 400mg three times daily capsules (GIII) for a 16 week trial. Acetaminophen up to 3,750mg daily was a rescue medication. Primary outcome (ITT) was patient reported pain intensity in the affected knee and variation of Lequesne's index (LI) at 16 weeks. Monthly secondary outcomes were mean changes from baseline in patient reported pain and LI, patient and physician global assessments of disease activity, acetaminophen consumption, and adherence. Sample size calculation considered a non-inferiority evaluation allowing a difference of less than 1.7 points in the LI and a decrease of pain less than 18mm in GI and GII, as compared to GIII. Safety evaluations were done at each monthly visit.

Results: The ITT population comprised 302, 301, and 306 patients in GI, GII and GIII, respectively, and 911 patients for safety. Demographic data were equally comparable in all groups. The criterion for non-inferiority analysis of GI and GII in relation to GIII, based on confidence interval (95%), was met for pain intensity and LI. The mean of pain reduction (GI: −30.9±1.5; GII: −28.7±1.5; GIII: −29.7±1.5 mm) was significant for all groups at week 16 (P<0.001). Similarly, the mean of LI decrease was significant in all groups (GI: −3.8±0.2; GII: −3.7±0.2; GIII: −3.9±0.2) (P<0.001). Moreover, reduction of acetaminophen consumption (−5, −3, and −5 weekly tablets for GI, GII, and GIII, respectively) was also significant in all groups (P<0.005). Withdrawal rate was 18.2%, 19.3%, and 19.3% for GI, II, and III. Patients that did not complete the study were 77 (44.8%) for lack of adherence, 16 (9.3%) consent withdrawal, 11 (6.4%) adverse events, 8 (4.7%) lost to follow-up, and 17 (9.9%) for other causes.

Conclusion: This is the largest study showing that GS/CS and GH/CS provide clinically meaningful and sustained analgesia in knee OA regardless of dose fractionation. GS/CS (capsule or sachet) and GH/CS formulations are equally effective and safe to treat symptomatic knee OA.

Disclosure: J. R. Provenza, None; **S. K. Shinjo**, Federico Foundation, 2; **J. M. Silva**, None; **C. R. Peron**, None; **F. A. Rocha**, None.

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Aesthetic Dissatisfaction in Hand Osteoarthritis Patients, Its Impact and Risk Factors. R. Liu, L.J.J. Beaart-van de Voorde, T.W.J. Huizinga and M. Kloppenburg. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Hand osteoarthritis (HOA) leads to aesthetic damage and is rarely studied. We aim to investigate in HOA patients the prevalence of dissatisfaction with the appearance of their hands, the impact and its risk factors.

Methods: Cross-sectional data were used of the ongoing HOSTAS (Hand OSTeoArthritis in Secondary care) study, in which consecutive patients are included, that are diagnosed by the treating rheumatologist with primary HOA. Participants underwent physical examination to assess number of joints with bony joint enlargements (0–30), deformities (0–22) and limitation in mobility (0–22).

The Michigan Hand Outcomes (MHQ) questionnaire involves a pain (range 0–100, higher scores=more pain) and an aesthetic scale, which measures satisfaction (range 1–5, lower scores=more dissatisfaction) with the appearance of the hands and its impact, namely discomfort in public, depression and/or the interference with normal social activities (range 3–12, lower scores = more impact). A score of <3 was considered as dissatisfaction and a score of <9 as experiencing impact. Scores for right and left hand were averaged.

Disability was assessed by the functional index for HOA (FIHOA) (0–30). Anxiety (0–21), depression (0–21) and illness perceptions were assessed with the Hospital Anxiety and Depression scales (HADS) and Illness Perception Questionnaire (IPQ), respectively.

Odds Ratio (OR) with 95% confidence intervals (CI) were calculated using multivariate logistic regression as measures of relative risk for reporting dissatisfaction with appearance or impact due to dissatisfaction of the appearance, adjusted for age, sex and BMI.

Results: Of 226 patients (87% women, mean age 61.5 yrs, median symptom duration 5.2(range 0.1– 58.7) yrs) 93% met ACR criteria for HOA. 25% were aesthetically dissatisfied and only 4% reported impact due to dissatisfaction. Mean pain score was 44 (SD 19) and median FIHOA score was 8 (range 0–24). Median depression and anxiety scores were 4 (range 0–18) and 2 (range 0–17), respectively.

Pain (OR 1.02 (1.00–1.04)), disability (OR 1.07 (1.01–1.12)), deformities (OR 1.24 (1.11–1.37)), number of joints with limitation in mobility (OR 1.05 (1.01–1.08) and the illness perception scale which involves negative feelings towards OA (OR 1.08 (1.02–1.15)) were associated with dissatisfaction, as well as with impact.

Bony joint enlargements (OR 1.09 (1.01–1.17)) and illness perception (belief in OA as a chronic disease) (OR 1.12 (1.01–1.23)) were associated with dissatisfaction, but not with impact.

Depression (OR 1.32 (1.13 –1.55)), anxiety levels (OR 1.37 (1.14 –1.64)) and illness perceptions (the belief in more severe consequences as a result of OA, less understanding of OA and attributing more psychological factors to their disease) were associated with impact.

Conclusion: HOA patients who consult secondary care report regularly aesthetic dissatisfaction with their hands. However, this dissatisfaction has negative impact only in a small group of patients, who also experiences more

pain, depression and anxiety and negative illness perceptions. These results have implications for management strategies in patients with HOA.

Disclosure: **R. Liu**, None; **L. J. J. Beaart-van de Voorde**, None; **T. W. J. Huizinga**, None; **M. Kloppenburg**, None.

1137

Clinimetric Properties of a New Outcome Measure: the Hand-Osteoarthritis Aesthetic Damage Index. N. Bellamy and Joan Hendrikz. The University of Queensland, Herston, Queensland, Australia

Background/Purpose: The 2006 OARSI Guidelines for hand OA clinical trials, recognised the potential value of an aesthetic damage assessment, but acknowledged the absence of any existing instrument to perform the measurement. In order to address this deficiency, a measure termed the Hand-Osteoarthritis Aesthetic Damage Index(HADIX) has been developed and its clinimetric properties explored. HADIX is a hexadimensional, Patient Reported Outcome Measure (PROM) of the aesthetic impact of hand OA (HADIX 1–6).

Methods: This study forms part of a larger longitudinal initiative involving clinical profiling, digital photography and radiography. The development of HADIX has been reported previously (1). In the current study, test-retest reliability (TRR) and construct validity of re-test HADIX data (except HADIX 4 which is a relative measure) using the Michigan Hand Outcomes Questionnaire - MHOQ, were evaluated using Pearson's rho or Kendall's tau-b. Time to completion was also examined.

Results: The study involved 28 subjects with hand OA 25 females and 3 males), who fulfilled the Altman Criteria for hand OA, with mean age last birthday70 yrs (min = 52 yrs; max = 87 yrs; SD = 9.5). TRR correlation coefficients were: HADIX1 = 0.89: HADIX2 = 0.77: HADIX3 = 0.86: HADIX4 = 0.68: HADIX5 = 0.76: HADIX6 = 0.87. Correlations between the re-test HADIX and MHOQ scores were HADIX1 = 0.55: HADIX2 = 0.52: HADIX3 = 0.44: HADIX5 = 0.72: HADIX6 = 0.45. Mean time to completion for HADIX on first presentation was 8.6 mins (min = 2.33 mins; max = 22.22 mins; SD = 4.57 mins). On the second occasion information was available for 5 patients who were 34 seconds faster on average.

Conclusion: HADIX provides a novel approach to the evaluation of the aesthetic impact of hand OA. These observations suggest that the HADIX Index is reliable, valid and feasible, and may have a role in the evaluation of structure modifying interventions in hand OA.

(1) Bellamy N. Osteoporosis International 2012;23(Suppl 2):S60.

Disclosure: **N. Bellamy**, None; **J. Hendrikz**, None.

1138

Nonpharmacologic and Pharmacologic Therapy Utilization by Primary Care Providers for Hand Osteoarthritis-Comparative Review by Electronic Health Record Data Mining and in-Home Visit Verification. Gale A. McCarty, President. Rheum.Ed Consulting, Harborside, ME

Background/Purpose: To compare current utilization of usual nonpharmacologic (NP) and pharmacologic (P) therapies for hand osteoarthritis (OA) by primary care providers (PCPs) and patients (Pts) based on American College of Rheumatology (ACR) 2012 Recommendations in 2 age- and gender-matched populations.

Methods: From voluntary in-home health visit (problem list, history, exam, medication reconciliation) with electronic health record assessment over 3 yrs for ascertainment of Medicare Advantage general health maintenance and quality benchmarking (Cty 1-Sacramento County CA, N = 50, and Cty 2-Cumberland County ME, N = 50), age- and gender-matched pts were identified. Pts were unaware the examiner was a rheumatologist. Discussion vs. Use vs. Source (PCP or pt) of NP recommendations (Activities of Daily Living, ADLs/Jt Protection/Assistive Device Provision for ADLs/Thermal Modalities/TrapezioMCP Splints) and P recs (Top. Capsaicin/Top. NSAIDs/PO NSAIDs/Tramadol) were queried. Descriptive statistics and/or SPlus were used where applicable: p value significance was $</=$ 0.05.

Results: Results: Behavior Risk Factor Surveillance System 2009/10 data confirmed no significant differences (nsd) from Cty 1 vs Cty 2 in: population (281,674 vs 265,012), % pop. > 65 (10.6 vs 11.2%), white ethnicity (78% vs 80%), female gender (70 vs 72%), mean age (72.4 vs 74.1 yrs-range 65–98), no. of pts. w/doctor-diagnosed arthritis b/w ages of 65 and 74 (45 vs 53%), no. of pts. w/activity limitation due to arthritis (48 vs 44%), no. of pts w/social participation restriction due to arthritis (17 vs 14%), no. of pts w/severe pain due to arthritis-non-site specified (27 vs 21%), obesity by BMI (32 vs 33%), the no. of Rheumatologists available for referral in network (6 vs 7), and the % of benchmarks attained for major health metrics (96 vs 95% capture). Latino ethnicity was statistically different (16.6 vs 1.9%). No significant differences from Cty 1 vs Cty 2 were noted for: Dx of OA-Hands (88 vs 92%); all had discussed OA as an issue with their PCPs at least once in the prior 3 yrs. Presence of hand OA was confirmed by Rheumatology exam in 88 vs 92% of pts. At least 1 NP Rec (Thermal Modalities) and 1 P Rec (Top NSAIDS) had been discussed at least once for all pts. by PCPs (100 vs 100%), but utilization was significantly different (44 vs 22%). Jt Protection and ADLs had not been discussed or utilized (80 vs 80%); only Assistive Device Provision (cane/walker) had been done (33 vs 30%). PO NSAIDs were actively discouraged even in low dose/Cox2 selective/H2 blocker usage by providers (80% vs 80%).

Conclusion: Current NP and P recommendations from OA experts are variably implemented with pts, despite confirmed presence of OA by their own PCPs as an Active Problem, and pts. reporting pain and social restriction due to arthritis.

Disclosure: **G. A. McCarty**, None.

ACR/ARHP Poster Session B
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Inhaled Nitrous Oxide Facilitates Access to Intra-Articular Corticosteroid Injections in Children with Juvenile Idiopathic Arthritis. Mercedes O. Chan[1], Ruth Wyllie[2] and H. E. Foster[3]. [1]University of British Columbia and British Columbia's Children's Hospital, Vancouver, BC, [2]Newcastle Hospitals, NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom, [3]Newcastle Hospitals NHS Foundation Trust, Great North Children's Hospital and Newcastle University, Newcastle Upon Tyne, United Kingdom

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood affecting 1 in 1000 children. Medical management for arthritis often includes intra-articular corticosteroid injections. The inhalation of nitrous oxide (N_2O) in painful procedures is widely recognised in adults, yet is underused in children and young people (CYP). N_2O is quickly absorbed, having low solubility in water and fat, and rapidly eliminated from the body when inhalation stops. It is safe, fast-acting, and non-invasive, reducing apprehension and anxiety. The use of N_2O has increased access for CYP requiring painful procedures such as joint injections (JIs) that may have previously required a general anaesthetic. We aimed to describe a population of children receiving JIs with N_2O at our center and the wait time for JIs with N_2O once a decision to inject was made.

Methods: Data was collected retrospectively from available charts of children receiving JIs with N_2O from January 2002 to April 2012 at our centre. Demographics, number of JIs (including types of joints injected), and number of repeat JIs within a year were recorded. Time from decision point (DP) to JI was calculated for JIs performed in 2011–2012.

Results: 397 JIs with N_2O on 292 occasions (140 males, 152 females) were performed from 2002–2012. The median age at time of JI was 13.78 (range 6.38 to 18.97 years). The median number of JIs performed with N_2O per year was 24 (range 14–53). On 48 occasions JIs were performed subsequent to one done earlier that calendar year. The median number of repeat JIs per patient requiring them was 1.

From 2011–2012, 79 JIs were performed with N_2O. The median number of days from a DP to a JI with N_2O was 0 (range 0–87 days). 62 patients had JIs within 2 weeks; 11 between 2 and 4 weeks; 2 between 4 to 6 weeks; and, 3 after 6 weeks from DP. One patient receiving a JI after 6 weeks (87 days) from DP required imaging to confirm synovitis before proceeding with the procedure. Reasons for other JIs performed after 6 weeks from DP were unable to be elicited from charts. Documentation of a DP for JIs with N_2O was present in 77/79 patients (97.5%).

Joints most commonly injected were: knees (80.05%), ankles (14.4%), elbows (3.28%), wrists (1.26%), subtalar (0.5%), fingers (0.31%) and shoulders (0.20%). There were no major adverse events (including septic arthritis) reported. An increase in trainee procedures was seen after 2009 consistent with the introduction of a paediatric rheumatology (PRh) training program.

Conclusion: Use of N_2O for JIs in children with JIA allows for expeditious, safe and efficient sedation and analgesia. At our centre, children assessed in clinic and who need JIs may be offered one at that visit, performed by the PRh team (clinician and nurse specialist). This has benefits for clinical care (rapid access to the procedure); the patient and family (less time off school/college or work, no anaesthetic risk); health care costs (reduced need for day case access and theatre time); and, optimal use of resources (preferential access to general anaesthetic lists for younger children; or those requiring multiple JIs or use of image intensifiers; or, quick procedures reducing PRh time).

Disclosure: **M. O. Chan**, None; **R. Wyllie**, None; **H. E. Foster**, None.

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Response to Adalimumab in 40 Patients with refractory juvenile Idiopathic Arthritis-Associated Uveitis. A Multicenter Study. Vanesa Calvo-Río[1], Ricardo Blanco[1], Manuel Díaz-Llopis[2], David Salom[3], Carmen García-Vicuña[4], Miguel Cordero-Coma[5], Norberto Ortego[6], Marta Suarez-de-Figueroa[7], J. Carlos Fernandez-Cid[8], A. Fonollosa Calduch[9], Ángel M. García-Aparicio[10], Jose M. Benítez-del-Castillo[11], Jose L. Olea[12], Javier Loricera[13] and Miguel Angel González-Gay[13]. [1]Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, Spain, [2]Hospital Universitario La Fe de Valencia, Valencia, Spain, [3]Hospital Universitario La Fe de Valencia, Valencia, Spain, [4]Hospital Sant Joan de Déu, Barcelona, Barcelona, Spain, [5]Hospital de León, León, Spain, [6]Hospital Santa Cecilio, Granada, Spain, [7]Hospital Ramon y Cajal, Madrid, Spain, [8]Hospital de Pontevedra, Pontevedra, Spain, [9]Hospital de Cruces, Barakaldo, Spain, [10]Hospital Virgen Salud, Toledo, Toledo, [11]Hospital Clínico San Carlos, Madrid, [12]Hospital Son Dureta, Palma de Mallorca, Spain, [13]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain

Background/Purpose: To assess the efficacy and safety of treatment with adalimumab therapy in patients with refractory Juvenile Idiopathic Arthritis (JIA)-associated uveitis.

Methods: Multicenter study on 40 patients diagnosed as having JIA-associated uveitis refractory to treatment with corticosteroids therapy and at least other systemic immunosuppressive drug. Standard adalimumab therapy was started (40 mg subcutaneously every-other-week); for children aged between 4 and 12 years, the recommended dose was 24 mg/m^{2} body surface area up to a maximum single dose of 40 mg sc every other week. The associated immunosuppressive therapy and the prednisone dose were reduced if there was no evidence of inflammation. Degree of anterior and posterior chamber inflammation (SUN criteria), corticosteroid dose, and macular thickness (optical coherence tomography) were assessed. Definite outcomes were assessed at six months in all patients. All expressed comparisons are between baseline and after 6 months of adalimumab therapy (Wilcoxon test).

Results: Forty patients (11 males, 29 females), mean age of $11,4\pm7,9$ years (range: 4 to 44 years), with active intraocular inflammation at baseline were studied. Thirty-six of 40 patients had inflammation in the anterior camera, and treatment with adalimumab achieved a significant improvement in mean tyndall from $1,8\pm1,1$ to $0,41\pm0,6$; p $=0.000001$.

Also, 17 (42,5%) patients had macular thickness with Optic Coherence Tomography (OCT)>250 microns. These cases had a significant improvement in OCT from $370,8\pm133,9$ to $249,3\pm28,0$ microns; p$=0,0007$. In addition, 9 patients with Cystoid Macular Edema (CME) (OCT>300) also had a significant improvement in OCT $(463,1\pm123,8$ to $254,4\pm30,2,$ p$=0,007)$. The dose of corticosteroids also was decreased from 0.26 ± 0.4 to 0.004 ± 0.02 mg/day (p$=0.00061$).

Adalimumab was usually well tolerated, and only local minor side-effects at the injection site were observed. Twelve patients (30%) had a mild relapse during the 6 months of therapy whereas only 2 patients (5%) had a moderate-severe relapse.

Conclusion: Adalimumab appears to be an effective and safe drug for the treatment of refractory JIA-associated uveitis and may reduce steroid requirement. Further controlled studies are warranted.

Disclosure: **V. Calvo-Río**, None; **R. Blanco**, None; **M. Díaz-Llopis**, None; **D. Salom**, None; **C. García-Vicuña**, None; **M. Cordero-Coma**, None; **N. Ortego**, None; **M. Suarez-de-Figueroa**, None; **J. C. Fernandez-Cid**, None; **A. Fonollosa Calduch**, None; **M. García-Aparicio**, None; **J. M. Benítez-del-Castillo**, None; **J. L. Olea**, None; **J. Loricera**, None; **M. A. González-Gay**, None.

1141

Safety of Celecoxib and Non-Selective Non-Steroidal Anti-Inflammatory Drugs in Juvenile Idiopathic Arthritis. Rachel E. Sobel[1], D. J. Lovell[2], Hermine I. Brunner[3], Jennifer E. Weiss[4], Paula W. Morris[5], Beth S. Gottlieb[6], Elizabeth C. Chalom[7], Lawrence K. Jung[8], Karen Onel[9], Lisa Petinoit[10], Donald P. Goldsmith[11], Staci Abramsky-Risman[12], James P., Young[13] and Edward H. Giannini[14]. [1]Pfizer, Inc., New York, NY, [2]Cincinnati Children's Hospital, Cincinnati, OH, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Hackensack Univ Med Ctr, Hackensack, NJ, [5]Univ of Arkansas for Med Sci, Little Rock, AR, [6]Cohen Children's Medical Center of New York, New Hyde Park, NY, [7]St. Barnabas Medical Center, Livingston, NJ, [8]Children's National Medical Center, Washington, DC, [9]University of Chicago, Chicago, IL, [10]'Specially for Children, Dell Children's Medical Center, Austin, TX, [11]St Christopher's Hospital for Children/Drexel College of Medicine, Philadelphia, PA, [12]Pfizer Inc, New York, NY, [13]United BioSource Corporation, Ann Arbor, MI, [14]PRCSG-Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Celecoxib, a selective COX-2 inhibitor, was approved by the FDA for the treatment of the signs and symptoms of JIA in children aged 2–17 years in December, 2006. As a condition of approval, Pfizer conducted a Phase IV study, the Safety in Idiopathic Arthritis: NSAIDs and Celebrex Evaluation Registry (SINCERE), to collect longer-term safety and developmental data on patients with JIA treated in routine clinical practice with celecoxib or non-selective NSAIDs (nsNSAIDs).

Methods: Children aged between 2 and 18 years with RF(+) or RF(−) polyarthritis, persistent or extended oligoarthritis, or systemic juvenile arthritis (without features of extra-articular features for '6 months) were enrolled into this prospective, observational, multi-centered, standard-of-care registry. To be eligible, patients had to be receiving newly or recently prescribed (≤6 months) nsNSAID or celecoxib. Duration of previous nsNSAID or celecoxib exposure, or use of concomitant DMARD or biologic therapy did not affect eligibility. Once enrolled, patients were to remain in the study whether they continued on the original NSAID, switched, or discontinued NSAIDs altogether. Visits were scheduled at 0, 4, 8, 12 months, and at 6 month intervals thereafter for a minimum of 2 years. All adverse events (AEs) regardless of severity were captured in the SINCERE database.

Results: A total of 274 patients (219 in the nsNSAID and 55 in the celecoxib group) were observed for 410 patient-years of observation (PYO) at study termination. Sixty percent of patients in the celecoxib group, and 53% in the nsNSAID group had oligoarthritis. Naproxen, meloxicam, and nabumetone were the most frequently used nsNSAIDs. At baseline, the celecoxib group had numerically longer disease duration, was older, and had a higher median weight and height. This is consistent with the practice of using celecoxib as the second or third NSAID in JIA. A numerically higher proportion of celecoxib patients had a history of intolerance to nsNSAIDs, mostly due to gastrointestinal side effects. The analysis of AEs reported during the study showed a similar incidence of AEs across groups (44 and 53/100 PYO for nsNSAID and celecoxib respectively, and 50/100 PYO for those off-NSAID [≥29 days after final dose]). AEs were those frequently observed with NSAID treatment. Two patients on nsNSAID and 2 off-NSAID experienced AEs of special interest. Twelve unique patients experienced a total of 18 serious adverse events (SAEs), the most frequent of which were infections; none were attributed to NSAID. Incidence rates (95% CI) of SAEs per 100 PYO were 3.4 (1.2, 5.6) and 2.9 (0, 7.0) for the nsNSAID and celecoxib group respectively, and 4.0 (0, 8.6) for the off-NSAID cohort. Overall, the study results indicate no important difference in the safety profiles between celecoxib and nsNSAIDs.

Conclusion: The total study population of 274 patients followed for a total of 410 PYO is one of the largest JIA NSAID cohorts, and adds substantially to the safety experience of NSAID treatment of JIA. The safety profile of celecoxib appears similar overall to that of nsNSAIDs and the benefit-risk for celecoxib treatment in JIA remains positive.

Disclosure: **R. E. Sobel**, Pfizer Inc, 3; **D. J. Lovell**, Centocor, Inc., 5, AstraZeneca, 5, Wyeth Pharmaceuticals, 8, Amgen, 9, Bristol-Myers Squibb, 5, Abbott Immunology Pharmaceuticals, 5, Pfizer Inc, 5, Regeneron, 5, Hoffmann-La Roche, Inc., 5, Novartis Pharmaceutical Corporation, 5, Forest Laboratories, 9, horizon pharmaceuticals, 5; **H. I. Brunner**, None; **J. E. Weiss**, None; **P. W. Morris**, None; **B. S. Gottlieb**, Pfizer Inc, 5; **E. C. Chalom**, None; **L. K. Jung**, None; **K. Onel**, None; **L. Petinoit**, None; **D. P. Goldsmith**, None; **S. Abramsky-Risman**, None; **J. P. Young**, None; **E. H. Giannini**, None.

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Efficacy of Biologic Agents in Juvenile Idiopathic Arthritis: A Systematic Review Using Indirect Comparisons. Janneke Anink[1], Marieke H. Otten[1], Sandra Spronk[2] and Lisette W.A. Van Suijlekom-Smit[1]. [1]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Erasmus MC, Rotterdam, Netherlands

Background/Purpose: During the last decade the availability of biologic agents for the treatment of juvenile idiopathic arthritis (JIA) increased substantially. Because direct head-to-head trials comparing biologics are lacking, physicians face difficulties to choose between these agents. In order to provide some scientific guidance, we indirectly compared the short-term efficacy of biologic agents.

Methods: In a systematic review, all available efficacy data from randomized controlled trials performed in JIA were retrieved. The following biologics were included: etanercept, adalimumab, infliximab, abatacept, anakinra, rilonacept, canakinumab and tocilizumab. Indirect between-drug comparisons (based on the Bucher's method) were conducted only if trials were comparable with regard to design and patients' characteristics related to treatment outcome.

Results: Eleven trials that evaluated biologic agents in JIA were selected. Quality of trials varied greatly: earlier trials for registration gained best scores, trials evaluating treatment strategies performed worst. For 5 trials, no match for an indirect comparison could be found due to design and patient characteristics. The remaining trials could be divided into two networks of evidence. Network 1 included withdrawal trials that evaluated etanercept, adalimumab and abatacept in poly-articular course juvenile idiopathic arthritis. Indirect comparisons identified no significant differences in short-term efficacy. Etanercept seemed superior to adalimumab (relative risk (RR) disease flare, etanercept vs. adalimumab, 0.59, 95% CI 0.28–1.24) and abatacept better than adalimumab (RR disease flare, abatacept vs. adalimumab, 0.64, 95% CI 0.34–1.23), especially considering the case-mix of adalimumab-treated patients, associated with better outcomes. Network 2 indirectly compared anakinra, tocilizumab and canakinumab in systemic juvenile idiopathic arthritis and no differences could be identified. Canakinumab tended to be superior to tocilizumab (RR 2.44, 95% CI 0.81–7.37).

Conclusion: The short-term efficacy of etanercept, adalimumab and abatacept seemed similar for poly-articular course JIA and anakinra, canakinumab and tocilizumab seemed similar for systemic JIA. Because of the observed differences between trials, head-to-head trials comparing 2 biologic agents directly are highly needed. For now, the pediatric rheumatologist has to rely on these indirect comparisons supplemented by observational data derived from cohort studies and safety, practical, and financial arguments.

Disclosure: J. Anink, None; **M. H. Otten**, Pfizer Inc, 9, Pfizer Inc, 9, Abbott Immunology Pharmaceuticals, 9, Roche Pharmaceuticals, 9, Novartis Pharmaceutical Corporation, 9; **S. Spronk**, None; **L. W. A. Van Suijlekom-Smit**, Pfizer Inc, 2, Abbott Immunology Pharmaceuticals, 2, Pfizer Inc, 5, Pfizer Inc, 9.

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Tocilizumab Therapy in Children with Systemic Onset Juvenile Idiopathic Arthritis. Russian Experience. Ekaterina Alekseeva, Rina Denisova, Saniya Valieva, Tatyana Bzarova, Kseniya Isayeva, Alexandra Chomakhidze, Evgeniya Chistyakova, Tatyana Sleptsova and Elena Mitenko. Scientific Center of Children's Health, Moscow, Russia

Background/Purpose: Systemic Juvenile Idiopathic Arthritis (sJIA) is classified as an acquired autoinflammatory disease. The interleukin-1 and interleukin-6 play a pivotal role in pathogenesis of this disease. The systemic manifestations as well as arthritis in sJIA are related to interleukin-6 action. Tocilizumab is promising drug for the treatment of systemic arthritis refractory to immunosuppressive drugs.

Objectives: To evaluate safety and efficacy of tocilizumab treatment in children with systemic juvenile idiopathic arthritis.

Methods: A prospective observational study in patients with sJIA taking tocilizumab. A total of 94 patients (49 boys and 45 girls) were included in this study. Median age was 5,5 years (range; 2 to 15 years) and median disease duration was 3,5 years (range; 0.5 to 12 years). Tocilizumab was administrated intravenously at a dose of 8–10 mg/kg every 2 weeks during 2 months then every 4 weeks. All patients received DMARDs. Efficacy end points included the American College of Rheumatology (ACR) Pediatric criteria for improvement 30 (ACR30), ACR50, ACR70 and criteria of inactive disease and remission.

Results: 39 of 94 patients (41%) entered 52 weeks and 69 patients - 24 weeks of continuous tocilizumab treatment. Tocilizumab treatment was discontinued in 15 patients. 40 patients continue to receive Tocilizumab therapy and have not entered 52 weeks yet. The ACR Pedi 30, 50 and 70 improvement were achieved by 100%, 100% and 75% of patients at Week 24 (n=69) and by 100%, 100% and 87% of patients at Week 52 (n=39), respectively. Inactive disease was achieved by 55% of patients at week 24 (n=69) and by 65% of patients at week 52 (n=39). Remission was achieved by 59% of patients (n=39). The mean dose of oral glucocorticoid was decreased from 0,6 (0,4; 0,5) mg/kg (n=45) to 0,2 (0,1-0,3) mg/kg (n=20) at week 52. The frequently observed non-severe adverse events were nasopharyngitis, upper respiratory tract infections and gastroenteritis. No cases of opportunistic infections, malignancies or death were reported. There were three cases of pneumonia and cellulitis. 30 patients had incidences of neutropenia. Tocilizumab treatment was discontinued in 15 patients. The causes for cancellation were relapse of disease (n=7), inefficacy (n=3), remission (n=1), parent's refusal (n=1), infusion reaction (n=2) and Crohn's disease (n=1).

Dynamics in systemic features

	Background	1 m	6 m	12 m
Number of systemic features per patient	3,1	1,1	0,5	0,2

Conclusion: The results of the annual prospective observational study have shown the high efficiency of tocilizumab in patients with the severe sJIA. Drug induced remission of extra-articular manifestations, arthritis and normalized laboratory parameters of the disease activity without initiation of treatment with oral prednisolone and increase its dose, thus avoiding severe irreversible complications of glucocorticoid therapy. Tocilizumab induced disease remission in 59% of patients at Week 52.

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Phenotypic Characterization of Childhood Onset Rheumatoid Arthritis. Emily G. Ferrell[1], Lori Ponder[2], Lauren Minor[3], Sheila T. Angeles-Han[3], Christine W. Kennedy[2], Kelly A. Rouster-Stevens[4], Mina Pichavant[2], Larry B. Vogler[4] and Sampath Prahalad[2]. [1]Emory University School of Medicine, Atlanta, GA, [2]Emory Children's Center, Atlanta, GA, [3]Emory University, Atlanta, GA, [4]Emory Univ School of Medicine, Atlanta, GA

Background/Purpose: Rheumatoid Factor positive polyarthritis (RF+ poly) is the JIA subtype that resembles adult seropositive RA. However, the ILAR classification criteria for RF+ polyarthritis do not capture all children with childhood onset RA due to specific exclusion criteria: lack of 2 (+) RF tests, <5 active joints in the first 6 months, family history of psoriasis, and (+) HLA-B27 in boys with onset after age 6. The ACR/EULAR criteria used for diagnosing adult RA do not have these exclusions, and they include the highly specific anti-CCP antibodies (ACPA). The current ILAR classification system does not include ACPA. Hence, children who are RF (−) but ACPA (+) may be treated less aggressively and develop complications secondary to undertreated disease. Our objectives are to 1) determine whether RF and/or ACPA (+) children meet ILAR criteria for RF+ poly JIA and 2) assess for significant differences between children who meet RF+ poly criteria and those who are classified as other subtypes.

Methods: Demographic and disease-related data were collected from charts of RF and/or ACPA (+) children. Each child was classified using ILAR criteria, and the ACR/EULAR classification was used to determine whether each child met criteria for adult RA. Children with RF+ poly JIA were compared to those with other subtypes. Nominal variables were compared using Chi square or Fisher's exact tests, and continuous variables were compared using Student's T test.

Results: Of 49 children with RF and/or ACPA (+) JIA, 29 (59%) met criteria for RF+ poly JIA (Table 1). Of the 20 who did not, 9 (45%) met criteria for undifferentiated JIA, 6 (30%) for RF- polyarthritis, 3 (15%) for persistent oligoarthritis, and 2 (10%) for extended oligoarthritis. All children with undifferentiated JIA were ACPA (+); 7 had presentations consistent with oligoarthritis, but had 2 positive RF tests; 1 had a father with psoriasis; 1 was an HLA-B27 (+) boy with onset after age 6. Comparison of children who met criteria for RF+ poly JIA to those who did not revealed significant differences in subtype distribution, number meeting ACR/EULAR criteria for RA, and use of steroids. All other features were not significantly different.

The ACR/EULAR criteria for RA captured more children with RF and/or ACPA (+) JIA than the ILAR RF+ poly classification (92% vs. 59%).

Table 1. Characteristics of ACPA and RF positive children with JIA*

	RF positive polyarticular JIA	Non-RF positive polyarticular JIA	P value**
Total number	29 (59)	20 (41)	
Age at symptom onset (mean±SD)	10.3 ± 3.4	9.3 ± 3.9	0.34
Demographic features			
Female gender	22 (76)	15 (75)	0.95
Hispanic ethnicity	7 (14)	1 (5)	0.08
African ancestry	9 (18)	8 (40)	0.52
Birth weight (kg; mean±SD)	3.4 ± 0.5	3.3 ± 0.5	0.60
ACPA value (mean±SD)	174.5 ± 100.0	163.2 ± 100.2	0.70
ILAR subtype			
RF + poly	29 (100)	0 (0)	**<0.0001**
RF - poly	0 (0)	6 (30)	**0.002**
Oligo extended	0 (0)	2 (10)	0.09
Oligo persistent	0 (0)	3 (15)	**0.03**
Undifferentiated	0 (0)	9 (45)	**<0.0001**
Meets 2010 ACR/EULAR criteria for RA	29 (100)	16 (80)	**0.01**
Imaging evidence of damage	18 (62)	7 (35)	0.07
Number of affected joints in first 6 months (mean & range)	13 (5-30)	11 (1-48)	0.48
Treatment			
Use of systemic steroids	20 (69)	7 (35)	**0.02**
Use of DMARD	28 (97)	17 (85)	0.15
Use of biologic	19 (66)	8 (40)	0.08

* All values are N(%) of those tested/reporting data for particular variables, except as indicated.
ACPA: anti-citrullinated protein antibody.
** P<0.05 was considered statistically significant

Conclusion: A significant number of children (41%) with RF and/or ACPA (+) JIA did not meet criteria for RF+ poly JIA, though many of their demographic features and disease measures were similar to children who did. The ACR/EULAR criteria allow a positive RF *or* ACPA to qualify as positive serology, and these criteria capture more children with RF and/or ACPA (+) JIA. We propose the inclusion of ACPA in future revisions of the JIA classification criteria to improve the specificity of diagnosing childhood onset RA, and we suggest replacing RF+ polyarthritis with RF/ACPA+ JIA.

Disclosure: E. G. Ferrell, None; **L. Ponder**, None; **L. Minor**, None; **S. T. Angeles-Han**, None; **C. W. Kennedy**, None; **K. A. Rouster-Stevens**, None; **M. Pichavant**, None; **L. B. Vogler**, None; **S. Prahalad**, None.

1145

Use of Non-Etanercept Biologics in Children with Juvenile Idiopathic Arthritis: Results From the Biologics for Children with Rheumatic Diseases Study. Lianne Kearsley-Fleet[1], Eileen Baildam[2], Michael Beresford[3], Rebecca Davies[1], Helen E. Foster[4], Katy Mowbray[1], Taunton R. Southwood[5], Wendy Thomson[1] and Kimme L. Hyrich[6]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [3]Institute of Translational Medicine (Child Health), Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [4]Musculoskeletal Research Group, Newcastle upon Tyne, United Kingdom, [5]University of Birmingham and Birmingham Children's Hospital, Birmingham, United Kingdom, [6]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom

Background/Purpose: The management of juvenile idiopathic arthritis (JIA) has been revolutionised by the introduction of biologic therapy, although the majority remain unlicensed for children. Until recently, etanercept (ETN) was the only choice of licensed therapy in the UK, with recent additions of adalimumab (age ≥ 4 years), abatacept (age ≥ 6 years) and tocilizumab (systemic arthritis). It is not yet known how and when non-ETN biologics are being prescribed in JIA. The purpose of this analysis was to describe the pattern of use of non-ETN biologics in children with JIA.

Methods: Since 2010, the Biologics for Children with Rheumatic Diseases (BCRD) study, an ongoing prospective observational cohort study, has been collecting detailed information on children <18 years newly starting a non-ETN biologic therapy for JIA. There are no other exclusion criteria. At baseline, detailed demographic and disease information, including details of past biologic therapies, are collected. The use of non-ETN therapy as a first-line or subsequent biologic therapy was compared, including patterns of prescription, use under licensed indications, ILAR subtypes and disease activity/severity using non-parametric descriptive statistics.

Results: To 06/21/2012, 136 children across the UK had been recruited: median age 10 years, 65% female. The most common ILAR subtypes were systemic arthritis (26.5%) and rheumatoid factor (RF) negative polyarthritis (27.2%) (see Table). Sixty four patients (47.1%) were starting a non-ETN biologic as first-line biologic therapy, of which 33 (51.6%) were prescribed off-license. Off-license use was more common among first-line users (p=0.047), largely accounted for by infliximab and anakinra. All patients on anakinra had systemic arthritis, whereas only 67.7% of those were prescribed tocilizumab. Forty-eight percent of first line users versus 26% of subsequent users had a history of chronic anterior uveitis (p=0.028). Of those registered at the point of starting a subsequent biologic, 71% had received prior ETN. The majority had received only 1 prior biologic although 17 children had received 2 prior biologics, 3 children had received 3 and 1 child (RF negative) had received 5 previous biologics. Disease severity was moderate to high and largely comparable between first-line and subsequent biologic users, although subsequent biologic users had a higher limited joint count.

Biologic Patients Characteristic, med(IQR) or n(%)	First Line	Subsequent	Total	p-value
n	64 (47.1)	72 (52.9)	136	
Age at Registration, years	8.5 (4.5-12)	11.5 (8-14)	10 (6-13.5)	0.0006
Female	37 (57.8)	51 (70.8)	88 (64.7)	0.113
ILAR subtype				
Systemic arthritis	19 (29.7)	17 (23.6)	36 (26.5)	0.001
Oligoarthritis: persistent	16 (25.0)	1 (1.4)	17 (12.5)	
Oligoarthritis: extended	9 (14.1)	14 (19.4)	23 (16.9)	
Polyarthritis: RF Negative	11 (17.2)	26 (36.1)	37 (27.2)	
Polyarthritis: RF Positive	1 (1.6)	6 (8.3)	7 (5.2)	
Enthesitis Related Arthritis	4 (6.3)	2 (2.8)	6 (4.4)	
Psoriatic arthritis	2 (3.1)	5 (6.94)	7 (5.2)	
Undifferentiated arthritis	1 (1.6)	0	1 (0.7)	
Not Recorded	1 (1.6)	1 (1.4)	2 (1.5)	
Biologic Drug at Registration				
Adalimumab	25 (39.1)	25 (34.7)	50 (36.8)	0.002
Infliximab	18 (28.1)	14 (19.4)	32 (23.5)	
Tocilizumab	11 (17.1)	20 (27.8)	31 (22.8)	
Abatacept	1 (1.6)	9 (12.5)	10 (7.4)	
Anakinra	9 (14.1)	1 (1.4)	10 (7.4)	
Rituximab	0	3 (4.2)	3 (2.2)	
Licensed Use	31 (48.4)	47 (65.3)	78 (57.4)	0.047
Prior Biological Treatment				
1 previous	0	51		
2 previous	0	17		
3 previous	0	3		
5 previous	0	1		
Ever had Chronic Anterior Uveitis	31 (48.4)	19 (26.4)	50 (36.8)	0.028
Active Chronic Anterior Uveitis at Registration	25 (39.1)	17 (23.6)	42 (30.9)	0.141
Disease activity				
Active joint count	2 (0-6)	3 (1-8.5)	2 (0-7)	0.1030
Limited joint count	1 (0-6)	3 (1-8)	2 (0-7)	0.0061
Physician Global Assessment (10cm VAS)	3.1 (1.5-4.9)	3 (1.8-6)	3 (1.8-5.5)	0.5603
Parent Global Assessment of Well-being (10cm VAS)	3 (0.8-5)	4.4 (2-6)	4 (1.1-5.9)	0.3414
CHAQ	1 (0.3-2)	1.3 (0.3-1.6)	1.1 (0.3-1.8)	0.8697
Pain (10cm VAS)	3.8 (0.5-6.1)	3.7 (1-6.6)	3.7 (0.8-6.5)	0.7833
ESR, mm/hr	10 (6-42)	14 (5-52)	12 (6-50)	0.6820
CRP mg/L	5 (3-20)	5 (4-28)	5 (3-20.4)	0.7292

Conclusion: Many children are now receiving non-ETN biologics in the UK, although almost half of these are being prescribed off-license. Ongoing

follow-up will help to address the question of best choice of biologic therapy for children with JIA, both as first-line and subsequent use, as well as determine the safety of these drugs in children, for which limited clinical experience exists.

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Choice of Systemic JIA Treatment Among Childhood Arthritis and Rheumatology Research Alliance (CARRA) Rheumatologists.

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Background/Purpose: Despite recent advances in identifying effective treatments for systemic Juvenile Idiopathic Arthritis (sJIA), many pediatric rheumatologists continue to use corticosteroids and methotrexate. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed standardized consensus treatment plans (CTPs) for sJIA with the goal of comparing their effectiveness using data collected for the CARRA Registry. Since physicians will select CTPs without randomization, each CTP must be used with sufficient frequency to allow for meaningful comparisons of efficacy. We aimed to ascertain the current anticipated frequency of CTP use by CARRA pediatric rheumatologists, and whether a clear standard of care exists for sJIA treatment.

Methods: An electronic survey was sent to voting members of CARRA regarding CTP choice for new-onset sJIA which has failed NSAID therapy alone. Respondents were asked to select one or more of the following CTPs for each clinical case scenario: (a) systemic corticosteroids (CS) only; or (b) methotrexate, (c) anti-IL1 or (d) anti-IL6 therapy, each with or without CS. Respondents could choose more than one CTP if factors such as insurance limitations or family preference might affect treatment. Features of the clinical case scenarios are summarized in the Table.

Table. Clinical Cases

	Systemic symptoms	Arthritis	Anemia	Acute Phase Reactants	Disability
Case 1	+	+	+	++	+
Case 2	++	+++	+++	+++	++
Case 3	+	++++	+	+	+++
Case 4	+++	++++	++++	++++	++++

Results: 134 of 247 (54%) CARRA members responded. The figure depicts treatment selections sorted by case, demonstrating wide variability in preferred treatment for new-onset sJIA. IL1 and IL6 inhibitors have become important treatment choices. Methotrexate use increases with more prominent arthritis features; however, methotrexate and CS usage are frequent regardless of presenting disease features. Overall, concurrent CS use was indicated by the majority of respondents across all CTPs (Case 1: 74%; Case 2: 87%, Case 3: 66%; Case 4: 91%).

Figure: CTP Choices by Case
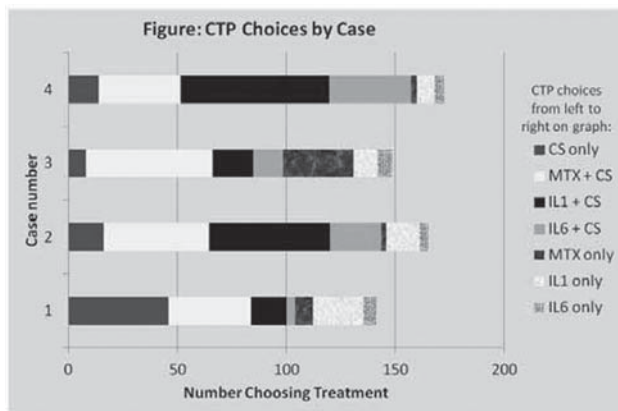
Conclusion: There is still significant variability in sJIA treatment approaches and no clear standard of care among CARRA members, with widespread use of methotrexate and CS. There is likely to be sufficient utilization of each of the CTPs for new-onset sJIA to establish comparative treatment effectiveness using the observational CARRA Registry.

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Definition of Improvement Thresholds in Juvenile Idiopathic Arthritis Using the JADAS.

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Background/Purpose: Evaluation of disease activity in JIA is fundamental in clinical assessment. The ACR paediatric response measure used in clinical trials are validated to analyse the response to a treatment in comparison to a baseline disease activity but does not judge about the absolute disease activity or the absolute improvement.

Methods: The JADAS has been calculated in patients of the BIKER registry newly starting treatment with etanercept or MTX. The JADAS10 was preferred because it values all 4 domains equally. Physicians + parents were requested to judge on treatment efficacy as very good, good, weak, none or worse. Improvement was assumed if judgement of both were very good or good. No improvement was assumed if at least one judgement was for none or poor. Inconclusive judgements or those with a difference >1 point were excluded from analysis.

Results: Initially, ANOVA of JIA categories showed no significant differences of mean DJADAS in all baseline classes and IQRs also showed good overall limits. So, all JIA categories were combined for a joint cutoff. Analysis was restricted to the 3 month evaluation because of a time dependence of the judgement of improvement in terms of the JADAS. Restriction to the 3 month results left 1340 patients. JADAS at baseline was finally put into 4 classes, class 0 for JADAS <5, "low" for 5≤JADAS<15, "moderate" for 15 ≤JADAS<25 and "high" for 25≤JADAS≤40. An initial JADAS of <5 was assumed as only minor or no disease activity. An improvement cutoff was only defined for baseline classes "low", "moderate" and "high". Cutoffs for defining improvement were chosen by calculating interquartile ranges (IQR) of the judgement groups and considering accuracy as well as sensitivity/specificity of the resulting model. Analysis by baseline class revealed clear cutoff points. According to the baseline JADAS class the following minimum decreases of the JADAS (DJADAS) are proposed for definition of improvement: For baseline class "low": DJADAS of 4, for baseline class "moderate": DJADAS of 10, for baseline class "high": DJADAS of 15. Alternatively a relative decrease of the JADAS by 42% for JADAS class "low", by 51% for JADAS Class "moderate" and 56% for JADAS class "high" were found to define improvement (table 1).

Table 1. Inter quartile ranges of variable DJADAS10 by improvement and baseline class, absolute and relative values. Chosen cutoff for improvement and goodness-of-fit parameters. Higher DJADAS10 indicate better treatment efficacy. Only integer cutoffs were considered.

	JADAS10 baseline class				
	Low (5-15)	Moderate (15-25)	High (25-40)		
Improvement	DJadas10 absolute values IQR (n)				
Yes	4.1-9.5 (502)	10.4-17.2 (450)	17.8-27.2 (148)		
No	-31.-3.7 (85)	1.5-10.2 (94)	4.6-15.0 (35)		
Cutoff for improvement	4	10	15		
Accuracy [%]	76.2	74.8	85.8		
Sensitivity	75.9	76.2	88.5		
Specificity	76.5	73.4	74.3		
Improvement	DJadas10 relative values [%] IQR				
Yes	45-86	55-88	65-94		
No	-32-42	8-50	18-49		
Cutoff for improvement	42	51	50	53	56
Accuracy [%]	76.8	78.5	88.0	87.4	87.4
Sensitivity	77.1	78.4	90.5	88.5	87.2
Specificity	75.3	78.7	77.1	82.9	88.6

Conclusion: Disease improvement on therapy can efficiently be defined by the decrease of the JADAS depending on the initial JADAS score defining low, moderate or high disease activity. Our model demonstrates clear cut off values. After cross validation these cutoffs may be used in clinical trials and for decisions in clinical practice.

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Adalimumab — Effective Control under Refractory JIA Associated Uveitis.

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Background/Purpose: Treatment of juvenile idiopathic arthritis (JIA)-associated uveitis is one of the serious problems of paediatric rheumatology. JIA associated uveitis often is refractory to MTX, CiA and topical NSAIDs and GC. Humanised anti-TNFα monoclonal antibody (adalimumab) may be effective drug for the treatment of JIA-associated uveitis refractory to immunosuppressive drugs.

Objectives: To evaluate clinical efficacy and safety of adalimumab therapy in patients with JIA-associated uveitis.

Methods: It was prospective, observational trial. 48 patients with uveitis were enrolled in the study, 8 boys and 40 girls, 32-with bilateral and 16-with unilateral uveitis, 27 had poly-, 21-oligoarthritis. Mean age of patients was 11,8 (range 4-18) y; mean of disease duration-5,7 (range 1-16) y. Before adalimumab therapy 10 patients were treated with MTX (range of dose 15–25 mg/m^2/w), 38-with MTX in combination with CiA (range of dose 4-4,5 mg/kg/d), 5—with oral GC (range of dose 5–12 mg/kg/d), all of them-with topical GC drops, NSAID drops, 27 -received retrobulbar injections of GC. Adalimumab was administrated by subcutaneous injection at dose 40 mg every 2 w during 1y. Adalimumab use was approved by the Local Ethics Committee. The efficacy of therapy was measured by ACR-pedi criteria. Changes in ocular inflammation were graded by M.J.Hogan's criteria. The main target—remission of uveitis and arthritis.

Results: Prior to administration of adalimumab, injection of conjunctiva, edema of iris, corneal precipitations, areas of inflammation in lens and optical nerve disk edema were found in all children with uveitis. After 8 w of treatment complete management of conjunctiva injection, iris edema and optical nerve disk edema were reported in 55% (44/80) of the affected eyes—corneal precipitations disappeared in 45% (36/80); inflammation-associated changes of lens—in 18% (14/80) of eyes. Treatment-associated improvement of vision was found in 63 of 80 of the affected eyes; no changes of vision acuity were reported in 33 (41%) of the affected eyes. GC eye drops were discontinued in 45% (22/48) of patients, NSAIDs eye drops—in 50% (24/48) of children; the dose of GC eye drops was reduced in 86% (41/48) of patients. The exacerbation of uveitis was persisting in 10% (8/80) of the affected eyes, subacute uveitis—in 25%(20/80); remission was found in 65%(52/80) of the affected eyes. After 24 w of treatment the cases of uveitis were not reported; subacute disease was observed in 22%(21/96) of eyes; remission was diagnosed in 78%(62/80) of the affected eyes. After 52 w of treatment remission was diagnosed in 83% of the affected eyes (66/80) The ACR-Pedi 30, 50, 70 were achieved 100%, 80%, 60% of patients at w 4, respectively. After 24 w of therapy ACR-Pedi 30,50,70 and 90 improvements rates was registrated in 100 %,92 %,78 % of patients. The remission was achieved by 63% of patient at w 52. Serious adverse events were not found.

Conclusion: Adalimumab is effective in patients with JIA associated uveitis. Reduction in uveitis activity and remission were reported in 83% of affected eyes. Remission of disease—in 63% of patients.The high efficacy of adalimumab allowed avoiding oral prednisolone and discontinuing topical GC therapy in patients with uveitis.

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Long-Term Safety of Etanercept in Patients with Juvenile Idiopathic Arthritis (JIA).

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Background/Purpose: Etanercept (Eta) has been the most frequently used biologic drug in patients with JIA. In Germany, about one in three patients with polyarticular JIA received Eta in 2010. However, published data on its long-term safety are limited. The data of the German JIA biologic registers BiKeR and JuMBO were used to determine the rates of serious adverse events or events of special interest in order to assess the long-term safety of Eta.

Methods: Patients who were included at start with Eta in the BiKeR registry until March 2007 and have been half-yearly observed into adulthood were considered for this analysis. All adverse events recorded by physicians over the whole observation period (mean 7.5 years) were categorized on the basis of MedDRA. Total exposure-adjusted rates for serious adverse events (SAEs) and for events of special interest (i.e., deaths, malignancies, medically important infections [MII], and newly emerged other immune-mediated inflammatory diseases [IMID]) per 100 patient years (PY) were calculated.

Results: During the 1,815 years of Eta exposure in 386 patients (mean age 23 years, mean disease duration 14 years) 77 SAEs were recorded (4.2 SUEs/100 PY), of which 8% were possibly related to therapy. The SAE rates for each year of Eta exposure per 100 PY varied somewhat over the first nine years of treatment, but did not differ significantly (p=0.312). The JIA-associated mortality rate was 1% in this study population. Two deaths occurred in patients treated with Eta within the last three months before death, but no patient died in suspected causal relationship to Eta. Two malignancies were reported (that were already published[1]), resulting in 0.11 event per 100 PY of exposure. Twenty MII were recorded which led to drug discontinuation in five patients. 75% of the MII occurred within the first three years of Eta treatment. The exposure-adjusted MII rate was 1.1 per 100 PY. Tuberculosis or other opportunistic infections were not registered. A total of 17 incident IMID (0.9/100 PY) were reported: among them were eight cases with new onset inflammatory bowel disease (0.44/100 PY) and eight cases with uveitis (0.44/100 PY).

Conclusion: The hitherto most comprehensive study of the long-term safety of Eta confirms the good tolerability of the substance. SAEs with possible relationship to therapy occur only rarely (0.3/100 PY). However, reliable risk rates for events of particular interest can only be calculated in larger patient cohorts. Moreover, a comprehensive control group is necessary to put the results into perspective.

Reference

1 - Horneff G, Foeldvari I, Minden K, Moebius D, Hospach T. Report on malignancies in the German juvenile idiopathic arthritis registry. Rheumatology (Oxford) 2011;50:230-6.

Disclosure: **K. Minden**, Pfizer Inc, 2, Pfizer Inc, Abbott, Novartis, Chugai, Roche, Medac, 5; **M. Niewerth**, None; **J. Klotsche**, None; **M. Hammer**, None; **J. P. Haas**, Abbott, Novartis, Chugai, 5; **G. Ganser**, Pfizer, Abbott, Chugai, Actelion, 5; **G. Horneff**, Abbott, Pfizer, 2, Abbott, Pfizer, Novartis, Chugai, Swedish orphan, 5.

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Adverse Events in Juvenile Idiopathic Arthritis: Results From the Enhanced Drug Safety Surveillance (EDSS) Pilot Project.

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Background/Purpose: There are few data available regarding the rates of serious and important medical events (SAEs and IMEs) for most of the medications used to treat JRA/JIA (Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis), including nonsteroidal anti-inflammatory drugs. These data are of particular importance as the use of biologic disease modifying antirheumatic drugs (DMARDs) in JRA/JIA has increased significantly over the past several years along with the number of medications that are FDA-approved for the treatment of these diseases. While the FDA has a voluntary MedWatch reporting system in place, only a small proportion of physicians fill out these reports and these data cannot be used to calculate SAE/IME rates. The Enhanced Drug Safety Surveillance (EDSS) Pilot Project was developed in partnership with Pfizer, as one of the US FDA post-marketing commitments for celecoxib in JIA, to implement a pilot process to capture of SAEs and IMEs, and to calculate SAE/IME rates in children with JRA/JIA utilizing the CARRA (Childhood Arthritis and Rheumatology Research Alliance) physician network. The objective of this analysis is to summarize the data resulting from the 4-year (2008–2012) EDSS Pilot Project.

Methods: Physicians at participating sites were surveyed monthly to determine whether any of their JIA/JRA patients had experienced a SAE or IME during the prior month. MedWatch forms were subsequently completed for each event, including attribution to medication(s). SAEs and IMEs were categorized by the primary organ system and/or the dominant symptoms (e.g. disease flare, infusion reaction). Each site was surveyed every 6 months regarding the number

of JRA/JIA patients per site, to provide a denominator for the SAE/IME rates. Reporting rates were calculated per 100 person-years (p-y) and 95% CI were calculated based on a Poisson distribution.

Results: 37 sites with 115 physicians contributed at least one year of data. The overall response rate to the monthly surveys was 65% and the overall response to the 6 month surveys was 86%. There were a total of 139 total SAEs and 139 IMEs. The largest proportion of SAEs and IMEs occurred in children with polyarticular JIA (39% and 38%, respectively). The majority of SAEs and IMEs were reported for patients receiving biologic DMARDs (73% and 68%, respectively). NSAIDs and non-biologic DMARDs were the next most commonly reported medications, with 1 SAE and 2 IMEs attributed to celecoxib, and 12 SAEs and 11 IMEs attributed to other NSAIDs. Infection accounted for the largest proportion of both SAEs and IMEs (52% and 20%). The next most common categories of SAE were disease flare and macrophage activation syndrome. The next most common categories of IME were neurologic and elevated liver function tests. The total event rate for SAEs and IMEs combined was 1.2 SAE/IME per 100 p-y (95% CI: 1.1–1.4). The rate for SAEs was the same as IMEs (0.6 per 100 p-y; 95% CI: 0.5–0.7).

Conclusion: The EDSS provided a simple and effective tool for SAE/IME reporting. These data support the development of a long-term registry of children with JRA/JIA in North America to continue the collection of these critical data.

Disclosure: **S. Ringold**, None; **A. F. Hendrickson**, None; **C. A. Wallace**, Pfizer Inc, 1, Amgen, 2, Pfizer Inc, 2, Genentech and Biogen IDEC Inc., 5, Novartis Pharmaceutical Corporation, 5; **R. E. Sobel**, Pfizer Inc, 3.

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Low-Dose Methotrexate and the Selective Accumulation of Intracellular Aminoimidazolecarboxamide Ribotide. Ryan S. Funk, Leon van Haandel, Mara L. Becker and J.S. Leeder. Children's Mercy Hospital, Kansas City, MO

Background/Purpose: Current evidence suggests that the anti-folate methotrexate (MTX) mediates its anti-inflammatory effects through inhibition of the purine synthesis pathway causing the accumulation of aminoimidazolecarboxamide ribotide (AICAR). Meanwhile, the anti-proliferative effects of MTX have primarily been attributed to inhibition of the pyrimidine synthesis pathway, marked by the accumulation of deoxyuridine monophosphate (dUMP). Therefore, identification of factors that affect MTX selectivity for purine synthesis pathway inhibition may be important in predicting and enhancing drug response in immuno-inflammatory diseases.

Methods: K562 erythroblastoid cells (2.5×10^5 cells/mL) were exposed to 0, 10, 100 and 1000 nM MTX under normal culture conditions for up to 24 hr. Cell samples (2.5×10^6 cells) were harvested after 1, 2, 4, 8 and 24 hr of MTX exposure. Cell lysates were analyzed for AICAR, dUMP, MTX and six different oxidation/methylation states of tetrahydrofolate, including 5-methyltetrahydrofolate (5mTHF); the polyglutamate distribution was also determined for each folate species and MTX. Mean concentrations and standard deviations from three independent experiments are reported. Statistical evaluations were conducted by unpaired Student's t-tests and statistical significance was defined by a P-value < 0.05.

Results: The primary effect on intracellular folates was a depletion of 5mTHF to levels at 24 hr that were 80%, 3% and 1% of control (0 nM MTX) in response to 10, 100 and 1000 nM MTX challenge, respectively with no effect on cell viability. Similarly, intracellular dUMP accumulated to levels 29-, 343- and 486-fold greater than control after a 24 hr exposure to 10, 100 and 1000 nM MTX, respectively. In the presence of 10 nM MTX, AICAR accumulated 93-fold compared to vehicle treated cells at 24 hr, however, increasing [MTX] had a paradoxical effect, resulting in lower AICAR concentrations. Across all experimental conditions intracellular [MTX] correlated with the intracellular accumulation of dUMP ($r^2=0.854$) and depletion of 5mTHF ($r^2=0.860$), but poorly with intracellular AICAR accumulation ($r^2=0.122$).
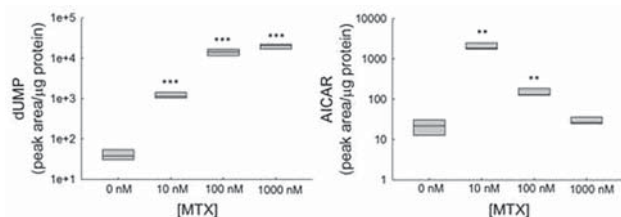
Figure. Intracellular dUMP and AICAR in K562 cells following a 24 hr exposure to MTX (**, P-value < 0.01; ***, P-value < 0.001).

Conclusion: Under these experimental conditions, increasing concentrations of MTX beyond 10 nM did not result in concentration-dependent increases in AICAR accumulation, and higher doses of MTX appeared to minimize the effects on the purine pathway, despite having profound effects on pyrimidine synthesis. Although the mechanism for this paradoxical effect on AICAR accumulation is currently under investigation, these findings support the hypothesis that low-dose MTX selectively targets the purine biosynthesis pathway and may result in improved anti-inflammatory effects.

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Improvement in Health-Related Quality of Life for Children with Juvenile Ideopathic Arthritis After Start of Treatment with Etanercept. Jens Klotsche[1], Kirsten Minden[2] and Gerd Horneff[3]. [1]German Rheumatism Research Center, a Leibniz institute, Berlin, Germany, [2]German Rheumatism Research Center, a Leibniz Institute, Berlin, Germany, [3]Centre of Pediatric Rheumatology, Sankt Augustin, Germany

Background/Purpose: The concept of Health-related quality of life (HrQoL) has been widely accepted as a burden of disease measure in recent years. The improvement in HrQoL is an important therapy goal in the treatment of patients with juvenile idiopathic arthritis (JIA). We investigated the 12-month course of HrQol in an unselected cohort of patients with JIA after therapy start with Etanercept and identified its associated factors.

Methods: Children were enrolled in the BiKer (Biologics in Paediatric Rheumatology) registry. A random subset of children completed the Pediatric Quality of Life Inventory (PedsQL) after the start of Etanercept treatment and was followed-up monthly for 6 monthly and bimonthly thereafter for up to one year. The 12-month course of the PedsQL total score and predictors for the change in HrQoL were investigated by growth curve modeling. The role of the depending predictor variables of an inactive disease and level of pain were studied in the course of HrQoL. The criteria by Wallace (2004) were applied to define inactive disease, the level of pain was assessed on a visual analogue scale (0–100) and functioning was measured by the CHAQ.

Results: Data were available for 61 patients with a mean age of 10.5 years (sd=3.9) and a mean disease duration of 3.2 years (sd=3.2). At baseline, the mean PedsQL total score was 75.5 (sd=16.7), mean number of swollen joints was 7.2 (sd=6.2), the mean rating of disease activity was 56.9 (sd=19.5) and 80% of the children reported functional restrictions indicated by a CHAQ above 0. A lower HrQol for patients at baseline was significantly associated with the number of swollen joints (beta=-1.1, p=0.016), functional restrictions (beta=-18.9, p<0.001), a high disease activity (beta=-0.31, p=0.002) and the existence of at least one comorbid condition (beta=11.5, p=0.021). The PedsQL total score increased at a rate of 2.8 units per month (p<0.001) in the first 6 months of treatment up to a level of 89.7 (sd=10.7), whereas the increase flattened (0.3 units per month, p=0.144) from 6-month to 12-month follow-up. A total of 16 (26%) children were already in remission after one year Etanercept treatment. The achievement of remission at the second month (beta=6.7, p<0.001) and fourth month (beta=5.2, p=0.029) yielded a significant increase in HrQoL. A high level of pain was associated with a lower HrQoL at each occasion.

Conclusion: HrQoL significantly improved after starting an Etanercept therapy in children with JIA. Adequate disease control and a low level of pain predicted a higher HrQoL in the 12-month course. But, both time dependent predictor variables did not fully explain the improvement in HrQoL.

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Perceived Health-Related Quality of Life and Its Determining Factors in Children with Recent-Onset JIA. Jens Klotsche[1], Ina Liedmann[1], Martina Niewerth[2], Gerd Horneff[3], Johannes Peter Haas[4] and Kirsten Minden[5]. [1]German Rheumatism Research Center, a Leibniz institute, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Centre of Pediatric Rheumatology, Sankt Augustin, Germany, [4]German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, [5]German Rheumatism Research Center, a Leibniz Institute, Berlin, Germany

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease and a major cause of chronic disability in children aged below 16 years. Health-related quality of life (HrQoL) has become an important

outcome measure for the perceived burden of disease and therapy effectiveness in the field of pediatric rheumatology. There is little knowledge about its diversification and determining factors in children with recently diagnosed JIA.

Methods: The diversification and determining factors of HrQoL were investigated by latent class analyses (LCA) in the ICON (Inception Cohort Of Newly-diagnosed patients with JIA) study, a prospective controlled observational multicentre study for long-term observation of patients diagnosed as JIA within the last 12 months. The evaluation comprised a self assessment by patients and parents via standardized questionnaires and clinical examinations by pediatric rheumatologists and ophthalmologists. HrQoL was measured by the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and the PedsQL 3.0 Rheumatology Module. The PedsQL was completed by patients above an age of eight years and parents. The difference between both ratings and determining factors for the difference was investigated.

Results: Information about HrQoL was available for 426 patients. Differences in the patients and parents ratings could be investigated for 198 children aged above 8 years. More than half of the children (58.4%) were assigned to a group characterized by high PedsQL scores (range: 79.4, 95% CI: 76.3;82.5 for treatment problems to 98.3, 95% CI: 97.5;99.2 for daily activity) by LCA. Only 9% of the children were classified into a group with low HrQoL scores (mean total score 50.6, 95% CI: 45.3;55.9) and were diagnosed with polyarthritis. High HrQoL scores were associated with the ILAR category oligoarthritis (p<0.001) and a low disease activity (mean 2.7 on NRS 0–10, p<0.001). Patients with high HrQoL scores had significantly less emotional difficulties as measured by the Strength and Difficulties questionnaire. Interestingly, parents of patients with higher HrQoL scores had more likely a higher educational level (57% with more than 10 years of schooling). In general, the parents rating of HrQoL was lower than the rating of the children (difference in total score = 4.1, 95%CI: 2.5;5.7). The most pronounced differences were observed in the rating of emotional problems (Δ=8.3, 95%CI: 5.3;11.2) within the age groups (Δ=6.0 for age group 8–12 years versus 1.8 for age group 13–16 years, p<0.001). Children in the two ILAR categories systemic arthritis (Δ=8.8, 95%CI: 3.6;14.1) and psoriatic arthritis (Δ=6.6; 95%CI: 1.2;13.5) reported better HrQoL compared to the parents report.

Conclusion: More than half of the children report high HrQoL scores at the beginning of JIA. Disease related parameters as well as social and personal factors independently affect the patients' overall well-being. Parents of younger children rated HrQoL remarkably lower than the children themselves, both patient- and proxy-reporting is therefore required to get a full picture of the burden of illness.

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Impact of FokI VDR and TNFalpha-308 Polymorphism On Disease Severity and Long Term Outcome in JIA Patients On Anti-TNF Treatment.
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Background/Purpose: Genetic contribution of SNP (single nucleotide polymorphism) of TNFα-308 promoter and FoxI for VDR (vitamin D receptor) polymorphism on disease severity and outcome in JIA is not yet well established. VDR polymorphisms correlations with different autoimmune diseases have been implicated and found to be different in some populations but data for JIA are missing. Primary endpoint of this study was to evaluate influence of these promoter polymorphisms, as possible biomarkers, on disease severity and long term outcome in JIA patients on anti-TNF treatment.

Methods: Genomic DNA was extracted and TNFα-308 promoter and FokI VDR polymorphism was evaluated using the PCR-RFLP method in 60 JIA patients included in Serbian JIA registry who donated blood samples before commencement of etanercept treatment. Time cut of point for outcome data analysis was 4 years after first dose of anti-TNF agent (etanercept).

Results: At enrolment JIA patients mean age was 14.7±4.22, disease duration 6.59±2.76, and average dose of MTX 11.91±6.68 mg/m2/week. Disease subtype distribution was 6.78% systemic, 54.24% polyRF- and extended oligo, 18.64% polyRF+, 16.95% ERA and 3.38 PsA. The distribution of TNFα308 and VDR genotypes was not significantly different among JIA subtypes. TNFα308 genotypes distribution was 6.78% AA, 30.51% GG and 62.71% GA. After 4 years treatment could be stopped (remission) in 35.14%, had to be reintroduced due to disease worsening in 16.22%, disease was in remission under medication in 21.62% or still active in 24.32% GA patients while respectively in 38.9%, 16.7%, 27.8% and 11.1% in GG patients. Average duration of etanercept treatment was 34.61±12.11 months and there was significantly shorter need for treatment duration if GG polymorphism group. VDR genotypes distribution was 51.6% FF, 38.7% Ff and 9.7% ff while in 20 healthy controls only FF (wild type) genotype was present. Presence of ff genotype significantly correlated with worse outcome and disease severity. We have found significant correlations with disease severity and presence of TNFα308 and/or FokI VDR genotypes.

Conclusion: Our results indicate that JIA patients, more frequently than healthy controls, have Ff or ff VDR FokI polymorphism. Heterozygote or homozygote presence of f variant for FokI polymorphism of VDR in JIA patients was associated with more severe disease and worse outcome. JIA patients with GG TNFα308 genotype can achieve better outcome and etanercept treatment can be stopped earlier compared to GA genotype. Both genotypes could be useful clinical predictive biomarker for disease severity and treatment response.

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A New Measure of Visual Function for Children with Juvenile Idiopathic Arthritis-Associated Uveitis.
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Background/Purpose: Studies on outcomes of children with juvenile idiopathic arthritis-associated uveitis (JIA-U) focus on the clinical ocular exam and physical disability secondary to arthritis. This assessment could improve by including measures of the impact of uveitis on daily life. However, until recently, there were no instruments that measured visual function in this population. Our objective is to validate a measure of visual function, the "Effects of Youngsters' Eyesight on Quality of Life (QOL)" (EYE-Q), in children with uveitis.

Methods: Focus groups were held to modify the old EYE-Q for children with uveitis. The new EYE-Q contains items specific to uveitis. A parent-proxy version was also developed. Children with JIA, JIA-U, and idiopathic uveitis (I-U) participated. Medical record reviews were performed. Questionnaires were completed on QOL (Pediatric QOL Inventory - PedsQL), physical function (Childhood Health Assessment Questionnaire - CHAQ), and visual function (EYE-Q).

Results: Participants were 104 children with JIA, 19 with JIA-U and 9 with I-U (Table 1). There were significant differences in the child and parent EYE-Q scores in children with uveitis compared to children with JIA (Table 2). For the child report, there were mild correlations between EYE-Q scores and logmarVA (r = −0.35) and moderate correlations with the PedsQL (r = 0.50) and CHAQ (r = −0.53) (Table 3). Similar results were found with the parent report. There were strong correlations between the parent and child EYE-Q (r = 0.74), and the old and new versions of the EYE-Q (r = 0.96, r = 0.94).

Table 1. Characteristics of children with JIA-associated uveitis, JIA alone, and idiopathic uveitis

	JIA alone N = 104	JIA-U N = 19	I-U N = 9
Demographic Characteristics			
Age, mean years ±SD	11.6 ± 4.8	10.5 ± 4.5	11.7 ± 4.9
Gender, female, N (%)	74 (71.8)	16 (84.2)	5 (55.6)
Hispanic, N (%)	10 (9.7)	4 (22.2)	0 (0)
Disease characteristics			
Age at arthritis onset, mean years ±SD	7.4 ± 4.5	4.0 ± 4.6	
Age at uveitis onset, mean years ±SD		6.8 ± 5.1	8.0 ± 4.4
Duration of JIA, mean years ±SD	3.99 ± 3.51	6.48 ± 3.74	
Duration of uveitis, mean years ±SD		3.68 ± 3.56	3.65 ± 3.12
Ophthalmology exam, most recent	N = 34	N = 15	N = 7
LogMarVA mean±SD, worse eye	0.17 ± 0.24	0.24 ± 0.22	0.74 ± 0.98
Intraocular pressure, worse eye	11.5 (7.8)	19.0 (7.5)	18.7 (8.6)
Slit lamp exam, worse eye			
Cells			
0 (<1 cell in field)	34	114	
0.5+ (1-5 cells in field)	0	2	2
1+ (6-15 cells in field)	0	1	0
2+ (16-25 cells in field)	0	2	0
3+ (26-50 cells in field)	0	0	0
4+ (>50 cells in field)	0	0	0
Complications, N (%)		N = 17	N = 9
Cataracts		5 (29.4)	6 (66.7)
Glaucoma		0 (0)	2 (22.2)
Synechiae		6 (36.3)	7 (77.8)
Band keratopathy		2 (11.8)	5 (55.6)
Cystoid macular edema		0 (0)	3 (33.3)
Other complications		3 (17.7)	4 (57.1)
Surgeries, N (%)			
Cataract extraction		0 (0)	3 (33.3)
Periocular steroid injection		2 (11.8)	3 (33.3)
Other ocular surgeries		1 (5.9)	2 (22.2)

Table 2. Mean scores on standard quality of life and function measures in JIA

	JIA N = 102	JIA-U N = 19	I-U N = 9	P value
Child Reports[+]				
EYEQ[a] (range 0-4)**	3.64 ± 0.44	3.31 ± 0.44	3.37 ± 0.79	0.043*
CHAQ[b] (range 0-3)[++]	0.59 ± 0.61	0.72 ± 0.67	0.00 ± 0.00	0.046*
PedsQL[c] Physical scale (range 0-100)**	70.3 ± 24.4	60.47 ± 24.7	91.5 ± 5.3	0.023*
PedsQL Psychosocial scale	74.5 ± 18.8	69.0 ± 17.9	81.8 ± 18.4	0.334
PedsQL Total scale	73.1 ± 19.5	65.98 ± 18.90	85.31 ± 18.89	0.102
Parent Reports				
EYEQ[a] (range 0-4)**	3.78 ± 0.37	3.37 ± 0.57	3.33 ± 0.89	0.002*
CHAQ[b] (range 0-3)[++]	0.57 ± 0.63	0.56 ± 0.62	0.08 ± 0.17	0.077
PedsQL[c] Physical scale (range 0-100)**	69.48 ± 25.44	67.29 ± 22.57	98.2 ± 3.54	0.010
PedsQL Psychosocial scale	76.29 ± 20.15	67.75 ± 19.99	84.29 ± 23.80	0.135
PedsQL Total scale	73.83 ± 20.49	67.64 ± 19.50	89.13 ± 15.42	0.061

± data are missing
ANOVA, *p-value <0.05
[a] Effects of Youngsters Eyesight on QOL; [b]Childhood Health Assessment Questionnaire;
[c]Pediatric Quality of Life Inventory
** Greater scores indicate better QOL; [++]Greater scores indicate worse QOL

Table 3. Correlations of the EYEQ with standard measures of quality of life and function in JIA

	R [95% CI]**	P value
EYEQ[a] child		
LogmarVA[b]	-0.35 [-0.60 – (-0.03)]	0.029*
CHAQ[c]	-0.53 [-0.78 – (-0.57)]	<0.0001*
PedsQL[d] Total scale	0.50 [0.33-0.63]	<0.0001*
EYEQ parent	0.74 [0.63 – 0.81]	<0.0001*
New EYE-Q	0.96 [0.94 – 0.97]	<0.0001*
EYEQ[a] parent		
LogmarVA[b]	-0.22 [-0.46 – 0.046]	0.101
CHAQ[c] score	-0.34 [-0.48 – (-0.18)]	<0.001*
PedsQL[d] total	0.43 [0.28 – 0.57]	<0.001*
New EYEQ[a]	0.94 [0.916 – 0.96]	<0.001*

Spearman's correlation coefficients, *p-value <0.05
** Mild correlations: R <0.3; Moderate correlations: R = 0.3 - 0.7; Strong correlation: R = >0.7
[a] Effects of Youngsters Eyesight on QOL; [b] Logmar visual acuity; [c] Childhood Health Assessment Questionnaire; [d] Pediatric Quality of Life Inventory

Cronbach's α for the old EYE-Q child and parent reports was 0.89. Cronbach's α for the new EYE-Q child report was 0.91 and for the parent report was 0.90.

Conclusion: The new EYE-Q, with items specific to uveitis, is a valid measure of visual function in children with uveitis. There were differences in child and parent perception of disease hence the inclusion of both perspectives in disease assessment is important. The EYE-Q may be an important measure in the assessment of outcomes in this population and a better measure than the clinical exam and arthritis specific measures alone. Longitudinal studies examining the performance of the EYE-Q in children with JIA-U and I-U are ongoing.

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Effectivity of Methotrexate in Therapy of Juvenile Idiopathic Enthesitis-Related Arthritis. Katharina Geitz and Ivan Foeldvari. Hamburger Zentrum Kinder-und Jugendrheumatologie, Hamburg, Germany

Background/Purpose: Juvenile idiopathic enthesitis related arthritis (enthJIA) represents 5 to 10% of children with JIA. Most patients present with peripheral arthritis and enthesitis. Methotrexate was not formally studied regarding effectivity for the peripheral joint involvement of this subset. Aim of our study was to assess the effectivity of methotrexate in peripheral joint involvement of enthesitis related JIA.

Methods: We conducted a chart review of patients with juvenile idiopathic enthesitis related arthritis, who have been treated at least for 3 months with MTX since 2005. The clinical and demographic parameters of the patients were assessed.

Results: We identified 73 patients with confirmed diagnosis of enthJIA, who were treated at least for 3 months with MTX. At the initiation of the therapy the average active joint count was 2,5 and the number of active enthesitis sites were 0,9. The mean CHAQ value was 0,55 and the mean pain score was 1,20 and the mean well being score was 1,26. The mean physician global was 1,74. At 3,6 and 9 months the active joint count was reduced by 18%, 44% and 53%, the number of painful joints by 22%, 36% and 47% and the number of swollen joints by 70%, 70% and 65%. The number of active enthesitis sites were reduced by 3,6 and 9 months by 44.5%, 61% and 50%. The CRP was reduced at 3,6 and 9 months by

49%, 70% and by 76%.The CHAQ score decreased at 3,6 and 9 months by 45%, 63% and 62%, the pain-score by 38%, 62% and 51% and the well-being score by 52%, 66% and 49% and the physician global by 58%, 65% and 65%.

Conclusion: In this retrospective chart review we could demonstrate the effectivity of MTX for peripheral joint involvement and for enthesitis. Interestingly only after 6 months of MTX therapy was the highest rate of improvement reached. Prospective controlled trial would be important to prove our results.

Disclosure: **K. Geitz**, None; **I. Foeldvari**, None.

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The Phenotypic Characterization of Juvenile Idiopathic Arthritis in African American Children. Lauren Minor[1], Lori Ponder[2], Emily G. Ferrell[1], Sheila Angeles-Han[1], Christine W. Kennedy[2], Kelly Rouster-Stevens[1], Mina Pichavant[2], Larry B. Vogler[1] and Sampath Prahalad[1]. [1]Emory University School of Medicine, Atlanta, GA, [2]Emory Children's Center, Atlanta, GA

Background/Purpose: JIA, a common childhood arthropathy, with an estimated prevalence of 1 in 1000 in children under the age of 16, affects children of all ages and races. There is limited data describing the characteristics of JIA in African-American (AA) children. The purpose of this study was to compare phenotypic characteristics of AA and Non-Hispanic White (NHW) JIA patients in our rheumatology clinic.

Methods: Charts of children with JIA, who were enrolled in a genetic study between June 2009 and June 2012 were reviewed. At time of enrollment, demographic and disease-related data were collected. Patients who identified as Hispanic or multi-racial were excluded. Disease characteristics compared between AA and NHW children included: age at onset and diagnosis, family history, JIA subtype, laboratory tests, associated features, medications, and radiographic changes. Fischer's exact test or Chi-Square tests were used to compare nominal variables, and student's T test was used to compare continuous variables.

Results: 150 NHW children and 62 AA children with JIA were studied. Table 1 compares demographic and disease characteristics of NHW and AA children. AA children with JIA were significantly older both at disease onset and presentation to a pediatric rheumatologist. JIA subtypes differed significantly between AA children and NHW children, with the AA being predominantly polyarticular RF+, and NHW being predominantly persistent oligoarticular. Both groups had a female predominance. Significantly more AA children had Medicaid and lived closer to their rheumatologist. AA children were less likely to have a family history of autoimmunity. Laboratory studies demonstrated that AA children were more likely to have positive RF and CCP antibodies. AA children were more likely to be treated with methotrexate at diagnosis, and more likely to have received systemic steroids during the course of their disease. These children were also more likely to have joint space narrowing and osteopenia on x-ray than NHW children. AA children were more likely to have rheumatoid nodules and chronic anemia as manifestations of their disease. The prevalence of uveitis was not significantly different between AA and NHW children with JIA. Even excluding the polyarticular RF+ subtype, AA children were older at onset and had more cumulative joints affected.

Table 1. Characteristics of NHW and AA children with JIA*

	NHW	AA	P value
Total Number	150	62	
Age at onset (mean ±SD)			
Including RF+ poly JIA	6.6 ± 4.4	8.7 ± 4.4	1.8×10^{-3}*
Excluding RF+ poly JIA	6.5 ± 4.4	8.0 ± 4.4	0.05*
Age at baseline visit (mean ±SD)			
Including RF+ poly JIA	7.5 ± 4.7	9.4 ± 4.4	6.9×10^{-3}*
Excluding RF+ poly JIA	7.2 ± 4.7	8.5 ± 4.4	0.10
Gender: females	102 (68)	48 (73)	0.19
Insurance type			
Medicaid	43 (29)	37 (60)	1.9×10^{-5}*
Private	105 (70)	24 (39)	1.7×10^{-4}*
Both	2 (1)	1 (1)	0.44
Distance from rheumatologist			
< 30 miles	35 (23)	44 (71)	$<1.0 \times 10^{-4}$*
> 30 miles	115 (77)	18 (29)	$<1.0 \times 10^{-4}$*
Management prior to rheumatology			
Managed by Pediatrician	12 (8)	8 (13)	0.1
Seen by Orthopedics	56 (37)	6 (10)	1.7×10^{-5}*
Alternate diagnosis	16 (11)	9 (15)	0.13
Family history of autoimmunity	39 (26)	9 (15)	0.03*
JIA subtype			
ERA	19 (13)	6 (10)	0.16
Oligoarticular extended	20 (13)	10 (16)	0.14
Oligoarticular persistent	45 (30)	6 (10)	6.8×10^{-4}*
Polyarticular RF-	37 (35)	12 (19)	0.1
Polyarticular RF+	9 (6)	18 (29)	1.4×10^{-5}*
Psoriatic	7 (5)	1 (2)	0.21
Systemic-onset	8 (5)	7 (11)	0.07
Undifferentiated	5 (3)	2 (3)	0.32
Uveitis	20 (13)	7 (11)	0.4

Joint involvement (excluding RF+ polyarticular JIA)			
Joints at onset	5.2 ± 6.4	7.2 ± 9.5	0.08
Cumulative joints involved	8.4 ± 8.3	11.9 ± 11.0	0.01*
JADAS-27 joint count ever	6.5 ± 5.7	9.3 ± 8.2	4.9×10^{-3}*
Laboratory tests			
Positive ANA	43 (29)	19 (32)	0.9
Positive HLA-B27	17 (16)	3 (6)	0.6
Confirmed RF positive	12 (8)	18 (30)	8.3×10^{-4}*
Anti-CCP positive	13 (9)	18 (36)	1.8×10^{-3}*
Radiographic findings			
Osteopenia	31 (21)	20 (32)	0.08
Joint space narrowing	18 (12)	16 (26)	8.5×10^{-3}*
Treatment			
Use of systemic steroids	62(41)	43 (69)	1.2×10^{-4}*
Use of DMARD ever	113 (75)	51 (83)	0.08
Use of biologic ever	73 (49)	36 (58)	0.06

* All values are N(%) of those tested/reporting data for particular variables, except as indicated. Significant P- values considered <0.05.

Conclusion: Using a large cohort of AA and NHW children with JIA, we confirm reports of the differences in disease characteristics reported in smaller earlier studies. AA children with JIA demonstrate significant differences in disease characteristics; they are older at disease onset, more likely to have RF/CCP + polyarthritis, more likely to use systemic steroids, more likely to have a higher joint count involvement, and more likely to have radiographic evidence of disease. These observations support earlier observations that the phenotype of JIA is different in AA children.

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Development of Cut-off Values for High Disease Activity in Juvenile Idiopathic Arthritis Based On the Juvenile Arthritis Disease Activity Score. Alessandro Consolaro[1], Stefano Lanni[1], Sara Verazza[1], Maria C. Gallo[1], Marta Bertamino[1], Giulia C. Varnier[1], Serena Calandra[2], Nicolino Ruperto[3], Alberto Martini[2] and Angelo Ravelli[4]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]University of Genova, Genova, Italy, [3]Paediatric Rheumatology International Trials Organisation [PRINTO], Genova, Italy, [4]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: In the last decade, there have been major advances in the management of juvenile idiopathic arthritis (JIA), including the shift towards early aggressive interventions and the development of new therapeutic agents and combination treatment strategies. A reliable documentation of the advances in therapeutic effectiveness creates the need for validated and clinically useful criteria that describe precisely the clinical state of the patient. The study was aimed to determine cut-off values for the state of high disease activity (HDA) in JIA based on the Juvenile Arthritis Disease Activity Score (JADAS).

Methods: For the selection of cut-offs, data from a clinical database including 618 children with JIA followed between 2007 and 2011 were used. Patients were defined as being in HDA when one of the following therapeutic interventions was prescribed: 1) start of methotrexate; 2) intraarticular corticosteroid therapy; 3) start of a biologic medication; 4) start of systemic corticosteroid therapy. Patients were defined as having low disease activity (LDA) when they were receiving no therapy or had therapy discontinued, tapered or left unchanged for > 1 year. For each patient, 1 visit in HDA and 1 visit in LDA were retained. Optimal JADAS cut-offs were determined by calculating the 25th percentile of cumulative score distribution in patients with HDA and by assessing their ability to discriminate between the states of HDA and LDA through ROC curve analysis (including calculation of Youden index and fixed 90% specificity). Cross-validation of cut-offs was performed in 490 JIA patients enrolled in the PRINTO methotrexate trial (Ruperto et al, A&R 2004;50:2191-201) and on 358 patients followed longitudinally at study centers for a median of 1.7 years, and was based on assessment of discriminative and predictive validity.

Results: The cut-offs were calculated separately for patients with oligoarticular and polyarticular course of joint disease (irrespective of ILAR category) owing to the different severity of these 2 JIA phenotypes. Complete clinical data were available for 258 visits of patients with oligoarthritis and 289 visits of patients with polyarthritis. JADAS-10 and JADAS-71 cut-offs were 7.6 for oligoarthritis and 10.6 for polyarthritis. JADAS-27 cutoffs were 7.7 for oligoarthritis and 8.9 for polyarthritis. Validation analyses showed that at baseline visit of methotrexate trial 94.7% of patients had a JADAS higher than the proposed cut-off for JADAS. At 6-month visit, the percentage of patients with a JADAS higher

than the cut-off was 85.6% among nonresponders and 23.8% among responders. Evidence of predictive ability of the cut-offs was obtained by demonstrating that in the longitudinal patient sample, the percentage of patients with inactive disease or with a C-HAQ score of 0 at final visit was significantly lower among patients who had a JADAS above the cut-off value at first visit than among those who did not.

Conclusion: We developed the JADAS cut-offs for HDA in JIA. The cut-offs revealed strong discriminative and predictive ability in a clinical trial and are, therefore, potentially applicable in clinical practice, observational investigations, and therapeutic studies.

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Reasons and Predictors of Methotrexate Discontinuation in Children with JIA: Results From the Childhood Arthritis Prospective Study (CAPS). Suzanne Verstappen[1], Lucy R. Wedderburn[2], H. E. Foster[3], Eileen Baildam[4], Janet Gardner-Medwin[5], Joyce Davidson[5], Alice Chieng[6], Wendy Thomson[7] and Kimme L. Hyrich[8]. [1]University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]University College London (UCL), London, United Kingdom, [3]Newcastle Hospitals NHS Foundation Trust and Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom, [4]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [5]Royal Hospital for Sick Children, Glasgow, United Kingdom, [6]Manchester Children's Hospital, Manchester, United Kingdom, [7]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [8]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom

Background/Purpose: Methotrexate (MTX) is the DMARD of first choice in patients with juvenile idiopathic arthritis (JIA). However, limited data is available on MTX survival, including reasons for stopping MTX, and predictors for stopping MTX.

Objectives: The objectives of this study were to i) describe survival time and reasons for stopping MTX and ii) to identify possible predictors for stopping MTX due to adverse events (AE) or inefficacy.

Methods: Consecutive children with JIA treated with MTX from the Childhood Arthritis Prospective Study (CAPS), a large prospective longitudinal inception cohort study, were included. At baseline, 6 months and at annual follow-up visits a clinical examination was performed including the physician's global assessment (PGA) and number of active and limited joints. The CHAQ, was completed by the parent or the child. Start and stop dates and reasons for stopping MTX were also collected. For the present study the following definitions were applied: 1) AE, stopped due to AE and MTX not restarted for at least one month; 2) inefficacy, stopped MTX due to inefficacy or added a biologic; 3) efficacy, stopped MTX because of efficacy and MTX not restarted for at least one year; 4) other. Kaplan Meier survival curves were calculated to determine the survival probability at two years for overall, AE, inefficacy or efficacy survival. Patients were included until the date of stopping MTX or until the last follow-up date when MTX treatment was continued. Cox proportional hazards regression analyses were applied to assess the predictive ability of demographic and clinical variables assessed at time of starting MTX treatment with AE or inefficacy. Since data on disease activity were not always collected at time of MTX therapy start, disease activity and CHAQ-score assessed for a maximum of three months prior to MTX start was used, otherwise data was defined missing.

Results: 501 children (median [IQR] age at MTX start was 8.3 [4.0-12.2] yrs) received MTX after a median time since symptom onset of 7.1 [3.5-19.1] months. 244 (49%) stopped MTX, reasons: AE (n=58), inefficacy (n=121), efficacy (n=34) and other reasons (n=31). Overall median survival time was 2.4 [1.1-4.4] yrs. The estimated survival rates at two yrs were 0.87 (95%CI 0.83 to 0.90) for AE, 0.75 (95%CI 0.70 to 0.79) for inefficacy and 0.93 (95%CI 0.88 to 0.95) for efficacy. Older children were more likely to stop MTX medication because of AE (HR 1.08, 95%CI 1.01 to 1.14) or inefficacy (HR 1.06, 95%CI 1.01 to 1.10) and a high PGA score measured at MTX start (HR 1.21, 95%CI 1.04 to 1.42 (n=236)) was associated with MTX related AE survival. No other associations with AE or inefficacy survival were found, probably due to lack of power, respectively: female gender (HR, 95%CI; 0.83 (0.48 to 1.43) and 0.98 (0.66 to 1.44)), active joint count (HR, 95%CI; 0.99 (0.95

to 1.03) and 1.02 (0.99 to 1.04) (n=323)), limited joint count (HR, 95%CI, 0.99 (0.95 to 1.04) and 1.02 (0.99 to 1.04) (n=321)), and CHAQ-score (HR, 95%CI, 0.71 (0.36 to 1.41) and 1.03 (0.64 to 1.66) (n=147)).

Conclusion: In this cohort of patients with JIA starting MTX we found that children stayed on MTX therapy for a median of 2.5 years. Older age was a predictor for stopping MTX due to AE and inefficacy.

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Assessment of Subclinical Synovitis by Power Doppler Ultrasonography in Patients with Juvenile Idiopathic Arthritis. Maria Teresa Terreri[1], Vanessa M. Bugni[2], Claudio A. Len[2], Sônia de A.V. Mitraud[3], Rita NV. Furtado[4] and Jamil Natour[5]. [1]Universidade Federal de São Paulo/UNIFESP, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo/UNIFESP, São Paulo, Brazil, [3]Universidade Federal de São Paulo/UNIFESP, São Paulo, [4]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [5]Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood, leading to physical disability and poor quality of life. Advances in the treatment of JIA have led to higher remission rates. However despite clinical remission articular ultrasonography (US) can sometimes detect subclinical synovitis (SS). The aim of this study was to evaluate patients with JIA in remission and healthy controls for the presence of SS by US Power Doppler (PD), and evaluate its association with demographic and clinical variables.

Methods: Cross-sectional study of patients with JIA in remission and healthy controls, matched for age and gender. Inclusion criteria: oligoarticular and polyarticular JIA, clinical and laboratory remission (Wallace et al), between the ages 5 to 18 years. Clinical assessment: active/limited joint count, functional capacity by the Childhood Health Assessment Questionnaire (CHAQ), physician global visual analogue scale (VAS), patient global VAS, medications in use. US assessment evaluated 17 joints bilaterally. Ultrasonographic parameters included synovitis and synovial blood flow in PD. A moderate to severe degree of synovitis and/or any synovial flow present at the PD indicated the presence of SS. P-values were calculated based on the chi-square test, Fisher's exact test, student's T test and Mann-Whitney U test.

Results: Thirty-six patients (mean age 11.5 ± 3.7 years) and 36 controls (mean age 11.3 ± 3.7 years) were included and a total of 2448 joints were assessed. There were 36 JIA patients, 29 were girls, with a mean age at assessment of 11.5 ± 3.7 years and a mean age at disease onset of 4.3 ± 3.2 years. Sixteen patients had persistent oligoarticular JIA, 11 extended oligoarticular and 9 polyarticular with negative rheumatoid factor. Nine patients were off medication and 27 were on medication, with an average time of remission of 1.8 ± 2.2 years. SS was present in 46/2448 (1.8%). SS was more common in patients (41.6%) than in controls (13.9%) (p=0.009). The most frequently affected joints were the wrists (15), followed by elbows (9), ankles (8), toes (7), knees (4) and fingers (3). There were differences between patients and controls related to the presence of SS in elbows (p=0.033) and ankles (p=0.006). On ultrasonographic evaluation of JIA patients, 38/1224 (3.1%) had SS joints. Patients with JIA polyarticular/extended oligoarticular subtypes and age at onset older than 6 years old had more SS (p=0.026 and p=0.018, respectively). There were no differences in terms of gender, age at evaluation, presence of antinuclear antibodies, type of remission, duration of remission, type of medication, previous uveitis, previous intra-articular injections, physician VAS, patient VAS and CHAQ.

Conclusion: SS was present in 3.1% of joints from JIA patients considered to be in remission especially in wrists, elbows, ankles, knees, fingers and toes. Although SS was shown to be more frequent in all JIA joints than in controls, we only observed significant difference in elbows and ankles joints. SS was more common in patients with polyarticular involvement (polyarticular and extended oligoarticular) and later age of JIA onset (greater than 6 years old).

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Current Evidence of Anti-TNFα Treatment Efficacy in Childhood Chronic Uveitis: A Systematic Review and Meta-Analysis Approach Comparing the Different Drugs. Gabriele Simonini[1], Kate Druce[2], Rolando Cimaz[1], Gary J. Macfarlane[2] and Gareth T. Jones[2]. [1]Anna Meyer Children's Hospital-University of Florence, Firenze, Italy, [2]University of Aberdeen, Aberdeen, United Kingdom

Background/Purpose: To summarize evidence regarding the effectiveness of anti-TNFα treatments in childhood autoimmune chronic uveitis (ACU), non responder and/or failure to previous DMARD course.

Methods: A systematic search of articles between January 2000 and June 2012 was conducted using EMBASE, Ovid MEDLINE, Evidence Based Medicine Reviews-ACP Journal Club, Cochrane libraries, and EBM Reviews. Studies were eligible for inclusion if they investigated the efficacy of anti-TNFα therapy as the first biologic modifier immunosuppressant medication, among children ('16 yrs) naïve to any anti-TNFα, therapy in the treatment of ACU, refractory to therapy with topical treatment and/or systemic treatment and at least one immunosuppressive treatment (MTX, and/or Azathioprin and/or CSA and/or Clorambucil and/or Micofenolate Mofetil). The primary outcome for this review was the proportion of patients classified as having improved intraocular inflammation, expressed as Tyndall, as defined by the Standardization of Uveitis Nomenclature (SUN) working group criteria. We determined a combined estimate of the proportion of children in the eligible studies responding to anti-TNFα treatment: Etanercept (ETA), Infliximab (INF), or Adalimumab (ADA).

Results: The initial search identified 959 articles, of which 144 were potentially eligible. 26 eligible articles, all retrospective chart reviews, but one RCT, remained in the analysis. 245 children were included in the analysis (ADA n=27; ETA n=62 and INF n=156) and the number of children in studies ranged from 1 to 47. The pooled analysis suggested that INF and ADA have favorable effects in the improvement of intraocular inflammation: the proportion of responding subjects was 82% (95% CI: 68–96%) and 68% (61–76%) for ADA and INF respectively. In contrast, only 28% (16–40%) showed improvement with ETA. There was no difference in the proportion of responders between ADA and INF (χ^2 2.17,p=0.14), although both showed superior efficacy compared to ETA (ADA *vs* ETA χ^2 =21.1, p<0.001; INF *vs* ETA χ^2=25.5, p<0.001)

Conclusion: Although randomized controlled trials are needed, the available evidence does not support the use of ETA in the treatment of childhood ACU.; ADA and INF seem instead reliable approach for their treatment.

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Patients with Juvenile Idiopathic Arthritis From a Low Socio-Economic Background Perceive Their Disease Activity and Physical Limitations Higher Than Patients from a High Socio-Economic Background. Suzanne Verstappen[1], Joanna Cobb[2], H. E. Foster[3], Eileen Baildam[4], Lucy R. Wedderburn[5], Janet Gardner-Medwin[6], Alice Chieng[7], Joyce Davidson[6], Wendy Thomson[8] and Kimme L. Hyrich[9]. [1]University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [3]Newcastle Hospitals NHS Foundation Trust and Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom, [4]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [5]University College London (UCL), London, United Kingdom, [6]Royal Hospital for Sick Children, Glasgow, United Kingdom, [7]Manchester Children's Hospital, Manchester, United Kingdom, [8]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [9]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom

Background/Purpose: It has been suggested that socio-economic status (SES) may be associated with delayed to access to rheumatology care and with worse disease severity in patients with juvenile idiopathic arthritis (JIA). The objectives of this study were to examine the association between SES and delay to rheumatology clinic and disease severity in patients with JIA in England.

Methods: Consecutive children from the Childhood Arthritis Prospective Study (CAPS), a large prospective longitudinal inception cohort study, were included. At baseline, a clinical examination was performed including the physician's global assessment (PGA), number of active and limited joints and

JADAS71. The CHAQ, pain score, the parental general evaluation (PGE) and the CHQ, including several physical and psychosocial concepts (higher scores indicate better functioning and well-being), were completed by the child or parent. Using postcode data, SES was determined by calculating the Index of Multiple Deprivation score (IMD). Based on the ranking of the IMD score, patients were included in the low SES group (lowest quartile), middle SES group (two middle quartiles) and high SES group (highest quartile). Differences in demographic and disease characteristics between these three groups were statistically tested applying the Kruskal-Wallis test or Chi-square test for gender.

Results: 934 JIA patients with a median age of 6.8 [IQR 2.9-10.9] yrs at baseline were included in this study. At baseline the percentage of patients according to the ILAR subtypes for the low, middle and high SES classes were, respectively: systemic (3.6%, 6.8%, 8.0%), oligoarthritis (54%, 51%, 48%), extended oligoarthritis (1.6%, 2.4%, 2.5%), polyarthritis RF- (13.6%, 18.4%, 19.0%), polyarthritis RF+ (4.2%, 2.9%, 2.5%), enthesitis related arthritis (4.2%, 5.8%, 5.5%), psoriatic arthritis (6.1%, 4.2%, 5.5%), undifferentiated (7.2%, 5.8%, 4.9%), other (5.5%, 3.2%, 4.3%). There was no difference in delay to first rheumatology consultation between the three SES groups. Although no significant differences in diseases activity scores assessed by the rheumatologist were observed between the three SES groups, children and/or parents of children with JIA in the low SES group recorded higher pain scores, disease activity scores and lower physical function scores than those in the high SES group. SES did not seem to impact on psycho-social outcomes as measured in the CHQ.

Table. Demographic clinical and self-reported outcomes of disease related factors in JIA patients from low, middle and high socio-economic background

	Low SES group N = 177	Middle SES group N = 419	High SES group N = 338	P-value
Age at onset, yrs	7.6 [3.5–115]	6.1 [2.5–10.8]	6.3 [2.8–10.3]	0.0103
Gender, female	211 (62%)	265 (63%)	112 (63%)	0.843
Delay to 1st rheumatology consultation, yrs	0.37 [0.19–0.86]	0.41 [0.19–0.86]	0.35 [0.17–0.91]	0.3929
JADAS71	12.2 [5.6–16.7]	10.8 [6.0–18.1]	20.3 [5.5–16.0]	0.6620
PGA, mm	28 [17–50]	29 [15–51]	29 [13–53]	0.9744
No. limited joints	1 [1–3]	1 [1–3]	1 [0–3]	0.8891
No. active joints	2 [1–5]	2 [1–5]	2 [1–4]	0.7333
CHAQ-score	0.875 [0.312–1.625]	0.625 [0.125–1.375]	0.375 [0–0.875]	0.0001
Pain score, mm	39 [14–64]	30 [6–55]	18 [4–49]	0.0003
PGE, mm	30 [7–52]	20 [3–50]	15 [4–36]	0.0013
CHQ score				
Physical functioning	56 [28–89]	72 [33–94]	89 [39–100]	0.0016
Role social limitations	50 [33–100]	75 [33–100]	86 [67–83]	0.0043
Bodily pain/discomfort	40 [20–60]	50 [20–70]	50 [30–80]	0.0081
Behaviour	73 [56–83]	68 [56–83]	77 [60–85]	0.3698
Mental health	75 [55–85]	75 [60–85]	75 [65–85]	0.3379
Self esteem	73 [54–88]	71 [50–83]	75 [67–88]	0.1167
General health perception	60 [43–75]	64 [52–73]	70 [60–81]	0.0028
Parental impact-emotional	67 [33–83]	58 [33–83]	67 [42–83]	0.4277
Parental impact - time	89 [56–100]	89 [56–100]	89 [67–100]	0.3193
Family activities	71 [48–88]	79 [50–96]	83 [58–96]	0.0176
Family cohesion	85 [60–85]	85 [60–85]	85 [60–85]	0.9630

Scores are median [IQR] or %

Conclusion: Patients from lower SES background score their disease activity and functional disability higher than patients from higher SES background, whereas no differences were found in disease activity scores obtained in clinic between the different SES groups. This study suggests that it is important to take SES background into account when patients with JIA present to the clinic for the first time.

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Risk Factors for Radiologic Progression in Polyarticular Juvenile Idiopathic Arthritis Patients Treated with Biologic Agents. Tomohiro Kubota[1], Tsuyoshi Yamatou[1], Yukiko Nonaka[1], Harumi Akaike[2], Tomokazu Nagakura[3], Yuichi Yamasaki[1], Tomoko Takezaki[1], Yasuhito Nerome[1], Hiroyuki Imanaka[1] and Syuji Takei[1]. [1]Kagoshima University, Kagoshima City, Japan, [2]Kagoshima University, Kagoshima, Japan, [3]House of Megumino-seibo, Usuki, Japan

Background/Purpose: Progression of joint damage is sometimes observed in JIA patients during the biologic therapy. However, it is difficult to evaluate the radiographic progression by simple radiographs because the width of joint space and ossification varies with age. Carpal length (CL) is a useful measure component for identifying joint space narrowing due to cartilage damage of the wrist in children[1–2].

Therefore, the risk factors for radiologic progression during the biologic therapy were investigated by evaluating the CL in polyarticular JIA patients.

Methods: Forty-six polyarticular JIA patients initiating biologics were followed up prospectively for mean 3.1 years. RF was positive in 36 out of 46, and all had active arthritis in the wrist at starting biologic therapy. Duration from the onset to initiating biologics was mean 3.1 years, and the 1st biologic agents used were etanercept in 21, adalimumab in 7, infliximab in 9, and tocilizumab in 9. CL was measured from radiographs of the wrist obtained at baseline (n=46), at 1year (n=36), and at 3 year (n=20), and the standard deviation (SD) of CL calculated by Poznanski's formula established from healthy children[1] was analyzed.

Results: 1) Changes in CL (SD) from baseline (Figure).
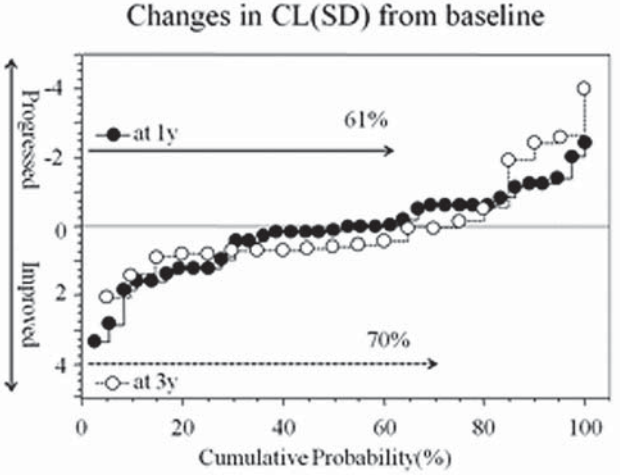
At 1 year after starting biologics, incidence of patients with increased (improved) or sustained CL(SD) was 61%, which indicated that 61% patients had no radiographic progression of joint damage of the wrist during the first year of biologic therapy. At 3 year from baseline, 70% of patients showed no radiographic progression of joint damage.

2) Risk factors for progression of joint damage.

Background, clinical features, disease activity by $DAS28_{ESR}$, and the biologic therapy were compared between two groups of patients with improved/sustained CL(SD) and with non-improved CL(SD) to determine the risk factors for radiologic progression after 1 year biologic therapy.

As the result, incidence of the patients showed no statistical difference between the two groups as to sex (male, female), onset age (<10 y, ≥10 y), RF (positive, negative), disease duration at initiating biologic therapy (<1 y, $1-<3$ y, ≥3 y), 1st biologic agent used, and episode of switching to the 2nd biologic agent. However, the incidence of patients who attained $DAS28<2.6$ remission was significantly higher in improved/sustained CL(SD) group (100%) than that of non-improved CL(SD) group (46%) (Qui square=7.038, P=0.0080).

Conclusion: Biologics can prevent the radiologic progression of wrist in only patients who attained the $DAS28<2.6$ remission during the first year treatment. Switching to the 2nd biologic agent may be needed in polyarticular JIA patients who failed to complete the $DAS28<2.6$ remission.

1) Poznanski AK et al. Radiology 1978;129:661-8.
2) Ravelli A, et al. J Pediatr 1998; 133:262-5

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Orofacial Anomalies in Children with Confirmed Juvenile Idiopathic Arthritis. Bernd Koos[1], Franka Stahl de Castrillon[2], Robert Ciesielski[1] and Nikolay Tzaribachev[3]. [1]University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany, [2]Department of Orthodontics, University of Rostock, Germany, Rostock, Germany, [3]Center for Rheumatic Diseases, Bad Bramstedt, Germany

Background/Purpose: In children with juvenile idiopathic arthritis (JIA) temporomandibular joints (TMJ) are affected in up to 96% of the patients,

where TMJ arthritis is frequently asymptomatic. Despite that, orofacial anomalies occur in many patients and tend to be correlated with dysfunction and excessive mechanical strain, which may complicate treatment and aggravate TMJ destruction.

To examine the prevalence and severity of relevant orofacial anomalies in patients with JIA compared to healthy children and to assess the correlation with Gadolinium (Gd) enhanced MRI.

Methods: TMJ data of 216 consecutive JIA patients (69% female, median age 12.9 years) were compared to TMJ data of 3756 healthy children (Stahl, Grabowski et al., 2007; Hirsch et al., 2009). JIA patients were divided into group I (2-10 years) and group II (10-18 years). The following measurements were taken: occlusal relations, mandibular position, deep and open bite (group I) and TMJ noise, tenderness to palpation of the TMJ or the masticatory muscles, reduced mouth opening (group II). In a subgroup (37 consecutive JIA patients, 57% female, median age 11.1 years) Gd MRI examinations were analyzed and compared to functional measurements. Sensitivity and specificity of the functional measurements were determined.

Results: Mandibular asymmetry was found in 35% of patients (15% right, 20% left; no correlation with sex; $p = 0.76$). Inhibited mandibular growth (distocclusion) was seen in 59% of patients (no correlation with sex; $p = 0.57$). Open bite was seen in 6.5%, deep bite in 33% of the children.

TMJ arthritis was demonstrated in 81% of the children from the MRI subgroup. Pathological TMJ sounds were present in 26% of the patients, but showed no statistical significance ($p = 0.16$). TMJ and masticatory muscles tenderness were present in 46.8% and 40.2%, respectively. Limitation of the interincisal opening was found in 14.4% of the patients. A positive statistical correlation was found for these functional measures (tenderness to palpation $p \leq 0.001$ and limitation of interincisal opening $p = 0.002$), but sensitivity was low at 53% (specificity: 89%).

Conclusion: The prevalence of orofacial abnormalities is noticeably increased in JIA patients compared to healthy children, particularly inhibition of the mandibular growth and mandibular asymmetries. Clinical findings and inflammatory state of TMJ does not reliable correlate. This mandates interdisciplinary TMJ treatment including orthodontics especially with respect to the high prevalence of TMJ dysfunction.

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Factors Associated with Achievement of Inactive Disease in Children with Juvenile Idiopathic Arthritis Treated with Etanercept. Nicoletta Solari[1], Elena Palmisani[1], Alessandro Consolaro[1], Sara Dalprà[1], Benedetta Schiappapietra[1], Giulia Bracciolini[1], Silvia Rosina[1], Giorgia Negro[1], Alberto Martini[2] and Angelo Ravelli[3]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]University of Genova, Genova, Italy, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: The advent of new therapies for juvenile idiopathic arthritis (JIA), particularly the introduction of biologic medications, has increased considerably the potential for treatment benefit, with clinical remission being now a realistic goal for a substantial proportion of patients. However, the assessment of remission has seldom been incorporated in clinical trials of biologics in JIA. Moreover, little information exists on predictors of the effectiveness of biologic medications. The study aim was two-fold: 1) to evaluate the rate of inactive disease (ID) in children with juvenile idiopathic arthritis (JIA) treated with etanercept (ETN); 2) to identify clinical characteristics associated with attainment of ID.

Methods: The clinical chart of all consecutive JIA patients who were given ETN between 2002 and 2011, and had a follow-up of at least 6 months after ETN start were reviewed. For each patient, all visits made from ETN initiation to the last follow-up evaluation in which the patient was still receiving ETN were examined to establish whether the patient had reached the state of ID, defined by the Wallace criteria (J Rheum 2004;31:2290-4), and to identify the first visit in which ID was documented. Clinical characteristics associated with achievement of ID were sought for by means of univariate analyses and Cox regression procedures. Predictive factors included sex, age at disease onset, age and disease duration at treatment baseline, interval between first observation at study center and start of ETN, ILAR category, antinuclear antibody status, JIA outcome measures at ETN start, joints affected before ETN start, and medications administered before ETN start and administered concomitantly during ETN therapy.

Results: A total of 173 patients who received ETN for a median of 2.2 years (range 0.5–10.5 years) were included in the study. Eighty-seven patients (50.3%) achieved ID a median of 0.6 years (range, 0.1–2.5 years) after the initiation of ETN therapy. The rate of ID was much lower in children with systemic JIA than in those with non-systemic categories altogether (29.6% vs. 54.1%). At last follow up visit, 0.5 to 10.5 years after ETN start (median, 2.2 years), 85 patients (49.1%) still had ID and 70 patients (40.5%) met the criteria for clinical remission on medication. The probability of achievement of ID after 6, 12 and 24 months of therapy was 24%, 46% and 57%, respectively. On Cox regression analysis, the attainment of ID was associated with lack of wrist involvement [HR_{Adj} (95% CI): 2.19 (1.38-3.48), p=0.0006] and an age at onset < 3.6 years [HR_{Adj} (95% CI): 1.61 (1.04- 2.49), p=0.03]. A secondary analysis made after the exclusion of the 27 children with systemic JIA led to identify the same predictors

Conclusion: Around half of our JIA patients treated with ETN in standard clinical care were able to achieve the state of ID. Children who lacked wrist involvement and had a younger age at disease onset had a greater likelihood of achieving ID during ETN administration. Thus, the presence of wrist disease and an older age at disease presentation may constitute an indication for the earlier introduction of ETN or its administration in combination with methotrexate.

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Clinical and Therapeutic Features of 312 Patients with Macrophage Activation Syndrome Enrolled in a Multinational Survey. Sergio Davì[1], Francesca Minoia[1], Erkan Demirkaya[2], Chiara Suffia[1], Mario Abinun[3], Amita Aggarwal[4], Nuray Aktay Ayaz[5], Maria Alessio[6], Jordi Anton[5], Maria Apaz[5], Tadej Avcin[7], Patrizia Barone[8], Blanca E. Bica[9], Isabel Bolt[10], Luciana Breda[11], Vyacheslav Chasnyk[12], Rolando Cimaz[5] Fabrizia Corona[5], Ruben Cuttica[13], Gianfranco D'Angelo[14], AnnaCarin Horne[15], Nicola Ruperto[1], Alberto Martini[1], Randy Q. Cron[16] and Angelo Ravelli[5]. [1]Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova, Italy, [2]International Investigator Consortium for MAS Diagnostic Criteria, Ankara, Turkey, [3]International Investigator Consortium for MAS Diagnostic Criteria, Newcastle upon Tyne, United Kingdom, [4]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [5]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [6]University of Naples Federico II, Naples, Italy, [7]International Investigator Consortium for MAS Diagnostic Criteria, Ljubljana, Slovenia, [8]International Investigator Consortium for MAS Diagnostic Criteria, Catania, Italy, [9]International Investigator Consortium for MAS Diagnostic Criteria, Rio de Janeiro, Brazil, [10]International Investigator Consortium for MAS Diagnostic Criteria, Zurich, Switzerland, [11]International Investigator Consortium for MAS Diagnostic Criteria, Chieti, Italy, [12]International Investigator Consortium for MAS Diagnostic Criteria, Saint-Petersburg, Russia, [13]International Investigator Consortium for MAS Diagnostic Criteria, Buenos Aires, Argentina, [14]International Investigator Consortium for MAS Diagnostic Criteria, Ancona, Italy, [15]Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden, [16]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: A multinational collaborative effort aimed to develop a new set of criteria for macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (sJIA) has been recently started. The first step of the project, based on a Delphi survey, has been completed (Davì S et al. J Rheumatol 2011;38:764-8). The second step, whose goal is to collect the data of a sizable sample of children with MAS and with potentially 'confusable' conditions, is currently under way. The study aim is to describe the demographic, clinical, laboratory, histopathologic, therapeutic and prognostic features of children with MAS collected so far in the data-collection phase of the project.

Methods: Investigators who participated in the Delphi survey were asked to enter the information of their patients with MAS collected retrospectively in a web-based database, developed by the Pediatric Rheumatology International Trials Organization (PRINTO).

Results: At the 31st of May, 2012, 312 patients with sJIA-associated MAS have been entered in the study website by 87 investigators from 27 countries. 181 (58%) patients were females and 131 (42%) were males. The age at onset of sJIA ranged from 0.2 to 15,9 years (median 5,1 years) and the disease duration from onset of sJIA and onset of MAS ranged from 0 to 15,6 years (median 0,3 years). MAS occurred at onset of sJIA in 50 (20,2 %)

patients. The frequency of the clinical, laboratory and histopathologic features of MAS is reported in the Table. The most frequently reported trigger of MAS was active disease (35,3%), followed by infection (26,3%) and medication toxicity (3,7%). 69 (37,1%) patients were admitted in the ICU. Therapeutic interventions included iv steroids (88.0%), oral steroids (74.1%), cyclosporine (65.5%), other immunosuppressants (13.8%), iv Ig (36.3%), etoposide (11.1%), anakinra (6.8%), and plasma exchange (5.4%). The mortality rate was 8.2%.

Table. Frequency of clinical, laboratory, histopathologic features of 312 patients with MAS.

Feature	No. with info available	Percentage
Falling platelet count ($\leq 262 \times 10^9$/l)	286	74.8
Hyperferritinemia (≥ 500 ng/ml)	256	91.4
Bone marrow hemophagocytosis	214	60.7
Increased liver enzymes (AST > 59UI/L)	275	74.9
Falling leukocyte count ($< 4 \times 10^9$/l)	285	21.1
Persistent continuous fever $\geq 38°C$	302	63.9
Hypofibrinogenemia ($\leq 2,5$ g/l)	250	48.4
Hypertrigliceridemia (≥ 265 mg/dl)	221	43.9
Central nervous system dysfunction	302	36.1
Increased D-dimer (≥ 500 ng/ml)	105	88.6
Hemorrhagic manifestations	301	20.9
Liver enlargement	305	70.5
Spleen enlargement	301	59.5

Conclusion: Hyperferritinemia, increased liver enzymes and falling platelet count were the most frequently observed laboratory abnormalities. The frequency of falling leukocyte count was unexpectedly low. Also unexpectedly, liver and spleen enlargement were recorded more frequently than persistent continuous fever. Hemophagocytosis was noticed in around two third of patients who underwent bone marrow aspirate. As expected, corticosteroids and cyclosporine were the most commonly administered medications.

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Golimumab in 25 Young Adults Affected by Juvenile Idiopathic ARTHRITIS NON Responders to OTHER Biological Agents: Preliminary DATA. Irene Pontikaki[1], Orazio De Lucia[1], Maurizio Gattinara[1], Alessandra Salmaso[1] Pier Luigi Meroni[2] and Valeria Gerloni[1]. [1]Orthopedic Institute Gaetano Pini, Milano, Italy, [2]Istituto G. Pini, University of Milan, Milano, Italy

Background/Purpose: Biological agents licensed in JIA have demonstrated a favourable benefit-to-risk profile. Nevertheless, intolerance, loss and lack of efficacy or adverse events have led to try other therapeutic options. Ultrasound can help in the assessment of active synovitis. The purpose of this study was to evaluate efficacy and safety of Golimumab in young adults affected by JIA with active polyarthritis (with or without uveitis), non responders to MTX, antiCD20 and anti-IL-1 and intolerant to the first generation of antiTNF (Infliximab, Etanercept and Adalimumab) by EULAR criteria and power Doppler ultrasound (PDUS).

Methods: In our Centre, since november '99 to dicembre 2011, 288 patients affected by refractory JIA were treated with TNF inhibitors and since May 2011, 25 patients (16 F, 9 M) affected by refractory JIA, non responders to other biologic agents, were enrolled in Golimumab (Simponi).

Patients had failed MTX as monotherapy, previous TNF inhibitors, Rituximab and anti-IL1 therapy. Two patients had been treated with 8 different biologic agents, 1 patient with 7, 2 patients with 6, 5 patients with 5, 3 with 3, 7 with 2 and 3 patients with just one previous biologic agent.

Two patients had a Systemic onset of JIA, 4 polyarthritis RF negative, 3 enthesitis related arthritis, 1 psoriatic arthritis, 6 oligoarthritis persistent and 9 oligoarthritis extended. Median age was of 28.7 years, median onset age 7.3 years, median disease duration 19.8 years. All patients had active

disease according to EULAR criteria, 8 patients had a previous history of chronic Iridociclitis. Patients received Golimumab at the dose of 50 mg subcutaneously every month, as in RA. Fifteen patients receive Golimumab in association with MTX. All patients underwent basal assessment of DAS 28 and after 4 months DAS 28 and PDUS assessment of the same 28 joints. Presence of synovitis at PDUS examination was considered in presence of at least one between joint effusion, synovial thickening and power Doppler signal detected in accordance to OMERACT criteria.

Results: Seventeen patients (68%) were responders according both to DAS 28 and PDUS, 5 patients were not evaluable because of follow-up less than 12 weeks and 3 patients were non responders (1 of these 3 pts dropped-out). In non responder patients PDUS showed a higher number of joints involved. No adverse events were observed. No adverse events occured.

Conclusion: Golimumab seems to be effective and well tolerated and could be a good treatment of long lasting refractory JIA in young adults who failed other biologics. Data found are confirmed by PDUS examination. This study seem to be one of the first experiences in the use of Golimumab in young adults affected by JIA.

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Cost-Effectiveness Analysis of Early Biologic Treatment in Polyarticular Juvenile Idiopathic Arthritis. Nadia Luca[1], Heather Burnett[2], Wendy Ungar[2], Timothy Beukelman[3], Brian M. Feldman[2], Gwen Schwartz[4] and Ahmed Bayoumi[5]. [1]Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]Univ of Alabama-Birmingham, Birmingham, AL, [4]St. Michael's Hospital, Toronto, ON, [5]Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON

Background/Purpose: The optimal timing of high cost biologic therapies in the treatment of polyarticular juvenile idiopathic arthritis (JIA) is uncertain. We evaluated the economic and health outcomes of initial compared with step-wise use of anti-tumor necrosis factor (TNF) agent, etanercept (ETN), in this setting.

Methods: We conducted a cost-utility analysis of two strategies from a Canadian health care payer perspective. In one strategy, initial therapy was with methotrexate (MTX) alone. ETN was added in a step-wise fashion for patients who did not respond to MTX. In the other strategy, initial therapy was with MTX in combination with ETN; patients who did not respond switched to another anti-TNF agent. In both strategies, third and fourth line therapies were modeled with additional biological agents. Our base case was a 12-year-old child (weight 40 kg) with newly diagnosed polyarticular JIA naïve to disease-modifying and biological agents. We simulated the course of the disease over 5 years using a Markov model with a cycle length of 1 month. Treatment response was defined as achieving an ACR Ped 70 response or better after 4 months of therapy. If this response was sustained over 12 months, without flare, patients entered a remission state. We derived model parameters, including treatment efficacy, disease flares, adverse events, costs, and quality of life weights from the medical literature. Effects were calculated as quality-adjusted life years (QALYs); costs and QALYs were discounted at a rate of 3% per year. We conducted sensitivity analyses on all model parameters to assess the robustness of our results and used a $50,000/QALY threshold for cost-effectiveness.

Results: Our model predicted that the proportion of patients entering remission after 5 years was 89% with initial MTX and 93% with initial MTX and ETN combination. Median time to remission was 20 months in the MTX monotherapy group and 16 months in the combination group. The combination of initial MTX and ETN, compared to MTX alone, resulted in a discounted incremental cost of $14,498 per patient over 5 years and yielded a discounted incremental effect of 0.15 QALYs, for an incremental cost-effectiveness ratio of $97,517 per QALY. The results were sensitive to the cost of ETN and estimates of the efficacy of initial combination therapy.

Conclusion: Our model suggests that using initial combination therapy of MTX and ETN is unlikely to be cost-effective compared to using MTX alone, but more research is needed on key model parameters, including efficacy of initial anti-TNF agents and their impact on quality of life. A reduction in the cost of ETN by 33% would make initial use of this drug cost-effective.

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Obstetrical Complications in Women with Juvenile Idiopathic Arthritis.
Evelyne Vinet[1], Sasha Bernatsky[2], Mohammed Kaouache[2], Christian A. Pineau[1], Ann E. Clarke[3], Elizabeth Hazel[1], Ciaran M. Duffy[4], Anick Bérard[5] and Debbie Ehrmann Feldman[6]. [1]McGill University Health Centre, Montreal, QC, [2]Research Institute of the McGill University Health Ctre, Montreal, QC, [3]MUHC, Montreal, QC, [4]Children's Hospital of Eastern Ontario, Ottawa, ON, [5]Université de Montréal, [6]Université de Montréal, Hampstead, QC

Background/Purpose: Juvenile idiopathic arthritis (JIA) most often affects women before childbearing age. Patients with JIA and their parents often ask about the potential impact of the disease on future pregnancies. Little is known about the risk of obstetrical complications in women with JIA. In a large population-based study, we aimed to determine if women with JIA have an increased risk of obstetrical complications compared to women without JIA.

Methods: We identified all women who had a hospitalization for their first delivery after JIA diagnosis using Quebec's physician billing and hospitalization databases (1996–2008). Women were defined as JIA cases if they had ≥ 1 hospitalization with the *International Classification of Diseases, Ninth Revision* (ICD-9) code 714, as a primary or secondary diagnosis, or ≥ 2 physician visits with the ICD-9 code 714, occurring 2 months to 2 years apart, both prior to the age of 18 years and prior to the delivery. We randomly selected a general population control group, composed of women with their first delivery and matched at least 3:1 for age and year of delivery, without a preceding diagnosis of JIA.

We ascertained the length of hospitalization for delivery, the occurrence of gestational diabetes, premature rupture of membranes (PROM), preeclampsia/eclampsia, and caesarean section (c-section), at the time of hospitalization for delivery, based on relevant diagnostic or procedures codes.

Results: We identified 1406 women with JIA. Of these women, 90 had their first delivery after JIA diagnosis, during database follow-up, and were matched to 448 controls. Mean age at JIA diagnosis was 15.3 years (95% CI 14.8, 15.8) and mean age at delivery was 22.9 years (95% CI 22.3, 23.5). There was no difference in the length of hospitalization for delivery between women with JIA and controls [3.2 days (95% CI 2.9, 3.5) vs 2.8 days (95% CI 2.7, 3.0)]. Compared to controls, women with JIA did not experience more gestational diabetes [1.1% (95% CI 0.1, 6.9) vs 1.1% (95% CI 0.4, 2.7)], PROM [8.9% (95% CI 4.2, 17.3) vs 8.3% (95% CI 6.0, 11.3)], preeclampsia/eclampsia [3.3% (95% CI 0.9, 10.1) vs 4.7% (95% CI 3.0, 7.2)], or c-section [20.0% (95% CI 12.6, 30.0) vs 20.5% (95% CI 17.0, 24.6)].

Conclusion: Our findings suggest that women with JIA do not seem to have an increased risk of obstetrical complications compared to the general population. We are currently expanding this study by performing mother-child linkage to further assess neonatal outcomes in children born to women with JIA and their controls.

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Folate Usage in Methotrexate - Treated Juvenile Idiopathic Arthritis Patients Is Inconsistent and Highly Variable.
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Background/Purpose: Low-dose weekly methotrexate (MTX) is the first-choice second-line drug in the treatment of juvenile idiopathic arthritis (JIA). Folate (as either Folic acid (FA) or Folinic acid (FLA)) effectively ameliorates or prevents some of MTX's adverse events (AE) in adults with RA. Folate supplementation in JIA, therefore, has become the standard of care in many medical centers. Although widely used in JIA patients, including in research studies, the evidence for folate-use in JIA to prevent AEs is based on only one-43 patient, non-randomized retrospective case series. To begin defining the most commonly used folate regimens, we examined the methods of folate supplementation in MTX-treated JIA patients among pediatric rheumatologists around the globe, using an electronic survey.

Methods: An Internet-based survey was distributed among the registrants of the pediatric rheumatology list serve, an electronic forum and mailing list, which hosts 1040 subscribers worldwide. The survey was initiated between March and April 2011 and followed up with 3 subsequent electronic reminders. Chi-square tests of proportions were used to compare the distribution of responses between US and Non-US populations. A Bonferroni corrected significance level of 0.0125 was used to account for repeated testing.

Results: 214 pediatric rheumatologists from 25 countries responded to the survey (table 1). 11.7% of respondents do not routinely use ANY folate supplementation unless the patient experiences AEs during the course of treatment; 72.5% prescribe only FA; 5.1% prescribe only FLA; and 10.7% use both forms of folate supplementation.

Table 1. Folate supplementation in MTX-treated JIA

Regimen	Total (%, n=214)	US (%, n=128)	Non-US (%, n=86)	p-value
Folic acid	72.5	62.5	87.2	0.0001
Folinic acid	5.1	5.5	4.7	0.9600
Both	10.7	16.4	2.3	0.0024
None*	11.7	15.6	5.8	0.0484

* Only if the patient experiences adverse events during the course of treatment

An extremely wide spectrum of prescribing regimens (71 unique regimens) for folate supplementation was reported:
1) Folic acid (FA): Some physicians used multivitamin supplements as the source of their FA. Others used FA in doses between 400 mcgs and 10 mg daily, 6 days per week or only 24–48 hours after MTX intake.
2) Folinic Acid (FLA): FLA was generally used in dose ranges of 5–10 mg once a week (24 hours after MTX intake).

A majority of the responders (53.6%) agreed with the statement that they did not know which supplementation regimen was superior.

Conclusion: We found a high degree of variability among pediatric rheumatologists in how and whether folate supplementation is used in JIA. This variability, often arising from a lack of evidence and certainly true in this case, emphasizes the need for a well-designed clinical trial to support a rational regimen of either FA or FLA supplementation in MTX-treated JIA patients.

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Validation of BASDAI and BASFI in Children with Spondyloarthritis.
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Background/Purpose: Juvenile-onset Spondyloarthritis (JSpAs), referred to as Enthesitis-Related Arthritis (ERA) subtype under the International League of Associations for Rheumatology (ILAR) classification is characterized by arthritis and enthesitis largely affecting the lower limbs. Axial involvement is uncommon at presentation, but may develop later in life. Although there are validated instruments assessing spinal disease in adults with Ankylosing Spondylitis (AS) such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI), there are no validated tools to measure disease activity or functional impairment in this population of children. We have previously reported excellent intra-rater reliability of the BASDAI and BASFI. The aims of the current study were to measure the validity and responsiveness of these two adult scores in ERA.

Methods: Patients diagnosed with ERA followed in the JSpA Clinic at The Hospital for Sick Children (June 2009 - June 2010) were enrolled into the study. The BASDAI and BASFI were measured prospectively at baseline and again at 4 to 6 months. At each study visit, joint and entheseal clinical exams were performed according to a standardized protocol. The data collected at baseline and follow up visit were used to assess construct validity and were expressed using Pearson's correlation coefficient. Responsiveness (sensitivity to change) was calculated in a subgroup of patients who showed changes in their joint and entheseal counts over time by dividing the mean change between the two assessments by the standard deviation of the change scores and was expressed by effect size.

Results: There were 41 patients (85% male) with a mean age at diagnosis of 12.1 ± 7.6 years and average age at enrollment of 14.5 ± 2.5 years.

Average disease duration at the time of the study was 5.1 ± 2.4 years. 46% were HLA B27 positive, 17% had a family history of Spondyloarthritis. 70% had SI involvement confirmed radiographically. The average time between baseline and follow up clinic visits was 4.6 ± 2.3 months. Correlations between both the BASDAI and the BASFI and active joint counts were found to be high ($r = 0.6$) while correlations with sites of enthesitis were found to be moderate (r = 0.3 – 0.4). Responsiveness was greatest in effect size for the BASDAI for detecting worsening arthritis (0.8) and improving enthesitis (0.7). For the BASFI, effect size was large for detecting worsening arthritis (0.9) and was moderate for improving enthesitis (0.4).

Conclusion: Our study demonstrates that the BASDAI and the BASFI show adequate construct validity and responsiveness and may be used in the evaluation of disease activity and functional impairment in children with JSpA. Correlations were higher for both measures in arthritis than in enthesitis, and sensitivity to changes over time showed the largest effect sizes for detecting worsening arthritis. For enthesitis, the BASDAI showed a larger effect size for detecting improving enthesitis than the BASFI. The results of this study illustrate that these two instruments validated in adults may become an objective addition to developing Paediatric JSpA core sets.

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Delineating the Role of Multiple Corticosteroid Joint Injections in the Management of Juvenile Idiopathic Arthritis in the Biologic Era.
Charalampia Papadopoulou[1], Maria I. Gonzalez[1], Juan C. Nieto[1], Mikhail Kostik[1], Marek Bohm[1], Stefano Lanni[1], Valentina Muratore[2], Alessandro Consolaro[1], Alberto Martini[3] and Angelo Ravelli[3]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [3]University of Genova, Genova, Italy

Background/Purpose: Intra-articular corticosteroid injection (IACI) therapy in juvenile idiopathic arthritis (JIA) is generally considered for the treatment of children with arthritis in a small number of joints, particularly large joints. However, the current place of multiple IACIs in the management of JIA is still uncertain. The aim of this study was to investigate the efficacy and safety of multiple IACIs, and to seek for factors associated with sustained remission of synovitis in injected joints.

Methods: The clinical charts off all JIA patients who received an IACI in ≥ 3 joints and had a follow-up ≥ 6 months after the IACI were reviewed. The corticosteroid preparation used was triamcinolone hexacetonide for large joints and methylprednisolone acetate for small or difficult to access joints. In each patient, the follow-up period after the IACI was censored when one of the following two events occurred: 1) first visit with flare of synovitis in ≥ 1 injected joint; 2) last follow-up visit with sustained remission of synovitis in all injected joints. Flare of synovitis was defined as recurrence (or persistence) of joint inflammation in ≥ 1 joint that required a new IACI or the initiation or change of systemic therapy, and remission of synovitis as complete resolution of all signs and symptoms of joint inflammation.

Results: A total of 220 patients (79.5% females) who underwent an IACI in 1086 joints (median 4 joints per patient) were included. The median age at IACI was 3.7 years and the median disease duration was 0.6 years. The most common ILAR categories were RF-negative polyarthritis (37.1%) and extended oligoarthritis (34.1%). The most frequently injected joints were the knee (84.5% of patients), ankle (76.4%), subtalar (30.5%), elbow (29.1%), and proximal interphalangeal (PIP) (26.4%) joints. Concomitant therapy included methotrexate in 56.8% of patients and biologic medications in 9.5% of patients. Seventy (31.8%) of patients had sustained remission in all injected joints after a median follow-up of 1 year, whereas 150 patients (68.2%) experienced flare of synovitis after a median of 0.5 years. Univariate analyses showed that patients with sustained remission had more frequently a positive ANA status (p=0.04) and an oligoarticular disease course (p=0.004), and had received more frequently general anesthesia (p=0.03) and concomitant methotrexate therapy (0.003) than did patients who experienced flare of synovitis. Flare of synovitis was seen more frequently in the ankle (45.2%), wrist (40.2%), and subtalar (34.5%) joints, than in the knee (20.8%), metacarpophalangeal (26.2%), PIP (21.3%), and elbow (15.5%) joints. Side effects occurred in only 1% of joints and were represented by skin hypopigmentation or subcutaneous atrophy.

Conclusion: Around one third of the patients who received multiple IACIs experienced long-lasting remission of synovitis in all injected joints.

General anesthesia and concomitant administration of methotrexate may increase the effectiveness of IACI procedures. The presence of ankle, subtalar and wrist joint involvement may constitute an indication to the simultaneous initiation of a more aggressive systemic therapy at the time of the injection.

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Targeting Remission in Juvenile Idiopathic Arthritis in Routine Clinical Care: Experience in 175 Newly-Diagnosed Patients.
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Background/Purpose: The recent advances in the management of juvenile idiopathic arthritis (JIA) have increased considerably the potential to achieve disease remission or, at least, low levels of disease activity, and have consequently moved the therapeutic aims increasingly towards the attainment of an inactive disease (ID) status. Complete disease quiescence is regarded as the ideal therapeutic target because its achievement helps preventing further joint damage and disability and may enhance physical function and quality of life. These issues have led to suggest that a tight control approach be adopted in the management of children with JIA. We describe our experience with treating JIA patients to specified targets.

Methods: Starting in March 2007, a treat-to-target approach to the management of all children with JIA first seen in the senior author's clinic was implemented, setting achievement of ID as primary goal and achievement of minimal disease activity (MDA) or parent-acceptable symptom state (PASS) as secondary goal. In case primary goal was not reached, treatment was intensified as deemed necessary. For the purpose of this study, patient records were reviewed to evaluate the frequency of achievement of primary and secondary therapeutic goals at 6, 12, 18 and 24 months following initial evaluation. ID, MDA and PASS were defined according to both established criteria and Juvenile Arthritis Disease Activity Score (JADAS) cutoffs. The outcome of patients who achieved or did not achieve ID at last follow-up visit was compared by means of the Juvenile Arthritis Functionality Scale (JAFS) and the Pediatric Rheumatology Quality of Life scale (PRQL).

Results: A total of 175 patients (77.7% females) were enrolled. The most common ILAR subtypes were persistent oligoarthritis (53.1%), extended oligoarthritis (14.9%), and RF-negative polyarthritis (14.3%); 3.4% of patients had systemic arthritis. The median age at disease onset was 2.8 years. At baseline visit, the median age was 3.5 years and the median disease duration was 0.2 years. Initial therapeutic interventions included intra-articular corticosteroid injection (84%), methotrexate (28%), systemic corticosteroids (5.7%), and biologic medications (1.1%). The frequency of achievement of treatment goals at study endpoints is shown in the table. At last follow-up visit, patients who had achieved ID had better functional ability (p=0.007) and physical well-being (p=0.007) than those who did not. The frequency of clinical remission on medication was 29.2%.

	6 months N (%)	12 months N (%)	18 months N (%)	24 months N (%)
Inactive disease (ID)	50 (35.2)	48 (41)	46 (47.4)	45 (50.6)
Minimal disease activity (MDA)	62 (43.7)	71 (60.7)	60 (61.9)	53 (59.6)
Parent-acceptable symptom state(PASS)	76 (66.1)	77 (74.8)	69 (82.1)	53 (70.7)
JADAS10 ≤ 1 (ID)	43 (31.6)	46 (41.4)	43 (46.2)	33 (39.3)
JADAS10 ≤ 2/3.8 (MDA)	51 (37.5)	58 (52.3)	60 (64.5)	40 (47.6)
JADAS10 ≤ 3.5/5.4 (PASS)	64 (47.1)	66 (59.5)	67 (72)	52 (61.9)

Conclusion: At 2 years after initial visit, a substantial percentage of patients had reached the states of ID or MDA or were in PASS. Patients who achieved ID had better physical function and well-being than those who did not. These findings suggest that the implementation of a treat-to-target approach may help improve patient outcomes.

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Severe Adverse Events Associated with Use of Biologic Therapy in Juvenile Idiopathic Arthritis: A Single-Center Study. Ricardo A. G. Russo[1] and Marìa M. Katsicas[2]. [1]Hospital de Pediatrìa Garrahan, Buenos Aires, Argentina, [2]Hospital de Pediatrìa Garrahan, Buenos Aires, Argentina

Background/Purpose: biologic agents have revolutionized the treatment of Juvenile Idiopathic Arthritis (JIA) and other conditions due to their high efficacy and safety. However, with the increased and prolonged use of these agents there is uncertainty regarding adverse events, especially in the long-term. The purpose of this study is to describe and analyse SAEs occurring during biologic therapy in a cohort of patients with JIA.

Methods: unicenter, retrospective longitudinal study based on review of a prospectively built, ad-hoc database and medical records. Observation period was January 2000-December 2011. Demographic data, JIA class, disease duration at start of biologic treatment, time from start of biologic treatment to occurrence of SAEs, type and dosage of biologic agents, total time of biologic therapy, concomitant methotrexate (MTX) and prednisone therapy, system involvement during SAEs, and outcomes were recorded. SAEs were defined as any untoward medical occurrence that occurs during observation and results in death, a life-threatening illness, hospitalization, persistent or significant disability or incapacity, or a medically significant event that jeopardized the health of the patient and required intervention to prevent one of the other outcomes listed.

Results: 218 biologic treatments were administered to 145 JIA patients (83 girls; 63 systemic [SJIA], 35 RF −ve poly, 22 RF +ve poly, 16 enthesitis related, 5 extended oligo and 4 psoriatic). Age at start of biologic therapy: 12 years; disease duration at start of biologic therapy: 30 months. One biologic agent was prescribed to 101 children, 2 (sequentially) to 28, 3 to 11, 4 to 5 and 5 to 2 patients. Biologics used: etanercept (ETA, 136 treatments), infliximab (INF, 29), adalimumab (ADA, 25), tocilizumab (TOC, 12), abatacept (ABA, 10), anakinra (ANA, 5), and rituximab (2). MTX was used in combination with biologic therapy in 172 (79 %) cases, prednisone in 80 (37 %). Total time of biologic therapy: 4444 months (3342 corresponding to ETA); median duration of each biologic therapy: 13 months. Eighteen SAEs were recorded in 15 children (11 SJIA): 14 infectious (6 varicella zoster), 2 hematologic, 1 systemic autoimmune, 1 anafilaxis. Symptoms compatible with macrophage activation syndrome developed in 2 patients. SAEs occurred at 3.5 (median) months after start of biologic therapy. SAEs rate was 4.9 per 100 patient-years. SAEs were observed during ETA (11 episodes, 8% of treatments), TOC (3, 25%), and INF (1, 3%), ADA (1, 4%), ABA (1, 10%), ANA (1, 20%) therapy. Median dose of concomitant MTX was 15 mg/week, prednisone 0 mg. All patients required admission (2 ICU) and eventually improved after discontinuation of biologics and appropriate therapy. One SJIA patient on ETA developed a lupus-like disease. No malignancy or TB reactivation were observed.

Conclusion: SAEs arising during biologic therapy are infrequently observed in children with JIA They usually appear during the initial months of therapy. Patients with SJIA are at a higher risk of developing SAEs. Varicella zoster is the more common infection. Multicenter studies and international registries may provide evidence on short- and longer-term, comparative safety of different biologics.

Disclosure: R. A. G. Russo, None; **M. M. Katsicas**, None.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Human Etiology and Pathogenesis
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Decreased Frequency of Th17 Cells in Early Rheumatoid Arthritis. Irene Arroyo-Villa[1], M. Belén Bautista-Caro[1], Alejandro Balsa[1], Pilar Aguado[1], Laura Nuño[1], Gema Bonilla[1], Amaya Puig-Kröger[2], Emilio Martín-Mola[1] and M. Eugenia Miranda-Carús[1]. [1]Hospital La Paz-IdiPaz, Madrid, Spain, [2]Hospital Gregorio Marañon, Madrid, Spain

Background/Purpose: Our objective was to examine the frequency and phenotype of Th17 cells in the peripheral blood of early RA (eRA) patients.

Methods: CD4+ T cells were isolated from the peripheral blood of 33 eRA patients and 33 healthy controls (HC), and from the synovial fluid of 20 established RA patients (RASF), by ficoll-hypaque gradient and magnetical negative selection. After polyclonal stimulation, the frequency of Th17 and Th1 cells was determined by flow cytometry and concentrations of IL-17, IFN-g, TNF-a and IL-10 were measured by ELISA in cell-free supernatants.

Results: When all of our eRA patients were analyzed together, a significantly lower percentage of circulating Th17 cells and a lower CD4-derived IL-17 secretion were observed in comparison with HC. However, after stratifying by anti-CCP antibody status, circulating Th17 cells were decreased in anti-CCP(+) but not in anti-CCP(−)-eRA. All Th17 cells were CD45RO+CD45RA- and CCR6+. Dual Th17/Th1 cells were also exclusively decreased in anti-CCP(+)-eRA. Circulating Th17 and Th17/Th1 cells were negatively correlated with anti-CCP titres. When anti-CCP(+)-eRA patients were retested one year after initiating treatment with oral methotrexate, their circulating Th17 frequency was no longer different from HC. Of note, the percentage of circulating Th1 cells and the secretion of CD4-derived IFN-g, TNF-a and IL-10 were not different between eRA patients and HC. In RASF, both Th17 and Th1 cells were increased when compared with blood.

Conclusion: Decreased circulating Th17 levels in eRA seem to be a marker of anti-CCP seropositivity, and return to levels observed in healthy controls after treatment with methotrexate.

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Galactosylation, and Not Sialylation, of Immunoglobulin G Is Associated with Improvement of Rheumatoid Arthritis During Pregnancy. Albert Bondt[1], Maurice H.J. Selman[2], André M. Deelder[2], Johanna M.W. Hazes[1], Manfred Wuhrer[2] and Radboud J.E.M. Dolhain[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is known to improve during pregnancy and to flare after delivery [1]. Changes in the glycosylation of immunoglobulin G's fragment crystallizable (IgG-Fc) have been suggested to play a role in this phenomenon [2]. Animal studies indicate sialylation is the effector of galactosylation mediated immune suppression [3]. In this study technical advances allowed further insight into sialylation, a previously elusive feature. We aim to find new associations between IgG-Fc N-glycosylation (galactosylation and sialylation) and the improvement of rheumatoid arthritis during pregnancy, which can give more insight into RA pathogenesis.

Methods: Sera of RA patients (n=251 pregnancies) and healthy controls (n=32), all participating in a prospective cohort study on RA and pregnancy (PARA study), were collected before conception if possible, during pregnancy, and after delivery. At all time points disease activity (DAS28-CRP(3)) was measured, and medication was recorded. Using a newly developed mass spectrometric method [4] the glycosylation of IgG Fc-glycopeptides was measured in a subclass specific manner.

Results: In both patients and controls changes in glycosylation during pregnancy have been observed. In patients IgG1 galactosylation changed from 59.3 ± 1.1 to $64.9\pm1.0\%$ (mean$\pm$SEM); sialylation from 18.7 ± 0.5 to $21.4\pm0.5\%$. Similar results were obtained for IgG2/3 and IgG4. Patient galactosylation and sialylation levels are lower compared to controls. Our data show that in patients increased galactosylation, but not sialylation, is associated with lower disease activity. Increased sialylation rates are associated with higher DAS28-CRP(3).

Conclusion: In contrast to animal studies, in patients increased galactosylation, and not sialylation, is associated with low disease activity. Our data suggest sialylation could partially inhibit the positive effect of galactosylation. These data do not only have implications for understanding the pathogenesis of RA, but may also shed new light on how glycosylation determines the function of IgG. This latter could have major consequences for the development of new monoclonals to treat human disease.

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3. Kaneko, Y., F. Nimmerjahn, and J.V. Ravetch, *Anti-Inflammatory Activity of Immunoglobulin G Resulting from Fc Sialylation.* Science, 2006. **313**(5787): p. 670–673.
4. Selman, M.H.J., et al., *Fc specific IgG glycosylation profiling by robust nano-reverse phase HPLC-MS using a sheath-flow ESI sprayer interface.* Journal of Proteomics, 2012. **75**(4): p. 1318–1329.

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Talin Is Cleaved and Expressed As a Short Form in Patients with Rheumatoid Arthritis. Kensei Tsuzaka[1], Masako Takao[1], Naoshi Shinozaki[2] and Jiro Nishida[1]. [1]Ichikawa General Hospital,TDC, Ichikawa, Chiba, Japan, [2]Ichikawa, Japan

Methods: Western Blot analysis showed that the N-terminal 32kDa and the C-terminal 15kDa of calpain1 fragment of talin (32kDa and 15kDa short-talin, respectively) was expressed predominantly in RA patients [85.7% (36/42), 83.3% (35/42)] compared with NC [0% (0/31), 0% (0/31)] and SLE patients [25.0% (5/20), 30.0% (6/20)] (Fig. 1, Fig. 2). PBMC obtained from a NC was incubated with each of 4 RA patient PBMCs, lysed with the lysis buffer, incubated with calpain1, and were electrophoresed on a SDS-PAGE gel. Membrane was blotted with H-18. As a result, the wild-type calpain1 fragment (47kDa) of talin was degraded into 32kDa short-talin after incubating with each RA patient PBMC. Moreover, GST-talin fusion protein was cleaved into the short-talin after incubating with RA patient PBMC lysate, but was not cleaved with NC PBMC lysate. Surprisingly, Western Blot analysis using H-18 also showed predominant expression of the 32kDa short-talin in RA patient plasma. findings suggest that the intracellular talin in RA patients is cleaved into short-talin and expressed predominantly in RA patient PBMC and plasma (Fig.3). This short-talin might be related to the pathogenesis of RA.

Disclosure: **K. Tsuzaka**, None; **M. Takao**, None; **N. Shinozaki**, None; **J. Nishida**, None.

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IL-6 and IL-21 in Rheumatoid Arthritis. Gustavo Carbone[1], Augusta Wilson[1], Sean Diehl[2], Janice Bunn[3], Sheldon Cooper[4] and Mercedes Rincon[1]. [1]University of Vermont College of Medicine, Burlington, VT, [2]University of Vermont College of Medicine, [3]University of Vermont, Burlington, [4]Univ Vermont College of Med, Burlington, VT

Background/Purpose: Interleukin-6 (IL-6) levels are known to be increased in patients with rheumatoid arthritis (RA). Tocilizumab, a monoclonal antibody to the IL-6 receptor (IL-6R), reduces disease activity in RA, although its mechanisms of action remain unclear. IL-6 has been shown to regulate cytokine production by CD4 T cells during activation. The objective of this study was to determine if treatment with tocilizumab altered the phenotype and cytokine production by CD4 T cells in patients with rheumatoid arthritis.

Methods: RA patients who entered a six-month open-label Phase III clinical study of tocilizumab (ACT-STAR), also consented to enter an accompanying laboratory study. Clinical parameters were obtained at each study visit. Additional blood specimens were obtained prior to the first treatment (baseline, visit 1), second infusion (visit 2), fourth infusion (visit 4), and 1 month after the sixth infusion (visit 7). CD4 CD45RA (naïve) and CD4 CD45RO (memory/activated) cells were isolated from peripheral blood of RA patients at the above time points. Production of IL-2, IL-21, IFNg, and IL-17 upon activation *in vitro* was determined. In addition, serum was also collected to determine the levels of specific immunoglobulins.

Results: There was significant reduction in tender and swollen joint counts, and DAS28 scores with tocilizumab treatment. The relative frequency of naïve and memory CD4 T cells was not altered over the treatment period. There was no change in the production of any of the examined cytokines by CD45 RA naïve T cells during the study. In contrast, there was a marked reduction of IL-21 production by memory/activated CD4 T cells with tocilizumab treatment. In addition, tocilizumab treatment led to a profound decrease in the levels of IgG4-specific anti-CCP autoantibodies. We also show that IL-21 is a powerful inducer of IgG4 production by B cells.

Conclusion: Treatment of RA with tocilizumab selectively lowers both the production of IL-21 by the memory/activated CD4 T cell population and serum IgG4-specific autoantibody levels. Since IL-21 promotes IgG4 production by B cells, these results suggest that IL-21 may play a role in B cell activation in patients with RA, and blockade of IL-6 may down-regulate this pathway.

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Vitamin D Receptor Polymorphisms Are Associated with Clinical Outcomes and IgM Responses to Common Pathogens but Not Baseline Disease Activity in Early Inflammatory Arthritis. Carol A. Hitchon[1], Linda Larcombe[1], Neeloffer Mookherjee[1], Christine A. Peschken[1], Marianna M. Newkirk[2] and Hani S. El-Gabalawy[1]. [1]University of Manitoba, Winnipeg, MB, [2]McGill University Health Centre, Montreal, QC

Background/Purpose: Vitamin D (VitD) exerts immunoregulatory activities of potential importance to rheumatoid arthritis and acts by binding to nuclear vitamin D receptors (VDRs) and regulating gene expression including cathelicidin an important mediator of host innate responses to infection. VDR genetic polymorphisms (VDrP) have been variably linked to disease activity in rheumatoid arthritis and to chronic infections. Altered host response to infection may break tolerance leading to disease. We sought to assess the association of VDR polymorphisms (Fokl, Bsm1, Apa1 and Taq1) with clinical disease activity at baseline and one year, baseline serum vitD levels, and antibody responses to common pathogens in a cohort of patients with inflammatory arthritis of less than 1 year symptom duration.

Methods: VDR SNPs at the restriction sites Bsm1 (B/b (T/C)) (rs1544410), Apa1(A/a (T/G)) (rs7975232), Taqa1(T/t (T/C)) (rs731236), Fok1 (F/f (C/T)) (rs10735810) and Cdx-2 (G/A) (rs11568820) were detected by polymerase chain reaction sequencing and analyzed using genotypic (DD vs Dd vs dd), dominant (DD, Dd vs dd), and recessive (DD vs Dd, dd) models. At first visit before DMARD treatment, 25OH VitD levels, antibody titers to E Coli and P. mirabilis (IgG, IgA and IgM), and CCP2 antibodies were measured in serum by ELISA. Smoking was assessed by self report and serum cotinine levels. Associations of VDR snps with clinical disease activity at baseline and one year and achievement of remission (DAS28CRP (3variable) <2.6) or EULAR treatment response at one year were tested.

Results: Subjects (n=228) were predominantly female (72%) and Caucasian (87%), with mean age at first visit of 47.8 years (range 17–82, SD 14), a mean DAS28CRP (3variable) 3.91 (1.35), (31% low, 50% moderate 19% high disease activity) and were RF (54%) or CCP2 positive (44%). Of the 154 subjects with one year follow-up data, 67% achieved low disease activity. The VDR minor allele frequencies were Fokl 0.42, Bsm1 0.55, Apa1 0.51, and Taq1 0.37. There was an association between Taq1 dominant alleles (TT,Tt) and at least one copy of shared epitope allele (p=0.01). No robust associations were seen between VDR polymorphisims and gender, age at first visit, RF or CCP2 or baseline disease activity. Fokl dominant alleles (FF,Ff) had higher baseline anti-E.Coli IgM titers (0.51 vs 0.34 units p<0.01) and anti-proteus IgM titers (1.34 vs 1.18 units p<0.05), and at one year had higher DAS28CRP (3 variable) scores (2.92 vs 2.44 p<0.05) and were less likely to achieve remission (41% vs 73% p<0.01). In multivariate models including CCP2, rheumatoid factor, shared epitope, smoking (ever), and baseline serum VitD, only lower baseline DAS28CRP (3 variable) (p=0.001), Fokl recessive alleles (ff) (p<0.01) and higher IgM E.Coli titers (p<0.05) predicted remission at one year.

Conclusion: Vitamin D receptor polymorphisms, especially Fokl, associate with IgM immune responses to common pathogens and associate with disease outcome in EIA but do not associate with baseline disease activity. Vitamin D receptor mediated regulation of immune responses may be important for the predisposition to inflammatory arthritis by breaking immune tolerance.

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The Sex-Determining Region Y Box 6 Locus: Shared Genetic Susceptibility Between Rheumatoid Arthritis and Psychotic Disorder. Tony R. Merriman[1], Nicola Dalbeth[2], Andrew Harrison[3], John Highton[4], Lisa K. Stamp[5], Malcolm D. Smith[6], Benedicte A. Lie[7], Tore K. Kvien[8], Timothy Radstake[9], Marieke J.H. Coenen[10], Barbara Franke[10], Jasper Broen[11], Piet Van Riel[10], Pilar Barrera[10], Sophia Steer[12], Marilyn E. Merriman[1], Amanda Phipps-Green[1], Ruth Topless[1], Mansour Zamanpoor[1] and Wan Rohani Wan Tain[13]. [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Hutt Hospital, Lower Hutt, New Zealand, [4]Univ of Otago Med Sch, Dunedin, New Zealand, [5]University of Otago, Christchurch, Christchurch, New Zealand, [6]Rheumatologist, Adelaide, Australia, [7]Oslo University Hospital, Oslo, Norway, [8]Diakonhjemmet Hospital, Oslo, Norway, [9]Radboud University Nijmegen Medical Centre, University Medical Center Utrecht, Nijmegen, Utrecht, Netherlands, [10]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [11]Department of Rheumatology & Clinical Immunology, University Medical Center, Utrecht, Netherlands, [12]1 Sloane Ct East Flat 7, London, United Kingdom, [13]Universiti Sains Malaysia, Malaysia

Background/Purpose: Rheumatoid arthritis (RA) is a common auto-immune disease and schizophrenia (SZ) is a common psychotic disorder. There is an established negative association between RA and SZ, with some evidence for a similar relationship in bipolar disorder (BPD) (Oken and Schulzer, *Schiz Bull* 25:625, 1999). We hypothesize that the negative relationship is determined by disease-specific mutually-exclusive (genetic and environmental) factors that provide input into a common pathway, driving disease progression in both the brain and immune system. An allele confer-

ring susceptibility to RA will stimulate the hypothetical disease-causing pathway in the immune system, but will protect from SZ by preventing activation of the pathway in the brain, and *vice versa*. Our hypothesis predicts a molecular pathway(s) containing shared genetic risk variant(s) driving the pathogenesis of both diseases.

Methods: We exploited genome-wide association scan (GWAS) data by comparing the top 1000 associations from the Genetic Association Information Network (GAIN) SZ dataset and the Wellcome Trust Case Control Consortium (WTCCC) RA dataset for candidate SNPs associated with both RA and SZ in the same direction of association. Replication in RA was done over Australasian, UK, Dutch and Norwegian Caucasian case-control sample sets (3755 cases and 3084 controls) using TaqManÒ technology. For psychotic disorder, replication was done *in silico* from publicly-available non-GAIN SZ and BPD datasets (3770 cases and 5269 controls).

Results: SNP *rs900865* from the chromosome 11 INSC-SOX6 region fitted the selection criteria of consistent direction of association (OR=1.14, P=0.002 in WTCCC RA and OR=1.22, P=5×10^{-4} in GAIN SZ). In replication there was evidence for association in both the meta-analyzed RA replication dataset (OR=1.09, P=0.009) and in the combined SZ/BPD replication dataset (OR=1.09, P=0.004). Meta-analysis of all datasets (psychotic disease datasets GAIN Sz, non-GAIN Sz and BPD; and RA datasets Australasian, UK, Dutch, Norwegian and WTCCC) provided evidence of association with *rs900865* at the genome-wide level of significance (OR=1.11, P=1.8×10^{-8}).

Conclusion: We conclude that the minor allele (C) of SNP *rs900865* confers susceptibility to both RA and psychotic disease. The SNP maps between the INSC *(*inscuteable homolog) and SOX6 (sex-determining region Y box 6) genes. *INSC* is not well characterized, but is known to be involved in retinal development. *SOX6* encodes a transcriptional factor that plays a role in a number of cell developmental processes including development of the central nervous system and human skeletal development (chondrogenesis), and is expressed in both the immune and central nervous systems. Whilst the mechanism is unclear, our data do suggest a genetic relationship between RA and psychosis, perhaps in a common signaling pathway.

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The Role of á-Defensin-1 and Its Signal Transduction Mechanisms in the Production of IL-6, IL-8 and MMPs in Rheumatoid Fibroblast-Like Synoviocytes. Joong Kyong Ahn[1], Bo Huang[2], Eun-Jung Park[2], Jiwon Hwang[2], Jaejoon Lee[2], Chan Hong Jeon[3], Eunmi Koh[2] and Hoon-Suk Cha[2]. [1]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea

Background/Purpose: Fibroblast-like synoviocytes (FLS) play an essential role in the pathophysiology of rheumatoid arthritis (RA). Also, neutrophils are the most abundant cell type of synovial fluid (SF) in flare-up of RA patients, suggesting that this cell plays an important role in overt inflammation in RA. α-defensin-1 is released into the extracellular milieu from neutrophils during inflammation. However, little is known of the role of α-defensin-1 in RA. We investigated the effect of α-defensin-1 on the expression of IL-6, IL-8, and MMPs and the signal transduction mechanisms responsible for these expressions in RA FLS.

Methods: The concentrations of SF α-defensin-1 from 51 RA patients and 21 OA patients were measured using ELISA. In rheumatoid FLS, IL-6, IL-8, and MMPs mRNA expression was examined using real-time PCR. The activation of signaling molecules was evaluated by Western blotting and EMSA.

Results: SF α-defensin-1 concentration was significantly increased in RA patients compared to OA patients (39.3±3.5 vs. 18.0±5.6 ng/ml, p=0.002). IL-6, IL-8, MMP-1 and MMP-3 mRNA expressions were significantly increased in RA FLS after α-defensin-1 stimulation compared to control (n=5)(all p <0.05). JNK and ERK were significantly phosphorylated in FLS stimulated with α-defensin-1 compared to control (n=3)(25.2±3.4-fold,

p=0.008 and 1.42±0.24-fold, p=0.05, respectively), while no significant change was found in p38 activity. Treatment of RA FLS with ERK inhibitor prior to α-defensin-1 stimulation significantly resulted in approximately 71% and 98% reduction, respectively, in IL-6 and MMP-1 production compared with control (p <0.05 for each). Blocking JNK pathway significantly suppressed α-defensin-1-induced MMP-1 production by approximately 73% compared with control (p<0.01). α-defensin-1-induced IL-8 expression was reduced by approximately 68% and 52% by inhibition of ERK and JNK, respectively. Also, α-defensin-1-induced MMP-3 expression was reduced by approximately 22% and 50% by ERK and JNK inhibitor, respectively. However, these differences did not reach statistical significance. In addition, there was a significant induction of NF-κB DNA binding activity in response to the stimulation of α-defensin-1 in rheumatoid FLS.

Conclusion: Our results are notable to suggest that increased SF α-defensin-1 released mainly by neutrophils can induce the expression of IL-6 and MMP-1 in rheumatoid FLS and these processes were dependent on the regulation of JNK and/or ERK and NF-κB pathway. These data provide new insight regarding the mechanism by which α-defensin-1 participates in joint inflammation and destruction in RA.

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Familial Aggregation and Heritability of Rheumatoid Arthritis in Taiwan: A Nationwide Population Study. Chang-Fu Kuo[1], Matthew J. Grainge[1], Kuang-Hui Yu[2], Lai-Chu See[3], Shue-Fen Luo[2], Ana M. Valdes[4], I-Jun Chou[2], Hsiao-Chun Chang[2], Weiya Zhang[1] and Michael Doherty[1]. [1]University of Nottingham, Nottingham, United Kingdom, [2]Chang Gung Memorial Hospital, Taoyuan, Taiwan, [3]Chang Gung University, Taoyuan, Taiwan, [4]St. Thomas' Hospital, King's College London, London, United Kingdom

Background/Purpose: The present study was to estimate the familial relative risk (RR) of rheumatoid arthritis (RA) in individuals with affected first-degree relatives compared to individuals with no affected first-degree relatives. We also estimated the heritability to assess the magnitude of genetic contribution to susceptibility to RA.

Methods: Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of data collected from 11,449,138 men and 11,800,070 women in 2010. RA cases were those receiving a catastrophic illness certificate for RA. The identification of first-degree relatives of each individual was determined using the NIHRD registry for beneficiaries. This specifies relationships between the insured person who paid the insurance fee and his/her dependents, allowing first-degree relatives (father, mother, son, daughter, brother, sister, twin) to be identified directly. Full siblings were identified as individuals who shared the same parents. Twins were full siblings who shared the same date of birth. The marginal Cox proportional hazard model with an equal follow-up time, adjusting for age and sex, was used to estimate RR (95% confidence interval [95% CI]) of RA in individuals with affected first-degree relatives. This model was used to account for shared environment and case clustering within families with robust variance. Heritability was estimated using multifactorial polygenic model.

Results: There were 8,010 men (0.07%) and 30,200 women (0.26%) who had RA catastrophic illness certificate in 2010. The prevalence of RA was higher in individuals with affected first-degree relatives (0.51%) than those without (0.16%). The overall familial RR was 4.79 (95% CI, 4.08-5.63). An individual's risk for RA varied depending on which of their family members were affected. The RRs (95% CIs) for an individual with an affected twin, sibling, offspring and parent were 20.95 (6.59-66.62), 8.93 (5.59-14.27), 4.46 (3.63-5.47) and 4.60 (3.90-5.44), respectively. The RR (95% CI) increased with the number of affected first-degree relatives, from 4.65 (3.95-5.46), 44.46 (18.90-3.09) and 118.34 (13.11-1068.55) for one, two or three or more affected relatives. The heritability of RA was 0.54 (95% CI, 0.42-0.67).

Conclusion: This population-based study confirms that RA aggregates within families and the heritability of RA is high. Genetic predisposition contributes to a significant proportion of RA development.

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Podoplanin-Mediated Interaction of Rheumatoid Arthritis Synovial Fibroblasts with Platelets Modulates IL-8 Expression. Manuel J. Del Rey[1], Elena Izquierdo[1], Regina Faré[1], Alicia Usategui[1], Vanessa Miranda[1], Gabriel Criado[1], J. D. Cañete[2] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Hospital Clínic de Barcelona,, Barcelona, Spain

Background/Purpose: Synovial fibroblasts (SF) are the most abundant resident stromal cells in the synovium. In rheumatoid arthritis (RA), SF expand and undergo phenotypic changes that contribute to the pathogenesis of chronic arthritis. Among these changes, expression of podoplanin, a membrane protein expressed by normal lymphatic endothelium and cancer cells, has been reported (Ekwall, Arthritis Res Ther 2011). Podoplanin is up-regulated on the invasive front of tumors and participates in tumor cell migration. The only known specific receptor for podoplanin is the platelet membrane signaling protein CLEC-2. We have analyzed the expression and potential functions of podoplanin in rheumatoid arthritis synovial fibroblasts (RASF).

Methods: Podoplanin expression was analyzed by immunohistochemistry (IHC), immunofluorecence labeling (IF), quantitative real-time polymerase chain reaction (qRT-PCR) and flow cytometry in synovial tissue and SF cultures from RA and osteoarthritis (OA) patients and healthy donors. Podoplanin RASF expression was silenced with podoplanin specific and control siRNA lentiviral expression vectors. Transduced cells were used in RASF-cartilage co-culture experiment to measure cartilage glycosaminoglycan degradation products in supernatants (Blyscan Assay; Biocolor, Northern Ireland, UK). Matrigel invasion and *in vitro* wound healing assays were performed to evaluate migration capability of silenced fibroblasts. Finally, silenced RASF were co-cultured for 24h with human platelets prepared from healthy donors and RASF RNA was extracted to quantify IL-6, IL-8, MCP-1, MMP-1 and MMP-3 mRNA expression by qRT-PCR. Quantitative data from at least three independent experiments were analyzed by Mann-Whitney U-test or t-test as required and p-value<0.05 was considered significant.

Results: Abundant podoplanin expression was detected by IHC in synovial lining and sublining fibroblasts in RA biopsies (n=40) whereas minimal or absent expression was observed in OA (n=15) or healthy synovium (n=6) respectively. Cultured SF displayed abundant podoplanin membrane expression irrespective of their source (RA, OA or healthy synovium). Treatment of cultured SF with TNF-α induced up-regulation of podoplanin mRNA and protein expression, as determined by qRT-PCR and flow cytometry. Podoplanin expression was effectively down-regulated by specific siRNA lentiviral transduction. Cell migration in matrigel and wound healing assays and *ex vivo* cartilage degradation were not modified in RASF transduced with podoplanin siRNA compared to RASF transduced with scrambled control siRNA. Co-culture of RASF with platelets induced a significant increase in IL-6 and IL-8 but no MCP-1, MMP-1 or MMP-3 mRNA expression in RASF. siRNA podoplanin silencing in RASF blocked the up-regulation of IL-8 but not IL-6 mRNA expression in response to platelet co-culture.

Conclusion: Our results confirm previous data on the up-regulation of podoplanin in RASF. Functional studies do not support a role for podoplanin on RASF migratory and invasive properties as reported in cancer cells. Podoplanin is potentially involved in the pro-inflammatory response that results from RASF/platelet interaction.

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Negative Association Between Testosterone Levels and Risk of Future Rheumatoid Factor Negative Rheumatoid Arthritis in Men. Mitra Pikwer[1], Aleksander Giwercman[2], Ulf Bergström[1], Jan-Åke Nilsson[1], Lennart T.H. Jacobsson[1] and Carl Turesson[1]. [1]Lund University, Malmö, Sweden, [2]Skåne University Hospital, Malmö, Sweden

Background/Purpose: Rheumatoid arthritis (RA) is a heterogeneous disease with female predominance. Sex hormones have been suggested to play a part in the pathogenesis. We have previously identified hormonal predictors (breast-feeding and early menopause) that influence predominantly rheumatoid factor (RF) negative RA in women. The increasing incidence with age of RA in men parallels age related drops in androgens. Lower levels of testosterone have been demonstrated in men with RA compared with controls,

but it has not been known whether this pattern precedes the disease or if it is a consequence of inflammation.

Methods: A nested case-control study was performed, using information and blood samples from a community based health survey performed between 1974 and 1992, which included 22 444 males. Blood samples were drawn between 8.00 and 10.00 a.m. after an overnight fast and stored at −20 degrees Celsius. Height and weight was measured and self-reported smoking habits were noted. Incident cases of RA were identified by linking the cohort to local and national RA-registers, and verified by a structured review of their medical records. Two controls for each validated case, matched for age, sex and year of screening, were selected from the health survey. Testosterone (T), sex hormone-binding globulin (SHBG), follicle stimulating hormone (FSH) and luteinizing hormones (LH) were analysed with standard immunoassays. Free testosterone was calculated from T and SHBG levels.

Results: Serum was available from 105 cases (mean age at diagnosis 59 years; median time from screening to RA diagnosis 12.7 years (range 1–28); 73 % RF positive at diagnosis or later) and 174 matched controls. Mean age at screening was 46 years. Mean free and total T levels were lower in pre-RA cases compared to controls, in particular in the subset who subsequently developed RF negative RA. T correlated negatively with body mass index (BMI), and smokers had significantly higher levels of both free and total T, as well as FSH and LH. In conditional logistic regression models, adjusted for smoking and BMI, lower levels of T were associated with RF negative RA (Odds Ratio (OR): 0.31 per standard deviation (SD), 95% Confidence Interval (CI): 0.12–0.85), with a similar tendency for RA overall (OR: 0. 77 per SD; 95% CI: 0.52–1.12). The same patterns were seen for free T. The differences were more pronounced in individuals screened > 12.7 years before diagnosis. Compared to matched controls and adjusted for smoking, significantly higher levels of FSH were seen in pre-RF-negative RA cases (p=0.02), whereas FSH levels were lower in pre-RF-positive RA cases (p=0.02),

Conclusion: Lower levels of total and free T were predictive of RF negative RA in men, adjusted for smoking and BMI. FSH levels were higher before onset of RF-negative RA, indicating a hypothalamus-pituitary response to testicular dysfunction. By contrast, lower FSH levels were found before onset of RF-positive RA, implicating an impaired hypothalamus-pituitary function as a possible factor in the pathogenesis of RF positive RA. Our results suggest that distinct hormonal patterns are associated with different phenotypes of RA, and that changes in androgens precede the onset of RA in men.

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Regulatory Role of 1, 25 Dihydroxyvitamin D3 in the Pathogenesis of Autoimmune Arthritis. Siba P. Raychaudhuri[1], Ananya Datta Mitra[2], Anupam Mitra[1], Christine Abria[2] and Smriti K. Raychaudhuri[2]. [1]VA Sacramento Medical Center/UC Davis School of Medicine, Mather, CA, [2]VA Sacramento Medical Center, Mather, CA

Background/Purpose: Fibroblast like synoviocytes (FLS) and T lymphocytes are considered as major effector cells in the pathogenesis of autoimmune arthritis (AA) such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA), due to their significant contribution in formation of pathognomonic "pannus"[1,2]. Several studies suggest deficiency of Vitamin D in RA and its correlation with disease severity[1,3]. 1,25 dihydroxyvitamin D3 (Vit D) is an active metabolite of Vitamin D3 and induces immuomodulatory effect through Vitamin D3 receptor (VDR) which is expressed on antigen presenting cells, lymphocytes, FLS. Here we are reporting the anti-proliferative and pro-apoptotic potential of Vit D in FLS and T lymphocytes of AA patients.

Methods: PBMC and FLS were isolated respectively from blood and synovial tissues of RA (n=5) and PsA (n=5) patients. $CD3^+$ T cells were magnetically sorted from PBMC. FLS were cultured in presence or absence of growth factor (PDGF), pro-inflammatory cytokine (IL-17) and Vit D (10^{-6}M) for 5 days. T cells were stimulated with CD3/CD28 cocktail and treated with Vit D (10^{-6}M) for 5 days. MTT and flow cytometric (CFSE) based proliferation assays were performed. T cell apoptosis was assessed by flow cytometry using Annexin V and propidium iodide (PI). Staurosporine was used as a positive control for apoptosis assay.

Results: In MTT assay (n=5), Vit D significantly inhibited the PDGF (OD: 0.61 $\pm$ 0.06 vs. 0.23 $\pm$ 0.01, p<0.01) and IL-17 (0.55 $\pm$ 0.05 vs. 0.32 $\pm$ 0.01, p<0.01) induced proliferation of RA-FLS (Figure 1). Similar results were observed with PsA-FLS. CD3/CD28 stimulation induced significant proliferation of $CD3^+$ T lymphocytes (17.54 $\pm$ 2.48% vs. 6.06 $\pm$ 1.13%, p<0.01) and Vit D significantly inhibited activated T lymphocytes

proliferation (11.21 ± 2.28 vs. $17.54 \pm 2.48\%$, $p<0.01$) (Figure 2A). We also observed that Vit D significantly induced apoptosis (Annexin V^+ PI^-) of T lymphocytes ($26.1 \pm 2.05\%$ vs. $3.28 \pm 0.17\%$, $p<0.001$) (Figure 2B).
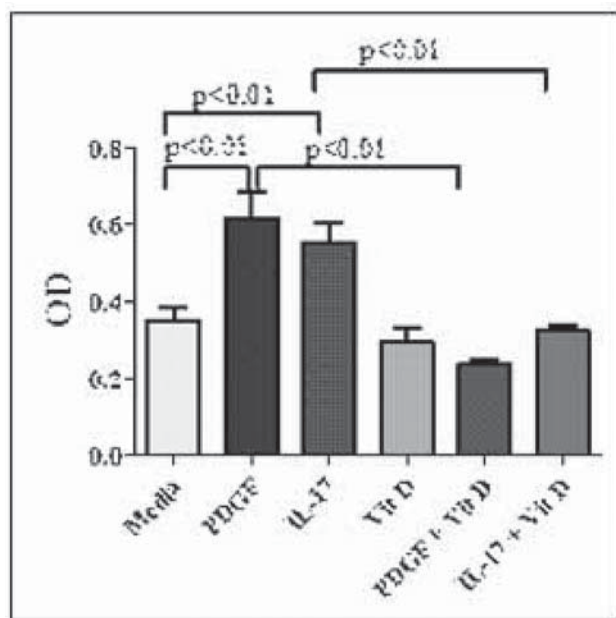
Figure 1. Anti-proliferative effect of Vit D in RA-FLS.
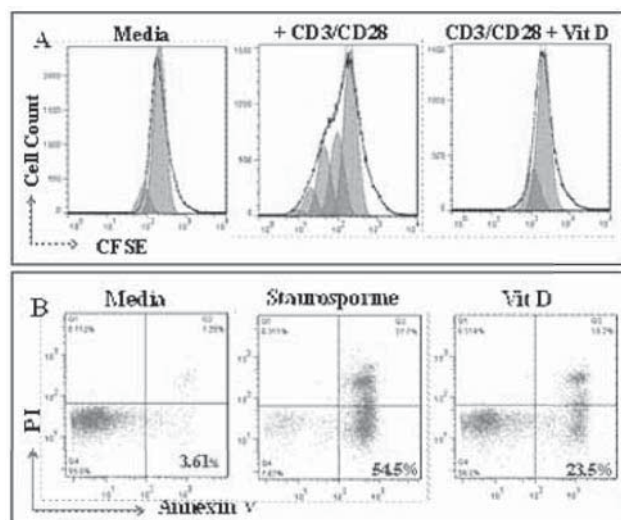
Figure 2. Representative histogram showing the anti-proliferative (A) and pro-apoptotic (B) effect of Vit D.

Conclusion: This demonstrates showed that Vit D has a regulatory role in pannus formation by exerting anti-proliferative effect on two major effector cells of AA such as FLS and T lymphocytes. Moreover the pro-apoptotic effect of Vit D on activated T lymphocytes further suggests its immunomodulatory effect in AA.

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A Single Nucleotide Polymorphism of Tumor Necrosis Factor Receptor-Associated Factor 1 Predicts Clinical Response to Anti-Tumor Necrosis Factor Treatments in Japanese Patients with Rheumatoid Arthritis.
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Background/Purpose: Recent genome-wide association studies have disclosed several single nucleotide polymorphisms (SNPs) associated with rheumatoid arthritis (RA) susceptibility. Among them, it is reported that the SNP of tumor necrosis factor (TNF) receptor-associated factor 1 (TRAF1) (+16860A/G) is associated with pathophysiology of RA in both Asians and Caucasians. Therefore, in this study, we assessed the usefulness of TRAF1 genotyping as a genetic predictor of the response to anti-TNF treatments in Japanese RA patients, and examined an underlying mechanism of the association between TRAF1 polymorphism and the clinical response to anti-TNF treatments.

Methods: TRAF1 (+16860A/G) was genotyped using TaqMan® SNP genotyping assay. 101 Japanese RA patients were enrolled, and retrospectively analyzed the association between the SNP and the clinical response to treatment with anti-TNF drugs as a first biologic agent, such as infliximab, etanercept and adalimumab. The clinical response was assessed by the 28-joint Disease Activity Score (DAS28)-ESR response criteria at 24 weeks after the initiation of anti-TNF treatments. To investigate the effect of the SNP on the expression of TRAF1, $CD4^+$, $CD8^+$, $CD14^+$ or $CD19^+$ cells were isolated using magnetic activated cell sorting from peripheral blood mononuclear cells obtained from healthy subjects with AA (n=6), AG (n=6), or GG (n=3) genotype, and then the mRNA expression of TRAF1 in $CD4^+$, $CD8^+$, $CD14^+$ or $CD19^+$ cells were evaluated by TaqMan™ quantitative RT-PCR. The expression of TRAF1 was evaluated by intracellular staining in combination with staining for CD4, CD8, CD14 or CD19 using flowcytometry.

Results: In 101 RA patients received anti-TNF treatments, 63 (62.4%), 28 (27.7%), and 10 (9.9%) patients achieved good, moderate, and no response, respectively. There was no statistical difference in DAS28-ESR at baseline among each patient group with AA, AG, or GG genotype. However, the relative change in DAS28-ESR from baseline to 24 weeks after the initiation of anti-TNF treatments tended to be decreased in patients with GG genotype compared to those with AA or AG genotype (1.27 versus 2.16, P=0.057). GG genotype was more frequently detected in patients with no response compared to those with good or moderate response (30.0% versus 5.5%, P=0.031, OR 7.4, 95%CI 1.5–37.5). Patients with no response more frequently possessed G allele than those with good or moderate response (55.0% versus 25.8%, P=0.006, OR 3.5, 95%CI 1.4–9.0). Quantitative RT-PCR revealed that mRNA for TRAF1 was highly expressed in $CD8^+$ or $CD14^+$ cells with AG or GG genotype compared to those with AA genotype (P=0.045). Flowcytometric analysis also showed that the expression of TRAF1 tended to be increased in $CD14^+$ cells with AG or GG genotype compared to those with AA genotype (p = 0.09).

Conclusion: TRAF1 (+16860A/G) is possibly useful for prediction of the clinical response to anti-TNF treatments, and may contribute to resistance to anti-TNF treatments in RA patients with G allele via increased expression of TRAF1 in circulating inflammatory cells.

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Smoking Status Is Associated with Inflammatory Cytokine Profile and Disease Activity in Anti-Citrullinated Protein Antibody Positive Rheumatoid Arthritis: Decreased Inflammation and Disease Improvement with Smoking Cessation?
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Background/Purpose: Smoking is a major risk factor for rheumatoid arthritis (RA) and has been associated with increased disease severity and lower rates disease remission. We hypothesized that levels of disease activity would be associated with smoking status and this would be related to levels of anti-citrullinated protein antibodies (ACPA) and/or serum cytokines.

Methods: The Veterans Affairs RA (VARA) registry was initiated in 2003 with routine collection of clinical demographics including disease activity score (DAS28) as well as baseline serum sampling. 1468 veterans with RA were included in the current study (76.9% anti-CCP2+, 90.7% male, mean age median age 63 (IQR 57–72), Median disease duration 8.45 years (IQR 2.8–18). Baseline serum samples were evaluated for levels of 19 distinct ACPA and 17 cytokines using the BioPlex platform on the Luminex 200 instrument. Smoking status was recorded as current, former, or never smokers. We evaluated the association of smoking status with disease activity (DAS28) by ANOVA and with levels of ACPA and cytokines using significance analysis of microarray (SAM) and output sorted based on false discovery rates (FRDs) in order to identify cytokines or autoantibodies with the greatest difference between different categories of smoking status.

Results: RA disease activity was significantly higher among current compared with former or never smokers ($P<0.01$). Among anti-CCP2 positive patients, levels of several cytokines associated with RA pathogenesis including TNFα, IL-17, IFNγ, GM-CSF, MCP-1, IL-2, and IL-7 were found to be significantly higher among current smokers compared with both former and non-smokers (FDR (q-value) <0.1%). Cytokine levels were similar between former and never smokers. Notably, levels of many ACPA were higher among current compared with never smokers, but similar between current and former smokers. Though number of subjects was smaller, the effect of smoking status on cytokine profile was not observed in the anti-CCP2 negative population.

Conclusion: Among anti-CCP2 positive RA patients, current smoking status is strongly associated with increased RA disease activity as well as elevation in several serum cytokines. This effect does not seem to be related to level of ACPA. The observation that higher levels of DAS28 and serum cytokines was only seen in current, and not former, smokers suggests that the effect of smoking may be minimized by smoking cessation. The effect of smoking cessation on RA disease activity should be evaluated in a prospective manner and multiplex cytokine profiling may provide a surrogate endpoint for efficacy of this intervention.

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Fibrinogen Induced Inhibition of Osteoclastogenesis Is Reversed by Citrullination of Fibrinogen by Peptidylarginine Deiminase. Eun Young Lee[1], Ji Soo Kim[1], Hye Won Kim[1], Sung Hae Chang[1], Jin-Su Song[2], Hie-Joon Kim[2], Kyung-Hyun Park-Min[3], Lionel B. Ivashkiv[3], Eun Bong Lee[2] and Yeong Wook Song[1]. [1]Seoul National University College of Medicine, Seoul, South Korea, [2]Seoul National University, Seoul, South Korea, [3]Hospital for Special Surgery, New York, NY

Background/Purpose: There are increasing evidences that autoantibodies and immune complexes (ICs) containing citrullinated fibrinogen are present in rheumatoid arthritis (RA) patients' sera and contribute to synovitis. We have in vitro data that fibrinogen can inhibit osteoclastogenesis from precursor cells. In this experiment, we investigated the effect of citrullinated fibrinogen, which are abundant in RA, on the in vitro osteoclastogenesis.

Methods: Fibrinogen (human and bovine; 1mg/ml) was citrullinated *in vitro* by reacting with rabbit skeletal muscle peptidylarginine deiminase (rmPAD2). Soluble fibrinogen, citrullinated or non-citrullinated, were applied with increasing doses to buffy coat-derived CD14+ cells, and osteoclastogenesis was induced in the presence of M-CSF (20 ng/ml) and RANKL (40 ng/ml). To confirm a migration shift due to citrullination, western blotting was performed. The citrullinated sites of fibrinogen were analyzed using mass spectrometry.

Results: Fibrinogen inhibited osteoclastogenesis in a dose-dependent manner. In contrast, citrullinated fibrinogen via rmPAD2 did not show inhibition of osteoclastogenesis, which were evident with non-citrullinated fibrinogen (Figure). Several osteoclastogeneisis related genes, especially DC-STAMP, were suppressed by fibrinogen during osteoclastoegenesis, but restored by citrullinated fibrinogen. Citrullination of fibrinogen was confirmed by Western blot analysis and Mass spectrometry, showing peak changes between citrullinated and non-citrullinated fibrinogen at 1576 and 1593 m/z. Western blot with anti-citrullinated antibody showed that proteins from RA synovial fluid were more citrullinated than those from osteoarthritis (OA) synovial fluid.
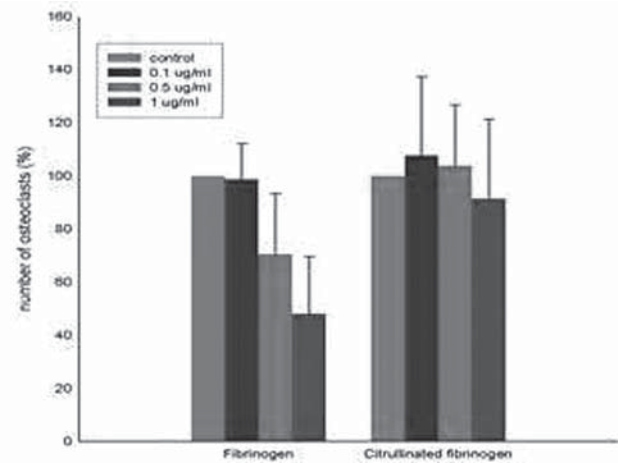
Conclusion: Fibrinogen was successfully citrullinated by PAD and confirmed by Western blot and Mass spectrometry. In contrast to fibrinogen, citrullinated fibrinogen did not show inhibition of osteoclastogenesis. These results may suggest that citrullinated fibrinogen can contribute to osteoclastogenesis in RA patients.

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Stromal Cell Markers in the Synovial Tissue of Patients with Early Arthritis and Preclinical Rheumatoid Arthritis. Yuen Kei Choi[1], Olga N. Karpus[1], Paul Peter Tak[2], Jörg Hamann[1], Christopher D. Buckley[3], Andrew Filer[4] and Danielle M. Gerlag[1]. [1]Academic Medical Center, Amsterdam, Netherlands, [2]Division of Clinical Immunology and Rheumatology, Department of Experimental Immunology, Academic Medical Center/University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands, [3]School of Immunity and Infection, MRC Center for Immune Regulation, Birmingham, United Kingdom, [4]Rheumatology Department, Birmingham, United Kingdom

Background/Purpose: Stromal cells in synovial tissue (ST) of patients with arthritis may have an important role in the initiation and persistence of the inflammatory infiltrate. Previous studies showed increased expression of stromal markers in ST of patients with established rheumatoid arthritis (RA) *(Maia et al, Arthritis Rheum 2010:62:3595; Ekwall et al, Arthritis Res Ther 2011:13:R40)*. Here we investigated the expression of CD248, gp38, CD55 and PDI in early arthritis in relationship to diagnosis and outcome. Furthermore, these markers were tested in the ST of individuals without clinically apparent arthritis who are at risk for developing RA.

Methods: Forty-seven patients with early inflammatory arthritis (<1 year disease duration) and 19 IgM rheumatoid factor and/or anti-citrullinated peptide antibody (ACPA) positive individuals with arthralgia but without arthritis were included in this study. Of the latter group, 9 individuals developed arthritis after a mean follow-up time of 3.4 years. In the early arthritis cohort, patients were diagnosed at baseline and at 2 years follow up as gout (n = 10), psoriatic arthritis (PsA, n = 9), undifferentiated arthritis (UA-UA, n = 10), UA-RA (n = 4) and RA-RA (n = 14). Patients were also classified based on prognostic outcome after 2 years into self-limiting, persistent non-erosive and persistent erosive disease. Synovial tissue was obtained by miniarthroscopy and analyzed by immunofluorescence to detect CD248, gp38, CD55 and PDI on stromal cells.Slides were examined by confocal microscopy. Expression was quantified as pixel/um². Kruskal-Wallis test and Mann-Whitney U test were used for statistical analysis. A *P*-value <0.05 was considered statistically significant.

Results: We observed clear expression of CD248, gp38, CD55 and PDI in ST of patients with early arthritis, independent of diagnosis or outcome (table 1). In the autoantibody positive subjects at risk of developing RA, the expression of gp38 was lower compared to early RA (p = 0.0025). Expression levels were not different between individuals who developed RA after follow up (n = 9) compared to those who did not (n = 10).

Table 1. Median expression levels in early arthritis and preclinical RA

Median expression (in pixel/ um²)	Expression levels in early arthritis in relationship to diagnosis						Expression levels in early arthritis in relationship to outcome				Expression levels in preclinical RA		
	Gout	PsA	RA-RA	UA-RA	UA-UA	P*	Erosive	Non-erosive	Self limiting	P*	Arthritis+	Arthritis-	P*
CD248	0.037	0.056	0.026	0.080	0.043	ns	0.018	0.026	0.053	ns	0.015	0.051	ns
Gp38	0.007	0.030	0.008	0.003	0.009	ns	0.010	0.008	0.005	ns	0.000	0.000	ns
CD55	0.014	0.027	0.014	0.017	0.006	ns	0.016	0.011	0.016	ns	0.017	0.019	ns
PDI	0.056	0.075	0.026	0.022	0.037	ns	0.025	0.044	0.037	ns	0.004	0.004	ns

*ns: not significant, p-value ≥0.05
Arthritis +: Seropositive individuals who developed arthritis during follow-up time of 3.4 years
Arthritis −: Seropositive individuals who did not develop arthritis after a mean follow-up time of 3.4 years

Conclusion: The stromal cell markers CD248, gp38, PDI and CD55 are all expressed in the earliest stages of clinically manifest arthritis, independent of the diagnosis and outcome after follow up. In preclinical RA the expression of gp38 is lower compared to early RA. Stromal markers seem to be expressed in a stable way in the ST during the development from being at risk of RA to early RA.

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Fine Specificity of Anti-Citrullinated Peptide Antibodies Discloses a Heterogeneous Antibody Population in Rheumatoid Arthritis (RA). John D. Goules, Andreas V. Goules and Athanasios G. Tzioufas. School of Medicine, National University of Athens, Athens, Greece

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are highly specific for the diagnosis of patients with RA. However, the predominant B cell epitopes have not yet been defined. The aim of this study was to examine in parallel the individual ACPA antibodies against different peptides derived from citrullinated proteins and investigate whether these antibodies constitute a homogenous population.

Methods: Sera from patients with RA (n = 141), systemic lupus erythematosus (n = 60), Sjögren's syndrome (n = 54), and healthy controls (n = 100) were tested for their reactivity against 6 citrullinated peptides (pep#2-pep#7) derived from peptidyl arginine deiminase (PAD), vimentin, alpha-enolase, fibrin, type II collagen and filaggrin respectively. A non citrullinated-control peptide derived from PAD was used as control (pep#1). Antibody reactivity was evaluated for each individual peptide by ELISA. Third generation anti-cyclic citrullinated peptide (anti-CCP3) antibodies were also determined. Specificity and sensitivity for anti-peptide antibody were tested by homologous and cross inhibitions assays. Cross reactivity between anti-peptide antibodies was evaluated, after affinity purification, by cross-inhibitions assays.

Results: Sera from patients with RA reacted diversely with the six citrullinated peptides. More specifically, pep#2 PAD (210–230aa) displayed 29.08% sensitivity, pep#3 vimentin (60–75aa) 29.08%, pep#4 alpha-enolase (5–21aa) 37.59%, pep#5 fibrin (617–631aa) 31.21%, pep#6 type II collagen (358–375aa) 29.97% and pep#7 filaggrin (306–324aa) 28.37% while control pep#1 PAD (621–640aa) showed no reactivity. All reactive peptides were found to be specific for RA (specificity: 91.59%, 93.93%, 95.33%, 95.79%, 97.20% and 97.73% respectively). The sensitivity of anti-CCP3 antibodies and antibodies against equamolar peptide mixture (containing six citrullinated peptides) for RA was 60.78% and 46.08% respectively and specificity 94.12% and 82.22%. Minimal cross reactivity between antibodies against the majority of citrullinated peptides was observed, ranging from 5.43% to 44.98%. A notable cross reaction (>60%) was observed between antibodies to pep#2 and antibodies to other peptides.

Conclusion: This study showed that ACPA in RA, using as substrates peptides from different citrullinated proteins, constitute a heterogeneous population with limited cross reactivity and without a predominant epitope. Studies to evaluate the significance of these findings are now under study in our laboratory.

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Nicotinamide Adenine Dinucleotide Phosphate Oxidase Mediated Angiogenesis and Inflammation in the Arthritic Joint. Monika Biniecka[1], Wei Gao[2], Chin Teck Ng[2], Emese Balogh[2], Douglas J. Veale[2] and Ursula Fearon[2]. [1]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Translation Rheumatology Research Group, Dublin, Ireland

Background/Purpose: To examine the role of Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH oxidase)-derived Reactive Oxygen Species (ROS) and NADPH oxidase-dependent redox signaling events in regulating angiogenesis and inflammation in the arthritic joint. Moreover to examine the effects of hypoxia, TNFi treatment and NADPH inhibitors on NADPH oxidase mediated angiogenesis and inflammation.

Methods: Patients with inflammatory arthritis (IA; n=48) underwent arthroscopy and synovial tissue oxygen (tpO₂) measurements, synovial tissue biopsies and clinical assessment were obtained. Sixteen patients pre/post-TNFi therapy were also recruited. Macroscopic synovitis/vascularity was measured by visual analogue scale. Synovial levels of NADPH oxidase (isoform NOX2), cell-specific markers of inflammation (CD3, CD8, CD20, CD68), vascular factors (VEGF, Ang2, Factor VIII) and redox signaling factors (NF-κB, Akt, STAT3) were quantified by immunohistology/ immunofluorescence. Using IA synovial explant cultures ex-vivo, the effect of the NOX2 inhibitors (DPI and APO) on IL-8 release was measured by ELISA. NOX2 protein levels were assessed in K4 cells (immortalised human synoviocytes) under normoxia and hypoxia (3%) by Western Blot.

Results: Low in vivo pO₂ levels in the inflamed joint (median [range] 26.6 [3.2-63] mm Hg) were related to increased microscopic expression of NOX2 (p=0.01; r=-0.43). In biologic responders in vivo tpO₂ levels increased post treatment, which was associated with a significant reduction in NOX2 level (p<0.05). In contrast in non-responders where tpO2 levels remained the same or were reduced, no significant change in NOX2 expression was observed. Furthermore in vitro hypoxia (3%) induced NOX2 protein expression in K4 cells. High synovial NOX2 expression correlated with high macroscopic vascularity (p=0.005; r=0.46), synovitis (p=0.03; r=0.37), and with increased number of cell-specific markers of T cells (CD4 p=0.0001, r=0.90; CD8 p=0.002, r=0.72), B cells (CD20 p=0.003; r=0.82) and macrophages (CD68 p=0.01; r=0.44). There was a colocalisation and strong association between synovial NOX2 and expression of VEGF (p=0.005; r=0.52), Ang2 (p=0.05; r=0.32) and a number of blood vessels (p=0.004; r=0.50). In addition, synovial NOX2 expression was linked to redox activation of NF-κB, Akt, and STAT3 signaling pathways. Functionally, stimulation of synovial explants with DPI and APO alone or in combination with TNF significantly decreased secretion levels of IL-8.

Conclusion: NADPH oxidase is strongly expressed in synovial tissue and NADPH oxidase-derived ROS may mediate angiogenic and proinflammatory processes in the inflamed joint. Furthermore these effects may in part be mediated through hypoxic activation of downstream redox sensitive signaling events.

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IL-21 Regulates B Cell Proliferation and Differentiation in Rheumatoid Arthritis. Lingyun Sun, Rui Liu and Xia Li. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Interleukin (IL)-21 is a member of type I cytokine family. Recent studies have indicated that IL-21 is an important regulator for human B cell activation, proliferation, plasma cell (PC) differentiation, immunoglobulin (Ig) production and isotype switching. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by abnormal production of cytokines and autoantibodies including rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP), suggesting that B cells play a key role in pathogenesis of RA. The aim of this study was to investigate the effect of IL-21 on B cell proliferation and differentiation of RA patients.

Methods: Concentrations of IL-21 in serum were measured by ELISA. The correlation between serum IL-21 levels and clinical features of RA patients were assessed. The percentages of IL-21R⁺CD19⁺ cells were analyzed by flow cytometry (FACS) in peripheral blood mononuclear cells (PBMC) from RA patients and healthy controls. PBMC from RA patients were stimulated with rIL-21 (50 or 100ng/ml) after motivation with anti-CD40 and anti-IgM. The percentages of IL-21R, activation markers (CD40, CD69 and CD25) on B cells and the proliferation labeled with CFSE as well as differentiation of B cells were determined by using FACS analysis

Results: The results showed that serum IL-21 concentrations in RA patients (191.3±34.42pg/ml, n=104) were significantly higher than in healthy controls (10.33±11.43pg/ml, n=56, p<0.01). The levels of IL-21 in RA patients were positively related to RF-IgM (r=0.23, p<0.05), RF-IgA (r=0.34, p<0.05), RF-IgG (r=0.35, p<0.05) and anti-CCP (r=0.32, p<0.05). Moreover, the

percentages of IL-21R$^+$CD19$^+$ cells were found to be markedly higher in PBMC of RA patients (48.55%±2.63%, n=50) compared to healthy controls (34.12%±2.37%, n=40, p<0.01) and IL-21 could up-regulate IL-21R expression on B cells in vitro. Meanwhile, IL-21 stimulated the proliferation of B cells and activated marker expressions (CD40, CD69 and CD25). IL-21 induced more production of CD138$^+$CD19$^{+/low}$ cells in RA patients, indicating that IL-21 can promote B cell differentiation.

Conclusion: These results suggest that increased IL-21 expression from RA patients might support B cells proliferation, activation and antibody secretion. Thus, antagonizing IL-21 may be a novel strategy for treating RA.

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Podoplanin Expression in Rheumatoid Stroma Correlates with Lymphoid Neogenesis and Is Downregulated by Anti-TNF-α Therapy. Regina Faré[1], Elena Izquierdo[1], Manuel J. Del Rey[1], Raquel Celis[2], Alicia Usategui[1], Juan D. Cañete[2] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Hospital Clínic of Barcelona, Barcelona, Spain

Background/Purpose: In rheumatoid arthritis (RA), synovial fibroblasts (SF) expand and undergo phenotypic changes that contribute to chronic inflammation and joint destruction. Podoplanin (Pdp) is a transmembrane glycoprotein normally expressed by lymphatic endothelium and stromal cells of the T-cell zone in lymph nodes. Recent studies have shown that Pdp is inducible by TNF-α in SF and its expression is increased in RA synovium. Pdp-deficient mice have defective development of both lymphoid organ and ectopic inflammation-associated lymphoid follicles. The aim of this study was to investigate the clinical and pathological significance of increased podoplanin expression in RA patients with particular focus on ectopic lymphoid neogenesis (LN).

Methods: Pdp expression was quantified by immunohistochemistry with specific anti-human podoplanin antibody (clone D2–40) in synovial arthroscopic biopsies from RA patients with active knee arthritis and variable disease characteristics (n=39) and healthy synovial tissues (n=6). Pdp expression was quantified as the fractional immunostained area using ImageJ software. Variation in Pdp expression was analyzed regarding the presence of LN (defined as large grade 2–3 T/B aggregates with MECA79+ high endothelial venules), pathological data including CD68, CD3, CD20 and CD31 cell density, and clinical variables such as disease duration and severity or activity variables. Changes in Pdp expression in a subgroup of 16 patients that underwent a second arthroscopic biopsy after anti-TNF-α therapy were also analyzed. Correlation between Pdp expression and other quantitative variables was analyzed by Spearman's test and changes in Pdp expression in different patient groups by Mann Whitney U-test.

Results: Pdp was abundantly expressed by lining cells of all RA synovial tissues whereas it was undetectable in healthy synovial tissues. In 54% of the patients, Pdp expression extended to sublining fibroblasts and reticular stromal cells within lymphoid aggregates of LN structures. Pdp expression was significantly increased in the group of patients (64%) with ectopic LN (13.7±2.4% vs 21.9±1.7%, mean±SEM, p=0.006). We also found significantly increased Pdp expression in the groups of patients with rheumatoid factor (14.6±2.3% vs 23.2±2.5%, p=0.02) or ACPA autoantibodies (10.7±1.9% vs 21.8±2.1%, p=0.01). No other clinical or pathological correlations were found. Therapy with TNF-α antagonists induced a significant reduction in Pdp expression (18.6±2.4% to 6.8±1.5%, p=0.0002).

Conclusion: Pdp is ectopically expressed by stromal cells of the lining and sublining in RA tissues, a phenomenon partially reversed by anti-TNF-α therapy. A higher level of Pdp expression is present in the subgroup of patients with LN providing a potential mechanistic link between stromal cell changes and LN.

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Prevalence of Anti-Peptidylarginine Deiminase Type 4 Antibodies in Rheumatoid Arthritis and Unaffected First-Degree Relatives in Indigenous North American Populations. Elizabeth D. Ferucci[1], Irene Smolik[2], Tammy L. Choromanski[1], David B. Robinson[2], Marianna M. Newkirk[3], Marvin J. Fritzler[4], Antony Rosen[5], Erika Darrah[5] and Hani S. El-Gabalawy[2]. [1]Alaska Native Tribal Health Consortium, Anchorage, AK, [2]University of Manitoba, Winnipeg, MB, [3]McGill University Health Centr, Montreal, QC, [4]University of Calgary, Calgary, AB, [5]The Johns Hopkins University, Baltimore, MD

Background/Purpose: Antibodies directed against peptidylarginine deiminase type 4 (PAD-4) are present in a subset of patients with rheumatoid arthritis (RA) and are associated with more severe joint destruction. These autoantibodies have been detected preceding the clinical diagnosis of RA in some patients. The objective of this study is to determine whether anti-PAD-4 antibodies are present in first-degree relatives of RA patients in two indigenous North American (INA) populations with high prevalence of RA.

Methods: Participants were recruited from two INA populations. We included RA patients (probands), their unaffected first-degree relatives (FDRs), and healthy controls, including both INA and Caucasian controls. Participants were interviewed for the presence of joint symptoms and underwent a joint examination by a rheumatologist. Sera were tested for the presence of anti-PAD-4 antibodies, anti-cyclic citrullinated peptide (CCP) antibodies, and rheumatoid factor (RF) IgM by ELISA. HLA-DRB1 subtyping was performed and participants were classified according to the presence or absence of shared epitope alleles.

Results: Antibodies to PAD-4 were detected in 27 of 82 (32.9%) RA probands; 2 of 147 (1.4%) FDRs; and 0 of 64 controls, including 20 Caucasian and 44 INA controls (p <0.0001). Anti-CCP antibodies were present in 26/27 (96.3%) of probands with anti-PAD-4, as compared to 42/54 (77.8%) of probands without anti-PAD-4 (p=0.05). In the FDRs, anti-CCP was present in 39/144 (27.1%) and there was no overlap between positivity for anti-CCP and PAD-4. None of the controls had anti-CCP antibodies detected. CCP and RF were both positive in 80.8% of the probands, but the association between RF and PAD-4 positivity was not statistically significant (p=0.14). One or more copy of an HLA-DRB1 shared epitope allele was present in 92% of probands and 82% of relatives (p=0.13), and there was no association between the presence of a shared epitope allele and PAD-4 positivity in probands (p=0.65) or relatives (p=1.0).

Conclusion: Despite a significant prevalence of anti-CCP in FDRs of INA RA patients, anti-PAD-4 antibodies were almost exclusively found in existing RA, suggesting these autoantibodies may be highly specific for RA. The prevalence of anti-PAD-4 antibodies in INA people with RA is similar to the prevalence described in other populations and these autoantibodies are strongly associated with anti-CCP in RA.

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Identification of Follicular Helper T Cells As a Novel Cell Population Potentially Involved in the Pathogenesis of Rheumatoid Arthritis. Sharon Ing[1], Anika Alarakhia[1], Elvira Lindwall[1], Austin Fraser[1], Jerald M. Zakem[2], William E. Davis[2], Tamika A. Webb-Detiege[3], Robert Quinet[4] and Xin Zhang[5]. [1]Ochsner Medical Center, New Orleans, LA, [2]Ochsner Clinic, New Orleans, LA, [3]Ochsner Medical Ctr, New Orleans, LA, [4]Ochsner Medical Center - New Orleans, New Orleans, LA, [5]Ochsner Clinic Foundation, New Orleans, LA

Background/Purpose: Rheumatoid Arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the synovium, causing progressive joint destruction and reduction in quality of life for patients. The treatment of RA is largely based on management of the clinical consequences and manifestation of joint inflammation, which is likely to be remote from the fundamental pathophysiologic defects. Identification of cellular subsets or biomarkers that differentiate distinct clinic features according to the pathophysiologic defects is a necessary first step toward making a more accurate prognosis and better therapeutic decisions. Here, we identify a novel T cell subset, follicular helper T cells (Tfh) in RA patients and examine the hypothesis that Tfh cells may participate in the pathogenesis in RA by fostering an environment for self-reactive B cells, resulting in autoantibody production.

Methods: Peripheral blood was collected from 20 RA patients meeting 2010 ACR/EULAR RA classification criteria and age/gender matched healthy donors. Synovial fluid specimens from actively inflamed joints of RA patients were also collected. Clinical disease activity was quantified using the Disease Activity Score in 28 joints (DAS-28). RA patients were divided into remission, mild/moderate, and severe groups based on their DAS-28 score. Serum laboratory measurements including Rheumatoid factor, anti-cyclic citrullinated peptide, Erythrocyte sedimentation rate and C Reactive Protein levels were obtained. Tonsil specimens were obtained from discarded surgical tissue of non-RA patients and used as positive controls. Surface phenotype (CXCR5, CD57, ICOS, PD-1, BTLA) and intracellular cytokine (IL-21) production were used to identify Tfh cells in RA peripheral blood, RA synovial fluid, and normal tonsil by flow cytometry and/or immunohistochemical staining. Surface phenotype CD20 and CD38 were used to identify

plasmablasts. IgG production was measured by ELISA from the co-culture of autologous B cells with their respective tonsillar Tfh cells, or RA peripheral blood Tfh and non-Tfh cells.

Results: A novel T cell subset with Tfh cell surface molecule and signature cytokine was identified in both of the peripheral blood and the synovial fluid from RA patients. The percentage of these Tfh-like cells was expanded in the peripheral blood and synovial fluid of active RA patients (DAS-28 > 2.6) (P<0.05), compared to healthy donors and RA patients in remission (DAS-28 <2.6). The percentage of Tfh-like cells in CD4$^+$ T cells of the peripheral blood of RA patients correlated with the percentage of plasmablasts in the total lymphocyte population, and also with the level of pathogenic auto-antibody (anti-CCP) and DAS-28. IgG levels were significantly increased in co-culture of Tfh-like cells and peripheral blood B cells of RA patients, but not in co-culture of non-Tfh-like cells and RA peripheral B cells.

Conclusion: Identification of an expanded population of Tfh-like cells in RA patients provides evidence that a distinctive germinal center pathway maybe involved in RA pathogenesis resulting in autoimmunity. Targeting RA-Tfh-like cells may provide more precise treatment strategies.

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Analysis of Gene Expression Patterns in Rheumatoid Arthritis (RA) Synovial Macrophages From Patients Undergoing Disease Flare. Karen L. Berg[1], Adedayo Hanidu[1], Jon Hill[2], Xiaoyu Jiang[1], Tom Freeman[2], Jennifer Swantek[1], Anna Yarlina[3], George D. Kalliolias[3], Lionel B. Ivashkiv[3] and Gerald H. Nabozny[1]. [1]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [2]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, [3]Hospital for Special Surgery, New York, NY

Background/Purpose: Synovial macrophages play a key role in RA pathogenesis. Their numbers are greatly increased in RA synovium, their phenotype is consistent with a pro-inflammatory function, and clinical data indicate all efficacious RA therapies lead to a significant reduction of this cell type in the diseased joint. Studies probing global gene expression in RA synovial macrophages have been limited in scope. We set out to further our understanding of synovial macrophage biology—both in RA and additional arthropathies—through gene expression profiling, gene mining and pathway analysis in synovial macrophages from patients undergoing disease flare.

Methods: Synovial fluids were collected from 10 RA patients in disease flare (treatments included oral DMARDs and/or biologics), and CD14+ cells isolated by positive selection. Control macrophage samples were generated from CD14+ peripheral blood monocytes from healthy donors, and differentiated with M-CSF. Macrophages were also isolated from synovial fluid from patients with Psoriatic Arthritis and other arthropathies to allow for comparison of dysregulated genes and pathways across related diseases. RNAs were isolated, processed, and transcriptional profiling of the samples was performed using Affymetrix arrays. Statistical analysis was performed using principle component analysis (PCA) and upregulated genes defined as >2.0-fold increase in expression and an FDR p-value of <0.05. Internal genesets from cytokine-stimulated macrophages, and M1 or M2 polarized macrophages, were used as comparators to further characterize upregulated genes and pathways in RA macrophages.

Results: Approximately 1900 genes were significantly upregulated in RA synovial macrophages, and 70% demonstrated overlap with Psoriatic arthritis and other arthropathies. Forty percent of RA-upregulated genes were upregulated in M1 polarized macrophages, vs. 7% in M2 macrophages. Only 10% of RA-regulated genes were upregulated by chronic treatment of control macrophages with TNFa, indicating other factors impact gene expression to a greater extent in RA macrophages. Gene Set Enrichment and Ingenuity Pathway Analysis indicated that several immunoregulatory pathways previously linked to RA pathogenesis were upregulated in RA macrophages (including CD40, and FcR), independent of treatment. Interestingly, the LTb signaling pathway, which was highly upregulated in M1 macrophages was not significantly induced in RA macrophages indicating a unique inflammatory phenotype of these disease macrophages.

Conclusion: We performed a comprehensive study focused on identifying differentially regulated genes and pathways in synovial macrophages from patients with RA and related arthropathies. These results suggest a unique inflammatory phenotype of RA macrophages and maintenance of key inflammatory pathways during flare that is independent of treatment. These observations may shed light on novel intervention points for treatment of RA.

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***Porphyromonas Gingivalis* and the Pathogenesis of Rheumatoid Arthritis: Analysis of the Synovial Tissue and of Other Compartments.** Michele C. Totaro[1], Sara D'Onghia[2], Elisa Gremese[1], Luca Petricca[1], Simona Marchetti[2], Silvia Canestri[1], Barbara Tolusso[1], Stefano Alivernini[1], Paola Cattani[2] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [2]Laboratory of Clinical Analyses CIC, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: *Porphyromonas gingivalis* (Pg), a periodontal anaerobic intracellular pathogen, has been recently associated to rheumatoid arthritis (RA) and the pathogenesis of the disease, due to its unique characteristic of citrullinating host and bacterial peptides. Given the mainly intracellular life of the bacterium, the aim of the study was to evaluate the presence of Pg DNA in the synovial tissue (ST) of RA patients through synovial biopsy in comparison with patients affected by other arthritides. Possible links with clinical, immunologic and genetic features were assessed.

Methods: Peripheral blood (PB), sub-gingival dental plaque, synovial fluid (SF) and ST samples were collected from 69 patients with active knee arthritis (32 with RA and 37 with other arthritides, of which 14 with undifferentiated peripheral inflammatory arthritis–UPIA). Demographic, clinical, laboratory and immunological data were recorded. The presence of Pg DNA was evaluated through PCR. The HLA-DR haplotype was assessed for 45 patients with RA and UPIA.

Results: No differences arose in the positivity for Pg DNA in the sub-gingival plaque, PB and SF samples between RA and the cohort of other arthritides. Full PB samples showed a higher positivity for Pg DNA than plasma samples (11.8% vs. 1.5%, p = 0.04). Patients with RA showed a higher positivity for Pg DNA in the synovial tissue compared to controls (33.3% vs. 5.9%, p < 0.01). UPIA and RA patients carrying HLA DRB1*04 allele showed a higher positivity for Pg DNA in the ST compared to patients negative for the allele (57.1% vs. 16.7%, p = 0.04). RA patients positive for Pg DNA in the sub-gingival plaque had a lower disease duration and a higher peripheral blood leucocytes and neutrophils count. The presence of Pg DNA did not influence disease activity, disease disability or positivity for auto-antibodies.

Conclusion: The presence of Pg DNA in the synovial tissue of RA patients suggests a pathogenic role of the bacterium. The higher positivity of Pg DNA in full peripheral blood and synovial tissue samples compared to plasma and synovial fluid suggests a possible intracellular localization of Pg, thus contributing to the loss of tolerance, in particular in patients positive for HLA-DR4.

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Cardiovascular Risk Factors and Events Are More Frequent Prior to the Onset of Rheumatoid Arthritis Than in the General Population. Helen Pahau[1], Vibeke Videm[2], Sanjoy Paul[3] and Ranjeny Thomas[1]. [1]University of Queensland Diamantina Institute, Brisbane, Australia, [2]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, and Department of Immunology and Transfusion Medicine, Trondheim University Hospital, Trondheim, Norway, [3]University of Queensland School of Population Health, Brisbane, Australia

Background/Purpose: Patients with the inflammatory autoimmune disease Rheumatoid Arthritis (RA) have a higher mortality and morbidity than the general population, predominantly related to cardiovascular disease (CVD). RA patients experience a 2-fold increased risk of myocardial infarction, due to the effects of traditional risk factors combined with inflammation. Since systemic inflammation, as determined by increases in multiple serum cytokines and chemokines, is evident prior to the onset of clinical RA but not osteoarthritis (OA), we hypothesized that cardiovascular events and risk factors would also occur more frequently prior to diagnosis of RA.

Methods: The HUNT population-based surveys were conducted in the county of Nord-Trøndelag in Norway. Detailed information pertaining to RA and OA diagnosis were obtained from 36493 subjects at baseline (HUNT 2, 1995–1997) and at 10-year follow-up (HUNT 3, 2006–2008). In subjects who did not have RA or OA at baseline, we evaluated the effects of cardiovascular and other relevant risk factors on the likelihood of developing RA or OA at follow-up. The risk factors included age, sex, smoking, BMI, blood pressure, diabetes and previous CVD.

Results: The 33567 individuals studied without RA or OA at baseline were mean (SD) age 46 (13) years old, 54% female, 50% current or ex-smokers, had BMI 26.1 (3.8) kg/m^2, 3.2% had previous CVD (angina, myocardial infarction or stroke), 1.4% had diabetes and 36% had hypertension. In this cohort, 786 (2.3%) individuals self-reported RA and 3586 (10.7%) self-reported OA at follow-up. Female were 41% and 136% more likely to develop RA and OA respectively. Individuals with previous CVD were 41% more likely to develop RA (p=0.03), but not OA. Current and previous smoking, and increased BMI, but not hypertension or diabetes, were significantly associated with both conditions. We evaluated the cardiovascular outcomes and associated risk factors in patients diagnosed with RA (n=429) or OA (n=2497) at baseline and follow-up. Adjusted for the cardiovascular risk factors, individuals with RA had 69% increased risk of stroke (p=0.02) and 45% increased risk of myocardial infarction (p=0.12) during follow-up. Individuals with OA had 35% increased risk of angina (p=0.003), but no increased risk of vascular events.

Conclusion: Although diagnosis was self-reported and not confirmed by chart review, these data suggest that individuals developing OA and RA among the Norwegian population share common cardiovascular risk factors, but only RA is pre-dated and associated with increased cardiovascular events. The development of RA at population level is associated with previous cardiovascular events and suggests the need for screening individuals with events for auto-antibodies and inflammatory features of RA.

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Proteases Produced by *Porphyromonas Gingivalis* Can Cleave and Citrullinate Substrates Found in the Joint and Oral Mucosa: Implications for Autoimmunity in Rheumatoid Arthritis.
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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterised by inflammation followed by tissue rebuilding or fibrosis. Failure by the body to effectively regulate inflammation is a hallmark of RA. It has been suggested that periodontal disease is one mechanism whereby tissue inflammation is triggered in RA. One of the organisms implicated in periodontal disease: *Porphorymonas gingivalis*, is an anaerobic pathogen that is known to produce peptidyl arginine demiminase (PAD), the only known bacterial PAD which causes citrullination. Cleavage of extracellular matrix (ECM) substrates in RA is known to lead to the production of ECM damage-associated molecular patterns, or DAMPs that can then be available for citrullination, thereby mediating chronic inflammation in RA.

Methods: We investigated the ability of proteases produced by *Porphorymonas gingivalis* to cleave extracellular matrix substrates which are found in the joint and also the human oral mucosa: fibrinogen, fibronectin and type I collagen. Culture supernatants of the anaerobe *Porphorymonas gingivalis* (strain W83 from ATCC) were produced from 24 hour cultures using full anaerobic conditions (3M Concept Plus anaerobic incubator). After culture, bacterial supernatants were extracted and incubated with the substrates at 0.5 mg/ml at 37° C, with collection of digestion products from 0–320 mins. The cleavage patterns of the substrates described was evaluated by SDS-PAGE and Western blotting in the presence of selective protease inhibitors.

Results: We found that culture supernatants *from Porphorymonas gingivalis* are effective at cleaving all the substrates tested. The substrate demonstrating the most rapid digestion profile in conditions of 37° C were in order of rapidity of cleavage: fibrinogen (30 mins for complete cleavage), fibronectin (180 mins for complete cleavage) and type I collagen (320 mins for complete cleavage). In the presence of arginine inhibitor (100 micromolar NMLA, *NG-methyl-L-arginine*) and 50 nM 1400 W (a potent selective inducible NOS *inhibitor)*, digestion of all three substrates was strongly inhibited. In the presence of gingipain inihibitors KYT-1 and KYT-36, greater inhibition of cleavage was demonstrated for KYT-36 than for KYT-31.

Conclusion: Our data demonstrate that selective proteases can cleave extracellular matrix protein substrates shared in the oral mucosa and the arthritic joint. Inhibition of cleavage of such substrates may delay the production of ECM DAMPs that can then be available for citrullination in RA. Therapeutic strategies aimed at inhibiting such cleavage of ECM substrates may be a novel therapeutic target in RA.

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Anti-Cyclic Citrullinated Peptide Antibodies in Idiopathic Pulmonary Fibrosis Are Not Citrulline-Specific: Implications for the Pathogenesis of Rheumatoid Arthritis.
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Background/Purpose: The association of rheumatoid arthritis (RA) with smoking and silica exposure has led to the hypothesis that the lung is the site where RA autoimmunity is initiated. In support of this, anti-citrullinated protein/peptide antibody (ACPA) positive RA is associated with a high prevalence of lung abnormalities at presentation, and airway changes have recently been reported in subjects with ACPA in the absence of joint disease. There are also reports of ACPA occurring in lung diseases in the absence of joint symptoms. Investigation of early lung associated citrullinated antigens may therefore give insight into RA pathogenesis.

Methods: Sera from 42 patients with idiopathic pulmonary fibrosis (IPF), but no arthritis, were tested for anti-CCP2 antibodies by commercial ELISA. Sera were further tested for antibodies to immunodominant peptides from 3 citrulllinated autoantigens in RA, α-enolase (KIHA-cit-EIFDS-cit-GNPTVE), vimentin (VYAT-cit-SSAV-cit-L-cit-SSVP) and fibrinogen (NEEGFFSA-cit-GHRPLDKK), as well as filaggrin (CCP1; SHQEST-cit-G-cit-SRGRSGRSGS) by in-house ELISA, with cysteines at the end of each peptide to facilitate cyclisation. Arginine-containing control peptides for all assays were run in parallel. A549 alveolar epithelial cells and HL-60 cells were cultured and lysates citrullinated in vitro with rabbit PAD2. Citrullinated and non-citrullinated lysates were separated by SDS-PAGE and probed with the anti-CCP2 positive sera.

Results: Six patients were anti-CCP2 positive (14%) with a mean antibody level of 44 AU/ml (range 29–61; normal <25). None of these 6 sera were positive for antibodies to the α-enolase, vimentin and fibrinogen peptides and only one was positive for the CCP1 peptide. No reactivity of the anti-CCP2 positive sera against the in vitro citrullinated A549 cell lysates was observed, however with the HL-60 lysates, reactive bands were identified in 3/6 sera (molecular weight approx. 52, 60 and 62 kDa) which were not citrulline-dependent. Sera were re-tested with the arginine-containing control peptide for CCP2, using a previously published method. This demonstrated that reactivity was not citrulline-dependent. Serum from a patient with RA-associated lung disease was used as a positive-control and had antibodies to CEP-1, cVim, cFib and CCP1, reacted predominantly with the citrullinated but not uncitrullinated A549 (bands at approx. 45, 50, 102 and 300 kDa) and HL-60 lysates, and showed citrulline-dependent specificity for the CCP2 peptides.

Conclusion: Our findings suggest that anti-CCP2 antibodies occurring in lung disease are not specific for citrullinated peptides. They may represent non-specific reactions, with correspondingly low antibody levels, as has previously been reported in autoimmune hepatitis. However, it remains a possibility that immunity to native antigens might breach tolerance to citrullinated proteins, as we have previously observed in DR4 transgenic mice immunised with α-enolase. Here we have identified candidate immunoreactive bands in the HL-60 lysates. In some individuals, this autoreactivity may be followed by epitope spreading to citrullinated protein, a corresponding rise in anti-CCP2 antibody levels, and the clinical onset of RA.

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Anti-Citrullinated Protein Antibody Specific Fc Glycosylation Patterns in Arthralgia Patients. Hans Ulrich Scherer[1], Yoann Rombouts[2], Ewoud Ewing[2], Lotte van de Stadt[3], Maurice H.J. Selman[2], André M. Deelder[2], Tom W.J. Huizinga[2], Manfred Wuhrer[2], D. van Schaardenburg[3] and René E.M. Toes[1]. [1]Leiden University Medical Centre, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) exhibit a specific, pro-inflammatory Fc glycosylation profile characterized by a low content of galactose and sialic acid residues. The absence of these residues from the Fc-linked core glycan could influence the biological activity of ACPA in rheumatoid arthritis. As ACPA can be detected in sera several years before disease development, we hypothesized that a change in ACPA Fc-glycosylation might precede the onset of arthritis.

Methods: Serum samples (n=300) of patients with ACPA positive arthralgia (n=184) were obtained at various time points. ACPA were isolated by affinity purification using cyclic citrullinated peptides as antigen. Isolated ACPA and total serum IgG molecules were subjected to trypsin digest, and glycan profiles of IgG1 Fc glycopeptides were analyzed by mass spectrometry. 96 patients in this cohort developed arthritis after an average duration of arthralgia of 14.7 months. At the time of the onset of arthritis, patients were defined as having rheumatoid arthritis (RA, n=51) based on the 1987 ACR criteria for RA, or undifferentiated arthritis (UA, n=45).

Results: No difference was found between ACPA-specific and total serum IgG1 Fc glycosylation patterns at the time of the patients' first presentation with arthralgia (baseline). At diagnosis of arthritis, RA patients, but not patients with undifferentiated arthritis, exhibited increased hypogalactosylation of the ACPA Fc fragment compared to healthy donors. Although a similar degree of Fc hypogalactosylation was found for total IgG in RA patients, hypogalactosylation of the ACPA Fc-tail occurred at 6 months before diagnosis, and was significantly more pronounced at 3 months before diagnosis than that of total IgG. No significant changes were noted for sialylation or fucosylation of the Fc tail.

Conclusion: ACPA acquire specific Fc-glycosylation patterns prior to disease onset, with a change towards hypogalactosylation occurring around 6 months before RA development. Of interest, ACPA hypogalactosylation was more pronounced than that of total IgG, indicating specific changes in the ACPA immune response several months before disease onset.

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1202

Antibodies Against *Porphyromonas Gingivalis* Correlate with Rheumatoid Arthritis-Specific Auto-Immunity in Arthralgia Patients. M. J. de Smit[1], L. A. van de Stadt[2], J. Westra[1], B. Doornbos-van der Meer[1], K.M.J. Janssen[1], A. Vissink[1], A. J. van Winkelhoff[1], E. Brouwer[1] and D. van Schaardenburg[2]. [1]University of Groningen, University Medical Center, Groningen, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands

Background/Purpose: In the disease association between rheumatoid arthrtitis (RA) and periodontitis a potential role is suggested for the periodontal pathogen *Porphyromonas gingivalis* (PG). PG is a major pathogen in periodontitis and has the unique feature of protein citrullination. Anti-cyclic-citrullinated-protein (CCP) antibodies are found not only in established RA but are also known to precede RA development. Aim of this study was to assess the levels of anti-PG antibodies in rheumatoid factor (IgM-RF) and/or anti-CCP positive arthralgia patients.

Methods: A cohort of 318 adult IgM-RF and/or anti-CCP positive arthralgia patients (mean age 50 years SD 12, 80% female) was prospectively followed for arthritis development during a median follow-up of 30 months. Patients with the possibility of a false-positive result for IgM-RF were excluded. Baseline analysis of serum samples was done by commercial (anti–CCP2; Axis-Shield) or in-house ELISA (IgM-RF, IgM-, IgG- and IgA-anti-PG). Baseline variables included age, gender, smoking, carriage of shared epitope (SE), and CRP/ESR levels by routine analysis. Anti-PG titers were compared to control subjects with severe periodontitis (disease controls, n=90) and control subjects with a healthy periodontium (healthy controls, n=23).

Results: 32% (n=103) of the patients developed arthritis, at median 15 months after baseline. After correction for age, gender, smoking and SE carriage, these patients had significantly higher mean anti-CCP levels compared to those who did not develop arthritis (p<0.001). No differences in levels of IgM-RF, anti-PG, CRP and ESR were found between groups of patients who did or did not develop arthritis.

Arthralgia patients had higher mean IgG-anti-PG levels than the healthy controls, as had the disease controls (p<0.001) (table 1). IgA anti-PG levels were only different between disease- and healthy controls (p<0.05), and no differences were seen between arthralgia patients, disease controls, and healthy controls in IgM-anti-PG levels (table 1). However, in the subgroup of arthralgia patients who developed arthritis there was a correlation of IgM-anti-PG with both anti-CCP and IgM-RF levels (ρ=0.2, p<0.05). No correlations were found between IgG- and IgA-anti-PG and anti-CCP.

Table 1. Mean (SD) anti-PG titers (mg/l) of different patient groups

Patients (n)	Arthralgia (318)	Arthritis+ (103)	Arthritis- (215)	Disease controls (90)	Healthy controls (23)
IgM-anti-PG	12.9 (12.9)	12.9 (12.4)	12.8 (13.1)	10.3 (8.71)	9.5 (7.44)
IgG-anti-PG	8.78 (17.5)**	7.94 (19.9)**	13.4 (29.6)**	23.8 (45.5)**	6.27 (23.6)
IgA-anti-PG	6.2 (11.5)	5.5 (15.5)	19.3 (133)	59.1 (292)*	8.88 (31)

** p<0.001 or *p<0.05 compared to healthy controls
Arthritis+: arthralgia patients who developed arthritis
Arthritis−: arthralgia patients who did not develop arthritis

Conclusion: IgM-RF and/or anti-CCP positive arthralgia patients have elevated IgG-anti-PG titers, and there is a significant correlation of IgM-anti-PG and RA-specific auto-antibodies in arthralgia patients who developed arthritis. This might indicate a role for the periodontal pathogen *P. gingivalis* in arthritis development.

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1203

High Expression of Genes in the Toll-Like Receptor and Interferon Pathways Are Associated with Radiographic Damage in African-Americans with ACPA-Positive RA. Maria I. Danila[1], A. D. Steg[2], Xiangqin Cui[2], David Redden[3], M. R. Johnson[2], Richard J. Reynolds[3], D. van der Heijde[4], Doyt L. Conn[5], Beth L. Jonas[6], Leigh F. Callahan[7], Larry W. Moreland[8], P. K. Gregersen[9] and S. Louis Bridges Jr.[10]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Emory Univ School of Medicine, Atlanta, GA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, [7]University of North Carolina, Chapel Hill, NC, [8]University of Pittsburgh, Pittsburgh, PA, [9]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [10]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: The clinical phenotype of rheumatoid arthritis (RA) ranges from mild joint inflammation to severe joint destruction, but molecular factors responsible for variability are incompletely understood, particularly in African-Americans. We tested the hypotheses that expression of immune-related genes in PBMCs differ in: a) severe vs mild radiographic damage; b) early or longstanding disease; c) RA vs control.

Methods: We analyzed total RNA from the PBMC of 60 African Americans from the CLEAR Registry (of a total of ~1,060 RA patients and 550 controls). Extremes of phenotype were analyzed: 10 RA with early disease/low damage (EL); 10 RA with early disease/high damage (EH); 10 RA with late disease/low damage (LL); late disease/high damage (LH) and 20 age, race and gender matched healthy controls. Early disease was defined as disease duration < 2 years. Late disease ranged from 9.5 to >60 years duration (Table 1). Radiographic severity was defined as total Sharp/van der Heijde scores of hands/feet. All participants had ACPA positive RA. We performed TaqMan qRT-PCR for 165 independent genes using panels based on specific pathways: SAB Innate and Adaptive Immune Signaling, and AB Immune Panel. The normalized gene expression levels (dCt) were compared between each RA group and the controls using a two-group t test.

Table 1. Clinical and demographic characteristics.

Variable	Control Group	EH Group	EL Group	LH Group	LL Group
Age (years)	35–69	23–75	34–62	35–76	47–68
Disease duration (months)	NA	2–23	0–5	114–522	189–339
Anti-CCP antibody status (ACPA)	Negative	Positive	Positive	Positive	Positive
Total Sharp/van der Heijde score	NA	11–53	0	181–341	0

Results: Preliminary results (Table 2) indicate a statistically significant increase (compared to controls) in gene expression in the EH category for the following genes: *TLR2, TLR4, TLR8, INFGR1, INFGR2, MAPK14*. In addition, EH subjects had lower expression of *MIF* and *IKBKB*. High expression of *TLR8* was associated with the LH group, while low expression of *TOLLIP* was associated with both the EL and LL groups. The expression of these genes is rarely increased in mild disease, especially in the LL goup. These preliminary results suggest that high expression of genes in the Toll-like receptor and interferon pathways are associated with radiographic damage in African-Americans with RA.

Table 2. Gene expression difference between RA groups and the control group*.

Gene	Control	EH Group		EL Group		LH Group		LL Group	
	dCT	dCT	p value	dCT	p value	dCT	p value	dCT	p value
TLR2	2.608	1.278	*0.00012*	2.561	0.9	2.244	0.32	2.234	0.31
TLR4	2.909	1.679	*0.0011*	2.345	0.13	2.334	0.12	2.247	0.076
TLR8	2.797	1.689	*0.00012*	2.391	0.17	2.129	*0.029*	2.402	0.19
TOLLIP	2.233	2.452	0.54	3.153	*0.012*	2.657	0.25	3.049	*0.027*
IFNGR1	2.58	1.364	*0.00048*	2.21	0.28	2.023	0.11	2.329	0.47
IFNGR2	2.171	1.447	*0.018*	2.2	0.92	1.83	0.24	2.284	0.7
MAPK14	2.548	1.641	*0.0011*	2.333	0.42	2.086	0.089	2.323	0.41
MIF	1.896	2.661	*0.012*	2.187	0.32	2.402	0.09	2.174	0.35
IKBKB	2.182	3.513	*0.0011*	2.767	0.14	2.509	0.41	2.464	0.48

*The CT values from qRT-PCR experiment were normalized against multiple house-keeping genes to obtain dCT values. Each RA group was compared with the control group. P values less than 0.05 are shown in italics.

Conclusion: These results will inform further studies of predictors of RA severity in African Americans using ~300 subjects from the CLEAR Registry, and have important implications regarding pathogenesis of radiographic damage of RA.

1204

Porphyromonas Gingivalis Antibody Responses and Clinical Associations in Patients with Early Rheumatoid Arthritis.
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Background/Purpose: Three prior studies have demonstrated an increased frequency of antibody responses to *P. gingivalis* (*Pg*), a leading agent of periodontal disease (PD), in RA patients, lending further evidence for a "mouth-joint connection" in RA pathogenesis. However, in these studies, patients had longstanding disease and were receiving DMARD therapy, which may affect serum antibody responses to *Pg* as well as infection with PD pathogens. Our goal was to determine the frequency of *Pg* antibody responses and their clinical associations early in the course of RA, prior to DMARD therapy.

Methods: We have established an early RA cohort study. To date, 45 adult patients with <1 year of symptoms have been enrolled prior to DMARD treatment and enrollment is ongoing. Sera from the early RA patients and 60 healthy controls were tested for *Pg* IgG antibodies by ELISA using sonicate antigen of whole *Pg* (ATCC 33277). A positive *Pg* antibody response was defined as >2SD above the mean absorbance of the 60 control subjects.

Results: The 45 early RA patients were typical of an RA cohort; 73% were female and 80% had positive test results for anti-CCP antibodies or rheumatoid factor (RF). Thirteen (29%) had a smoking history, but only 6 (13%) were current smokers. At study entry, 14 of the 45 patients (31%) had positive IgG antibody responses to *Pg* and the levels were significantly higher compared to healthy controls (P<0.0001). History of smoking was slightly lower in patients with *Pg* antibodies (3/13, 23%) than in those without such antibody responses (13/32, 41%), and median levels of *Pg* antibodies were not different between these groups. At study entry, early RA patients with *Pg* antibodies tended to have higher DAS-28-ESR scores (median values, 5.2 versus 4.3), more frequent anti-CCP antibody responses (86% versus 68%), and higher ESR values (median values 35 versus 20 mm/h, P=0.05) than those without *Pg* antibodies. Moreover, the magnitude of *Pg* antibody responses correlated directly with anti-CCP antibody levels (R^2=0.147, P=0.009) and ESR values (R^2=0.179, P=0.004), while showing no correlation with RF or CRP levels. During 12 months of DMARD therapy, DAS-28-ESR scores and *Pg* antibody responses declined in most patients, and no patient who had a negative *Pg* antibody response at entry became seropositive. At 12 months, there was still a trend toward higher DAS-28-ESR scores in patients with *Pg* antibody responses than those without *Pg* antibody (median score, 3.9 versus 2.4, P=0.08), and fewer patients in the Pg+ group achieved DAS remission (31% versus 56%).

Conclusion: A subset of patients with early untreated RA had IgG antibody reactivity to *Pg*. The high *Pg* antibody responses at this time demonstrate that immunosuppressive therapy does not explain the *Pg* antibody reactivity. In these patients, higher anti-CCP antibody responses and ESR values suggested that *Pg* infection may be associated with a specific inflammatory response. Finally, *Pg* antibody positivity was associated with a trend toward greater disease activity and less likelihood of achieving remission by 12 months. These findings support a role for *Pg* in both the initiation and persistence of disease activity in a subset of patients with early RA.

1205

Study of Association of CD40-CD154 Gene Polymorphisms with Disease Susceptibility and Cardiovascular Risk in Spanish Rheumatoid Arthritis Patients.
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased cardiovascular (CV) mortality. Since *CD40-CD154* binding has direct consequences on inflammation process initiation, we aimed to replicate previous findings related to disease susceptibility in Spanish RA population. Furthermore, as the major complication in RA disease patients is the development of CV events due to accelerated atherosclerosis, and elevated levels of CD40L/CD154 are present in patients with acute myocardial infarction, we assessed the potential association of the *CD40* (rs1883832, rs4810485 and rs1535045) and *CD154/CD40L* (rs3092952 and rs3092920) gene variants with CV risk in Spanish RA patients.

Methods: One thousand five hundred and seventy-five patients fulfilling the 1987 ACR classification criteria for RA and 1600 matched controls were genotyped for the *CD40* rs1883832, rs4810485 and rs1535045 and *CD154* rs3092952 and rs3092920 gene polymorphisms, using predesigned TaqMan single nucleotide polymorphism genotyping assays. Afterwards, we investigated the influence of *CD40-CD154* gene variants in the development of CV events. Also, in a subgroup of 273 patients without history of CV events, we

assessed the influence of these polymorphisms in the risk of subclinical atherosclerosis determined by carotid ultrasonography.

Results: Statistically significant differences in the allele frequencies for the rs1883832 CD40 gene promoter polymorphism between RA patients and controls were found. Although we did not observe a significant association of CD40-CD154 gene variants with the development of CV events, an ANCOVA model adjusted for sex, age at the time of the ultrasonography assessment, follow-up time, traditional CV risk factors and anti-cyclic citrullinated peptide antibodies disclosed a significant association between CD40 rs1535045 polymorphism and carotid intima media thickness, a surrogate marker of atherosclerosis (p= 0.0047).

Conclusion: Our data indicate a potential association of rs1883832 *CD40* gene polymorphism with susceptibility to RA. Also, the *CD40* rs1535045 gene variant may influence development of subclinical atherosclerosis in RA patients.

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1206

Gp96 Exacerbate the Inflammation of Rheumatoid Arthritis. Qi Quan Huang[1], Robert Birkett[2], J.-P. Jin[3] and Richard M. Pope[4]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Wayne State University, Detroit, MI, [4]Northwestern Univ Med School, Chicago, IL

Background/Purpose: The mechanisms that contribute to the persistent activation of macrophages in rheumatoid arthritis (RA) are incompletely understood. Toll-like receptors (TLRs) have been implicated in the regulation of innate immunity and inflammation, and to play an important role in the pathogenesis of RA. We have recently identified that gp96 as an endogenous TLR2 ligand that contributes to the persistent inflammation of RA. Employing RA synovial fluid (SF) macrophages, we demonstrated synergistic activation between the microbial TLR2 ligand peptidoglycan (PGN) and the TLR4 ligand lipopolysaccharide (LPS). This study was performed to determine the synergistic effect of gp96 in macrophages activation and in the K/BxN serum transfer model of arthritis.

Methods: Recombinant N' terminal fragment (aa 22–337) of gp96 was expressed from *E.coli* and purified with extensive endotoxin removing procedures (final product < 1EU/mg protein). Suboptimal concentrations of LPS, Pam3CSK4, PGN, and RA SFs containing low concentrations of gp96 (<300ng/ml) were employed individually or in combination to activate control or RA SF macrophages. Except when LPS was added, cell activation was performed in media supplemented with endotoxin inhibitor Polymyxin-B. Macrophage activation was determined by the expression of TNFa mRNA employing quantitative RT-PCR or by examining culture supernatants for TNFa and IL6 by ELISA. Arthritis was induced employing the K/BxN serum transfer model in wild type C57Bl/6 mice. Gp96 (20 mg/in 5ml of PBS) was injected intraarticularly into mice on days 3 and 10, with/without injection of K/BxN serum on day 0. Heat inactivated gp96 (65°c for 2 hour) severed as the negative control. Arthritis was evaluated by ankle swelling and clinical score from day 0 to 17 post-induction.

Results: Macrophage activation by low concentrations of gp96 (2.5–5 mg/ml) were synergistically enhanced by very low or trace amount of LPS, Pam3CSK4 and PGN. Pre-incubation of RA SFs (10% in RPMI medium) with gp96 (1mg/ml) synergistically increased TNFa expression in control and RA SF macrophages, compared with SF only or SF preincubated with heat inactivated gp96. C57Bl/6 mice that received K/BxN serum plus gp96 intraarticularly developed more severe arthritis, compared with the group received K/BxN serum plus heat inactivated gp96. Although gp96 or heat inactivated gp96 was administered at day 3 and boosted at day 10 post arthritis induction, the difference between these two groups was not observed until day 10 and afterward. Gp96 or heat inactive gp96 ankle injection alone only caused mild ankle swelling at 24 hours that resolved in 2–3 days.

Conclusion: These observations suggest that gp96 synergizes with low levels of microbial TLR2 and TLR4 ligands in promoting of macrophage activation. The intraarticular injection of gp96 exacerbated serum transfer arthritis. Gp96 may also interact with endogenous TLR ligands or other inflammatory molecules present in RA SF resulting in enhanced macrophage

activation. These observations suggest that gp96 does not act alone, but cooperates with other factors within the joint to promote inflammation and joint destruction.

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1207

Impact of Anti Tumor Necrosis Factor-Alpha Therapy in Rheumatoid Arthritis On Osteoclast Activation and B Cells. Ezinma Ezealah[1], Jennifer Hossler[1], Jamie Biear[1], Christopher A. Cistrone[1], Teresa Owen[1], Nida Meednu[1], Kelly Callahan[1], Arumugam Palanichamy[1], Ignacio Sanz[2], Allen P. Anandarajah[1], Ralf G. Thiele[1], Darren Tabechian[1], R. John Looney[1] and Jennifer H. Anolik[1]. [1]University of Rochester Medical Center, Rochester, NY, [2]Emory University, Atlanta, GA

Background/Purpose: Serum receptor activator of NFkB ligand (RANKL) and its natural decoy receptor, osteoprotegerin (OPG), play key roles in osteoclast activation. In a group of patients with active RA, we tested the hypothesis that initiation of TNF blockade would improve osteoclast activation (reflected by the serum OPG:RANKL ratio). DAS response was correlated with markers of B cell activation and musculoskeletal ultrasound.

Methods: 18 patients with RA failing methotrexate therapy (disease activity score (DAS) > 4.4) were randomized to receive either etanercept or adalimumab as part of a larger NIH sponsored Autoimmunity of Excellence (ACE) study (n=60). Soluble serum RANKL and OPG were measured by ELISA at baseline, 24, and 52 wk (pg/ml). RA disease activity was followed by DAS28 at baseline, 12 and 24 weeks. Peripheral blood (PB) B cells were phenotyped by flow cytometry using the following surface markers: CD19, IgD, CD27, CD24, CD38, CD95, and CD21. High frequency gray scale (GS) and power Doppler (PD) musculoskeletal ultrasound (MSK US) was performed on a subset of subjects (n=8) on the wrists, MCP, and PIP joints of both hands according to EULAR guidelines by a rheumatologist (DT and RT) certified in MSK US at baseline 4, 12, and 24 wk. GS US and PD US were scored semiquantitatively (on a severity scale from 0–3).

Results: In the current analysis of the Rochester cohort (n=18), 61% of patients were good DAS responders, 28% moderate responders, and 11% non-responders at 24 weeks. Good DAS responders had higher baseline RANKL levels than moderate/non-responders (2653 vs. 1218). Serum RANKL decreased significantly with anti-TNF treatment (2381+3025 at baseline vs. 921+1630 at 52 wk, p=0.03, n=8 longitudinal), as did OPG (150+92 at baseline vs. 82+51 at 52 wk, p=0.01), regardless of DAS response. Interestingly, the OPG:RANKL ratio was very low in these active RA patients (0.76+1.2 compared to historic healthy controls 3.0) and did not change significantly with anti-TNF treatment. On MSK US, the higher the baseline # of GS+ joints the less likely patients were to achieve a good DAS response. Additionally good DAS responders tended to have a low # of GS+ joints/absent PD on follow-up US (12 and 24 wk) in contrast to moderate/non-responders. Finally, RA patients at baseline had an expansion of activated memory B cells in the PB (CD95+ on CD27+IgD- memory in RA [n=13] 50.5+19.5% vs. HC [n=14] 29.6+9.5%, p=0.001; also significant for CD95+ on CD27-IgD- memory p<0.0001 and CD21- on CD27+IgD- memory p=0.02). There was a strong negative correlation between OPG:RANKL ratio and B cell activation (R2=−0.62 for correlation with CD95+ on CD27-IgD- memory), suggesting that activated B cells may contribute to RANKL activation. Longitudinal assessment of B cell subsets in response to anti-TNF is underway.

Conclusion: In our study, the OPG:RANKL ratio was considerably lower than the ratio reported for control subjects and similar to that observed in patients with multiple myeloma. B cell activation was characteristic of active RA and correlated with RANKL activation. These results support the notion that OPG:RANKL and B cells have a central role in RA-associated joint destruction.

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1208

Stable Synovial Fluid Phenotype for Anti Citrullinated-Protein Antibodies in Established Rheumatoid Arthritis. Vijay Joshua[1], Lena Israelsson[2], Lars Klareskog[2], Anca Irinel Catrina[1] and Vivianne Malmström[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden

Background/Purpose: Presence of anti citrullinated-protein antibodies (ACPA) in the peripheral blood of patients with rheumatoid arthritis is a validated disease biomarker. We have previously shown local synovial production of these antibodies in the synovial fluid of active RA. We aimed to investigate longitudinal stability of ACPA and ACPA fine specificities in SF of active established RA patients.

Methods: A cohort of 30 RA patients (n=30) with established RA (median disease duration 11 years at inclusion) was followed up for a median of 9 years. Half of the included patients were testing positive for CCP2 ELISA in the SF when screened at one arbitrary time point and half were negative. Longitudinal SF samples of these patients (a median of 5 samples/patient, median follow-up time of 9 years) were analyzed for the presence of anti CCP2 antibodies and for fine ACPA specificities using ELISA against citrullinated forms of alpha-enolase (aa5–21; cep-1), fibrinogen (aa566–580; cit-fib573) and vimentin (aa60–75; cit-vim60–75) peptides. Cut off of these ELISAs were set at the 98th percentile, based on analysis of sera from healthy controls.

Results: SF ACPA quantification using the CCP2 ELISA kit demonstrates a highly stable phenotype during time, with all patients selected on the basis of ACPA positivity at one time point (15/30, 100%) being positive on all tested occasions. The same was true for ACPA negative SF (15/30, 100%). Among fine specificities presence of anti citrullinated a-enolase was stable (with 5/30 positive and 25/30 negative patients on all tested occasions). Same trend was observed for antibodies against citrullinated vimentin with 25/30 patients being either positive (3) or negative (22) on all tested occasions and citrullinated fibrinogen with 28/30 patients being either positive (3) or negative (24) on all tested occasions.

Conclusion: We demonstrate that both ACPA and ACPA fine specificities have a stable phenotype in SF of patients with longstanding RA suggesting continuous local production of antibodies during disease progression.

1209

Functional Role of Chondrogenic Progenitor Cells in Rheumatoid Arthritis. Sabine Blaschke[1], Sandra Trautmann[1], Alexander W. Beham[2], Burkhard Mai[3], Sebastian Koelling[1], Caroline Breysach[4], Gabriele Wolf[1], Gerhard A. Mueller[1] and Nicolai Miosge[5]. [1]University Medical Center Goettingen, Goettingen, Germany, [2]Department of Surgery, Germany, [3]Vitos Orthopaedic Clinic Kassel, Kassel, Germany, [4]Department of Surgery, Goettingen, Germany, [5]Dept. of Prosthodontics, Goettingen, Germany

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease of still unknown etiology leading to progressive cartilage and bone destruction. Proinflammatory cytokines, immunoregulatory cells and synoviocytes were previously shown to play an important role in RA pathogenesis. Recently, a novel progenitor cell population, termed chondrogenic progenitor cells (CPCs), were isolated from repair tissue in later stages of osteoarthritis (OA). In this study, we analyzed the presence and functional characteristics of this cell type in human RA.

Methods: Cartilage tissue specimens were obtained from 10 RA patients (age 44–85y) after total joint replacement surgery. All patients met the American College of Rheumatology criteria for established RA. The study was approved by the local ethics committee. CPCs were isolated as previously described (1) and subjected to flow cytometry and immunocytochemistry for stem cell surface markers and the interleukin-17 receptors (IL-17RA/RC). Expression of transcription factors was analyzed by quantitative RT-PCR and multipotency was characterized by in vitro chondrogenic, osteogenic and adipogenic differentiation. Functionally, in vitro effects of IL-17A/F-stimulation (50ng/ml for 24h) in RA-CPCs were assessed.

Results: RA-CPCs could be isolated from tissue specimens in 10/10 RA cases. Flow cytometry revealed the expression of cell surface markers CD13, CD29, CD44, CD73, CD90 and CD105, but CPCs were negative for CD34 and CD45. Furthermore, RA-CPCs were shown to express the IL-17RA and -RC receptor. Transcription factors RUNX-2 and SOX-9 were detected by quantitative RT-PCR and immunocytochemistry. Multipotency differentia-

tion revealed that RA-CPCs harbour a chondrogenic, osteogenic and adipogenic potential. In vitro stimulation with IL-17A/F resulted in significant upregulation of NF-kB, TRAF-6, MMP-3 and IL-6.

Conclusion: Our study results demonstrate that CPCs are also present in RA cartilage tissue and express stem cell characteristics already described for OA-CPCs. Functional analysis revealed that these cells may also play a role in RA pathogenesis by IL-17-induced upregulation of MMP- and proinflammatory cytokine expression.

1210

Effect of HLA-DRB1*0901 Suggest Distinctive Mechanisms of Rheumatoid Arthritis Susceptibility. So-Young Bang[1], Hye-Soon Lee[2], Kyung Wha Lee[3] and Sang-Cheol Bae[4]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Hanyang University Guri Hospital, Guri, South Korea, [3]Hallym Institute for Genome Application, Hallym University Sacred Heart Hospital, Anyang, South Korea, [4]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea

Background/Purpose: Although HLA-DRB1 shared epitope (SE) alleles and DRB1*0901 have repeatedly been shown to be associated with RA susceptibility, the effect of each allele on levels of anti-cyclic citrullinated peptide autoantibodies (anti-CCP) and interaction with smoking in RA remains to be fully defined. We aimed to investigate whether DRB1 risk alleles influence anti-CCP levels and whether each allele interacts with smoking in anti-CCP positive or negative RA.

Methods: All RA patients (n =1,924) and controls (n = 1,119) were Korean. Odds ratios and biologic interactions as departure from additivity or multiplicity were analyzed by logistic regression.

Results: The *0901 allele significantly decreased anti-CCP levels in both the SE-negative and SE-positive group. We found a hierarchy of anti-CCP levels depending upon the combination of RA risk alleles ($P=5.55\times10^{-11}$). In the hierarchy, individuals carrying SE/SE had the highest (614 units/ml) and *0901/*0901 had the lowest levels (189 units/ml). The SE alleles interacted with smoking strongly in anti-CCP positive RA (AP=0.48 [0.25–0.71] and slightly in anti-CCP negative RA (AP=0.43 [0.02–0.81]). In addition, each of the SE alleles significantly interacted with smoking in anti-CCP positive RA. In anti-CCP negative RA, only *1001 interacted with smoking. However, DRB1*0901 did not interacted with smoking in both anti-CCP positive and negative RA groups. Interestingly, interactions between the two most significant risk alleles, *0405 and *0901, (AP=0.68 [0.46–0.89], multiplicity p=0.012) significantly increased RA susceptibility regardless of anti-CCP and smoking status. Moreover, smoking amplified the risk for RA by significant synergistic interaction with the heterozygote *0405/*0901 in anti-CCP negative RA (AP=0.80 [0.32–1.28]) but not in anti-CCP positive RA.

Table 1. Risk of anti-CCP positive and anti-CCP negative RA according to HLA-DRB1 and smoking

HLA-DRB1/ Smoking	anti-CCP positive RA		anti-CCP negative RA	
	No. of cases/ controls	OR† (95% CI)	No. of cases/ controls	O† (95% CI)
SE				
−/−	188/502	reference	58/502	reference
−/+	30/63	2.17 (1.25–3.77)	13/63	3.76 (1.74–8.15)
+/−	826/328	7.28 (5.85–9.06)	99/328	2.66 (1.87–3.79)
+/+	166/46	16.31 (9.96–26.74)	22/46	9.05 (4.43–20.37)
AP‡	0.48 (0.25–0.71)		0.43 (0.02–0.81)	
RERI‡	7.87 (0.53–15.21)		4.08 (−2.34–10.50)	
S‡	2.06 (1.28–3.31)		1.92 (0.84–4.41)	
*0901				
−/−	188/502	reference	58/502	reference
−/+	30/63	2.54 (1.41–4.60)	13/63	2.90 (1.30–6.45)
+/−	292/162	4.97 (3.83–6.44)	41/162	2.19 (1.41–3.40)
+/+	47/33	7.77 (4.12–14.63)	13/33	5.66 (2.38–13.45)
AP‡	0.16 (−0.32–0.65)§		0.28 (−0.32–0.87)§	
RERI‡	1.25 (−3.21–5.72)		1.57 (−2.85–0.87)	
S‡	1.23 (0.63–2.38)		1.51 (0.54–4.20)	

Table 2. Synergistic effect of having *0405 and *0901 alleles in RA according to anti-CCP status

Genotype	anti-CCP positive RA		anti-CCP negative RA	
	No. of cases/ controls	OR† (95% CI)	No. of cases/ controls	OR† (95% CI)
non-risk/non-risk	220/574	reference	71/574	reference
*0901/non-risk	173/151	2.94 (2.24–3.87)	31/151	1.63 (1.03–2.59)
*0405/non-risk	359/135	7.54 (5.82–9.77)	51/135	3.11 (2.07–4.67)
*0901/*0901	29/11	6.92 (3.36–14.24)	2/11	1.44 (0.31–6.64)§
*0405/*0405	61/9	20.22 (9.77–41.82)	2/9	1.85 (0.39–8.74)§
*0405/*0901	90/10	28.03 (14.17–55.45)	16/10	13.66 (5.93–31.44)
AP‡		0.66 (0.43–0.89)		0.73 (0.49–0.96)
RERI‡		18.69 (−0.28–37.66)		9.98 (−1.23–21.20)
S‡		3.19 (1.57–6.52)		4.63 (1.75–12.26)
Multiplicity‡		$P = 0.025$		$P = 4.32 \times 10^{-4}$

† All odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by comparing each group with the corresponding reference group [individuals without SE &*0901] adjusted for age and sex.

Conclusion: DRB1*0901 differs from SE alleles regarding to anti-CCP levels and interaction with smoking, suggesting a distinct mechanism of *0901 in RA pathogenesis, which may bypass anti-CCP formation. In addition, significant increase of *0405/*0901 heterozygote in RA susceptibility may be attributable to the synergistic contribution of two different pathways in which two alleles participate independently.

Disclosure: S. Y. Bang, None; **H. S. Lee**, None; **K. W. Lee**, None; **S. C. Bae**, None.

1211

ANTI-Cyclic Citrullinated Protein Antibodies Induce Inflammation and Oxidative Stress in WHITE Blood CELLS of Rheumatoid Arthritis Patients. Chary Lopez-Pedrera[1], Carlos Perez-Sanchez[2], Patricia Ruiz-Limon[1], Mª Angeles Aguirre[1], Rosario M. Carretero-Prieto[1], Antonio Rodriguez-Ariza[1], Nuria Barbarroja[3], Pilar Font[1], Francisco Martinez[1], Inmaculada Gomez-Gracia[1], Mª Jose Cuadrado[4] and Eduardo Collantes-Estevez[1]. [1]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [2]Research Unit, IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [3]IMABIS and Virgen de la Victoria Hospital, Malaga, Spain, [4]The Rayne Institute, London, United Kingdom

Background/Purpose: Anti-cyclic citrulinated protein antibodies (anti-CCP) are the most specific autoantibody markers in rheumatoid arthritis (RA) patients. However no previous studies have evaluated their role in the atherogenic process and cardiovascular (CV) risk in RA. The aim of this study was to investigate the role of anti-CCP antibodies in the induction of a pro-oxidative and inflammatory status in white blood cells, and their relationship with chronic inflammation and early atherogenesis in RA.

Methods: Fifty three RA patients and 31 healthy donors were included. Tissue factor (TF), protease activated receptors (PARs) expression, peroxides and peroxinitrites levels, and mitochondrial membrane potential (MMP), were analyzed by flow cytometry in white blood cells; glutathione peroxidase activity (GPx) was evaluated in cell lysates. Atherosclerosis/CV risk markers were also evaluated. RT-PCR was performed to elucidate the cellular origin of plasma inflammatory molecules. The carotid-intimate media thickness (CIMT) was measured as a surrogate marker of atherosclerosis. In parallel in vitro studies, isolated monocytes, lymphocytes, or neutrophils were incubated with non-specific human IgG or with purified anti-CCP antibodies.

Results: Increased expression of TF and PAR2 was found in neutrophils from RA patients, with higher plasma levels of VEGF, tPA, MCP1, MIP1α, TNFα, IL-2, -6, -8, -17A and -23. RA monocytes and neutrophils had higher peroxides and peroxynitrite levels, more depolarised mitochondria and lower GPx activity. Significantly higher levels of mRNA MCP-1, IL-1β, -6, -8, and TF were found in monocytes, pointing to the main cell sources of inflammatory molecules in RA. Notably, augmented titres of anti-CCPs were not only directly related to increased expression of protrombotic, pro-inflammatory and oxidative stress markers, but also to increased CIMT. Moreover, in vitro treatment with anti-CCP increased peroxide production in monocytes and neutrophils, as well as on the percentage of cells with increased MMP. Anti-CCP treatment in monocytes induced elevated cell surface TF expression and increased mRNA levels of MCP-1, IL-1β, -6, and -8 while in lymphocytes provoked increased IL-1β, -2, -6, -8, TNFα, and VEGF mRNA expression levels. No changes in cytokine mRNAs were found in neutrophils.

Conclusion: 1) Anti-CCP antibodies directly induce inflammation and oxidative stress in RA patients. 2) Monocytes and lymphocytes are key mediators of the anti-CCP-induced inflammatory state by expressing particular cytokines, which may constitute promising therapeutical targets for the

prevention of atherosclerosis and CVD in RA patients. Support: JA0246/2009, P08-CVI-04234, PS09/01809, Spanish Foundation of Rheumatology.

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1212

Elevated Fecal Secretory Immunoglobulin A, Anti-Cyclic Citrullinated Peptide Antibodies, and Cytokine Levels in Rheumatoid Arthritis Patients. Sam Dalvi, Jose U. Scher*, Mukundan Attur, Jyoti Patel and Steven B. Abramson. NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Rheumatoid arthritis (RA) is a complex auto-immune disease with genetic and environmental contributions. There has been increasing interest in the microbiome and its potential contribution to the pathogenesis of the inflammatory arthritides. Our recent study suggest that RA patients have altered intestinal microbiota compared to healthy controls. Here we aimed to investigate the local immunologic response in the intestinal tract of RA patients, including humoral signatures and pro-inflammatory cytokine profile. Mucosal response against enteric bacteria may offer insights into the pathogenesis of RA and the potential identification of subsets of patients amenable to therapeutic interventions.

Methods: *RA status, clinical activity and sociodemographic factors were determined in patients with New-onset RA (NORA; n=15), Chronic-established RA (CRA; n=14), and matched healthy subjects (n=14).* Fecal samples were obtained and total protein was extracted. ELISA assays were performed to determine concentrations of secretory (s) IgA, anti-cyclic citrullinated peptides antibodies (anti-CCP3.1), and various pro-inflammatory cytokines by multiplex assay**.**

Results: RA patients show aberrant intestinal humoral responses manifested by elevated fecal sIgA levels. Elevated levels of anti-CCP antibodies were found in fecal samples of these patients (mean= 64.9 Units vs 14.7 Units in healthy controls; P=0.03), suggesting that the intestinal tract is a potential site for peptide citrullination. Intriguingly, the gut anti-CCP3.1 levels in CRA patients were higher compared to NORA (p=0.10). NORA patients have significantly elevated fecal IL-1β compared to controls (mean= 4.2 pg/ml vs 1.67, p=0.02) as well as other pro-inflammatory cytokines including TNFa. These changes are associated with an intestinal microbiota alteration in NORA patients, characterized by a higher prevalence of Prevotella spp.

Conclusion: Our results show evidence of an amplified adaptive immune response and subclinical inflammation within the intestinal tract of patients with RA. To our knowledge, detection of the aforementioned fecal immunoglobulins and cytokines in RA patients has not been previously described. These findings suggest that immunologic defense mechanisms against intestinal bacteria may play a role in the pathogenesis of RA and that the intestinal tract is a potential site of peptide citrullination. Further studies are warranted to validate our findings.

Disclosure: S. Dalvi, None; **J. U. Scher***, None; **M. Attur**, None; **J. Patel**, None; **S. B. Abramson**, None.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Clinical Aspects II:
Clinical Features & Comorbidity/Cardiovascular Disease
Monday, November 12, 2012, 9:00 AM–6:00 PM

1213

The Serum Cytokine Profile of Interstitial Lung Disease in Rheumatoid Arthritis. Jose Felix Restrepo[1], Inmaculada del Rincon[2], Roy Haas[3], Daniel F. Battafarano[4] and Agustin Escalante[5]. [1]University of Texas Health Science Center, San Antonio, TX, [2]University Of Texas, Health Science Center, San Antonio, TX, [3]TX, [4]Brooke Army Medical Ctr, San Antonio, TX, [5]University of Texas Health Science Center at San Antonio, San Antonio, TX

Background/Purpose: Interstitial lung disease (ILD) is associated with significant morbidity and mortality in rheumatoid arthritis (RA). There are currently no proven biomarkers for ILD in RA. Cytokines, because of their important role in RA pathogenesis, as promising candidates to serve as biomarkers for ILD. In the current analysis, we examined the association between multiple cytokines and ILD in an RA cohort.

Methods: We studied members of an RA cohort recruited during a visit to a rheumatologist. All patients had comprehensive assessments at baseline

and annual follow-up, including collection of a serum sample which was stored. Medical records, including imaging reports, were reviewed thoroughly to assess comorbidity. We considered ILD to be present if an X-ray or computed tomography of the chest, or a lung biopsy were diagnostic of ILD. We measured the concentration of 38 cytokines in stored serum, using ELISA. We used stepwise logistic regression to identify cytokines associated with ILD, adjusting for age and sex as covariates. We show odds ratios (95% CI) to show strength of association.

Results: We studied 1328 patients, of whom 1204 had a stored serum sample for cytokine measurement. Of these, 86 had ILD (6.5%). Using stepwise logistic regression, the concentration of six cytokines was independently associated with ILD. The following three were associated with increased odds of ILD: growth-related oncogene (GRO), 2.14 (1.33, 3.44); tumor necrosis factor-alpha (TNF-a), 1.56 (1.12, 2.17); and interleukin-2 (IL-2), 1.73 (1.4, 2.15). The following three were associated with decreased odds of ILD: macrophage inflammatory protein-1-alpha (MIP1-a), 0.79 (0.62, 1.00); macrophage-derived chemokine (MDC) 0.48 (0.32, 0.72); and granulocyte colony stimulating factor (GCSF), 0.51 (0.34, 0.78). (Table 1). The area under the ROC curve for a model containing these cytokines plus age and sex was 0.776, while that for a model containing only age and sex was 0.63.

Table 1. Cytokines in RA-ILD patients.

Cytokine	OR (95% CI)	P-Value
GRO	2.14 (1.33, 3.44)	0.004
IL-2	1.73 (1.40, 2.15)	≤0.001
TNF-A	1.56 (1.12, 2.17)	0.021
MIP 1A	0.79 (0.62, 1.00)	0.043
GCSF	0.51 (0.34, 0.78)	0.006
MDC	0.48 (0.22, 0.72)	0.001

Conclusion: The profile of serum cytokine concentrations is significantly associated with the presence of ILD, with some cytokines being associated with increased risk, others with decreased risk. These findings may indicate the potential pathogenic of these cytokines in ILD among RA patients. In addition, these cytokines offer promise as potential biomarkers that could be used for the early identification of patients at risk for developing ILD.

Disclosure: Nothing to disclose

Disclosure: J. F. Restrepo, None; **I. del Rincon**, None; **R. Haas**, None; **D. F. Battafarano**, None; **A. Escalante**, None.

1214

The Impact of Periodontal Disease On Early Inflammatory Arthritis Persists Even After All Teeth Are Lost. Gisela Westhoff[1], Paola de Pablo[2], Thomas Dietrich[3], Georg Schett[4] and Angela Zink[5]. [1]German Rheumatism Research Center Berlin, Berlin, Germany, [2]University of Birmingham, Birmingham, United Kingdom, [3]The School of Dentistry, University of Birmingham, Birmingham, UK, Birmingham, United Kingdom, [4]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]German Rheumatism Research Center and Charité University Medicine, Berlin, Germany

Background/Purpose: Data suggests that individuals with periodontal disease (PD) may be more likely to develop rheumatoid arthritis (RA) and have worse disease activity. PD is a common inflammatory disease characterized by gingival accumulation of inflammatory cells with endothelial cell proliferation and matrix degradation that may worsen joint inflammation. Since PD is a major cause of tooth loss, tooth loss may be a surrogate marker for chronic PD, an inflammatory process that may possibly end when the last tooth is lost. We therefore hypothesized that partial vs. complete tooth loss (edentulism) may be differentially associated with disease activity in persons with early arthritis naive to DMARD-therapy.

Methods: The study sample included 1,009 patients with early arthritis (<6 months) naive to DMARD-treatment, enrolled in an ongoing longitudinal study (CAPEA 2010–2013). Data collection included disease activity (DAS28 calculated by TJC28, SJC28, ESR and Patient Global (PG; NRS 0–10)), the 2010 ACR-EULAR RA classification criteria and self-reported number of teeth. Patients were categorized according to number of teeth at study entry (no teeth, 1–19, 21–27, all teeth). Analysis of covariance was done to determine baseline disease activity by number of teeth.

Results: Study participants (65% female) were 55 ±14 years old and had mean symptom duration of 12 ±7 weeks. 56% were RF and/or ACPA positive and 66% fulfilled the 2010 criteria for RA. No patient had received any DMARDs at baseline. Sample characteristics by tooth loss categories are shown on Table 1. Significantly more participants with edentulism met ACR/EULAR classification compared with those with complete dentition (OR 1.9, 95% CI 1.01–3.35; adjusted for age, sex, BMI, smoking, and DAS28). Edentulous patients had neither lower nor higher disease activity (DAS28) than patients with considerable tooth loss (1–19 teeth left). However, compared with those with moderate tooth loss (20–27; P = 0.046) or complete dentition (P = 0.006), they had significantly worse disease activity.

Number of teeth	N	%	Age*	§RF/ ACPA pos. %	# RA %	& ESR*	~CRP mg/l*	TJC28*	PG*	DAS28 ESR*# (95% CI)
edentulous	77	7.6	68.2	65	75	45	28	10.0	5.5	5.2 (4.8–5.5)
1–19	289	28.6	63.7	54	70	39	27	10.0	5.3	5.3 (5.1–5.4)
20–27	401	39.7	53.6	55	65	28	18	7.8	4.9	4.8 (4.7–4.9)
all teeth	242	24.0	43.9	56	60	24	13	7.7	4.8	4.6(4.4–4.8)
Total	**1.009**	**100.0**	**55.3**	**56**	**66**	**32**	**22**	**8.6**	**5.0**	**4.9**
P = no vs. 1–19 teeth			0.001	0.055	0.270	0.080	0.828	0.955	0.578	0.470
P = no vs. all teeth			<0.001	0.101	0.011	<0.001	0.017	0.013	0.055	0.006

§ rheumatoid factor and/or anti citrullinated peptide antibody; # ACR-EULAR RA classification criteria points (0–10; ≥6 =RA);; & erythrocyte sedimentation rate; ~ C-reactive protein; *means, adjusted to 55.0 years of age

Conclusion: Tooth loss was associated with disease activity at disease onset in a large cohort of patients with early inflammatory arthritis (IA) naïve to DMARD-therapy. Contrary to the assumption that exposure to periodontal disease ends once all affected teeth are lost, edentulism does not improve the interrelation of dental health and IA. The impact of PD on IA starts before IA onset, and obviously persists even after all teeth have been lost. The data also support the notion that there might be a common underlying pathobiology for both conditions.

Disclosure: G. Westhoff, None; **P. de Pablo**, None; **T. Dietrich**, None; **G. Schett**, None; **A. Zink**, None.

1215

Rates of Orthopaedic Interventions for Rheumatoid Arthritis Have Changed Over the Last 25 Years. A Report From Two UK Inception Cohorts Reflecting Treatment Changes From Sequential DMARD Monotherapy to Anti-TNF Agents (1986–2011). Elena Nikiphorou[1], Lewis Carpenter[2], Sam Norton[3], David James[4], Patrick D. Kiely[5], David Walsh[6], Richard Williams[7] and Adam Young[3]. [1]ERAS, St Albans City Hospital and University College London (UCL), London, United Kingdom, [2]University of Hertfordshire, Hatfield, United Kingdom, [3]ERAS, St Albans City Hospital, St Albans, United Kingdom, [4]Diana Princess of Wales Hospital, Grimsby, United Kingdom, [5]St. Georges Hospital, London, United Kingdom, [6]City Hospital, Nottingham, United Kingdom, [7]County Hospital, Hereford, United Kingdom

Background/Purpose: Orthopaedic surgery is considered an important, although uncommonly reported, outcome measure in rheumatoid arthritis (RA) and a surrogate marker for joint destruction. The expectation is that orthopaedic surgical rates will decline over time with greater and earlier use of more intensive treatments for RA.

Methods: The Early RA Study (ERAS) recruited from 1986–1999 (n=1465), the Early RA Network (ERAN) from 2002–2011 (n=1236). Standardised clinical, laboratory and X-ray measures were performed at baseline prior to initiation of DMARD therapy and then yearly in both cohorts. Treatment of patients included disease modifying, steroid and biologic therapies according to standard UK practices for management of hospital based RA patients, based on sequential published guidelines over 1986–2011. Source data of all orthopaedic interventions included clinical datasets (patient reports and medical records from 1986), and national data from Hospital Episode Statistics and the National Joint Registry. Length of follow up was based on the National Death Registry. For the analysis, recruitment years were grouped into 6 periods and interventions categorized into major (large joint replacements), intermediate (mainly synovectomies and arthroplasties of wrist/hand, hind/forefoot), and minor (soft tissue/ tendon surgery).

Results: A total of 1602 procedures were performed in 770 patients (29%) over maximum 25 year follow up. The 25 year cumulative incidence rate of major interventions was 21.7% (19.4–24.0%), and 21.5% (17.8–25.5%) for intermediate. Secular changes in orthopaedic surgical rates per year from 1987–2011 will be displayed graphically, showing a small, non-significant decline in major interventions (0.02%; p>0.05), but the regression model fitted for intermediate interventions indicated a significant decline (0.03%, p <0.05), and a small but non-significant increase for minor interventions (0.02%; p>0.05). There were only minor differences in demographic and baseline features over the recruitment periods examined, but definite treatment trends showed a gradual change from sequential monotherapy to combination therapies and biologics, and greater and earlier use of methotrexate and steroids in later recruitment periods. Methotrexate

and combination therapies as first DMARD were used in 1% and less than 1% respectively in recruitment period 1986–1989, and in 70% and 13% in 2006–2011. Anti-TNF agents were used in the first 3 years of disease only the latter two recruitment periods: 2002–2005, 7.8% and 2006–2011, 19.4%.

Conclusion: Orthopaedic surgery is an important and common outcome in RA by 10years. Only hand/foot surgery rates showed a consistent decline from 1986–2011. Possible explanations include differences in pathophysiological processes affecting joints; variations in responses to therapy between large and small joint destructive processes; changes in service provision and thresholds for different types of orthopaedic surgery over time.

1216

Flare Self Management Strategies Used by Patients with Rheumatoid Arthritis. Susan J. Bartlett[1], Clifton O. Bingham III[2], Juan Xiong[3], Ernest Choy[4], Gilles Boire[5], Carol A. Hitchon[6], Janet E. Pope[7], J. Carter Thorne[8], Diane Tin[8], Boulos Haraoui[9], E. Keystone[10], Vivian P. Bykerk[11], OMERACT Flare Working Group[12] and CATCH[13]. [1]McGill University, Montreal, QC, [2]Johns Hopkins University, Baltimore, MD, [3]Mount Sinai Hospital, Toronto, ON, [4]Cardiff University School of Medicine, Cardiff, United Kingdom, [5]CHUS - Sherbrooke University, Sherbrooke, QC, [6]University of Manitoba, Winnipeg, MB, [7]Western University of Canada, St. Joseph's Health Care, London, ON, [8]Southlake Regional Health Centre, Newmarket, ON, [9]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [10]University of Toronto, Toronto, ON, [11]Hospital for Special Surgery, New York, NY, [12]Ottawa, [13]Toronto, ON

Background/Purpose: Though disease flares are common, very little is known about strategies RA patients use for self management (SM) of flares. We asked patients to identify SM strategies and explored potential predictors of strategies.

Methods: 512 patients in the Canadian early ArThritis CoHort (CATCH) completed the OMERACT preliminary flare questionnaire (PFQ) at clinic visits from 11–2011 through 4–2012. Patients who self-identified as being in a flare provided ratings of flare severity, pain, disability (HAQ) and identified SM strategies they were using. Strategies were selected from those previously reported during OMERACT RA Flare patient focus groups. Rheumatologists rated whether their patient was in a flare and performed joint counts. Groups were stratified based on Patient-MD agreement of flare status and compared using ANOVA. Multivariable logistic regression was used to identify potential predictors of flare SM.

Results: 512 patients with early RA who were mostly female (75%), white (82%) and well educated (57% > HS) answered the PFQ. Patients had a mean (SD) age of 53 (14) yr, 18% smoked, 65% RF+, 53% CCP+ and 24% had erosions. Mean HAQ was 1.03 (.70) and pain was 56 (27). 149 (29%) patients self-identified flare whereas MDs identified 169 cases of flare (31%); patients and MDs agreed about flare status 72% of the time (K=.34). Patients who were female, current smokers, RF+, Anti-CCP+, minority, living alone and ≤ HS education were significantly (p<.05) more likely to be classified as being in a flare.

The most common SM strategy was taking more analgesics (51%); in contrast, few patients reported taking more steroids (5%) and 34% tried to manage the flare without medications. Other strategies differed by patient/MD agreement on flare status (see Table). When patients and MDs agreed the patient was in a flare, 87% reported using SM strategies; whereas when patients but not MDs identified flare, 65% used SM strategies (p=.001). Patient/MD agreement about flare status was also associated with a significantly (p<.05) greater likelihood of activity reduction/avoidance. Although few patients contacted the care team for help prior to the visit, patient/MD agreement about flare status was associated with >5 fold increase in asking for help. Across strategies, predictors of SM included patient/MD agreement, female sex, and higher disability; other sociodemographic and disease characteristics were not reliably associated with SM.

As a result of this flare, I:	Patient Flare MD Flare (n=86)	Patient Flare MD Non-Flare (n=63)	p-value
Didn't do anything different	11 (13%)	22 (35%)	.001
Reduced the amount of activities	49 (57%)	24 (38%)	.023
Avoided doing activities that I had planned to do	32 (37%)	15 (24%)	.082
Tried to manage my flare without medications	28 (33%)	23 (37%)	.616
Took more painkillers	48 (56%)	28 (44%)	.170
Took more steroid tablets	6 (7%)	2 (3%)	.468
Asked for help from nurse or my rheumatologist	14 (16%)	2 (3%)	.014

Conclusion: Disease flares are common at routine care visits in early RA. Most patients recognize when they are flaring and their rheumatologists agree. Patients report using several flare SM strategies including taking more analgesics and reducing activities. Patient/MD agreement, female sex and higher disability are predictors of flare SM efforts. Notably, few patients (11%) experiencing flare in this early RA sample reported asking care providers for help prior to the routine clinic visit.

1217

Decreased Survival in Rheumatoid Arthritis Complicated with Bronchiectasis: A Family-Based Cohort Study. Xavier Puéchal[1], Emmanuelle Génin[2], Thierry Bienvenu[1] and Daniel J. Dusser[1]. [1]Hôpital Cochin, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [2]INSERM UMR-S946, Université Paris Diderot, Paris, France

Background/Purpose: In cystic fibrosis, mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene lead to diffuse bronchiectasis (DB) and decreased survival. DB is also associated with rheumatoid arthritis (RA), in which the role of *CFTR* mutations in predisposition to DB has been established (Puéchal et al. ARD 2011,70: 653–9). The prognosis of RA-associated DB (RA-DB) has not been well described.

Methods: We report on long-term mortality in a French nationwide prospectively followed, well-characterized, family-based association study of patients with a diagnosis of RA, DB or RA-DB. Families of probands with RA-DB were included if one first-degree relative had RA and/or DB. We assessed the overall mortality according to clinical characteristics and *CFTR* mutations among 138 subjects from 24 kindreds enrolled in the cohort. The association of potential risk factors with death was tested by Cox proportional-hazard analysis.

Results: During a median follow-up time after the inclusion of 10.6 years, 18 patients in the study cohort died, mainly due to respiratory involvement. The survival of RA-DB patients was significantly lower than the one of the RA patients and DB patients (P=0.006) (Fig A). In RA patients, the presence of DB was the main poor prognostic factor (hazard ratio for death, 8.7; 95% CI, 1.6 to 48.5; P=0.01). Among the RA-DB patients, an early onset of DB (hazard ratio, 18.6; 95% CI, 2.2 to 156.9; P<0.01) and *CFTR* mutation (hazard ratio, 8.3; 95% CI, 1.5 to 45.7; P=0.02) had an independent, significant association with decreased survival (Fig B and C). A *CFTR* mutation in RA patients with early-onset DB defined a subgroup of patients with increased mortality (hazard ratio, 9.4; 95% CI, 2.5 to 35.0; P<0.001).
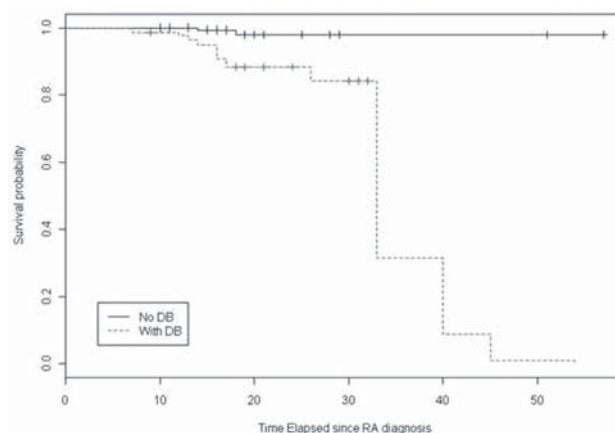
Figure A. Survival curves in RA patients using Cox proportional Hazard model and two strata (with and without DB) (p=0.006).
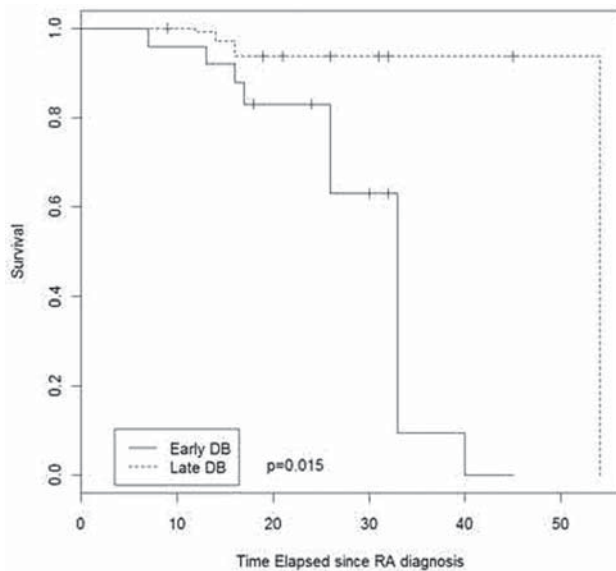
Figure B. Cox survival curves in RA patients with DB according to age of DB onset.
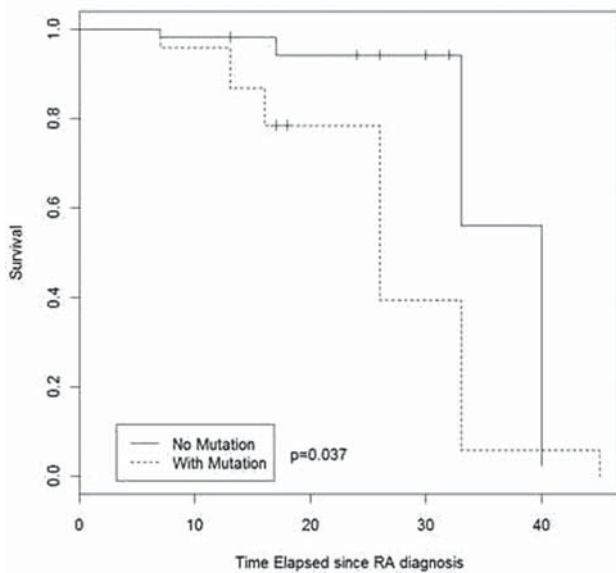
Figure C. Cox survival curves in RA patients with DB according to *CFTR* mutational status.

Conclusion: In this prospective family cohort, DB in RA patients was associated with decreased overall survival. *CFTR* mutation in early-onset DB was strongly associated with shortened survival in RA patients and provides a new biomarker for risk stratification and design of future therapeutic interventions.

Disclosure: X. Puéchal, None; **E. Génin**, None; **T. Bienvenu**, None; **D. J. Dusser**, None.

1218

Genetic Markers of Functional Stress Response in Patients with Rheumatoid Arthritis. Olga Malysheva and Christoph G. Baerwald. University Hospital, Leipzig, Germany

Background/Purpose: Stress is recognized as an important risk factor in the pathogenesis of rheumatoid arthritis (RA). However, it is still incompletely understood how the stress response and interactions between the autonomic nervous system, the hypothalamus-pituitary-adrenal axis and the immune system contributes to the pathogenesis of RA. The purpose of our study was to characterise neuroimmune interactions common variants in the genes of the beta2-adrenergic receptor (beta2AR) and corticotropin releasing hormone (CRH) together with functional stress responses in RA patients and controls.

Methods: An allele-specific polymerase chain reaction was used to determine the polymorphisms of the beta2AR at position 16, 27, and 164, as well as the polymorphic sequences in the 5' flanking region of the human CRH gene in patients with RA (n = 310) and ethnically matched healthy controls (n = 305). In a subgroup of RA patients (n = 100) the autonomic response upon various standardised stressors was performed by utilising the heart rate variability (HRV) test (ProSciCard III, Version 2.2a, Medi-Syst GmbH, Germany) and compared to 45 age and sex matched osteoarthritis patients. To evaluate the impact of CRH promoter polymorphisms on the stress response in a subgroup of RA patients (n=18) an insulin hypoglycaemia test (IHT) was performed studying the dynamics of blood glucose levels, CRH, adrenocorticotropin (ACTH) and cortisol production.

Results: There was a highly significant distortion in the distribution of the beta2AR polymorphism at codon 16 between RA patients and controls, contributing to the genetic background of RA. Arginine (Arg) at codon 16 was present in 89.7 % of RA patients compared to 66.2 % controls (OR 4.43, 95 % CI 2.81 to 7.02, p = 0.00001). Stratifying RA patients for the amino acid sequence at position 16 and their autonomic reactivity revealed a statistically significant decrease of parasympathetic activity, in particular for the deep breathing test, in patients with homozygosity for Glycine (Gly) 16 compared to RA patients being heterozygous (Arg16Gly). However, RA patients with homozygosity for Glycine 16 showed a normalisation of the sympathetic reactivity upon mental stress test. On the other hand, polymorphisms of CRH 5' regulating region are differentially distributed in RA patients and healthy subjects. The CRH promoter polymorphisms exerted a significant influence on the stress response of RA patients undergoing an IHT. The integrated cortisol response to hypoglycaemia expressed as area under the curve was significantly lower in RA patients bearing the A1B1 allele (64154 ± 5768 nmol/l) compared to the A2B2 allele (91273 ± 7298 nmol/l, p=0.016).

Conclusion: Polymorphisms of the beta2AR and CRH contribute to the genetic background of RA and is associated with disturbed functional stress reactivity on various levels in these patients. Further studies are warranted to determine the role of genetic factors on stress response in the disease process of RA.

Disclosure: O. Malysheva, None; **C. G. Baerwald**, None.

1219

Periodontal Disease Is Associated with Rheumatoid Arthritis but Its Severity Is Not Correlated with Rheumatoid Arthritis Disease Activity.
In Ah Choi[1], Jin-Hee Kim[2], Kyung Hwa Kim[2], Hye Won Kim[1], Myeong Jae Yoon[1], Bon Seung Ku[1], Hyejin Oh[1], Joo Youn Lee[1], Eun Young Lee[1], Eun Bong Lee[1], Yong-Moo Lee[2] and Young Wook Song[1]. [1]Department of Internal Medicine, School of Medicine, Seoul National University, Seoul, South Korea, [2]Department of Periodontology, School of Dentistry, Seoul National University, Seoul, South Korea

Background/Purpose: The prevalence of periodontal disease is known to be increased in patients with rheumatoid arthritis (RA) compared to the general population. We investigated whether severity of periodontal disease is associated with RA and correlated with RA disease activity, ACPA status or treatment medication.

Methods: We conducted a cross-sectional study comparing 295 RA patients and 88 non-arthritis controls. In RA patients, serum RF, anti-CCP antibody, CRP and ESR were measured. Clinical parameters including tender joint count (TJC), swollen joint count (SJC), DAS28 and presence of erosive changes in X- ray were evaluated at the time point obtaining samples. In all subjects, a number of teeth (0~28, 3rd molars excluded) was checked. Subjects who had 15 or more teeth were evaluated for dental exam and checked for P. gingivalis antibody. Plaque index (PI) was evaluated as a marker of dental hygiene and gingival index (GI), probing pocket depth (PPD), bleeding on probing (BOP) and clinical attachment loss (CAL) were evaluated as index of periodontitis. Periodontitis was defined as mild (CAL 1~2 mm), moderate (CAL 3~4 mm) and severe (CAL ≥ 5mm) by American Academy of Periodontology 2004 Classification.

Results: The mean number of teeth (±SD) in 295 RA patients and 88 controls were 23.4 ± 6.2 vs. 25.8 ± 2.9, respectively (p= 0.001). Among 290 RA patients, 28 patients (8.8%) had less than 15 teeth and 3 patients had ongoing dental care, both were excluded from the dental exam. Mean PI in 264 RA patients and 88 controls were 0.84 ± 0.49 and 0.70 ± 0.34

(p=0.014), mean GI 0.51 ± 0.43 vs. 0.15 ± 0.18 (*p < 0.001*), mean PPD 2.0 ± 0.4 vs. 1.7 ± 0.2 (*p < 0.001*) and mean CAL 3.2 ± 0.8 vs. 2.9 ± 0.5 (*p < 0.001*). The prevalence of moderate or severe periodontitis was significantly higher in RA patients compared to controls (63.6% vs. 33.3%, *p*< 0.001). Mean P. gingivalis antibody level (±SD) was higher in RA compared to control (34227 ± 55100 vs. 18341 ± 13147 unit/mL, p< 0.001). In RA patients, presence of dry mouth was associated with higher BOP (*p*= 0.022). Disease duration was associated with higher GI (r^2= 0.044, *p*= 0.002) and BOP (r^2= 0.022, *p*= 0.016). The patients with high positive anti-CCP antibody (≥ 15 IU/mL) showed higher GI than patients with negative (< 5 IU/mL, *p*= 0.002) or low positive (≥ 5 and < 15 IU/mL, *p*=0.046) anti-CCP antibody. There was no significant association between severity of periodontitis and RA disease activity markers (TJC, SJC, ESR, CRP, DAS28), presence of bone erosion, rheumatoid factor or use of steroid or biologic agents.

Conclusion: Patients with RA had more severe periodontal index than controls. Severity of periodontitis was associated with the presence of dry mouth, anti-CCP antibody and RA disease duration but not with disease activity.

Disclosure: **I. A. Choi**, None; **J. H. Kim**, None; **K. H. Kim**, None; **H. W. Kim**, None; **M. J. Yoon**, None; **B. S. Ku**, None; **H. Oh**, None; **J. Y. Lee**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. M. Lee**, None; **Y. W. Song**, None.

1220

Occurrence and Morbidity of Lower Extremity Ulcer in Rheumatoid Arthritis - A Population Based Study. Adlene Jebakumar, Cynthia S. Crowson, Prabhu D. Udayakumar, Sherine E. Gabriel and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Lower extremity (LE) ulcer is a known complication of rheumatoid arthritis (RA). However, little is known regarding the magnitude and morbidity associated with this complication. We aimed to assess the occurrence, risk factors, morbidity and mortality associated with LE ulcers in RA.

Methods: We retrospectively reviewed a population-based incidence cohort of patients who fulfilled 1987 ACR criteria for RA in 1980–2007. All subjects were longitudinally followed through their complete community medical records until death, migration or April 2012. Ulcers in the lower extremities that developed after the diagnosis of RA were included. Foot ulcers due to surgery, biopsy, burns, animal bites, ingrowing toe nail, toe nail removal, abrasion, cellulitis, foreign body or herpes zoster were excluded. Cumulative incidence of lower extremity ulcers adjusted for the competing risk of death was estimated. Cox models were used to assess risk factors for LE ulcers and their impact on mortality.

Results: The study population included 813 patients, 537 (66%) were rheumatoid factor positive; during follow-up, 33% had rheumatoid nodules and 53% had erosive joint disease. During 9771 total person-years of follow-up (mean 12.0 years per patient), 125 patients developed LE ulcers with total occurrence of 171 episodes. The cumulative incidence of LE ulcers in RA patients was 4.8 % (± 0.8%) at 5 years after diagnosis of RA and increased to 26.2% (± 2.5%) by 25 years. Mean age of RA patients with at first LE ulcer occurrence was 73.5 years (74% female). The most common ulcer locations were between ankle and knee (58 ulcers, 34%) and in the tips of toes (46 ulcers, 27%). Majority were pressure (62 ulcers, 36%) or traumatic (49 ulcers, 29%) in etiology; 22 (13%) were ischemic ulcers and only 2 (1%) were vasculitic ulcers. The incidence of LE ulcers was higher among patients diagnosed with RA in 1995–2007 compared to those diagnosed in 1980–1994 (hazard ratio [HR] 2.03; p=0.001). Median time for the LE ulcer to heal was 30 days. 10 (6%) of 171 episodes lead to amputation. LE ulcers in RA were associated with increased mortality (HR 2.42; p < 0.001) adjusted for age, sex and calendar year.

Risk factors for LE ulcers in RA were: age (HR 1.90 per 10 year increase; p<0.001); current smoking (HR 1.51; p = 0.048); diabetes mellitus (HR 1.65; p = 0.015); coronary heart disease or heart failure (HR1.56; p = 0.035); presence of rheumatoid nodules (HR 1.64; p = 0.010); ESR ≥ 60 mm/hour on three occasions (HR 1.78; p = 0.022); venous thromboembolism (HR 2.08; p = 0.014); severe extra-articular manifestations (HR 1.67; p = 0.048). 79 (46%) of 171 ulcer episodes occurred in patents on corticosteroid therapy.

Conclusion: LE ulcers are common among patients with RA. The cumulative incidence increased by 1% per year, and the incidence of LE ulcers in RA has doubled in the recent years. A significant number require amputation. LE ulcers are associated with double the mortality rate in RA patients. Clinicians should be aware of the significance of LE ulcers in RA for better management of these patients.

Disclosure: **A. Jebakumar**, None; **C. S. Crowson**, None; **P. D. Udayakumar**, None; **S. E. Gabriel**, None; **E. L. Matteson**, None.

1221

Low Muscle Density in Rheumatoid Arthritis and Modified Association with Total Fat Mass, Results of a Pilot Study. Joshua Baker[1], Joan Marie Von Feldt[2] and Mary Beth Leonard[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA, [3]The Children's Hospital of Philadelphia, Philadelphia, PA

Background/Purpose: Fatty infiltration of muscle (*myosteatosis*) results in a decrease in muscle density. Prior studies documented that skeletal muscle attenuation determined by CT was associated with skeletal muscle lipid content on tissue biopsy. Low muscle density is associated with insulin resistance and is independently associated with an increased fracture risk. We evaluated muscle density as measured by peripheral quantitative CT (pQCT) in 28 subjects with rheumatoid arthritis (RA) compared to 464 well-characterized controls.

Methods: RA subjects and healthy controls from the Philadelphia area underwent whole-body Dual X-ray Absorptiometry (DXA) and pQCT of the tibia. The pQCT measure of muscle density (mg/cm^3) was used as a composite index of intra and extra-myocellular fat content as previously described. Edge-detection and threshold techniques were used to separate tissues (fat, muscle, and bone) based on attenuation characteristics. Images were filtered prior to being analyzed using contour mode 3 (-101 mg/cm^3) to find skin, and peel mode 2 (40 mg/cm^3) to separate adipose and muscle/bone, respectively. Whole body DXA measures of total fat mass were converted to an index to adjust for height (kg/m^2). Muscle density was compared between RA and controls after adjusting for age, sex, and race using multivariable linear regression analysis. Linear regression was further utilized to assess for differences in RA and controls after adjustment for differences in total fat mass and to evaluate for modification of the association between fat and muscle density among RA subjects.

Results: Adjusted mean muscle density in RA and controls was 73.3 (2.08) and 74.5 (2.01), respectively (p=0.003). There was significant modification of the effect of fat mass on muscle density in RA [Interaction β: 0.0038 (0.0018–0.0057) p<0.001]. In healthy controls, muscle density was negatively associated with total fat mass index (FMI), while among RA, there was no such association (Figure 1). This interaction suggested that differences in muscle density between RA and controls were most pronounced among subjects with lower fat mass. Use of steroids, use of biologics, disability scores, C-Reactive Protein (CRP) and disease activity (DAS28) were not significantly associated with muscle density in this small sample of RA.
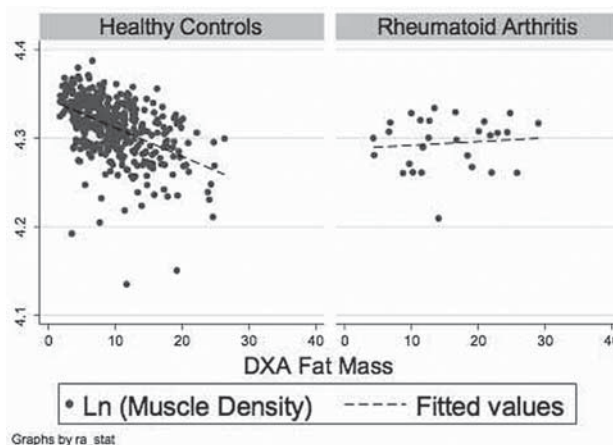
Figure 1. Association between DXA fat mass index (FMI) and muscle density among Healthy Controls and Rheumatoid Arthritis after adjustment for age, sex, and race.

Conclusion: Muscle density is lower in RA subjects compared to healthy controls of similar age, sex, and race. Differences in muscle density are not dependent on the greater fat mass observed among RA subjects. The interaction observed between RA status and FMI suggests that the mechanism of myosteatosis in RA may be distinct from that of healthy controls.

Disclosure: **J. Baker**, None; **J. M. Von Feldt**, American Board of Internal Medicine, 6; **M. B. Leonard**, None.

1222

Incidence and Time Trends of Malignancy in Rheumatoid Arthritis: A Population Based Study 1980–2007. Kerry Wright, Cynthia S. Crowson, Sherine E. Gabriel and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: to determine the incidence and time trends of malignancy in patients with rheumatoid arthritis (RA) in 1980–2007 compared to individuals without RA from the same population.

Methods: A population based inception cohort of patients with RA who fulfilled 1987 ACR criteria in 1980–2007 and an age and sex matched cohort of non-RA subjects from the same population was assembled and followed until death, migration or 12/31/2008. Incidence rates of overall and site specific malignancy were collected. Cumulative incidence of malignancy adjusted for the competing risk of death was estimated for RA and non-RA subjects and compared using Gray's test.

Results: The study consisted of 813 RA and non-RA subjects (mean age 55.9 years, 68% female, 66% rheumatoid factor positive). Prior to RA incidence/non-RA index date, 53 RA and 66 non-RA subjects had a malignancy (p=0.22). The prevalence of hematologic malignancy was lower among RA subjects compared with non-RA subjects prior to the incidence/index date, (n=0 vs n=7, p=0.015). Excluding patients with prior malignancies, the remaining RA patients were followed for a mean of 9.1 years (mean 10.3 years for non-RA) during which 109 RA and 94 non-RA subjects developed a malignancy. The cumulative incidence for hematologic malignancy was higher among RA than non-RA subjects (2.0% ± 0.6% vs 0.7% ± 0.3% at 10 years, p=0.009). There was no significant difference in the cumulative incidence of overall malignancy between RA and non-RA subjects (13.0% ± 1.5% vs 9.1% ±1.2% at 10 years, p=0.10). There was no significant difference in the rate of lung or colon cancer in RA subjects relative to non-RA subjects. The cumulative incidence of breast cancer was lower among RA subjects compared to non-RA in the first 10 years after diagnosis of RA (2.9% ± 0.8% vs 1.6% ± 0.7% at 10 years), but this difference did not achieve statistical significance (p=0.63). Individuals diagnosed with RA more recently (1995–2007) were more likely to develop a hematologic malignancy compared with RA subjects diagnosed in earlier years (1980–1994) (hazard ratio [HR]: 2.28; 95% CI 0.95, 5.51). Similar changes were not seen over the same time period among subjects without RA.

Conclusion: Patients diagnosed with RA more recently appear to be at higher risk of developing a malignancy relative to patients diagnosed in earlier years. There was no significant difference in the rate of solid organ malignancies including breast, lung and colon cancer between RA and non-RA subjects in this population. The rate of hematologic malignancy is higher among patients with RA relative to non-RA subjects.

Disclosure: K. Wright, None; **C. S. Crowson**, None; **S. E. Gabriel**, None; **E. L. Matteson**, None.

1223

Frequency of Deep Vein Thromboses and Pulmonary Emboli in Rheumatoid Arthritis. Christian A. Pineau[1], Evelyne Vinet[1] and Sasha Bernatsky[2]. [1]McGill University Health Centre, Montreal, QC, [2]Research Institute of the McGill University Health Ctre, Montreal, QC

Background/Purpose: There are few data regarding the frequency of deep vein thromboses (DVTs) and pulmonary emboli (PE's) in patients with rheumatoid arthritis (RA). To determine the frequency of DVTs and PE's within RA patients in a population-based sample from Quebec, Canada.

Methods: We conducted a study using Quebec's provincial administrative health care databases (including physician billing claims and hospitalization records for all eligible Quebec residents (over 7.8 million individuals) from 1996 to 2008.

Cohort definition: The definition for RA was based on at least 2 physician billing diagnoses for RA (ICD-9 code 714, ICD-10 code M05), at least 8 weeks apart but within 2 years, OR at least one hospitalization code (primary or secondary) with an RA diagnostic code. Of these subjects, we excluded any with subsequent evidence (based on 2 billing codes or a hospitalization) of a different systemic rheumatic disease (including seronegative arthropathies and connective tissue diseases). We also excluded any patients who had seen a rheumatologist but who did not have the RA diagnosis confirmed on at least one of the rheumatology visits.

Outcome definitions: Our outcome definition for DVT was: Two or more physician billing diagnoses for ICD-9 code 451 or 453 (ICD10 code 180.2], or at least one hospitalization diagnosis (primary or secondary) indicating one

of these codes. Our outcome definition for PE was: Two or more physician billing diagnoses for ICD-9 code 415.1 (ICD-10 code I26) or one or more hospitalization diagnoses (primary or secondary), based on the same ICD codes.

We compared the number of observed events, to the number of events that would be expected, based on recent estimates of thromboembolic events (DVT's and PE's) within a general population (which were also based on physician billing and hospitalization administrative data sources. * The ratio of observed to expected events provides the standardized incidence ratio, and 95% confidence intervals were generated assuming a Poisson distribution for the observed events.

Results: In total over the period of study, we identified 170,021 Quebec residents who met our RA definition (suggesting a period prevalence of about 2%). The subjects were followed for a total of 1,074,854 patient-years, averaging 6.3 years (standard deviation 3.9) of observation per subject. Within this time, 12278 RA subjects had at least one event (1.18 events per 100 person-years), with 9,846 DVT's being recorded over the interval (0.94 events per 100 person-years), and 3756 PE's (0.35 events per 100 person-years).

RA cohort experience	Observed events	Expected Events*	Standardized Incidence rate	95%	CI
Any event	12278	9054	1.36	1.33	1.38
DVT	9846	7229	1.36	1.34	1.39
PE	3756	2996	1.25	1.21	1.29

* Expected rates generated from Boulet et al, ARCH INTERN MED 2010: 170 (19)

Conclusion: Our preliminary work suggests that patients with RA have about a 30% increase in thromboembolic events, compared to published general population rates. Further work is in progress to provide results stratified by age and sex.

Disclosure: C. A. Pineau, None; **E. Vinet**, None; **S. Bernatsky**, None.

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Rheumatoid Arthritis Disease Activity During Pregnancy Affects the Postnatal Catch-up Growth of the Child. Florentien D.O. de Steenwinkel[1], Anita C.S. Hokken-Koelega[2], Maria A.J. de Ridder[1], Johanna M.W. Hazes[1] and Radboud J.E.M. Dolhain[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus Medical Center- Sophia Children's Hospital, Rotterdam, Netherlands

Background/Purpose: Active rheumatoid arthritis (RA) during pregnancy is associated with lower birth weight. Active RA during pregnancy can be treated with prednisone. However, studies have shown that prednisone use during pregnancy reduces gestational age thereby indirectly creates lower birth weight[1]. In general, newborns with a lower birth weight will catch-up in growth after they are born. Literature shows that a fast catch-up growth pattern of the child is associated with cardiovascular risk and metabolic disorders in early adulthood[2]. The purpose of this study: "Is maternal RA and/or prednisone use during pregnancy associated with fast catch-up growth in the first 2 years of the child?"

Methods: Current study is a continuation of a prospective nationwide study on RA during pregnancy. Growth charts were collected from children born from mothers participating in this study. Dependent variable: height standard deviation score (SDS) and weight SDS on different time points. Independent variable: prednisone use and RA disease activity (DAS28) during pregnancy.

Results: 161 growth charts were analyzed; 67 women used prednisone at some point during their pregnancy. The mean DAS28 during pregnancy was significantly higher in the prednisone group, 3.88 (SD: 1.01) than in the group without prednisone 3.02 (SD: 1.03) (p<0.0001).

An association was found between elevated DAS28 during pregnancy and fast catch-up growth (>0.50 SDS) of the child within the first half year. An increase of one point DAS28 during pregnancy resulted in a catch-up weight of 0.16 (p=0.03) and a catch-up height of 0.12 (p=0.04) at the age of 3 months. No effect was shown for prednisone use.

Conclusion: Our study suggests that elevated RA disease activity during pregnancy is associated with fast catch-up growth. This might have lifelong consequences for the child. Minimizing the disease activity during pregnancy is therefore crucial and should be striven at all times.

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2. Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *JAMA.* Jun 3 2009;301(21):2234–2242.

1225

Self Reported Comorbidity Is Common in Early Inflammatory Arthritis and Associated with Poorer Function and Quality of Life and Greater Disease Activity: Results From the Canadian Early Arthritis Cohort.
Carol A. Hitchon[1], Gilles Boire[2], Boulos Haraoui[3], Edward Keystone[4], Janet E. Pope[5], Vivian P. Bykerk[6] and Canadian Early Arthritis Cohort (CATCH) Investigators[7]. [1]University of Manitoba, Winnipeg, MB, [2]CHUS - Sherbrooke University, Sherbrooke, QC, [3]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [4]University of Toronto, Toronto, ON, [5]Univ of Western Ontario, London, ON, [6]Hospital for Special Surgery, New York, NY, [7]Toronto

Background/Purpose: Chronic comorbid medical conditions may contribute to poor outcomes in rheumatoid arthritis. The extent of comorbidity, in particular cardiovascular disease (CVD), may be related to the burden of inflammation and may influence initial treatment choice. We report the association of baseline comorbidity with clinical disease activity, functional status and quality of life in early inflammatory arthritis (EIA) using data from the Canadian Early Arthritis Cohort (CATCH).

Methods: Subjects (n=779) with EIA of symptom duration 6–52 weeks, $\geq$ 2 effused joints *or* 1 swollen MCP or PIP and $\geq$ 2 of: +RF, +CCP, morning stiffness > 45 minutes, response to NSAIDS, or painful MTP squeeze test report comorbid medical conditions at baseline, quality of life indices (SF12) annually, and functional status (HAQ), pain visual analogue scale, detailed arthritis clinical assessments and arthritis treatment at each visit. Although there is no formal treatment protocol, participating rheumatologists aim for minimal disease activity. The influence of baseline comorbidity on outcomes while controlling for age and disease duration was tested by linear regression.

Results: Comorbidity was reported by 538 subjects (69%; median conditions 1 range 0–8). Patients with vs without comorbidity were older (45 vs 54 years p<0.0001) and had higher baseline disease activity primarily due to ESR (37 vs 21 p<0.001) and CRP (14 vs 11 p<0.02). Associations between CVD and higher DASCRP3v (4.42(1.3) vs 4.18(1.3) p=0.03) and worse HAQ (1.13(0.73) vs 0.94(0.71) p<0.001) at baseline were not significant after correcting for age. Baseline SF12 scores (all patients) were below population averages (Physical Composite Score (PCS) 37(11) and Mental Composite Score (MCS) 47(12)). SF12 correlated with the number of comorbidities: PCS (−0.2 p<0.0001); MCS (−0.11 p=0.003). All domain scores were significantly worse in patients with any comorbidity vs without. Patients with CVD (vs without) (34 (10) vs 38 (11) p<0.0001) endocrine disease (diabetes, thyroid, dyslipidemia) (35(11) vs 38(11) p=0.001), GI or renal (stomach bowel, liver disease, hepatitis or renal; 35(11) vs 38(11) p=0.03) and respiratory (asthma, bronchitis) (p=0.005) had poorer PCS. Patients with neurologic (migraine, parkinson, seizures) (44(12) vs 47(11) p=0.03), mental health (depression or other)(39 (11) vs 48 (39) p<0.0001) and GI or renal (43(12) vs 47(11) p=0.005) comorbidities were associated with poorer MCS. Patients with any baseline comorbidity had higher DASCRP3v scores (3.15 (8.1) vs 2.94 (9.1) p=0.004), worse functional status (HAQ 0.67 (0.54) vs 0.47 (0.46) p<0.0001), and more pain (3.6 (2) vs 3.2 (2.1) p=0.001), averaged over the first year, than those without baseline comorbidity. Renal or GI disease had worse DASCRP3v (p<0.001) over the first year. Baseline cardiovascular disease was not associated with poorer outcomes. The number of comorbid conditions at baseline was inversely associated with one year PCS and MCS.

Conclusion: Patients with comorbid medical conditions have greater disease activity, poorer functional status and lower self reported quality of life over the first year of followup. This observation has implications for treatment of early arthritis.

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Transition Time to Osteoporosis in Patients with Rheumatoid Arthritis.
Jiwon Hwang[1], Joong Kyong Ahn[2], Ji Young Chai[3], Hoon-Suk Cha[1], Jaejoon Lee[1] and Eunmi Koh[1]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Jesang Hospital, Seongnam-si Gyeonggi-do, South Korea

Background/Purpose: Rheumatoid arthritis (RA) is an independent risk factor for osteoporosis. Although bone mineral density (BMD) testing is routinely performed in patients with RA, the optimal interval between BMD tests remains undetermined. The aim of this study was to evaluate the transition time to osteoporosis in RA patients with normal BMD and in those with osteopenia at baseline, and to estimate the optimal BMD testing interval.

Methods: We retrospectively analyzed 548 consecutive RA patients at a single tertiary hospital who underwent BMD testing on two or more occasions during October 1994 and December 2011. Patients were sorted into 5 groups; normal baseline BMD (T score, −1.00 or higher), mild osteopenia (T score, −1.01 to −1.49), moderate osteopenia (T score, −1.50 to −1.99), severe osteopenia (T score, −2.00 to −2.49) or osteoporosis (T score −2.50 or lower). The transition time to osteoporosis was defined as the estimated time for 10% of patients to make the transition to osteoporosis from normal BMD or from each subgroup of osteopenia. Risk factors for osteoporosis on initial BMD test were also assessed.

Results: Patients were mostly women (96.4%) and the mean age was 55.6 ± 10.6 years. The mean follow-up duration of RA was 8.8 ± 4.3 years. At initial visit, 9.1% of patients had a past history of steroid use for diseases other than RA. Rheumatoid factor was positive in 330 of 531 patients (62.1%) and anti-CCP antibodies in 138 of 206 patients (67%). The mean duration between the initial visit and the first BMD screening was 32.7 ± 40.2 months and the prevalence of osteoporosis was 31.7% at screening (95% confidence interval (CI) 27.6 to 36.1). Estimated transition time to osteoporosis was 72 months (95% CI 36 to 90) for patients with normal BMD, 62 months (95% CI 28 to 126) for patients with mild osteopenia, 34 months (95% CI 16 to 60) for patients with moderate osteopenia, and 17 months (95% CI 10 to 21) for patients with severe osteopenia. The adjusted odds ratio (OR) for osteoporosis at initial BMD testing was high for older age (OR 1.066, 95% CI 1.029 to 1.105, p < 0.0001), past steroid use (OR 2.033, 95% CI 1.174 to 3.520, p = 0.0159), and current steroid use (OR 3.987, 95% CI 2.092 to 7.597, p < 0.0001).

Conclusion: Our data indicate that osteoporosis would develop in less than 10% of RA patients within 6 years for patients with normal bone density, 5 years for patients with mild osteopenia, 2.5 years for patient with moderate osteopenia, and 1 year for patients with advanced osteopenia at baseline. Therefore, the interval for rescreening BMD testing should be adjusted based on the initial BMD result in patients with RA.

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Rheumatoid Arthritis-Associated Interstitial LUNG Disease: Clinical Spectrum of A Large Cohort From A Respiratory Referral Center.
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Background/Purpose: Rheumatoid arthritis (RA) has a myriad of pulmonary manifestations and RA-associated interstitial lung disease (RA-ILD) causes the most clinical concern. Subclinical ILD may be identified in up to 60% of individuals with RA, and lung disease is responsible for 10–20% of overall deaths and 80% of deaths in those with clinically significant lung disease. Known risk factors for RA lung disease include smoking and male gender. In this study, we sought to describe a large cohort of RA-ILD evaluated at our center.

Methods: We identified all subjects with a diagnosis of RA and ILD at our center between January 1987 and June 2012 (N=350). All subjects were confirmed to have RA by their treating rheumatologist. Patients without a high resolution computed tomography (HRCT) or surgical lung biopsy were excluded. The final cohort consisted of 135 subjects. All data were extracted from comprehensive medical review. Kaplan Meier survival analysis was performed on those with usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP).

Results: Table 1 displays the cohort characteristics as a whole and Table 2 displays the comparison of those with UIP and NSIP. There was no significant difference among those with UIP (median 100.3 months) compared to NSIP (median 58.3 months) (p=0.5).

Table 1. Baseline Demographics and Pulmonary Function Tests

Age at Initial Visit	63 (21 to 90)
Gender (%male)	42%
Current or Past Smokers	67%
RF Positivity	79%
RF Level	822 (0 to 13300)
CCP Positivity	76%
CCP Level	134 (0 to 323)
ANA positivity	14%
%FEV1	67% (22 to 113%)
%FVC	66% (30 to 122%)
%TLC	84% (45 to 143%)
%DLCO	70% (31 to 127%)
ILD Subtypes	
Usual Interstitial Pneumonia	31% (43)
Nonspecific Interstitial Pneumonia	30% (41)
Fibrosis NOS	12% (17)
Cryptogenic Organizing Pneumonia	2% (3)
Other	22.5% (31)

Table 2. Usual Interstitial Pneumonia vs Nonspecific Pneumonia

	Usual Interstitial Pneumonia	Nonspecific Interstitial Pneumonia
Age at initial visit	63 (39–84)	62 (26–84)
Gender (% male)	70%	22%
Past or current smokers	63%	60%
RF positivity	100%	76%
CCP positivity	83%	68%
%FVC	59% (30–100%)	67% (32–112%)
%DLCO	62% (39–96%)	75% (31–111%)
%TLC	76% (53–105%)	80% (45–128%)

Conclusion: In contrast to prior studies that suggest UIP is the most common pattern in RA-ILD, equal numbers of subjects with UIP and NSIP were identified in our large cohort. We also found a significant number of subjects in whom lung disease was either too mild to classify or had fibrotic features both of NSIP and UIP (28% of our cohort). Furthermore, in contrast to prior studies that suggest RA-UIP has worse survival than RA-NSIP, underlying histologic pattern did not impact survival in our cohort. Prospective studies are needed to further understand the impact of histopathology on the natural history of RA-ILD.

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1228

Contributions of Inflammation, Inactivity, and Low Dose Prednisone Use to Skeletal Muscle Insulin Resistance in Well-Controlled Rheumatoid Arthritis. Hiba Abouassi, Lori Bateman, Gary E. McDaniel, Lorraine Elliott-Penry, Michael Muehlbauer, E. William St. Clair, William E. Kraus and Kim M. Huffman. Duke University Medical Center, Durham, NC

Background/Purpose: Rheumatoid arthritis (RA) is associated with a high prevalence of insulin resistance. Most prior investigations of insulin resistance in RA have examined fasting glucose and insulin. However, because glucose uptake is performed predominantly by skeletal muscle, skeletal muscle insulin resistance is best assessed with a glucose challenge. We determined if persons with RA exhibit more skeletal muscle insulin resistance than age, gender, race, and BMI–matched controls, and if inflammation, inactivity, and low dose prednisone use mediated skeletal muscle insulin resistance.

Methods: We enrolled 50 participants with RA and 50 matched controls; all had no history of diabetes or cardiovascular disease. The patients with RA had not changed their anti-rheumatic therapy in the previous 3months and may have been taking low doses of prednisone (5 mg or less per day); any steroid tapers were completed at least three weeks prior to study enrollment. Participants completed questionnaires for medication information, a visual analog scale for health rating, and the Stanford Brief Activity Survey for physical activity. Each underwent anthropomorphic measures, a 28 joint exam, and fasting blood collection for glucose, insulin, and an erythrocyte sedimentation rate (ESR), used to compute a disease activity score (DAS-28). Fasting glucose and insulin were used to calculate the Homeostasis Model of Assessment (HOMA). A frequently-sampled

intravenous glucose tolerance test was performed with glucose and insulin measured in each sample. Bergman's minimal model was used to determine insulin sensitivity (SI), indicative of skeletal muscle insulin sensitivity. SI was logarithmically transformed prior to group comparisons with a t-test and predictor identification with linear modeling.

Results: Persons with RA reported less physical activity (P=0.046) than controls, and had a slightly higher median (IQR) ESR [4 (1, 5) vs. 8 (1, 18) mm/h, P=0.05]. The median (IQR) DAS-28 was 2.9 (2.1, 3.8). Daily low dose prednisone use was reported by 27%.

Persons with RA were more insulin resistant than controls (geometric mean (SD) 4.4 (2.39) versus $4.8(2.1)*10^{-5}\text{min}^{-1}/[\text{pmol/l}]$), but this difference was not statistically significant (P=0.37). Prednisone use was related to SI independent of the contributions of BMI, fasting insulin, HOMA, gender and physical activity ($R^2 = 0.56$, model P<0.0001, prednisone use, partial R^2=0.10, P=0.03). Prednisone use was associated with more than a 41% lower SI. There was a trend for an independent relation for physical activity with SI (partial R^2=0.03, P=0.09). Age, ESR, DAS-28, NSAID, DMARD, or biologic use did not contribute to SI in the aforementioned model.

Conclusion: Although persons with RA showed higher insulin resistance, this difference did not achieve statistical significance. However, in persons with RA, the use of low dose prednisone therapy did appear to increase skeletal muscle insulin resistance independent of BMI and physical activity. Future studies should determine if interventions, such as regular physical activity, can counteract the effect of low dose prednisone use on skeletal muscle insulin resistance.

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Rheumatoid Arthritis and Risks of Malignant Lymphoma - Are Risks Still Increased? Karin Hellgren[1], Eva Baecklund[2], Karin E Smedby[3], Carin Backlin[4], Christer Sundstrom[5] and Johan Askling[6]. [1]Unit of Rheumatology, Stockholm, Sweden, [2]Unit of Rheumatology, Uppsala, Sweden, [3]Clinical Epidemiology Unit, Stockholm, Sweden, [4]Department of Medical Sciences, Uppsala, Sweden, [5]Department of Genetics and Pathology, Uppsala, Sweden, [6]Rheumatology Unit & Clinical Epidemiology Unit, Stockholm, Sweden

Background/Purpose: Patients with established Rheumatoid Arthritis (RA) are at increased risk of malignant lymphomas. We have previously demonstrated a strong association between inflammatory intensity and lymphoma risk in a historical RA cohort, but also that the lymphoma risk was increased in patients diagnosed 1997 and followed through 2006. Given the dramatic changes in treatment strategies and goals over the last decade, it may be that lymphoma risks in more recently diagnosed patients have changed. We therefore aimed at assessing lymphoma risks in a more contemporary patient population with respect to year of RA onset and duration of RA disease.

Methods: 10,367 patients with incident RA (ACR criteria, >18 years age, symptom duration ≤ 13 months) diagnosed 1997 through 2010 were identified within the national Swedish Rheumatology Register (SRQ) including information on disease characteristics, disease activity, and therapy. Each patient was matched to 5 general population comparators, by gender, age and residence (n=49,825).To identify the lymphomas, all individuals were linked to the nationwide Swedish Cancer Register. Relative risks (RR) of lymphoma were assessed using Cox models. The RA lymphomas were reviewed and reclassified (WHO classification).

Results: Overall, the risk of lymphoma in RA was almost doubled (RR= 1.7 (95% CI 1.2–2.4)), based on 45 lymphomas in RA versus 126 in the general population comparator cohort (person time 58,825 versus 283,903). When stratified by RA disease duration, a statistically significantly increased risk (p value=0.04) was noted > 5 years after RA diagnosis. When relative risks were cross-tabulated according to year of RA onset and time since RA diagnosis, we noted that this risk increase was significant only among patients in calendar period 1997–2001. Short-term risks for lymphoma were similar across calendar periods. (see Table).

Calender Period, years of inclusion in SRQ RR (95% CI) (No. of events)	Time period since RA diagnosis (years) RR (95% CI) (No. of events)			
	0-<3	3-<6	6–14	Total
1997–2001	1.3 (0.5–3.7) (4/13)	1.3 (0.5–3.3) (5/21)	2.7 (1.4–4.9) (15/27)	1.9 (1.2–3.1) (24/61)
2002–2005	1.2 (0.4–3.3) (4/16)	1.7 (0.8–3.8) (7/17)	2.0 (0.6–6.7) (3/8)	1.6 (0.9–3.0) (14/41)
2006–2010	1.6 (0.7–3.7) (6/20)	1.3 (0.2–9.4) (1/4)	not applicable	1.4 (0.6–3.3) (7/24)
Total study period 1997–2010	1.2 (0.7–2.1) (14/49)	1.6 (0.9–2.9) (13/42)	2.9 (1.7–4.7) (18/35)	1.7 (1.2–2.4) (45/126)

Conclusion: Overall, the risk increase for malignant lymphomas in RA patients diagnosed 1997–2010 was of a similar magnitude as that reported from historical RA cohorts. Whereas our results suggested a declining point estimates for lymphoma risk in successive calendar periods of RA diagnosis 1997–2010, this observation was confounded by differences in length of follow-up, i.e., that risks increased with RA duration. It will be an important task to monitor future risks over longer follow-up time.

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The Role of Sleep Problems in Conditioned Pain Modulation in Rheumatoid Arthritis.
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Background/Purpose: Among rheumatoid arthritis (RA) patients, pain may exist out of proportion to peripheral inflammation. This observation suggests that central nervous system pain amplification mechanisms, such as diminished conditioned pain modulation (CPM), may play a role in enhancing pain perception among some RA patients. We examined CPM, pressure pain threshold and pressure pain tolerance among RA patients compared to controls.

Methods: Fifty-eight female RA patients and 54 age-matched controls without chronic pain underwent quantitative sensory testing to assess CPM, pressure pain threshold and pressure pain tolerance. We induced CPM using a cold water bath, and we assessed pain threshold (when patients first felt pain) and tolerance (when pain was too much to bear) with an algometer. Associations between RA and quantitative sensory testing measures were analyzed using linear regression models. Sleep problems, mental health and inflammation were assessed as mediators of the relationship between RA and quantitative sensory testing measures, according to the Baron and Kenny criteria (J Pers Soc Psychol 1986).

Results: Median CPM levels were 0.5 kg/cm^2 (interquartile range (IQR) -0.1, 1.6) among RA patients compared to 1.5 kg/cm^2 (IQR -0.1, 2.5) among controls ($P = 0.04$). Relative to controls, RA patients had lower pain threshold ($P = 0.03$) and tolerance ($P \leq 0.004$) at the wrists and knees. Spearman's correlations between clinical pain scores and quantitative sensory testing measures of pain varied from -0.08 for CPM to -0.31 for wrist tolerance. Compared to controls, RA patients had greater problems with sleep, catastrophizing, depression and anxiety ($P < 0.0001$). Mediation analyses showed significant associations between: 1) RA and CPM (Baron and Kenny criterion #1), 2) RA and sleep problems (Baron and Kenny criterion #2) and 3) sleep problems and CPM, adjusted for RA (Baron and Kenny criterion #3) (Figure 1). Catastrophizing, depression and anxiety did not mediate the association between RA and CPM.
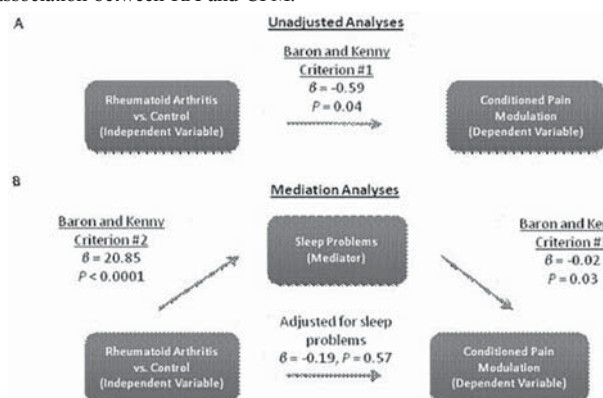
Figure 1. A. Unadjusted association between RA and conditioned pain modulation. B. Mediation analyses for the role of sleep problems in the association between RA and conditioned pain modulation. The change in β between the unadjusted analyses and the analyses adjusted for sleep problems indicates potential mediation, which is supported by the Baron and Kenny criteria: 1) the significant unadjusted association between RA and conditioned pain modulation, 2) the significant association between RA and sleep problems and 3) the significant association between sleep problems and conditioned pain modulation, adjusted for RA.

Conclusion: RA patients have impaired CPM relative to pain-free controls. Sleep problems may contribute to low CPM levels. Future studies are needed to determine whether interventions to improve sleep may improve pain in RA.

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Rheumatoid Arthritis Is Associated with Likelihood of Being Overweight in Women.
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Background/Purpose: Adipose tissue is metabolically active producing adipokines, which, along with locally attracted cytokines, are active participants in inflammation and its regulation. Since RA a systemic inflammatory disease, we postulated that obesity might be a risk factor for developing RA. The objective of this study was to evaluate the association of obesity with risk of incident RA.

Methods: We conducted a case control study using incident RA cases from 2001 to 2011 in a health system using electronic health records. Patients with a primary care physician in the health system with at least 3 documented body mass index (BMI, in kg/m^2) measurements were eligible. A 1:5 (case:control) age, gender, and calendar year match design was performed. An index date was created such that for cases it was the date of RA diagnosis and for the controls it was the date of RA diagnosed in the matching case. Current obesity was defined using the most recent prior, BMI measurement to the index date. History of obesity was defined using all historical BMI measurements, prior to the index date. Any prior BMI >30 was considered as meeting criteria. This was repeated for current and history of overweight classification (BMI > 25). The association between BMI in RA patients and the controls was calculated using a conditional logistic regression model adjusting for current smoking status.

Results: 523 patients with incident RA and 2615 age, gender, calendar year matched controls were included in the analysis. The baseline characteristics revealed similar average BMI measurements in the two groups; current and past smoking was more prevalent in the RA group than controls. Of the RA patients, 63% and 41% were positive for RF and ACPA, respectively. The odds ratio (OR) for the association between RA and obesity or overweight overall, and stratified by gender, is shown in Table 1. Subgroup analysis according to RF positivity is shown in Table 2. Similar results were found for ACPA positivity.

Table 1. Odds of obesity or overweight in RA patients according to gender

	All		**Female**		**Male**	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value
BMI	1.01 (0.99, 1.02)	0.19	1.01 (1.00, 1.03)	0.12	0.99 (0.96, 1.03)	0.73
Current Obesity	1.07 (0.88, 1.29)	0.50	1.21 (0.97, 1.51)	0.10	0.79 (0.56, 1.12)	0.19
History of Obesity	1.18 (0.98, 1.43)	0.08	1.24 (0.99, 1.56)	0.06	1.04 (0.74, 1.48)	0.81
Current Overweight	**1.31 (1.03, 1.66)**	**0.03**	**1.38 (1.05, 1.82)**	**0.02**	1.11 (0.68, 1.80)	0.67
History of Overweight	**1.43 (1.09, 1.88)**	**0.01**	**1.60 (1.17, 2.18)**	**0.003**	0.92 (0.52, 1.62)	0.77

Table 2. Odds of RF positivity in RA patients according to gender

	RF-negative vs. Control		**RF-positive vs. Control**	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
BMI	1.03 (1.00, 1.05)	0.04	1.00 (0.99, 1.02)	0.72
Current Obesity	1.18 (0.86, 1.62)	0.30	1.01 (0.79, 1.29)	0.93
History of Obesity	**1.44 (1.04, 2.01)**	**0.03**	1.05 (0.83, 1.34)	0.69
Currently Overweight	**1.68 (1.09, 2.58)**	**0.02**	1.15 (0.85, 1.54)	0.37
History of Overweight	**1.72 (1.06, 2.78)**	**0.03**	1.22 (0.87, 1.71)	0.25

Conclusion: RA is associated with 43% and 31% increase in odds of historical or current overweight status in women. This is consistent with other previously reported data and it is a significant observation that can help shed light in the pathogenesis of RA. Further, the observed association of being currently overweight or historically overweight or obese with specifically

sero-negative RA may be relevant to the reported protective effect of a higher BMI on joint erosion in RA. These results need to be replicated in prospective RA cohorts.

Disclosure: **I. M. Idrees**, None; **H. L. Kirchner**, None; **A. Bili**, None.

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Association of Actometer Assessed Physical Activity and Fatigue in Patients with Rheumatoid Arthritis: Patients with a Lower Daily Activity Have More Fatigue. Sanne van Dartel, Han Repping-Wuts, Dewy van Hoogmoed, Hans Knoop, Gijs Bleijenberg, Piet L.C. van Riel and J. Fransen. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Fatigue in rheumatoid arthritis (RA) is related to pain and disability, and several psycho-social factors such as coping strategies. In Chronic Fatigue Syndrome (CFS), increased fatigue is associated with reduced physical activity. Apparently, cognitive behavioral therapy and exercise are the only effective interventions in CFS. It is unclear whether, also in RA, fatigue and physical activity are related. Therefore, the objective of this study was to investigate whether there is an association between objectively measured physical activity and patient assessed fatigue in RA patients.

Methods: Consecutive RA patients of the rheumatology clinic of the Radboud University Nijmegen Medical Centre (N=181) were enrolled. Fatigue severity was measured using the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS20). Physical activity was measured during 12 consecutive days with an ankle-worn actometer and a daily activity score was calculated from the number of accelerations. The group mean of the physical activity score over the 12-day period acted as predefined reference score. All patients with at least 10 daily measurements of activity were included in the analyses. Patients with at least 90% of their daily activity scores below the group mean were classified as pervasively passive, while the remaining patients were labeled as active. Linear regression was performed with CIS-fatigue as dependent and physical activity as independent variable with correction for confounders. Fatigue was also analyzed classified as severely fatigued (CIS-fatigue score $\geq$ 35) and not severely fatigued (CIS-fatigue score $<$ 35).

Results: A total of 167 patients had at least 10 daily measurements of activity and were included in the analysis. Mean activity score ($\pm$SD) of all 167 patients was 73$\pm$27, and 42 (25%) patients were classified as pervasively passive and 125 (75%) patients were classified as active. Active patients showed less fatigue: the mean ($\pm$SD) CIS-fatigue was 30.9 (12.3) in active patients and 35.7 (12.8) in pervasively passive patients (p=0.028). Similarly, there was a significantly higher percentage of severely fatigued patients in the passive group (60%) compared to the active group (38%), (p=0.017). The relation between activity and fatigue was linear ($\beta=$ -0.077) and significant (p=0.012), with correction for the confounders age, gender and pain.
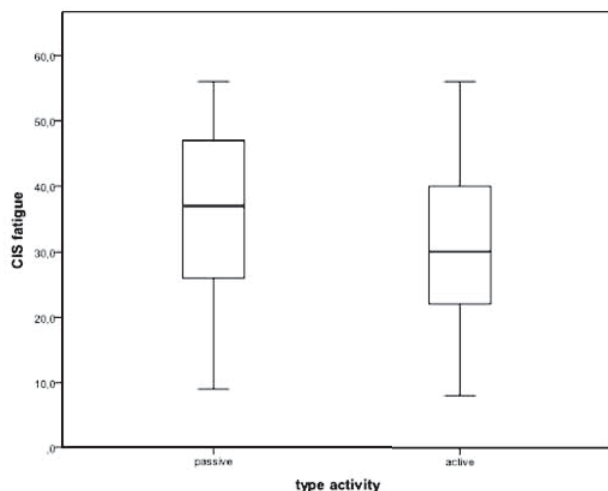
Figure 1. Box plots: bold horizontal bars indicates the medians, the end of the boxes indicates the quartiles.

Conclusion: In RA, a higher level of physical activity was associated with less fatigue. Active patients had a significantly lower CIS-fatigue score than the pervasively passive patients. To study whether this relationship is causal

and clinically relevant, an intervention trial aiming at increasing activity may be performed.

Disclosure: **S. van Dartel**, None; **H. Repping-Wuts**, None; **D. van Hoogmoed**, None; **H. Knoop**, None; **G. Bleijenberg**, None; **P. L. C. van Riel**, None; **J. Fransen**, None.

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Effect of Insoles On the Rheumatoid Foot. Emilia Moreira[1], Anamaria Jones[1], Hilda A. Oliveira[1], Fabio Jennings[1], Artur R.C. Fernandes[2] and Jamil Natour[3]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by peripheral polyarthritis, which may cause joint destruction and deformities, resulting in reduced function and disability. The joint involvement of the foot occurs in 85–100% of the patients with RA. The use of insoles has been a routine in the treatment of rheumatoid feet, despite the weak evidence of its use in randomized controlled trials. The aim of the present study were to evaluate the effectiveness of the use of insoles for foot pain, function, gait, foot load distribution, quality of life and patient satisfaction regarding the use of the insoles in patients with RA.

Methods: Eligible patients included women classified as RA according to the ACR criteria, aged 18–65 years old with pain in feet between 3 and 8 on a 10-cm pain scale (VAS) for walking; functional classes I, II, and III. Of the 208 patients evaluated, 80 met the eligibility criteria and were randomized into experimental (EG) or control groups (CG). The EG group made use of EVA insoles with medial arch and retrocapital support, and CG group employed flat insoles during the study. Pacients were evaluated for pain (VAS) when walking and at rest, function (HAQ), function of the feet (FFI), quality of life (SF-36), 6-minute walk test, satisfaction with the treatment (Likert scale) and dynamics baropodometry (Pro FootWalk, AMcube®, Gargas, France) at baseline, 45 days (T45), 90 days (T90) and 180 days after randomization by a blinded evaluator.

Results: Thirty-nine and 41 patients were randomly divided into EG and CG groups, respectively. The groups were homogeneous at baseline regarding clinical and demographic characteristics. In the comparison between the groups over time, we found better results for the EG with a statistical difference for pain during walking and at rest on the right and left foot (p $<$0.001), stride length (p $=$ 0.001), and satisfaction with the treatment (p $=$ 0.039). For other variables, we found no statistically significant difference between groups.

Conclusion: The use of insoles with medial arch and retrocapital support is effective in reducing pain during walking and at rest on both feet, increasing stride length and satisfaction with the use of insoles.

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Barriers, Benefits and Preferences for Exercise in RA Patients: A Cross Sectional Study. Yves Henchoz[1], Pascal Zufferey[2] and Alexander So[2]. [1]Université du Québec à Trois-Rivières, Trois-Rivières, QC, [2]Lausanne University Hospital, Lausanne, Switzerland

Background/Purpose: Physical exercise is safe and effective as an adjunctive nonpharmacological treatment modality in the management of rheumatoid arthritis (RA). It is well established that patients with RA are less active compared to healthy controls. The transtheoretical model of health promotion, based on five stages of change, provides a useful framework to better understand patients' motivation towards regular exercise. The purpose of this study was to determine the distribution of exercise stages of change in a RA cohort, and to examine barriers, benefits and preferences for exercise.

Methods: One hundred and twenty consecutive patients with RA followed at a hospital-based rheumatology practice were invited to participate in the study. Those who accepted to participate filled in a questionnaire to determine their exercise stage of change, their perceived benefits and barriers to exercise, and their preferences for various features of exercise. Disease activity was measured using the disease activity score (DAS28). Other variables included the Health Assessment Questionnaire (HAQ), the short version of the Arthritis Impact Measurement Scales 2 (AIMS2-SF), pain and

fatigue visual analogue scales (VAS), the number of comorbidities and demographic characteristics. Characteristics of patients in the maintenance and precontemplation stages of change were compared using two-sample t tests, Wilcoxon rank-sum tests and Chi-square tests.

Results: Eighty nine (74%) patients were finally included in the analyses. Mean age was 58.4 (SD 11.7) years, mean RA duration was 10.1 (9.8) years and mean DAS28 was 2.8 (1.2). The distribution of exercise stages of change was as follows: precontemplation (n=30, 34%), contemplation (n=11, 13%), preparation (n=5, 6%), action (n=2, 2%), and maintenance (n=39, 45%). Compared to patients in the maintenance stage of change, precontemplators were less often at work (P<0.05), exhibited a higher body mass index (P<0.01), poorer HAQ (P<0.01), higher pain VAS (P<0.05), poorer scores of physical (P<0.001), symptom (P<0.01), affect (P<0.01) and role (P<0.01) dimensions of the AIMS2-SF, and reported less exercise benefits (P<0.05) and more barriers to exercise (p<0.01). Most participants preferred exercising alone (40%), at home (29%), at a moderate intensity (64%), with advice provided by a rheumatologist (34%) or a specialist in exercise and RA (34%). Walking was by far the preferred type of exercise, in both the summer (86%) and the winter (51%).

Conclusion: This study provides new insight into how RA interferes with exercise participation. Our cohort of patients with RA was essentially distributed across the precontemplation and maintenance exercise stages of change. These subgroups of patients exhibit psychological and functional differences that make their needs in terms of exercise counseling different. Walking appears to be a simple but promising way of promoting physical activity among RA patients.

Disclosure: Y. Henchoz, None; **P. Zufferey**, None; **A. So**, None.

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Orthopedic Surgery Among Patients with Rheumatoid Arthritis 1980–2007: A Population-Based Study to Identify Predictors of Large Joint Vs Small Joint Surgeries. Ashima Makol, Cynthia S. Crowson and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Despite improvements in medical management of rheumatoid arthritis (RA) in recent years, arthritis related orthopedic surgery is often needed to relieve pain and improve function. We aimed to identify risk factors for orthopedic surgery in RA, and ascertain if predictors for large joint surgery differ from those for small joint surgery and soft-tissue procedures.

Methods: A population-based inception cohort of patients fulfilling 1987 ACR criteria for RA between 1980–2007 was assembled and followed until death, migration or 12–31–2008. A retrospective medical record review was performed of all orthopedic surgeries since RA incidence, including primary total joint arthroplasty (TJA), large joint surgery (LJS), small joint surgery (SJS) and soft tissue procedures (STP). Demographics, clinical characteristics of RA, extra-articular manifestations and comorbidities were recorded. Risk factors for surgery were examined using Cox models adjusted for age, sex and calendar year.

Results: The study included 813 RA patients (mean age 56 years; 68 % female; mean follow-up 9.6 years), 189 of who underwent ≥1 joint surgeries during follow-up.

Age was associated with a significantly higher risk of TJA (hazard ratio [HR] per 10 years 1.18; p=0.01) and hip/knee surgery (HR 1.3; p<0.001) but lower risk of SJS (HR 0.84; p=0.03). Female sex (HR 1.38; p=0.05) was predictive of a higher risk for any joint surgery. Obesity at incidence was predictive of higher rates of TJA (HR 2.0; p=0.001), LJS (HR=1.8; p=0.001) and hip/knee surgery (HR=2.6; p<0.001), but not SJS (HR=0.8; p=0.4) or STP (HR=1.0; p=0.9). ESR at RA incidence was associated with increased risk for any joint surgery (HR per 10 mm/hr 1.12; p=0.002), TJA (HR=1.2; p<0.001) and LJS (HR=1.15; p=0.001) but not SJS (HR=1.0; p=0.7). Presence of rheumatoid factor (HR=2.0; p<0.001) and radiographic erosions (HR 3.1; p<0.001) predicted a significantly higher risk for any joint surgery.

Large joint swelling was associated with elevated risk of TJA (HR 1.85; p=0.02), LJS (HR 2.1; p=0.001) and STP (HR 2.0; p=0.02) but not SJS. Rheumatoid nodulosis was predictive of SJS (HR 3.3; p<0.001) and STP (HR 3.0; p<0.001) but not LJS (HR=1.3; p=0.2). Severe extra-articular manifestations of RA were marginally associated with a higher risk of SJS (HR 1.8; 95% confidence interval [CI] 0.93–3.6) but not LJS (HR 1.0; p=0.98). Smoking history predicted a marginally higher risk for STP (HR 1.57; 95% CI 0.98–2.5) but not other procedures.

Conclusion: Women with RA are more likely than men to undergo joint surgery. Female sex, increasing age and obesity were predictive of LJS (especially hip and knee TJA) in RA, similar to the general population. Older patients were less likely to undergo SJS. Rheumatoid nodulosis and radiographic erosions are strong predictors especially for SJS and STP but are also associated with increased risk for any joint surgery. These results indicate that need for LJS in patients with RA is similar to the general population, and that SJS is less desirable for older patients despite long standing disease. Aggressive control of disease activity in the early years after RA incidence to lessen development of erosive changes may decrease future need for joint surgery.

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Important Prognostic Factor in Rheumatoid Arthritis Patients with Interstitial Lung Disease Is Not Usual Interstitial Pneumonia Pattern but Interstitial Lung Disease Extent On Chest High-Resolution Computed Tomography. Hwajeong Lee[1], Jung-Yoon Choe[1], Seong-Kyu Kim[1], Sung Hoon Park[1], Ji Hun Kim[1], Dae Sung Hyun[2], Kyung Jae Jung[3] and Jisuk Bae[4]. [1]Division of Rheumatology, Department of Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, South Korea, [2]Division of Pulmonology, Department of Internal Medicine, Catholic University of Daegu School of Medicine, South Korea, [3]Radiology, Catholic University of Daegu School of Medicine, South Korea, [4]Department of Preventive Medicine, Catholic University of Daegu School of Medicine, South Korea

Background/Purpose: Interstitial lung disease (ILD) is a common pulmonary manifestation of rheumatoid arthritis (RA), and an important cause of morbidity and mortality in RA patients. We categorized ILD to two groups, as the usual interstitial pneumonia (UIP) pattern and the nonspecific interstitial pneumonia (NSIP) pattern, using chest high-resolution computed tomography (HRCT) scanning. We compared demographic and clinical characteristics of UIP pattern and NSIP pattern in rheumatoid arthritis patients and determined the important prognostic factors that influence the survival of RA-ILD patients.

Methods: We enrolled 51 RA patients (male n=21, female n=30) with ILD underwent HRCT, between January 2002 and December 2011 in Catholic University Hospital of Daegu.

Results: Demographics and the clinical characteristics of the 51 RA-ILD patients showed no significant difference between the UIP pattern and NSIP pattern. Comparing the two groups, there were no differences in age at which RA was diagnosed, age at which ILD was diagnosed, RA duration, ILD duration, proportion of steroid and DMARD medication, laboratory study, pulmonary function test and ILD extent on chest HRCT. But RA-NSIP group was younger than RA-UIP group (62.3±11.7 vs 68.2±8.4).

Of the 51 RA-ILD patients, 21(UIP pattern 16 cases, NSIP pattern 5 cases) patients died. More patients died in UIP pattern, but there were no significant differences in survival time between RA-UIP pattern and RA-NSIP pattern (Log rank p=0.985).

Cox's regression analysis was performed to find out prognostic factors that affects survival of RA-ILD patients. ILD extent on chest HRCT was strongly associated with mortality (HR=1.044, 95% CI 1.019–1.069). Patients that was diagnosed ILD in older age (HR=1.518, 95% CI 1.109–2.077), high LDH(HR=1.007, 95% CI 1.000–1.014) and high rheumatoid factor (HR=1.004, 95% CI 1.000–1.008), the use of MTX (HR=5.539, 1.332–23.041) were associated with worse survival time. UIP pattern on HRCT, age, sex, smoking history, anti-CCP antibody didn't have an effect on survival. We divided the extent of the lung disease in to 4 groups; 1–15%, 16–20%, 21–25%, >25% and compared the survival rate. Comparing four groups, there were significant differences in survival estimates (Log-rank p value= 0.0) based on ILD extent of 15%. The median survival time for ILD extent of less than 15% was 89.4 months, ILD extent of excess of 15% was 49 months.

Conclusion: Our case studies reveal that the relationship of the UIP pattern to survival is unclear but the extent of ILD on chest HRCT was found to be significantly associated with poor prognosis of RA-ILD patients.

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Baseline Evaluation of Insulin Resistance in Patients with early Non-Treated Rheumatoid Arthritis. Sara Manrique-Arija[1], María América López-Lasanta[1], Pilar Espiño- Lorenzo[1], Pedro Valdivielso[2], José Rioja[2], Inmaculada Ureña[1], Francisco Gabriel Jimenez- Núñez[1], Carmen M. Romero-Barco[1], Veronica Rodríguez-García[1], Laura Nieves[1], Mari Carmen Ordoñez-Cañizares[1], Laura Cano[1], Maria Victoria Irigoyen[1] and Antonio Fernández-Nebro[1]. [1]Hospital Carlos Haya. University of Malaga, Malaga, Spain, [2]Department of Medicine. University of Malaga, Malaga, Spain

Background/Purpose: High levels of inflammatory cytokines are associated with insulin resistance syndrome in long-standing AR. The aim was to analyze insulin resistance (IR), adipokines, inflammatory cytokines and baseline clinical and laboratory features in patients with early rheumatoid arthritis (ERA) who have not received any treatment for their underlying disease.

Methods: Cross-sectional, case-control, study. Forty-six consecutively patients with ERA (disease duration <1 year) according to 2010 ACR/EULAR criteria, older than 16 years of age and 45 sex and age-matched controls were included. Patients with Diabetes (2010 ADA Criteria) and in prior or current treatment with DMARDs or corticosteroids were excluded. All participants signed an informed consent. Baseline blood and urine samples were collected; Glucose, lipid profile, RF, anti-CCP, ESR, CRP and other parameters were measured in fresh samples; serum was stored at −80°C for later analysis of insulin, ultrasensitive CRP, IL6, TNFα, resistin, adiponectin y leptin. Insuline resistance was estimated by the Homeostasis model assesment for insulin resistance (HOMA-IR), HOMA β, McAuley and QUICKI index. A cardiovascular risk factors (CVRF) questionnaire and a dietary survey were also completed. Measurement of abdominal and hip circumference was performed. Statistical analysis: T-test or Mann Whitney test and Pearson or Spearson's correlation analysis were performed.

Results: Among 103 subjects twelve were excluded (6 were other types of arthritis, 6 had type 2 diabetes) and finally, 91 subjects were included; 46 had RA (50.5%) and 45 were healthy controls (49.5%). Most of them were women (~76%) and there were not differences in age, sex and BMI, between groups but hypertension was higher in patients than controls (30 vs 13%, p < 0.05). Regarding baseline characteristics of patients with RA, the average time of evolution of RA was 6 months, and more than 70% had positive RF and anti-CCP. Concerning laboratory parameters, CRP and ESR were higher in RA patients than in controls (p<0,001). In relation to CVRF and IR, total cholesterol was higher in controls [215 (SD±40,3) mg/dl vs 195(SD±39,5) mg/dl (p< 0,05)], and HDL cholesterol lower in RA patients [52(SD±14,8)mg/dl Vs 59 (SD±16,7) mg/dl(p< 0,05)], and also levels of cytokines such as IL6, TNF-alpha and Resistin in blood were higher in patients than controls. No statistically significant differences were found in leptin, adiponectin or atherogenic index between cases and controls neither in insulin resistance estimated by HOMA-RI, HOMA β, QUICKI nor McAuley. Bivariate analysis revealed a statistically significant correlation between the different indices of IR and parameters of inflammatory activity (PCR, TNF), leptin and body composition.

Conclusion: Although patients showed higher blood pressure, total cholesterol and resistin levels and lower HDL cholesterol than age, sex and BMI matched controls, we were unable to show differences in leptin, adiponectin and any of the insulin resistance indexes assessed, in spite of the expected high levels of systemic inflammatory molecules, such as TNFα and IL-6 in patients group. Lack of association between AR and IR indexes might be due to the short course of the disease.

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Effects of Stress On Clinical Presentation of Patients with Early Rheumatoid Arthritis. Yun A. Kim[1], Jane E. Salmon[2], Juan Xiong[3], Boulos Haraoui[4], Carol A. Hitchon[5], Edward Keystone[6], Janet Pope[7], Diane Tin[8], J. Carter Thorne[8], Gilles Boire[9], Vivian P. Bykerk[2] and CATCH[10]. [1]Hospital for Special Surgery (and Kwangju Christian Hospital, Gwangju, Korea), New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Mount Sinai Hospital, Toronto, ON, [4]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]University of Toronto, Toronto, ON, [7]Schulich School of Medicine and Dentistry, Western University, London, ON, [8]Southlake Regional Health Centre, Newmarket, ON, [9]CHUS - Sherbrooke University, Sherbrooke, QC, [10]Toronto

Background/Purpose: Stress is related to pathogenesis and progression of inflammatory autoimmune disorders. The aim of this study is to evaluate the role of patient (pt) self reported stress within a year of clinical presentation, particularly pt reported outcomes (PROs) in patients (pts) with early rheumatoid arthritis (ERA).

Methods: 951 pts in CATCH (Canadian Early Arthritis Cohort), a prospective multicentre observational cohort, who answered a modified stress & life events questionnaire, were included. Psychological (Psych) stress was defined as death of family member, divorce, separation, family stress and financial stress. Physical stress was defined as motor vehicle accident, surgery, major illness and infection. Differences in baseline characteristics and PROs in pts at 6 months and 1 year reporting exposure or not to stress were compared. Differences were compared using Chi-Square tests for categorical and Wilcoxon rank sum test for continuous variables.

Results: Mean age (SD) was 53.8(14.2). Mean symptom duration (SD) was 6.0 (3.1) months, 83% were Caucasian, 73% female and 18% smokers. Features distinguishing pts with exposure to either stress vs. none are noted in Table 1. More pts reporting psych stress were female, living alone, employed and fatigued (p<0.05). More pts reporting physical stress and were female, older, had a higher HAQ score, and more co-morbidities (p<0.05). Symptom duration, AM stiffness, smoking, race, education, income and marital status were not associated with stress. Pain, fatigue and HAQ scores were elevated at 0,6 and 12 months in patients exposed to stress vs. non-exposed though these improved to a similar degree in both groups. (Table2).

Table 1. Patients reporting exposure to psychological or physical stress versus no stress

Variables	No stress n=454	Psychological stress n=307	Physical stress n=69
Age	54.2 ± 15.0	53.0 ± 12.49	**58.5 ± 12.8***
Female sex	318 (70.0%)	**239 (77.9%)***	**39 (56.5%)***
Living alone, n (%)	51 (11.4%)	**54 (17.7%)***	11 (16.2%)
Employed, n (%)	238 (52.4%)	**191 (62.2%)***	32 (46.4%)
Pain (0–10mm)	5.4 ± 2.8	5.7 ± 2.7	5.5 ± 3.0
Fatigue (0–10mm)	4.8 ± 3.0	**5.6 ± 2.9***	4.9 ± 2.7
DAS28 score	5.0 ± 1.5	5.0 ± 1.5	5.2 ± 1.6
HAQ score	0.96 ± 0.70	1.01 ± 0.66	**1.14 ± 0.71***
Erosions, n (%)	100 (27.4%)	72 (28.0%)	18 (32.1%)
Co-morbidities, n (%)	384 (84.6%)	268 (87.3%)	**66 (95.7%)***

*p-value <.05, Values are mean ± SD unless indicated

Table 2. Outcomes after 6 months and 1 year in patients exposed to stress versus no stress

Variables	6 month stress + (n=447)	6 month Stress − (n=392)	1 year stress + (n=463)	1 year stress − (n=423)
Pain (0–10mm)	**3.5 ± 2.8***	3.0 ± 2.6	**3.0 ± 2.6***	2.7 ± 2.5
Fatigue (0–10mm)	**3.7 ± 3.0***	3.3 ± 2.9	**3.3 ± 2.8***	2.9 ± 2.7
DAS28 score	3.3 ± 1.5	3.3 ± 1.5	3.0 ± 1.5	2.9 ± 1.3
HAQ score	**0.6 ± 0.6***	0.5 ± 0.6	**0.5 ± 0.6***	0.4 ± 0.6

* p <.05, Values are mean ± SD unless indicated

Conclusion: Exposure to stress in ERA pts negatively affects PROs. Given that patient self report of stress may be affected by recall bias and attribution prospective studies on the prevalence and impact of stress in early inflammatory arthritis are needed. Stress may be a significant contextual factor to consider when assessing PROs in long term observational studies of RA.

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Soluble Glycoprotein VI: A Novel Risk Marker for Thrombosis in Patients with Inflammatory Arthritis. Leann Bell[1], Anne M. Madigan[1], Paul A. MacMullan[1], Eimear Dunne[2], Dermot Kenny[2] and Geraldine M. McCarthy[1]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]RCSI, Dublin 2, Ireland

Background/Purpose: Patients with inflammatory arthritis (IA) such as rheumatoid arthritis (RA) are at high risk of cardiovascular mortality. Increased platelet reactivity is a risk marker for adverse cardiovascular events.

We and others have demonstrated that there is increased platelet reactivity in blood from patients with IA. Recent data has shown that platelets amplify inflammation in the joint in IA via the collagen receptor, glycoprotein(GP)VI followed by the production of proinflammatory platelet microparticles[1]. When platelets are activated, the GPVI receptor is shed and detectable in plasma as soluble GPVI (sGPVI) Our hypothesis was that both plasma and synovial fluid (SF) sGPVI would be raised in patients with IA compared to those with osteoarthritis (OA).

Methods: Following ethics approval and informed consent healthy normal donors (n=20) were compared to 43 consecutively recruited patients (OA, n=15, IA, n=28). SF samples were obtained from knee joints when indicated for clinical evaluation and/or joint injection. Plasma and SF samples were centrifuged at 720g and then 20000g to ensure that no platelets or platelet derived microparticles were present in the sample and sGPVI levels were measured by ELISA[2].

Results: Mean plasma sGPVI was similar in normal controls and patients with OA (30$\pm$6 ng/ml vs 31$\pm$6 ng/ml respectively). In contrast, mean plasma sGPVI was 51$\pm$14 ng/ml in patients with IA compared to both normal and OA individuals (P<0.005). SF sGPVI was assayed in 14 patients (IA, n=8, OA, n=6). Seven patients (IA n=4, OA, n=3) had plasma and synovial fluid samples taken simultaneously. SF sGPVI was significantly elevated in patients with IA compared to those with OA. Moreover plasma levels of sGPVI closely correlated with SF levels in these matched samples (rs = 0.995).

Conclusion: Our data shows that sGPVI is easily measured in both plasma and SF. It also suggests the potential value of sGPVI as a marker of both disease activity and platelet reactivity in arthritis. Finally, it further supports an active role of platelets in promoting inflammation locally within the joint.

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Serum Anti-Müllerian Hormone Can Be Used to Determine Ovarian Reserve in Women with Rheumatoid Arthritis. Jenny Brouwer, Johanna M.W. Hazes, Joop S.E. Laven, Izaäk Schipper and Radboud J.E.M. Dolhain. Erasmus Medical Center, Rotterdam, Netherlands

Background/Purpose: Planning of pregnancy is important in women with rheumatoid arthritis (RA). It is preferred to start a pregnancy after adjustment of medication and when disease activity is low. Therefore, it is important to know the ovarian reserve in these women, since a reduced ovarian reserve is associated with subfertility and early menopause. It has been shown in healthy women, that anti-Müllerian hormone (AMH) is a good biomarker for ovarian reserve. Prior to using AMH for this purpose in women with RA, the influence of disease activity and medication use, in particular methotrexate, should be assessed.

Methods: Serum levels of anti-Müllerian hormone were measured in women aged 18 to 42 years with recent onset RA (according to the 2010 ACR/EULAR rheumatoid arthritis classification criteria) at time of diagnosis (before treatment was started) and six months later. The control group existed of 509 healthy women aged 18 to 42 years. The relationships between AMH and presence of rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), erosions, values of C-reactive protein (CRP), disease activity (measured by DAS28) and use of methotrexate (MTX) were assessed.

Results: Serum samples were available for 72 patients at time of diagnosis. Patients were older (median age 35,1 years (IQR 30,1–39,2)) than controls (29,4 years (IQR 23,8–34,4)) (p<0,001). Serum values of AMH, adjusted for age, did not differ significantly between patients (1,71 μg/L (IQR 0,81–4,39 μg/L)) and controls (2,82 μg/L (IQR 1,64–4,38 μg/L)) (p=0,254). AMH levels were not related to the presence of RF (p=0,487), anti-CCP (p=0,686) or erosions (p=0,350) and did not show a significant correlation with serum CRP levels (r = $-$0,207, p=0,083) or disease activity scores (DAS28, r = 0,007, p=0,955).

After six months of treatment, serum was available for 53 patients, of whom 31 patients (58%) were prescribed MTX. AMH levels after six months were significantly lower in these patients (1,92 μg/L (IQR 0,84–3,75)) than at

time of diagnosis (2,57 μg/L (IQR 0,90–5,30)) (p<0,001), but did not differ from the controls after adjustment for age (p=0,741). There was no significant difference in AMH values after six months of treatment between patients who did or did not receive MTX (p=0,287).
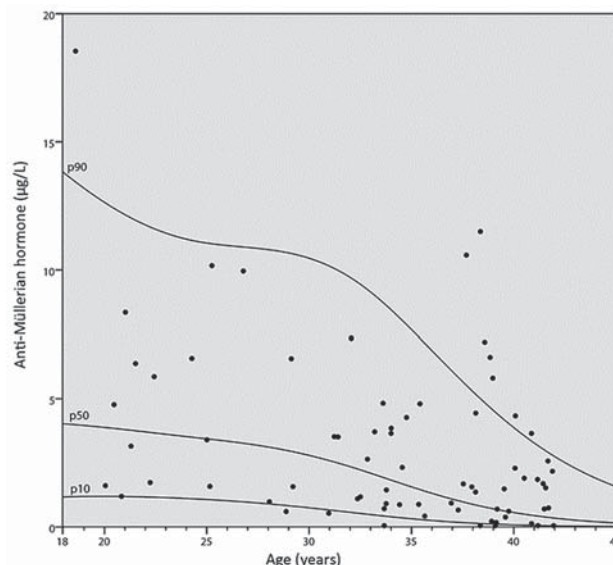
Serum values of anti-Müllerian hormone in women with recent onset rheumatoid arthritis at time of diagnosis compared to the 10th, 50th and 90th percentile lines of healthy controls

Conclusion: In women with recent onset RA, serum AMH levels are not affected by disease activity or short term use of methotrexate. Therefore, serum AMH levels can be used as a marker for ovarian reserve in women with RA. AMH levels are not reduced in women with recent onset RA compared to controls. Further research is needed to study the long term effects of rheumatologic disease and medication use on ovarian reserve in women with RA.

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Glucocorticoid use Is associated with increase in HDL in Rheumatoid Arthritis Patients. Lisa L. Schroeder[1], Xiaoqin Tang[2], Mary Chester Wasko[3] and Androniki Bili[4]. [1]Geisinger Health System, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Temple University School of Medicine, Pittsburgh, PA, [4]Geisinger Medical Center, Danville, PA

Background/Purpose: Atherogenic lipid profiles are common in active RA, with most common being decreased HDL. Glucocorticoids (GC) use is reported to have variable associations with lipid profiles in RA, and the potential differential effect of GC dose on lipid levels is unknown. We sought to evaluate the association of GC dose with lipid changes in RA.

Methods: Patients with RA diagnosed between 1/1/01–11/30/11, receiving oral or intravenous GC and having lipid levels tested prior to and at least 1 year after treatment with ongoing GC were identified. A cohort of RA patients not on GC was constructed for comparison. GC exposure was calculated as a weighted daily dosage in prednisone equivalents. GC exposure was analyzed as a continuous and as a dichotomous <7.5mg/day (low) vs. $\geq$7.5mg/day (high) GC dose. Primary outcome was change in HDL in the low vs. high GC groups. Secondary outcomes were changes in LDL, total cholesterol (TC), triglycerides (TG) and TC/HDL in the same fashion. A similar analysis between the patients on GC vs. not on GC was performed. Linear regression models were used to calculate the outcome, adjusting for age, gender, body mass index (BMI), diabetes, HTN, hyperlipidemia, RF, ESR, statin, NSAID, methotrexate (MTX), hydroxychloroquine (HCQ) and TNF-α inhibitor use.

Results: 202 patients on GC and 463 patients not on GC were included. Baseline characteristics are shown in Table 1. The changes in lipid levels according to GC use are shown in Table 2. Any GC and high dose GC use were associated with increased HDL, but no other significant lipid changes,

compared to non-GC users. There were no significant differences in HDL or other lipids between the low vs. high GC groups. Sensitivity analysis, excluding patients on statins, showed similar results.

Table 1. Baseline patient characteristics

	Patients on GC			**No GC**
	All **N=202**	**GC <7.5** **N=87**	**GC ≥7.5** **N=115**	**No GC** **N=463**
GC dose* (median)	8.4 (5.6–11.1)	5.2 (5.0–6.2)	10.4 (9.3–14.5)	
Age (mean ± SD years)	64.7 (11.7)	64.5 (11.2)	64.8 (12.1)	62.8 (11.4)
Female	137 (67.8)	61 (70.1)	76 (66.1)	293 (67.2)
BMI	30.6 (6.5) N=166	30.4 (6.5) N=66	30.7 (6.6) N=100	30.5 (6.2) N=358
ESR	35.6 (24.8) N=154	30.8 (22.5) N=60	38.6 (25.9) N=94	34.2 (24.5) N=313
RF	124 (61.4)	41 (47.1)	83 (72.2)	254 (58.3)
Diabetes	88 (43.6)	39 (44.8)	49 (42.6)	161 (36.9)
HTN	136 (67.3)	59 (67.8)	77 (67.0)	302 (69.3)
Hyperlipidemia*	141 (69.8)	53 (60.9)	88 (76.5)	316 (72.5)
HCQ use	42 (20.8)	20 (23.0)	22 (19.1)	106 (24.3)
NSAID use	96 (47.5)	41 (47.1)	55 (47.8)	196 (45.0)
Statin use	74 (36.6)	29 (33.3)	45 (39.1)	163 (37.4)
Anti-TNF use	23 11.4)	10 (11.5)	13 (11.3)	47 (10.8)
MTX use	107 (53.0)	49 (56.3)	58 (50.4)	184 (42.2)

Table 2. Change in lipids according to GC use [1]

	Any GC	**GC <7.5**	**GC ≥ 7.5**	**No GC**
Pre-treatment HDL	52.4 (15.8)	55.4 (16.0)	50.1 (15.4)	52.2 (15.3)
Highest post-treatment HDL	58.1 (16.6)	60.1 (15.6)	56.5 (17.2)	55.4 (16.0)
Change in HDL	5.7 (11.6)*	4.7 (12.1)	6.5 (11.3)*	3.2 (10.5)*
Pre-treatment TC	191 (43)	197 (34)	187 (48)	194 (43)
Lowest post-treatment TC	189 (41)	193 (36)	186 (45)	186 (41)
Change in TC	2.4 (36.5)	3.6 (3.9)	1.5 (40.3)	7.8 (37.7)
Pre-treatment TC/HDL	3.9 (1.2)	3.8 (1.2)	4.0 (1.2)	4.0 (1.2)
Lowest post-treatment TC/HDL	3.5 (1.0)	3.4 (1.0)	3.5 (1.1)	3.6 (1.2)
Change in TC/HDL	0.39 (0.91)	0.37 (0.94)	0.40 (0.89)	0.35 (0.93)
Pre-treatment LDL	106 (35)	110 (33)	103 (36)	110 (35)
Lowest post-treatment LDL	96 (33)	103 (30)	97 (34)	100 (33)
Change in LDL	6.4 (32.3)	6.9 (28.5)	6.0 (34.8)	9.9 (32.6)
Pre-treatment TG	160 (113)	151 (84.1)	167 (130)	157 (90)
Lowest post-treatment TG	149 (81)	147 (81)	152 (82)	149 (83)
Change in TG	11.1 (90.3)	4.3 (78.4)	16.2 (98.3)	7.8 (68.4)

*Statistically significant findings p-value<0.05:
GC vs. No GC: change in HDL: p=0.006
High GC dose vs. No GC: change in HDL: p=0.012
[1]Adjusted for age, gender, BMI, ESR, RF, DM, HTN, hyperlipidemia, and use of TNF-α inhibitors, MTX, statins, HCQ, and NSAIDs

Conclusion: In this RA cohort, any GC and high dose GC (median 10.4 mg/day) use were associated with increased HDL, whereas low dose was not. Although our results need to be replicated in other RA cohorts, these findings are reassuring in this patient population at high risk for cardiovascular disease.

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Use of Anti-Tumor Necrosis Factor Therapy Is Associated with Reduced Cardiovascular Event Risk in Rheumatoid Arthritis. Mike Nurmohamed[1], Yanjun Bao[2], James Signorovitch[3], Parvez M. Mulani[2] and Daniel E. Furst[4]. [1]VU University Medical Center & Jan van Breemen Research Institute, Amsterdam, Netherlands, [2]Abbott Laboratories, Abbott Park, IL, [3]Analysis Group, Inc., Boston, MA, [4]David Geffen School of Medicine at UCLA, Los Angeles, CA

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased risks for cardiovascular (CV) comorbidities because of an increased prevalence of traditional CV risk factors and the underlying chronic inflammatory process. We assessed the effects of treatment with anti–tumor necrosis factor (anti-TNF) therapy, methotrexate (MTX), or other nonbiologic DMARDs on CV event risk in patients with RA.

Methods: Adult patients with ≥2 RA diagnoses (ICD-9 CM: 714.xx) and ≥1 filled prescription of anti-TNF therapy, MTX, or other nonbiologic DMARD were identified in the Thomson Reuters MarketScan® database

(2003–2010). Patients were assessed from index fill date to first inpatient CV diagnosis of myocardial infarction (MI), stroke, unstable angina, or congestive heart failure (CHF) to the end of health plan enrollment or to 6 months after the discontinuation of their index drug, whichever came first. Cox proportional-hazards models assessed the effect of cumulative exposure to anti-TNF therapy, MTX, and other nonbiologic DMARDs on occurrence of CV events. We adjusted for baseline (ie, 1 year before index prescription) demographics, use of therapies for RA (eg, MTX, corticosteroid), CV-related medications and smoking deterrents, comorbidities (eg, dyslipidemia, hypertension, diabetes), history of CV events, and medical resource use. Subgroup and sensitivity analyses also were conducted.

Results: The study identified 109,462 patients with 105,920 total patient-years (PYs) of follow-up, including 48,621 PYs of exposure to anti-TNF therapies (31,466 as monotherapy), 35,480 PYs of exposure to MTX (18,325 as monotherapy) and 52,994 PYs of exposure to other nonbiologic DMARDs (9,441 as monotherapy). A total of 1743 patients (1.6%) had a CV event after their index prescription. In the multivariate regression model, each additional 6 months of anti-TNF therapy significantly reduced the risk for any study CV event (hazard ratio [HR]=0.87, 95% confidence interval [CI]=0.80–0.96, P=.005) and for MI (HR=0.80, CI=0.67–0.95, P=.013), compared with patients without anti-TNF biologics. The effects of cumulative use of MTX and other nonbiologic DMARDs were not statistically significant. In the subgroup analyses, each additional 6 months of anti-TNF therapy use was significantly associated with a reduction in CV events in patients aged ≥50 years (HR=0.86, CI=0.77–0.96, P=.007) and in those without prior MTX use (HR=0.85, CI=0.73–0.98, P=.022). When assessed individually, significant event risk reduction was also observed with MI, unstable angina, and CHF for patients with longer exposure to anti-TNF therapies compared with nonuse of anti-TNF therapies. In the full sample, the model predicted that cumulative use of anti-TNF therapy for 1, 2, or 3 years would reduce CV event risks by 24%, 42%, and 56%, respectively, compared to nonuse of anti-TNF therapies.

Conclusion: Use of anti-TNF therapies vs. nonuse was associated with significantly lower risks for CV events (ie, inpatient diagnoses for MI, stroke, unstable angina, or HF) in patients with RA, older patients with RA, and patients without prior exposure to MTX, adjusting for use of MTX and other nonbiologic DMARDs.

Disclosure: **M. Nurmohamed**, Abbott Laboratories, 2, Abbott Laboratories, 5, Abbott Laboratories, 8; **Y. Bao**, Abbott Laboratories, 3, Abbott Laboratories, 1; **J. Signorovitch**, Analysis Group, 3; **P. M. Mulani**, Abbott Laboratories, 3, Abbott Laboratories, 1; **D. E. Furst**, Abbott Laboratories, 5, Abbott Laboratories, 8, Abbott Laboratories, 9.

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Effect of Tocilizumab Treatment On Regional Left Ventricular Function, As Assessed by Cardiac Magnetic Resonance Imaging, in Rheumatoid Arthritis Patients without Cardiac Symptoms. Hitomi Kobayashi[1], Isamu Yokoe[1], Hiroshi Sato[1] and Yasuyuki Kobayashi[2]. [1]Itabashi Chuo Medical Center, Tokyo, Japan, [2]St Marianna Univ Sch of Med, Kawasaki, Japan

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased risk of congestive heart failure, possibly via shared mechanisms of inflammation. This study was undertaken to test the hypothesis that the powerful anti-inflammatory effect of anti-interleukin 6 (tocilizumab: TCZ) therapy might lead to a reduction in left ventricular (LV) dysfunction in patients (pts) with RA. We sought to measure LV regional function by using a cardiac magnetic resonance imaging (CMR) approach in RA pts without cardiac symptoms, and also to evaluate the changes in these measurements at 52 wks of TCZ treatment.

Methods: This was an open-label prospective pilot study to directly evaluate the effect of TCZ on LV function in RA pts without a clinical diagnosis of cardiovascular disease. Consecutive RA pts with active disease and healthy control subjects were enrolled. The RA pts each had inadequate clinical response to non-biologic DMARDs or non-TNF directed therapy, and were prescribed TCZ therapy (8 mg/kg IV every 4 wks). All subjects underwent baseline evaluation of LV function, as measured by non-contrast CMR on a 1.5 T scanner. Peak systolic regional radial strain (Err, %) was calculated by feature tracking of cine MRI in the six segments of the mid-slice of LV. After the baseline (BL) CMR, treatment with the prescribed TCZ was initiated and pts were followed for 52 wks. Pts underwent follow-up CMR evaluation at 52 wks of treatment with TCZ. We examined the differences in peak Err between the control subjects and RA pts. We compared peak Err of RA pts at BL and at 52 wks, and determined the association of peak Err with disease activity and severity measures.

Results: All RA pts received TCZ treatment for 52 wks. We compared 11 RA pts (100% female; mean age 52.6±10.4 y) at BL and at 52 wks, with 10 non-RA controls (100% female; mean age 55.7±4.6 y). DAS28-ESR, SDAI, and Swollen Joint Count (SJC) were significantly lower in RA pts at 52 wks than at BL ($p<0.0001$, $p<0.0001$, $p=0.003$, respectively). Mean peak Err in RA pts at BL was significantly lower than in normal subjects (0.58±0.13 vs. 0.69±0.10; $p=0.04$); mean peak Err in RA pts at 52 wks was not significantly different from those of normal subjects (0.65±0.12 vs. 0.69±0.10; $p=0.56$) (figure). Mean peak Err tended to be lower at BL than at 52 wks, but not significantly ($p=0.26$). Percentage change of mean peak Err in RA pts was significantly associated with percentage change of SJC ($r=0.74$, $p=0.009$) and DAS28-ESR ($r=0.70$, $p=0.017$).

Peak Err in control subjects, in patients at baseline and after 52 weeks of TCZ treatment
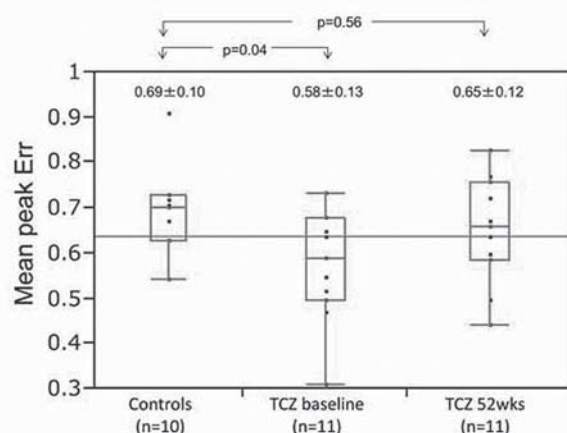
Conclusion: Our findings suggested sub-clinical LV regional dysfunction in RA pts without cardiac symptoms. Furthermore, we demonstrated that improvements in LV regional function by TCZ treatment correlated with reduction in measures of systemic inflammation and RA disease activity. This suggests that systemic inflammation contributes to myocardial dysfunction in RA.

Disclosure: H. Kobayashi, None; **I. Yokoe**, None; **H. Sato**, None; **Y. Kobayashi**, None.

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Group Cycling in Rheumatoid Arthritis: Positive Effects On Aerobic Capacity and Blood Pressure. Lars Ångström, Kristina Hörnberg and Solveig Wållberg Jonsson. Dept of Rheumatology, Umeå, Sweden

Background/Purpose: Cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA) (1). Strong evidence shows that exercise reduces the CVD risk in the general population (2). In the present study we examined the effect of group cycling on risk factors for CVD in patients with RA.

Methods: 13 subjects (12 women and 1 man, median age 57 years) with RA exercised on stationary bikes at medium to high intensity for 45 min, 3 times a week for 10 weeks. A control group of 10 subjects continued their previous activities. The following measurements were made at baseline, at 10 weeks and at 25 weeks: Aerobic capacity calculated by a sub-maximal ergometer test according to Åstrand; Visual analogue scale (VAS) for self-assessment of pain and general health; self-assessments of functional ability, using the health assessment questionnaire (HAQ), and the number of tender and swollen joints (28-joint count). Analyses of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipids (cholesterol, % high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides), insulin and glucose according to routine methods; Body mass index (BMI) and disease activity score (DAS 28) were calculated; Pulse wave analysis (PWA) (Arteriograph™) was used to register augmentation index (AIx), a measure reflecting early endothelial dysfunction shown to predict future cardiovascular events, pulse wave velocity (PWV), a proxy for arterial stiffness, and systolic blood pressure in aorta (SBPao) besides peripheral blood pressure.

Results: In the exercise group there were significant improvements at 10 weeks compared to baseline regarding aerobic capacity (33 vs 26 ml O2/kg ×

min; $p<0.05$), systolic (126 vs 137.8 mm Hg; $p<0.01$) and diastolic (73 vs 83.8 mm Hg, $p<0.05$) peripheral blood pressure, SBPao (118 vs 137.7 mm Hg; $p<0.01$) and tender joint count ($p<0.05$). The improvement of the diastolic blood pressure was significantly larger in the exercise group compared to the controls at 10 weeks (-7.0 vs $+2.6$ mm Hg; $p<0.05$). Low aerobic capacity at baseline correlated with high disease activity (ESR; $r_s=-.687$, $p<0.01$, CRP; $r_s=-.727$, $p<0.01$) and low physical function (HAQ; $r_s=-.572$, $p<0.05$) at baseline. Swollen joint count at baseline correlated with AIx at 10 weeks ($r_s=.641$, $p<0.05$). Improvements in blood pressure correlated with high physical function (HAQ) at baseline and at 10 weeks and with low disease activity (tender joints, VAS pain, CRP, DAS 28) at 10 weeks.

Conclusion: Regular exercise on stationary bikes on medium to high intensity for 10 weeks increased aerobic capacity in a group of RA-subjects and produced changes of blood pressure to a level that is described to be clinically relevant (3). Subjects also reported fewer tender joints after the exercise period.

Reference
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Disclosure: L. Ångström, None; **K. Hörnberg**, None; **S. Wållberg Jonsson**, None.

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Age-Specific Association Between Disease-Related Measures and Incident Cardiovascular Events and All-Cause Mortality in Early Rheumatoid Arthritis. Sofia Ajeganova[1], Maria LE Andersson[2], Johan Frostegård[3] and Ingiäld Hafström[1]. [1]Karolinska Institutet, Unit of Rheumatology, Department of Medicine Huddinge, Stockholm, Sweden, [2]R&D Center, Spenshult Hospital, Oskarström, Sweden, [3]Karolinska Institutet, Section of Immunology and chronic disease, Institute of Environmental Medicine, Stockholm, Sweden

Background/Purpose: Increased risk of cardiovascular disease (CVD) and premature mortality in rheumatoid arthritis (RA) has been established, but the impact of inflammatory and disease related factors has been inconsistent across studies.

Here, we determined if occurrence of subsequent CVD and mortality outcomes was influenced by disease related factors at RA onset and the first years of disease, and if the impact of these factors differed between age groups. Further we investigated the role of antibodies against phosporylcholine (anti-PC), a promising atheroprotective biomarker.

Methods: This is a cohort study derived from the BARFOT inception RA cohort, to which patients were consecutively recruited from 1994 through 1999, disease duration <13 months. Participants with prevalent CVD at study enrollment or aged <20 years were excluded. The outcomes were an incident CVD event (myocardial infarction, cardiac arrest, angina pectoris, peripheral arterial disease, coronary or vascular surgery, stroke and transient ischemic attack) and all-cause mortality, and were tracked through the Swedish Hospital Discharge Registry and the National Cause of Death Registry until December 2010.

Area under the curve (AUC) was calculated for disease measures assessed at inclusion and after 1 and 2 years, and differences (D) between inclusion and 1 year after enrollment. IgM anti-PC was determined by ELISA.

Cox proportional regression models in age groups <65 and ≥65 years at RA onset, adjusted for age, gender, smoking, presence of hypertension, diabetes or hyperlipidemia, and Kaplan Meier analysis were used for statistical tests.

Results: The study population comprised 741 patients with early RA, whose mean age at entry was 55 years (SD 14.7), range 20–93 years, 67.5% of the participants were women, and 60% were RF positive. The median observation was 13 years (range 2–17). During follow-up, 177 patients developed an incident CVD event, and 151 deceased, corresponding rates of 2.1 (1.8–2.4) and 1.7 (1.4–1.9) per 100 person-years.

Only in the younger individuals, RF or ACPA positivity, CRP-AUC, ESR-AUC, and VAS pain-AUC were associated with higher risk of CVD event, adjusted hazard ratios (HRs) 2.72 (95% CI, 1.48–5.02), 1.87 (1.01–3.34), 1.07 (1.01–1.14), 1.10 (1.02–1.17), and 1.06 (1.00–1.13), respectively. On the other hand, only in the older patients, DCRP, DESR, DHAQ, and also regular use of methotrexate and daily oral glucocorticoids were associated with incident CVD, respective HRs 0.94 (0.89–1.00), 0.90 (0.82–0.97), 0.71/0.52–0.97), 0.64 (0.43–0.96), and 1.69 (1.13–2.51). Similarly, RF or ACPA positivity and VAS pain-AUC were associated with higher death risk

in the younger patients, while CRP-AUC, ESR-AUC and HAQ-AUC were independently related to risk of death in both age groups.

CVD outcome but not mortality was associated with the levels of anti-PC at baseline, the 10-year CVD event-free survival rates were 66%, 74% and 76% in the first (lowest), second and third anti-PC tertiles, respectively, p=0.024.

Conclusion: In early RA, age stratification could improve evaluation of risk factors for CVD and mortality. The IgM anti-PC antibodies may perform atheroprotective in RA.

Disclosure: S. Ajeganova, None; **M. L. Andersson**, None; **J. Frostegård**, Frostegård is named as inventor on patents and patent applications relating to anti-PC, 9; **I. Hafström**, None.

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Cardiovascular Risk Assessment in Rheumatoid Arthritis (RA) Patients Treated by Biologic Response Modifiers. Majed M. Khraishi[1], Rana Aslanov[2] and Katie Doyle[1]. [1]Memorial University of Newfoundland, St Johns, NF, [2]Memorial University of Newfoundland, St.John's, NF

Background/Purpose: We aimed to assess the 10-year CV event risk in patients with RA at the baseline and 1 year after the initiation of treatment with biologic DMARDs.

Methods: RA patients receiving biologic therapy were included. Participants were divided into 2 groups aged 21 to 49 years and 50 to 84. The Framingham Risk Score (FRS) was used for the assessment of 10-year CVD risk. The presence of CV risk factors (fasting serum TC, HDL levels, history of HTN, DM and Dyslipidemia, and CV events) were ascertained by a medical records review and throughout a 1 year follow-up. Regression analyses of the relationship between lipids and inflammatory indices (CRP & DAS28) before and after treatment, as well as of biologic modifiers were performed.

Results: The mean (SD) age of 215 patients (73.5% females) was 55.6 (12) years. The age at RA diagnosis was 41.6 (13.3) years with a mean (SD) duration of symptoms at 14 (8.7) years. 7 cases with previously documented MI and 3 cases with TIA/Stroke were analysed. All patients had their CV events prior to the initiation of treatment with biologics with predicted 10-year CVD risk more than 30%. Smoking was documented in 19% of patients (61% females) at baseline and 1-year. TJC and SJC were significantly reduced after 12 months of treatment (12.5 ± 8.6 vs. 9.0 ± 7.5; $p<0.001$ and 4.3 ± 3.8 vs. 1.9 ± 2.4; $p<0.001$, respectively). The means of TC, HDL and the Atherogenic Index (AI) at the baseline and 12 months were compared: TC was not significantly increased from 3.1 ± 2.8 to 3.3 ± 2.6 (p=0.185); HDL increased from 0.7 ± 0.7 to 0.9 ± 0.7 (p=0.005); and AI was significantly reduced from 4.6 ± 1.7 to 4.0 ± 1.2 ($p<0.001$). CRP, ESR and DAS28 levels were significantly reduced from baseline (p=0.002; $p<0.001$ and $p<0.001$, respectively). Patients were grouped by their 10-year CVD risk level: Low Risk ($<10\%$), Moderate Risk (10% to 19%), High Risk (20% and more). The trend analysis of 10-year CVD risk by gender showed that 7% of men in a 12-month period moved from the low/moderate risk to the high risk (38.6% vs. 45.6%; $p<0.001$) while 4% of females significantly lowered their risk from the high to the moderate/low (11.4% vs. 7.6%; $p<0.001$). The analysis of relationship between lipids and inflammation indices as well as biologics did not show significance at the baseline and 1 year follow-up.

RA Characteristics and lipid levels at baseline and 12-month

RA Characteristics	Baseline, mean (SD)	1-year F-Up, mean (SD)	P
Total Joint Count (TJC)	12.47 (8.550)	8.97 (7.52)	<0.001
Swollen Joint Count (SJC)	4.33 (3.77)	1.94 (2.43)	<0.001
C-Reactive Protein (CRP), mg/l	16.24 (29.73)	9.92 (15.81)	0.002
ESR, mm/h	30.67 (23.20)	22.86 (20.77)	<0.001
DAS28 score	3.95 (1.34)	3.39 (1.25)	<0.001
CDAI score	17.44 (9.90)	13.00 (10.00)	<0.001
HAQ score	1.18 (0.73)	1.08 (0.75)	0.007
Total Cholesterol, mmol/l	3.10 (2.80)	3.30 (2.62)	0.185
HDL Cholesterol, mmol/l	0.73 (0.70)	0.86 (0.71)	0.005
Atherogenic Index (TC/HDL)	4.64 (1.68)	3.99 (1.18)	<0.001

Conclusion: Our results showed a trend in reducing a 10-year CV event risk over 12-month of treatment with biologic disease modifiers. No serious cardiovascular events were observed during the study period. This improvement was influenced by many factors such as lipid-lowering treatment (30.7% of patients) and proper control of blood pressure and plasma glucose level

(28.4% and 11.6% of patients, respectively). Females appeared to be more successful in reducing the CVD risk. Biologic DMARDs effectively decreased inflammation and possibly played a pivotal role in reducing the risk for CV event in patients with chronic RA.

Disclosure: M. M. Khraishi, Abbott, Roche, Pfizer, Amgen, 2; **R. Aslanov**, None; **K. Doyle**, None.

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Delay in Diagnosis of Rheumatoid Arthritis Increases the Cardiovascular Risk. Chan-Bum Choi[1], Yoon-Kyoung Sung[2], Soo-Kyung Cho[2], Dae-Hyun Yoo[2], Shin-Seok Lee[3], Jisoo Lee[4], Jinseok Kim[5], Hye-Soon Lee[6], Tae-Hwan Kim[2], Bo Young Yoon[7], Wan-Hee Yoo[8], Jung-Yoon Choe[9], Sang-Heon Lee[10], Seung-Cheol Shim[11], Won-Tae Chung[12], Seung-Jae Hong[13], Choong Ki Lee[14], Eunmi Koh[15], Jae-Bum Jun[16], So-Young Bang[6], Seong-Kyu Kim[17], Hoon-Suk Cha[18], Jeeseon Shim[19], Sang-Cheol Bae[20] and Korean Observational Study Network for Arthritis (KORONA)[21]. [1]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Chonnam National University Medical School, Gwangju, South Korea, [4]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [5]Jeju National University Hospital, Jeju, South Korea, [6]Hanyang University Guri Hospital, Guri, South Korea, [7]Inje University Ilsan Paik Hospital, Goyang, South Korea, [8]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [9]Catholic university of Daegu School of mediine, Arthritis and autoimmunty research center, Daegu, [10]Konkuk University School of Medicine, Seoul, South Korea, [11]Eulji University Hospital, Daejeon, South Korea, [12]Dong-A University Hospital, Busan, South Korea, [13]Kyung Hee University, Seoul, South Korea, [14]Yeungnam University, Daegu, South Korea, [15]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [16]Hanyang University Hospital for Rheumatic Disease, Seoul, South Korea, [17]and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu, South Korea, [18]Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea, [19]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [20]Hanyang University Hospital for Rheumatic Disease, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [21]Seoul

Background/Purpose: Patients with rheumatoid arthritis (RA) are known to be at increased risk for cardiovascular diseases. Inflammation as well as traditional risk factors contributes to this risk and adequate control of the disease activity of RA will decrease it. We investigated whether earlier diagnosis and earlier initiation of treatment would decrease the risk of cardiovascular diseases in patients with RA.

Methods: RA patients from the KORONA (Korean Observational Study Network for Arthritis) prospective multicenter cohort were assessed. Information on RA onset to diagnosis, disease duration, disease activity, functional impairment, smoking status, cardiovascular comorbidities, and cardiovascular risk using SCORE (Systematic Coronary Risk Evaluation) risk chart were obtained from questionnaires and medical records. Regression models were used to assess the association between delay in diagnosis of RA and cardiovascular risk, adjusting for disease duration, disease activity, radiographic damage, functional impairment, body-mass index, and methotrexate, steroids, NSAIDs, and biologics use.

Results: The mean delay from RA onset to diagnosis was 1.8 ± 4.1 years. A total of 2,465 patients were diagnosed within a year from onset with a mean delay of 0.2 ± 0.3 years and diagnosis was delayed more than a year in 1,023 patients with a mean of 5.5 ± 6.1 years. Patients with delayed diagnosis were significantly older at assessment, younger at diagnosis, and had longer disease duration. There was no difference in current disease activity assessed by DAS28, but patients with delayed diagnosis showed significantly higher functional impairment (p < 0.01). Proportion of patients smoking, taking corticosteroids and/or NSAIDs were significantly lower in the delayed diagnosis group (p < 0.01, p = 0.03, p <0.01, respectively). SCORE risk score was significantly higher in patients with delayed diagnosis with 1.3 ± 1.7 compared to 1.1 ± 1.7 in patients with diagnosis within a year (p < 0.01). The association between delay in diagnosis of RA and increase in cardiovascular risk calculated by SCORE risk score remained significant in women after adjustment (p < 0.01), but it was lost in men (p = 0.12).

Conclusion: Delay in diagnosis of rheumatoid arthritis can lead to increase in major cardiovascular risk, especially in women.

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Accelerated Aging Influences Cardiovascular Disease Risk in Rheumatoid Arthritis. Cynthia S. Crowson, Terry M. Therneau, John M. Davis III, Veronique L. Roger, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Background/Purpose: People with rheumatoid arthritis (RA) suffer an excess burden of cardiovascular disease (CVD), yet standard risk assessments designed for the general population do not accurately predict their CVD risk. The purpose of this study was to identify traditional CVD risk factors that have a significantly different impact on CVD development in the presence of RA. Recognition of potentially distinctive contributions of CVD risk factors in RA could inform the development of improved CVD risk assessment tools for patient management.

Methods: A population-based inception cohort of RA subjects aged ≥ 30 years who fulfilled 1987 ACR criteria for RA between 1-1-1988 and 1-1-2008 was assembled and followed until death, migration, or 12-31-2008. Medical records were reviewed to ascertain the presence of CVD risk factors (age, blood pressure, lipids, smoking, and diabetes mellitus) at RA incidence and to ascertain the development of CVD (myocardial infarction, CVD death, angina, heart failure, stroke and intermittent claudication) during follow-up. The 10-year Framingham risk score (FRS) for CVD was calculated. Cox models were used to examine the effects of CVD risk factors included in the FRS in patients with RA, and whether RA disease characteristics (e.g., rheumatoid factor [RF] positivity, acute phase reactants, extra-articular manifestations) modify the effects of CVD risk factors. Models were adjusted for the FRS and stratified by sex.

Results: The study included 525 patients with RA without prior CVD (mean age: 55 years, 71% women; 68% RF positive). The patients were followed for a mean of 8.4 years, during which 84 developed CVD (47 women, 37 men). The FRS predicted only 45.7 events (23.3 women, 22.4 men). Essentially all of the excess events (37.2 of 38.3) were among the RF-positive patients. Analysis of CVD risk factors revealed a greater effect of age on the risk of developing CVD among RF-positive but not RF-negative patients. As estimated by the FRS, the effect of age on CVD risk in the RF-positive group was nearly double its effect in the general population (p<0.001). The impact of this additional aging effect was negligible for patients younger than 50 years, when CVD risk in the general population is generally low. However, the impact was observed to increase exponentially as CVD risk rose with age. For example, patients over 65 years with RF-positive RA had similar CVD risk as persons in the general population aged >90 years. The unique influence of age in RF-positive RA was not explained by other CVD risk factors or RA disease characteristics. Acute phase reactants and severe extra-articular manifestations also appear to influence CVD risk in RF positive RA after accounting for this additional age effect.

Conclusion: The results revealed an exponentially increasing effect of age on CVD risk in patients who have seropositive RA, supporting prior reports of accelerated aging in this disease. In contrast, the impact of age on CVD risk among RF-negative patients was similar to the general population. These findings suggest that the advent of CVD risk scores that better account for accelerated aging and other factors in RF-positive patients could improve CVD risk assessment for persons with RA.

Disclosure: **C. S. Crowson**, Pfizer Inc, 2; **T. M. Therneau**, Pfizer Inc, 2; **J. M. Davis III**, None; **V. L. Roger**, None; **E. L. Matteson**, Pfizer Inc, 2; **S. E. Gabriel**, Pfizer Inc, 2, Roche Pharmaceuticals, 5.

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The Impact of Statin Use On Lipid Levels in Statin-Naive Patients with Rheumatoid Arthritis (RA) Vs. Non-RA Subjects: Results From a Population-Based Study. Elena Myasoedova, Cynthia S. Crowson, Abigail B. Green, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Background/Purpose: Dyslipidemia in patients with rheumatoid arthritis (RA) is well recognized. The impact of lipid-lowering medications on lipid levels in patients with RA vs non-RA subjects has not been comprehensively studied in large population-based cohorts. We aimed to examine lipid profiles among statin naive patients with RA and those without RA before and after the initiation of statins.

Methods: Lipid measures were abstracted in a population-based incident cohort of RA patients (1987 ACR criteria first met between 1/1/1988 and 1/1/2008) and in a cohort of non-RA subjects from the same underlying population. Information regarding statin use was gathered in both cohorts. Only patients with no history of statin use who started a statin for dyslipidemia between 1 year prior to RA diagnosis/index date and last follow-up were included. Target lipid levels for both cohorts were defined as follows: total cholesterol (TC) <200 mg/dL, low density lipoprotein cholesterol (LDL) <160 mg/dL, triglycerides <150 mg/dL, high density lipoprotein (HDL) ≥ 50 mg/dL. T-tests and linear regression models were used to compare changes in lipid profiles between the RA and non-RA cohorts.

Results: The study included a cohort of 161 patients with RA (mean age 56.3 years, 57% female, 66% rheumatoid factor positive) and 221 non-RA subjects (mean age 56.0 years, 66% female). Prior to the start of statins, the levels of TC (mean+/−standard deviation, 225.3+/−54.7 mg/dL) and LDL (141.0+/−53.4 mg/dL) in the RA cohort were significantly lower than in the non-RA cohort (TC: 242.3+/−45.8 mg/dL, p<0.001, and LDL: 155.2+/−40.6 mg/dL, p=0.004). The decrease in absolute LDL values after at least 90 days of statin use was less pronounced in the RA vs non-RA cohort (−33.7+/−42.8 mg/dL vs −44.7+/−38.5 mg/dL, respectively, p=0.025); a similar trend was observed for TC (−35.6+/−46.3 mg/dL vs −43.5+/−41.4 mg/dL, p=0.08). There were no significant differences in baseline and/or follow-up levels of triglycerides, HDL, and TC/HDL in RA vs non-RA cohorts. During the 90-day follow-up, the percentage change in LDL, but not in other lipids, was significantly smaller (by 9%) in RA than in the non-RA cohort (p=0.039), adjusting for age, sex, smoking, diabetes mellitus, hypertension, and coronary heart disease. However, RA patients with altered lipid levels were as likely to reach lipid targets with statin use as non-RA subjects (all p > 0.05). A total of 89% of RA vs 91% of non-RA subjects met the target levels for LDL after 90 days of statin use (p=0.53). There were no apparent changes in the use of disease-modifying antirheumatic drugs and biologics in RA patients during the study period.

Conclusion: Before statin initiation, patients with RA had significantly lower TC and LDL levels than non-RA subjects. Absolute and relative decreases in LDL values following statin initiation were smaller in RA than in non-RA subjects. Nonetheless, patients with RA were as likely to achieve conventional lipid goals as non-RA subjects suggesting the potential for clinical benefits of statins in RA. More studies are needed to determine the impact of improvement in lipid profile with statin use on cardiovascular risk reduction in RA.

Disclosure: **E. Myasoedova**, None; **C. S. Crowson**, Pfizer Inc, 2; **A. B. Green**, None; **E. L. Matteson**, Pfizer Inc, 2; **S. E. Gabriel**, Pfizer Inc, 2, Roche Pharmaceuticals, 5.

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Heightened Aortic Wall Inflammation in Patients with Rheumatoid Arthritis Versus Patients with Established Coronary Artery Disease without Autoimmune Disease. Jeffrey D. Greenberg[1], Zahi Fayad[2], Victoria Furer[3], Michael Farkouh[2], Michael J. Colin[3], Pamela B. Rosenthal[3], Jonathan Samuels[3], Svetlana Krasnokutsky Samuels[4], Soumya M. Reddy[3], Peter M. Izmirly[3], Cheongeun Oh[3], Manish Jain[3] and Venkatesh Mani[2]. [1]New York University School of Medicine, New York, NY, [2]Mount Sinai School of Medicine, New York, NY, [3]NYU School of Medicine, New York, NY, [4]NYU School of Medicine, New York

Background/Purpose: Rheumatoid arthritis (RA) has been associated with premature atherosclerosis and increased prevalence of cardiovascular disease. 18-fluoro-deoxyglucose positron emission tomography (18-FDG-PET) is a promising imaging technique that has been used previously to evaluate vascular inflammation. Individuals with coronary artery disease (CAD) have been shown to have increased 18-FDG-PET uptake in previous studies. In this study we compare vascular inflammation in individuals with RA with inflammation versus patients with established CAD without underlying autoimmune disease.

Methods: 27 RA patients (aged 35–64)and 70 CAD patients (aged 41–76) without autoimmune disease were recruited as two separate cohorts and underwent PET scans after injection of 10mCi of FDG to measure vascular inflammation. Metrics of PET uptake, the mean, maximum and most diseased segment (MDS) target to background ratios (TBR) were computed

for the aorta and carotid arteries and compared across the two groups. Multivariate regression models were run to adjust for differences in age, gender and BMI between the groups. P-values < 0.05 were considered significant.

Results: The RA cohort had a mean disease duration of 11.3 years and mean DAS28 of 4.6, with 10 (37%) on biologic DMARDs. None of the RA patients had a history of CAD, MI or stroke. The table shows the median +/− standard deviations of the mean, maximum and MDS FDG-PET uptake (TBR values) in the two groups both without and with adjustments for age gender and BMI. For the carotids, no differences were detected in mean, maximum or MDS comparisons in adjusted models. For the aorta, we found that the mean, maximum and MDS TBR values were significantly higher in RA patients than CAD patients in both unadjusted and adjusted analyses.

Table. Comparison of RA Patients versus CAD Patients Target to Background Ratios

Target to Background Ratio (TBR) Measures	RA patients (median ± SD)	CAD Patients (median ±SD)	p-value (unadjusted)	p-value (adjusted)*
Aorta Mean TBR	1.46 ± 0.40	1.25 ± 0.12	**0.003**	**<0.0001**
Aorta Max TBR	2.08 ± 0.57	1.75 ± 0.22	**0.014**	**<0.0001**
Aorta MDS TBR	2.23 ± 0.62	1.87 ± 0.27	**0.015**	**0.0004**
Carotids Mean TBR	1.47 ± 0.19	1.47 ± 0.21	0.261	NS
Carotids Max TBR	1.69 ± 0.25	1.84 ± 0.30	**0.018**	NS
Carotids MDS TBR	1.79 ± 0.25	1.87 ± 0.31	**0.005**	NS

* Adjusted for age, gender and BMI; **bold font** indicates significant differences

Conclusion: Our data indicates that RA patients without known CVD have heightened aortic wall inflammation and similar levels of carotid wall inflammation when compared to CAD patients without autoimmune disease. Increased aortic inflammation might be a mechanism for increased risk for atherosclerosis in RA patients.

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Vulnerability Features Are Common in Coronary Plaques of Asymptomatic Patients with Rheumatoid Arthritis Compared to Controls: Associations with Lipid and Oxidative Stress Biomarkers. George A. Karpouzas[1], Jennifer Malpeso[2], Tae-Young Choi[2], Silvia Munoz[1] and Matthew Budoff[2]. [1]Harbor-UCLA, Torrance, CA, [2]Harbor-UCLA Medical Center, Torrance, CA

Background/Purpose: Computed tomography angiography (CTA) reliably evaluates coronary plaque presence, severity, burden, and composition. CT characteristics of culprit lesions in acute coronary syndromes (ACS) include low attenuation plaques (LAP) consistent with necrotic core, positive remodeling (PR) and spotty calcifications. Increasing numbers of those vulnerability features yields progressively higher risk for future ACS (within 2 years) compared to their absence. We studied 150 asymptomatic, patients with Rheumatoid Arthritis (RA) and an equal number of age and sex-matched controls for plaque vulnerability features using CTA.

Methods: A standard 15-segment American Heart Association model was used for evaluation. Plaque composition was defined as non-calcified (NCP), mixed- partially calcified (MP), or fully calcified (CP). Plaques in both groups were evaluated for all 3 vulnerability features. Fasting lipid assessments, including total Cholesterol (TC), HDL-c, LDL-c, VLDL-c, particle sizes thereof, and apolipoproteins B100 and A1 were completed. Both IgG and IgM antibodies against oxidized LDL in relative light units (RLU), as well as oxidized phospholipids on apoB100 particles were measured as indicators of oxidative stress. Non-parametric ANOVA and Fisher's tests were used as appropriate for comparisons among groups.

Results: In the RA group, 107 (71%) patients had a total of 303 plaques, compared to 68 (45%) in the controls with 135 plaques (p<0.0001). Twenty-four (16%) RA subjects had 41 plaques with ≥1 vulnerable characteristic (VP+) compared to none in the control group (p<0.0001, table); 8 (5.3%) had plaques with≥2, and 6 (4%) had all 3 characteristics. Thirty-one of 84 (37%) MP in RA had ≥1 VP characteristic, compared to 10/156 (6.4%) of NCP (p<0.0001); higher numbers of VP features were only present on MP. In general, VP were moderately sized and 66% rendered <50% luminal stenosis. Subjects with vulnerable plaque features (VP+) had higher Framingham scores, TC/HDL-c (pro-atherogenic index), small particle LDL

(LDL4), and apoB/A1 ratio, compared to those with plaque lacking vulnerability characteristics (VP-), or those without plaque (table).

Parameter	VP (+)	VP (−)	Plaque (−)	p-value
RA-n patients=150	24	83	43	**<0.0001**
Controls-n patients=150	0	68	82	
RA-n plaques=303	41	262	n/a	**<0.0001**
Controls-n plaques=135	0	135	n/a	
Parameters in subjects with RA (mean± SEM)				
Framingham Score	6.3 ± 1.3	3.6 ± 0.5	2 ± 0.5	**<0.0001**
Total Cholesterol (mg/dl)	175.7 ± 8.2	170.2 ± 3.9	161.5 ± 4.8	0.26
HDL-c (mg/dl)	46.7 ± 2.5	53.2 ± 1.5	49.9 ± 2.4	0.07
Total Chol/HDL ratio	3.92 ± 0.21	3.36 ± 0.11	3.43 ± 0.14	**0.026**
HDL2 (md/dl)	12.1 ± 1.2	15.2 ± 0.8	13.5 ± 1.1	0.06
HDL3 (mg/dl)	34.7 ± 1.5	38.1 ± 0.8	36.3 ± 1.4	0.15
LDL-total (mg/dl)	104 ± 6.5	94.6 ± 3.7	92.6 ± 3.6	0.2
LDL1 (mg/dl)	14.2 ± 1.4	13.2 ± 0.8	12.8 ± 0.9	0.7
LDL2 (mg/dl)	21 ± 2.7	21.9 ± 1.4	22.7 ± 1.7	0.7
LDL3 (mg/dl)	37.1 ± 2.8	30.6 ± 1.5	31.4 ± 1.6	0.09
LDL4 (mg/dl)	12.5 ± 1.5	9.1 ± 0.7	8.4 ± 1.1	**0.01**
Triglycerides (mg/dl)	163.4 ± 20.5	142.5 ± 10	144.7 ± 11.9	0.6
VLDL1, 2 (mg/dl)	11.3 ± 1.3	9.9 ± 0.5	9.5 ± 0.5	0.5
VLDL3 (mg/dl)	13.7 ± 0.8	12.7 ± 0.4	11.7 ± 0.4	0.1
ApoB/A1 ratio	0.64 ± 0.03	0.56 ± 0.02	0.59 ± 0.02	**0.045**
OxPL/apoB100 (NanoM PC)	11.4 ± 1.2	11.7 ± 0.5	11.4 ± 0.9	0.7
Ox-MDA-LDL IgG (RLU)	14,366 ± 2,490	11,095 ± 707	10,587 ± 1,011	0.7
Ox-MDA-LDL IgM (RLU)	28,195 ± 2,833	28,082 ± 1,169	27,036 ± 1,365	1

Conclusion: Coronary plaques of asymptomatic patients with RA frequently display vulnerability features, by contrast to controls, and increasing numbers of those segregate preferentially on moderate sized, non-occlusive MP. Their presence associates with higher Framingham scores, pro-atherogenic index, smaller sized oxidation-prone LDL, and apoB/A1 ratios.

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Association of Paraoxonase 1 Gene Polymorphisms and Enzyme Activity with Carotid Plaque in Rheumatoid Arthritis. Christina Charles-Schoeman, Yuen Yin Lee, Veena K. Ranganath, John D. FitzGerald, Mihaela B. Taylor, Maureen A. McMahon, David Elashoff and Srinivasa T. Reddy. University of California, Los Angeles, CA

Background/Purpose: Paraoxonase 1 (PON1) is a high density lipoprotein (HDL) associated enzyme, which promotes the anti-oxidant and anti-inflammatory properties of HDL. PON1 polymorphisms and enzyme activity have previously been associated with cardiovascular (CV) events in the general population. Since abnormal HDL function has been proposed to contribute to CV risk in patients with rheumatoid arthritis (RA), the current work investigated the relationship of genetic and biochemical determinants of PON1 activity with carotid plaque as a surrogate marker of CV risk in RA patients.

Methods: PON1 activity, PON1 genotype (for the functional polymorphism at position 192), and carotid plaque presence were determined in 168 patients with RA. Fasting blood was collected for lipoprotein analysis, and PON1 activity was measured using paraoxon as the substrate. Genotyping for the PON1 Q192R polymorphism (SNP rs662) was done for all patients as described previously (Bhattacharyya et al. *JAMA* 2008). Lipoprotein cholesterol levels were measured by standard methods and traditional cardiovascular risk factors, medication use, and RA disease characteristics were assessed for all patients.

Results: The PON1 genotype demonstrated a significant dose dependent association with PON1 activity (RR192 > QR192 > QQ192) (p<0.001). Compared to patients with either the PON1 QQ192 or QR192 genotype, patients with the RR192 genotype demonstrated decreased risk of carotid plaque in multivariate analysis controlling for traditional CV risk factors, high-sensitivity C-reactive protein levels, prednisone use, and cholesterol lowering medication use (p<0.05). Separate multivariate logistic regression analysis controlling for the above factors also revealed a significant association of plasma PON1 activity with carotid plaque in RA patients. Lower plasma PON1 activity was associated with increased risk of carotid plaque (p <0.05).

Conclusion: The current work suggests a relationship between the genetic determinants and activity of PON1 with cardiovascular risk in RA patients as assessed by the presence or absence of carotid plaque. Further CV outcome studies may be warranted to determine if PON1 is a useful biomarker of CV risk in patients with RA.

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Identifying Vulnerable Plaque in Rheumatoid Arthritis: A Pilot Study Using Novel Microbubble-Contrast Enhanced Carotid Ultrasonography.
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Background/Purpose: Rheumatoid arthritis (RA) is independently associated with a higher risk of cardiovascular disease (CVD). Markers of systemic inflammation, as seen in RA, are associated with plaque vulnerability. Recently, increased vasa vasorum neovascularization has been identified as a common feature of inflammation and plaque vulnerability, and independently predicts future CV events in the non-RA general population. Excess CVD risk in RA may be caused by disease-related factors leading to vulnerable plaque characterized by increased vasa vasorum neovascularization, which is not assessed by traditional imaging modalities. Microbubble contrast-enhanced carotid ultrasound (CU) is a novel imaging technique that has been validated in detecting measures of vulnerable plaque, namely increased adventitial vasa vasorum density (aVVD), in non-RA subjects.

Our objective was to establish feasibility of measuring aVVD in RA patients; to determine whether RA patients have higher aVVD compared to non-RA controls, and whether disease-related RA measures correlate with increased aVVD, using CU.

Methods: We performed a preliminary cross-sectional study of 23 RA cases and 28 non-RA controls; this project is ongoing. All 51 subjects underwent CU with measurement of intima-media thickness (IMT, using maximum of both sides) and the mean common carotid artery adventitial to lumen videointensity ratio (using maximum of both sides) to quantify aVVD. Demographic and CV risk factor data were collected on all subjects, and tested for differences between cases and controls, using the Wilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data. RA disease activity measures (CDAI and DAS28), erythrocyte sedimentation rate, high sensitivity C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (CCP), were collected systematically on RA subjects. Spearman correlations were assessed between disease activity measures and aVVD and IMT within RA cases.

Results: Demographic and CV risk factors between RA and controls were similar, except for mean age (58.0 years in RA, 66.1 years in controls; p<0.01); systolic blood pressure (138 in RA, 120 in controls; p<0.01); and race (91.3% white in RA, 64.3% white in controls; p=0.02). We successfully measured aVVD, which was higher in RA (mean=0.634; SD=0.097) versus controls (mean=0.595; SD=0.112), although so far non-significantly (p=0.31). IMT was also higher, although again non-significantly so far (p=0.65), in RA (mean = 0.85; SD=0.28) versus controls (mean=0.80; SD=0.18). After adjusting for age and personal history of CVD, results did not qualitatively change. As expected, CRP, RF and CCP were all significantly higher in RA than controls (p<0.001). No correlations between disease activity measures with aVVD and IMT were significant.

Conclusion: Measurement of aVVD to quantify plaque vulnerability in RA patients is feasible utilizing the novel CU technique. In this pilot study, the aVVD was slightly higher in RA than control subjects, though not significantly. Our study is ongoing, with plans for targeted enrollment of larger numbers of subjects and further adjustment for differences in demographic and CV risk factors.

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In Treatment-Naive Early RA the Left Ventricular Function Is Correlated to CRP, Doctors Global and Anti-CCP Status.
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Background/Purpose: The role of inflammation and anti-CCP status in the pathogenesis of cardiovascular disease in RA remains unclear. Previous studies have suggested that both disease activities as well as disease duration are associated with atherosclerosis and a higher mortality rate caused by coronary artery disease.

We wanted to investigate how disease activity and anti-CCP status in treatment-naive early RA impacts the left ventricular (LV) systolic function.

Methods: 41 patients (18 men, median age 60 range (28–81)) with steroid and DMARD-naive early RA. Disease activity was scored by the use of the Danish national DANBIO registry (number of swollen joints (NSJ) (28), number of tender joints (NTJ) (28), CRP, HAQ. Visual analog scales 1–100 was used to assess pain, fatigue and global assessment by the patient as well as global assessment by doctor and as composite score DAS28(CRP)). IgMRF and anti-CCP titers were evaluated by standardized techniques. One experienced senior rheumatologist and one experienced cardiologist performed all the clinical assessments as well as all the transthoracical echocardiography (TTE). We performed an extensively TTE measuring conventional measurements of LV systolic function including the novel technology, global longitudinal strain (GLS) analysis.

Results: Disease activity before treatment at baseline NSJ(28) median 7 range (1–16), NTJ(28) 8 (1–15), CRP 9 mg/l (0–42), HAQ 2.625 (0.5–2.625), pain VAS 54 (7–100), fatigue VAS 48 (2–100), doctor global assessment 55 (28–79), DAS28(CRP) 4.7 (3.3–6.2), pulse 65 (50–87), diastolic blood pressure (BP) 88 mmHg (66–158), systolic BP 147 mmHg (78–158). 18 (43.9%) patients was IgMRF positive and 26(63.4%) was anti-CCP positive.

We found LV systolic function by conventional Ejection Fraction (EF), median 52% (24–74), non-significant correlated to disease activity (CRP: r= 0.19, p=0.23; baseline NSJ: r=-0.11, p=0.5; NTJ: r=-0.04, p=0.81; HAQ: r=0.27, p=0.1; pain VAS: r=-0.1, p=0.53; fatigue VAS: r=0.1, p=0.56; doctor global assessment: r=-0.07, p=0.67 and DAS28: r=0.03, p=0.86). However using a more sensitive measurement of the longitudinal systolic LV function (s') we found a significant correlation, in means of CRP (r=0.40; p=0.015) and doctor global assessment VAS (r=0.47; p=0.003), to disease activity; both corrected for relevant confounders (age, gender, pulse and blood pressure). Furthermore using strain analysis of LV function we found a significant difference in global LV GLS values in 11(26.8%) patients with high values of anti-CCP (values ≥ 340 (GLS: −18.7% (−20.6–14.4)) vs. in 30(73.2%) patients with anti-CCP <340; p=0.04. For patients with high IgMRF the result was non-significant.

Conclusion: We observed a significant correlation between increasing CRP, doctors global, anti-CCP anti-CCP <340 and increased longitudinal LV systolic function.

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Vascular Calcification On Hand and Feet X-Rays, VFA Imaging of the Spine, and Cardiovascular Disease in Rheumatoid Arthritis.
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Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of osteoporosis (OP) and cardiovascular disease (CVD), and have increased cardiovascular mortality compared with the general population. Vascular calcification (VC) is independent predictor of incident CVD and mortality in RA patients. While VC may be present on plain films of the hands and feet, little is known about the significance of this entity in RA patients. We evaluated the prevalence of VC on hands and feet radiographs, the association with VFA-detected abdominal aortic calcification (AAC) and other CVD risk factors, and the prevalence of CVD in RA patients.

Methods: We conducted a cross-sectional study on our RA subjects ≥40 years of age, who met 1987 ACR criteria for RA classification, and had hands and feet radiographs available for analysis. Risk factors and details of CVD were recorded, and DXA and VFA scans were reviewed where available. Study was approved by local I.R.B. Two blinded musculoskeletal radiologists examined all radiographs for the presence of VC as either "present" or "absent", and VFA scans to detect and quantify the presence of AAC. We compared the prevalence of VC between RA patients with and without CVD using multivariable logistic regression, and determined if VC on hands and feet radiographs was independently associated with VFA-detected AAC and prevalent CVD.

Results: 854 RA patients met the inclusion criteria, 603 of whom also had a VFA scan available for analysis: 69% female mean age 59 years and 77% seropositive (Table 1). 230 subjects had ≥1 documented CVD event. VC was observed on radiographs in 94(11%) and a higher proportion of subjects had prevalent CVD (49% Vs 24%). Of the 603 who had a VFA scan available, 211(35%) of the subjects had AAC. A greater proportion of those with VC on plain films had AAC on VFA (36% Vs 23%). In multivariable analyses, VC presence was significantly and independently associated with AAC (OR 1.80; 95% CI 1.55 to 1.98; p< 0.05) and prevalent CVD (OR 2.30; 95% CI 1.8 to 2.8; p<0.05).

Table 1. Demographics and Clinical Features of 854 RA Patients According to the Presence of VC on Hand and Feet X-rays

Variables	VC positive (n = 94)	VC negative (n = 760)	p Value
Age (years)	59 ± 12.74	56 ± 9.67	0.012
Women–n (%)	65 (69)	525 (69)	0.890
Smokers–n (%)	60 (64)	396 (52)	0.003
RA duration (years)	15 ± 9	13 ± 6	0.006
Family history of CVD–n (%)	39 (41)	200 (26)	0.003
Diabetes–n (%)	15 (16)	112 (15)	0.540
Dyslipidemia–n (%)	41 (43)	260 (34)	0.003
Prevalent CVD	46 (49)	184 (24)	<0.001
Hypertension–n (%)	45 (48)	167 (22)	<0.001
Glucocorticoid use–n (%)	23 (24)	120 (16)	0.017
RF positive–n (%)	69 (73)	590 (78)	0.021
Anti-CCP positive–n (%)	71 (76)	540 (71)	0.013
C-reactive protein (mg/l)	5.50 ± 3.52	3.31 ± 1.86	<0.001
DAS28, mean ± SD	2.98 ± 0.90	1.92 ± 0.86	<0.001
AAC on VFA–n (%)	34 (36)	177 (23)	0.034

Conclusion: We found a significant association between VC on hands and feet radiographs and abdominal aortic calcification and CVD in our RA cohort. The presence of VC should alert physicians to the presence of CVD in patients with RA.

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High Inflammation May Condition the Antiatherogenic Function of Small, Dense HDL in Patients with Active Rheumatoid Arthritis. Carla Saucedo[1], Leonardo gomez Rosso[2], Tomas Meroño[2], Fernando Brites[2], Anatol Kontush[3], Luis J. Catoggio[1], Enrique Soriano[4], Laurent Camont[5], Marie Lhomme[5], Veronica Malah[6], Patricia Sorroche[7], Sandrine Chantepie[5], Paul Robillard[8] and John Chapman[5]. [1]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Laboratory of Lipids and Lipoproteins, School of Pharmacy and Biochemistry, Buenos Aires, Argentina, [3]Université Pierre et Marie Curie-Paris, Paris, France, [4]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [5]Université Pierre et Marie Curie, Paris, France, [6]Rheumatology section, Hospital de Clínicas "José de San Martín", Buenos Aires, Argentina, [7]Central Laboratory, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [8]Université Pierre et Marie Curie, Paris, Argentina

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased mortality, mainly due to cardiovascular disease. High grade inflammation might drive to premature atherosclerosis. High-density lipoprotein (HDL) possesses multiple biological activities, including antioxidative actions. Small, dense HDL3c particles exert potent antiatherogenic activities, which can be compromised under conditions of chronic inflammation. It remains indeterminate as to whether the level of such functional HDL deficiency is related to the degree of inflammation. Our objective was to evaluate HDL antioxidative function in normolipidemic RA active patients and controls.

Methods: serum from normolipidemic female patients with active RA (DAS28 >3.2; n=12) and normolipidemic age-matched female controls (n=10) was analized. Plasma levels of total cholesterol (TC), triglycerides (TG), HDL, LDL, apo-A, apo-B, plasma C-reactive protein (PCR), and serum amyloid A (SAA), subfractions of LDL and HDL were obtained. Small, dense HDL3b and 3c particles were isolated by density gradient ultracentrifugation. The capacity to protect LDL from oxidative stress induced by free radicals was assessed in small, dense HDL3b and HDL3c subpopulations, and in total HDL.

Results: sera from 12 active female RA patients and 10 age-matched female controls were analized. No significant differences were observed in plasma levels of TC, TG, LDL, HDL, apo-A and apo-B. Active RA patients exhibited a wide range of plasma C-reactive protein (CRP) levels, which were elevated relative to controls (8.4 mg/l, CI 3.5–11.4 vs. 0.47 mg/l, CI 0.30–0.89, p<0.001). Antioxidative activity and total chemical composition of small, dense HDL did not differ between RA patients and controls (p>0.05). Nonetheless, subgroup analyses revealed that RA patients featuring high levels of inflammation (CRP>10mg/l) possessed small, dense HDL with reduced antioxidative activities (up to −23%, p<0.01). Furthermore, antioxidative activity of HDL was inversely correlated with plasma CRP and SAA levels. HDL3b and 3c were depleted of free cholesterol (FC) in high-inflammated RA patients. This FC depleted HDL particles were less efficient in preventing LDL oxidation.

Conclusion: only RA patients who displayed high circulating levels of inflammatory biomarkers (CRP and SAA) possessed small, dense HDL3 particles with reduced antioxidative activity. This reduction in antioxidative action of HDL3 particles, along with reduced capacity of HDL to promote cholesterol efflux, and depletion of free cholesterol in HDL, may enhance development of atherosclerosis in active RA patients. These pathophysiological features are intimately linked to the inflammatory state, supporting that uncontrolled chronic inflammation leads to increased cardiovascular risk.

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Subclinical Atherosclerosis in Hispanic Patients with Rheumatoid Arthritis. Correlation with the Presence of Anti-Oxidized LDL Antibodies and Serum Levels of CD40L. Yurilis Fuentes-Silva[1], Soham Al Snih[2], Natali Serra-Bonett[1], Juan De Sanctis[3] and Martin A. Rodriguez[4]. [1]Centro Nacional de Enfermedades Reumáticas, Caracas, Venezuela, [2]University of Texas Medical Branch, Galveston, TX, [3]Instituto de Inmunología, Caracas, Venezuela, [4]Hospital Universitario de Caracas, Caracas, Venezuela

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease, associated with an excess of cardiovascular morbidity and mortality due to accelerated atherosclerosis. The appearance of antibodies (Abs) against anti-oxLDL may be a pathogenic link between inflammation and atherosclerosis. An excessive CD40L/CD40 interaction is thought to play a pathogenic role in RA. The aim of this study was to search for the presence of subclinical atherosclerosis in a group of Venezuelan patients with RA and examine its correlation with anti-oxLDL Abs and serum levels of CD40L.

Methods: Sixty-five RA patients and 26 healthy volunteers participated in the study. The presence and total serum levels of anti-oxLDL Abs and CD40L were examined by ELISA. The biologically active CD40L was measured by an assay testing induction of nitric oxide production in vitro by RAW mouse 264.7 cells. The presence of subclinical atherosclerosis was detected by the measurement of intima-media-thickness (IMT) of the common carotid arteries using a Doppler ultrasound system (Esaote MyLab, 12 Mhz). Subclinical atherosclerosis was defined by an IMT ≥ 0.6 mm. Statistical analysis was performed by Student's t test and Chi-square and the Exact Fisher's test for continuous and dichotomous variables, respectively. The study was approved by our hospital Ethics Committee and all patients signed an informed consent.

Results: We compared 65 RA patients (92.3% female; mean age 50,58±8,96) with 26 healthy controls (96.15% female; mean age 43.42±9.62). DMARDs and DMARDs plus biologics were received by 98.46% and 18.46% of patients, respectively. Mean disease duration was 7.32±6.04 years and mean and Disease Activity Score (DAS) 28-ESR was 3.19±1.5. Serum levels of anti-oxLDL were significantly higher in the RA patients than in healthy controls (34.48±9.83 vs. 24.74±6.4; P= 0,01). Serum levels of total CD40L and biologically active CD40L were also significantly higher in RA patients than in controls (9.13±2.74 vs. 3.86±1.21; P < 0,0001 and 3.81±1.94 vs. 1.6±1.11; P = 0,002). Patients with RA showed a higher proportion of an IMT ≥ 0.6 mm (P = 0,006). There was no correlation between serum levels of anti-oxLDL or CD40L with IMT.

Conclusion: To our knowledge this is the first study showing the presence of subclinical atherosclerosis in Hispanic patients with RA. Elevated serum titers of anti-oxLDL Abs and both total and soluble CD40L were features observed in this patient population suggesting their potential utility as biomarkers in this disease. Our preliminary results do not support a role for anti-oxLDL Abs or CD40L in the premature atherosclerosis observed in RA patients.

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Association Between Low Vitamin D Levels and Indicators of Osteoporosis and Atherosclerosis.
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Background/Purpose: Osteoporosis and cardiovascular disease are complications of chronic rheumatoid arthritis (RA). It is not known if these processes share pathogenetic mechanisms. Low levels of vitamin D predispose to bone fragility. Recent data suggest that they may also be linked to vascular disease.

Methods: A cross-sectional study of RA patients and age-/sex-matched controls was carried out. None had any history of cardiovascular disease or diabetes mellitus. Levels of 25-hydroxy vitamin D were recorded and DXA scans were performed. Evidence of sub-clinical atherosclerosis was obtained with pulse wave analysis (PWA) and carotid intimal-medial thickness (CIMT). Serum markers of vascular disease (ICAM1, oxidized LDL, HSP60, IL6), a lipid profile and body mass index (BMI) were measured. Early RA was defined as those with disease duration less than 2 years. Data were analysed using SPSS 16.0.

Results: 99 people were included in this study (74 RA and 25 controls). Fifty-two (70%) of the RA group and 8 (31%) of the control group were taking calcium/vitamin D supplements (average vitamin D level 400iu/day). Only 12 (13%) had normal vitamin D levels (>80nmol/l). Vitamin D levels were deficient (<25nmol/l) in 21% and insufficient (>25 <80nmol/l) in 65%. All patients with early RA were vitamin D deplete (n = 18); 33% had insufficient levels and 67% deficient amounts. In contrast, 20% (n = 11) of those with established RA had normal vitamin D levels, while 65% had insufficient and 15% deficient levels. Mean vitamin D measurements were 38.5nmol/l in early RA versus 58nmol/l in established RA (p = 0.02).

Bone mineral density was similar between RA and controls. In the RA cohort, 29% had evidence of osteoporosis, while 46% had osteopenia and 25% had a normal DXA scan. In those with early RA, osteoporosis was present in 3 (18%) versus 16 (32%) patients with chronic RA (p = 0.3)

In RA, there was a negative correlation between vitamin D levels and DXA T-scores (p = 0.02), and BMI (p = 0.007). While RA patients had significantly greater levels of serum markers of vascular disease (IL6, ICAM1, oxidized LDL, HSP60) compared with controls, there was no correlation with vitamin D levels. CIMT measurements correlated negatively with vitamin D (p=0.06). Using multiple linear regression controlling for age, CIMT and DXA T-scores, and calcium/vitamin D supplements, vitamin D levels were negatively correlated with PWV (p=0.04), across the entire study group. Triglyceride levels were inversely related to vitamin D across the study group (cc −0.3, p<0.01).

Conclusion: Low levels of vitamin D were common in this population, particularly in those with early RA. Vitamin D supplementation at current dosages does not achieve normal vitamin D levels. The association between low vitamin D levels and markers of both osteoporosis and atherosclerosis needs to be further explored. In particular, a lack of sunlight in relation to insufficient exercise exposure may be relevant in exploring this link.

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Association Between Subclinical Atherosclerosis and Bone Mineral Density in Rheumatoid Arthritis.
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Background/Purpose: Rheumatoid arthritis (RA) is associated with a higher risk of osteoporosis (OP) and cardiovascular disease (CVD). This cross-sectional study was undertaken to identify links between the subclinical evidence of these processes.

Methods: RA patients without known cardiovascular disease or diabetes were included. Measures of osteoporosis risk (DXA, bone turnover markers) and sub-clinical atherosclerosis (pulse wave analysis, carotid intimal-medial thickness (CIMT)) were recorded in addition to serum markers of systemic inflammation and lipid profiles. Data were analysed using SPSS 16.0 for Windows.

Results: Seventy four RA patients and 26 controls were included in the analysis. Gender and age were similar between RA and controls and between sub-groups of RA duration. The RA group had significantly higher oxidized LDL titres (p<0.001), interleukin-6 (p<0.001), heat shock protein (HSP) 60 (p=0.008), and soluble ICAM-1 (p=0.016) compared with controls. HDL levels were significantly lower in those with RA for <10 years (p=0.026), while LDL (p = 0.014) and HSP60 levels (p = 0.024) were higher. Levels of vitamin D (p = 0.008), TNFα (0.016) and P1NP, a marker of bone formation (p = 0.03), were higher in those with long-standing RA.

In RA, femur T-scores were inversely related to mean CIMT (cc −0.3, p=0.02), mean common carotid artery IMT (cc −0.3, p=0.02), aortic augmentation index (AAIx) (cc −0.3, p=0.01), CRP (cc −0.4, p=0.002), oxLDL (cc −0.3, p=0.01) and anti-CCP antibody titre (cc −0.25, p=0.046). T-scores for the spine were also negatively correlated with AAIx (cc −0.4, p<0.001), anti-CCP antibody (cc −0.3, p=0.03), and oxLDL (cc −0.25, p=0.04). For those with osteoporosis, oxLDL was significantly higher compared to those with normal bone density (p=0.016). However, femur T-scores correlated positively with BMI (cc 0.5, p<0.001), waist (cc 0.4, p=0.002) and hip (cc 0.6, p<0.001) circumference, total fat mass (cc 0.4, p=0.01) and trunk fat mass (cc 0.4, p=0.02). T-scores for the spine also correlated with BMI (cc 0.3, p=0.008), waist (cc 0.4, p=0.002) and hip (cc 0.3, p=0.03) circumference.

Conclusion: Disease duration in RA correlated significantly with risk factors for atherosclerosis, independent of age. Furthermore, reduced bone mineral density was associated with evidence of sub-clinical atherosclerosis. These results suggest that early recognition of such complications may help to improve quality of life and longevity in patients with RA.

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Hydroxychloroquine Reduces the Risk of Coronary Artery Disease in Patients with Rheumatoid Arthritis.
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Background/Purpose: Disease modifying anti-rheumatic drugs (DMARDs) can alter cardiovascular risk in RA by inflammation or by influencing cardiovascular risk factors indirectly. However, previous studies predominantly focused on methotrexate(MTX) and ignore the other major conventional DMARDs, such as hydroxychloroquine (HCQ).To assess the complication of coronary artery disease (CAD) and identify the risk factors of CAD in a large population of RA in China.

Methods: One thousand and ninety-six patients were enrolled in the study. Data were obtained from a retrospective survey of patients with RA, randomly selected from rheumatology practice of 21 university hospitals in China. The patients' social conditions, clinical conditions, medications associated with RA such as DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoid, biologic agents were collected. The χ^2test was used to compare the frequency of CAD risk factor, manifestations and medications of RA. Logistic regression modeling was used to examine the influence of risk factors on the development of CAD outcomes.

Results: Of the 1096 patients 34 developed CAD with a incidence of 3.1%. Compared to the control group, the CAD group patients had higher age (64.8±9.3yrs *vs* 52.0±14.1yrs, *P*=0.000), longer disease duration (13.3±11.4yrs *vs* 8.0±8.9yrs, *P*= 0.011), higher prevalence of diabetes

mellitus (29.4% *vs* 7.0%, *P*=0.000), hypertension (38.2% *vs* 16.2%, *P*=0.001), rheumatoid nodules (14.7% *vs* 2.7%, *P*=0.003) and lung interstitial disease (17.6% *vs* 7.0%, *P*=0.023). Patients with CAD were less likely to use hydroxychloroquine (HCQ)(5.9% *vs* 20.3%, *P*=0.038). Multivariate analysis showed higher age and rheumatoid nodules were independent predictors of CAD and HCQ was a protective factor of CAD.

Conclusion: CAD is a major concern for RA patients. HCQ reduces the risk of CAD in RA patients, higher age and rheumatoid nodules are independent risk factors for CAD in RA.

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Epicardial Adipose Tissue Is Associated with Cardiometabolic Risk and the Metabolic Syndrome in Patients with Rheumatoid Arthritis. Michelle J. Ormseth[1], Aliza Lipson[2], Nikolaos Alexopoulos[2], Gregory R. Hartlage[2], Annette M. Oeser[1], Aihua Bian[1], Tebeb Gebretsadik[1], Ayumi Shintani[1], Paolo Raggi[2] and C. Michael Stein[1]. [1]Vanderbilt Medical Center, Nashville, TN, [2]Emory University, Atlanta, GA

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased coronary atherosclerosis and this may be related to their increased prevalence of visceral adiposity, insulin resistance, and metabolic syndrome. Epicardial adipose tissue (EAT), a type of visceral fat, may contribute to insulin resistance, and through local paracrine effects, to coronary atherosclerosis. We measured EAT volume in patients with RA (n=162) and a matched control group (n=89) to define the relationship between EAT and markers of cardiometabolic risk in RA.

Methods: Clinical characteristics, inflammatory cytokines, lipids, fasting insulin and glucose, and homocysteine were measured. The homeostatic model of insulin resistance (HOMA) was calculated as a measure of insulin resistance and presence of metabolic syndrome defined by the National Cholesterol Education Program Adult Treatment Panel III criteria. EAT volume and coronary artery calcium score were measured by non-contrast cardiac computed tomography. EAT volume was compared in RA patients and controls, and the relationships between EAT volume and markers of cardiometabolic risk in RA defined.

Results: EAT volume was 108.2 cm^3 [77–144.6] (median [IQR]) in patients with RA and 93.9 cm^3 [69.9–133.1] in controls (P=0.06). RA patients with metabolic syndrome had significantly higher EAT volume than those without (P<0.001) and each increase in metabolic syndrome criteria count was associated with a 20% increase (95% CI, 14–26%) in EAT volume (p<0.001) independent of age, race and sex. Among RA patients, EAT volume was positively associated with IL-6 (P=0.03), triglycerides (P=0.004), presence of hypertension (P=0.01), HOMA (P<0.001), smoking history (P=0.04), and homocysteine (P=0.001) and negatively associated with HDL (P=0.005) after adjustment for age, race and sex. However, there was no significant association between EAT volume and current use and cumulative dose of corticosteroids (P=0.72 and P=0.90, respectively) or coronary artery calcium score (P=0.24), after adjustment for age, race and sex. With further adjustment for waist circumference as a measure of visceral obesity, EAT was independently positively associated with triglycerides, HOMA, current smoking and homocysteine (all P<0.05).

Conclusion: In patients with RA, EAT volume is associated with metabolic syndrome and independently associated with cardiometabolic risk factors including: insulin resistance, triglycerides, current smoking, and homocysteine levels, but not with coronary artery calcium.

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Rheumatoid Arthritis Patients with Higher Disease Severity and Subclinical Carotid Plaque Experience More Cardiovascular Events Despite a Favorable Conventional Cadiovascular Risk Profiles. Yeon-Ah Lee[1], Somi Kim[1], Sang-Hoon Lee[2], Ran Song[2], Hyung In Yang[2] and Seung-Jae Hong[1]. [1]Kyung Hee University, Seoul, South Korea, [2]Hospital at GANG-DONG, Kyung Hee University, Seoul, South Korea

Background/Purpose: It has been shown that patients with rheumatoid arthritis (RA) experience cardiovascular (CV) events more often than expected. Increased risks of CV diseases in RA patients cannot be fully explained by conventional CV risk factors. This raises the possibility that the systemic inflammatory burden in RA may bring about its high CV event rate by causing accelerated atherosclerosis. This study was designed to evaluate the extent of subclinical atherosclerosis by measuring intima-media thickness of the carotid arteries (C-IMT) and the presence of plaque among RA patients and controls and to determine whether subclinical atherosclerosis, RA associated features, and other conventional CV risk factors are associated with later development of CV diseases (CVDs) in RA patients.

Methods: C-IMT was measured in 126 RA patients and 85 OA patients as controls who had no experience of CV events. The C-IMT was evaluated at common carotid arteries (CCAs), carotid bifurcation (BF) and internal carotid arteries (ICAs), bilaterally. Mean and maximal (max) IMTs were calculated from three measurements at each site. The following data were obtained for every patient: age, sex, body mass index (BMI), presence of bone erosions, rheumatoid factor, anti-CCP, medications, hypertension, hypercholesterolemia, diabetes mellitus, smoking status, family history of CVDs, ESR and CRP levels. Thereafter, these patients have been followed-up and examined the CV event rate during seven years. The CVD was defined as myocardial infarction, unstable angina, cardiac arrest, or death due to ischemic heart diseases.

Results: Although CV risks were fewer in RA than in OA, the mean and max C-IMT did not show a significant difference between two diseases groups. We found the higher presence of carotid plaques in RA patients than in OA patients. During follow-up, 21 patients experienced CV events. The incidence of CV events was higher in RA than OA (15.0% vs. 3.5%, p=0.004). But, the conventional CV risk factors such as DM, hypertension and high BMI were fewer in RA than in OA (10.3%, 27.7%, 34.1% vs. 28.2%, 55.2%, 57.6%, p=0.000). More CV events occurred in RA patients who initially showed the presence of subclinical plaques. The duration of CV event-free survival was shorter in RA patients with carotid plaque than those without (10 vs. 31 months, p=0.051). The RA patients who developed CVD later had more bony erosions, higher positivity for rheumatoid factor or anti-CCP, higher doses of steroid and higher levels of ESR and CRP, than those who did not.

Conclusion: Despite a favorable conventional CV risk profile, RA patients had a significantly higher incidence rate of CVD than OA patients. RA itself was an independent risk factor for CVD. Especially, RA patients with carotid plaque, seropositivity, bony erosion, higher ESR and CRP are at higher risk of CVD.

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Carotid Arterial Wall Inflammation Is Associated with a Specific Profile of Inflammatory Biomarkers and Anti-Citrullinated Protein Antibodies in Rheumatoid Arthritis Patients. Caroline Grönwall[1], Gregg Silverman[1], Zahi Fayad[2], Venkatesh Mani[2], Victoria Furer[1], Michael Farkouh[2], Manish Jain[1], Cheongeun Oh[1], John Todd[3], Mukundan Attur[4], Steven B. Abramson[4] and Jeffrey D. Greenberg[5]. [1]NYU School of Medicine, New York, NY, [2]Mount Sinai Hospital, New York, NY, [3]Singulex, Alameda, California, Alameda, CA, [4]NYU Hospital for Joint Diseases, New York, NY, [5]New York University School of Medicine, New York, NY

Background/Purpose: Patients with RA are at increased risk of cardiovascular (CV) comorbidity and premature mortality. While generally attributed to accelerated atherosclerosis, the pathogenesis remains poorly understood.

Methods: To investigate cardiovascular disease in RA, we measured carotid and aortic wall inflammation by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) uptake and vessel wall morphology by MRI in a cross-sectional study (N=30 pts). We calculated Mean and Maximum Target to Background Ratio (TBR) values as measures of arterial wall inflammation. Left and right carotid TBRs were combined as mean carotid values. Inflammation-related serum analytes were measured by commercial ELISA (sRAGE), and with a custom plasma panel for inflammation-related proteins, including cytokines, matrix metalloproteinases (MMPs), MMP inhibitors and trophic factors (Singulex Inc.). High-sensitivity cardiac troponin I (cTn-I) was also measured (Singulex Inc) as a marker of myocardial injury. IgG antibodies to citrullinated (cit) peptides from fibrinogen (Fib), histone 2A, filaggrin, a-enolase, and vimentin were determined by quantitative ELISA, and CCP3 using a commercial clinical assay (Inova

Diagnostics Inc.). Protein peptide-specific ACPA assays were validated with a panel of sera from RA, OA and healthy individuals.

Results: The mean age was 51.2 years, mean DAS28 score 6.7 (range 2.2–6.7), 80% female and 11(36%) were on biologic DMARDs. Carotid Max TBR was associated with higher levels of cTn-I ($r=0.566$, $p=0.01$), indicating an association of carotid wall inflammation with subclinical myocardial injury. Of the 15 inflammatory biomarkers assessed, carotid max TBR values was associated with elevations of sRAGE, VEGF, MMP8, proMMP9 and IL-1b. **(Table 1)**. Similar results were obtained for carotid mean TBR. Strikingly, there was a strong correlation between carotid max TBR and cit-Fib IgG ($R=0.72$, $p=0.0005$). Furthermore, patients with a positive Cit-Fib IgG test ($n=10$) had higher levels of carotid wall inflammation [max TBR (p-0.04), mean TBR ($p=0.03$)] than Cit-Fib IgG negative pts. No correlation was found between carotid TBR values and levels of IgG CCP3. Neither IgG antibodies nor any of the inflammatory biomarkers correlated with aorta TBR measures. By MRI, we found significant correlations between wall thickness and ACPA IgGs specific for citrullinated fibrinogen, filaggrin, and enolase, as well as plasma hsCRP and pMMP9.levels ($p<0.05$).

Table. Associations of carotid wall inflammation (max TBR) and biomarkers

Biomarker	Spearman (r)	P-value
cTn-I	0.57	0.01
sRAGE	0.43	0.07
VEGF	0.59	0.008
MMP8	0.62	0.004
pMMP9	0.58	0.008
IL1β	0.48	0.03
IgG anti-Cit-Fib	0.72	0.0005

Conclusion: These FDG-PET studies indicate that a subset of RA patients exhibit inflammatory carotid artery disease. Carotid inflammation was associated with elevations of a distinct profile of innate inflammatory markers and citrullinated self-protein-specific IgG. These data may provide insights into the immunopathogenesis of RA-associated CV disease.

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Vascular Age in Rheumatoid Arthritis Patients. Jl Rosales-Alexander. César Magro Checa, Juan Salvatierra, Silvia Montes García, Jesús Cantero Hinojosa and Enrique Raya Álvarez, University Hospital San Cecilio, Granada, Spain

Background/Purpose: The European League Against Rheumatism (EULAR) recommends cardiovascular risk (CV) assessment using the systematic coronary risk evaluation (SCORE) chart in rheumatoid arthritis (RA) patients. However, the absolute 10 years CV risk is a statistical and epidemiological concept that could be difficult to understand by our patients, resulting in a lack of adherence to treatment. The Framinghan heart study (FHS) incorporated the concept of vascular age, as the age of the arteries, a concept more easily understood by all patients. Recently, a calibrated vascular age chart (VAC) according to the SCORE scales was published for european people.

Objectives: To assess vascular age (VA) in RA patients without CV risk factors/previous ischemic events using the VAC comparing it with healthy controls. To assess the correlation of several clinical and serological variables with VA.

Methods: We included 101 consecutive RA patients, according to the 1987 ACR classification criteria, without CV risk factors neither previous ischemic events and matched to 98 healthy controls according to sex, age and gender. We recorded demographic data, clinical and laboratory parameters of disease activity like ESR, CRP, tender and swollen joint counts, DAS28, patient global assessment by visual analogue scale, lipid profile and RA characteristics. We assessed VA using the VAC. Data was analyzed with the statistical software SPSS 15. Descriptive data were shown as percentages and mean±SD. To analyze data, we use simple lineal regression test with correlation and the multiple lineal regression analysis. The limit of statistical significance was located in the α error of 0,05.

Results: In RA patients, the median chronologic age (CA) was 53,83±8,28 years, VA was 56,67±9,84 and absolute CV risk was 1,43±1,1. Of these patients, 20% fulfilled EULAR criteria for higher CV risk (20% had more than 10 years of disease, 9% had extra articular manifestations, 77% were positive RF and 48% had ACPA). In controls, CA was 53,52±8,37, VA

was 55,78±9,82 and absolute CV risk was 1,1±1. After applying lineal regression test, VA was correlated with CA (beta 1.096, $p=0.000$); however, there were not differences in VA between both groups (beta −0.62, $p=0,232$). Of interest, after adjusting for confounding factors, VA seem to be correlated with presence anti-citrullinated peptide antibodies (ACPA) $p<0,021$.

Conclusion: In our study we did not find differences between VA in RA patients without CV risk factors in comparison to healthy controls, but we found a well correlation between VA and the CA. Presence of ACPA seems to predict higher vascular age.

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Lipoprotein Subclass Particles and Small Vessel Elasticity As a Potential Marker for Early Atherosclerosis in Rheumatoid Arthritis: a Prospective, Controlled Study. Marty T. Mertens[1] and Elie Gertner[2]. [1]University of Minnesota, Minneapolis, MN, [2]Regions Hospital and University of Minnesota Medical School, St. Paul, MN

Background/Purpose: Rheumatoid arthritis (RA) has increased rates of cardiovascular (CV) events. However, standard CV risk factors, such as routine lipid profiles, are not different in RA patients. It is still unclear how to best evaluate CV risk in RA.

Lipoprotein subclass determination differentiates lipoproteins by size and density. Small, dense LDL particles have been associated with an increased risk of CV disease in a number of population studies. Recently, small, dense HDL particles have been shown to be potentially anti-atherogenic. In RA, lipoprotein subclasses have been evaluated in three studies with conflicting results. No studies have prospectively evaluated lipoprotein subclasses in RA. Further, no studies have attempted to correlate these findings with a marker of endothelial function.

In this study, we evaluated lipoprotein subclasses and small arterial elasticity (SAE) in patients with RA over a 12 month period in comparison to healthy controls. SAE is a marker for vascular function and reduction in SAE is predictive of development of atherosclerosis.

Methods: Thirty-five seropositive RA and thirty-one control subjects without a history of coronary artery disease, diabetes mellitus, or active statin therapy were recruited. DAS28-CRP was measured as a marker for disease activity. Lipoprotein subclass concentrations were measured by nuclear magnetic resonance spectroscopy. SAE was measured from pulse-wave analysis by radial artery tonometry. After 12 months, the RA group underwent repeat DAS28-CRP, lipoprotein subclass determination, and SAE evaluations.

Results:

1. There was no significant difference between the RA and control groups in small arterial elasticity.
2. The RA group had significantly lower total LDL and lower small LDL particle concentration as compared to the control group.
3. Average HDL size was significantly larger in the RA group compared to controls.
4. Within the RA group, there was a statistically significant correlation of increased DAS28-CRP with a lesser number of small HDL particles ($R = -0.07$, $p = 0.047$). No significant correlations were seen between changes in DAS28-CRP with small LDL particles or HDL size. Changes in small LDL, small HDL particles, HDL size and DAS28-CRP did not correlate with changes in SAE.

	Rheumatoid Arthritis (SD) N = 35	Controls (SD) N = 31	p-value
Small Arterial Elasticity (ml/mmHg ×100)	5.90 (2.74)	6.48 (2.68)	0.42
Total LDL (nmol/L)	1008 (317)	1210 (389)	**0.028**
Small LDL (nmol/L)	504 (308)	753 (445)	**0.012**
LDL size (nm)	21.4 (0.7)	21.1 (0.8)	0.085
Total HDL (nmol/L)	32.5 (5.4)	33.3 (5.3)	0.57
Small HDL (nmol/L)	18.5 (5.2)	19.6 (5.9)	0.38
HDL size (nm)	9.3 (0.4)	9.1 (0.5)	**0.039**

Conclusion:

1. In the RA group, there was lower total LDL and lower small LDL particle concentration as compared to controls. HDL size was significantly larger in the RA group as compared to controls.

2. Within the RA group, increased disease activity significantly correlated with a reduced number of small HDL particles.
3. Small arterial elasticity did not differentiate RA from controls in assessing potential cardiovascular risk. SAE was not affected by changes in lipoprotein subclasses.

Alterations in LDL subclass populations may not account for the increased cardiovascular risk seen in RA. However, reduction in the potentially anti-atherogenic small HDL particles may be a potential factor.

Disclosure: **M. T. Mertens**, None; **E. Gertner**, None.

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Evaluation of Metabolic Syndrome in 97 Patients with Rheumatoid Arthritis. Fernanda G. G Chaer[1], Juliana Lucena[1], Rogerio Castro Reis[1], Fabiola Brasil[1], Murilo Melo[2], Amanda Callegari[2] and Branca Souza[2]. [1]Irmandade da Santa Casa de Misericordia de Sao Paulo, São Paulo, Brazil, [2]Irmandade da Santa Casa de Misericordia de São Paulo, São Paulo, Brazil

Background/Purpose: Rheumatoid arthritis (RA) is an independent risk factor for cardiovascular disease (CVD), which is the leading cause of death in this group. Thus, the investigation of metabolic syndrome (MS) is critical, as designating a number of other cardiovascular risk factors: abdominal obesity, dyslipidemia, hypertension and hyperglycemia.To evaluate the frequency of MS in patients with RA and their relationship with disease activity and the different therapies used, in particular blocking tumor necrosis factor alpha (anti-TNF).

Methods: We selected 107 consecutive patients diagnosed with RA and included only patients with data necessary for determining the MS according to NCEP-ATPIII. Disease activity was determined using the 28-joint Disease Activity Score (DAS28). Score greater than 3.2 and was considered the cutoff point for disease activity.

Results: The study included 97 patients. 47 (48.5%) were using anti-TNF in combination with methotrexate (MTX). 50 (51.5%) patients were using only synthetic DMARDs: 36 (72 %) MTX, 22 (44%), leflunomide, 19 (38%) chloroquine and 8 (16%) sulphasalazine. The overall frequency of MS was 37.1%. There was no significant difference between the prevalence of MS in patients using synthetic DMARDs only or anti-TNF. We did not observe any association between RA disease activity and MS in our study. The use of chloroquine was associated with a lower frequency of MS (p = 0.005), and BMI was higher in this group (p <0.001). In multivariate analysis including all variables with p <0.200, only the use of chloroquine and BMI remained in the model (r = 0.465, p <0.001).

Conclusion: The use of anti-TNF was not associated with lower incidence of MS compared to the use of synthetic DMARDs only, and among these, chloroquine was associated with a lower frequency of MS. Considering these results, the safety profile and low cost, chloroquine remains a valuable adjuvant therapy in this patient population at high risk for CVD.

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Inflammatory Burden Predicts Progression of Carotid Plaque in Rheumatoid Arthritis: A 24-Month Longitudinal Analysis. Churl Hyun Im, Na Ri Kim, Jong Wan Kang, Young Ji Kim, Kyung Hye Kim, Eon Jeong Nam and Young Mo Kang. Kyungpook National University School of Medicine, Daegu, South Korea

Background/Purpose: Carotid atherosclerosis, which is associated with the increased risk of cardiovascular (CV) disease, is increased in rheumatoid arthritis (RA) patients. In our previous study, an inflammatory burden, measured by area under the curve of erythrocyte sedimentation rate (ESR-AUC), increases the risk of carotid plaque formation in RA, independently with traditional CV risk factors. The aim of this study was to evaluate the role of inflammatory burden in the progression of carotid plaques during 2 years of follow up in a RA patient cohort.

Methods: We measured the intima-media thickness (IMT) and plaques using carotid artery ultrasound at baseline and after 2 years in 279 RA patients, who were enrolled in the Kyungpook National University Hospital Atherosclerosis Risk in Rheumatoid Arthritis (KARRA) cohort. Surveys for traditional CV risk factors were performed using the same questionnaire. Clinical and laboratory variables relevant to RA activity were obtained. To assess inflammatory burden, ESR-AUC during 2 years of follow up (ESR-AUC2), 5 years before baseline enrollment (ESR-AUC5, 140 females, ≥ 40 years old), and summation of these two periods (ESR-AUC7) were calculated.

Results: The study population included 227 females and 52 males RA patients. Mean and maximal common carotid IMT was increased during 2 years of follow up (0.799 ± 0.173 vs. 0.809 ± 0.173 mm; $P = 0.010$ and 0.918 ± 0.214 vs. 0.936 ± 0.210 mm; $P = 0.002$, respectively). Frequency and number of carotid plaque were also increased from 34.7% to 46.4% ($P < 0.001$) and from 0.7 ± 1.3 to 1.0 ± 1.7 ($P < 0.001$), respectively. Plaque presence at 2 years of follow up was associated with tender joint count (TJC), swollen joint count (SJC), disease activity score (DAS) 28, and ESR level at baseline, after the adjustment with age and gender. ESR-AUC2, ESR-AUC5, and ESR-AUC7 were significantly associated plaque at 2 years ($P = 0.035$, $P = 0.018$, and $P = 0.025$ respectively), after the adjustment with age and gender). After multivariate logistic regression analysis, the factors found to be significantly associated with plaque at 2 years were ESR-AUC5 ($P = 0.015$) and TJC28 at baseline ($P = 0.048$). In the second step analysis of 71 patients with newly developed plaque at 2 years (33 patients with no plaque at baseline and 38 patients with increased number of plaques from baseline), the factor significantly associated with plaque progression was ESR-AUC5 ($P = 0.038$) in multivariate logistic regression analysis.

Conclusion: Our findings indicate that residual inflammatory burden increases the risk of carotid plaque progression during 2 years of follow up in RA.

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Lipid Alterations and Measurement of Arterial Stiffness in Rheumatoid Arthritis. Marina Scolnik[1], Carla Saucedo[1], David A. Navarta[1], Leandro Ferreyra Garrott[1], Erika Catay[1], Maria L. Acosta Felquer[1], Eliana Lancioni[1], Cristian Quiroz[1], Federica Varela Guidetti[1], Zaida Bedran[1], Mirtha Sabelli[1], Javier Rosa[1], Maria Victoria Garcia[1], Patricia M. Imamura[1], Patricia Sorroche[2], Jose Alfie[3], Margarita Morales[3], Gabriel Waisman[3], Luis J. Catoggio[1] and Enrique Soriano[4]. [1]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Central Laboratory, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Hypertension Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease. Increased arterial stiffness, an independent risk factor for premature coronary artery disease, has been reported in patients with RA. The objectives of this study were first to assess, in patients with RA and controls, the prevalence of lipid alterations and to measure arterial stiffness. And second, to investigate the relationship between arterial stiffness, disease activity, disease duration and other traditional cardiovascular (CV) risks factors.

Methods: Between January 2010 and May 2011, 91 consecutive adult RA patients (fulfilling 2010 ACR/EULAR criteria) and 79 controls (patients seen at the rheumatology section with diagnoses of non-inflammatory diseases) were included. Exclusion criteria were previous history of cardiovascular disease, using of lipid-altering drugs and uncontrolled hypothyroidism. Data from each patient of smoking, blood pressure, weight, height, body mass index (BMI), waist size, glucose levels, HDL cholesterol, LDL cholesterol, triglycerides (TG), total cholesterol (TC), DAS28, sedimentation rate (ESR) and medication were obtained. Carotid femoral pulse wave velocity (PWV) was measured in 56 RA patients and 25 controls. RA patients were divided in active patients (DAS28>=2.6, n=39) or patients in remission (DAS28<2.6, n=17). Reference values for PWV were those published by the European Society of Cardiology. Patients with PWV over the value expected for age and optimal blood pressure were considered to have arterial stiffness.

Results: Patients characteristics are shown in table 1. Mean RA duration was 7.5 years (SD 4.5). RA patients and controls had similar values of lipids and other classic CV risk factors (table 1). Arterial stiffness measured by PWV was found in 1 control (4%) and 6 RA patients (10.7%) (p=0.3). Mean carotid femoral PWV was 8,78 m/s (SD 2.1) for controls and 9.3 m/s (SD 2,6) for RA patients (p=0.4). PWV was similar in remission RA patients and active RA patients, means 9,23 m/s (SD 3.4) and 9.3 m/s (SD 2.3) respectively (p=0,9). Patients with hypertension had an increased PWV compared with non-hypertensive patients (p=0.0003). In fact in multivariate analysis, only arterial hypertension correlated independently with arterial stiffness (OR 19.9, CI 2.2–178). No relationship was found between carotid femoral velocity and DAS 28, ESR, disease duration, medications or other CV risk factors.

Table 1.

	CONTROLS (n=79)	RA PATIENTS (n=91)	P value
Age, years (SD)	58.6 (12.6)	58.4 (12.4)	0.92
Female, % (CI)	94.9 (87.5–98.6)	93.4 (86.2–97.5)	0.67
Hypertension, % (CI)	53.2 (41.6–64.5)	46.1 (37.4–57)	0.36
Hyperglycemia, % (CI)	6.5 (CI 2.1–14.5)	5.5 (CI 1.5–13.4)	0.8
Current smokers, % (CI)	19 (11–29.4)	11.3 (5.3–20.3)	0.17
BMI (SD)	27.9 (5.6)	26.02 (5.3)	0.02
Waist perimeter, cm (SD)	94.31 (14.08)	88.76 (14.28)	0.01
HDL <40 mmol/L, % (CI)	6.4 (2.1–14.3)	6.6 (1.8–15.9)	0.97
LDL >= 160 mmol/L, % (CI)	17.9 (10.2–28.3)	15.5 (7.3–27.4)	0.7
TG > 150 mmol/L, % (CI)	16.7 (9.2–26.8)	7.1 (2–17.3)	0.1
TC> 200 mmol/L, % (CI)	41 (30–52.7)	50.6 (39.4–61.8)	0.22
Dyslipidemia, % (CI)	58.2% (IC 46,6–69,2)	51.7% (IC 40,8–62,4)	0.39

Conclusion: in this cohort, RA patients and controls had similar CV risk factors and we found no differences in PWV between them. In RA patients, neither disease duration nor disease activity, measured by DAS28, was related to increased arterial stiffness. Arterial hypertension was the only CV risk factor associated with arterial stiffness. We did not find increased pulse wave velocity in RA patients as has been previously reported.

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Serum Cytokines Associated with Carotid Atherosclerosis in Rheumatoid Arthritis. Inmaculada del Rincon[1], Roy W. Haas[1], Daniel H. O'Leary[2], Joseph F. Polak[2], Daniel F. Battafarano[3] and Agustin Escalante[1]. [1]University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]Tufts University-Boston Campus, Boston, MA, [3]Brooke Army Medical Ctr, San Antonio, TX

Background/Purpose: The mechanism for the increased cardiovascular morbidity and mortality in rheumatoid arthritis (RA) is incompletely understood. In a previous analysis, we found that both the erythrocyte sedimentation rate and the C-reactive protein were associated with the carotid intima-media thickness (IMT) in RA patients, suggesting that systemic inflammation plays a role. Cytokines are important mediators in inflammation and can be measured in the serum. We examined the association between the serum concentration of cytokines/chemokines and the carotid IMT in patients with RA.

Methods: We performed a high-resolution carotid ultrasound in patients with RA for measurement of the internal and common carotid IMT, expressed as a composite. A subset of patients returned for a repeat ultrasound of the common carotid IMT, following a protocol designed to assess change. A stored sample of patients' serum at baseline was used to measure 38 cytokines using a multiplex ELISA technique. We used a multivariable stepwise selection process to identify cytokines associated cross-sectionally with the composite carotid IMT, and with rapid progression of the common carotid IMT.

Results: A baseline scan was performed on 1,162 RA patients, 873 of whom were women. The mean composite carotid IMT was 1.040 mm (SD 0.181 mm). A subset of 566 patients was eligible for a follow-up scan, which we performed in 487 (86%). The mean (SD) common carotid IMT at baseline was 0.571 mm (0.151), and after a 3 year follow-up, the common carotid IMT increased to a mean of 0.621 mm (0.171), an increase of 0.050 mm (0.055), P < 0.001. Among patients in the highest progression quartile, the common carotid IMT increased by 0.119 mm (0.062). The following serum cytokines were independently associated with the cross-sectional composite IMT, adjusted for age and sex: IL-8, 0.047 (0.018, 0.076); soluble IL-2 receptor-alpha, 0.054 (0.020, 0.089); IL1-receptor antagonist, −0.053, −0.087, −0.018); and macrophage-derived chemokine −0.027 (−0.052, −0.001). Values shown are regression coefficients in mm per SD (95%CI). Few cytokines were associated with rapid progression of the common carotid IMT, with only the IL-12p40 reaching statistical significance with an odds ratio of 1.67 per SD, 95% CI (1.14, 2.29).

Conclusion: A number of inflammatory cytokines measured in the serum, notably IL-8, were significantly associated with the carotid IMT. However, in contrast with other RA outcomes, the number of cytokines and the strength of their association with the carotid IMT were modest. This may indicate that cytokines and chemokines exert their effect at the level of the vascular wall rather than though the systemic circulation. These findings help clarify the role of inflammation in rheumatoid atherosclerosis.

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Role of Inflammation, Serologic Status and Low Density Lipoprotein in Coronary Heart Disease Among Patients with Rheumatoid Arthritis: Data From the National Veterans Health Administration. Iris Navarro-Millan[1], Shuo Yang[2], Scott L. DuVall[3], Lang Chen[2], John Baddley[2], Grant W. Cannon[4], Elizabeth S. Delzell[2], Jie Zhang[2], Monika M. Safford[2], Nivedita M. Patkar[5], Ted R. Mikuls[6], Jasvinder A. Singh[2] and Jeffrey Curtis[2]. [1]University of Alabama Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]VA Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [4]Salt Lake City VA and Univeristy of Utah, Salt Lake City, UT, [5]Univ of Alabama-Birmingham, Birmingham, AL, [6]Omaha VA and University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Rheumatoid arthritis (RA) increases the risk for coronary heart disease and ischemic events like myocardial infarction (MI). The association between traditional cardiovascular risk factors in this population remains unknown. Objective: To determine the association between myocardial infarction (MI), low density lipoprotein (LDL), seropositive RA and inflammation as determined by C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) among patients with RA.

Methods: Retrospective data from the national Veterans Health Administration (VHA) from 1998–2011 was used for this study. Identification of the RA population and incident hospitalized MI was done using a validated algorithm using ICD-9 codes for RA from outpatient rheumatology visits and MI primary diagnosis code on hospitalization. Patients eligible for this analysis included RA patients with no previous MI. Baseline characteristics were determined during the first 12 months of observation in the VHA system, after which follow-up time for this analysis began. Laboratory data was examined in a time-varying fashion and updated on a daily basis and assessed at each event time. Seropositivitiy was characterized by having either positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody. Cox proportional hazard models were used to determine the hazard ratios (HR) between first hospitalized MI and LDL (in quartiles and using ATP III cutpoints); CRP, ESR in quartiles (to avoid assumptions of linearity) and seropositivity using age as the time axis.

Results: A total of 38,694 VHA patients with RA were identified. They were 90.3% male; mean ± SD age was 63.5 (± 12.1) years. Mean CRP, ESR and LDL levels at baseline were 10.4 mg/L (± 20.5), 30.1 mm/h (SD ± 24.9) and 100 mg/dL (SD ± 31.7) respectively; 85% of the RA cohort was seropositive. The baseline prevalence of diabetes was 12.5% and hypertension 33.9%.

The number of usable MI events varied according conditional on the availability of laboratory results. The crude rates of MI by each exposure variable are listed (table). A strong relationship was seen with increasing ESR. Trends in MI rates associated with increasing CRP were observed only for the 4th quartile. Higher HDL appeared protective, and patients in the lowest LDL quartile had the highest rates of MI.

Table. Myocardial Infarction Incident rates by ESR, CRP, LDL, High Density Lipoprotein (HDL) and Serologic Status by Quartiles

ESR (mm/hour) Quartile	MI Events	Person Years	Iincident Rate per 1,000 Person year
1st (<11)	80	2406	3.3
2nd (≥11 and <23)	87	21131	4.1
3rd (≥23 and <42)	133	20247	6.6
4th (>42)	171	18896	9.0
CRP (mg/L) Quartile			
1st (< 0.89)	26	4975	5.2
2nd (≥ 0.89 and <3.1)	17	4302	4.0
3rd (≥3.1 and <9.5)	20	3941	5.1
4th (>9.5)	30	3483	8.6
LDL 9mg/dL) Quartile			
1st (< 77.4)	245	31437	7.8
2nd (≥ 77.4 and ≤ 97.2)	184	32797	5.6
3rd (≥ 97.2 and ≤ 121)	143	31965	4.5
4th (>121)	162	30392	5.3
HDL (mg/dL) Quartile			
1st (< 34.4)	220	27241	8.1
2nd (≥ 34.4 and 41.0)	190	30203	6.3
3rd (≥ 41.0 and ≤ 50.4)	180	35294	5.1
4th (>50.4)	153	34345	4.5
Serologic status (RF/CCP)			
Seronegative	43	14588	2.9
Seropositive	443	84193	5.3

After controlling for age, the HR for ESR (comparing the highest to lowest quartile) was 2.4 (p < 0.001), and the HR for CRP (highest to lowest quartile) was 1.6 (p = 0.08). The HR for sepositive RA was 1.7 (p < 0.001). HR for LDL ≥160 mg/dL compared to LDL < 100 was 1.2 (p= 0.30).

Conclusion: In this U.S., predominantly male RA cohort, ESR and seropositivity were significantly associated with a risk for MI and trends suggested CRP was as well. Higher LDL was not associated with a significantly increased risk for MI.

ACR/ARHP Poster Session B
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Two-Year Drug Survival and Treatment Effect of Abatacept and Tocilizumab in the Treatment of Rheumatoid Arthritis in Routine Care. Results From the Nationwide Danish Danbio Registry. HC Leffers[1], Mikkel Østergaard[1], Bente Glintborg[2], Niels Steen Krogh[3], Ulrik Tarp[4], Tove Lorenzen[5], Annette Hansen[2], Michael Sejer Hansen[2], Lene Dreyer[2], Martin S. Jakobsen[2] and Merete L. Hetland[6]. [1]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Glostrup, Denmark, [2]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Copenhagen, Denmark, [3]ZiteLab ApS, Copenhagen, Denmark, [4]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Aarhus, Denmark, [5]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Silkeborg, Denmark, [6]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark

Background/Purpose: Abatacept and tocilizumab have been shown to be efficacious for the treatment of rheumatoid arthritis (RA), even in patients refractory to tumor necrosis factor inhibitor (TNFi). However, reports on their long term efficacy in clinical practice are scarce. The aim of this study was to describe two-year drug survival and clinical response in RA patients treated with abatacept or tocilizumab in routine care. It is an extension of previously published 48-week data[1], based on data from the nationwide Danish DAN-BIO registry

Methods: In the DANBIO registry we identified 230 and 447 RA patients treated with abatacept and tocilizumab, respectively. The clinical efficacy was assessed by drug survival and by changes in DAS28 and EULAR response rates after 48 and 96 weeks. No imputation of missing values was done. No direct comparison of the 2 drugs was made.

Results: Of the patients receiving abatacept and tocilizumab, respectively, 22%/25% (abatacept/tocilizumab) were male, median (interquartile range, IQR) age 55(45–64)/57(46–65) years, disease duration 5(1–13)/5(1–11) years and number of previous biological drugs 2(2–3)/2(1–3), >99%>/99% of patients, had previously received ≥1 TNFi. Rheumatoid factor was positive in 79% and 77% of patients with available data (143/230 and 290/447), respectively.

After 48 and 96 weeks, 54%/66% and 39%/58% of patients treated with abatacept/tocilizumab were still receiving the drug, respectively.

Among patients with available response data, median DAS28 was in the abatacept group 5.2, 3.2 and 2.9 at baseline, week 48 and week 96, respectively, while 5.3, 2.7 and 3.0 in the tocilizumab group.

At week 48 and 96, the remission rates for abatacept/tocilizumab were 29%/49% and 38%/41%, respectively and rates of good-or-moderate EULAR response was 76%/87% and 79%/97% at week 48 and 96. Response rates after correction for proportion of patients still on drug (LUNDEX values[2]) are presented in **figure 1**.

Conclusion: In RA patients (>99% TNFi failures) treated with abatacept and tocilizumab, 54%-66% of patients were still receiving the drug after 48 weeks, and 39%-58% after 96 weeks. Due to the non-randomised study

design, no direct comparison of the drugs were made. Both drugs significantly decreased the disease activity, and a good-or-moderate EULAR response was seen in the majority (76%-87%) of patients after 48 weeks (87%-97% after 96 weeks). After correction for patients who had withdrawn, response rates were lower. This stresses the importance of transparency in the reporting of observational data.

References
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2. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum 2006;54(2):600–606.

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Rheumatoid Arthritis (RA) Incomplete Secondary Responders to TNF-Alpha Safely Achieve Efficacy by Switching to Certolizumab Pegol in a 24-Week Study: A Phase IV, Randomized Multicenter, Double-Blind, Twelve-Week Study Followed by a 12 -Week Open-Label Phase. M. Schiff[1], Ronald Goldblum[2] and John RP Tesser[3]. [1]University of Colorado, Denver, CO, [2]CPC, Inc, Carlsbad, CA, [3]AZ Arthritis Rheum Assoc, Paradise Valley, AZ

Background/Purpose: Certolizumab pegol (CZP), an inhibitor of TNF-alpha, has demonstrated rapid and sustained efficacy in RA patients. Switching from one anti-TNF therapy to another has been investigated in many open-label (OL) uncontrolled studies, but in few controlled trials. This 24-week study (12 weeks double-blind (DB) CZP or placebo followed by 12 weeks OL CZP) examined the effect of treatment with CZP or placebo on measures of disease activity in patients with active RA on stable concomitant DMARD therapy who had discontinued a TNF-alpha inhibitor other than CZP due to a secondary loss of efficacy.

Methods: The initial 12-week phase randomized 37 subjects (2:1 ratio) who were secondary non-responders (primary non-responders were excluded) or intolerant of TNF-alpha inhibitors to either CZP (27 subjects) or placebo (10 subjects) in addition to background MTX or other DMARDs. CZP was administered subcutaneously in approved doses. The pre-specified primary endpoint was the ACR 20 response at Week 12. After the Week 12 visit, all subjects could continue (blinded to initial treatment) with OL CZP for an additional 12 weeks. (NCT01147341).

Results: 37 subjects were randomized; 35 (26 on CZP and 9 on placebo) completing at least 4 weeks of dosing were analyzed for efficacy. Demographic/baseline characteristics (mean) of the 2 treatment groups were similar: age 56 vs 59 years, disease duration 12 vs 14 years, MTX dose 16.4 vs 16.1 mg/week, and DAS-CRP 5.48 vs 5.44 (placebo vs active). Efficacy results (initial 12 weeks) are as follows:

Efficacy Endpoints	Placebo n/N (%)	CZP n/N (%)	p-value*
ACR 20 (primary)	0/9 (0)	16/26 (61.5)	0.001
CDAI Decrease ≥10	2/9 (22.2)	22/26 (84.6)	0.001
ACR 50	0/9 (0)	5/26 (19.2)	N.S.
CDAI LDAS+Remission	0/9 (0)	6/26 (23.1)	N.S.
EULAR good and moderate	0/9 (0)	17/26 (65.4)	0.001
DAS28 (CRP) ≥1.2 Decrease	0/9 (0)	17/26 (65.4)	0.001
CDAI ≥13.9 Decrease	0/9 (0)	17/26 (65.4)	0.001

* two-sided p-value from Fisher's exact test

24-Week Data: 8 of the 9 subjects randomized to placebo (all non-responders) continued into OL; 5/8 (67%) attained ACR 20, 7/8 (87.5%) of these had CDAI improvement ≥13.9 after the switch to CZP. Five of the CZP-treated subjects who were initially ACR 20, but not ACR 50, responders improved to ACR 50 or 70 responses with OL treatment.

In the initial 12 weeks, adverse events occurred in 16/27 (59.3%) CZP subjects and 4/10 (40%) placebo subjects. One serious adverse event of G-I bleeding (considered unrelated to CZP) occurred in the open-label phase.

There were no other serious adverse events, deaths, neoplasms, opportunistic or serious infections.

Conclusion: In this controlled study of secondary non-responders to TNF inhibitors, the primary efficacy endpoint (ACR 20) and most secondary endpoints showed significant improvement with CZP compared to placebo. The ACR 20 response rate observed with CZP (>60%) is higher than that reported in most previous studies of incomplete TNF responders. With OL CZP dosing for the final 12 weeks, improved efficacy was seen in most subjects who had previously received placebo. In addition, CZP demonstrated good safety and tolerability. This study supports the use of CZP in RA patients who are secondary non-responders to anti-TNF therapies or intolerant to them.

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Can Response Duration After the First Rituximab Treatment Be Used in Timing of Rituximab Retreatment?
Noortje van Herwaarden[1], Aatke van der Maas[1], Tim L. Jansen[2], Ellen Dutmer[3], Andre Hartkamp[4], Piet L.C.M. van Riel[2], Wietske Kievit[2], Bart J.F. van den Bemt[1] and Alfons A. den Broeder[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Gelderse Vallei Hospital, Ede, Netherlands, [4]Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands

Background/Purpose: The optimal retreatment strategy for rituximab is not clear[1]. Different strategies are being used in clinical practice, including: on demand retreatment when disease activity increases and fixed interval retreatment. We investigated whether the response duration after the first rituximab course might be used for timing of retreatment by assessing the intra-individual variation in response duration after two subsequent rituximab courses in patients with rheumatoid arthritis (RA).

Methods: In this retrospective study, RA patients treated with at least three rituximab courses, according to the on demand retreatment strategy, were included. Difference in first and second interval between infusions and between duration until loss of response were analysed with student's paired t-test, Spearman correlation coefficient and limits of agreement. Date of loss of response was determined by two research physicians based on chart review.

Results: Seventy patients were included (table 1). The dosage of the first rituximab treatment cycle was 2 × 1000 mg in 69 patients (in 1 patient unknown), and of the second rituximab cycle 2 × 1000 mg in 57 patients, 2 × 500 mg in 6 patients and 1 × 1000 mg in 7 patients. Concomitant DMARD treatment changes were infrequent and comparable between first and second interval. Forty patients were treated with systemic corticosteroids at baseline; changes in systemic steroid treatment were also comparable between first and second interval.

Table 1. Baseline characteristics

	n = 70
Age, years (SD)	58 (10.2)
Woman, n (%)	57 (81)
Disease duration, years median [p25-p75]	13 [6 – 18]
Rheumatoid factor positive, n (%)	61 (87)
Anti-CCP positive, n (%)	53/65 (76)
DAS28 at first RTX (SD)	5.1 (0.99)
Previous DMARDs, n median [p25-p75]	5 [3 – 6]
Previous biologicals n, median [p25-p75]	2 [2 – 3]
Concomitant DMARD, n (%)	32 (46)
Concomitant MTX, n (%)	21 (30)
Concomitant corticosteroid, n (%)	40 (57)
Corticosteroid dose, mg (SD)	10 (4.0)
Concomitant statin, n (%)	7 (10)

anti-CCP= anti-cyclic citrullinated peptide; DAS28 = 28 joints disease activity score; RTX = rituximab; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate

The mean interval in days was 301 (SD 95) and 341 (SD 123) days for the first and second rituximab interval. Mean time until loss of response was 252 (SD 93) and 307 (SD 126) days respectively. Limits of agreement between 1st and 2nd infusion intervals were large, −190 and +272 days (figure 1). Of note, the second interval between infusions was longer than the first (40 days (SD 119) p = 0.003).
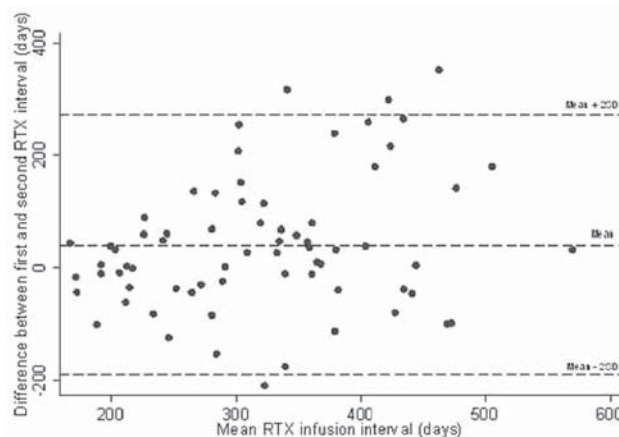
Figure 1. Difference against mean for RTX interval 1 and 2

Conclusion: Duration of response after the first rituximab course is not a useful parameter in timing of retreatment, because of the large intra-individual variation in response duration. The second rituximab interval seems to be longer than the first, which could lead to increasing overtreatment when fixed schedule retreatment is used.

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Relationship Between Morning Stiffness Duration and Severity, Pain Intensity, and Measures of Disease Activity in a 12 Week Efficacy Study of a Modified (Delayed-Release) Prednisone Plus Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis.
Frank Buttgereit[1], John R. Kirwan[2], Kenneth G. Saag[3], Reike Alten[4], Amy Grahn[5], Patricia Rice[6] and Maarten Boers[7]. [1]Charite University Medicine, Berlin, Germany, [2]Bristol Royal Infirmary, Bristol, United Kingdom, [3]Univ of Alabama-Birmingham, Birmingham, AL, [4]Charité Univ Medicine, Berlin, Germany, [5]Horizon Pharma, Deerfield, IL, [6]CliniRx Research, Naperville, IL, [7]VU University Medical Center, Amsterdam, Netherlands

Background/Purpose: RA patients typically present with pain and morning stiffness (MS). MS is predictive of both functional disability and escalated RA care, but the best way to evaluate MS in RA has yet to be determined. Data evaluating MS duration (MSD), MS severity (MSS), and pain intensity (PI) upon awakening with other RA measures representing disease progression and response would help to determine if one is more clearly related to disease activity. Chronotherapy with a modified (delayed)-release (MR) prednisone tablet given at bedtime has shown MS reduction compared to conventional, immediate-release (IR) prednisone with a sustainable effect up to 12 months. Data from the Circadian Administration of Prednisone in Rheumatoid Arthritis-2 (CAPRA-2) study in patients with active RA and on stable DMARD therapy provide the opportunity to evaluate possible relationships between measures of MS and PI with ACR20, DAS28 and HAQ-DI response criteria.

Methods: CAPRA-2 was a 12-week, double-blind, PBO-controlled study that randomized 350 RA patients to 5 mg MR-prednisone (n=231) or PBO (n=119) taken once daily at bedtime (eg, 10pm) in addition to their standard DMARD treatment (Buttgereit, ARD 2012). The primary endpoint was the proportion of patients achieving an ACR20 response after 12 weeks. A key secondary objective was reduction of MS at week 12, as measured in patient diaries. Pearson Correlations were performed to evaluate the relationships between change from baseline in MSD (minutes), MSS (VAS) or PI with DAS28 and HAQ-DI. Furthermore a Wilcoxon rank sum analysis was completed between responders and nonresponders based on ACR20, DAS28 (score < 2.6) and HAQ-DI (% change from baseline < −0.22) and MSD.

Results: MSD, MSS and PI showed correlation with DAS28 and HAQ-DI in all group analyses (p<0.0001). Stronger absolute correlations

were seen with MSS and PI than with MSD, whether the study groups were analyzed separately or together (all treatment, Table 1). Specifically, a moderately strong correlation (≥ 0.5) was seen between DAS28 and MSS and PI in the treatment and PBO groups. MSS and PI were strongly correlated (0.9). The ranges of correlations found are similar to previous studies showing joint impairment is moderately correlated with disability (0.42–0.50) as measured by self-report questionnaires (Yazici, J Rheumatol 2004). Responders had a greater relative reduction in MSD than non-responders, especially the MR-prednisone patients (Table 2).

Table 1. Change from Baseline Correlation between MSD, MSS, and PI with Disease Activity Measures

	All Treatment	MR-Prednisone + DMARD	PBO + DMARD
DAS28			
MSD	0.28	0.21	0.37
MSS	0.48	0.43	0.51
PI	0.47	0.42	0.50
HAQ-DI			
MSD	0.25	0.21	0.27
MSS	0.39	0.35	0.40
PI	0.43	0.41	0.41

Table 2. Analysis of MSD and Responder Status

	MR Prednisone + DMARD			PBO + DMARD		
	Responder	Non-responder	p-value	Responder	Non-responder	p-value
ACR20						
N	109	107		34	73	
Reduction MSD (%)	86.0	34.0	<0.0001	46.3	17.9	<0.001
DAS28						
N	25	101		8	99	
Reduction MSD (%)	100.0	50.8	<0.0001	67.3	31.0	0.1221
HAQ-DI						
N	110	106		32	75	
Reduction MSD (%)	73.9	48.1	<0.01	42.7	19.7	<0.01

Conclusion: MSD, MSS and PI are correlated with DAS28 and HAQ-DI in placebo and MR-prednisone treated patients on DMARDs, with stronger correlations seen with MSS and PI. Patients meeting ACR20, DAS28 and HAQ-DI response criteria had a significantly greater reduction in MS than non-responders. Morning pain and stiffness severity in addition to duration of morning stiffness are key patient reported outcomes for both treatment response and disease progression in RA patients.

1275

Fast Remission Response to Etanercept At Week 4 Predicts Better Long-Term Outcomes in Early and Established Rheumatoid Arthritis Compared to Slower Response At Week 12. Bernd Raffeiner, Costantino Botsios, Francesca Ometto, Mariagrazia Canova, Livio Bernardi, Cristiana Vezzari, Silvano Todesco, Paolo Sfriso and Leonardo Punzi. Rheumatology Unit - University of Padova, Padova, Italy

Background/Purpose: Achievement of clinical remission not only early in disease course but also early in treatment course may be critical for functional outcome of patients with rheumatoid arthritis (RA). Patients showing clinical response to certolizumab at week 6 demonstrated greater ACR responses, higher rates of remission, and improved patient-reported outcomes after 1 year compared to patients who had a response at week 12. Response to treatment as early as week 6 predicted continuation of treatment with TNFα blockers in long-term follow-up. Objective of study was to establish rate of patients on etanercept (ETA) achieving clinical remission at week 4 (fast) or week 12 of treatment (slow remission responders). To

determine effects of fast versus slow remission response on clinical and radiographic remission. To identify predictors for fast remission response.

Methods: Retrospective case control study was performed on RA patients who started ETA from 2004 to 2010 due to moderate-severe disease activity despite DMARDs. Patients having available control at first and third month were enrolled. Patients achieving DAS28 remission by first month were defined as fast remission responders. Patients reaching DAS28 remission at three month as slow remission responders. Patients not reaching remission within 3 months or not maintaining remission for at least one year were excluded because considered unresponsive. Fast remission responders were compared with slow responders regarding maintenance of clinical remission on ETA in longterm follow-up. Arrest of radiolgraphic progression was determined by Total Sharp Score modified van der Heijde (TSS) on X-rays performed at baseline and after 1 year. Clinical and therapeutic baseline characteristics were compared between fast and slow remission responders. Statistical analysis was performed by Student T-test and Pearson test as appropriate. Multivariate logistic regression was applied to find predictors for fast remission response.

Results: 74 of total 186 RA patients identified reached DAS28 remission within the first treatment month with ETA and were classified as fast remission responders (39.7%). Only 8 of 74 fast remission responders (10.8%) lost disease control by ETA in follow-up (mean 3.5 years) compared with 25% of slow remission responders (28 out of 112, p < 0.05). Considering patients with early RA (disease duration ' 1 year) difference was even more significant (14.3 vs 64.7%, p <0.05). Radiographic progression (ΔTSS>1) occurred in 5.8% of fast but 16.3% of slow remission responders (p < 0.05). No difference was found for analyzed patients' baseline characteristics or past and concomitant therapy. None of the baseline characteristics was predictive for fast remission response.

Conclusion: Fast remission response to ETA at week 4 was achieved in 39.7% of RA patients with early and established disease, and determined better outcome by greater maintenance of clinical and radiographic remission compared to slow remission responders at week 12. Fast remission response resulted to be an independent factor for outcome as it could not be predicted by other parameters but only clinically assessed by tight control.

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Changes in B Cell Populations and Serum Immunoglobulins and Their Relationship to Infections in a One Year, Uncontrolled Open Label Study of Tabalumab. Maria W. Greenwald[1], Melissa Veenhuizen[2], Wendy Komocsar[2], Rebecca Jones-Taha[3], Chin H. Lee[2] and Pierre-Yves Berclaz[2]. [1]Desert Medical Advances, Palm Desert, CA, [2]Eli Lilly & Company, Indianapolis, IN, [3]PharmaNet/i3, Blue Bell, PA

Background/Purpose: B cell activating factor (BAFF) is an important modulator of B cell development and proliferation and is secreted by neutrophils, monocytes, macrophages and dendritic cells. Tabalumab, a monoclonal antibody that neutralizes both membrane-bound and soluble BAFF, has previously been shown to reduce the signs and symptoms of rheumatoid arthritis (RA)[1,2]. In this open label, uncontrolled, extension study, we examined the effect of tabalumab on B cell populations, serum immunoglobulins (Ig) and the relationship between these parameters and infections.

Methods: One hundred eighty-six patients (pts) who completed one of two 24 week phase 2 trials of tabalumab versus placebo were elligible for this study, and 182 (98%) of those pts enrolled. Pts were methotrexate or TNF antagonist inadequate responders. All pts received open label 60 mg subcutaneous tabalumab every 4 weeks for 48 weeks. The dose could be increased to 120 mg and, if necessary, decreased to 60 mg one time at the investigators' discretion. B cell populations and serum Igs were compared to their pre-treatment baseline from the initial phase 2 studies. Total B cell counts were monitored during a post study follow-up period.

Results: Sixty pts (33%) received 60 mg throughout the study, and 121 pts (66%) escalated to 120 mg at different times (60/120 mg group). One pt escalated to 120 mg then returned to 60 mg. In all groups, total B cell and mature naïve B cell counts gradually declined over time but were not depleted at week 52 (table). Memory B cells increased $\sim$ 100% over baseline at week 12 and returned to $\sim$ 60–70% over baseline at week 52. Sixty-six pts had total B cell counts < 43 cells/μl and < 50% of baseline at week 52 or after and the Kaplan-Meier estimate of median time to recovery after the last injection was 40.6 weeks (CI: 39.6–51.3). All of these pts who completed follow up (n=47) recovered by 66 weeks. Among pts whose B cells decreased below

50% of baseline at any time during the treatment period, 37% had infections compared to 53% among pts whose B cells did not. Serum Igs (IgA, IgM, IgG) decreased for all groups at week 52 (table). Eleven pts had treatment-emergent serum Ig levels below the lower limit of normal (LLN) during the treatment period with no concurrent infections.

Change from Baseline in B Cell Populations and Serum Immunoglobulins at Week 52†

	60 mg (N=60)	60/120 mg (N=121)	All pts* (N=182)
Total B cells (CD20+)	(n=59) -41.1 %	(n=118) -34.7 %	(n=178) -37.1 %
Mature naïve B cells (CD19+ IgD+ CD27-)	(n=59) -65.8 %	(n=118) -72.0 %	(n=178) -70.1 %
Memory B cells (CD19+ IgD- CD27+)	(n=59) 58.4 %	(n=118) 78.6 %	(n=178) 71.8 %
Serum IgA	(n=57) −14.7 %	(n=121) -13.5 %	(n=179) -13.8 %
Serum IgG	(n=57) −10.9 %	(n=121) -11.2 %	(n=179) -11.1 %
Serum IgM	(n=57) −18.7 %	(n=121) -19.4 %	(n=179) -19.1 %

† Last observation carried forward method was used to impute missing values at week 52. Small 'n' indicates the number of patients with both baseline and post baseline assessments
* 1 pt that had dose escalated to 120 mg and decreased back to 60 mg is included in 'all pts' category

Conclusion: Tabalumab treatment reduced total B cells, mature naïve B cells and serum Igs, while memory B cells were increased. Total B cells were only partially depleted and recovered in all pts during the post treatment follow-up period. There was no indication that reductions in B cells or in serum Igs below the LLN were associated with an increased frequency of infections. Additional studies will help further understand the effect of tabalumab treatment on B cells, serum Igs and adverse events.

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2. Genovese et al. Ann Rheum Dis 2011;70(Suppl3):71

Disclosure: M. W. Greenwald, Eli Lilly and Company, 2; **M. Veenhuizen**, Eli Lilly and Company, 3, Eli Lilly and Company, 3; **W. Komocsar**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **R. Jones-Taha**, None; **C. H. Lee**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **P. Y. Berclaz**, Eli Lilly and Company, 1, Eli Lilly and Company, 3.

1277

Tofacitinib, an Oral Janus Kinase Inhibitor, in Combination with Methotrexate Reduced the Progression of Structural Damage in Patients with Rheumatoid Arthritis: Year 2 Efficacy and Safety Results From a 24-Month Phase 3 Study. D. van der Heijde[1], Y. Tanaka[2], R. M. Fleischmann[3], E. Keystone[4], J. M. Kremer[5], C. Zerbini[6], M. H. Cardiel[7], S. B. Cohen[8], P. T. Nash[9], Y. Song[10], D. Tegzova[11], B. Wyman[12], D. Gruben[12], B. Benda[13], G. Wallenstein[12], S. Krishnaswami[12], S. H. Zwillich[12], J. Bradley[12], C. A. Connell[12] and ORAL Scan Investigators[14]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Occupational and Environmental Health, Kitakyushu, Japan, [3]Metroplex Clinical Research Center, Dallas, TX, [4]Mount Sinai Hospital, Toronto, ON, [5]Albany Medical College, Albany, NY, [6]CEPIC–Centro Paulista de Investigação Clínica, São Paulo-SP, Sao Paulo, Brazil, [7]Centro de Investigacion Clinica de Morelia, Morelia, Mexico, [8]Metroplex Clinical Research Centre, Dallas, TX, [9]Nambour Hospital, Sunshine Coast, Australia, [10]Seoul National University Hospital, Seoul, South Korea, [11]Institute of Rheumatology, Prague, Czech Republic, [12]Pfizer Inc., Groton, CT, [13]Pfizer Inc., Collegeville, PA, [14]Groton

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. This 24-month (Mo) Phase 3 study compared efficacy, including inhibition of structural damage, and safety of tofacitinib vs placebo (PBO) in patients (pts) with active RA with inadequate response to methotrexate (MTX). Here we report 24-mo data to assess consistency of efficacy and safety.

Methods: Pts on stable-dose MTX were randomized 4:4:1:1 to one of four sequences (NCT00847613): tofacitinib 5 mg twice daily (BID); 10 mg BID; PBO advanced to 5 mg BID; PBO advanced to 10 mg BID. Pts on PBO advanced at Mo 6 or at Mo 3 if non-responsive (<20% reduction from baseline (BL) in swollen and tender joint counts). In the primary analysis, PBO structure data were imputed through linear extrapolation from the time of advancement (Mo 3 or Mo 6). As there is less relevance of imputing data long-term, mean change from BL for the modified Total Sharp Scores (mTSS) as well as ACR response and DAS28-4(ESR) <2.6 rates are shown with and without imputation.

Results: 797 pts were randomized and treated; 535 (67.1%) completed the 24-mo study. Pt treatment sequences were similar for BL characteristics including mTSS and its components. Primary efficacy endpoints and Mo 12 data have been reported previously;[1] here we report Mo 24 data. Only descriptive statistics are presented for these selected secondary endpoints (Table 1). Efficacy was maintained through Mo 24 as measured by ACR response, DAS28-4(ESR) <2.6, HAQ-DI and mTSS suggesting that pts maintain their response to tofacitinib for at least 2 years. Adverse events (AEs), serious AEs and serious infection events are shown in Table 2. Most AEs were mild or moderate and resolved while continuing tofacitinib treatment. During the 24-mo study, 36 pts (11.2%) on 5 mg BID, 37 pts (11.7%) on 10 mg BID, 8 pts (9.9%) on PBO to 5 mg BID, and 10 pts (12.7%) on PBO to 10 mg withdrew due to AEs related to study drug. There was one opportunistic infection (8 in total over 24 mo) and four deaths (all 5 mg BID; one considered not related: acute myocardial infarction; three considered related by the investigator: cardio-respiratory arrest; cardiac failure; congestive cardiac and renal failure) occurring after Mo 12. The incidence of laboratory abnormalities was similar in all treatment sequences.

Table 1. Selected secondary efficacy endpoints at Mo 12 and Mo 24

	Mo 12		Mo 24	
	NRI	Observed	NRI	Observed
ACR20	% (N)	% (N)	% (N)	% (N)
Tofacitinib 5 mg BID	48.5 (309)	75.4 (252)	41.1 (309)	73.5 (211)
Tofacitinib 10 mg BID	55.3 (309)	78.5 (265)	49.5 (309)	82.6 (218)
Placebo → 5 mg BID	30.4 (79)	74.6 (67)	25.3 (79)	83.3 (54)
Placebo → 10 mg BID	33.3 (75)	74.6 (63)	30.7 (75)	82.7 (52)
ACR50				
Tofacitinib 5 mg BID	32.4 (309)	46.0 (252)	28.8 (309)	48.8 (211)
Tofacitinib 10 mg BID	39.5 (309)	50.9 (265)	39.8 (309)	65.1 (218)
Placebo → 5 mg BID	21.5 (79)	52.2 (67)	20.3 (79)	53.7 (54)
Placebo → 10 mg BID	16.0 (75)	41.3 (63)	17.3 (75)	53.9 (52)
ACR70				
Tofacitinib 5 mg BID	18.8 (309)	24.6 (252)	17.2 (309)	27.0 (211)
Tofacitinib 10 mg BID	26.5 (309)	32.5 (265)	25.6 (309)	40.4 (218)
Placebo → 5 mg BID	10.1 (79)	31.3 (67)	10.1 (79)	31.5 (54)
Placebo → 10 mg BID	12.0 (75)	27.0 (63)	13.3 (75)	38.5 (52)
DAS28-4 (ESR) <2.6				
Tofacitinib 5 mg BID	9.8 (265)	12.8 (218)	10.9 (265)	16.8 (179)
Tofacitinib 10 mg BID	13.2 (257)	18.6 (221)	12.5 (257)	20.7 (179)
Placebo → 5 mg BID	3.1 (65)	13.0 (54)	3.1 (65)	12.2 (41)
Placebo → 10 mg BID	7.8 (64)	25.9 (54)	7.8 (64)	22.7 (44)
HAQ-DI *mean change from BL*[a]	Δ (N)		Δ (N)	
Tofacitinib 5 mg BID	−0.46 (251)		−0.50 (210)	
Tofacitinib 10 mg BID	−0.61 (265)		−0.65 (218)	
Placebo → 5 mg BID	−0.53 (67)		−0.56 (54)	
Placebo → 10 mg BID	−0.48 (63)		−0.59 (52)	
mTSS *mean change from BL*	LEP Δ (N)	Observed Δ (N)	LEP Δ (N)	Observed Δ (N)
Tofacitinib 5 mg BID	0.45 (287)	0.31 (252)	0.87 (287)	0.48 (210)
Tofacitinib 10 mg BID	0.10 (298)	0.20 (261)	0.36 (298)	0.23 (216)
Placebo → 5 mg BID	0.59 (71)	0.51 (62)	1.18 (71)	0.63 (52)
Placebo → 10 mg BID	0.65 (68)	0.16 (61)	1.31 (68)	0.37 (49)

All data are from the full analysis set; [a]mixed-effect, longitudinal model; BID, twice daily; BL, baseline; LEP, imputation using linear extrapolation; N, number of patients in each group; NRI, non-responder imputation (with advancement penalty); Observed, no imputation

Table 2. Treatment-related adverse events over the final 18-month study period, Mo 6–24

Adverse events, n (%)

Tofacitinib 5 mg BID (N = 321)	160 (49.8)
Tofacitinib 10 mg BID (N = 316)	165 (52.2)
Placebo → 5 mg BID (N = 81)	30 (37.0)
Placebo → 10 mg BID (N = 79)	36 (45.6)

Serious adverse events, n (%)

Tofacitinib 5 mg BID (N = 321)	18 (5.6)
Tofacitinib 10 mg BID (N = 316)	18 (5.7)
Placebo → 5 mg BID (N = 81)	3 (3.7)
Placebo → 10 mg BID (N = 79)	6 (7.6)

Serious infection events, n (%)

Tofacitinib 5 mg BID (N = 321)	9 (2.8)
Tofacitinib 10 mg BID (N = 316)	13 (4.1)
Placebo → 5 mg BID (N = 81)	1 (1.2)
Placebo → 10 mg BID (N = 79)	3 (3.8)

BID, twice daily

Conclusion: RA pts treated with tofacitinib 5 or 10 mg BID on stable background MTX maintained efficacy, including inhibition of structural damage, through 24 mo. No new safety signals emerged.

Reference
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1278

Tuberculosis and Tofacitinib Therapy in Patients with Rheumatoid Arthritis. Kevin L. Winthrop[1], S.-H. Park[2], A. Gul[3], M. Cardiel[4], JJ Gomez-Reino[5], D. Ponce de Leon[6], R. Riese[7], R. Chew[7], T. Kawabata[7], E. Mortensen[6] and H. Valdez[8]. [1]Oregon Health & Science University, Portland, OR, [2]The Catholic University of Korea, Seoul, South Korea, [3]Istanbul University, Istanbul, Turkey, [4]Centro de Investigación Clínica de Morelia SC, Morelia, Mexico, [5]Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [6]Pfizer Inc., Collegeville, PA, [7]Pfizer Inc., Groton, CT, [8]Pfizer Inc., New York, NY

Background/Purpose: Biologic therapies that block tumor necrosis factor-alpha (TNF) increase the risk of tuberculosis (TB), and screening for latent tuberculosis infection (LTBI) before their initiation can prevent LTBI progression to active TB disease. Tofacitinib, a novel oral Janus kinase inhibitor investigated as a targeted immunomodulator and disease-modifying therapy for RA, partially and reversibly inhibits cytokine signaling thought to be important in TB immunity. It was shown recently that incidence rates for TB in patients (pts) treated with tofacitinib are consistent with those of TNF inhibitors in RA.[1]

Methods: Phase 2, 3, and long-term extension (LTE) clinical trial data from the tofacitinib RA program were reviewed. Before study entry, potential participants were screened for TB per protocol with Quantiferon-TB Gold® or, if unavailable, a Mantoux PPD skin test (5 mm cutoff), and chest radiography performed within 3 months of screening. In Phase 3 trials, patients diagnosed with LTBI were allowed trial entry after completing 1 month of a planned 9-month isoniazid preventive therapy regimen. Active TB cases, reported by study investigators as of September 29, 2011, were identified and TB incidence rates (IRs; per 100 pt-years [95% CI]) calculated for patients exposed to tofacitinib, stratified by their region of enrollment. Regions were categorized according to background TB IR (per 100 person-years): low (≤0.01), medium (>0.01 to ≤0.05), and high (>0.05).[2]

Results: Twelve pts with active TB were identified in 4791 (0.25%) total subjects enrolled. Median time between drug start and TB diagnosis for all TB cases was 38 weeks (range 22–137 weeks). Ten cases (83%) occurred in countries with high background TB IR; 11 cases (92%) occurred in pts with negative screening results at study entry (Mantoux PPD skin test or Quantiferon-TB Gold®), and 4 cases (33%) were extrapulmonary or disseminated. Demographic characteristics and use of concomitant medications, including methotrexate and corticosteroids, were similar to those of the entire program population. Overall, the TB IR (95% CI) for tofacitinib-treated pts was 0.173 (0.098, 0.305), which varied according to regional background TB IR: low 0.037 (0.005, 0.261); medium 0.034 (0.005, 0.242); high 0.781 (0.420, 1.452). In Phase 3 studies, 209 tofacitinib-treated pts received concomitant isoniazid therapy for treatment of LTBI. None of these pts developed active TB and there was no apparent difference in the safety profile (eg elevated transaminases) in these pts.

Conclusion: Within the large global tofacitinib development program for RA, TB was rare in regions of low and medium TB incidence and occurred most frequently in pts receiving higher doses of tofacitinib in endemic regions. As with biologic therapy, pts should be screened for TB before tofacitinib treatment using either Quantiferon-TB Gold® or tuberculin skin test. Initial data indicate that pts diagnosed with LTBI can be successfully and safely treated with isoniazid while receiving tofacitinib.

References
1. Cohen S et al. Arthritis Rheum 2011; 63 (Suppl 10): S153.
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1279

First in Human Study with Recombinant Anti-IL-21 Monoclonal Antibody in Healthy Subjects and Patients with Rheumatoid Arthritis. Stanislav Ignatenko[1], Birte K. Skrumsager[2], Adam Steensberg[2] and Ulrik Mouritzen[2]. [1]Charité Research Organization GmBH, Berlin, Germany, [2]Novo Nordisk A/S, Copenhagen, Denmark

Background/Purpose: Interleukin-21 (IL-21), a cytokine produced by activated T cells (especially T$_{17}$ and T$_{FH}$ cells), has a proinflammatory and pleiotropic nature, and drives mainly activation and differentiation of adaptive immune cells. Both IL-21 and the IL-21 receptor (IL-21R) have been shown to be upregulated in patients with rheumatoid arthritis (RA). NNC0114-0005 is a human recombinant monoclonal immunoglobulin G1 (IgG1) antibody that binds to and neutralizes IL-21. It is currently in development for the treatment of RA. The primary objective of this trial was to assess safety and tolerability of single intravenous (i.v.) and subcutaneous (s.c.) doses of NNC0114-0005 in healthy subjects (HS) and patients with RA.

Methods: A phase 1, randomized, single-center, placebo-controlled, double-blind, single-dose, dose-escalation trial was conducted in male HS (n=44) aged 18–60 and patients with RA (n=20) aged 18–75 on stable methotrexate treatment (7–25 mg/wk for ≥4 wks) with a DAS28-CRP score >3.2. HS were randomized (3:1 active to placebo) to 8 increasing i.v. dose levels (range: 0.0025–25 mg/kg) and 3 s.c. dose levels (0.1, 1 and 4 mg/kg). Patients with RA were randomized (3:1) to 3 i.v. dose levels (0.25, 4 and 25 mg/kg). Key safety parameters included adverse events (AEs), injection-site reactions and detection of neutralizing antibodies against NNC0114-0005. Pharmacokinetic (PK), pharmacodynamic and efficacy parameters were also assessed.

Results: In total, 55 AEs were reported in 31/64 (48%) subjects: 32 AEs in 16/32 HS on i.v. treatment; 16 AEs in 10/20 RA patients on i.v. treatment; and 7 AEs in 5/12 HS on s.c. treatment. The most commonly reported AEs were headache (22%) and nasopharyngitis (16%). No dose dependency was detected for AEs. One serious AE (eczema) was reported 91 days post-dosing for a patient with RA exposed to 4 mg/kg NNC0114-0005; it was evaluated as unlikely related to the trial product by the investigator. No injection-site reactions or clinically significant antibodies against NNC0114-0005 were detected. No clinically relevant changes in laboratory parameters, vital signs or ECG were observed. Pharmacokinetic dose proportionality of the area under the curve (AUC) was shown after i.v. and s.c. dosing in HS and patients with RA. The mean terminal elimination half-life of NNC0114-0005 was ~3 weeks. Overall, no clinically relevant changes in lymphocyte subsets, B-cell subsets or total IL-21R expression on lymphocyte subsets were observed after NNC0114-0005 treatment. The reduction in DAS28-CRP was numerically favorable (but not statistically significant) for patients with RA treated with 25 mg/kg NNC0114-0005 compared to placebo.

Conclusion: NNC0114-0005 was safe and well tolerated in HS and patients with RA and did not raise any safety concerns during the trial. Linear PK of NNC0114-0005 was demonstrated in HS and patients with RA and the PK properties were similar for both populations. The improvements in DAS28-CRP for patients with RA at the highest dose level may suggest biologic and clinical activity of NNC0114-0005.

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Sustained Efficacy Responses and a Consistent Safety Profile with Rituximab Repeat Treatment Over 5 Years in Patients with Rheumatoid Arthritis and an Inadequate Response to Tumour Necrosis Factor Inhibitors. Edward Keystone[1], Stanley B. Cohen[2], Paul Emery[3], Joel M. Kremer[4], Maxime R. Dougados[5], James E. Loveless[6], Carol Chung[7], Pamela Wong[7], Patrica B. Lehane[8] and Helen Tyrrell[8]. [1]Mount Sinai Hospital, Toronto, ON, [2]Metroplex Clinical Research Center, Dallas, TX, [3]University of Leeds, Leeds, United Kingdom, [4]Albany Medical College, Albany, NY, [5]René Descartes University, Paris, France, [6]St Luke's Rheumatology, Boise, ID, [7]Genentech, Inc., South San Francisco, CA, [8]Roche Products Limited, Welwyn Garden City, United Kingdom

Background/Purpose: In the REFLEX study conducted in anti-TNF inadequate responder (TNF-IR) patients with RA, a single course of rituximab (RTX) in combination with methotrexate (MTX) significantly improved disease activity at 24 weeks vs placebo (PBO) + MTX. Patients were eligible for continued RTX treatment in an open-label extension (OLE). Efficacy and safety outcomes from REFLEX and its OLE over 5 years are presented.

Methods: This was an observational, post-hoc analysis of REFLEX from baseline to 5 years, open label from the second study treatment. Patients originally randomized to PBO were rescued with RTX as appropriate and included in the OLE. Patients with a response to initial RTX treatment were eligible for further RTX treatment courses. RTX retreatment was administered as needed based on SJC and TJC ≥ 8 and at the discretion of the physician (≥ 24 weeks following first RTX course and ≥ 16 weeks following additional courses). PBO patients were re-baselined prior to their first RTX treatment and for this analysis PBO data were pooled with RTX patient data from time of first RTX treatment. Efficacy outcomes 24 weeks after each RTX course were calculated relative to first RTX pre-treatment baseline. No imputations were made for missing data. Safety data included rates of AEs, serious AEs (SAEs), infections, and serious infections (SIEs).

Results: Overall, 480 patients received at least one course of RTX. Subsequent RTX courses were given to 317 (≥ 2 courses), 259 (≥ 3 courses), 195 (≥ 4 courses), and 122 (≥ 5 courses) patients. Most withdrawals occurred after course 1, mainly for non-safety reasons. ACR responses were improved after the first course of RTX and were maintained over 5 courses (Table) with a similar trend observed for EULAR responses.

ACR response rates (% patients) at 24 weeks after each course

Clinical measure	Course 1 (n=400)	Course 2 (n=279)	Course 3 (n=225)	Course 4 (n=161)	Course 5 (n=91)
ACR20	62.0	72.8	72.4	65.8	70.3
ACR50	30.8	41.2	47.6	44.7	41.8
ACR70	13.0	19.4	26.2	24.2	22.0

The proportion of patients achieving a minimal clinically important difference in HAQ-DI was maintained over 5 courses (66.0–71.1%). Over the 5 years, rates of AEs, SAEs, and infections did not increase and generally remained stable in the RTX-treated population (1768 pt-yrs), with overall rates per 100 pt-yrs (95% CI) of 344.87 (336.32–353.64) for AEs, 22.34 (20.24–24.65) for SAEs, 97.50 (93.01–102.21) for all infections, and 5.60 (4.60–6.82) for SIEs. The most frequent SIE was pneumonia, affecting 2% of RTX patients.

Conclusion: This post-hoc analysis shows that RTX repeat treatment is associated with 24-week clinical efficacy responses, sustained to 5 courses, with a trend towards improved efficacy over time. The safety profile of RTX was comparable with published RTX long-term safety data and with that of other biologics in RA populations. No increased incidence of significant AEs was observed in spite of RTX exposure and peripheral B-cell depletion over many years. The results confirm RTX as an effective long-term treatment option in this refractory RA population.

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IL-6 Signaling Inhibition Improves Abnormal Bone Homeostasis in Active Rheumatoid Arthritis. Masayasu Kitano[1], Sachie Kitano[1], Chieri Sato[1], Kazuyuki Fujita[1], Takahiro Yoshikawa[1], Yuki Katashima[1], Masahiro Sekiguchi[1], Naoto Azuma[1], Naoaki Hashimoto[1], Shinichiro Tsunoda[1], Kiyoshi Matsui[1] and Hajime Sano[1]. [1]Hyogo College of Medicine, Nishinomiya-city, Japan

Background/Purpose: Tocilizumab (TCZ) is a humanized monoclonal anti-IL-6 receptor antibody. TCZ has demonstrated efficacy in moderate to severe active rheumatoid arthritis (RA) with inadequate clinical response to disease-modifying anti-rheumatic drugs (DMARDs) or TNF inhibitors. Moreover, it is reported that TCZ combined with MTX reduces systemic bone resorption in RA. However, the detailed mechanism about improvement effect by TCZ on abnormal bone homeostasis in RA is poorly understood. In this study, we investigated the effect of TCZ on biomarkers of bone metabolism, soluble receptor activator of NF-kappa B ligand (sRANKL), osteoprotegerin (OPG), Dickkopf-1 (DKK-1), and osteopontin (OPN) in active RA.

Methods: Thirty four patients with active RA (25 females, 9 males; age 51.9 ± 7.9 years; disease duration 12.4 ± 12.6 years; DAS28-ESR 5.6 ± 1.6) were started on treatment with TCZ 8mg/kg intravenously every 4 weeks. All patients were treated with methotrexate, other DMARDs and prednisolone, and the treatments continued at the stable pretreatment doses. After 12 weeks of treatment with TCZ, we evaluated an effectiveness using DAS28-ESR. We appreciated DAS28-ESR<2.6 as a remission group and DAS28-ESR$\geq$a2.6 as a no-remission group, respectively. Additionally, we measured serum biochemical markers such as osteocalcin, type I collagen cross-linked N-telopeptides (NTx), sRANKL, OPG, and DKK-1 and plasma OPN by ELISA at baseline and 12 weeks.

Results: At 12 weeks after the treatment of TCZ, a disease activity reduced significantly from the baseline (DAS28-ESR 5.6 ± 1.6 vs 3.1 ± 1.7; p<0.01). Fifteen patients achieved the remission. In the analysis of bone metabolic markers at 12 weeks, average of serum NTx levels decreased significantly from the baseline (18.91nmol BCE/l vs 17.16nmol BCE/l; p<0.05) and osteocalcin levels increased significantly from the baseline (5.78ng/ml vs 6.68ng/ml; p<0.05). In addition, average of serum sRANKL, DKK-1, and plasma OPN levels decreased significantly from the baseline (sRANKL: 0.570pmol/l vs 0.480pmol/l; p<0.05, DKK-1: 2806pg/ml vs 2282pg/ml; p<0.01, and OPN: 117.0ng/ml vs 77.1ng/ml; p<0.01 respectively), however average of OPG levels did not change significantly from the baseline. TCZ decreased NTx, sRANKL, DKK-1, and OPN levels and increased osteocalcin levels regardless of remission group or no-remission group. Moreover, average of OPG levels in remission group increased significantly from the base line. Therefore, OPG/RANKL ratio tended to increase in remission group compared with no-remission group.

Conclusion: These findings suggest that TCZ therapy improves abnormal bone homeostasis in patient with active RA. We consider that this mechanism may result from the regulation of osteoclastic-bone destruction via the control of RANKL induced-osteoclastogenesis and OPN induced-osteoclast attachment of bone surface and the promotion of osteoblastic-bone formation via the regulation of DKK-1.

1282

Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Open-Label, Long-Term Extension Safety and Efficacy up to 48 Months. Jurgen Wollenhaupt[1], Joel C. Silverfield[2], Eun Bong Lee[3], Susan P. Wood[4], Koshika Soma[4], Lisy Wang[4], Hiroyuki Nakamura[5], Yoshihiro Komuro[5], Chudi I. Nduaka[4], David Gruben[4], Birgitta Benda[6], Samuel H. Zwillich[4], Richard Riese[4] and John D. Bradley[4]. [1]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Tampa Medical Group, Tampa, FL, [3]Seoul National University, Seoul, South Korea, [4]Pfizer Inc., Groton, CT, [5]Pfizer Japan Inc., Tokyo, Japan, [6]Pfizer Inc., Collegeville, PA

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy in RA. Here we report the safety and tolerability of tofacitinib and the durability of response up to 48 months (mo) in long-term extension (LTE) studies.

Methods: Data were pooled from two open-label studies (NCT00413699, NCT00661661) involving patients (pts) who had participated in randomized Phase (P)2 or P3 studies of tofacitinib. Treatment was initiated with tofacitinib 5 or 10 mg twice-daily (BID); data from doses are pooled. Baseline was that of the P2 or P3 study for pts enrolling within 14 days of participation; if enrollment was >14 days after participation, baseline was the start of the LTE study. Primary endpoints were adverse events (AE) and confirmed laboratory safety data. Secondary endpoints included ACR responses, DAS28-4(ESR), and HAQ-DI. Safety data were included over 60 mo of observation but efficacy data were only available up to Mo 48 (limited pt numbers [n=58] post-Mo 48).

Results: 4102 pts were treated for a total duration of 6034 patient-years (pt-y); mean (maximum) treatment duration was 531 (1844) days. 852 pts (20.8%) discontinued (AEs: 440 [10.7%]; lack of efficacy: 83 [2.0%]; other: 329 [8.1%]). The most commonly reported classes of AEs were infections and infestations (50.8%), gastrointestinal disorders (23.6%), musculoskeletal/connective tissue disorders (23.4%), and investigations (16.1%). The most frequent investigator-reported AEs (%) were nasopharyngitis (12.7%), upper respiratory tract infection (10.5%), and urinary tract infection (6.6%). Serious AEs (SAEs) were reported in 15.4% of pts with an incidence rate (IR) of 11.11 per 100 pt-y (95% CI 10.28, 12.02). Serious infection events (SIEs) were reported in 4.5% of pts with an IR of 3.07 per 100 pt-y (95% CI 2.66, 3.55). IRs for SAEs and SIEs did not increase between 36- and 48-mo observations.

Decreased hemoglobin (Hgb; ≥ 2 g/dL from baseline, or Hgb <8 g/dL) was observed in 3.5% of pts. Raised aminotransferases (>3 × upper limit of normal) were observed in 3.2% (ALT) and 1.5% (AST) of pts. Moderate-to-severe neutropenia (absolute neutrophil count [ANC] $0.5-1.5 \times 10^3/mm^3$) was reported in 0.7% of pts; there were no cases of confirmed ANC <0.5 × $10^3/mm^3$. Increases (>50% from baseline) in creatinine were noted in 3.2% of pts. Mean values for laboratory safety measures were consistent with observations in P2 and P3 studies, and were stable over time.

Efficacy was maintained through Mo 48. ACR20, ACR50, and ACR70 responses in pts treated with tofacitinib 5 and 10 mg BID (results pooled) at Mo 1 and Mo 48 were 67% and 69%, 44% and 47%, and 25% and 31%, respectively. Mean DAS28-4(ESR) was 6.2 at baseline, and was reduced to 3.8 at Mo 1, and 3.6 at Mo 48. Mean HAQ-DI score was 1.4 at baseline and improved to 0.85 at Mo 1, and 0.81 at Mo 48.

Safety and efficacy were similar for pts receiving tofacitinib as monotherapy or with background DMARDs.

Conclusion: Tofacitinib dosed at 5 or 10 mg BID in pts with RA demonstrated a consistent safety profile and sustained efficacy over 48 mo in open-label LTE studies.

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Effects of Tofacitinib On Patient-Reported Outcomes in Patients with Active Rheumatoid Arthritis Receiving Stable-Dose Methotrexate: Results of Two Phase 3 Studies.

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Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. The efficacy and safety of tofacitinib were evaluated in patients (pts) with active RA in Phase 3 trials. Primary efficacy analyses have previously been described.[1,2] Here we show patient-reported outcomes (PROs) from two Phase 3 studies.

Methods: Pts on stable-dose methotrexate (MTX) from the ORAL Step (NCT00960440; tumor necrosis factor inhibitor-inadequate responder [TNFi-IR] pts) and ORAL Scan (NCT00847613; MTX-IR pts) studies were randomized to tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or placebo (PBO) advanced to either tofacitinib 5 mg BID or 10 mg BID. All PBO pts in ORAL Step advanced at Month 3. In the ORAL Scan study, non-responder PBO pts (<20% reduction from baseline in swollen/tender joint counts) were advanced to tofacitinib 5 or 10 mg BID at Month 3, and all remaining PBO pts were advanced to tofacitinib at Month 6. Non-responding tofacitinib patients remained on the same treatment and dose. Excepting the Health Assessment Questionnaire-Disability Index, the PROs were secondary endpoints and included patient global assessment of disease activity (visual analog scale [VAS]), pain (VAS), health-related quality of life (Medical Outcomes Study Short-Form [36-Item] Health Survey), and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue).

Results: In total, 1196 pts received treatment (399 in ORAL Step and 797 in ORAL Scan). Within each study, baseline demographic and disease characteristics were generally similar across treatment groups; differences were noted between studies: ORAL Step pts were required to have failed at least one TNFi and had longer RA disease duration and higher disease activity at baseline relative to pts in ORAL Scan. Treatment with tofacitinib 5 and 10 mg BID resulted in significant improvements in all PROs when compared with PBO (Table 1). Improvements with both tofacitinib doses were observed at 3 months and continued through study end. Based on pts reporting improvements $\geq$ minimally clinically important differences, numbers needed to treat at Mo 3 for tofacitinib 5 and 10 mg BID, were 3.7–7.8 and 3.1–10.6, respectively, across various PROs in both studies.

Table 1. PROs at Month 3 (least squares means of change from baseline)

PRO	ORAL Step			ORAL Scan		
	PBO	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	PBO	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
PtGA (VAS)	−9.19	−23.39***	−25.05***	−8.59	−22.29***	−27.66***
No. of pts reporting improvements ≥MCID [−10]	49	74***	71***	63	198***	227***
NNT		4.3	5.8		4.2	3.1
Pain (VAS)	−8.26	−27.16***	−24.95***	−8.84	−23.31***	−28.04***
No. of pts reporting improvements ≥MCID [−10]	45	79***	78***	61	204***	221***
NNT		7.0	6.1		3.7	3.1
Physical function (HAQ-DI)	−0.18	−0.43***	−0.46***	−0.15	−0.40***	−0.54***
No. of pts reporting improvements ≥MCID [0.22]	55	71*	81*	63	184***	222***
NNT		7.1	5.5		5.1	3.2
Health-related quality of life (SF-36)						
SF-36 PCS	2.03	5.65***	6.57***	2.20	5.31***	7.39***
No. of pts reporting improvements ≥MCID [2.5]	57	80*	83*	64	198***	215***
NNT		5.4	5.8		4.2	3.6
SF-36 MCS	0.37	3.52*	3.96**	0.69	3.49*	4.71***
No. of pts reporting improvements ≥MCID [2.5]	43	64*	62*	57	152*	170***
NNT		5.8	8.0		7.8	5.7
FACIT-F	1.11	6.27***	4.57*	0.58	5.13***	6.28***
No. of pts reporting improvements ≥MCID [4]	44	72	60	49	167	176
NNT		4.4	10.6		4.3	4.0

*p < 0.05; ***p < 0.001 versus PBO
FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCID, minimal clinically important difference; MCS, mental component score; NNT, number needed to treat; PCS, physical component score; PRO, patient-reported outcome; PtGA, patient global assessment of arthritis; SF-36, Medical Outcomes Study Short-Form (36-Item) Health Survey; VAS, visual analog scale
PROs for full analysis set, longitudinal model; NNTs for full analysis set, no imputation

Conclusion: In two Phase 3 studies of tofacitinib in combination with MTX, treatment with tofacitinib 5 and 10 mg BID resulted in consistent statistically significant and clinically important improvements in multiple PROs vs PBO.

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Evaluation of Influenza and Pneumococcal Vaccine Responses in Patients with Rheumatoid Arthritis Receiving Tofacitinib. K. L. Winthrop[1], A. Racewicz[2], E. B. Lee[3], B. Wilkinson[4], S. H. Zwillich[4], K. Soma[4], S. Rottinghaus[4], T. Kawabata[4], R. Riese[4], S. Wood[4], J. Bradley[4] and C. O. Bingham III[5]. [1]Oregon Health and Science University, Portland, OR, [2]Department of Internal Medicine and Osteoarthrology, Bialystok Regional Hospital, Bialystok, Poland, [3]Seoul National University, Seoul, South Korea, [4]Pfizer Inc., Groton, CT, [5]Johns Hopkins University, Baltimore, MD

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. Clinical guidelines recommend the use of influenza and pneumococcal vaccines in patients with RA; however, the effect of tofacitinib on vaccine immunogenicity is unknown.

Methods: Patients with RA taking tofacitinib 10 mg twice daily (BID) were recruited from an open-label, long-term extension trial (NCT00413699). In this vaccine substudy, participants were randomized into 2 groups and stratified by methotrexate (MTX) use: 1) those who continued tofacitinib 10 mg BID during and after randomization ("continuous"); or 2) those who interrupted tofacitinib use for 1 week prior to and 1 week after vaccination ("withdrawn"). Vaccination baseline serum pneumococcal and influenza antibody titers were measured and all patients were vaccinated with the 2011–2012 influenza vaccine and PNEU-MOVAX® 23 (PCV23, Merck & Co., Inc) at 1 week post-randomization; antibody titers were measured at 35 days post-vaccination. The primary endpoint was the proportion of continuous and withdrawn patients who achieved a satisfactory humoral response to (a) pneumococcal vaccine (≥2-fold increase in antibody concentrations against ≥6 of 12 pneumococcal antigens [serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 19A, 19F, 23F, 18C]) and (b) influenza vaccine (≥4-fold increase in antibody titers against at least 2 of 3 influenza antigens). Secondary endpoints included comparison of pre- and post-vaccine hemaglutination titers (HI), and influenza and pneumococcal serotype-specific Geometric Mean Fold Rise (GMFR) between groups.

Results: Of 199 patients enrolled, 183 (continuous, N=92; withdrawn, N=91) completed vaccination and antibody titer evaluations and were included in the analysis. The proportion of patients achieving a satisfactory humoral response to pneumococcal and influenza vaccines was similar between patients who continued tofacitinib and those who were temporarily withdrawn (Table). Post-vaccination pneumococcal antigen GMFRs trended higher in patients withdrawn from tofacitinib, while GMFRs were similar between groups for influenza (Table). Protective influenza HI titers (≥1:40 influenza antibody titer in ≥2 of three antigens) were similar for continuous (75%) and withdrawn patients (82%) at 35 days post-vaccination.

Table. Percentage of satisfactory humoral responders (%) (evaluable population) and pneumococcal and influenza antigen GMFR at 35 days post-vaccination

Satisfactory humoral responders, %

	Responders n/N (%) tofacitinib 10 mg BID		Difference between treatment group % (95% CI)
	Continuous	**2-week withdrawn**	
PCV23*			
Overall	69/92 (75.0)	77/91 (84.6)	−9.6 (−24, 4.7)
Stratified by MTX use at BL			
Yes	36/55 (65.5)	44/55 (80.0)	−14.5 (−33.3, 5.0)
No	33/37 (89.2)	33/36 (91.7)	−2.5 (−25.2, 20.0)
Influenza vaccine*			
Overall	61/92 (66.3)	58/91 (63.7)	2.6 (−12.2, 16.6)
Stratified by MTX use at BL			
Yes	38/55 (69.1)	34/55 (61.8)	7.3 (−12.2, 26.4)
No	23/37 (62.2)	24/36 (66.7)	−4.5 (−27.8, 17.7)

Pneumococcal and influenza antigen GMFR at 35 days post-vaccination

Tofacitinib 10 mg BID

	Continuous			**2-week withdrawn**		
	N	**GMFR**	**95% CI**	**N**	**GMFR**	**95% CI**
Pneumococcal vaccine						
1	89	5.87	(4.57, 7.55)	86	9.26	(6.89, 12.44)
3	91	2.34	(1.97, 2.79)	89	4.20	(3.31, 5.32)
4	91	5.32	(4.22, 6.71)	89	6.29	(4.65, 8.51)
5	92	2.02	(1.75, 2.34)	91	2.53	(2.12, 3.02)
6B	92	2.32	(1.98, 2.73)	91	3.06	(2.53, 3.69)
7F	92	4.69	(3.73, 5.90)	89	6.41	(4.97, 8.28)
9V	92	3.17	(2.70, 3.72)	90	4.39	(3.62, 5.34)
14	92	5.23	(4.00, 6.86)	91	7.34	(5.50, 9.79)
18C	92	3.97	(3.28, 4.79)	91	7.41	(5.77, 9.53)
19A	92	2.33	(1.99, 2.72)	91	2.93	(2.46, 3.50)
19F	90	2.97	(2.44, 3.62)	90	4.60	(3.64, 5.80)
23F	92	2.74	(2.27, 3.32)	90	4.54	(3.58, 5.75)
Influenza vaccine						
B	92	3.33	(2.57, 4.32)	91	4.17	(3.25, 5.34)
H1N1	92	7.94	(5.96, 10.58)	91	6.71	(4.94, 9.12)
H3N2	92	7.80	(5.58, 10.91)	91	8.51	(6.45, 11.21)

*Primary endpoints, 35 days post-vaccination; BID, twice daily; BL, baseline; CI, confidence interval; GMFR, Geometric Mean Fold Rise; MTX, methotrexate; PCV23, PNEUMOVAX®, influenza vaccine for 2011–2012

Conclusion: Among patients with RA, continuous tofacitinib use did not significantly impair overall responsiveness to pneumococcal and influenza vaccines, although the pneumococcal antigen GMFRs trended higher in patients who discontinued tofacitinib. A study limitation is the absence of a MTX-only control group or group lacking tofacitinib exposure. These data suggest that it is not necessary to discontinue tofacitinib in order to attain meaningful responses to pneumococcal and influenza vaccines.

Disclosure: K. L. Winthrop, Oxford Immunotech; Pfizer, 2; Abbott; Pfizer; UCB; Amgen; Cellestis, 5; **A. Racewicz**, None; **E. B. Lee**, Pfizer Inc., 5; **B. Wilkinson**, Pfizer Inc., 1, Pfizer Inc., 3; **S. H. Zwillich**, Pfizer Inc., 1, Pfizer Inc., 3; **K. Soma**, Pfizer Inc., 1, Pfizer Inc., 3; **S. Rottinghaus**, Pfizer Inc., 1, Pfizer Inc., 3; **T. Kawabata**, Pfizer Inc., 1, Pfizer Inc., 3; **R. Riese**, Pfizer Inc., 1, Pfizer Inc., 3; **S. Wood**, Pfizer Inc., 1, Pfizer Inc., 3; **J. Bradley**, Pfizer Inc, 1, Pfizer Inc, 3; **C. O. Bingham III**, Pfizer Inc., 5.

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Short-Term Efficacy of Etanercept Plus Methotrexate Vs.Various Disease-Modifying Anti-Rheumatic Combinations with Methotrexate in Established Rheumatoid Arthritis. Roy Fleischmann[1], Andrew S. Koenig[2], Annette Szumski[2], Henk Nab[3], Lisa Marshall[2] and Eustratios Bananis[2]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Pfizer Inc., Collegeville, PA, [3]Pfizer Europe, Rome, Italy

Background/Purpose: The objective of this study was to assess the short-term benefit of etanercept (ETN) + methotrexate (MTX) vs. various disease-modifying anti-rheumatic drugs (DMARDs; hydroxychloroquine [HCQ], leflunomide [LEF], or sulfasalazine [SSZ]) + MTX in subjects with established rheumatoid arthritis (RA).

Methods: Data from subjects with moderate-to-severe RA and an inadequate response to MTX were pooled from the APPEAL[1] (ETN 25 mg twice weekly + MTX or DMARD + MTX) and LatinRA[2, 3] (ETN 50mg once weekly + MTX or DMARD + MTX) studies. At week 16, proportions of subjects for each pair of treatments were compared using Fisher's exact test for the following endpoints: American College of Rheumatology (ACR) 20, 50 and 70 responses, disease activity score in 28 joints (DAS28, both C-reactive protein [CRP; DAS28-CRP] and erythrocyte sedimentation rate [ESR; DAS28-ESR] methods) low disease activity (LDA; DAS28-CRP or DAS28-ESR ≤3.2), remission (DAS28-CRP or DAS28-ESR <2.6), Clinical Disease Activity Index (CDAI) of LDA (CDAI ≤10), CDAI remission (CDAI <2.8), and a Health Assessment Questionnaire (HAQ) score of ≤0.5.

Results: 478 subjects received ETN + MTX and 245 subjects received a DMARD + MTX (HCQ + MTX, n=81; LEF + MTX, n=69; SSZ + MTX, n=95). Baseline demographics were similar between the 2 treatment groups, with a mean age of 48.5 years (standard deviation [SD], 11.7; p=0.983) and disease duration of 7.6 years (SD, 7.5; p=0.437). At week 16, significantly more subjects receiving ETN + MTX achieved ACR 20/50/70, DAS28-CRP LDA and remission, DAS28-ESR LDA and remission, CDAI LDA and remission, and HAQ ≤0.5 compared with subjects on DMARDs + MTX (**Table**). Significantly greater proportions of subjects in the ETN + MTX group vs. the HCQ + MTX, LEF + MTX, and SSZ + MTX groups reached these endpoints with the exception of CDAI remission for all DMARD types and DAS28-CRP LDA, DAS28-ESR remission, CDAI LDA, and HAQ ≤0.5 in the LEF + MTX group. In addition, significantly more subjects on LEF + MTX achieved ACR50, DAS28-CRP LDA, DAS28-CRP remission, and CDAI LDA than subjects on SSZ + MTX.

Table. Proportions (%) of Subjects Achieving Endpoints at Week 16

Endpoint	ETN + MTX (N = 478)	DMARD + MTX			
		Overall (N = 245)	HCQ + MTX (N = 81)	LEF + MTX (N = 69)	SSZ + MTX (N = 95)
ACR 20	82	58[a]	59[a]	62[a]	54[a]
ACR 50	56	29[a]	31[a]	38[b,c]	20[a]
ACR 70	24	8[a]	12[d]	7[a]	6[a]
DAS28-CRP LDA	53	28[a]	28[a]	43[e]	17[a]
DAS28-CRP remission	35	15[a]	16[a]	22[c,d]	9[a]
DAS28-ESR LDA	39	18[a]	20[f]	20[b]	14[a]
DAS28-ESR remission	18	7[a]	7[d]	9	4[a]
CDAI LDA	54	29[a]	30[a]	42[e]	18[a]
CDAI remission	7	3[d]	2	3	3
HAQ ≤0.5	48	34[a]	32[d]	37	34[d]

[a]p < 0.001 vs. ETN + MTX; [b]p < 0.01 vs. ETN + MTX; [c]p < 0.05 vs. SSZ + MTX; [d]p < 0.05 vs. ETN + MTX; [e]p < 0.001 vs. SSZ + MTX; [f]p = 0.001 vs. ETN + MTX; p values calculated using Fisher's exact test.

Conclusion: Combination ETN + MTX was more effective in treating subjects with established moderate-to-severe RA regardless of the DMARD combination (HCQ, LEF, or SSZ) + MTX. LEF + MTX and HCQ + MTX had some greater benefits over SSZ + MTX at 16 weeks.

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Antibodies to Etanercept and Adalimumab in Rheumatoid Arthritis Inadequate Responders and Clinical Outcomes After an Active Switch to Infliximab.

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Background/Purpose: To determine if RA patients (pts) who had an inadequate response to etanercept(ETN) or adalimumab(ADA) and developed antibodies (Abs) to ETN or ADA responded clinically in the RESTART Trial after switching without a washout to infliximab(IFX) and if the presence of Abs to ETN or ADA correlated with differences in the levels of IFX or Abs to infliximab(ATI) compared to pts who had not developed Abs to ETN or ADA.

Methods: RESTART is a Phase 4, multicenter, open-label, assessor-blinded, active switch study of IFX+MTX (methotrexate) in pts with active RA who had an inadequate response (DAS28 score ≥3.6 and ≥6 SJC and TJC) to ETN or ADA+MTX. EULAR response was evaluated at wk 10 post-induction (1° endpoint). Pts adequately responding by EULAR criteria remained on IFX 3 mg/kg; incremental increases in IFX dose in pts not achieving/maintaining EULAR response occurred at wks 14 and/or 22, with a final efficacy assessment at wk 26. Assays were developed to measure Abs against ADA, ETN and IFX. Antibodies to anti-TNFs were measured at wks 0, 14 and 26 for ADA and wks 0, 6, 14 and 26 for ETN and IFX. IFX levels were measured at wks 0, 6, 14 and 26.

Results: Among the evaluated patients, 40.3% (50/124) of previously treated ETN pts and 46.8% (37/79) of the previously treated ADA pts of ADA pts demonstrated measureable Abs before exposure to IFX. No cross-reactivity was observed between anti-ADA Abs and IFX. By Week 26, 71% (88/124) of ETN inadequate responders demonstrated Abs to ETN (median titer = 1280) and 50.6% (40/79) of ADA inadequate responders had demonstrated Abs to ADA (median titer = 320). Of these pts, 195 pts had samples available for ATI testing, of which 24 pts (12.3%) had detectable ATI. Of these 24 pts, 23 had evidence of prior Abs to ETN (12/12) or ADA (11/12). Interestingly, the median wk26 serum conc of IFX was significantly lower in those pts who had developed Abs to ADA vs those who had not (2.1 mg/mL vs 11.9 ug/mL; p<0.0001) and contrasted with pts with or without Abs to ETN (8.8 ug/ml vs 11.7 ug/ml, respectively; p = 0.4768). Also, in pts who received IFX dose escalation to 5 or 7 mg/kg, the anti-ADA⁺ pts who were ATI⁻ had a median wk26 IFX serum conc (1.8ug/ml) lower than that observed for the dose escalated pts who were anti-ADA⁻ (13.9ug/ml). Overall, the combined EULAR responses at wks 10 and 26 were 49.7% and 51.8%, resp. Pts with Abs to ADA showed lower EULAR responses to IFX early on, but following incremental dose increases of IFX, these pts reached responses by wk26 (55.3%) similar to pts who were anti-ADA⁻ (59%).

Conclusion: Although Abs develop in 6% and 5% of adult pts treated with ETN and ADA (ETN PI 2011, ADA PI 2012, resp), in this pt population of refractory RA pts who had an inadequate response to either ADA or ETN, the majority of pts had developed moderate to high titer Abs to either ETN or ADA. In these pts, 12.3% developed ATI through 26wks after switching to IFX. Since no cross-reactivity was observed between anti-ADA Abs and IFX, the data suggest that some pts who developed Abs to ADA cleared IFX more rapidly than those pts who were anti-ADA⁻ and did so independent of ATI. Overall, a majority of IFX-treated pts demonstrated a EULAR response by wk26 regardless of the presence of Abs to ETN, ADA or IFX.

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Rheumatoid Arthritis Comparison of Active Therapies in Methotrexate Suboptimal Responders: Validation of the Strategy of Conventional Disease Modifying Anti-Rheumatic Drugs Before Biologicals.

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Background/Purpose: Double-blind placebo controlled randomized trials have demonstrated the efficacy of 15 different therapies in RA patients with active disease despite methotrexate (MTX). No blinded trials have compared conventional combination therapy to biologicals. Biologicals are roughly 100-fold more expensive than conventional therapy and have a different toxicity profile. We examine the strategy of starting conventional combination therapy followed by switch to a biological only in the subset of non-responders.

Methods: This multinational double-blind non-inferiority trial randomized 353 patients with active disease despite MTX equally to treatment with triple therapy (MTX, sulfasalazine and hydroxychloroquine) or etanercept plus MTX. Treatment continued for 48 weeks, with blinded treatment switch at 24 weeks allowed for patients in both groups if their DAS28 had failed to improve by a clinically significant amount (ΔDAS28 of <1.2). The primary end point of the trial was DAS28 improvement at week 48 based on the initial randomization group. Radiographs were obtained at 0, 24 and 48 weeks and scored by the modified Sharp method (secondary endpoint). Patients were enrolled from 16 VA centers, 12 other US sites and 8 sites in Canada.

Results: Study population baseline: mean age 57 yrs., 54% males, DAS28 = 5.8, disease duration 5.2 years and mean initial MTX dose of 19.6 mg week. There was no significant difference between groups at baseline. Both groups improved significantly from 0 to 24 weeks (p=0.001). The percentage of patients who switched therapy at 24 weeks was nearly identical (27.9% for triple therapy group vs. 27.0% for etanercept group). In those patients who switched both groups had significant improvement after the switch (p <0.0001) and the response was not different across therapies (p=0.08). At 48 weeks Δ DAS28 was not different between the groups (−2.1 [triple] and- 2.3 [etanercept]). Importantly, in patients in both groups who did respond and continued on their original assignment (73% of the patients in both groups) the response was maintained at 48 weeks. Radiographic progression (week 0 to week 48) was not different between the groups (+ 0.87 for triple vs. + 0.23 for etanercept, [p=0.09]). Secondary patient-reported outcomes including HAQII and pain were also not different between groups. Toxicities were similar across groups.

Conclusion: The strategy of conventional combination therapy before biological therapy provides benefit, both clinically and radiographically, that are similar to initial use of etanercept. For the first time data support the premise that patients who respond poorly to MTX and a biological (etanercept) have significant improvement with conventional DMARD combinations (triple therapy) and vice versa. At the health system level, the cost-saving potential and ultimately the cost-effectiveness of the

strategy of starting with conventional DMARD combinations and then switching to biologicals in those who do not respond is enormous.

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A Significant Number of Patients with Chronic Arthritis Received a Reduced Dosage of Biological Drugs: an Observational Study in Clinical Practice. Jose Inciarte-Mundo[1], Maria Victoria Hernández[1], Violeta Rosario[1], Sonia Cabrera[2], Virginia Ruiz-Esquide[1], Maria Eugenia Gomez-Caballero[1], Jose A. Gómez-Puerta[1], Julio Ramirez[1], Juan D. Cañete[1] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Hospital Clínic of Barcelona., Barcelona, Spain

Background/Purpose: Biological agents are used to treat chronic arthritis according to the standard dosages from phase III clinical trials. However, in some patients, a good response to treatment may allow the dosage to be reduced, the timing lengthened, and costs reduced. Our objective was to analyze a strategy of dosage reduction of biological agents in patients with chronic arthritis attended by the rheumatology department of a tertiary hospital.

Methods: Cross-sectional study which included all patients attended consecutively between June 2011 and November 2011 by a single clinician, and who had received ≥1 dose of a biological agent in 2011. Data analyzed were: demographic characteristics, diagnosis and disease duration, DMARD therapy, dosage, type and duration of biological agent used; time on reduced dosage and reason for dosage reduction. In rheumatoid arthritis (RA) patients we also analyzed disease activity (DAS28 score) and serum levels of C-reactive protein (CRP). The reduced dosage was defined as a lower dosage than recommended in the summary of product characteristics and was not based on a structured protocol.

Results: We included 170 patients (67% female); mean age: 51.1 ± 14.3 years. Diagnoses were: 56.5% RA, 18.8% ankylosing spondylitis (AS), 11.8% psoriatic arthritis (PsA) and 12.9% miscellaneous (MISC), including 9 juvenile idiopathic arthritis, 3 undifferentiated spondyloarthropathy, 3 uveitis, 2 connective tissue disorder and 1 SAPHO. Mean disease duration was 14.5 ± 8 years, with no differences between diagnoses. Mean duration of current biological therapy was 47.7 ± 35.6 months, with 134 patients receiving TNF blockers and 36 patients receiving non anti-TNF (abatacept, rituximab and tocilizumab). 53% of patients received concomitant therapy with DMARDs, mainly in the RA group, and 28.2% had received ≥1 biological agent. At the time of analysis, 76 patients (44.7%) were receiving low dosages of biologicals (56% of etanercept patients, 55% adalimumab, 45% tocilizumab, 39% infliximab and 11% abatacept). Of the 76 patients, 51.3% had RA, 23.7% AS, 13.2% PsA and 11.8% MISC. Most commonly used low dosages were 50 mg every 15 days for etanercept, 40 mg every 3 weeks for adalimumab, 5mg every 9–10 weeks for infliximab and 6 mg every 4 weeks for tocilizumab. The reason for dosage reduction was disease remission in 68 patients (89.5%) and low activity in 8 (10.5%). Mean time of dosage reduction was 17.2 ± 21.1 months. In RA patients, mean DAS28 score and CRP levels were lower in patients with reduced dosage than in patients with standard dosage (2.57 vs 3.47, p=0.09) and (0.37 vs 1.09, p=0.007), respectively, and the percentage of remission was higher (76.3% vs 30.7%, p=0.000). The medical decision at the time of data collection was to maintain low-dosage biological treatment in 63 patients (82.9%) due to low disease activity and/or remission, assessed by clinical judgment and regular scores.

Conclusion: Near half our chronic arthritis patients receiving biological therapy were able to reduce the dosage to below that of established clinical guidelines, preserving remission or low disease activity in many cases. This dosage reduction was observed both in RA and spondyloarthropathies, and with different biological drugs.

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Abatacept Biologic-Free Remission Study in Established Rheumatoid Arthritis Patients. Orion Study. Tsutomu Takeuchi[1], Tsukasa Matsubara[2], Shuji Ohta[3], Masaya Mukai[4], Koichi Amano[5], Shigeto Tohma[6], Yoshiya Tanaka[7], Hisashi Yamanaka[8] and Nobuyuki Miyasaka[9]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Matsubara Mayflower Hospital, Hyogo, Japan, [3]Taga General Hospital, Ibaraki, Japan, [4]Sapporo City General Hospital, Sapporo, Japan, [5]Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, [6]Sagamihara National Hospital, Sagamihara City, Japan, [7]University of Occupational and Environmental Health, Kitakyushu, Japan, [8]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [9]Tokyo Medical and Dental University, Tokyo, Japan

Background/Purpose: Abatacept (ABA) has comparable efficacy to TNF inhibitors in achieving clinical remission in rheumatoid arthritis (RA) patients. However, although clinical evidence suggests that biologic-free remission is achievable for RA patients treated with TNF inhibitors, no evidence for biologic-free remission is available for ABA. To evaluate the efficacy of ABA in terms of biologic-free remission in RA patients who achieved clinical remission with ABA.

Methods: We conducted a multi-center, non-randomized, 12-month, prospective observational study that recruited RA patients who achieved DAS28-CRP < 2.3 at the end of a Japanese phase II/III study. ABA was continued or discontinued based on the patients' decision. During a 12 month follow-up period, ABA treatment was restarted in patients who experienced disease flare (DAS28-CRP >2.7 at two consecutive visits) or according to doctors' decisions. The primary endpoint was the proportion of patients who maintained biologic-free remission 1 year after ABA discontinuation. DAS28-CRP and change in van der Heijde-modified Sharp Score (ΔTSS) were compared between the discontinuation and continuation groups.

Results: A total of 51 RA patients were enrolled in the study, of which 34 discontinued and 17 continued ABA treatment. The mean age was 57.1 ± 11.3 and 61.4 ± 9.4 years, mean disease duration at entry was 6.6 ± 5.3 and 12.0 ± 10.5 years, and mean duration of ABA treatment was 3.3 ± 0.3 and 3.3 ± 0.3 years for the discontinuation and continuation groups, respectively. Twelve patients (35.3%) in the discontinuation group maintained biologic-free remission for 12 months. Among the other 21 patients in the discontinuation group, 14 patients experienced disease flare, with 9 of them restarted ABA treatment. Seven patients dropped out from the study and one was excluded due to data deficiency, even though the patient discontinued ABA during the entire follow-up period (included in the analysis). The overall remission rate at month 12 for the discontinuation and continuation groups did not significantly differ (p=0.058, 23.5% and 52.9%, respectively). The least square mean (LS) means for DAS28-CRP at month 12 were 3.1 and 2.1 in the discontinuation and continuation groups, respectively, and the longitudinal profiles of the two groups were significantly different (P=0.030). ΔTSS of the discontinuation and continuation groups was 0.64 and 0.32, respectively, which did not statistically differ (p=0.19). The proportion of patients with non-radiological progression (ΔTSS≤0.5) was 52.9% and 70.6%, respectively, and no marked differences in HAQ-DI at month 12 were detected (0.68 and 0.56, respectively; p=0.46).

Conclusion: Biologic-free remission occurred in 35.3% of ABA discontinuation patients, with over 50% of both groups achieving non-radiographic progression. Moreover, functional remission was also maintained among patients in biologic-free remission compared to those in the continuation group. Our findings suggest that ABA may achieve biologic-free remission in RA patients.

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Effects of Tofacitinib On Lipid Profiles and Cholesterol and Lipoprotein Kinetics in Patients with Rheumatoid Arthritis.
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Background/Purpose: Tofacitinib is a novel oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. In RA patients (pts), suppression of total (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels during inflammation has been described. Tofacitinib has shown significant efficacy in reducing RA disease activity and inflammation in Phase 2/3 studies, during which a proportion of pts displayed increases in cholesterol levels. This Phase 1 study aimed to understand the mechanisms for suppression of cholesterol levels in active RA pts compared with healthy controls, and to investigate changes in cholesterol and lipoprotein kinetics following 6 weeks of tofacitinib treatment in RA pts.

Methods: Baseline lipid profiles and cholesterol and lipoprotein kinetics were assessed in 36 RA pts and 33 matched healthy controls (of similar age, race, sex, and menopausal status) and were repeated in RA pts after treatment with oral tofacitinib 10 mg twice daily for 6 weeks. Fasting blood samples were collected for apolipoprotein (Apo) and lipoprotein cholesterol concentrations, HDL and LDL particle size, and biomarkers of HDL dysfunction. In vivo cholesterol and lipoprotein kinetics were assessed with a 22-hour infusion of [^{13}C]cholesterol and [^{13}C]leucine.

Results: At baseline, HDL cholesterol, LDL cholesterol, TC and ApoA1 concentrations in RA pts were lower than in controls (Table). The cholesterol ester (CE) fractional catabolic rate (FCR) was significantly greater in RA pts vs controls without differences in cholesteryl ester transfer protein mass/activity or CE production rate. HDL-ApoA1 and LDL-ApoB100 FCR were similar between the groups. HDL biomarkers indicated HDL dysfunction in RA pts compared with controls as shown by higher HDL-associated serum amyloid A and myeloperoxidase, and lower in vitro lecithin cholesterol acyltransferase activity/mass. After tofacitinib therapy, the HDL-ApoA1 production rate was increased. Additionally, the CE FCR and cholesterol levels approached levels of controls with increases in plasma ApoA1 and ApoB concentrations. Increased CE FCR in the absence of changes in HDL-ApoA1 or LDL-ApoB100 FCR suggests increased selective CE uptake by scavenger receptor Class B Type 1 in RA pts, which was normalized by tofacitinib. Total HDL particle number and LDL size increased, and markers of HDL dysfunction improved after tofacitinib.

Table. Lipid parameters, cholesterol kinetics, and particle size in RA pts before and after treatment with tofacitinib, and in healthy controls

Mean (standard deviation)	RA patients Baseline	RA patients Tofacitinib-treated[a]	Baseline healthy controls
Lipid and lipoprotein concentrations			
Total cholesterol (mg/dL)	194 (33)†	220 (41)*	222 (42)
CE (mg/dL)	106 (20)†	122 (23)*	123 (30)
LDL-cholesterol (mg/dL)	125 (29)†	143 (39)*	145 (36)
HDL-cholesterol (mg/dL)	54 (13)†	62 (15)*	63 (17)
ApoB1 (mg/dL)	81 (42)	93 (42)*	82 (48)
ApoA1 (mg/dL)	117 (56)†	135 (58)*	128 (68)
Cholesterol and lipoprotein kinetics			
CE FCR (%/h)	2.43 (0.39)†	2.23 (0.31)*	2.17 (0.36)
CE production rate (mg/kg BW/h)	1.09 (0.24)	1.12 (0.24)	1.11 (0.26)
LDL-ApoB100 FCR (%/h)	1.61 (0.37)	1.57 (0.41)	1.50 (0.35)
LDL-ApoB100 production rate (mg/kg BW/h)	0.49 (0.12)	0.52 (0.12)	0.50 (0.13)
HDL-ApoA1 FCR (%/h)	1.08 (0.22)	1.11 (0.28)	1.02 (0.22)
HDL-ApoA1 production rate (mg/kg BW/h)	0.57 (0.11)	0.65 (0.15)*	0.59 (0.16)
HDL dysfunction			
HDL serum amyloid A (mg/L)	35 (63)†	18 (35)	3 (2)
Myeloperoxidase (pmol/L)	1092 (1017)†	943 (943)	736 (345)
LCAT activity (nmol/mL/h)	596 (139)†	642 (134)*	688 (121)
Particle size			
Total HDL particles (μmol/L)	30.7 (4.8)†	33.9 (5.51)*	35.0 (5.92)
LDL size (nm)	21.0 (0.85)	21.2 (0.97)*	21.4 (0.89)

*p < 0.05 vs baseline for RA pts; †p < 0.05 paired difference vs healthy controls
[a]Tofacitinib 10 mg twice daily for 6 weeks
Note: all pts had a body mass index <40 kg/m^2. Apo, apolipoprotein; BW, body weight; CE, cholesterol ester; FCR, fractional catabolic rate; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein

Conclusion: This is the first study to assess cholesterol and lipoprotein kinetics in pts with active RA and matched healthy controls. The data suggest that low cholesterol levels in RA pts with active disease may be explained by increases in CE catabolism. Treatment with tofacitinib decreased CE catabolism and normalized cholesterol levels to those of healthy controls while improving markers of HDL function, including increased HDL-ApoA1 production.

1291

A Phase Ib Clinical Trial with F8-IL10, an Anti-Inflammatory Immunocytokine for the Treatment of Rheumatoid Arthritis (RA), Used in Combination with Methotrexate (MTX).
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Background/Purpose: Interleukin 10 (IL10) is an anti-inflammatory cytokine potentially efficacious for RA. F8-IL10 is a fusion protein in which the cytokine is fused with the antibody F8 specific to the alternatively-spliced EDA domain of fibronectin, a marker of angiogenesis. The conjugation of IL10 to the antibody F8 allows the selective delivery and accumulation of the cytokine to sites of inflammation, therefore increasing the therapeutic index. In mouse models of collagen-induced arthritis, F8-IL10 was able to selectively localize at sites of inflammation and showed a clear therapeutic activity by drastically reducing paw swelling when combined with MTX. A Phase Ib clinical trial is now on-going involving the administration of F8-IL10 in combination with MTX in patients with RA who have previously failed at least one TNF blocker. Objectives of the study are to establish the maximum tolerated dose of the combined treatment (F8-IL10 + MTX), to study safety and tolerability, to obtain preliminary information on efficacy and to assess the pharmacokinetic behavior of the drug. Here, we report the results obtained in 5 patients who have already completed the study. A sixth patient is under treatment at the time of writing.

Methods: Cohorts of 3–6 patients with active RA are assigned to receive escalating doses of F8-IL10 (6, 15, 30, 60 μg/kg respectively) in combination with 15mg of MTX. The treatment is given as once weekly sc injection for up

to 8 weeks. Safety evaluation performed on days 1 through 28, including AEs, SAEs, and standard laboratory assessments, are used to determine the dose limiting toxicity. Response is assessed after 4 and 8 weeks of treatment according to ACR and DAS28 criteria. The pharmacokinetic profile and formation of human anti-fusion protein antibodies are measured using standard methods.

Results: All three patients enrolled in the first cohort (6 μg/kg weekly of F8-IL10) achieved an ACR 50 response at more than one evaluation time point. In cohort 2 (15 μg/kg weekly of F8-IL10), patient I005 even resulted in ACR 70 response whereas patient I004 did not reach ACR20, however a moderate EULAR response was seen and treatment stopped after only 4 weeks. ACR responses are summarized in the attached table. DAS 28 significantly improved in all patients but to a lesser extent in pt I004. An excellent tolerability of F8-IL10, at the doses used, was observed in all treated patients, as of now no grade ≥2 adverse drug reactions have been reported.

ACR RESPONSE TO THE TREATMENT

Patient ID	week 5	week 9	F.U. 1 (week 14)	F.U. 2 (week 22)	Cohort and Dose Level
I001	ACR0	ACR0	ACR50	ACR50	Cohort 1, 6 μg/kg weekly
I902	ACR0	ACR50	ACR50	ACR20	Cohort 1, 6 μg/kg weekly
I903	ACR0	ACR50	ACR50	ongoing	Cohort 1, 6 μg/kg weekly
I004	ACR0	-	-	-	Cohort 2, 15 μg/kg weekly
I005	ACR50	ACR70	ACR70	ongoing	Cohort 2, 15 μg/kg weekly
I006	ongoing				Cohort 2, 15 μg/kg weekly

Conclusion: The promising safety data regarding the clinical use of F8-IL10, together with preliminary positive signs of activity may be favored by the targeted delivery of IL10 to the site of inflammation. These results also warrant future developments of the product in randomized clinical trials, which are currently in planning. An update of clinical data will be presented at the ACR meeting.

1292

Fatigue Is an Independent Variable Predicting Physical Function and Disease Activity Score-28 Remission for Patients with Rheumatoid Arthritis Treated with Intravenously Administered Golimumab: Results From Phase 3, Placebo Controlled Clinical Trial. Rene Westhovens[1], Michael Weinblatt[2], Chenglong Han[3], Tim Gathany[3], Lilianne Kim[4], Michael Mack[5], Jiandong Lu[5], Daniel Baker[5], Alan Mendelsohn[5] and Clifton O. Bingham[6]. [1]University Hospital KU Leuven, Leuven, Belgium, [2]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [3]Johnson & Johnson Pharmaceutical Services, LLC, Malvern, PA, [4]Janssen Research & Development, LLC, Malvern, PA, [5]Janssen Research & Development, LLC, Spring House, PA, [6]Johns Hopkins University, Baltimore, MD

Background/Purpose: To evaluate the association of fatigue with physical function and disease activity in patients with rheumatoid arthritis (RA), and the impact of treatment with intravenously administered golimumab (GLM) on fatigue using data from the Phase III clinical trial GO- FURTHER.

Methods: GO-FURTHER was a multicenter, randomized, placebo-controlled study. Adult patients with active RA despite MTX therapy were randomized to placebo + MTX (placebo group) or GLM 2mg/kg plus MTX (GLM group) at week 0, 2, and every 8 week thereafter. Patients in placebo group with <10% improvement in tender and swollen joint count from baseline at week 16 entered early escape and received a 2 mg/kg GLM infusion at Weeks 16 and 20. Impact on physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ). Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and clinically meaningful improvement in FACIT-Fatigue was defined as ≥ 4 points increase in the scores. Correlation of FACIT-Fatigue with HAQ and disease activity and remission (DAS28 using CRP<2.6) were analyzed using Pearson correlation, or multiple linear and logistic regression models to adjust for other confounding variables (age,

CRP, swollen and tender joints counts). Comparisons between groups were performed using ANOVA on van der Waerden normal scores for continuous outcomes or Chi-square test for binary outcomes.

Results: At baseline, mean (SD) FACIT-Fatigue score was 25.5 (10.54), indicating significant fatigue. Significant correlations of FACIT-Fatigue with HAQ (r=-0.62, p<0.01) and DAS28 score (r=-0.42, p<0.01) were observed at baseline. In multiple regression models, baseline FACIT-Fatigue score or change in FACIT-Fatigue at week 24 were correlated with change in HAQ and DAS28 score. Patients with higher FACIT-Fatigue scores at baseline were more likely to achieve DAS28 remission at week 24 (p=0.024). Compared to the placebo group, GLM-treated patients had significantly greater improvement in FACIT-fatigue at week 12 (5.4 ± 10.3 vs. 2.1 ± 9.0), which was sustained through week 16 (7.5 ± 10.5 vs. 2.2 ± 9.7) and 24 (8.0 ± 10.8 vs. 2.5 ± 10.2) (all p-values<0.001). Compared with the placebo group, a greater proportion of patients in the GLM group achieved clinically meaningful improvement in FACIT-Fatigue score at week 12 (57.5% vs. 42.8%) and at week 24 (65.8% vs. 40.3) (all p-values<0.001).

Conclusion: RA patients inadequately responsive to MTX experienced severe fatigue. Fatigue was a significant independent predictor of physical function and disease activity in patients with RA. Treatment with intravenously administered GLM significantly improved clinical symptoms of fatigue in patients with RA inadequately responsive to MTX.

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Importance of Steady-State Trough Concentrations After Intravenous Golimumab with Concomitant Methotrexate in Subjects with Active Rheumatoid Arthritis. J. H. Leu, Z. Xu, C. Hu, Alan Mendelsohn, J. Ford, Hugh M. Davis and H. Zhou. Janssen Research and Development, LLC, Spring House, PA

Background/Purpose: To determine an optimized dosing regimen for IV golimumab in subjects with active RA using population pharmacokinetic (PK) modeling and simulation.

Methods: Two Phase 3 trials were performed for IV golimumab. In the first trial, IV infusions of 2 mg/kg golimumab every 12 weeks (Q12W) or 4 mg/kg Q12W with concomitant methotrexate (MTX) were investigated in RA subjects. Population PK modeling was conducted using data from this first trial. Simulations were performed to identify an optimized IV regimen that would result in steady-state trough golimumab concentrations similar to the approved subcutaneous (SC) dosing regimen of 50 mg Q4W. Absolute bioavailability of 50% and Ka of 0.658 day^{-1} were used for simulating the SC golimumab profile. The dosing regimen for the second trial was then modified to shorten the dosing interval to Q8W.

Results: In the first trial, although there were strong trends towards clinical benefit, the primary endpoint (ACR 50) was marginally missed. It was found that Q12W dosing was inadequate to maintain adequate trough golimumab concentrations at the later part of the dosing interval. Using population PK analysis, a two-compartment IV infusion model with first-order elimination was developed. Parameter estimates for the model were: CL: 0.654 L/day; V1: 4.33 L; V2: 2.82 L and Q: 0.215 L/day. Simulations showed that IV golimumab 2 mg/kg Q8W + MTX and currently approved SC golimumab 50 mg Q4W + MTX resulted in similar steady-state trough golimumab concentrations. When the IV regimen of 2 mg/kg golimumab at Weeks 0, 4 followed by Q8W was studied in the second trial, the primary efficacy endpoint (ACR 20) was achieved.

Conclusion: Population PK modeling and simulation aided in the determination of an optimized dosing regimen for IV golimumab in subjects with active RA. Both observed data and population PK modeling and simulation corroborate the importance of maintaining adequate steady-state trough concentrations of golimumab for robust clinical efficacy.

A Phase Ib Multiple Ascending Dose Study Evaluating Safety, Pharmacokinetics, and Early Clinical Response of Brodalumab (AMG 827), a Human Anti-Interleukin 17 Receptor (IL-17R) Antibody, in Rheumatoid Arthritis.

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Background/Purpose: The cytokine IL-17A is an innate inflammatory cytokine implicated in the pathogenesis of several human autoimmune diseases including rheumatoid arthritis (RA). Brodalumab is a human, immunoglobulin G2 (IgG2) monoclonal antibody that binds with high affinity to human IL 17RA and blocks the biological activity of IL 17A, IL-17F, IL-17A/F heterodimers, and IL-25. Increased levels of IL-17A have been detected in the synovial fluid of patients with RA and furthermore, blockade of IL-17A signaling can inhibit osteoclast formation induced by culture media of RA synovial tissues. The aim of this study was to evaluate safety, pharmacokinetics, and preliminary efficacy of brodalumab in subjects with moderate to severe RA.

Methods: This phase Ib, randomized, placebo-controlled, double-blind multiple ascending dose study enrolled subjects with a moderate to severe RA (>6/66 swollen and >8/68 tender joints). Subjects were randomized 3:1 to receive multiple doses of brodalumab (50mg, 140mg or 210mg subcutaneously every two weeks for 6 doses, or 420mg or 700mg intravenously every 4 weeks for two doses) or placebo. The primary endpoint was safety and tolerability of brodalumab, including incidence of adverse events (AEs). Multiple dose pharmacokinetics was a secondary endpoint. Exploratory endpoints included pharmacodynamics, and improvements in RA clinical metrics. Assessments were performed up to end of study on day 127.

Results: 40 subjects were randomized and received at least one dose; there was one dropout on day 85 due to worsening RA (placebo). Treatment with brodalumab resulted in receptor occupancy by brodalumab on circulating leukocytes and inhibition of IL-17 receptor signaling. Dose-dependent increases in the magnitude and duration of mean receptor occupancy were observed. Treatment-related AEs were reported by 3 (30.0%) of 10 placebo subjects and 7 (23.0%) of 30 brodalumab subjects. The most common treatment-related adverse event was headache (20%) for placebo subjects and leukocytosis (7%) for brodalumab subjects. Serious AEs occurred in 2 subjects during the study [complicated migraine (placebo) and non-cardiac chest pain (brodalumab, 420 mg IV)]; neither was considered by the investigator related to investigational product. On day 85 (week 13) ACR20 was achieved by 11 (36.7%) of 30 subjects receiving brodalumab and 2 (22.0%) of 9 subjects receiving placebo. Few ACR50 or ACR70 responses were observed in either active or placebo group at day 85.

Conclusion: This small ascending dose phase 1b study demonstrates that multiple dose administration of brodalumab was tolerated in subjects with active RA. Conclusions about efficacy cannot be reached given the study design.

Effectiveness and Tolerability of Subcutaneous Tocilizumab in Rheumatoid Arthritis Patients Switched From Intravenous Tocilizumab: Results From the Extension Period of the Musashi Study.

Atsushi Ogata[1] and the MUSASHI study group[2]. [1]Osaka University Graduate School of Medicine, Suita, Japan, [2]Japan

Background/Purpose: In the MUSASHI study (i.e., Double-blind, parallel-group, Phase III non-inferiority study comparing subcutaneous tocilizumab [SC-TCZ] monotherapy versus intravenous tocilizumab [IV-TCZ] monotherapy), the effectiveness and safety of SC-TCZ monotherapy were proved to be comparable to those of IV-TCZ monotherapy in Japanese patients with rheumatoid arthritis (RA). The aim of the current study was to investigate the effectiveness and safety of SC-TCZ in the patients who had received IV-TCZ in the MUSASHI study.

Methods: This study enrolled RA patients who had received TCZ monotherapy for 24 weeks in the MUSASHI study (prior-IV group: 8 mg/kg IV-TCZ every 4 weeks; prior-SC group: 162 mg SC-TCZ every 2 weeks). They received open label SC-TCZ (162 mg every 2 weeks) starting at Week 24 without any concomitant use of synthetic or biologic DMARDs. Disease activity as measured by DAS28-ESR and ACR response rates and safety were assessed.

Results: A total of 319 patients (160 patients in the prior-IV group and 159 patients in the prior-SC group) were enrolled. Baseline demographics were comparable between the prior-IV group and the prior-SC group: body weight (kg, mean $\pm$ SD), 54.3 ± 10.1 vs. 53.9 ± 8.8; proportion of patients who previously used TNF-α inhibitors before the MUSASHI study, 23.1% vs. 18.2%. At 12 weeks after starting the extension period (36 weeks after the beginning of the MUSASHI study), 158 patients in the prior-IV group and 157 patients in the prior-SC group were still receiving SC-TCZ. The mean change of DAS28-ESR in the prior-IV group was comparable to that in the prior-SC group over the whole 36 weeks, and was maintained after switching from IV-TCZ to SC-TCZ (Table). ACR response rates at Week 24 were also maintained for the 12 weeks following the switch from IV-TCZ to SC-TCZ. The incidences of new onset AEs and SAEs between Weeks 24 and 36 were, respectively, 59.4% (95/160) and 4.4% (7/160) in the prior-IV group and 57.9% (92/159) and 2.5% (4/159) in the prior-SC group. The safety profiles in both groups were comparable. Among AEs, the incidence of new onset injection-site reactions (ISRs) was 5.6% (9/160) in the prior-IV group. No case of serious ISR was seen during the extension period in the prior-IV group and the prior-SC group. Anti-TCZ antibodies were detected in 1 patient who switched from IV to SC administration. However this patient had no case of serious anaphylaxis or anaphylactoid reactions.

Table. DAS28-ESR over time (mean $\pm$ SD)

week	Double blind period			Extension period
	0	12	24	36
Prior-SC[*1]	6.1 ± 0.9	3.1 ± 1.2	2.7 ± 1.3	2.6 ± 1.4
Prior-IV[*2]	6.2 ± 0.9	2.8 ± 1.0	2.5 ± 1.1	2.6 ± 1.2

[*1]Prior-SC: SC-TCZ 162 mg q2w
[*2]Prior-IV: IV-TCZ 8 mg/kg q4w for 24 weeks and then switched to SC-TCZ 162 mg q2w

Conclusion: There was no sign of effectiveness being reduced after switching to SC-TCZ in this short extension period. Switching of TCZ treatment from IV-TCZ to SC-TCZ was tolerable. These findings are useful consideration for the clinical application of SC-TCZ.

An Interim Analysis of the Efficacy of Abatacept in Japanese Biologics-naïve Rheumatoid Arthritis Patients (results from ABROAD study): Comparison of CRP and MMP-3 Level After Treatment with Abatacept Versus Anti-TNF Agents.

Masahiro Sekiguchi[1], Kiyoshi Matsui[1], Masayasu Kitano[1], Mitsuo Namiki[1], Koichiro Ohmura[2], Takao Fujii[2], Hideko Nakahara[3], Keiji Maeda[3], Hideo Hashimoto[4], Takanori Kuroiwa[5], Kenji Miki[6], Masanori Funauchi[7], Kazuhiro Hatta[8], Kenshi Higami[9], Shunzo Namiuchi[10], Ichiro Yoshii[11], Teruyuki Nakatani[12], Takashi Ikawa[13], Takaji Matsutani[14], Kosaku Murakami[15], Satoshi Morita[16], Yutaka Kawahito[17], Norihiro Nishimoto[14], Tsuneyo Mimori[2] and Hajime Sano[1]. [1]Hyogo College of Medicine, Nishinomiya, Japan, [2]Kyoto University, Kyoto, Japan, [3]NTT West Osaka Hospital, Osaka, Japan, [4]Rinku Hashimoto Rheumatology, Osaka, Japan, [5]Yukioka Hospital, Osaka, Japan, [6]Amagasaki Central Hospital, Amagasaki, Japan, [7]Kinki University Faculty of Medicine, Osaka, Japan, [8]Tenri Yorozu Sodansyo Hospital, Nara, Japan, [9]Higami Hospital, Nara, Japan, [10]Saiseikai Nakatsu Hospital, Osaka, Japan, [11]Yoshii Hospital, Shimanto, Japan, [12]Kishiwada City Hospital, Osaka, Japan, [13]Kobe-Konan Yamate Clinic, Kobe, Japan, [14]Wakayama Medical University, Ibaraki, Japan, [15]Osaka Red Cross Hospital, Osaka, Japan, [16]Yokohama City University, Kanagawa, Japan, [17]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Background/Purpose: Abatacept (ABA) is a recombinant fusion protein consisting of the extracellular domain of human CTLA-4, binding to

CD80/86 on antigen presenting cells (APCs) and thereby inhibits the interaction between these molecules and CD28 on T cells. ABA suppresses T cell activation and has been reported to have the therapeutic benefit for patients with rheumatoid arthritis (RA). However, there are limited data to compare the efficacy of ABA and anti-TNF agents. We conducted the ABROAD study (Abatacept Research Outcomes as a first-line biological Agent in the real worlD) in collaboration with 37 institutions in Japan. In this study, we confirmed the efficacy of ABA and compared CRP and MMP-3 levels after treatment with ABA versus anti-TNF agents in Japanese biologics-naïve RA patients.

Methods: We analyzed multicenter 100 biologics-naïve RA patients treated with ABA (ABROAD study) from January 2010 to May 2012. Patients received 500mg of abatacept for patients weighted less than 60kg or 750mg for patients with more than 60kg with or without MTX (mean dosage:6.0±3.7mg/week) for 24 weeks. To evaluate the efficacy of the treatment, we measured SDAI, DAS28-CRP (DAS), CRP and MMP-3 levels at week 0, 4, and 24 after treatment. We also compared CRP and MMP-3 levels after treatment with ABA versus anti-TNF agents using propensity score matching of sex, age and duration of the disease in 48 biologic-naïve RA patients, respectively.

Results: At week 0, 4, and 24 after ABA treatment, the mean SDAI/DAS score and CRP/MMP-3 levels were SDAI (26.2±14.9→16.6±11.1→10.4±9.6), DAS (4.5±1.3→3.5±1.2→2.8±1.2), CRP (2.1±2.2→1.1±1.6→0.8±1.8 mg/dl), and MMP-3 (219.1±202.5→169.7±140.3→114.1±117.0 ng/dl), respectively. We observed statistically significant reduction of SDAI/DAS/CRP/MMP-3 levels at week 4 compared to those of the baseline. The proportions of patients who achieved low disease activity or remission at week 24 were 65.7% and 17.2% based on SDAI score, and 49.0% and 39.2% based on DAS, respectively. In the comparison of propensity score matching 96 biologics-naïve RA patients (48 patients received ABA: ABROAD group; 48 patients received anti-TNF agents: anti-TNF group), the mean CRP levels at week 0, 4 and 24 after treatment were (1.75±1.99→0.71±0.88→0.39±0.67 mg/dl) in ABROAD group and (1.60±1.78→0.52±1.24→0.45±0.78 mg/dl) in anti-TNF group, respectively. The mean MMP-3 levels at week 0, 4 and 24 after treatment were (217.4±194.5→166.3±124.7→90.7±64.0 ng/dl) in ABROAD group and (225.9±163.8→164.4±177.2→127.9±128.2 ng/dl) in anti-TNF group, respectively. Although statistically not significant, CRP and MMP-3 levels in ABROAD group were lower than those in anti-TNF group at week 24 after treatment.

Conclusion: We observed the efficacy of ABA at week 4 after treatment of biologic-naïve RA patients. We also observed that CRP and MMP-3 levels in ABROAD group were lower than those in anti-TNF group at week 24 after treatment. These results indicate the possibility that ABA could become as a first-line biologic for the treatment of RA patients.

Disclosure: M. Sekiguchi, Bristol-Myers Squibb, 2; **K. Matsui**, Bristol-Myers Squibb, 2; **M. Kitano**, Bristol-Myers Squibb, 2; **M. Namiki**, Bristol-Myers Squibb, 2; **K. Ohmura**, Bristol-Myers Squibb, 2; **T. Fujii**, Bristol-Myers Squibb, 2; **H. Nakahara**, None; **K. Maeda**, None; **H. Hashimoto**, None; **T. Kuroiwa**, None; **K. Miki**, None; **M. Funauchi**, Bristol-Myers Squibb, 2; **K. Hatta**, None; **K. Higami**, None; **S. Namiuchi**, None; **I. Yoshii**, None; **T. Nakatani**, None; **T. Matsutani**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 8; **K. Murakami**, None; **S. Morita**, Bristol-Myers Squibb, 8; **Y. Kawahito**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 8; **N. Nishimoto**, Bristol-Myers Squibb, 2; **T. Mimori**, Bristol-Myers Squibb, 2; **H. Sano**, Bristol-Myers Squibb, 2.

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Tofacitinib and Adalimumab Achieve Similar Rates of Low Disease Activity in Rheumatoid Arthritis—Lack of Improvement in Disease Activity Score by 3 Months Predicts Low Likelihood of Low Disease Activity At 1 Year.
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Background/Purpose: Tofacitinib is a novel oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. This post-hoc analysis of the Phase 3 active-controlled randomized ORAL Standard trial (NCT00853385) determined the relationship between changes in the Disease Activity Score (28 joints, 4 components, ESR; DAS28) during the first 3 months (mo) of treatment with tofacitinib or adalimumab (ADA), and the likelihood of achieving low disease activity (LDA) at Mo 6 or Mo 12 in patients (pts) with RA.

Methods: Pts on stable background methotrexate (MTX) were randomized 4:4:4:1:1 to one of five sequences: tofacitinib 5 mg twice daily (BID); 10 mg BID; ADA 40 mg sc biweekly (q2w); placebo (PBO) advanced to tofacitinib 5 mg BID; or PBO advanced to 10 mg BID. All pts self-administered injections q2w (ADA or PBO). Pts on PBO advanced to tofacitinib at Mo 6, or at Mo 3 if they did not show ≥20% reduction from baseline (BL) in swollen/tender joint counts.

Results: Overall, 717 pts were treated. Primary results have been reported previously.[1] Mean BL DAS28 values across sequences were 6.4–6.6. Tofacitinib 5 and 10 mg BID and ADA all showed statistical superiority to PBO at Mo 3 and Mo 6, and achieved numerically similar responses, including rates of LDA (DAS28 ≤3.2) (Table). In the current analysis of pts with a DAS28 improvement from BL <0.6 by Mo 1, less than 5% receiving tofacitinib 5 mg BID and approximately 10% receiving tofacitinib 10 mg BID achieved LDA at Mo 12. In pts with a DAS28 improvement from BL <0.6 by Mo 3, none achieved LDA at Mo 6 or Mo 12 on either dose of tofacitinib, while approximately 10% (n=2) of ADA pts with DAS28 improvement <0.6 by Mo 3 achieved LDA at Mo 12 (Table).

Endpoint	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab 40 mg q2w	Placebo
LDA (%), all pts[a]				
Mo 3	14.7**	13.6**	14.6**	2.2
Mo 6	17.0*	19.3**	15.7*	4.4
Mo 12	17.5	22.7	26.4	NA
LDA (n/N) at Mo 12 in pts achieving <0.6 DAS28 improvement from BL at Mo 1	1/42	5/49	8/54	NA
LDA (n/N) at Mo 12 in pts achieving <0.6 DAS28 improvement from BL at Mo 3	0/19	0/19	2/21	NA

*p≤0.001; **p≤0.0001 vs placebo. [a]Non-responder imputation BL, baseline; DAS28, Disease Activity Score (28 joints, 4 components, erythrocyte sedimentation rate); LDA, low disease activity defined as DAS28≤3.2; Mo, month; n, number of patients achieving LDA; N, total number of patients with DAS28 improvement from baseline < 0.6; NA, not applicable

Conclusion: LDA rates were similar between tofacitinib and ADA. In this post-hoc analysis of the ORAL Standard study, failure to achieve ≥0.6 improvement from baseline in DAS28 within the first 3 months of tofacitinib treatment was predictive of a low probability of achieving LDA at 1 year.

Reference
1. van Vollenhoven RF et al. Arthritis Rheum 2011; 63: S153.

Disclosure: R. F. van Vollenhoven, Abbott; BMS; GSK; HGS; MSD; Pfizer; Roche; UCB, 2, Abbott; BMS; GSK; HGS; MSD; Pfizer; Roche; UCB, 5; **S. Krishnaswami**, Pfizer Inc., 1, Pfizer Inc., 3; **B. Benda**, Pfizer Inc., 1, Pfizer Inc., 3; **D. Gruben**, Pfizer Inc., 3, Pfizer Inc., 1; **B. Wilkinson**, Pfizer Inc., 1, Pfizer Inc., 3; **C. A. Mebus**, Pfizer, Inc., 1, Pfizer, Inc., 3; **S. H. Zwillich**, Pfizer, Inc., 1, Pfizer, Inc., 3; **J. Bradley**, Pfizer Inc., 1, Pfizer Inc., 3.

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Improvement of Treatment Outcome of Rheumatoid Arthritis with Salazosulfapyridine by Pharmacogenetic Approach.
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Background/Purpose: Salazosulfapyridine (SASP) is acetylated in liver by N-acetyltransferase2 (NAT2) in the track of metabolism. Previous studies have shown that genotyping of NAT2 is adequate to classify its acetylation activity into fast (FA), intermediate (IA), and slow acetylator (SA). Prediction of SASP efficacy/adverse events (AEs) based on NAT2 genotype has been demonstrated in retrospective studies, but has not been validated by prospective study. Thus, the purpose of this study is to investigate the association of efficacy and NAT2 genotype prospectively.

Methods: NAT2 genotype was determined by typing following SNPs, C341T, G590A, and G857A, using Q-probe method (i-densy; Arkray Inc.). Wilcoxon rank-sum test and Pearson's chi-square test were used for statistical analysis.

1.) Retrospective Study: AEs and efficacy were retrospectively investigated based on physician's reports and medical records for 102 RA patients (male/female; 29/73, mean age; 60.2±14.6 years), whose mean DAS28-CRP (DAS28) was 4.26±1.08 at baseline.

2.) Prospective Study: Forty three RA patients who initiated SASP between Jan 2010 and Mar 2012 (male/female; 15/28, mean age; 64.4ΔDAS28 was significantly greater in IA than that of FA (FA; −1.03±0.86, IA; −1.88

Results: Between Oct 2001 and Apr 2012, 9,905 CORRONA patients initiated biologic therapy for RA, of which 40% were previously bio naïve. Demographics and disease activity characteristics in the Bio naïve and Bio

experienced patients respectively were as follows; age (years; mean±SD): 57±14 vs 57±13, females: 76% vs 81%, duration of RA (years; mean±SD): 8±9 vs 13±10, seropositivity: 75% vs 73%, and CDAI (mean±SD): 19± 14 vs 22± 15.

Of the 9,905 patients, 25% received Bio MT and 75% received Bio CMB. Among patients that were previously bio naïve, 19% initiated a biologic as MT whereas MT initiation rates for patients who had received one prior biologic was 29%; two prior biologics, 26%; and three or more prior biologics, 31%. Higher rates of MT initiations were observed with prior Bio experience (unadjusted OR 2.01 [95% CI 1.70, 2.37]). Higher proportion of patients starting their biologic therapy after 2006 received MT as compared to those who started their biologic therapy prior to 2006 but was not statistically significant (unadjusted OR 1.20 [95% CI 0.99, 1.45]).

In the multivariate model (Table 1), Bio experienced patients continued to be significantly more likely to receive MT as compared Bio naïve. Median odds ratio showing the effect of individual physician's prescribing patterns on initiating bio MT was 2.40 [95% CI 2.08, 2.86].

Table 1. Adjusted Odds ratios for initiating Bio MT versus Bio CMB

	OR (95% CI) for initiating Bio MT vs Bio CMB
Prior number of biologics	1
0 (reference)	2.12 (1.76, 2.54)
1	1.63 (1.30, 2.04)
2	2.20 (1.68, 2.89)
≥3	
After 2006 vs. up to 2006	1.03 (0.84, 1.25)
Effect of physician prescribing patterns	2.40 (2.08, 2.86)

Abbreviations: Bio–biologic, MT–monotherapy, CMB–combination therapy.

Conclusion: Monotherapy remains a common strategy of biologic prescription to treat RA. Prior biologic experience and individual physician's prescribing patterns were associated with increased likelihood of initiating a biologic as monotherapy warranting further investigation to understand factors influencing decisions to initiate biologic monotherapy.

Disclosure: D. A. Pappas, CORRONA,; G. W. Reed, Corrona, 2, University of Massachusetts Medical School, 3, Corrona, 5, Harvard Medical School,; K. C. Saunders, Corrona, 3; A. John, Genentech, 3; A. Shewede, Genentech and Biogen IDEC Inc., 3; J. Devenport, Genentech and Biogen IDEC Inc., 3; J. D. Greenberg, Corrona, 4, AstraZeneca, Novartis, Pfizer, 5; J. M. Kremer, Pfizer Inc, 2, Pfizer Inc, 5.

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Rituximab Versus Abatacept in Rheumatoid Arthritis Patients with an Inadequate Response to Prior Biologic Therapy: A Retrospective, Single-Center Study. Edward Keystone, Juan Xiong, Deborah Weber and Ye Sun. Mount Sinai Hospital, Toronto, ON

Background/Purpose: Patients with RA who experience an inadequate response to TNF inhibitor (TNFi) therapy (TNF-IR) may be successfully treated using an alternative TNFi or a biologic with a different mode of action such as rituximab (RTX) or abatacept (ABA). The relative effectiveness of these approaches has not been determined in head-to-head trials. Evidence from real-world experience would help to guide treatment decisions for TNF-IR patients.

Methods: This was a retrospective chart review of patients from a single site (Rebecca MacDonald Center) with ACR-defined RA who initiated RTX or ABA after failure of at least one TNFi. The relative effectiveness of RTX and ABA was evaluated by analyzing drug survival distribution. Kaplan-Meier survival curves were compared using the log rank test (p-values <0.05 indicated statistical significance).

Results: The study cohort comprised 61 patients, of whom 37 and 24 were treated with RTX and ABA, respectively. In the RTX group, 10 patients had also received prior therapy with ABA. Demographics and disease characteristics were generally similar in the two groups, although RTX patients had higher disease activity compared with ABA patients (mean CDAI: RTX 32.5 vs ABA 26.9) and had received more prior TNFis (1.8 vs 1.7) and/or ABA (2.1 vs 1.7). After excluding the 10 RTX patients who had received prior ABA, survival rates over time were generally better with RTX vs ABA (table).

Estimated survival rates

Time (years)	RTX (n=27)	ABA (n=24)
0.5	0.92	0.83
1.0	0.79	0.74
1.5	0.74	0.54
2.0	0.68	0.54
3.0	0.68	0.54
4.0	0.68	0.41

Overall survival distribution (figure) was not significantly different between the RTX and ABA groups (p=0.658); however, RTX patients who had also failed ABA had significantly reduced survival compared with those who had not received ABA (p=0.015).
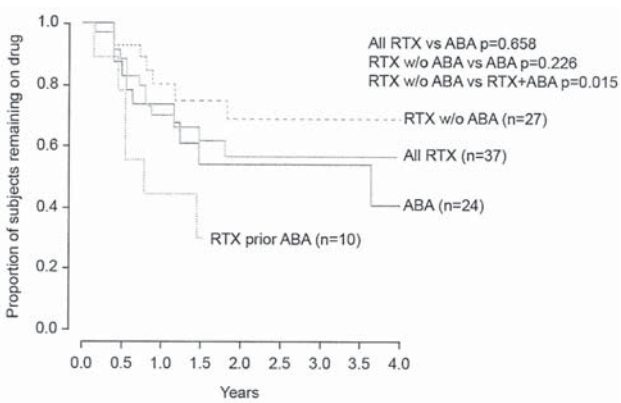
Stratification of survival data according to number of prior TNFi failures indicated that RTX (excluding patients with prior ABA) was superior to ABA among patients who had failed 3 TNFis. Survival was also numerically greater with RTX vs ABA in patients who had failed 1 prior TNFi. Finally, survival was better on both RTX and ABA when compared with that seen in a separate cohort of patients (n=88) who received a second TNFi after first TNFi failure.

Conclusion: These results from real-life practice suggest that in RA patients who have failed one or more TNFi, RTX may have better long-term survival than either ABA or an alternative TNFi. Prior ABA appears to reduce the efficacy of RTX. Further data are needed.

Disclosure: E. Keystone, Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Centocor, Roche, Genzyme, Merck, Novartis, Pfizer, UCB, 2, Abbott, AstraZeneca, Biotest, Bristol-Myers Squibb, Centocor, Roche, Genentech, Merck, Nycomed, Pfizer, UCB, 5; J. Xiong, None; D. Weber, None; Y. Sun, None.

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Characteristics Associated with Biologic Initiation As Monotherapy Versus Combination Therapy in Patients with Rheumatoid Arthritis (RA) in a US Registry Population. Dimitrios A. Pappas,[1] George W. Reed,[2] Katherine C. Saunders,[3] Ani John, [3] Ashwini Shewede,[3] Jenny Devenport,[4] Jeffrey D. Greenberg,[5] and Joel M. Kremer.[6] [1]Columbia University, College of Physicians and Surgeons, New York, NY, [2]University of Massachusetts Medical School, Worcester, MA, [3]CORRONA, Inc., Southborough, MA, [4]Genentech Inc., South San Francisco, CA, [5]NYU Hospital for Joint Diseases, New York, NY, [6]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Approximately one-third of RA patients were prescribed biologic (Bio) monotherapy (MT) i.e. without concomitant disease-modifying anti-rheumatic drugs (DMARD) (Yazici et al., 2008). The purpose of this abstract is to summarize characteristics associated with Bio MT and Bio combination therapy (CMB) initiation in a cohort of previously bio naïve and experienced RA patients in US and evaluate if previous treatments, increased availability of biologics approved for MT after 2006, and individual physician-prescribing patterns influence the decisions to initiate Bio MT and Bio CMB.

Methods: Data were obtained from the Consortium of Rheumatology Researchers of North America (CORRONA) registry, an independent prospective observational cohort with >30,000 RA patients enrolled from over 100 academic and private practices across the US. Odds ratios (OR) (adjusted and unadjusted) for initiating MT in Bio experienced compared to Bio naïve patients were estimated using logistic regression models. A Median OR to account for random effects from variation in individual physician's prescribing patterns and the effect of the availability of more biologics approved for MT after 2006 were also estimated.

Results: Between Oct 2001 an Apr 2012, 9,905 CORRONA patients initiated biologic therapy for RA, of which 40% were previously bio naïve. Demographics and disease activity characteristics in the Bio naïve and Bio experienced patients respectively were as follows; age (years; mean±SD): 57±14 vs 57±13, females: 76% vs 81%, duration of RA (years; mean±SD): 8±9 vs 13±10, seropositivity: 75% vs 73%, and CDAI (mean±SD): 19±14 vs 22±15.

Of the 9,905 patients, 25% received Bio MT and 75% received Bio CMB. Among patients that were previously bio naïve, 19% initiated a biologic as MT whereas MT initiation rates for patients who had received one prior biologic was 29%; two prior biologics, 26%; and three or more prior biologics, 31%. Higher rates of MT initiations were observed with prior Bio experience (unadjusted OR 2.01 [95% CI 1.70, 2.37]). Higher proportion of patients starting their biologic therapy after 2006 received MT as compared to those who started their biologic therapy prior to 2006 but was not statistically significant (unadjusted OR 1.20 [95% CI 0.99, 1.45]).

In the multivariate model (Table 1), Bio experienced patients continued to be significantly more likely to receive MT as compared Bio naïve. Median odds ratio showing the effect of individual physician's prescribing patterns on initiating bio MT was 2.40 [95% CI 2.08, 2.86].

Table 1. Adjusted Odds ratios for initiating Bio MT versus Bio CMB

	OR (95% CI) for initiating Bio MT vs Bio CMB
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≥3	
After 2006 vs. up to 2006	1.03 (0.84, 1.25)
Effect of physician prescribing patterns	1.40 (1.08, 2.86)

Abbreviations: Bio - biologic, MT - monotherapy, CMB - combination therapy.

Conclusion: Monotherapy remains a common strategy of biologic prescription to treat RA. Prior biologic experience and individual physician's prescribing patterns were associated with increased likelihood of initiating a biologic as monotherapy warranting further investigation to understand factors influencing decisions to initiate biologic monotherapy.

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Predictors of Significant Disease Activity Score-28 (Using C-reactive protein) Remission Achieved with Intravenous Golimumab in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: Results of the Phase 3, Multicenter, Double-Blind, Placebo-Controlled Trial. Clifton O. Bingham III[1], Michael Weinblatt[2], Alan Mendelsohn[3], Lilianne Kim[3], Michael Mack[3], Jiandong Lu[3], Daniel Baker[3] and Rene Westhovens[4]. [1]Johns Hopkins University, Baltimore, MD, [2]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [3]Janssen Research & Development, LLC, Spring House, PA, [4]University Hospital KU Leuven, Leuven, Belgium

Background/Purpose: To evaluate the efficacy of intravenous(IV) golimumab(GLM) 2mg/kg+ methotrexate(MTX) in patients(pts) with active RA despite MTX in achievement of DAS remission and ACR/EULAR remission.

Methods: Pts (n=592) with active RA (≥6/66 swollen joints, ≥6/68 tender joints, CRP≥1.0mg/dL, RF and/or anti-CCP antibody-positive) despite ≥3months of MTX(15–25mg/wk) participated in this multicenter, randomized, double-blind, placebo(PBO)-controlled phase 3 study. Pts were randomized (2:1) to receive IV GLM 2mg/kg or PBO at wks0&4 and q8wks; all pts continued their stable MTX regimen. Clinical remission was defined by DAS28-CRP score <2.6 (prespecified; not validated) and recently developed ACR/EULAR remission[1] using SDAI≤3.3 (post hoc; validated). DAS28-CRP analyses used last-observation-carried-forward.

Results: Statistically significantly higher DAS28-CRP remission rates were observed with GLM+MTX vs. PBO+MTX at Wk14 (15.4% vs. 4.6%, respectively; p<0.001) and Wk24 (17.7% vs. 5.1%, respectively; p<0.001). Similar trends were seen when remission was defined by a SDAI score ≤3.3 (Wk14: 4.8% vs.1.0%, respectively; p<0.05 and Wk24: 7.3% vs. 2.0%, respectively; p<0.01). Moderate (approx.10%-15%) increases in Wk24 DAS28-CRP remission rates were observed among subgroups of pts defined by HAQ score <1.625 (24%) vs ≥1.625 (12%), baseline physical Functional Class I (27%) vs Class II and III (17% each), swollen joint count <12 (23%) vs ≥12 (14%), tender joint count <24 (25%) vs ≥24 (11%), and CRP <1.5 mg/dL (29%) vs ≥1.5 mg/dL (15%).

Table. No. (%) of pts achieving DAS28-CRP <2.6 at Wk24 by baseline characteristics*

No. randomized GLM pts	495
Age (yrs): < 65/≥ 65	61/336 (18%)/9/59 (15%)
Sex: Female/Male	58/326 (18%)/12/69 (17%)
Body weight (median: 70kg): < 70 kg/≥ 70 kg	34/198 (17%)/36/197 (18%)
Disease duration (median:4.7yrs):< 4.7yrs/≥ 4.7yrs	35/196 (18%)/35/199 (18%)
Functional class: I/II/III	9/33 (27%)/48/284 (17%)/13/78 (17%)
Rheumatoid factor: Negative/Positive	6/30 (20%)/64/365 (18%)
Anti-CCP: Negative/Positive	6/32 (19%)/64/362 (18%)
CRP (mg/dL): ≤ 1.5/> 1.5	20/69 (29%)/50/326 (15%)
Swollen joint count (median: 12): < 12/≥ 12	40/174 (23%)/30/221 (14%)
Tender joint count (median: 24): < 24/≥ 24	48/195 (25%)/22/200 (11%)
HAQ score (median 1.625): < 1.625/≥ 1.625	46/193 (24%)/24/202 (12%)
Oral corticosteroids at baseline: Yes/No	38/251 (16%)/32/144 (22%)
DMARDs at baseline: Yes/No	38/206 (18%)/32/189 (17%)
NSAIDs at baseline: Yes/No	57/323 (18%)/13/72 (18%)
Methotrexate at baseline (mg/wk): <15/≥ 15	46/268 (17%)/24/127 (19%)

* Cutpoints for baseline characteristic subgroups were determined by the median value among patients randomized to GLM+MTX

Conclusion: In pts with active RA despite ongoing MTX, IV GLM 2 mg/kg+MTX yielded significantly higher DAS28-CRP remission rates and higher ACR/EULAR remission rates vs PBO at Wk14 and Wk24. Achievement of DAS28-CRP remission appeared to be enhanced in pts with lower levels of baseline physical function impairment and lower joint counts. Confirmation of these hypothesis-generating data are required.

Ref
[1]Felson et al, Arthritis Rheum 2011;63:573–86.

1302

Early Neutropenia Is Associated with Clinical Response in Patients Receiving Tocilizumab in Rheumatoid Arthritis. Marie Kostine[1], Thomas Barnetche[2], Elodie Ardouin[3], Marlene Joly[4], Emilie Rabois[5], Baptiste Glace Sr.[6], Delphine Nigon[7], Thierry Schaeverbeke[8] and Christophe Richez[9]. [1]Rheumatology, CHU Pellegrin, Bordeaux, France, [2]CHU Bordeaux Pellegrin, Bordeaux, France, [3]Rheumatology, Limoges University Hospital, Limoges, France, [4]Rheumatology, Montpellier University Hospital, Montpellier, France, [5]CHU Gabriel Montpied, Clermont-Ferrand, France, [6]Rheumatology CHU Gabriel Montpied, Clermont-Ferrand, France, [7]CHU Purpan, Toulouse, France, [8]Groupe Hospitalier Pellegrin, Bordeaux, France, [9]Hôpital Pellegrin and Université Victor Segalen Bordeaux, France

Background/Purpose: A reduction in peripheral blood neutrophils count is usually observed with the anti-interleukin (IL) 6 receptor antibody tocilizumab. This often appears few days after first administration, but mechanisms are not completely established. Objective is to evaluate the evolution of neutrophils count under tocilizumab (anti IL-6R) treatment for rheumatoid arthritis affected patients and to correlate this evolution with clinical response.

Methods: We performed a multicentric retrospective study including patients with RA treated by tocilizumab +/− DMARDs in 5 University French Centers (Bordeaux, Clermont-Ferrand, Limoges, Montpellier and Toulouse). Neutrophils, inflammatory parameters and DAS28 (ESR) were recorded at baseline, and after one and three months of treatment. The comparisons were performed using Student's t-test or Mann-Whitney test when appropriate. A statistical significant p-value of 0,05 was selected.

Results: 158 patients were included with mean age of $59,7 \pm 12,6$ years-old and a mean disease duration of $13,4 \pm 8,8$ years. The mean DAS28 (ESR) at inclusion was about $5,32 \pm 1,27$, and decreased significantly after one month of treatment to $3,74 \pm 1,38$ ($p<10^{-4}$), and to $3,18 \pm 1,33$ ($p<10^{-4}$) after three months of treatment. According to the EULAR response criteria, 3 patients were classified as good responders (1,9%), 126 as moderate responders (79,7%) and 29 as non-responders (19,4%). The neutrophils count shows a significant decrease between the introduction of tocilizumab therapy and after one month of treatment ($5972 \pm 2736/\text{mm}^3$ vs. $3972 \pm 2436/\text{mm}^3$, $p<10^{-4}$), whereas it stays at the same level between the first and the third month of treatment ($3972 \pm 2436/\text{mm}^3$ vs. $3963 \pm 2255/\text{mm}^3$, p=0,94). The frequency of neutropenia (neutrophils$<=1500/\text{mm}^3$) was about 1,3% (2/155) at inclusion, 5,9% (9/154) after one month and 3,5% (5/142) after three months of treatment.

The neutrophils count decreases significantly between the inclusion and first month of treatment in the subgroup of Month 3 responders ($6095 \pm 2823/\text{mm}^3$ vs. 3946 ± 2450, $p<10^{-4}$ with Mann-Whitney test), whereas this decrease is not significant in the subgroup of month 3 non-responders ($5438 \pm 2292/\text{mm}^3$ vs. $4087 \pm 2415/\text{mm}^3$, p=0,05 with Mann-Whitney test). The DAS (ESR) difference between Month 0 and Month 3 was positively correlated with the difference of the neutrophils count between Month 0 and Month 1 (p=0,03; r=0,19)

Conclusion: This study reveals correlation between neutrophils decrease and clinical response during tocilizumab therapy. Accordingly with our previous report showing decrease of myeloid dendritic cells and monocytes during tocilizumab therapy, these new data suggest a specific effect of tocilizumab on cells from myeloid lineage.

Disclosure: M. Kostine, None; **T. Barnetche**, Roche Pharmaceuticals, 8; **E. Ardouin**, None; **M. Joly**, None; **E. Rabois**, None; **B. Glace Sr.**, None; **D. Nigon**, None; **T. Schaeverbeke**, Roche Pharmaceuticals, 5; **C. Richez**, Roche Pharmaceuticals, 8.

1303

Achieving Comprehensive Disease Control in Long-Standing or Early Rheumatoid Arthritis Patients Treated with Adalimumab Plus Methotrexate Versus Methotrexate Alone. Edward C. Keystone[1], Ferdinand C. Breedveld[2], Désirée van der Heijde[2], Ronald F. van Vollenhoven[3], Stefan Florentinus[4], Freddy Faccin[5], Shufang Liu[5], Hartmut Kupper[6] and Arthur Kavanaugh[7]. [1]University of Toronto, Toronto, ON, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Karolinska Institute, Stockholm, Sweden, [4]Abbott, Rungis, France, [5]Abbott, Abbott Park, IL, [6]Abbott GmbH and Co. KG, Ludwigshafen, Germany, [7]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Effective treatment of rheumatoid arthritis (RA) patients (pts) aims to suppress inflammation, preserve physical function, and prevent structural damage, which together represent the hallmarks of comprehensive disease control (CDC).[1] Advances in therapies and application of targeted approaches to disease management have made CDC a realistic treatment goal for many pts.[2] The present analysis evaluated CDC attainment following 1 year of treatment with adalimumab (ADA) + methotrexate (MTX) vs MTX alone in 3 different randomized, controlled trials (RCTs).

Methods: Pt data originate from the DE019, OPTIMA, and PREMIER RCTs. DE019 enrolled pts with long-standing RA (mean =11 years) and an inadequate response (IR) to MTX; OPTIMA and PREMIER enrolled early RA (mean =0.4 and 0.7 years, respectively) and MTX-naïve pts. All studies included a comparison of ADA+MTX vs placebo (PBO)+MTX and were of at least 1 year duration. Changes to assigned treatment strategy were not allowed in DE019 or PREMIER but were made on the basis of achieving a stable low disease activity [LDA, DAS28(CRP) <3.2] target at weeks 22 and 26 in OPTIMA; PBO+MTX-IR could receive open-label (OL) ADA+MTX for an additional 52 weeks (Rescue ADA arm). CDC was defined for this analysis as the simultaneous achievement of LDA, normal function (HAQ-DI <0.5), and the absence of radiographic progression (ΔmTSS ≤0.5). This post hoc analysis assessed the proportion of pts achieving CDC and the individual criteria following 1 year of treatment with ADA+MTX combination therapy or MTX monotherapy in DE019, in the Rescue ADA arm of OPTIMA, or in PREMIER.

Results: Approximately one-fifth (19%) of ADA+MTX-treated pts in DE019 achieved CDC at 1 year vs 5% of PBO+MTX-treated pts ($P <.001$, **Table**). The addition of OL ADA+MTX to PBO+MTX-IR in the Rescue ADA arm of OPTIMA permitted 29% (n/N=102/348) of early RA pts to achieve CDC following 1 year of treatment, a proportion that was comparable with the proportion of MTX-naïve early RA pts treated with ADA+MTX in PREMIER achieving CDC at 1 year (32%, n/N=87/268). Significant differences between treatment groups in DE019 and PREMIER were still apparent when the disease activity component was replaced by DAS28(CRP) remission (<2.6).

Table. Attainment of Individual and Composite Criteria for Comprehensive Disease Control (CDC) Following 1 Year of Treatment With ADA + MTX or MTX Alone

Study	DE019		OPTIMA	PREMIER	
Outcome	ADA + MTX (N = 207)	PBO + MTX (N = 200)	Rescue ADA (N = 348)	ADA + MTX (N = 268)	MTX (N = 257)
DAS28 (CRP)[a], n (%)					
<3.2 (LDA)	100(48)	29 (15)***	209 (60)	171 (64)	91 (35)***
<2.6 (remission)	56 (27)	12 (6)***	154 (44)	125 (47)	56 (22)***
HAQ-DI <0.5[a], n (%)	77 (37)	35 (18)***	136 (39)	157 (59)	99 (39)***
ΔmTSS ≤0.5[b], n (%)	164 (79)	116 (58)***	287 (82)	169 (63)	89 (35)***
CDC[c], n (%)					
LDA	40 (19)	10 (5)***	102 (29)	87 (32)	29 (11)***
remission	28 (14)	5 (3)***	82 (24)	67 (25)	22 (9)***

[a]Last observation carried forward.
[b]Linear extrapolation, with nonresponder imputation for patients with no data.
[c]Comprehensive disease control, the simultaneous attainment of LDA [DAS28(CRP) <3.2] or remission [DAS28(CRP)<2.6], normal function (HAQ-DI <0.5), and no radiographic progression (ΔmTSS ≤0.5).
***$P < .001$ for differences between initial treatments from chi-square; no comparisons were made with the Rescue ADAgroup from OPTIMA.
ADA, adalimumab; MTX, methotrexate; PBO, placebo; DAS28 (CRP), 28-joint disease activity score with C-reactive protein; LDA, low disease activity; HAQ-DI, disability index of the health assessment questionnaire; ΔmTSS, change in modified total Sharp score.

Conclusion: CDC appears to be a realistic treatment goal in RA. Treatment with the combination of ADA+MTX led to significantly higher rates of CDC following 1 year than treatment with MTX alone, and earlier treatment appeared to increase the likelihood of CDC. A targeted treatment approach aiming at stable LDA at 6 months enabled MTX-IR who received OL ADA+MTX for an additional 1 year to achieve CDC in a proportion that was comparable with MTX-naïve early RA pts initiated with ADA+MTX, underscoring the utility of treat-to-target approaches in maximizing long-term outcomes.

References
1. Smolen, *et al. ARD* 2010;69:631–7.
2. van der Heijde, *et al. J Rheum* 2010;37:2237–46.

Disclosure: E. C. Keystone, Abbott, Amgen, AstraZeneca, BMS, Centocor, Genzyme, Merck, Novartis, Pfizer, Roche, and UCB, 2, Abbott, AstraZeneca, Biotest, BMS, Centocor, Genentech, Merck, Nycomed, Pfizer, Roche, and UCB, 5, Abbott, Amgen, BMS, Janssen, Merck, Pfizer, Roche, and UCB, 8; **F. C. Breedveld**, Centocor, Schering-Plough, Amgen/Wyeth, and Abbott, 5; **D. van der Heijde**, Abbott, Amgen, AstraZeneca, BMS, Centocor, Chugai, Eli-Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth, 5, Imaging Rheumatology bv, 4; **R. F. van Vollenhoven**, Abbott, BMS, Glaxo SmithKline, Human Genome Sciences, Merck, Pfizer, Roche, and UCB Pharma, 5, Abbott, BMS, Glaxo SmithKline, Human Genome Sciences, Merck, Pfizer, Roche, and UCB Pharma, 2; **S. Florentinus**, Abbott Laboratories, 1, Abbott Laboratories, 3; **F. Faccin**, Abbott Laboratories, 1, Abbott Laboratories, 3; **S. Liu**, Abbott Laboratories, 1, Abbott Laboratories, 3; **H. Kupper**, Abbott Laboratories, 1, Abbott Laboratories, 3; **A. Kavanaugh**, Abbott, Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB, 2, Abbott, Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB, 5.

1304

Long-Term Use of Adalimumab As Monotherapy Following Attainment of Low Disease Activity with Adalimumab Plus Methotrexate. Edward C. Keystone[1], Ferdinand C. Breedveld[2], Hartmut Kupper[3], Shufang Liu[4] and Stefan Florentinus[5]. [1]University of Toronto, Toronto, ON, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Abbott GmbH and Co. KG, Ludwigshafen, Germany, [4]Abbott, Abbott Park, IL, [5]Abbott, Rungis, France

Background/Purpose: There has been increased interest in understanding whether biologics can be safely withdrawn from patients (pts) receiving combination therapy with MTX once a clinical target has been achieved. The ability of the biologic to maintain the target as monotherapy following MTX withdrawal has received less consideration. The purpose of this analysis was to evaluate long-term clinical, functional, and radiographic outcomes in pts

treated with open-label (OL) adalimumab (ADA) as monotherapy following attainment of low disease activity (LDA) with ADA+MTX.

Methods: PREMIER was a 2-year (yr), phase 3, randomized, controlled trial (RCT) in MTX-naïve pts with early RA who were randomized to MTX, ADA, or ADA+MTX.[1] Pts completing the RCT were eligible to receive OL ADA for up to an additional 8 yrs (this trial is ongoing); MTX could be added at the investigator's discretion. This post hoc analysis included data from pts treated with ADA+MTX during the RCT who reached at least an LDA state [defined as DAS28(CRP) <3.2] at Yr 2 (ie, the end of the RCT) and received OL ADA as monotherapy up to Yr 5. The percentages of pts remaining in LDA or with normal function (HAQ-DI <0.5) at Yr 5 were summarized using non-responder imputation based on the population entering the OL period and as observed for pts with data available at Yr 5. Mean ΔmTSS and the proportion without radiographic progression (ΔmTSS ≤0.5) from Yrs 2–5 were summarized as observed. Conditional logistic regression analysis based on propensity score matching was used to identify variables significantly associated with MTX use.

Results: Of the 183 ADA+MTX-treated pts who enrolled in the OL extension, 140 (83%) reached an LDA state at Yr 2. Among the LDA responders, 84 (60%) received ADA as monotherapy during the OL period, and 56 (40%) reinitiated MTX during the OL extension (time to 1st MTX use: mean/median=28/5 weeks). Higher physician's global assessment appeared to predict MTX use during the OL extension (P <.01). A total of 60 pts (75%) completed 3 yrs of OL ADA monotherapy. Adverse events were the most frequently cited reason for study discontinuation (n=9); no pt withdrew citing loss of efficacy. The majority of pts retained LDA at Yr 5 with ADA monotherapy (63%; **Table**); 50% of the 84 pts were in DAS28(CRP) remission and 58% had normal function at Yr 5. Of the pts with Yr 5 data available, 88% were in LDA. Further, OL ADA monotherapy was associated with clinically insignificant radiographic progression for pts completing Yr 5 (mean annual mTSS progression rate from Yrs 2–5 =0.5 units/yr).

Table. Year 5 Outcomes for Year-2 LDA Responders Who Received Up to 3 Years of Treatment With Open-label ADA Monotherapy

Assessment Parameter	OL ADA Monotherapy	
	Non-responder imputation[a]	Observed
DAS28(CRP), mean ± SD	N/A	2.3 ± 0.9
DAS28 (CRP) <3.2, % (n/N)	63 (53/84)	88 (53/60)
HAQ-DI, mean ± SD	N/A	0.3 ± 0.5
HAQ-DI <0.5, % (n/N)	58 (49/84)	78 (49/63)
ΔmTSS, mean ± SD	N/A	1.5 ± 5.6
ΔmTSS ≤0.5, % (n/N)	50 (42/84)	72 (42/58)

[a]Patients with missing data at the Yr 5 assessment were imputed as non-responders.
LDA, low disease activity; ADA, adalimumab; OL, open-label; DAS28(CRP), 28-joint disease activity score with C- reactive protein; SD, standard deviation; N/A, not applicable; HAQ-DI, disability index of the health assessment questionnaire; ΔmTSS, change in modified total Sharp score from Year 2.

Conclusion: Following attainment of an LDA state at Yr 2 with ADA+MTX combination therapy, treatment with OL ADA as monotherapy for 3 yrs was sufficient for most pts to retain LDA and have minimal radiographic progression. Thus, MTX withdrawal appears possible for some pts whose disease activity is responsive to ADA monotherapy.

Reference
[1]*Arthritis Rheum* 2006;54:26–37.

1305

Three-Year Follow-up of Rituximab in Rheumatoid Arthritis: Results From the Belgian MIRA (MabThera in Rheumatoid Arthritis) Registry.
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Background/Purpose: The MIRA registry was set up to collect safety, efficacy and (re)treatment practice data for Belgian RA patients treated with rituximab.

Methods: All rheumatologists from Belgium and Luxemburg were invited to participate in the study. Patient demographics were collected at baseline. Follow-up data included disease activity measures, attrition and reasons for discontinuation. Evolution of disease activity is reported here for the subpopulation followed for at least 3 years. Data are presented as mean±standard error (SE) or as percentages. Data analysis was performed with SPSS 20.0 software.

Results: The MIRA registry includes 649 patients (treated by 80 rheumatologists in 52 centers), who started rituximab therapy between November 2006 and October 2011. The study population consisted for 75% of females; 55.3% were RF positive and 33.9% anti-CCP positive. Patients starting rituximab were on average 57.4±0.5 years old with a mean disease duration of 12.8±0.4 years. Patients received on average 2.82±0.07 (range 1–9) rituximab treatments, over a median follow up time of 82 weeks (range 0–254 weeks). At database lock, 433 patients (66.72%) were still on rituximab treatment, 182 (28.04%) had stopped, and 34 patients (5.24%) were lost to follow up.

Over the study period, a clear evolution was observed in the baseline characteristics of patients starting rituximab treatment. The number of previously failed anti-TNF drugs used before starting rituximab significantly decreased over time (chi-square p<0.001). In 2006, 50.0 % of patients had previously been treated with more than one anti-TNF, whereas in 2011 only 33.4% of patients had received more than one anti-TNF before switching to rituximab. In parallel, the DAS28 values at baseline significantly decreased, from 6.31±0.59 in 2006 to 5.65±0.17 in 2011 (ANOVA, p<0.001).

Evolution of disease activity was analysed in a subset of 139 patients who were followed for at least 3 years. DAS28 showed significant changes over the study period (ANOVA, p<0.001), declining in the first 8 weeks after rituximab treatment, and stabilising afterwards. DAS28 in this subgroup with 3-year follow-up at weeks 0, 8, 52, 104 and 156 respectively were 6,16±0.09, 4.47±0.45, 3.79±0.18, 3.85±0.29 and 3.58±0.42.

Conclusion: Data from the MIRA registry shows that over the last 5 years, less alternative anti-TNF treatments were used in Belgium before switching RA patients to rituximab. Additionally, rituximab treatment tended to be started in patients with lower disease activity. Furthermore, this clinical practice study demonstrates that rituximab treatment results in adequate long-term disease control.

1306

How well Do Patients with Rheumatoid and Psoriatic Arthritis Tolerate Methotrexate? A Retrospective Review of Discontinuation Data From a Large UK Cohort.
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Background/Purpose: Due to its efficacy and safety, methotrexate (MTX) has become the first-line disease-modifying drug for rheumatoid (RA) and psoriatic arthritis (PsA). Although deemed safe, few studies have analysed MTX tolerability. The objective of our study was to ascertain the proportion of RA and PsA patients that discontinue MTX and the reasons for this.

Methods: A retrospective review of the Rheumatology departments electronic database was undertaken to identify all patients who had received MTX for RA or PsA. This was followed by review of both the electronic and paper records to identify patients in whom MTX had been discontinued. The reasons for this were then classified into several categories. Every effort was made to ensure that the correct reasons for drug withdrawal were documented. Discrepancies were discussed with a senior member of the team. Cases with insufficient data were excluded from the final analysis.

Results: 1257 patients on MTX were identified. Of these 762 had RA and 193 had PsA. MTX had been stopped in 260 patients with RA and 71 patients with PsA. In RA patients, the mean dose at the time of discontinuation of MTX was 14.1mg/week (dose range 5–30mg, SD 5.6mg) and in PsA patients 13.6mg/week (dose range 5–25mg, SD 5.0mg) (missing data in 80 and 26 patients respectively). The reasons for discontinuation and differences between the rheumatoid and psoriatic arthritis groups are highlighted in Table 1 & 2. Our data suggests that about a third of patients with RA and PsA eventually stop methotrexate, most of whom cite intolerance as a reason. In addition a statistically significant difference between the RA and PsA cohorts was seen, with abnormalities in blood counts (leucopenia and thrombocyto-

penia) being reported more frequently in RA patients (11.5% vs 6.8%; p<0.05) and more PsA patients having liver enzyme abnormalities (27% vs 12%; p<0.05).

Table 1. Reasons for methotrexate discontinuation in patients with RA and PsA

Reason for discontinuation	RA (% of all withdrawals)	PsA (% of all withdrawals)	p-value (X^2-test)
Adverse events	200 (77.5)	44 (62.0)	0.4430
Ineffective	32 (12.4)	13 (18.3)	0.2061
No longer indicated	17 (6.6)	1 (1.4)	–
Patient choice	13(5.0)	10 (14.1)	0.0117
No reason stated	14 (5.4)	6 (8.5)	0.4168

Table 2. Side-effects leading to methotrexate discontinuation

	RA (% of all withdrawals) n=260	PSA (% of all withdrawals) n=71	p-value (X^2-test)
All gastrointestinal symptoms	65 (32.5)	12 (27.3)	0.93
Nausea	41 (20.5)	7 (15.9)	
Oral ulceration	12 (6.0)	1 (2.3)	
Diarrhoea	6 (3.0)	3 (6.8)	
Vomiting	4 (2.0)	2 (4.5)	
Abdominal pain	2 (1.0)	3 (6.8)	
Tenesmus	1 (0.5)	0 (0.0)	
All respiratory symptoms	50 (25.0)	6 (13.6)	0.68
Shortness of breath	19 (9.5)	4 (9.1)	
Cough	10 (5.0)	2 (4.5)	
Chest infection	11 (5.5)	0 (0.0)	
Abnormal LFT	24 (12.0)	12 (27.3)	0.029*
Abnormal FBC	23 (11.5)	3 (6.8)	
Neutropenia	11 (5.5)	1 (2.3)	
Thrombocytopenia	11 (5.5)	3 (6.8)	
Non-specifically unwell	21 (10.5)	5 (11.4)	
Neurological and psychological	16 (8.0)	3 (6.8)	
Headache	6 (3.0)	1 (2.3)	
Dizzyness	5 (2.5)	1 (2.3)	
Fatigue	12 (6.0)	3 (6.8)	
Cutaneous	11 (5.5)	2 (4.5)	
Rash	8 (4.0)	2 (4.5)	
Nodulosis	3 (1.5)	0 (0.0)	
Renal dysfunction	3 (1.5)	0 (0.0)	
Alopecia	2 (1.0)	1 (2.3)	
Miscellaneous AEs	7 (3.5)	6 (13.6)	
Non-specific intolerance	19 (9.5)	5 (11.4)	

Conclusion: Our data demonstrates that although MTX is safe, it is not well tolerated. The differences between MTX tolerability in RA and PsA is likely to be disease rather than therapy specific. We were unable to characterise patients who suffer from side-effects but continue therapy. Thus, the magnitude of the problem is likely to be substantially greater. Poor tolerability is also likely to impact on adherence and in these patients biologic therapy may be indicated.

1307

Anti-IL-6 Receptor Nanobody (ALX-0061) Seamless "First-in-Human" Phase I/II POC Study in Patients with Active RA On Stable MTX Treatment.
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Background/Purpose: ALX-0061 is a 26kD bispecific IL-6R targeting Nanobody® with monovalent binding to IL-6R and serum albumin. It effectively neutralizes IL-6 pathway activity in-*vitro* and in-*vivo*. Translational studies (PK/PD modelling) resulted in a novel FIM design combining single ascending dose (SAD), multiple ascending dose (MAD) and clinical POC using PK, biomarker and early clinical read-outs as decision tools.

Methods: Multicentre (6 sites in CEE), randomized, double-blind, placebo (PLC) controlled, dose escalation, Phase I/II study in patients with active RA on stable MTX therapy. Five treatment groups are tested in the SAD part and primary objectives are safety and tolerability of single ascending doses, MTD and/or biological effective doses (BED). Following SAD completion, an interim PK/PD analysis was performed to confirm the adequacy of the anticipated dosing regimen in MAD. Monthly or bi-monthly doses of ALX-0061 up to 12 and 24 weeks are tested in MAD with roll-over of PLC subjects after 12 weeks interim efficacy assessment to enrich the safety and efficacy population of ALX-0061. Biological and clinical efficacy is assessed with PK/PD, radiographic (MRI) and clinical scores at 12 weeks and end of study and correlated with pre-clinical modelling and literature data on IL-6R pathway inhibition.

Results: 28 patients with active RA were included in the SAD part and received single injections of 0.3mg/kg (2 pat), 1mg/kg (6 pat), 3mg/kg (6 pat), 6mg/kg (6 pat) and PLC (8 pat). Average age (52y) and BMI (25.6) were balanced between the groups; compared with PLC group, patients in ALX-0061 arm had higher disease activity (ACR Class II/III 85% vs 62.5%; DAS high disease activity 45% vs 12.5%). Safety: ALX-0061 was well tolerated. One subject reported an acute hypersensitivity event, no further SAEs were reported and no DLT occurred. The MTD was not reached. No clear increase in frequency or severity of AEs with increased doses of ALX-0061 observed. PK: Serum ALX-0061 concentrations and corresponding drug exposure increased with escalated dose. PD: CRP, ESR, fibrinogen and serum amyloid A showed rapid and marked decrease with highest effect observed at highest dose levels (3 and 6mg/kg). IL-6 and sIL-6R plasma concentrations increased with dose, representing a marker to monitor the biological effect of ALX-0061 on its target. Clinical effect: Following single injection, 16 ALX-0061 subjects (80%) and 3 PLC subjects (37.5%) achieved moderate/good EULAR response at 2 months. 10 ALX-0061 subjects (50%) achieved LDA (6 pat) or DAS28 remission (4 pat), 2 PLC subjects (25%) achieved LDA (1 pat) or DAS28 remission (1pat). Based on PK/PD modelling, three dose levels were selected for the MAD: 1 mg/kg Q4W, 3 mg/kg Q4W and 6 mg/kg Q8W. 36 patients are treated in MAD part and completion is expected before end of 2012.

Conclusion: Single injections of ALX-0061 were well tolerated at BED. The pre-clinical PK/PD modelling was confirmed and dose-dependent changes of early inflammation biomarkers were consistent with inhibition of the IL-6 pathway. The MAD study part will further assess early effect of ALX-0061 on disease activity with radiographic and clinical disease score evaluations.

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Opportunistic Infections in Patients with Rheumatoid Arthritis Treated with Rituximab: Data From the Autoimmunity and Rituximab Registry.
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Background/Purpose: Therapy with biological agents may be associated with opportunistic infections (OIs). Data on the occurrence of OIs in patients with RA treated with rituximab (RTX) are limited.
Objective: To describe the spectrum of OIs associated with RTX therapy.
Methods: The AutoImmunity and Rituximab (AIR) registry was set up by the French Society of Rheumatology. Patients are followed up every 6

months during 7 years. Data regarding serious infections are validated by the 2 coordinators of the study using chart copies.

Results: 1975 patients had already had at least 1 follow-up visit. The follow-up was 4937 patient/years on January 1st, 13 OIs occurred (0.3 OIs/100 patient years). 23.0% of OIs were due to intra-cellular bacterial (1 tuberculosis, 1 atypical mycobacteriosis, 1 non-typhoid salmonellosis), 38.6% were viral (2 severe herpes zoster, 1 varicella, 2 disseminated cytomegalovirus infections), 30.8% were fungal (2 pneumocystosis, 1 echinococcosis, 1 Scedosporium infection) and 7.6% were parasitic (1 disseminated scabies). 1 patient required admission to the intensive care unit and died from herpetic hepatitis.

Conclusion: Even in real life patients, the risk of tuberculosis remains very low in patients treated with RTX in Western Europe. However, some various and serious OIs, especially those with intracellular micro-organisms, may unfrequently develop in patients receiving RTX. This risk requires to be reevaluated with a longer follow-up.

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Predictive Risk Factors of Serious Infections in RA Patients Treated with Abatacept in Real Life: Results in the Orencia and Rheumatoid Arthritis (ORA) Registry. Jacques-Eric Gottenberg[1], Philippe Ravaud[2], Alain G. Cantagrel[3], Bernard Combe[4], René-Marc Flipo[5], Thierry Schaeverbeke[6], Eric Houvenagel[7], Philippe Gaudin[8], Damien Loeuille[9], Stephanie Rist[10], Maxime Dougados[11], Jean Sibilia[12], Xavier Le Loet[13], Christian Marcelli[14], Thomas Bardin[15], Isabelle Pane[16], Elodie Perrodeau[17], Gabriel Baron[18] and Xavier Mariette[19]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [3]Place du Docteur Baylac, Toulouse, France, [4]Hopital Lapeyronie, Montpellier, France, [5]Rheumatology Department, Lille University Hospital, Lille, France, [6]Groupe Hospitalier Pellegrin, Bordeaux, France, [7]St Philibert Hospital, Lomme 59462, France, [8]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [9]CHU Brabois, Vandoeuvre les Nancy, France, [10]Hospital University Orléans, France, [11]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [12]CHU Hautepierre, Strasbourg, France, [13]CHU de ROUEN, Rouen, France, [14]Rheumatology Department, Caen University Hospital, [15]Hôpital Lariboisière, Paris, France, [16]Hotel Dieu University Hospital Paris, France, [17]Epidemiologist, Paris, France, [18]Epidemiology, Paris, France, [19]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Little data is available regarding the rate and predicting factors of serious infections in patients with rheumatoid arthritis treated with abatacept (ABA) in daily practice. We therefore addressed this issue using real-life data from the Orencia and Rheumatoid Arthritis (ORA) registry.

Methods: ORA is an independent registry promoted by the French Society of Rheumatology which includes RA patients treated with abatacept. At baseline, 3, 6 months and every 6 months or at disease relapse, during 5 years, standardized information are prospectively collected by trained clinical nurses in each center. Central reviewing of charts of patients with SAEs is performed by the two coordinators of the study.

Results:

–Baseline characteristics and comorbidities

1032 patients (79.1% of women) were included in the ORA registry. Median age of patients was 58 years and median disease duration was 15 years. 5.8% of patients had a history of cancer, 34.6% a record of serious infection, and 11.8% had diabetes. 12.9% of patient had not received any anti-TNF prior to ABA. 29.8% of patients had previously received rituximab.

–Rate of serious infections

Among the 977 patients with a follow-up of at least 3 months (median follow-up of 1766 patient-years (PY)), 118 serious infections occurred in 99 patients during treatment with ABA (64 infections) and/or within the 6 months following ABA discontinuation (54 infections). Thus, 6.7 serious infections/100 PY were observed (3.6/100 PY during treatment with ABA and 3.1/100 PY within the 6 months following discontinuation of ABA).

–Predicting factors of severe infections

On univariate analysis, an older age, record of previous serious or recurrent infections, diabetes, chronic lung disease, a lower number of previous anti-TNF, and a higher corticosteroid dosage at initiation of ABA were associated with a higher risk of serious infections. Disease duration, previous treatment with rituximab, concomitant treatment with a synthetic DMARD, disease activity were not significantly associated with an increased risk of serious infections. On

multivariate analysis, only age (OR 1.5 CI95% [1.2–1.7], P<0.001) and record of previous serious or recurrent infections (2.2 [1.5–3.5], P< 0.001) were significantly associated with a higher risk of serious infections.

Conclusion: In ORA registry, severe infections in patients treated with abatacept were slightly more frequent than in clinical trials. This might be related to the fact that a high proportion of patients with comorbidities, who would have been excluded from controlled trials, are treated with ABA in real life. Characteristics of RA (duration, previous treatments including anti-TNF or rituximab, disease activity) were not associated with serious infections. Predictive risk factors of serious infections in patients treated for RA with ABA in common practice included age and previous record of serious infections.

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Analysis of Anti-JC Polyomavirus T-Cell Immune Response with JC-Feron in Patients with Rheumatoid Arthritis Treated with Rituximab or Anti-TNF. Raphaèle Seror[1], Houria Chavez[2], anne-Aurélie Mazet[1], Jeremie Sellam[3], Bruno Fautrel[4], Maxime Dougados[5], Yassine Taoufik[2] and Xavier Mariette[6]. [1]Bicetre university hospital, LE Kremlin-Bicetre, France, [2]Hopital Bicetre, Université Paris Sud, AP-HP, France, [3]Hopital Saint-Antoine, Pierre et Marie Curie University Paris 6, AP-HP, 75012, France, [4]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [5]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [6]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Some cases of progressive multifocal leukoencephalopathy (PML) have been described in patients with autoimmune diseases with profound immunosuppression, due to replication of JC polyomavirus within the CNS. Biologics such as natalizumab and efalzimab have been clearly associated with an increased risk of PML. Rare cases of PML have also been described in patients treated with rituximab (RTX), without any idea of the mechanisms which could support this association. Our objectives were to analyze JC viral load and anti-JC T-cell response in rheumatoid arthritis (RA) patients treated with RTX or anti-TNF.

Methods: In four French rheumatology departments, RA patients starting a new biological therapy with either RTX or anti-TNF were recruited to participate in this prospective study. All patients were screened at baseline, 3 to 6 months and 12 to 18 months after the beginning of biologic therapy during for JC tests, including urine, PBMC and plasma viral load (with quantitative PCR method) and specific IFN-g Elispot for JC (Elipsot was performed after overnight activation of T cells with purified JCV). It was planned to include half of patients treated with RTX and half with anti-TNF, and to compare evolution of anti-JCV T cell response and JC viral load between these 2 groups.

Results: Between February 2010 and January 2011, 42 patients were included: 19 received RTX and 23 anti-TNF (etanercept n= 15; adalimumab n=3; infliximab n=4; golimumab n=1). At baseline and during the whole follow-up, all patients had negative PBMC and plasma viral load, 19/42 (45.2%) had positive and stable urine viral load. At baseline, 5 patients had positive JCV Elispot, 2 before anti-TNF and 3 before RTX, 2 out of these 5 patients having also positive urine viral load, one in each group. To assess reproducibility of the JCV Elispot, at baseline 4 patients had been tested twice a few days apart, results were similar (3 had negative and one had positive results).

38/42 patients had a follow-up visit. The evolution of JCV Elispot is reported the table. Overall, 9 patients had a positive JCV Elispot once, 5 at baseline, 2 after RTX and 2 after anti-TNF during the follow-up, including 3 who with positive urine viral load, which remained positive during the whole follow-up.

Table. Evolution of JC-feron positive patients

Treatment	Evolution		JC virus IFNγ Elispot			
			Baseline	4–6 months	9–18 months	Urine JC viral load
Rituximab	Positive to negative	Patient 1	Positive	ND	Negative	Positive (6 log)
		Patient 2	Positive	Negative	Negative	Negative
		Patient 3	Positive	Positive	Negative	Positive (6 log)
	Negative to positive	Patient 4	Negative	Negative	Positive	Negative
		Patient 5	Negative	Positive	Negative	Negative
Anti-TNF	Positive to negative	Patient 6	Positive	ND	Negative	Negative
	Negative to positive	Patient 7	Negative	Negative	Positive	Negative
		Patient 8	Negative	Positive	ND	Positive (1.3 log)
	Always positive	Patient 9	Positive	Positive	Positive	Negative

Conclusion: The presence of anti-JCV T cell response has been found positive at least once in 9/42 (21%) of patients with RA treated with anti TNF or rituximab without any link with the use of one or the other type of biologics. These results suggest that in patients chronically infected with JC virus with long duration RA treated or not with biologics, transient reactivation of JC may occur leading to T-cell response Our data do not support a link with RTX or anti-TNF use. Long term follow up in larger cohorts of patients is necessary for indicating if a positive JCV Elispot could be predictive of further central neurological complication of JC virus.

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A Novel Individualized Treatment Approach in Open-Label Extension Study of Ozoralizumab (ATN-103) in Subjects with Rheumatoid Arthritis On a Background of Methotrexate. Roy M. Fleischmann[1], Steven De Bruyn[2], Christian Duby[2], Katrien Verschueren[2], Judith Baumeister[2], Laura Sargentini-Maier[2], Cedric Ververken[2] and Josefin-Beate Holz[2]. [1]University of Texas, Dallas, TX, [2]Ablynx N.V., Zwijnaarde, Belgium

Background/Purpose: Ozoralizumab (ATN-103), a novel TNFα inhibitor, is a trivalent, bispecific Nanobody® that potently neutralises TNF and binds to human serum albumin to increase its in vivo half-life. 2 singe ascending dose (SAD)/multiple ascending dose (MAD) studies in 313 patients (world-wide and Japan) with active RA on stable MTX background evaluated ozoralizumab's clinical activity and safety during 12 weeks of treatment. The 80mg Q4W dosing regimen significantly improved disease activity measures compared with placebo. Patients completing the MAD trials were allowed to enrol in this 48-week open-label extension (OLE) study to evaluate the long-term safety and tolerability of ATN-103. An innovative dosing concept with individual dose escalation from 10mg to max. 80mg during first 12 weeks of treatment was tested in this OLE.

Methods: Study start was defined as completion of 20-week follow-up visit in the MAD trials. Individualized dosing regimen was introduced with all patients starting on active treatment at 10mg SC monthly. Subsequently, dose escalation to 30mg and 80mg monthly SC was dependent on patient's CDAI and safety. Primary objective was long-term safety and tolerability of ATN-103. Efficacy measures, as well as PK/PD, were included as exploratory endpoints.

Results: 266/313 pat (85%) enrolled in the OLE. Baseline mean age was 52y, 80% female, DAS 6.11 and CDAI 42. Dropout rate was low with 13% and 231/266 pat completed the study. 93% of pat reached individual final dose at or before week 12, 56% completed at 80 mg, 29% at 30mg and 15% remained on the starting dose of 10mg. Safety: Treatment was well tolerated, most common AEs were infections (37.6%) with serious events in 3/100 pat years. Efficacy: At study endpoint, ACR20, 50 and 70 scores were 84%, 63% and 32% respectively; 38% had DAS28_CRP <2.6; 132/230 pat (57%) had low or no disease activity; EULAR good/moderate response rate was 97% with rapid and marked improvement of pain (47%) and morning stiffness (90%). 7/266 pat tested positive for neutralizing anti-drug antibodies (nADA) at any time during trial, all completed the study and 57% (4/7) had DAS28 <2.6. 0.75% of patients remained positive for nADA at end of study without effect on patient's safety or ability to achieve remission or improvement of disease activity.

Conclusion: The novel anti-TNFα inhibitor ATN-103 enabled highly effective and well-tolerated individualized treatment. Specific molecular features of Nanobodies (small size, low immunogenicity potential, manufacturability) contributed to the desired treatment outcome with the majority of patients showing marked improvement in their disease activity and, moreover, once induced remission could be maintained at doses less than 80mg monthly. This treatment approach could prove beneficial to patients and minimize treatment costs.

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Clinical Response At 12 Weeks Predicts Long-Term Remission and the Extent of Radiographic Progression in Japanese Patients with Rheumatoid Arthritis Treated with Certolizumab Pegol with and without Methotrexate Coadministration. Tsutomu Takeuchi[1], Kazuhiko Yamamoto[2], Hisashi Yamanaka[3], Naoki Ishiguro[4], Yoshiya Tanaka[5], Katsumi Eguchi[6], Akira Watanabe[7], Hideki Origasa[8], Toshiharu Shoji[9], Nobuyuki Miyasaka[10] and Takao Koike[11]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan, [5]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [6]Sasebo City General Hospital, Sasebo, Nagasaki, Japan, [7]Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi, Japan, [8]University of Toyama School of Medicine, Toyama, Toyama, Japan, [9]Otsuka Pharmaceutical Co., Ltd, Shinagawa-ku, Tokyo, Japan, [10]Tokyo Medical and Dental University, Tokyo, Japan, [11]Sapporo medical center NTT EC, Sapporo, Japan

Background/Purpose: The majority of patients (pts) with active rheumatoid arthritis (RA) have previously been shown to respond during the first 12 weeks (wks) of certolizumab pegol (CZP) treatment; additionally, a lack of DAS28 improvement by Wk12 predicts failure to achieve low disease activity (LDA) at later timepoints.[1] This post hoc analysis investigated whether the magnitude of DAS28(ESR) nonresponse to CZP at Wk12 of therapy can predict the likelihood of achieving remission (DAS28(ESR)<2.6) and extent of radiographic progression after 1 year (yr) (52–56 wks) of CZP treatment in Japanese pts receiving coadministered MTX (JRAPID, NCT00851318), DMARDs other than MTX or CZP monotherapy (HIKARI, NCT00850343).

Methods: Both studies included a 24 Wk double blind phase (CZP 400mg Wks 0, 2, 4, then CZP 200mg every other week (Q2W)), followed by open-label treatment for 28 Wks with CZP 200mg Q2W or CZP 400mg every 4 wks (Q4W). The mean change in mTSS and the proportion of pts who achieved remission at 1 yr was assessed according to the level of DAS28 response (ie, DAS28(ESR) change from baseline [CFB] ≥0.6 and ≥1.2 units) at Wk12. Last observation carried forward (LOCF) imputation was used for pts who withdrew.

Results: 82 J-RAPID and 116 HIKARI CZP treated pts were included. J-RAPID and HIKARI pts had a mean baseline DAS28(ESR) of 6.19 and 6.09, and mean mTSS total of 50.4 and 36.5, respectively. Overall, 77% of J-RAPID pts and 74% of HIKARI pts had a ≥1.2 DAS28(ESR) response at Wk12. Remission was achieved by 32.9% and 27.6% of the original J-RAPID and HIKARI CZP ITT populations at 1 yr. Pts who did not achieve a DAS28(ESR) change of ≥1.2 at Wk12, had a <7% chance of achieving remission at Wk52 (Table) and had greater radiographic progression at 1 yr than responders. Failure to achieve remission at 1 yr and the extent of radiographic progression was also dependent on the magnitude of DAS28(ESR) change at Wk12. Pts with a DAS28(ESR) response of <0.6 had a lower rate of remission and greater radiographic progression at 1 yr compared to pts with a DAS28(ESR) response of <1.2 (Table). Similar results were observed in both the J-RAPID and HIKARI populations.

Table. Wk 12 response predicts remission rate and mean mTSS total score change after 1 year

Change in DAS28 (ESR) at Wk 12	J-RAPID CZP 200 mg Q2W + MTX (N = 82)				HIKARI CZP 200 mg Q2W (N = 116)			
	N	DAS28 (ESR) remission rate n (%)	N	Mean change in mTSS total score	N	DAS28 (ESR) remission rate n (%)	N	Mean change in mTSS total score
<0.6	10	0 (0)	10	4.20	13	0 (0)	12	3.46
≥0.6	72	27 (37.5)	71	0.26	103	32 (31.1)	102	1.39
<1.2	19	1 (5.3)	19	2.23	30	2 (6.7)	28	2.79
≥1.2	63	26 (41.3)	62	0.29	86	30 (34.9)	86	1.23

Conclusion: The majority of Japanese pts responded to treatment with CZP at Wk12 in the broad pt population represented by these studies.

Likelihood of remission and extent of radiographic progression after 1 year could be predicted at Wk12 based on the magnitude of change in DAS28(ESR) in pts.

Reference
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Tolerance of Rituximab in Patients with a History of Cancer: Data From the Registry Air. Jacques-Eric Gottenberg[1], Marie-Odile Duzanski[2], Thomas Bardin[3], Patrice P. Cacoub Sr.[4], Alain G. Cantagrel[5], Bernard Combe[6], Maxime Dougados[7], Rene-Marc Flipo[8], Bertrand Godeau[9], Loic Guillevin[10], Eric Hachulla[11], Xavier Le Loet[12], Thierry Schaeverbeke[13], Jean Sibilia[14], Isabelle Pane[15], Philippe Ravaud[16], Gabriel Baron[17] and Xavier Mariette[18]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [3]Hôpital Lariboisière, Paris, France, [4]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [5]Hopital Purpan, Toulouse CEDEX 9, France, [6]Hopital Lapeyronie, Montpellier, France, [7]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [8]Hopital R Salengro CHRU, Lille CEDEX, France, [9]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [10]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [11]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [12]CHU de ROUEN, Rouen, France, [13]Groupe Hospitalier Pellegrin, Bordeaux, France, [14]CHU Hautepierre, Strasbourg, France, [15]Hotel Dieu University Hospital Paris, Paris, France, [16]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [17]Epidemiology, Paris, France, [18]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Data regarding tolerance of biologics in patients with a history of cancer are very limited. We therefore analyzed tolerance of rituximab (RTX) in patients with a history of cancer included in the AIR ("Autoimmunity and Rituximab") registry.

Methods: The French Society of Rheumatology has set up a nationwide prospective 7-year registry, AIR to investigate the long-term safety and efficacy in real life of RTX.

Results: Among the 2000 patients enrolled, 272 patients (13.6%) treated with RTX had a history of cancer prior to RTX. 33% of them had a history of breast cancer with a median duration of 6 years, 15% of skin cancer (6% melanoma), 14% of lymphoma, 7% a prostate cancer, 6% an uterus cancer, 5% a colorectal cancer, 3% a thyroid cancer and 17% another cancer (kidney, bladder, lung, blood malignancies, brain). The main baseline characteristics of these patients (disease duration 15 years, record of serious or recurrent infections: 35.2%, proportion of patients treated without a concomitant synthetic DMARD:38.2%) were comparable to those of patients without a history of cancer, except an older age (63 vs 58 years), a higher proportion of patients without anti-TNF prior to RTX (55% vs 83%) and a lower disease activity (median DAS28: 5.2 vs 5.6). The median time between the diagnosis of cancer and the first infusion was 4 [0–46] years. 270 patients with a history of cancer had at least 1 follow-up visit respectively, with a median follow-up period of 2.8 years (756 patient/years) and 1709 patients without a history of cancer had a follow-up visit with a median follow-up of 2.8 years (4785 patient/years).

–Cancers: Among the patients with a history of cancer, 20 patients had a recurrence of cancer or a second cancer (2.6 cancers/100 patient/years). 13 (5%, 1.7/100 patient/years) developed metastases or recurrence of their previous cancer (breast: 3, colon: 1, liver: 2, lung: 2, myeloma: 1, skin: 1, uterus: 1, bladder: 1, kidney: 1) and 7 (2.6%, 0.9 cancer/100 PY).) developed a new cancer (skin: 3, bladder: 2, colon: 1, pancreas: 1). Among the patients without a history of cancer, 43 cancers (0.9 cancer/100 patient/years) (skin: 10, breast: 6, lung: 5, prostate: 4, others: 18) occurred after a median duration of 22 months after the 1st RTX infusion.

–Serious infections: 25 and 214 patients with/without history of cancer had a serious infection (3.3 and 4.5 serious infections/100 patient/years, respectively).

–Deaths: 15 and 64 patients with/without history of cancer died (1.9 and 1.3 deaths/100 patient/years, respectively).

Conclusion: RTX is often used in common practice in patients with history of cancer, although data are limited except for lymphomas. After nearly 3 years of follow-up, overall safety of RTX seems comparable in patients with or without history of cancer. The risk of a new cancer is the same than in patients without any previous cancer. The risk of cancer recurrence is difficult to evaluate in the absence of a control group of RA patients with cancers of matched histology, severity and duration, non-treated with RTX. Collaboration between registries might help to address this issue.

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Validation of Algorithms Using Genome-Wide SNP Analysis for Prediction of Remission or Low Disease Activity for Infliximab or Etanercept-Treated RA Patients. Tsukasa Matsubara[1], Satoru Koyano[2], Keiko Funahashi[2], James E. Middleton[2], Takako Miura[1], Kosuke Okuda[1], Takeshi Nakamura[1], Akira Sagawa[3], Takeo Sakurai[4], Hiroaki Matsuno[5], Tomomaro Izumihara[6], Eisuke Shono[7], Kou Katayama[8], Toyomitsu Tsuchida[9], Mitsuyoshi Iwahashi[10], Tomomi Tsuru[11] and Motohiro Oribe[12]. [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [4]Inoue Hospital, Takasaki, Japan, [5]Toyama, Japan, [6]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [7]Shono Rheumatology Clinic, Fukuoka, Japan, [8]Katayama Orthopedic Rheumatology Clinic, Asahikawa, Japan, [9]Tsuchida Clinic, Chiba, Japan, [10]Higashi-Hiroshima Memorial Hospital, Higashi-hiroshima, Japan, [11]PS Clinic, Fukuoka, Japan, [12]Oribe Rheumatism and Internal Medicine Clinic, Oita, Japan

Background/Purpose: Achievement of remission or low disease activity with infliximab (IFX) and etanercept (ETN) treatment is currently one of the most important matters in RA treatment. However, there is no method for prediction of remission or low disease activity. Previously, we established and validated SNP algorithms for prediction of remission or non-remission among IFX or ETN-treated RA patients (Matsubara T, et al., *The 75th annual meeting of the American College of Rheumatology (ACR)*. Chicago, IL, USA (2011)). In this study, in order to predict remission or low disease activity with these biologics, we validated a third population sample by using the first and second population algorithms.

Methods: The first population sample included 187 RA patients, the second, 206 patients, and the third, 145 patients, for a total of 538 patients from eleven hospitals in different regions of Japan. Remission criteria and low disease activity were determined by DAS28(CRP) within 24–30 weeks after the initiation of treatment with the biologics. Case-control analyses between 285,548 SNPs and remission or low disease activity was examined by Fisher's exact test. For each biologic, IFX or ETN, we selected 10 SNPs associated with remission or low disease activity which were common in the analyses of both the first and second population ($p < 0.05$). We then scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in remission: +1 point, hetero allele: 0 points, and homo allele in the majority of non-remission: −1 point), and then examined relationship between remission, non-remission, and the total score.

Results: In the validation of the third population sample, accuracy ((true positive+true negative)/total) for prediction of IFX remission or low disease activity using the two combined algorithms was 88.9%. Also, in the validation of the third population sample, accuracy of prediction of ETN remission or low disease activity using two combined algorithms was 76.7%. Therefore, the accuracy of prediction of remission or low disease activity using the two combined algorithms is exponentially better than that of remission or low disease activity algorithms alone.

Conclusion: These highly accurate algorithms using SNP analysis may be useful in the prediction of remission or low disease activity before treatment with IFX or ETN, and in this way can contribute to future tailor-made treatment with biologic agents.

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Gene Expression Profiling and Pathway Changes Associated with Clinical Response to Tabalumab Blockade of Membrane Bound and Soluble B Cell Activating Factor in Rheumatoid Arthritis.

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Background/Purpose: Tabalumab, a monoclonal antibody neutralizing membrane bound and soluble B cell activating Factor (BAFF), has been shown to reduce the signs and symptoms of rheumatoid arthritis (RA)[1.] To better define tabalumab's molecular mechanism of action, gene expression profiling of whole blood RNA was performed to characterize individual gene expression signatures and to map the associated pathways involved with BAFF blockage in RA.

Methods: Whole blood RNA was obtained from 158 RA subjects with inadequate response to methotrexate enrolled in a phase 2 randomized trial in which patients received subcutaneous placebo, 1, 3, 10, 30, 60 or 120 mg of tabalumab every 4 weeks (wks) over 24 wks. At total of 669 RNA samples were obtained at baseline, wk 1, 4 and 16, and follow up visits at wk 32 and 44. Samples from 30 healthy blood donors controls were analyzed. Affymetrix U133 Plus 2.0 expression arrays were used to measure gene expression. Data were normalized using Robust Multichip Average (RMA) algorithm[2]. Following quality analysis a total of 676 samples were profiled. B cells from peripheral blood were enumerated using flow cytometry. Total serum IgG, A and M, rheumatoid factor (RF) and ACPA were measured using nepholometry. Statistical analyses were performed using a mixed effect model and p-values were adjusted for multiple hypotheses testing using False Discovery Rate (FDR) and Bonferroni techniques. Paired t-tests were used to generate a list of biologically relevant genes whose transcripts exhibited consistent changes in response to tabalumab treatment.

Results: The genes demonstrating significant changes with treatment over time are listed in the table. Many of these genes are represented by multiple probe sets. Most were down regulated. Several of these have been previously reported to be associated with RA susceptibility. The use of gene ontology, pathway and literature mining revealed that the most significant changes were related to B cell development and signaling. Changes in CD19 expression were correlated with CD19 enumeration. Additional genes related to B cell development and signaling were associated with changes in CD19 expression. Consistent with these changes, serum immunoglobulins IgM, IgA decreased significantly from baseline and IgG had a numerical decrease over time. There were no statistically significant changes in RF or ACPA levels from baseline.

Table. Top candidate genes whose gene expression changes were significant following treatment with tabalumab

Gene	Raw p-value/ Multiplicity Adjusted p-value	Gene	Raw p-value/ Multiplicity Adjusted p-value
T-cell leukemia/lymphoma 1A, TCL1A	5.40E-18/ 2.90E-13	phosphatidic acid phosphatase type 2 domain containing 1B, PPAPDC1B	6.00E-08/ 3.30E-03
MACRO domain containing 2, MACROD2	2.90E-09/ 1.60E-04	like-glycosyltransferase, LARGE	1.70E-10/ 9.10E-06
immunoglobulin heavy constant delta, IGHD	1.90E-10/ 1.00E-05	ATP-binding cassette, sub-family B (MDR/TAP), member 4, ABCB4	3.00E-10/ 1.60E-05
CD72 molecule, CD72	1.70E-09/ 9.20E-05	immunoglobulin heavy constant mu, IGHM	2.10E-09/ 1.10E-04
chronic lymphocytic leukemia up-regulated 1, CLLU1	3.20E-09/ 1.70E-04	sodium channel, voltage-gated, type III, alpha subunit, SCN3A	1.10E-08/ 5.80E-04
Fc receptor-like A, FCRLA	7.4 E-08/ 4 E-08	major histocompatibility complex, class II, DO beta, HLA-DOB	4.30E-08/ 2.30E-03
tetraspan 13, TSPAN13	4.30E-08/ 2.30E-03	CD79a molecule, CD79A	3.20E-07/ 9.20E-04
CD19 molecule, CD19	4.80E-07/ 1.20E-03	family with sequence similarity 129, member C, FAM129C	4.60E-07/ 1.20E-03
Fc fragment of IgE, low affinity II, receptor for (CD23), FCER2	1.10E-06/ 2.30E-03	protein kinase (cAMP-dependent, catalytic) inhibitor gamma, PKIG	7.30E-07/ 1.70E-03
CD200 molecule, CD200	9.80E-07/ 2.20E-03	sorting nexin 22, SNX22	6.70E-07/ 1.70E-03
coronin, actin binding protein, 2B, CORO2B	1.10 E-06/ 4.90 E-03	Fc receptor-like 2, FCRL2	2.40E-06/ 5.30E-03
probe 243780_at near the BAFF Receptor, BAFF-R	2.90E-06/ 5.50E-03	Fc receptor-like 1, FCR1	3.50E-06/ 6.30E-03

Conclusion: Using RNA gene expression profiling and pathway analysis, significant gene changes associated with the clinical response to tabalumab were identified. We observed changes in genes related to B cell development and maturation which is consistent with tabalumab's mechanism of action. These data may provide additional potential targets or biomarkers for future studies in RA.

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Disclosure: W. J. Komocsar, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **M. C. Genovese**, Eli Lilly and Company, 2, Eli Lilly and Company, 5; **E. R. Dow**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **P. Banerjee**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **M. A. Penny**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **E. P. Nantz**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **S. Stepaniants**, Eli Lilly and Company, 9; **A. Ho**, Eli Lilly and Company, 9; **P. Y. Berclaz**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **R. W. Hoffman**, Eli Lilly and Company, 1, Eli Lilly and Company, 3.

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Long-Term Safety and Efficacy of 4-Weekly Certolizumab Pegol Combination and Monotherapy in Rheumatoid Arthritis: 5 Year Results from an Open Label Extension Study.

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Background/Purpose: Certolizumab pegol (CZP) has been shown to be efficacious and have an acceptable safety profile when administered every 4 weeks (Q4W) as monotherapy (FAST4WARD, NCT00548834) or in combination with methotrexate (MTX) (Study 014, NCT00544154) for the treatment of rheumatoid arthritis (RA).[1,2] This post-hoc analysis evaluated long-term safety and efficacy of 400mg CZP Q4W monotherapy and in combination with MTX for RA over 5 years.

Methods: The open label extension (OLE) study (NCT00160693) enrolled patients (pts) who withdrew or completed the 24 week (Wk) FAST4WARD or 014 studies. The primary OLE objective was to monitor safety. Pts were permitted to take DMARDs in OLE. Pt retention rates and efficacy are reported up to Wk280 (5.4yrs) (last time point all sites open) and safety up to Wk364 (final data cut-point) of the OLE. Safety population included all pts who received CZP in OLE (patients completing or withdrawing early from either feeder study who entered OLE and those originally randomized to PBO in the double-blind phase [all pts N=402, all monotherapy pts N=126]). Analyzed efficacy population consisted of (1) FAST4WARD and 014 Wk 24 completers from CZP group who entered OLE (N=71; CZP completers) and (2) FAST4WARD completers from CZP group who entered OLE and did not receive MTX or another DMARD at any point (N=48; CZP monotherapy completers).

Results: 50% of the CZP monotherapy completers remained in OLE at Wk280 (Figure). These retention rates were similar to all CZP completers (Figure). For all monotherapy pts, the event rates per 100-pt yrs (ERs) for all adverse events (323.4), injection site reactions (2.8), all serious AEs (16.5) and serious neoplasms (0.8) were lower than for all pts (416.4, 3.6, 24.4 and 1.6). ER of serious infections, AEs leading to withdrawal and AEs leading to death were low and similar between populations (Table). In CZP completers and CZP monotherapy completers, respectively, DAS28-3(CRP) mean (SD) change from feeder study baseline was −1.8 (1.2) and −1.9 (1.4) at OLE entry, and −3.0 (1.4) and −3.1 (1.6) at Wk280. HAQ mean (SD) change from feeder baseline for the same groups were −0.4 (0.5) and −0.6 (0.7) at OLE entry, and −0.5 (0.6) and −0.7 (0.8) at Wk280, respectively.

A. Kaplan Meier plot showing drop-out rates due to any reason for CZP all patients and CZP monotherapy pts who completed 24-wks of double-blind CZP therapy
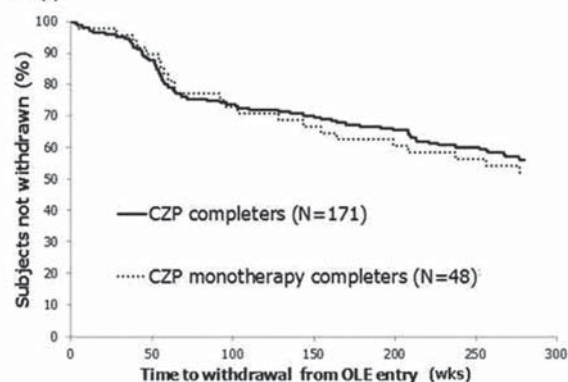
B. Safety of CZP: all patients compared to monotherapy subgroup (includes pts who completed or withdrew from either feeder and entered OLE, and pts who were originally on PBO)

Summary of adverse events	All pts in OLE N=402	All monotherapy in OLE N=126
ER-event rate per 100 pt-yrs		
Any AE	416.4	323.4
Injection site reaction	3.6	2.8
Any serious AE	24.4	16.5
Serious infection	4.4	4.2
Serious neoplasm*	1.6	0.8
AEs leading to withdrawal	6.7	6.3
AEs leading to death	0.6	0.6

*Neoplasms could be benign or malignant

Conclusion: Use of CZP 400mg Q4W monotherapy has been confirmed to have an acceptable long-term safety profile. Some AEs seem to be lower in the monotherapy subgroup than for all pts, but this requires confirmation as it could be a consequence of selection bias. Long-term CZP monotherapy is associated with similar improvement in disease activity and physical function to a population where the majority of pts received combination therapy. CZP monotherapy pts had a similar retention rate in the OLE to the overall population.

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One-Year Results From the Canadian Methotrexate and Etanercept Outcome Study: A Randomized Trial of Etanercept and Methotrexate Versus Etanercept Alone in Rheumatoid Arthritis.

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Background/Purpose: Combination therapy with a biologic and methotrexate (MTX) usually yields better outcomes than biologic monotherapy in rheumatoid arthritis (RA).[1,2,3] However, patients may be intolerant to MTX, or prefer fewer medications if doing well. As well, some data suggest monotherapy with etanercept (ETN) may be sufficient.[4] The objective of this open label, RA trial was to determine if withdrawing MTX after 6 months of combination ETN+MTX, in MTX inadequate responders, is as effective as continuing ETN+MTX.

Methods: TNF inhibitor naïve, RA patients with active disease ($\geq$3 swollen joints, DAS28$\geq$3.2) despite stable MTX therapy ($\geq$15 mg/wk, or 10 mg/wk if intolerant) for >12 weeks were enrolled. Combination therapy with ETN (50 mg/wk sc)+MTX was initiated for 6 months, followed by randomization of the patients to either continue with ETN+MTX or switch to ETN monotherapy for an additional 18 months. The primary end point was to show non-inferiority of ETN vs ETN+MTX, based on the change in DAS28-ESR, 6 months after randomization (non-inferiority margin in DAS28-ESR (-0.6)), with pre-specified analyses of subsets by disease activity (DAS28<3.2 vs DAS28$\geq$3.2).

Results: 258 patients with active RA were enrolled (76% female; mean age 54.7$\pm$12.5 yrs; DAS28 5.4$\pm$1.1; duration of RA 8.9$\pm$8.4 yrs). Mean duration of prior MTX treatment was 4.9$\pm$4.7 yrs; 48.4% of patients used $\geq$2 prior DMARDs and 43.8% used sc MTX. From baseline to 6 months, disease activity improved, with a change in mean DAS28 [95% CI] of -1.9 [-2.1, -1.7]. At 6 months, 205 patients were randomized with similar baseline characterisitics. Of 53 non-randomized patients, 40% discontinued treatment due to disease progression, 26% due to adverse events and 34% for other reasons. From 6 to 12 months, DAS28 was maintained in patients on ETN+MTX and increased slightly in patients on ETN monotherapy, (Table 1). The primary endpoint of non-inferiority was not achieved. However, if a low disease activity (LDA) was achieved (DAS28<3.2) at 6 months, the change in DAS28 from 6 to 12 months was similar for ETN+MTX and ETN (Figure 1). Conversely, for patients on ETN+MTX with DAS28$\geq$3.2 at 6 months disease activity continued to improve from 6 to 12 months, while patients on ETN monotherapy had slightly iincreased disease activity at 12 months (Figure 1).

Table 1. Change in DAS28 from 6 and 12 months (Intent to Treat–All randomized subjects)

	Total		Primary Non-Inferiority Endpoint (Adjusted difference between 6 to 12 months DAS28 change in ETN vs ETN+MTX)
	ETN (n = 98)	**ETN+MTX (n = 107)**	
Mean DAS28 [95%CI] 12 months	4.0 [3.7, 4.3]	3.6 [3.2, 3.8]	-0.4 [-0.7, -0.12]
Change [95%CI] from month 6 to 12 in mean DAS28	0.5 [0.3, 0.7]	0.04 [-0.2, 0.3]	
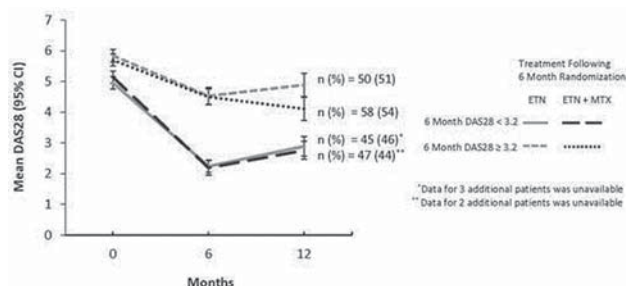
Figure 1. Mean DAS28–6 Month Randomization to 12 Months (Intent to Treat Analysis)

Conclusion: Patients who achieve DAS28<3.2 by 6 months on ETN+MTX have similar disease activity at 12 months, whether they continue or stop MTX. It is possible to discontinue MTX in the subset of patients who reach LDA, while it is preferable to continue MTX in those who do not achieve LDA.

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1318

Long-Term Benefits of 4-Weekly Certolizumab Pegol Combination and Monotherapy On Household Productivity and Social Participation in Rheumatoid Arthritis: 5 Year Results from an Open Label Extension Study. Vibeke Strand[1], Oana Purcaru[2], Ronald F. van Vollenhoven[3], Ernest Choy[4] and Roy Fleischmann[5]. [1]Stanford University, Portola Valley, CA, [2]UCB Pharma, Brussels, Belgium, [3]Karolinska Institute, Stockholm, Sweden, [4]Cardiff University School of Medicine, Cardiff, United Kingdom, [5]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Certolizumab pegol (CZP) monotherapy administered every 4 weeks (Q4W) for rheumatoid arthritis (RA) has been shown to be associated with rapid and sustainable improvements in productivity up to 2 years.[1] The current analysis evaluates the long-term impact on household productivity and social participation of CZP 400mg Q4W combination and monotherapy over 5 years.

Methods: In this open-label extension (OLE) (NCT00160693) patients (pts) originally enrolled in FAST4WARD (NCT00548834) or study 014 (NCT00544154) received CZP 400 mg Q4W for 24 weeks (wks). Pts who completed or withdrew on/after Wk12 in either study were eligible and were permitted to take DMARDs in OLE. Household productivity and social participation were assessed through the RA-specific Work Productivity Survey (WPS-RA); results are reported up to Wk268 (5.2yrs). The analyzed population consisted of (1) Wk 24 CZP completers from FAST4WARD or 014 who entered the OLE (all pts group) and (2) CZP completers from FAST4WARD who entered OLE and did not receive MTX or another DMARD at any point (monotherapy subgroup).

Results: From the CZP groups of the FAST4WARD (N=111) and 014 (N=124) feeder studies, 75 and 96 pts, respectively, completed the studies and entered the OLE. 48 pts who completed FAST4WARD and entered the OLE remained on monotherapy throughout their time in the OLE, and of these 26 remained in OLE at Wk268. In both populations analyzed, a rapid reduction in the number of days missed of household work per month was seen from feeder study baseline (BL, 7.4 and 11.1 mean days respectively) over 24wks of the feeder studies to OLE entry (3.5 and 4.1 mean days respectively) and continued to decline over time, up to Week 268 (1.2 and 1.4 mean days respectively; Table). A similar decrease was reported in the number of household days with reduced productivity per month, and in the rate of RA interference with household productivity per month (Table). Increased participation in family/social/leisure activities was reported in both populations, with a decrease in the number of days missed per month from feeder study baseline (4.4 and 6.2 mean days, respectively), to entry to OLE, at a mean of 1.3 and 1.1 days respectively for the 2 groups; these improvements continued over the 5 years to 0.4 and 0.2 days on average in the 2 populations respectively.

Table. Productivity at home and daily activities of CZP 400mg Q4W combination and monotherapy patients over 5 years[a]

Week	All pts					Monotherapy subgroup*				
	BL feeder study	Entry OLE	52	160	268	BL feeder study	Entry OLE	52	160	268
Number of subjects*	171	171	157	112	95	48	46	42	31	26
Household work days missed per month; mean [median/Q8]	7.4 [4/10]	3.5 [0/5]	1.7 [0/1.7]	1.3 [0/1.3]	1.2 [0/1.3]	11.1 [7/20]	4.1 [1.5/5]	1.6 [0/1.7]	0.9 [0/1]	1.4 [0.2/1.7]
Household work days with reduced productivity per month; mean [median/Q8]	10.2 [8.0/15]	3.8 [0/5]	2.4 [0/2.3]	1.3 [0/1.2]	1.6 [0/1.3]	11.9 [9/22.5]	3.6 [0.5/4]	2 [0/1.3]	0.8 [0/1]	1.2 [0/1.7]
Rate of RA interference with household productivity per month; mean [median/Q8]	5.5 [5/7]	3.2 [3/5]	2.8 [3/4]	2.3 [2/4]	2.4 [2/4]	5.9 [5/9]	3.2 [2.5/5]	2.6 [1.5/5]	1.8 [1/4]	2.3 [0.5/5]
Days missed of family/social/ leisure activities per month; mean [median/Q8]	4.4 [1.5/5]	1.3 [0/1]	0.5 [0/0.3]	0.3 [0/0]	0.4 [0/0]	6.2 [2.5/6.5]	1.1 [0/2]	0.9 [0/0.7]	0.3 [0/0.7]	0.2 [0/0]

Observed data; *Total possible pts at each time point shown, actual number of survey respondents may differ; 0–10 scale, 0 = no interference, 10 = complete interference; Pts from FAST4WARD who remain on monotherapy throughout the CLE

Conclusion: CZP treatment, in combination with MTX/DMARDs or as monotherapy, improved household productivity and increased participation in social/family/leisure activities, as shown by the decrease in the number of household work or social/family/leisure days missed or the number of days with reduced productivity per month. These improvements were maintained up to 5 years with open-label CZP following 24 wks double-blind CZP therapy.

Reference
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Certolizumab Pegol Plus Methotrexate Is Similarly Effective in Active Rheumatoid Arthritis Secondary Non-Responders to Anti-TNF Inhibitors: Post-Hoc Analysis of a Phase Iiib Trial. Daniel Furst[1], Saeed A. Shaikh[2], Maria W. Greenwald[3], Michael H. Schiff[4], Barbara Bennett[5], Owen Davies[6], Fabienne Staelens[6], Will Koetse[7] and Philippe Bertin[8]. [1]University of California at Los Angeles, Los Angeles, CA, [2]McMaster University, St Catharines, ON, [3]Desert Medical Advances, Palm Desert, CA, [4]University of Colorado, Denver, CO, [5]BABennett Consulting, LLC, Marietta, GA, [6]UCB Pharma, Brussels, Belgium, [7]UCB Pharma, Rtp, NC, [8]Dupuytren Hospital, Limoges, France

Background/Purpose: Certolizumab pegol (CZP) has demonstrated efficacy in patients (pts) with prior TNF inhibitor exposure.[1] In the Doseflex trial two maintenance dosing regimens of CZP were comparable at maintaining response and significantly better than placebo (PBO).[1] Data from pts with and without prior TNF inhibitor exposure are presented.

Methods: Doseflex was a 34 Wk Phase IIIb, open-label run-in and double-blind (DB) PBO-controlled randomized study in pts with active RA on stable dose MTX (NCT00580840). Secondary TNF inhibitor non-responders were included. All pts received 400 mg CZP at wks 0, 2, and 4 and 200 mg CZP every 2 wks (Q2W) to Wk16 + MTX. Wk16 ACR20 responders were randomized 1:1:1 at Wk18 to MTX plus 200 mg CZP Q2W, 400 mg CZP every 4 wks (Q4W) or PBO (CZP withdrawn) for 16 Wks. Primary end-point was ACR20 at Wk34; ACR responses and CDAI/SDAI/DAS28(ESR) remission were assessed using NRI for missing data imputation.

Results: Of 333 pts entering the run-in 91.9% were from the US and 53.5% had prior TNF inhibitor use. Mean DAS28(ESR), SDAI and CDAI at baseline were 6.4, 40.4 and 38.4. At Wk16, responder rates for pts with and without prior TNF inhibitor exposure were; ACR20 60.7% vs. 61.9%; ACR50 34.8% vs. 41.3%; ACR70 14.0% vs. 18.7%. Of pts randomized at Wk18, 42.0%, 61.4% and 55.7% had prior TNF inhibitor use in PBO, CZP 200 mg and CZP 400mg groups. Baseline characteristics were similar for randomized pts with and without prior TNF inhibitor exposure. At Wk34, ACR20/50/70 response rates were comparable between 200mg and 400mg groups (67.1/50.0/30.0% and 65.2/52.2/37.7%) and significantly higher than CZP→PBO (44.9/30.4/15.9%, p<0.05 for all). ACR20 at Wk34 in pts with vs. without prior TNF exposure was 37.9% vs. 50.0% with PBO, 74.4% vs. 55.6% with CZP 200 mg Q2W and 61.5% vs. 70.0% with CZP 400 mg Q4W. ACR50/70 and remission rates were similar in CZP pts with and without prior TNF inhibitor exposure receiving both dosage regimens; however, with PBO they were considerably lower for pts with prior TNF inhibitor exposure vs. without (Figure). CZP was well tolerated (adverse event (AE) rates in DB phase: 62.3% vs 62.9% vs 60.9%; serious AE rates: 0% vs 7.1% vs. 2.9% in the CZP→PBO, CZP 200mg and 400mg groups). The most common SAEs were infections and infestations (4.3% in the CZP 200mg groups; 0 in the other groups).

Figure. ACR50 response, CDAI and SDAI remission rates by prior TNF inhibitor at wk 34 in ACR20 responders at wk 18
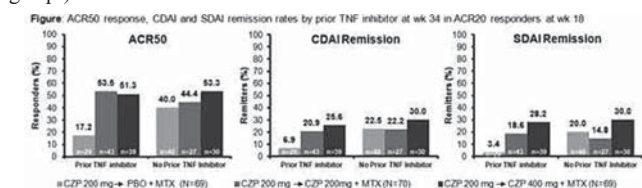
Conclusion: In RA pts with active disease and incomplete response to MTX, CZP 200mg Q2W and CZP 400mg Q4W showed comparable efficacy in maintaining clinical response to Wk34 following a 16 Wk run-in. CZP demonstrated similar efficacy in RA pts with or without prior exposure to TNF inhibitors over 34 Wks. When CZP was withdrawn at Wk16 in ACR20 responders (pts randomized to PBO), there appeared to be a greater maintenance of response in pts who had no prior TNF inhibitor exposure.

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Sarilumab, a Subcutaneously-Administered, Fully-Human Monoclonal Antibody Inhibitor of the IL-6 Receptor: Effects On Hemoglobin Levels in a Clinical Trial for the Treatment of Moderate-to-Severe Rheumatoid Arthritis.

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Background/Purpose: Anemia of chronic disease, a common extra-articular manifestation of rheumatoid arthritis (RA), which has a substantial impact on patient function, is driven in part by proinflammatory cytokines such as IL-6. Sarilumab, the first fully human monoclonal antibody directed against the alpha subunit of the IL-6 receptor (IL-6Rα), blocks receptor binding of IL-6. In the phase 2 MOBILITY Part A trial, sarilumab administered subcutaneously demonstrated significant and clinically relevant improvements in ACR20 at Week 12 relative to placebo in patients with active RA receiving methotrexate (MTX). The current analysis evaluated the effects of sarilumab on hemoglobin (Hb) levels.

Methods: MOBILITY Part A was a phase 2, 12-week, double-blind, placebo-controlled trial of adults with active RA despite MTX. Patients continued MTX and were equally randomized to placebo or 1 of 5 sarilumab doses: 100 mg every other week (q2w); 150 mg q2w; 100 mg weekly (qw); 200 mg q2w; or 150 mg qw. Blood samples collected at baseline and every 2 weeks during treatment were analyzed for Hb levels (ANCOVA model comparing Hb change over 12 weeks for each sarilumab group vs. placebo) and high sensitivity C-reactive protein (hs-CRP), an inflammatory marker.

Results: 306 patients were randomized. Baseline characteristics were similar across all groups: mean age 52.2 ± 12.3 years; 79% female; mean disease duration 7.8 ± 8.1 years; RF+ 79.7%; mean hs-CRP 2.8 ± 3.0 mg/dL. Week 0 Hb data were available for 295 patients: mean baseline Hb 12.6 ± 1.6 mg/dL; 25.4% of patients had low Hb, defined as ≤12.5 mg/dL. Increase in Hb levels was observed as early as Week 2 in all sarilumab groups, with significant increases vs. placebo ($P\leq0.0002$) at Week 12 (Figure). The effect was greatest with the 150 mg qw dose, followed by 200 mg q2w. All placebo patients who had low baseline Hb (n=17) still had low Hb at Week 12; 65.5% of the sarilumab patients low at baseline (n=58) had normalized Hb (n=38) at Week 12. Mean hs-CRP levels were ≤0.8 mg/dL by Week 12 in all treatment groups except placebo (2.6 mg/dL) and sarilumab 100 mg q2w (1.8 mg/dL); reductions in hs-CRP at Week 12 were also significant relative to placebo ($P<0.0001$), except for 100 mg q2w ($P=0.0661$). The most common treatment emergent adverse events (AEs) reported in the sarilumab arms were infections (non-serious) 12–26%, neutropenia 0–20%, and ALT increase 0–6%. Eight patients (3 receiving sarilumab 100 mg q2w, 3 receiving 100 mg qw, and 2 receiving placebo) experienced at least 1 treatment emergent serious AE (SAE); of these, 6 led to permanent treatment discontinuation, including 1 death in the sarilumab 100 mg q2w group (acute respiratory distress syndrome, cerebrovascular accident). There were no infection-related SAEs in patients with grade 3 or 4 neutropenia.
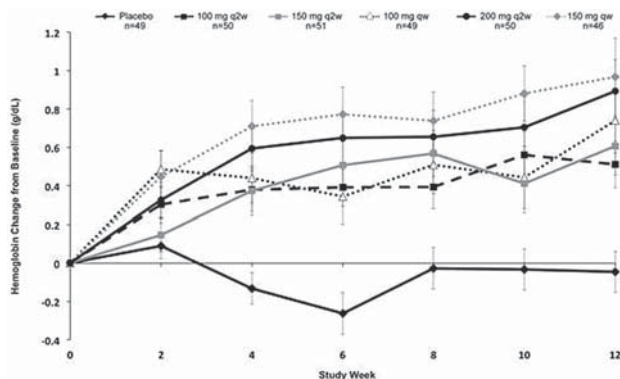
*P≤0.0002, change from baseline at week 12 for each dose group vs placebo

Conclusion: Sarilumab treatment for RA over 12 weeks resulted in significant improvements in hemoglobin relative to placebo.

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C-Type Lectin Domain Family 4, Member C Gene Expression Level Helps Predict Future Clinical Response to Tabalumab Blockade of B Cell Activating Factor in Rheumatoid Arthritis.

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Background/Purpose: Patients with rheumatoid arthritis (RA) exhibit substantial variability in both the magnitude and duration of their clinical response to treatment. Despite considerable research, no biomarker has reproducibly been shown to predict likelihood of clinical response to biologic therapy. There remains significant unmet medical need to identify patients who will have a meaningful response to treatment prior to drug exposure. We have recently shown the efficacy of tabalumab (previously known as LY2127399), a monocolonal antibody neutralizing membrane bound and soluble B cell activating factor (BAFF) in RA[1]. We have now used gene expression profiling of whole blood mRNA, obtained prior to drug exposure, to identify a predictive gene expression pattern that helps identify patients that are highly likely to respond to treatment with tabalumab.

Methods: Whole blood mRNA was obtained at baseline from 158 RA subjects with an inadequate response to methotrexate enrolled in a phase 2 randomized trial in which patients received placebo, 1, 3, 10, 30, 60 or 120 mg of tabalumab every 4 weeks over 24 weeks. Clinical results of BAFF blockade in RA of this study have recently been reported[1]. In addition to the RA subjects (152 samples passed quality control), samples from 30 healthy blood donor controls were analyzed using Affymetrix U133 Plus 2.0 expression arrays to determine gene expression, and data were compared after normalization using Robust Multichip Average (RMA) algorithm[2]. C-type Lectin Domain Family 4, Member C (CLEC4C) qPCR was performed in validated assays at Covance Genomics Seattle using primers and probes obtained from ABI. Statistical analyses were performed using Messina[3], two sample t-test and or regression modeling.

Results: There was a bimodal distribution of CLEC4C mRNA in whole blood from RA patients and controls at baseline. The mean level of CLEC4C gene expression measured by Affymetrix was lower in patients than in controls. Mean expression after normalization for patients (n=152) is 5.79 with a range of 3.18 to 9.69. Mean expression for control healthy blood donors (n=30) is 6.88, range is 4.36 to 9.02. Among patients, those with higher levels of CLEC4C gene expression were more likely to respond to tabalumab (as measured by ACR-N). Messina analysis[2] at baseline identified both CLEC4C probe sets as having the largest margin when comparing responder and non-responder group outcome at week 16 using ACR-N/DAS28. A two sample t-test on the same data was significant (p<0.0007). These expression findings from selected Affymetrix probe sets were validated using qPCR; for CLEC4C the change in threshold cycle versus ACR-N was statically significant after correction for multiple comparisons using False Discovery Rate (FDR) and Bonferroni techniques (FDR p=0.013, Bonferroni p=0.013).

Conclusion: The subgroup of RA patients with higher levels of CLEC4C mRNA expression at baseline were significantly more likely to respond to treatment with tabalumab. Independent replication of these hypothesis generating findings is now in progress in a large phase 3 clinical trial of tabalumab.

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Coadministration of ASP015K, a Novel Janus Kinase Inhibitor with Methotrexate Demonstrates Tolerability and Lack of Pharmacokinetic Interactions in Patients with Rheumatoid Arthritis. Tong Zhu[1], Kazuo Oda[2], Udaya Valluri[1], Bogie Moore[1], Ying Cao[1], Vishala Chindalore[3] and Bola Akinlade[1]. [1]Astellas Pharma Global Development, Inc., Northbrook, IL, [2]Astellas Pharma Inc., Osaka, Japan, [3]Pinnacle Research Group/Anniston Medical Clinic, Anniston, AL

Background/Purpose: ASP015K is an oral Janus kinase (JAK) inhibitor with selectivity for JAK1/3 in development for treatment of rheumatoid arthritis (RA) and other autoimmune diseases. Methotrexate (MTX) is the most common non-biologic DMARD therapy and recommended as first-line therapy in RA treatment guidelines. In humans, MTX is primarily excreted unchanged into urine. Transporter-mediated renal tubular secretion of MTX is thought to be a major mechanism of PK interaction with other drugs. In vitro experiments were performed to evaluate the effects of ASP015K on renal transporters. A clinical drug-drug interaction study was also conducted to evaluate the effect of multiple-dose of ASP015K on MTX PK, and the short-term safety and tolerability of coadministration in RA patients.

Methods: In vitro experiments were conducted to assess the inhibitory potency of ASP015K on human multidrug resistance-associated protein 2/4 (MRP2/4) and organic anion transporter 1/3 (OAT1/3). A phase 1, open-label, single-sequence study was conducted to confirm the in vivo effect of ASP015K on the PK of MTX, a substrate of MRP2/4 and OAT1/3. Fifteen subjects diagnosed with RA for ≥ 6 months and had been treated with MTX (15 to 25 mg weekly) for ≥ 28 days were enrolled. Subjects received their usual prescribed dose of MTX on day 1. They then received ASP015K 100 mg BID for 6.5 days (day 3 through the morning of day 9), and a second prescribed dose of MTX in combination with ASP015K on day 8. Serial blood samples were collected for MTX concentration assay after dosing on day 1 (MTX alone) and 8 (MTX+ASP), and for ASP015K concentration assay after dosing on day 7 (ASP alone) and 8 (MTX+ASP). Predose concentrations (C_{tough}) of ASP015K were measured on days 3, 4, 5, 6, 7 and 8. Urinary excretion of MTX was also assessed.

Results: ASP015K demonstrated no in vitro inhibitory effect on MRP2/4 or OAT1 ($IC_{50} > 100$ μM); it inhibited OAT3 with an IC_{50} of 5 μM. Fourteen subjects completed the phase 1 study for PK evaluation. Results showed that MTX exposure was not affected by coadministration of ASP015K; AUC_{inf} ratio (MTX+ASP/MTX alone) was 103% [90% confidence interval (CI) 93, 113]; C_{max} ratio was 92% [90% CI 83, 103]. Analysis of C_{trough} indicated ASP015K levels reached steady state on day 5. ASP015K $AUC_{12,ss}$ was not affected by coadministration of MTX with a ratio (MTX+ASP/ASP alone) of 98% [90% CI, 91, 106]. ASP015K C_{max} decreased by 8% with a ratio (MTX+ASP/ASP alone) of 92% [90% CI, 78, 108], which was considered not to be clinically significant. The unbound C_{max} of ASP015K at 100 mg BID was estimated to be $<1/10^{th}$ of the IC_{50} for OAT3 in vitro suggesting that ASP015K would not affect MTX PK. ASP015K was well tolerated when coadministed with MTX. One subject experienced an SAE (urinary tract infection) before receiving study drug and subsequently a second SAE (gastroenteritis) after receiving MTX on day 1 but before receiving ASP015K. This subject was discontinued from the study.

Conclusion: Coadministration of ASP015K and MTX was well tolerated in this short-term study exhibiting no clinically significant effect on the PK profile of either drug. Efficacy and safety of ASP015K/MTX combination therapy is being assessed in ongoing phase 2 trials in RA patients.

Disclosure: T. Zhu, Astellas Pharma Global Development, Inc., 3; **K. Oda**, Astellas Pharma Global Development, Inc., 3; **U. Valluri**, Astellas Pharma Global Development, Inc., 3; **B. Moore**, Astellas Pharma Global Development, Inc., 3; **Y. Cao**, Astellas Pharma Global Development, Inc., 3; **V. Chindalore**, None; **B. Akinlade**, Astellas Pharma Global Development, Inc., 3.

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Effects of Dose Escalation of Tocilizumab in Combination with Nonbiologic Disease-Modifying Antirheumatic Drugs: Sub-Analysis of a 24-Week Study in a United States Population. M. E. Weinblatt[1], Herbert S. B. Baraf[2], Ara H. Dikranian[3], Andrew M. Anisfeld[4], Jenny Devenport[4] and Sheldon Cooper[5]. [1]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [2]Arthritis & Rheumatism Associates, Wheaton, MD, [3]San Diego Arthritis Medical Clinic, San Diego, CA, [4]Genentech, South San Francisco, CA, [5]Univ Vermont College of Med, Burlington, VT

Background/Purpose: In the US, the recommended starting dose of Tocilizumab (TCZ) is 4 mg/kg (q4w) with an increase to 8 mg/kg (q4w) based on clinical response. However, analyses of responses experienced by patients increasing TCZ dose from 4 mg/kg to 8 mg/kg have been limited by a uniform escape escalation criterion used across phase III trials: patients randomized to 4 mg/kg who did not experience a 20% improvement in TJC and SJC at Week 16 increased the dose to 8 mg/kg. This sub-analysis of the ACTSTAR study evaluated the response of patients following an increase in TCZ dose after or at Week 8 based on joint counts or investigator discretion, respectively. Safety and efficacy outcomes of the full study were reported previously.

Methods: ACT-STAR was a phase 3b, 24-wk, open-label, multicenter US study that evaluated adults with active RA who had an inadequate clinical response or safety/tolerability issues with prior DMARD therapy. This sub-analysis examined patients initiating TCZ 4 mg/kg who continued their current synthetic DMARD. Per study protocol, patients who did not achieve $\geq 20\%$ improvement in TJC and SJC at Week 8 were to increase TCZ dose to 8 mg/kg. After Week 8, the protocol allowed TCZ dose escalation to 8 mg/kg per physician discretion. Study visits occurred at BL and 4 weeks after each infusion.

Results: Of the 363 patients randomized to receive TCZ 4 mg/kg, 68 increased to 8 mg/kg *after* Week 8, 142 patients increased to 8 mg/kg *at* Week 8 and 152 patients received only 4 mg/kg (1 patient was not dosed). Among patients who increased dose *after* Week 8, ACR20 response at Week 24 was achieved by 58.8% of patients, ACR50 by 36.8% of patients and ACR70 11.8% of patients. Mean DAS28 decreased from 5.76 at BL to 4.45, 4.20 and 3.77 at Weeks 8, 16 and 24, respectively. ACR core components improved initially and continued to improve following dose escalation (Table). Of these patients who escalated at Week 8, which was enriched for non-responders due to study design, ACR20, 50 and 70 responses were achieved in 30.3%, 12.0% and 3.5% of patients at Week 24. Mean DAS28 decreased from 5.69 at BL to 5.39 at Week 8 (prior to protocol defined dose escalation) and to 4.32 and 4.17 at Weeks 16 and 24 (after dose escalation), respectively. Similar improvements across ACR core components were observed (Table). The most common serious adverse events pre- and post-dose increase were serious infections (SI); 1/142 (0.7%) patient experienced SI prior to dose increase, 0 patients who escalated after Week 8 experienced SIs and 3/142 (2.1%) patients experienced SI post Week 8 dose increase. Eight patients withdrew from the study due to adverse events; 2 patients who escalated after Week 8 and 6 patients who increased at Week 8.

Table.

	Baseline	Change from baseline		
		Week 8	Week 16	Week 24
Patients who increased dose from 4 mg/kg to 8 mg/kg after Week 8 (n = 68)				
DAS28, mean (SD)–	5.76 (0.97) [68]	-1.29 (1.1) [66]	-1.59 (1.3) [66]	-1.95 (1.4) [61]
CRP, mg/dL (SD)–	1.08 (1.3) [68]	-0.19 (1.3) [66]	-0.36 (1.5) [67]	-0.62 (2.8) [62]
TJC, mean (SD)–	29.57 (13.5) [68]	-12.73 (10.0) [67]	-13.12 (14.3) [67]	-15.33 (14.3) [67]
SJC, mean (SD)–	19.32 (11.6) [68]	-9.07 (8.1) [67]	-8.72 (13.2) [67]	-10.34 (12.4) [67]
Patient Global VAS (SD)–	63.91 (20.7) [68]	-19.37 (22.8) [67]	-20.10 (26.3) [67]	-25.00 (25.3) [67]
Physician Global VAS (SD)–	64.93 (18.2) [68]	-24.12 (22.3) [67]	-22.36 (24.3) [66]	-29.82 (23.8) [67]
Patients who increased dose from 4 mg/kg to 8 mg/kg at Week 8 (n = 142)				
DAS28, mean (SD)–	5.69 (1.03) [142]	-0.31 (0.9) [139]	-1.38 (1.1) [134]	-1.47 (1.2) [120]
CRP, mg/dL (SD)–	1.64 (2.5) [142]	-0.15 (2.0) [139]	-1.19 (2.6) [134]	-1.02 (2.7) [120]
TJC, mean (SD)–	28.73 (14.6) [142]	0.27 (10.5) [142]	-8.33 (14.3) [138]	-9.37 (13.5) [127]
SJC, mean (SD)–	18.06 (11.0) [142]	0.56 (8.2) [142]	-5.10 (8.1) [138]	-5.96 (9.2) [127]
Patient Global VAS (SD)–	65.17 (19.4) [142]	-5.32 (20.4) [142]	-14.60 (23.4) [138]	-16.63 (23.5) [127]
Physician Global VAS (SD)–	63.91 (17.9) [142]	-8.45 (22.2) [142]	-23.02 (26.1) [133]	-25.92 (25.5) [127]

Conclusion: Patients who escalated TCZ dose from 4 mg/kg to 8 mg/kg after or at Week 8 based on joint counts or investigator discretion were observed to have improvements in DAS28 and ACR core components following dose escalation.

Disclosure: M. E. Weinblatt, Amgen, Abbott, Merck, Astra Zeneca, Centacor, UCB, Pfizer, Roche/Genentech, 5; **H. S. B. Baraf**, Abbott, Janssen, Sanofi, Pfizer, BMS, Genentech, 2, Abbott Laboratories, 8; **A. H. Dikranian**, Genentech, UCB, Abbott, BMS, 8; **A. M. Anisfeld**, Genentech and Biogen IDEC Inc., 3; **J. Devenport**, Genentech and Biogen IDEC Inc., 3, Genentech/Roche, 1; **S. Cooper**, IL-6, IL-21 in RA, 2, various, 5.

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Golimumab, A Human Anti-TNF Monoclonal Antibody, Administered Subcutaneously Every Four Weeks As Monotherapy in Patients with Active Rheumatoid Arthritis Despite Disease Modifying Antirheumatic Drug Therapy: Week 104 Results of Clinical, Radiographic and Safety Assessments.

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Background/Purpose: To assess the long-term efficacy and safety of golimumab (GLM) as monotherapy in Japanese patients (pts) with active rheumatoid arthritis (RA) despite DMARD therapy.

Methods: GO-MONO is a multicenter, randomized, double-blind, placebo (PBO)-controlled study in pts with active RA despite treatment with DMARDs. Pts were randomized to SC PBO, GLM50 mg, or GLM100 mg q4wks as monotherapy. At wk16, pts in the PBO group (grp) crossed over (CO) GLM50 mg q4wks. Treatment with GLM continued to wk120. Primary endpoint was the proportion of pts achieving ACR20 at wk14. Secondary endpoints included ACR50, ACR70, and ACR-N, DAS28 and HAQ and changes from BL to wks 24/52/104/120 in total modified vdH-Sharp (vdH-S) score. Data were analyzed using all patients receiving ≥ 1 dose of study treatment. Missing clinical response data were not imputed. For vdH-S score, treatment grp comparisons at wks 52/104 were based on initial randomized grps. Missing data were imputed using median change from BL in total vdH-S scores (TSS) of all pts or by linear extrapolation. Wk52 data have been reported; wk104 results of efficacy are now reported. Safety data from all treatment period are reported as incidence per 100-patient-years.

Results: Long-term efficacy and safety data are shown in the Table. Clinical remission was defined as DAS28(ESR) < 2.6 and HAQ remission was defined as HAQ < 0.5 maintained between wk52 and wk104. Median changes from baseline to wk52 were 1.0 in PBO and GLM 50mg, and 0 in GLM100 mg. Median changes from baseline to wk104 in PBO, GLM 50 and 100 mg were 1.5, 1.25 and 1.0, respectively. The proportions of pts with changes in TSS greater than the smallest detectable change (SDC) were also maintained from wk52 and wk104. Proportion of pts with no progression (change in TSS≤ 0) were slightly decrease from wk52 to wk104 in both of GLM 50 mg and 100 mg. Safety finding are also summarized in the Table. Two deaths were reported, one in GLM 50 mg (brain stem haemorrhage) and one in 100 mg (pancreatic carcinoma). Incidences of SAEs and AEs leading to discontinuation in GLM 50 mg were higher than 100 mg. There were no cases of tuberculosis or lymphoma reported.

	Evaluation at	PBO[a]	GLM 50 mg	GLM 100 mg
Efficacy results				
DAS(ESR) remission (<2.6)	Wk 52	17/85 (20.0)	18/84 (21.4)	26/94 (27.7)
n/N(%)	Wk 104	27/78 (34.6)	29/74 (39.2)	32/90 (35.6)
HAQ remission (<0.5)	Wk 52	46/85 (54.1)	37/84 (44.0)	52/94 (55.3)
n/N(%)	Wk 104	51/78 (65.4)	46/74 (62.2)	53/90 (58.9)
Change from BL in TSS[b]	Wk 52	83	82	93
n	Wk 104	2.81 (7.139)	3.31 (6.192)	1.56 (5.093)
Mean (SD)		1	1	0
Median		83	82	93
		3.61 (8.922)	4.34 (7.720)	2.64 (6.507)
		1.5	1.25	1
Pts with progression based on TSS >SDC[c]	Wk 52	17/83 (20.5)	16/82 (19.5)	16/92 (17.4)
n/N(%)	Wk 104	16/75 (21.3)	16/72 (22.2)	21/89 (23.6)
Pts with change ≤ 0 in TSS from baseline	Wk 52	37/105 (35.2)	46/101 (45.5)	54/102 (52.9)
n/N(%)	Wk 104	28/75 (37.3)	22/72 (30.6)	40/89 (44.9)
Safety results from all treatment period				
Avg duration of follow-up (wks)		15	97.1	110.9
Incidence per 100 patient-years (95%CI)		0.00 (0.00, 9.88)	0.28 (0.01, 1.55)	0.46 (0.01, 2.56)
Deaths		6.63 (0.80, 23.94)	14.47 (10.74, 19.08)	7.92 (4.61, 12.68)
SAEs		9.95 (2.05, 29.09)	7.83 (5.20, 11.32)	5.07 (2.53, 9.07)
Patients with AEs leading to discontinuation		3.30 (0.08, 18.38)	3.09 (1.54, 5.53)	3.75 (1.62, 7.39)
Patients with 1 or more serious infections				

a) All patients received placebo crossed over to GLM50 mg afer wk 16.
b) Missing data were imputed using median change from BL of all pts or by linear extrapolation.
c) SDC = 5.18 at wk 52, SDC = 5.65 at wk 104

Conclusion: Treatment with GLM50 mg and 100 mg monotherapy sustained the efficacy of signs/symptoms during 104wks. Inhibition of structural damage in GLM 100 mg was relatively greater than GLM 50mg, however the progression went on slowly during 104wks in both of the GLM groups. The GLM safety profile was similar to other anti-TNF agents.

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Prevention of Joint Destruction in Patients with High Disease Activity or High C-Reactive Protein.

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Background/Purpose: In Japan, 2 doses (50mg and 100mg) of golimumab (GLM) were approved for the treatment of rheumatoid arthritis (RA) patients (pts), used with methotrexate (MTX), based on the results from GO-FORTH study. However, differences in joint destruction between the GLM 100mg and 50mg groups remain unclear. In a sub analysis of the GO-FORTH study, we assessed the difference of suppression on joint destruction progression between 100mg and 50mg based on the baseline disease activity or CRP.

Methods: GO-FORTH is a multicenter, randomized, double-blind, placebo(PBO)-controlled study in pts with active RA despite MTX. Pts were randomized to SC PBO, GLM50 mg, or GLM100 mg q4wks. All pts received MTX 6–8 mg orally/wk. Pts with <20% improvement in SJC/TJC entered early escape(EE) at wk 16 so that PBO→GLM50 mg and GLM50 mg→GLM100 mg. Pts who did not enter EE continued initial therapy until wk 24. The ΔTSS and inhibition rates (IR, ΔTSS ≤ 0) on progression of joint destruction through wk 24 in MTX-resistant pts (n=261) by baseline DAS28ESR and CRP were compared. High disease activity pts (HDA) and high CRP pts were defined as DAS28ESR > 5.1 or CRP $\geq$ 1.5mg/dL, and moderate disease activity pts (MDA) and low CRP were defined as 3.2 < DAS28 (ESR) $\leq$ 5.1 or CRP < 1.5mg/dL.

Results: Mean ΔTSS (median) in placebo + MTX with HDA (n=57) or high CRP (n=40) were 3.48 (1.0) and 3.41 (1.0) which were higher than those in MDA (0.76 (0.0) (n=29)) and low CRP (1.76 (0.0) (n=48)), respectively (Table). In HDA and high CRP, mean ΔTSS in GLM 100mg + MTX was lower compared with GLM 50mg + MTX in HDA and high CRP individually, although MDA and low CRP were not. IR on progression in HDA and high CRP were 40.4% in placebo + MTX (n=57), 43.1% in GLM 50mg +

MTX (n=51) and 69.8% in 100mg + MTX (n=53) by HDA, and 40.0% (n=40), 38.2% (n=34) and 61.5% (n=26) by high CRP, respectively. IR on progression in MDA and low CRP were 69.0% (n=29), 81.8% (n=33) and 70.6% (n=34) by MDA and 58.3% (n=48), 73.1% (n=52) and 73.8% (n=61) by low CRP, respectively. Group differences in IR were only observed between GLM 50mg + MTX and 100mg + MTX in HDA or high CRP. The suppression on joint destruction in GLM 50mg + MTX was effective in MDA or low CRP, however it was not effective in HAD or high CRP. Pts whose ΔTSS >0 in GLM 50mg + MTX with HAD or high CRP had short disease duration and small TSS as baseline characteristics in comparison with pts whose ΔTSS ≤ 0.

Table. Change from baseline in vdH-S through wk 24.

		Placebo + MTX†	50mg + MTX	100mg + MTX
Overall	number of patients	88	86	87
	Δtotal vdH-S score			
	mean (SD)	2.51 (5.52)	1.05 (3.71)	0.33 (2.66)
	median (min, max)	0.25 [-8.5, 33.5]	0.00 [-6.3, 22.5]	0.00 [-3.5, 19.0]
	p value	–	0.0203	0.0006
	Change in vdH-S score ≤ 0	44 (50.0%)	51 (59.3%)	61 (70.1%)
	p value	–	0.2179	0.0066
DAS28 (ESR) >3.2 - ≤5.1	number of patients	29	33	34
	Δtotal vdH-S score			
	mean	0.76	−0.27	0.23
	median (min, max)	0.00 [-1.5, 8.0]	0.00 [-3.5, 3.5]	0.00 [-3.5, 6.2]
	p value	–	0.0257	0.1977
	Change in vdH-S score ≤ 0	20 (69.0%)	27 (81.8%)	24 (70.6%)
	p value	–	0.2384	0.8888
>5.1	number of patients	57	51	53
	Δtotal vdH-S score			
	mean	3.48	1.94	0.39
	median (min, max)	1.00 [-8.5, 33.5]	0.50 [-6.3, 22.5]	0.00 [-3.5, 19.0]
	p value	–	0.1127	0.0012
	Change in vdH-S score ≤ 0	23 (40.4%)	22 (43.1%)	37 (69.8%)
	p value	–	0.7069	0.0019
CRP (mg/dL) <1.5	number of patients	48	52	61
	Δtotal vdH-S score			
	mean	1.76	−0.04	0.02
	median (min, max)	0.00 [-1.5, 19.5]	0.00 [-6.3, 5.5]	0.00 [-3.5, 7.0]
	p value	–	0.0010	0.0007
	Change in vdH-S score ≤ 0	28 (58.3%)	38 (73.1%)	45 (73.8%)
	p value	–	0.1200	0.0889
≥1.5	number of patients	40	34	26
	Δtotal vdH-S scor			
	mean	3.41	2.71	1.15
	median (min, max)	1.00 [-8.5, 33.5]	1.00 [-4.5, 225]	0.00 [-2.0, 19.0]
	p value	–	0.6021	0.1151
	Change in vdH-S score ≤ 0	16 (40.0%)	13 (38.2%)	16 (61.5%)
	p value	–	0.8768	0.0871

Data shown are number (%) of patients or mean ±SD, median [range].
P values derived from comparisons versus placebo+MTX. Δtotal vdH-S score was tested by van der Waerden normal scores. Changes in vdH-S score ≤ 0 was tested by chi-square test.
† Pts with <20% improvement in SJC/TJC entered early escape(EE) at wk 16 so that PBO→GLM50 mg and GLM50 mg→GLM100 mg.

Conclusion: In the GO-FORTH study, joint destruction progression in RA pts with HAD or high CRP at baseline was more rapid than in RA pts with MDA or low CRP. GLM 100mg was more effective in preventing joint destruction than GLM 50mg, especially in RA pts with early and high disease activity or high CRP.

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Efficacy of Different Biologic Agents for Improving Physical Function As Measured by the Health Assessment Questionnaire: A Meta-Analysis with Indirect Comparisons.
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Background/Purpose: The Health Assessment Questionnaire (HAQ) is a patient-centred, validated measure of physical function. It is predictive for disability, morbidity and mortality. The efficacy of various biologics agents for improving HAQ in patients with Rheumatoid arthritis (RA) has been demonstrated in numerous trials. However, head-to-head comparisons of biologic agents are scarce. The objective of this study was to determine the comparative efficacy of biologic agents for improving HAQ in patients with established RA who failed Disease Modifying Anti-Rheumatic Drugs (DMARDs) or anti-Tumour Necrosis Factor alpha (TNF) agents and in patients with early RA (ERA).

Methods: We performed random effects meta-analyses (Mantel-Haenszel method) of randomized, placebo-controlled trials. Inclusion criteria were: age >15 years, clinically utilized biologic agents, HAQ score at baseline and 6 or 12 months. We searched PubMed, EMBASE and the Cochrane Library. Outcome was the mean difference in change in HAQ for biologic agents compared to controls (ΔHAQ_B-ΔHAQ_C). Indirect comparisons of the different biologic drugs compared to the control group were conducted using the Q-test based on analysis of variance. Meta-regression was performed using the method of moments.

Results: 31 trials were included: 23 with DMARD-failures; 5 with anti-TNF-failures and 6 ERA. The following biologics were represented: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. In established RA patients with DMARD failures: ΔHAQ_B-ΔHAQ_C = −0.28; 95%CI:-0.324, −0.237 (I^2=64%); abatacept and infliximab were less effective compared to the other anti-TNF agents and tocilizumab (p<0.01). In anti-TNF-failures: ΔHAQ_B-ΔHAQ_C was −0.254; 95%CI: −0.46, −0.049 (I^2=92%); golimumab was not effective compared to control and abatacept was superior to tocilizumab (p=0.0184); rituximab was equivalent to abatacept and tocilizumab. Heterogeneity was predominately due to differences in the efficacy of the different biologic agents. In ERA trials: ΔHAQ_B-ΔHAQ_C = −0.231; 95% CI: −0.323, −0.14 (I^2=0%); adalimumab, etanercept, infliximab and rituximab were equally effective. Using meta-regression, baseline HAQ did not significantly effect HAQ improvement.

Conclusion: Biologic agents were efficacious at lowering HAQ in established RA and ERA by at least the minimally clinically important difference of 0.22. However, infliximab and abatacept were less effective in DMARD-failures. The role of anti-TNF agents in anti-TNF failures and of biologics in DMARD-naïve patients remains unclear.

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Comparison of Four Different Intensive Treatment Strategies in Patients with Early Rheumatoid Arthritis in Korea.
Mi-Il Kang, Yoon Kang, Hee-Jin Park, Hyang-Sun Lee, Sang-Won Lee, Yong-Beom Park and Soo-Kon Lee. Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

Background/Purpose: The previous studies reported that intensive treatment-strategies, including biological agents and glucocorticoids, can improve the severity of early rheumatoid arthritis. However, there was no report on their efficacy in Korean patients with early rheumatoid arthritis. Hence, in this study, we investigated the clinical efficacy of intensive treatments in patients with early rheumatoid arthritis in Korea.

Methods: A total of 135 patients with rheumatoid arthritis (RA), who had not receive disease modifying anti-rheumatic drugs (DMARDs) and who had presented with joint symptoms within 1 year, were prospectively enrolled. Clinical outcome measurements and laboratory tests were performed monthly during one-year study period for adjusting treatment in order to achieve remission (Disease Activity Score in 28 joints, DAS28 (ESR) <2.6). All patients were randomly distributed to four treatment groups. Treatment groups were as followings: group1 = a step-up regimen starting with initial methotrexate (MTX) monotherapy and subsequent addition of sulfasalazine (SSZ) and hydroxychloroquine (HCQ); group 2 = initial triple therapy (MTX/SSZ/HCQ); group 3= initial high dose prednisolone with rapid-tapering schedule, combined with MTX; group 4 = initial tumor necrosis factor (TNF)-α blockades combined with MTX. At 12 months, functional ability (Health Assessment Questionnaire (HAQ)), mean differences in the DAS28 (ESR) score, proportion of patients meeting the American College of Rheumatology criteria for 50% improvement (ACR50) and DAS28 (ESR) remission were evaluated. Radiological progression was assessed by the modified Sharp scores after 12 months.

Results: Patients in group 3 and 4 had significantly lower HAQ score than those in group 1 or 2 at 6 months (0.06 and 0.14 vs 0.39 and 0.36, respectively, p=0.008). Furthermore, HAQ scores were still low in patients in group 3 and 4, compared to those in group 1 and 2 after 12 months, but they did not significantly differ (0.07 and 0.10 vs 0.27 and 0.23, respectively, p=0.056). Mean differences in DAS28 (ESR) scores between initial and final assessments were significantly greater in patients in group 3 and 4 than those in group 1 and 2 (-3.6 and -3.3 vs -2.3 and -2.9, respectively, p=0.029). Also ACR50 proportion of group 3 or 4 was significantly higher than that of group 1 or 2 (85 or 95% vs 54 or 76%, respectively, p=0.013). The percentages of patients fulfilling DAS28 (ESR) remission criteria or radiologic progression among study groups showed no significant differences.

Conclusion: In Korean patients with early RA, intensive initial therapy of either high dose prednisolone or TNF-α blockades exhibited rapid functional improvement and excellent disease control at 1 year, compared to a step-up regimen starting with initial MTX monotherapy or parallel triple therapy. Also the efficacy of prednisolone combination therapy was comparable to that of TNF-α blockades combination therapy. Further clinical studies are needed to evaluate whether the initial clinical efficacies of combination therapy including either high dose prednisolone or a TNF-α blockades could be maintained during the long-term follow-up of patients with early rheumatoid arthritis.

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1328

The Higher and Faster Increasing Schedule of Methotrexate May Not Be the Best: The Accumulation of Intracellular Longer Chain Methotrexate Polyglutamates Was Facilitated by the Extra-Low-Dose Methotrexate Treatment. Yoshinobu Koyama[1], Kazunori Hase[2], Daisuke Hidaka[2], Shuji Nagano[2], Toshiyuki Ota[2] and Ayumi Uchino[2]. [1]Okayama Red Cross General Hospital, Okayama, Japan, [2]Iizuka Hospital, Iizuka, Japan

Background/Purpose: Although data are conflicting with regard to the clinical utility of MTX polyglutamates (PGs) measurements as a predictor of the efficacy or toxicity in the treatment of rheumatoid arthritis (RA), it is considered to be essential for the therapeutic effect to achieve necessary concentrations of intracellular MTX-PGs. However, there is no universally accepted method of the optimal schedule for dose initiation and escalation. The higher starting dosage and faster increasing schedule is considered to be beneficial so far. In Japan, the officially approved dosage of MTX for RA treatment had been fixed up to 8mg/wk from 1996 to 2011, whereas the maximum doses of 20 to 30mg/wk were commonly used in the rest of world. As a result, we have very unique experience of extra-low-dose MTX (ExLD-MTX) treatment for RA. In this report, we evaluate the efficacy of ExLD-MTX treatment for RA, and we also investigate the concentrations of intracellular MTX-PGs after ExLD-MTX treatment.

Methods: RA cases treated with ExLD-MTX (n=133) were retrospectively investigated. After 12 months of the treatment, the rates of achieving remission criteria and of withdrawing from the initial treatment were calculated. Next, the concentrations of MTXGlu1–7 in red blood cell (RBC) lysates of 91 patients receiving long-term oral ExLD-MTX were quantitated with using HPLC method.

Results: After 12 months of ExLD-MTX treatment (mean MTX dosage: 6.68 ± 1.72 mg/wk), 72.2% of cases were still maintained with the same treatment. The remission criteria for DAS28 (<2.6) were achieved 31.4% of cases, which is comparable to those of MTX monotherapy arm (mean MTX dosage: 16.9mg/wk) in PREMIER study. The rates of withdrawal because of adverse events and of insufficient efficacy were 2.2% and 25.6% in ExLD-MTX group, while 7.4% and 17.9% in MTX monotherapy arm in PREMIER study. The analysis of intracellular MTX-PG after ExLD-MTX treatment revealed distinct distribution of MTX-PG subtypes, i.e., $88.2\pm19.5\%$ of MTX-PG was MTX-PG6–7, whereas the rate of MTX-PG6–7 was reported to be less than 1% after conventional MTX treatments. Although it did not reach statistical significance, the total concentrations of MTX-PG1–7 (nmoles/1g of Hb) after ExLD-MTX treatment were 8.3 ± 3.8 (range: 3.3–15.4) in the DAS<2.6 group and 6.55 ± 4.25 (range: 1.7–17.6) in the DAS>3.2 group. The percentages of low MTX-PG1–7 concentration (<5.0 nmoles/1g of Hb) were 7.7% in the DAS<2.6 group versus 44.8% in the DAS>3.2 group.

Conclusion: Although the higher starting dosage and faster increasing schedule for MTX has been considered to be better, we found that the efficacy of ExLD-MTX treatment is comparable to conventional MTX treatments. Since MTX exposure was known to induce up-regulation of folylpolyglutamate hydrolase, which removes glutamic acid from MTX-PG, the ExLD-MTX treatment could be favorable for accumulation of the longer-chain MTX-PG. Although it seems to be beneficial to escalate the MTX dosage for some of patients with active disease (DAS>3.2) after ExLD-MTX treatment, a majority of them may have already sufficient MTX-PG concentration to predict its maximal efficacy. Our findings prompt a re-evaluation of the conventional methods for dose initiation and escalation of MTX.

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1329

Differential Effect of 4 and 8 Mg/Kg Tocilizumab in Combination with Methotrexate On Serum Biomarkers of Cartilage, Connective Tissue and Bone Turnover. Anne C. Bay-Jensen[1], Inger Byrjalsen[2], Andrew Kenwright[3], Thierry Sornasse[4], Claus Christiansen[5] and Morten Asser Karsdal[1]. [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Nordic Bioscience, Herlev, Denmark, [3]Roche, Welwyn Garden City, United Kingdom, [4]Genentech, South San Francisco, [5]CCBR, Ballerup, Denmark

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by poly-articular inflammation, cartilage loss, synovial inflammation, subchondral bone erosion, and joint space narrowing. In this analysis, we investigated the effect of tocilizumab (TCZ; anti-IL-6R mAb) in combination with methotrexate (MTX) on serum biomarkers of bone, cartilage, and synovium turn over in patients with moderate to severe RA enrolled in the LITHE study.

Methods: The LITHE study (Roche WA17823) was a 2-year phase III, 3-arm randomized (1:1:1), double-blind, placebo-controlled, parallel group study of TCZ in moderate to severely active RA with inadequate response to MTX. 1196 patients were randomized to receive stable doses of MTX (10–25 mg/week) plus placebo, TCZ at 4 mg/kg (TCZ4), or TCZ at 8 mg/kg (TCZ8) every 4 weeks for 52 weeks. Patients who experienced less than 20% improvement in both swollen (SJC)/tender joint counts (TJC) at week 16 were given escape therapy. Serum samples were collected at baseline and week 2, 4, 16, 24, and 52. Following biomarkers were measured: C2M (cartilage degradation), C3M (synovial inflammation), MMP3, total CRP, CRPM (MMP-degraded CRP), VICM (Citrullinated and MMP degraded Vimentin), ICTP (MMP destroyed type I collagen), osteocalcin (bone formation) and CTX-I (Bone resorption). Analysis of dose- and time-dependent effect of TCZ on the release of biomarkers compared to placebo both including and excluding the escape patients was done by two-way ANOVA.

Results: In the TCZ8 group, the cartilage degradation marker C2M was rapidly reduced as compared to placebo (week 2: -12%) and remained low through weeks 4, 16, 24, and 52 (-13 to -16%, p<0.001). A similar pattern was observed for C3M, VICM, and CRPM, which were reduced at week 4 by -28, -50, and -30% (p<0.0001), respectively. The levels of these 4 markers were not affected in the TCZ4 group or in the placebo group. In contrast, MMP3 levels were strongly reduced in both TCZ4 and TCZ8 groups. The circulating level of total CRP was completely inhibited by TCZ8, but only inhibited by 50% in the TCZ4 group. Osteocalcin and CTX-I were both increased in response to TCZ8, but only osteocalcin was increased in response to TCZ4. No change in ICTP was observed. There was a significant difference (p<0.001) in the biomarker profiles between escape patients, non-responders and responders.

Conclusion: TCZ8 strongly inhibited serum markers of cartilage degradation, synovial inflammation, and inflammation mediated tissue turnover suggesting that TCZ actively suppresses key pathobiological processes at the site of inflammation in RA patients. TCZ4, on the other hand, had limited effect on the release of the markers. This might indicate that TCZ8 had a more beneficial effect on the joint health as compared to TCZ4. Furthermore, the difference in the biomarkers profiles of responders and non-responders were markedly different indicating that predictive profiles for responders and non-responders may exist.

Disclosure: A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **A. Kenwright**, Roche Pharmaceuticals, 3; **T. Sornasse**, Genentech and Biogen IDEC Inc., 3; **C. Christiansen**, Nordic, Bioscience A/S, CCBR/Synarc, Roche, Eli Lilly, Novartis, Novo Nordisk, Proctor and Gamble, Groupe Fournier, Besins EscoVesco, Merck Sharp and Dohme, Chiesi, Boehringer Mannheim, Pfizer, GlaxoSmithKline, Amgen., 5; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 4.

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High Body Mass Index Is Associated with Decreased Response to Initial Combination Therapy in Recent Onset RA Patients. Marianne van den Broek[1], L. Heimans[1], S. le Cessie[1], B. Siegerink[1], H.K Ronday[2], K.H. Han[3], P.J.S.M. Kerstens[4], T.W.J. Huizinga[1], W.F. Lems[5] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, Netherlands, [3]MCRZ hospital, Rotterdam, Netherlands, [4]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [5]VU University medical center, Amsterdam, Netherlands

Background/Purpose: A diminished response to combination treatment with a fixed dose of TNF-blocker infliximab (IFX) has been reported in patients with established RA and a high BMI. The association between BMI and response to therapy might also exist for other treatment regimens through inflammation and/or pain.

The association between high body mass index (BMI) and treatment response was assessed in a treat to target cohort with recent onset RA patients.

Methods: All patients from the BeSt study (n=508), in which patients were randomized to initial monotherapy or combination therapy with prednisone or infliximab (IFX) were included in the analyses. Response (DAS≤2.4) to disease activity steered treatment (first dose and after 1 year) was compared between patients with a BMI <25 and ≥25, using Poisson regression analyses. Several components of disease activity and functional ability during the first year were compared using linear mixed models. Joint damage progression in year 1 and over 8 years of treatment was compared using radiographs scored with the Sharp/van der Heijde Score.

Results: High BMI was independently associated with decreased treatment response to initial therapy, RR: 1.20 (95% C.I. 1.05–1.37). After stratification for initial treatment group, the effect was found for combination therapy with prednisone: RR 1.55 (1.06–2.28) and for combination therapy with IFX, RR 1.42 (0.98–2.06). The RRs for failure after one year in these groups were 1.46 (0.75–2.83) and 2.20 (0.99–4.92) respectively. A similar association was found for response to delayed combination therapy with IFX, after adjustment for selection bias related to previous failure on DMARDs. In the first year of treatment, patients with a high BMI had higher disease activity and worse functional ability, with more tender joints and a higher VAS global health, but not more swollen joints and similar systemic inflammation. Patients with high BMI did not have more damage progression over time (figure 1).
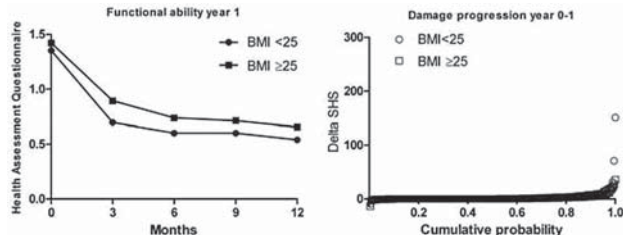
Figure 1. functional ability and joint damage progression in year 1 for patients with normal and high BMI

Conclusion: High BMI was independently associated with decreased response to initial combination therapy with prednisone and to initial and delayed treatment with infliximab, During DAS≤2.4 targeted treatment, patients with a high BMI experienced more pain, but not more swelling or systemic inflammation. Joint damage progression over 8 years was similar for patients with high and normal BMI.

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Once Daily High Dose Regimens of GLPG0634 in Healthy Volunteers Are Safe and Provide Continuous Inhibition of JAK1 but Not JAK2. Florence Namour[1], René Galien[1], Lien Gheyle[2], Frédéric Vanhoutte[3], Béatrice Vayssière[1], Annegret Van der Aa[3], Bart Smets[3] and Gerben van 't Klooster[3]. [1]Galapagos SASU, Romainville, France, [2]SGS Clinical Pharmacology Unit, Antwerp, Belgium, [3]Galapagos NV, Mechelen, Belgium

Background/Purpose: GLPG0634 is an orally-available, selective inhibitor of Janus kinase 1 (JAK1) with an IC_{50} of 0.6 μM and a 30-fold selectivity over JAK2 in human whole blood. Non-selective JAK inhibitors have shown long-term efficacy in treating rheumatoid arthritis (RA). However, doses and thereby efficacy are limited by JAK2-driven side effects. Selective inhibition of JAK1 may result in a cleaner safety profile while maintaining clinical efficacy. Based on its pharmacokinetic (PK) half life, both once-daily (QD) and twice-daily (BID) dosing regimens have been explored. In patients with active RA on methotrexate, 4 weeks daily dosing of 200 mg GLPG0634 has shown highly encouraging efficacy and safety.

Objectives: Evaluate the safety, PK, JAK pharmacodynamics (PD) and -selectivity of GLPG0634 at high dose QD regimens in healthy volunteers.

Methods: In a single-center Phase I study, 3 panels of 8 male healthy volunteers (2 on placebo) received QD dosing of 200 mg, 300 mg and 450 mg GLPG0634 for 10 days. Safety was monitored continuously and followed until 7 days after the last dose. Day profiles for PK and PD were evaluated on Days 1 and 10. GLPG0634 plasma concentrations were assessed by LC-MS/MS. Inhibition of JAK1 was measured by *ex vivo* IL-6 induced STAT1 phosphorylation (pSTAT1) in $CD4^+$ cells, and JAK2 by GM-CSF induced pSTAT5 in $CD33^+$ cells.

Results: GLPG0634 was safe and well-tolerated for 200 mg, 300 mg and 450 mg QD, following 10 days of dosing. Treatment-emergent adverse events over all dose groups were typical Phase I findings (mild and transient headache and abdominal discomfort), with a comparable incidence in GLPG0634- and placebo- treated subjects. There were no relevant findings regarding hematology (including reticulocytes), biochemistry (including LDL cholesterol, ALT/AST or creatinine) or other safety parameters (ECG and vital signs, including blood pressure). A maximal tolerated dose was not reached.

Steady state PK was dose proportional up to 450 mg QD, with an apparent mean half-life of 8 hours. The PK was similar in RA patients and healthy volunteers. There was no accumulation to steady state with low trough levels relative to GLPG0634's IC_{50}. Still, JAK1 signaling remained suppressed up to 24 hours from drug intake, whereas JAK2 signaling was not influenced up to the high dose of 450 mg QD.

GLPG0634 Steady state PK	RA patients (n=6) 200 mg QD	Healthy volunteers (n=6/cohort) 300 mg QD	450 mg QD	200 mg QD
C_{max} (ng/mL)	1,430	1,200	1,380	2,580
C_{24h} (ng/mL)	24	6.0	9.9	18
AUC_{24h} (ng.h/mL)	5,380	4,490	4,400	10,200

Conclusion: At high doses, exceeding those showing high level efficacy in a 4-week RA patient study, GLPG0634 was well tolerated and safe in healthy volunteers. No safety signals were found with GLPG0634; typical findings reported within 2 weeks of dosing of non-selective JAK inhibitors were not observed. Up to 450 mg QD, GLPG0634 was highly selective for inhibition of JAK1 over JAK2. The data suggest the PD half life to be longer than that for PK.

Ongoing studies in RA patients will determine the efficacy of low doses of GLPG0634 (30 mg QD) and the safety of high doses (300 mg QD).

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The Incidence of Exacerbation of Pre-Existing Interstitial Lung Disease (ILD) Is Higher in TNF Blockers Than in Non-TNF Blockers in RA. Tamao Nakashita[1], Shinji Motojima[2], Natsuki Fujio[2] and Akira Jibatake[2]. [1]Kameda Medical Center, Kamogawa City, Japan, [2]Kameda Medical Center, Kamogawa city, Japan

Background/Purpose: Exacerbation of interstitial lung disease (ILD) is a problem when biologics are administrated in patients with RA, and not a few fatal cases have been reported in Japan. According to the post-marketing surveillance report of TNF blockers, the development/exacerbation rate of ILD was 0.5 %. In our department, however, the rate was 5 % probably because we have many RA cases with ILD. We have shown that in patients with pre-existing ILD, the rate is nearly 30%. In japan there are 6 biologics available for the treatment of RA, 4 of which are TNF blockers and 2 are non-TNF blockers. Here we compared the incidence of exacerbation of pre-existing ILD in patients administrated with TNF blockers and non-TNF blockers.

Methods: Subjects were 58 patients with RA, with the mean age of 66. As a part of workup before administration of biologics, chest CT scan was done. After administration of biologics, chest X-ray film (CXR) was taken at least every 3 months. When newly developed shadows were found on CXR or when patients complained of respiratory symptoms for more than 2 weeks, chest CT scan was done again. The severity of ILD was graded into 3, grades 1 to grade 3, according to the extent of ILD on chest CT. The biologics administrated were infliximab (IFX) for 8, etanercept (ETN) for 36, adalimumab (ADA) for 2, tocilizumab (TCZ) for 9 and abatacept (ABT), respectively. The duration of observation was 12 months, except when the biologics were withdrawn because of exacerbation of ILD.

Results: The ILD of 30, 22 and 6 patients were graded into grade 1, 2 and 3, respectively. The ILD exacerbated in 14 subjects (24.1 %); the duration from the introduction of biologics to the exacerbation was from 1 to 12 months with the median of 7 months. The biologics used at the exacerbation of ILD were IFX in 5, ETN in 8, ADA in 1, TCZ in 0 and ABT in 0, respectively. The incidence of ILD exacerbation with TNF blockers and non-TNF blockers were 30.4 % (14/46) and 0 % (0/12), respectively, and there was a significant difference between them (p = 0.024).There were no differences between the subjects with ILD exacerbation and those without it in age, gender, RF titer, the ILD grade, KL-6 concentration, and the dose of prednisolone and MTX. The KL-6 concentration increased significantly when ILD exacerbated (p < 0.05). The biologics were withdrawn in 11 of 14 subjects with ILD exacerbation, and 2 subjects with ILD grade 2 and 3 died due to respiratory failure.

Conclusion: The exacerbation rate was high in patients with pre-existing ILD when TNF blockers were administrated.

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The Predictive Value of CD64 Counts for Infectious Disease in Patients Treated with Tocilizumab On the Infectious Disease Risk Management Cohort (ACT4U-study). Atsushi Ihata[1], Hiroyuki Hagiyama[2], Shouhei Naga-oka[3], Junichi Obata[4], Kiyomitsu Miyachi[5], Hidehiro Yamada[6], Shunsei Hirohata[7], Norihiko Koido[8], Masaomi Yamasaki[9], Kenichi Miyagi[10], Shigeru Ohno[11], Daiga Kishimoto[1], Reikou Watanabe[1], Takeaki Uehara[1], Kaoru Takase[1], Maasa Hama[1], Ryusuke Yoshimi[1], Atsuhisa Ueda[1], Mitsuhiro Takeno[1] and Yoshiaki Ishigatsubo[1]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Yokohama-city Bay Red Cross Hospital, Yokohama, Japan, [3]Yokohama Minami Kyosai Hospital, Yoko-hama, Japan, [4]Hikarichuo Clinic, Kawasaki, Japan, [5]Keigu Clinic, Kawasaki, Japan, [6]St. Marianna University, Kawasaki, Japan, [7]Kitasato University School of Medicine, Sagamihara, Japan, [8]Kawasaki Rheumatism & Internal Medecine Clinic, Kawasaki, [9]St Marianna University, Yokohama City Seibu Hospital, Yokohama, Japan, [10]Miyagi Naika Clinic, Yokohama, [11]Yokohama City University Medical Center, Yokohama, Japan

Background/Purpose: An administration of tocilizumab (TCZ) rapidly suppresses inflammatory markers such as CRP and ESR, which makes the diagnosis of infection difficult. There is a real need to establish the surrogate marker of infectious disease and to find how to reduce the infection risk./To validate the specificity of CD64 on polymorphonuclear neutrophils (CD64) and procalcitonin (PCT) levels as parameters for serious infection (SI) and deterrence effect of infectious disease risk management (IDRM) in RA patients with TCZ.

Methods: Forty-nine RA patients with were enrolled from 4 universities and affiliated clinics (Table). They were required to comply with IDRM policy during observation period. CD64 and PCT were measured at week 0, 4, 8 and the occurrence of infectious disease. Primary endpoint was occurrence frequency of SI (OFSI) and rate of increase in CD64 and PCT. Secondary endpoint was admission due to infection, the dose of concomitant medicines, CDAI and persistence rate of TCZ.

Table. Baseline characteristics of RA subjects at cohort entry

Cases (Male/Female)	49 (5/44)
Age (yr)	57.9 ± 2.1
Weight	8.0 ± 1.4 (6.0)
Steinblocker's Stage (1/2/3/4)	18.8/35.4/22.9/22.9
Steinblocker's Class (1/2/3/4)	22.9/62.5/14.6/0
Smoking	14.3%
Steroid use	± 0.6
Methotrexate use	± 0.5

Results: CD64 was 1477.3±199 and 1456.1±96.7 before and after TCZ administration, respectively. There was no significant difference of CD64 and PCT at baseline between patients with infectious disease and without infectious disease (1104.8±228.3 vs. 1501.4±191.5). Although the increase of CD64 was found in patients with infectious disease at week 8 compared with patients having no infectious disease, there were no significant difference between two groups (2091.2±934.9 vs. 1405.2±157.9). CRP was not as sensitive as CD64, which increased more than 2,000 when infection was complicated in some, but not all cases.

Neither pneumonia nor cellulitis occurred in 17 events of infection and 3 events of SI. CDAI was changed from 61.1±3.7 to 18.3±4.4 (Figure). The dose of CS was reduced by 41.8%. Persistence rate of TCZ was 69.4% at 48 weeks (Figure).
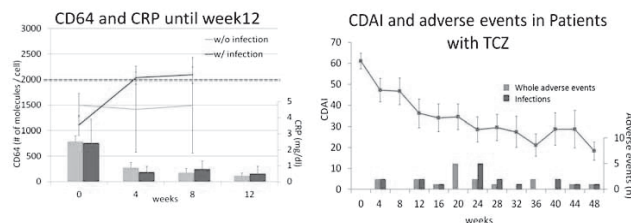
Conclusion: The present study showed that CD64 more sensitively moved than CRP at the complication with infection, suggesting that CD64 was a promising surrogate marker to detect infectious events in patients treated with TCZ. In spite of higher frequency of concomitant lung disease, the incidence of respiratory infection and OFSI were lower in our study than PMS, indicating that IDRM could contribute to reduction of OFSI especially in respiratory infection.

Disclosure: A. Ihata, None; **H. Hagiyama**, None; **S. Nagaoka**, None; **J. Obata**, None; **K. Miyachi**, None; **H. Yamada**, None; **S. Hirohata**, None; **N. Koido**, None; **M. Yamasaki**, None; **K. Miyagi**, None; **S. Ohno**, None; **D. Kishimoto**, None; **R. Watanabe**, None; **T. Uehara**, None; **K. Takase**, None; **M. Hama**, None; **R. Yoshimi**, None; **A. Ueda**, None; **M. Takeno**, None; **Y. Ishigatsubo**, None.

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Intra-Articular Etanercept Treatment in Inflammatory Arthritis: A Randomized Double-Blind Placebo-Controlled Trial. Caroline J. Aal-bers[1], Danielle M. Gerlag[1], Koen Vos[1], Gertjan Wolbink[2], R. Landewe[1] and Paul P. Tak[3]. [1]Academic Medical Center/University of Amsterdam, Amster-dam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [3]Academic Medical Center, University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: The use of intra-articular (IA) corticosteroid injections has been widely accepted as a therapy to control local inflamma-tion. Studies on the use of IA TNF inhibitors revealed conflicting results. Case-reports suggested long-term efficacy of single or repeated injections in inflammatory arthritides. Randomized controlled trials comparing the use of IA TNF inhibitors to IA corticosteroids, showed either inferior or comparable efficacy. It is unknown if IA TNF blockade is more effective than placebo treatment. The objective of this trial was to investigate efficacy and safety of a single IA etanercept injection in comparison to placebo.

Methods: Patients with rheumatoid arthritis (RA) (revised 1987 ACR criteria) or psoriatic arthritis (PsA) (CASPAR classification criteria) and arthritis of knee, ankle, wrist, elbow or MPC joint despite a stable dose of methotrexate and/or prednisone were included. Patients were randomized to receive an IA injection of etanercept (25 mg) or placebo (0.9% NaCl) in a 2:1 ratio. Target joint improvement was determined by a composite change index (CCI; score 0–10), including a visual analogue scale (VAS) for pain, clinical assessments (tenderness, swelling and disability, scored 0–3) and patient's and doctor's assessment of treatment effect. To evaluate the effect of treatment on the CCI as a dependent variable, generalised estimating equations was used with age, gender, disease duration, CRP at baseline and TJC at baseline as covariates, and an exchangeable working correlation structure was chosen. Safety and general disease activity parameters were evaluated weekly up to week 6, as well as systemic CRP level, ESR and etanercept levels.

Results: Thirty-two patients (RA=12; PsA=20) were included, 22 received etanercept and 9 placebo. At baseline both groups were comparable. Treatment with etanercept resulted in a prompt and statistically significant improvement of the CCI (p<0.001) in comparison with placebo, as well as a

decrease in general parameters. When analysed over time, this beneficial effect was transient and only statistically significant at week 1 and 2 after IA injection (Figure 1). Joint tenderness remained decreased up to week 6 (p < 0.01). Maximum serum etanercept levels measured after 1 week were 1.39 ± 0.46 ug/ml. Levels were comparable between CCI 'good'- and 'non-responders'. Mild transient adverse events were reported for 7 (32%) patients treated with etanercept and 2 (25%) with placebo (p=0,55). No serious adverse events were reported.
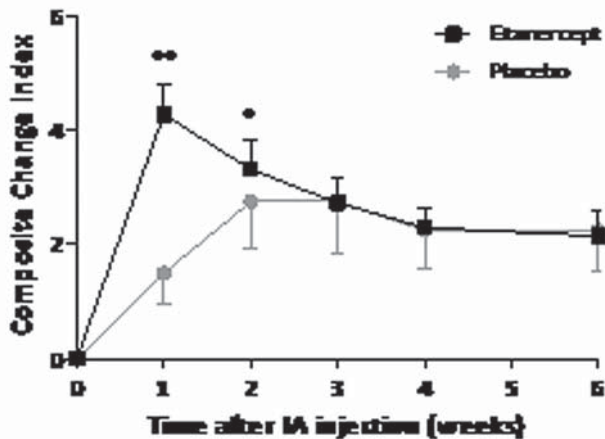
Figure 1. Effect over time of treatment on the composite change index (CCI). The CCI is calculated relative to the baseline visit. Etanercept has a significant effect on the CCI at 1 and 2 weeks after intra-articular injection. *p < 0.05; **p < 0.01.

Conclusion: A single IA etanercept injection is feasible and safe and results in transient improvement of disease activity in the target joint as well as general parameters. This treatment can benefit patients who do not respond to or do not tolerate IA corticosteroids. Due to the high costs associated with anti-TNF treatment, IA corticosteroids remain the preferred treatment option.

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Remission Induction in Early Active Rheumatoid Arthritis: Comparison of Tocilizumab Versus Methotrexate Monotherapy. Patrick Durez, Geneviève Depresseux, Marie Avaux, Adrien Nzeusseu Toukap, Bernard Lauwerys, Laurent Meric de Bellefon, Maria S. Stoenoiu and Frédéric A. Houssiau. Université catholique de Louvain, Brussels, Belgium

Background/Purpose: Tocilizumab (TCZ), as monotherapy and in combination with methotrexate (MTX), has been shown to be efficacious for rheumatoid arthritis patients with insufficient response to MTX or other disease-modifying antirheumatic drugs. These observations were extended to patients with early rheumatoid arthritis (ERA) or refractory to tumor necrosis factor inhibitors. This study was designed to compare the rate of remission induction and the cardiorespiratory endurance (CRE) in early RA patients treated with TCZ or MTX.

Methods: Eligible patients had disease duration ≤2 years, were MTX-naive, and had active RA (DAS28 ≥3.2). Thirty (23 women and 7 men) RA patients were randomized to received either TCZ 8 mg/kg every month or MTX 20 mg weekly for 6 months. After this first period, all patients were treated with MTX for an additional 6 months period. Baseline demographics did not differ between groups: mean age +/− SD (56.9 +/− 10.4) vs (49.4 +/− 14.0), mean disease duration (0.49 +/− 1.3) vs (0.99 +/− 2.3), mean DAS 28-CRP (4.7 +/− 1.3) vs (4.4 +/− 1.0), mean HAQ (1.4 +/− 0.7) vs (0.9 +/− 0.6). ACR and EULAR core set values were evaluated monthly by an independent joint assessor. Differences were statistically tested using Mann-Whitney or Wilcoxon rank tests.

Results: 13 and 17 ERA patients were included in the MTX and TCZ arm, DAS 28CRP promptly improved with a between group statistically significant difference observed at month 3 and 6. At week 24, respectively 76.5% (13/17), 75% (12/16) of patients in the TCZ group achieved DAS28CRP remission (<2.6) and SDAI remission (<3.3) vs 41.7% (5/12), 50% (6/12) in the MTX group. Interestingly, a SJC of 0 was achieved at 6, 9 and 12 month in a significantly greater proportion of patients in the TCZ group (88%) compared to the MTX group (36%) (p<0.012). According to the new ACR/EULAR Boolean definition, remission was achieved in **31.3% (5/16) of TCZ patients and 0% (0/13) of MTX patients** (p<0.048). The proportion of patients achieving HAQ scores within the norm (£0.5) was not significantly greater in the TCZ group (70.5% [12/17]) than in the MTX group (33.3% [4/12]). For the submaximal CRE test, 13 patients were excluded from the analysis because they were unable to perform the 3rd stage. The work capacity during the active treatment was not statistically improved at 6 months (W65%/kg: 1.86 +/−0.85 vs 1.57 +/−0.60 watts/kg for the MTX group and 1.55 +/−0.60 vs 1.57 +/− 0.49 for the TCZ group). Serious AEs were reported by only one patient in the TCZ group who developed an episode of diverticulitis at 24 weeks.

Conclusion: These results demonstrate that remission is a realistic therapeutic goal when TCZ monotherapy is administered early in the RA disease process. In this population of naive DMARDs ERA patients, TCZ was superior to MTX alone in producing prolonged clinical remission. We failed to demonstrate that early RA patients intensively treated with TCZ or MTX could restore their CRE despite a large clinical response.

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Changes in the Levels of Anti-Cyclic Citrullinated Protein Antibody and Immunoglobulins in Rheumatoid Arthritis Patients After Administration of Tocilizumab. Masao Sato, Masao Takemura, Ryuki Shinohe, Tsuneo Watanabe and Katsuji Shimizu. Gifu University, Gifu, Japan

Background/Purpose: The recently established scoring system of American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) early arthritis diagnosis criteria have assigned scores of 0, 1, and 2, respectively, for negative, positive (low titer), and positive (high titer) results of anti-cyclic citrullinated protein (anti-CCP) antibody tests. Thus, high anti-CCP antibody titer is unfavorable in the pathological condition of rheumatoid arthritis (RA). We investigated the changes of anti-CCP antibody and immunoglobulin titers after treatment using tocilizumab (TCZ), which is the biological product of an interleukin (IL)-6 inhibitor agent.

Methods: Subjects were 40 RA patients (6 men, 34 women). The patient backgrounds were as follows: age, 25–76 years; mean age, 58.1 ± 11.8 years; mean disease duration, 8.8 ± 8.4 years (range, 1–45 years). TCZ 8 mg/kg was intravenously administered every 4 weeks and was continued for 52 weeks. Evaluations were performed at 3 time points: at the start of the treatment, after 12 weeks, and after 52 weeks. The methods of evaluations were as follows: after calculation of the patient's disease activity score (DAS28), quantitative determination of serum C-reactive protein (CRP) and immunoglobulin levels was performed by TIA. Anti-CCP antibody was measured using CL-JACK with a designated reagent and an anti-CCP test kit. IL-6 was evaluated using CLEIA. In addition, lymphocyte phenotypes were analyzed for CD3/CD19, CD4/CD25, and CD8/CD11 levels with the corresponding antibodies by using a flow cytometer.

Results: Of the 40 RA patients, 34 patients showed effective improvement in the DAS28; further, although effective, 6 patients showed insufficient DAS28. All CRP values of effective cases after the 12-week evaluation were less than the cut-off value (0.02 μg/ml). Comparison of the immunoglobulin levels at the start of the treatment and after 52 weeks of treatment were respectively as follows: IgG, 1550.1 ± 518.9 mg/ml and 1162.2 ± 431.9 mg/ml, p < 0.0006; IgA, 287.9 ± 112.2 mg/ml and 234.7 ± 89.9 mg/ml, p < 0.002; IgM, 119.9 ± 68.0 mg/ml and 111.9 ± 59.1 mg/ml, not significant (NS). A significant decrease was observed in IgG and IgA levels. No changes were observed in the CD3 (68.2 ± 11.7% and 65.2 ± 11.2%; NS), CD19 (12.5 ± 8.1 and 14.3 ± 8.7%; NS), and number of lymphocytes. The results at the beginning and after 52 weeks of treatment for anti-CCP antibody were 207.0 ± 281.2 U/ml and 253.6 ± 336.4 U/ml (NS) and IL-6, 22.7 ± 35.6 pg/ml and 31.8 ± 40.1 pg/ml (NS). No statistically significant differences were observed.

Conclusion: It can be confirmed from our study results that administration of TCZ decreases immunoglobulin levels in all patients. This result is understood clearly by blocking the differentiation-inducing effect from B-cell lymphocytes to plasma cells, which originally is an action of IL-6. Despite the

possibility that a decrease in the levels of anti-CCP antibodies can be misinterpreted, no such observations were noted. A suppressive action on B-cell differentiation is assumed because of the changes in lymphocytes (CD19+) in the patient blood samples. However, TCZ is considered to have no suppressive action on anti-CCP antibody production at the local inflammation sites in RA patients.

Disclosure: M. Sato, None; M. Takemura, None; R. Shinohe, None; T. Watanabe, None; K. Shimizu, None.

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Sarilumab, a Subcutaneously-Administered, Fully-Human Monoclonal Antibody Inhibitor of the IL-6 Receptor: Pharmacokinetic Profile and Its Relationship to Changes in Pharmacodynamic Markers in Patients with Rheumatoid Arthritis. Pavel Belomestnov[1], Jennifer Hamilton[1], A. Thomas DiCioccio[1], Martine Jasson[2] and Allen R. Radin[3]. [1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Sanofi, Paris, France, [3]Regeneron Pharmaceuticals Inc, Tarrytown, NY

Background/Purpose: Sarilumab, a fully human monoclonal antibody targeting interleukin-6 receptor alpha (IL-6Rα), is being evaluated for the treatment of rheumatoid arthritis (RA) based on the role of IL-6 in RA pathogenesis. This study aims to characterize the pharmacokinetic (PK) profile of single subcutaneous (SC) doses of sarilumab, and determine its relationship to markers of pharmacodynamic (PD) effects in patients (pts) with RA.

Methods: In this phase 1 parallel group study, pts with active RA (N=32) on background methotrexate (MTX) received a single SC dose of 50, 100, or 200 mg sarilumab or placebo (PBO). Blood samples were drawn at baseline and post-treatment days 1, 4, 8, 12, 15, 22, 29, 36, and 43. The serum obtained was analyzed for concentrations of functional sarilumab, defined as antibody with 0 or 1 of the 2 binding sites occupied by soluble IL-6Rα, using a validated enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic parameters were determined using non-compartmental methods. The PD markers IL-6, high sensitivity C-reactive protein (hsCRP), and serum amyloid A (SAA) were assessed in parallel. Safety and tolerability were evaluated based on incidence of adverse events (AEs) and clinical/laboratory assessments.

Results: All pts were white and female; age ranged from 45.5–55.4 years and RA duration from 7.9–10.3 years. PK is characterized as non-linear with target-mediated elimination. An initial absorption phase, followed by a saturating beta phase and a terminal target-mediated elimination phase were observed. Patients in the higher dose groups had higher concentrations of functional sarilumab, and these concentrations were detectable for a longer period (Table). A greater than dose-proportional increase in the area under the concentration-time profile (AUC) and maximum serum concentration (C_{max}) was observed. The beta phase was well defined in the 200 mg dose group. While no meaningful changes over time were observed in hsCRP, SAA, or IL-6 with PBO, changes in the sarilumab groups reflected both the dose and PK profile. Reductions in hsCRP and SAA and increases in IL-6 were greater and of longer duration at higher doses, and were statistically significant compared to placebo. The largest % changes were seen in the 200 mg group: hsCRP −91.7%, SAA −92.5%, and IL-6 +647%. The most commonly reported treatment-related AEs in the combined sarilumab groups were neutropenia, increased alanine aminotransferase, and increased aspartate aminotransferase, which were transient and not associated with clinical sequelae. One pt receiving sarilumab 50 mg had a serious AE of RA flare requiring hospitalization.

Pharmacokinetic variable	Sarilumab 50 mg SC + MTX (n = 8)	Sarilumab 100 mg SC + MTX (n = 8)	Sarilumab 200 mg SC + MTX (n = 8)
C_{max}, mg/L	0.52 ± 0.26 (144)	3.96 ± 0.96 (68.2)	12.9 ± 1.7 (37.5)
C_{max}/Dose, 1/L	0.010 ± 0.005 (144)	0.040 ± 0.010 (68.2)	0.064 ± 0.009 (37.5)
t_{max}, days	2.56 ± 0.37 (24.7)[a]	3.77 ± 0.47 (35.4)	3.67 ± 0.49 (37.8)
C_{last}, mg/L	1.38 ± 0.23 (29.4)[a]	1.83 ± 0.55 (85.0)	2.55 ± 1.21 (134)
t_{last}, days	2.56 ± 0.37 (24.7)[a]	6.53 ± 0.53 (23.0)	15.9 ± 3.83 (68.1)
AUC_{all}, day · mg/L	1.79 ± 0.92 (145)	21.2 ± 5.43 (72.5)	102 ± 20.1 (55.6)
AUC_{all}/Dose, day/L	0.036 ± 0.018 (145)	0.21 ± 0.05 (72.5)	0.51 ± 0.10 (55.6)

Mean ± standard error (coefficient of variation %)

C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; C_{last}, concentration at time of last positive evaluation; t_{last}, time of last positive drug evaluation; AUC_{all}, area under the curve from time zero to the last concentration
[a]Five patients who had concentrations < lower limit of quantitation were excluded from this analysis.

Conclusion: Sarilumab has a nonlinear PK profile with parallel linear and target-mediated elimination. PD effects were dose-dependent, consistent with the PK profile, and showed substantial reductions in acute phase reactants relative to placebo.

Disclosure: P. Belomestnov, Regeneron, 1, Regeneron, 3; J. Hamilton, Regeneron, 1, Regeneron, 3; A. T. DiCioccio, Regeneron, 1, Regeneron, 3; M. Jasson, Sanofi-Aventis Pharmaceutical, 1, Sanofi-Aventis Pharmaceutical, 3; A. R. Radin, Regeneron, 1, Regeneron, 3.

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Anti-Tumor Necrosis Factor Therapy Reduces Serum Levels of Chemerin in Rheumatoid Arthritis: A New Mechanism by which Anti-Tumor Necrosis Factor Might Reduce Inflammation. M.M. Herenius[1], A.S.F. Oliveira[1], C.A. Wijbrandts[1], D. Gerlag[1], Paul P. Tak[2] and Maria C. Lebre[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center, University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: Chemerin is a specific chemoattractant for macrophages and dendritic cells (DC). In addition, it can rapidly stimulate macrophage adhesion to extracellular matrix proteins and adhesion molecules and is able to activate fibroblast-like synoviocytes (FLS), suggesting a role in the pathogenesis of rheumatoid arthritis (RA). Chemerin is also an adipocytokine that has been related to the inflammatory state of endothelial cells and as such could be involved in the changes in endothelial cells in RA and perhaps increased cardiovascular morbidity. We investigated whether anti-TNF treatment affects chimeric levels.

Methods: 49 patients with active RA (disease activity score evaluated in 28 joints (DAS28)) ≥3.2) were started on adalimumab therapy. Blood was drawn from patients while fasting at baseline and 16 weeks after treatment. Chemerin serum levels were measured by ELISA and related to disease activity, mediators of inflammation and known risk factors for cardiovascular disease

Results: Adalimumab therapy significantly reduced chemerin serum levels, which was correlated with the reduction in DAS28 ($r=0.37$, $p=0.009$), ESR ($r=0.55$ $p<0.001$), CRP ($r=0.40$, $p=0.005$). In addition, the decrease in chemerin serum levels after anti-TNF treatment was associated with the decrease in serum levels of IL-6 ($r=0.39$, $p=0.033$) and macrophage migration inhibitory factor (MIF) ($r=0.31$, $p=0.049$). Baseline chemerin serum levels were not related to traditional risk factors for atherosclerosis, except perhaps for smoking ($p=0.07$).

Conclusion: The present study suggests that anti-TNF therapy may exert its beneficial effects on synovial inflammation and cardiovascular morbidity in part via an effect on chemerin levels.

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A Pilot Study Investigating the Tolerability and Pharmacodynamic Effect of Single Intravenous/Subcutaneous Doses of Olokizumab, an Anti-Interleukin-6 Monoclonal Antibody, in Patients with Rheumatoid Arthritis. Roy Fleischmann[1], Alan J. Kivitz[2], Frank Wagner[3], Jeffrey A. Feinstein[4], Uwe Fuhr[5], Jürgen Rech[6], Jagdev Sidhu[7], Philip L. Hill[8], Ruth Oliver[8] and Kosmas Kretsos[9]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Charité Research Org GmbH, Berlin, Germany, [4]San Antonio, TX, [5]Hospital of the University of Cologne (AöR), Köln, Germany, [6]University of Erlangen-Nuremberg, Erlangen, Germany, [7]CSL Limited, Parkville, Australia, [8]UCB Celltech, Slough, United Kingdom, [9]UCB, Slough, United Kingdom

Background/Purpose: Olokizumab is a novel IL-6 inhibitor that selectively blocks the final assembly of the IL-6 signaling complex (gp80+gp130+IL-6). We report the safety, PK, and PD results from a pilot single-dose study in patients with rheumatoid arthritis (RA).

Methods: This was a randomized, double-blind, placebo-controlled study of RA patients who: were diagnosed by the 1987 ACR criteria; had >6 months' disease duration; were treated with methotrexate 5–25 mg/week for at least 3 months prior to screening; had an elevated baseline high-sensitivity C-reactive protein (CRP; median 3.37, range 0.6–27.2 mg/L) with a reasonable spread that allowed robust characterization of the PD effect. At baseline, the mean DAS28 (CRP) was 3.07 (olokizumab) and 2.87 (placebo). Patients were randomized (3:1) to a single dose of olokizumab, either iv (0.1 or 1.0 mg/kg) or sc (1.0 or 3.0 mg/kg), or placebo. Primary objectives of the study

included evaluating the PK/PD relationship between olokizumab and CRP, and the safety and tolerability of olokizumab over 12 weeks post dose.

Results: Of 40 randomized patients, 38 completed the 12-week follow-up. Dose-dependent and sustained suppression of plasma CRP followed all doses of olokizumab until the end of the study (except for the 0.1 mg/kg iv group). IL-6 levels were markedly reduced after olokizumab exposure, remaining suppressed for the duration of the study. Commonly reported AEs in olokizumab recipients included headache, infection, decreased white blood cells (WBC), and abnormal liver function tests (LFT), with no dose relationship to severity, grade, or frequency of reported events. Laboratory abnormalities included: reductions in WBC and elevated LFT, cholesterol, and triglycerides. Two serious AEs were reported: 1 for placebo (grade 2 Bowen's disease) and 1 for olokizumab 1.0 mg/kg sc (worsening of RA). Two patients withdrew: 1 placebo (worsening of RA) and 1 olokizumab 1.0 mg/kg sc (protocol deviation). Dose-related reductions in complement C3 and C4 were seen. The terminal elimination $t_{1/2}$ of olokizumab in plasma was consistent regardless of route of administration or dose, with an overall median of 31 days. For the 1.0 and 3.0 mg/kg sc dose groups, the mean C_{max} was 6.29 and 19.1 μg/mL, achieved within a median t_{max} of 13 and 7 days, respectively. Bioavailability determined from PK/PD modeling, pooling data from the first-in-human study[1] and this study, was 76%. Non-compartmental analysis, based solely on data from this study, yielded a bioavailability of 66%.
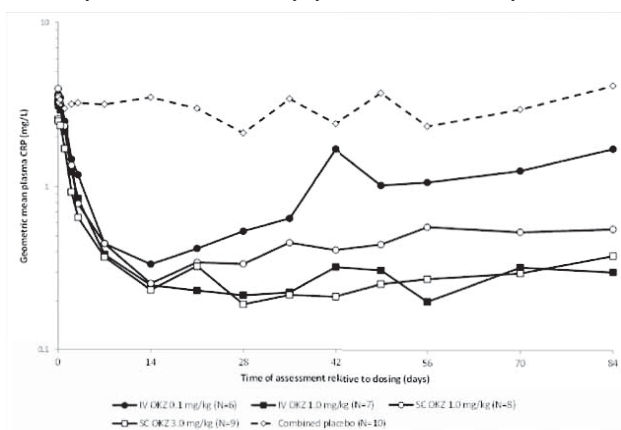
Conclusion: In RA patients, single doses of $\leq$3mg/kg sc olokizumab demonstrated prolonged suppression of CRP, a marker of inflammation, although CRP in the 0.1 mg/kg iv group showed some recovery after 28 days; all doses were well tolerated. These results provided the rationale for a further study to investigate the clinical efficacy of olokizumab in RA.

Reference:
1. *Ann Rheum Dis* 2011;70(Suppl3):471

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Effects of Subcutaneous Abatacept or Adalimumab On Remission and Associated Changes in Physical Function and Radiographic Outcomes: One Year Results From the Ample (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) Trial. Roy Fleischmann[1], Michael H. Schiff[2], Michael E. Weinblatt[3], Michael A. Maldonado[4], Elena M. Massarotti[5] and Yusuf Yazici[6]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]University of Colorado, Denver, CO, [3]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [4]Bristol-Myers Squibb, Princeton, NJ, [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [6]New York University, New York, NY

Background/Purpose: Advancements in the understanding of Rheumatoid Arthritis (RA) have led to the development of novel therapeutics and treatment guidelines that target remission as an achievable goal in RA.

Further, this has created a debate on the definition and dimensions of remission in RA. We report here, the impact of treatment with subcutaneous abatacept (ABA) or adalimumab (ADA) on remission in the AMPLE (**A**batacept Versus Adali**m**umab Com**p**arison in Bio**l**ogic Naiv**e** RA Subjects with Background Methotrexate) study, the first head-to-head trial in RA patients with inadequate response to methotrexate (MTX). AMPLE provides a novel opportunity to compare biologic agents with different mechanisms of action and their ability to achieve remission defined by multiple criteria.

Methods: AMPLE is an ongoing, phase IIIb, randomized, investigator-blinded study of 24 months duration with a 12 month primary efficacy endpoint. Biologic-naïve RA patients with an inadequate response to MTX were randomized to 125 mg ABA weekly or 40 mg ADA bi-weekly, in combination with a stable dose of MTX. The proportions of patients achieving remission defined as DAS28-CRP <2.6, SDAI ≤3.3, CDAI ≤2.8, RAPID3 <1, and Boolean score ≤1 were assessed. Patient function (assessed with the health assessment questionnaire disability index [HAQ-DI - responders defined as reduction ≥ 0.3]) and radiographic non-progression (defined as change in modified total Sharp score of ≤ 0.5 or ≤ 2.8, change in erosion or joint space narrowing score of ≤ 0.5) were then analyzed in patients achieving remission at 1 year.

Results: The baseline clinical characteristics of ABA (n = 318) and ADA (n = 328) treatment groups were balanced, as was clinical, functional and radiographic efficacy and safety at 1 year with minor differences. The proportions of patients meeting each of the remission criteria at 1 year were generally equal for both groups, but significantly more patients achieved DAS28-CRP remission compared to CDAI, SDAI or RAPID3 remission, and the smallest proportion achieved Boolean remission (Table). Across all assessed remission criteria, 76–85% of patients in both treatment arms were HAQ responders at year 1. Furthermore, 63–100% of patients were radiographic non-progressors depending on the remission criteria employed; however, similar radiographic outcomes were seen in both treatment arms.

Remission Criteria	SC Abatacept	Adalimumab
DAS28-CRP ≤ 2.6, n/m (%)	119/275 (43.3%)	112/267 (41.9%)
RAPID3 = 0–1.0	74/272 (27.2%)	66/263 (25.1%)
CDAI ≤ 2.8	65/277 (23.5%)	64/267 (24.0%)
SDAI ≤ 3.3	64/275 (23.3%)	66/266 (24.8%)
Boolean	6/275 (2.2%)	15/267 (5.6%)

Conclusion: Patients treated with SC abatacept or adalimumab in the AMPLE trial achieved comparable rates of remission as assessed across multiple criteria. Similar improvements in physical function and radiographic outcomes were observed in patients that achieved remission. Data reported here further highlight the difference in remission rates depending on the measure used and help illustrate the relationship between remission and functional and radiographic outcomes independent of choice of effective treatment in RA.

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Beneficial Effect of Anti-TNF Therapy in the Lipoprotein Atherogenic Risk Profile in Comparison with DMARD Standard Therapy in RA Patients. Jaime Calvo-Alen[1], Ignacio Villa[2], Victor M. Martinez-Taboada[3], Jose Luis Peña-Sagredo[4], Mario Agudo[4], Ana Carmen García[5] and Juan Gomez-Gerique[6]. [1]Hospital Universitario Sierrallana, Torrelavega, Spain, [2]Hospital Sierrallana, Torrelavega, Spain, [3]Hospital Universitario Marques de Valdecilla. IFIMAV, Santander, Spain, [4]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [5]Fundación 12 de Octubre, Madrid, Spain, [6]Hospital Universitario Marqués de Valdecilla, Santander, Spain

Background/Purpose: RA patients portend a greater risk of cardiovascular complications than general population. Although most probably diverse mechanisms are implicated, quantity and quality changes in the lipoproteins appear to have an important role.

Methods: RA patients in stable treatment with anti-TNF therapy at least during the last six months and a matched (by age, gender and rheumatoid factor status) with stable doses of standard DMARDs (most of them using methotrexate) were clinically evaluated using DAS28, as activity marker and MHAQ to assess disability. In addition, a complete standard lipid profile, a comprehensive lipoprotein assessment was carried out including: Lipoprotein, and apolipoprotein A1 (ApoA1) and B (ApoB) levels (total and lipoprotein specific), levels of paroxonase 1 (PON1), HDL, LDL, VLDL and total cholesterol, triglycerides and phospholipids levels as well as number of molecules of these lipids (mc, mt and mf respectively) in each lipoprotein, total mass (M) and number of particles (np) of the before mentioned lipoproteins, levels of PCSK9 receptor. Results of both subsets of patients were performed with standard statistical tests.

Results: Sixty-seven RA patients on anti-TNF and 63 matched RA patients on DMARD, mean age (58.7 ± 12.3 and 61 ± 12.1 years), gender distribution (81% females in both cases), disease duration (140 ± 165 and 143 ± 276 months) and RF status (64% in both cases) were comparable. Patients on DMARD were more active (DAS28 4.42 ± 1.35 vs 3.57 ± 1.27 and hsCRP 9.4 ± 15.2 vs 3.8 ± 5.8 mg/l respectively. Main findings in the lipoprotein analysis are shown in table 1.

	Apo-A (mg/dl)	MVLDL (mg/dl)	np VLDL
Anti-TNF	169.7	913.5	89513.1
DMARD	156.2	1360.8	112898.3
p value	.008	.001	.017

Multivariate analysis were performed with the three variables entering DAS28 as covariate and in all cases anti-TNF therapy remained as unique explicative variable.

Conclusion: RA patients treated with anti-TNF, regardless that they show lower levels of clinical activity, they have an improvement in their atherogenic risk profile showing higher levels of ApoA1 and therefore greater antioxidant capacity as well as lower levels of total mass and number of particles of VLDL which are atherogenic risk factors.

Disclosure: J. Calvo-Alen, None; **I. Villa**, None; **V. M. Martinez-Taboada**, None; **J. L. Peña-Sagredo**, None; **M. Agudo**, None; **A. C. García**, None; **J. Gomez-Gerique**, None.

1342

Changes in Patient Reported Outcomes in Response to Subcutaneous Abatacept or Adalimumab in Rheumatoid Arthritis: Results From the Ample (Abatacept Versus Adalimumab Comparison in Biologic Naive RA Subjects with Background Methotrexate) Trial. Roy Fleischmann[1], Michael E. Weinblatt[2], Michael H. Schiff[3], Dinesh Khanna[4], Daniel Furst[5] and Michael A. Maldonado[6]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [3]University of Colorado, Denver, CO, [4]University of Michigan, Ann Arbor, MI, [5]University of California at Los Angeles, Los Angeles, CA, [6]Bristol-Myers Squibb, Princeton, NJ

Background/Purpose: Rheumatoid arthritis (RA) is associated with pain, fatigue, disability and functional loss, which can significantly impact a patient's health-related quality of life (HRQoL). Patient-Reported Outcomes (PROs) are critical since patients and caregivers do not always perceive treatment effects equally. To highlight the patient's perspective, we report multiple PROs from the first head-to-head study, AMPLE (**A**batacept Versus Adali**m**umab Com**p**arison in Bio**l**ogic Naiv**e** RA Subjects with Background Methotrexate) comparing subcutaneous abatacept (ABA) and adalimumab (ADA) on background methotrexate (MTX).

Methods: AMPLE is an ongoing, phase IIIb, randomized, investigator-blinded study of 24 months duration with a 12 month efficacy primary endpoint. Biologic-naïve patients with active RA and inadequate response to MTX were randomized to either 125 mg ABA weekly or 40 mg ADA bi-weekly in combination with MTX. PROs assessed were patient pain, patient global assessment (PtGA), and fatigue, all assessed by 100mm visual analog scale (VAS), with a higher score indicating worse outcome (Minimal Clinically Important Difference [MCID]: reduction $\geq$10mm). Physical function was evaluated with the health assessment questionnaire disability index (HAQ-DI; MCID reduction $\geq$0.3). HRQoL was assessed using the SF-36 (including Physical and Mental Component Summary subscores [PCS and MCS]; MCID: improvement $\geq$5). The Routine Assessment of Patient Index Data (RAPID3), an index of 3 patient-reported core dataset measures (physical function, pain, and patient global estimate of status), was also assessed (MCID: reduction $\geq$2.0).

Results: A total of 646 patients were randomized and treated with ABA (n=318) or ADA (n=328) on background MTX. Patient characteristics were balanced. A similar proportion of patients achieved a HAQ-DI response from baseline to year 1 (60.4% patients in the ABA arm vs. 57.0% patients in the ADA arm). Improvements in patient pain (mean% $\pm$ SE) were 46.5 ± 4.2% vs. 35.6 ± 4.1% at 6 months, and 53 ± 6.1% vs. 39.2 ± 6.0% at 1 year for ABA and ADA, respectively. Improvements in PtGA were 40.2 ± 7.3% vs. 27.6 ± 7.2% and 46.1 ± 3.5% vs. 41.2 ± 3.4% for ABA and ADA at 6 months and 1 year. Fatigue decreased from baseline by -22.4 ± 1.5% vs. -19.9 ± 1.5% at 6 months, and -23.2 ± 1.5% vs. -21.4 ± 1.5% at 1 year for ABA and ADA respectively. Improvements in all domains of the SF-36 including PCS and MCS observed at 6 months were maintained at 1 year (Figure). For RAPID3, the ABA and ADA-treated groups demonstrated improvements (mean $\pm$ SE) of -2.7 ± 0.1 vs. -2.5 ± 0.1 at 6 months and -2.9 ± 0.1 vs. -2.7 ± 0.1 at 1 year.
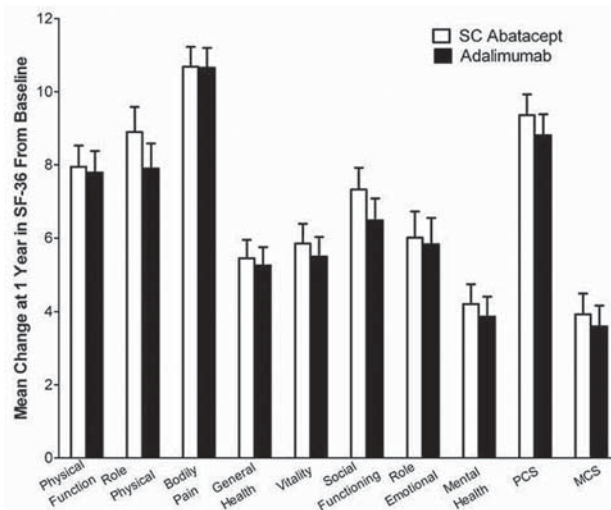
Figure 1. Mean Change from Baseline to Year 1 in Short From-36 Scores

Conclusion: In this first head-to-head comparison, subcutaneous abatacept demonstrated significant improvements with similar kinetics of response in patient-reported outcomes and HRQoL measures over 1 year which were comparable to adalimumab.

Disclosure: R. Fleischmann, Genentech Inc, Roche, Abbott, Amgen, UCB, Pfizer, BMS, Lilly, Sanofi Aventis, Lexicon, MSD, Novartis, BiogenIdec, Astellas, Astra-Zeneca, Jansen, 2, Roche, Abbott, Amgen, UCB, Pfizer, BMS, Lilly, Sanofi Aventis, Lexicon, Novartis, Astellas, Astra-Zeneca, Jansen, HGS, 5; **M. E. Weinblatt**, Bristol-Myers Squibb, Abbott, 2, Bristol-Myers Squibb, Abbott, 5; **M. H. Schiff**, Bristol-Myers Squibb, 5, Abbott Laboratories, 8; **D. Khanna**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5; **D. Furst**, Abbott, Actelion, Amgen, BMS, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 2, Abbott, Actelion, Amgen, BMS, BiogenIdec, Centocor, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5, Abbott, Actelion, UCB (CME ONLY), 8; **M. A. Maldonado**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1.

ACR/ARHP Poster Session B
Spondylarthropathies and Psoriatic Arthritis:
Clinical Aspects and Treatment
Monday, November 12, 2012, 9:00 AM–6:00 PM

1343

EARLY Improvements in the Lower Limbs Enthesis by Ultrasound Predicting Later Favorable Responses in TNF Inhibotors-Treated Patients with Spondyloarthritis. Kensuke Kume[1], Kanzo Amano[1], Kuniki Amano[2], Hiroyuki Ohta[3] and Noriko Kuwaba[4]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Sky Clinic, Hiroshima, Japan, [3]Hiroshima, Japan, [4]Sanki Clinical Link, Hiroshima, Japan

Background/Purpose: Lower limbs enthesis by ultrasound (US) detects inflammatory activity in patients with spondyloarthritis(SpA) and is a diagnostic tool of early SpA. The present objective was to follow SpA patients starting anti-TNF inhibitors with US and clinical assessments to

explore whether any variable in baseline or early stage could predict later favorable responses.

Methods: This study is prospective and US reader and clinical physician blinded study. Patients with SpA starting anti-TNF inhibitors were consecutively included and examined at baseline and, after 1 and 12 weeks with standardized bilateral ultrasound of six enthesis (Madrid sonography enthesitis index (MASEI)). In addition, the patients were assessed clinically with ASDAS, assessor global VAS (study nurse), ESR and CRP. Patients with ASDAS clinical important improvement at the 12 weeks examination was defined as responders. The results of US score (MASEI), clinical and laboratory assessments at baseline and after 1 week were explored by Mann-Whitney tests to examine for associations with the responders.

Results: A total of 45 patients were included (mean (SD) age 60.3 (25.2) years, disease duration 14.2 (6) years, and 35% women, with 73% using infliximab and 27% adalimumab). A total of 69 % of the patients were defined as ASDAS responders, and they had significantly lower US score (MASEI) (p=0.03), assessor global VAS (study nurse) (p=0.02), and CRP (p=0.02) at the 12 weeks examination. Baseline US score (MASEI), ASDAS, assessor global VAS, ESR or CRP did not separate between responders and non-responders. At 1 week examination the only variable differing between responders and non-responders was the US score (MASEI), with a significant reduction in US score (MASEI) in the responders versus non-responders 12.6 (5.4) versus 2.3(3.3) (p=0.03).

Conclusion: US enthesis images at 1 week after TNF inhibitors in patients with SpA are useful to identify later good responders.

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1344

Diagnostic Value of High Sensitivity C Reactive Protein for Early Axial Spondyloarthritis: Results From the Devenir Des Spondylarthopathies Indifferenciees Recentes Cohort. Victoria Navarro-Compán[1], Désirée van der Heijde[1], Bernard Combe[2], Claudine Cosson[3] and Floris van Gaalen[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Hopital Lapeyronie, Montpellier, France, [3]Hôpital Bicêtre, Assistance Publique Hôpitaux de Paris, Paris, France

Background/Purpose: The average delay in spondyloarthritis (SpA) diagnosis after symptom onset is one of the longest among the inflammatory rheumatic diseases. Elevated C-reactive protein (CRP) has been incorporated as one of the features for ASAS axial SpA criteria and in the Berlin diagnostic algorithm. However, CRP levels are elevated in only a minority of early SpA patients which limits its potential diagnostic value. More sensitive tests called high-sensitivity CRP (hsCRP) have been developed and can detect lower concentrations of CRP compared with traditional methods. Therefore, hsCRP could be more sensitive than traditional CRP for diagnosis in axial SpA. The aim of this study was to assess if hsCRP measurement contributes to early axial SpA diagnosis compared with traditional CRP measurement.

Methods: Baseline data from 648 patients with inflammatory back pain (IBP) duration >3 months but <3 years from DESIR cohort was used. Design and inclusion criteria have previously been reported (1). Levels of CRP and hsCRP were measured in serum at baseline. The cut-off values selected to define positive hsCRP and CRP were ≥ 2 mg/l and ≥ 5 mg/l, respectively.

Results: Based on the ASAS axial SpA criteria, 444 (69%) patients were classified as SpA and 203 (31%) patients as no SpA. Patients' characteristics and lab results are shown in table 1. Serum levels of CRP and hsCRP were higher in SpA versus no SpA. In the subgroup of patients with a negative CRP, mean serum levels of hsCRP were also higher in SpA patients compared with no SpA patients (1.7 mg/L vs 1.5 mg/L, p 0.03). Moreover, after dichotomizing hsCRP, more patients within the SpA group had a positive hsCRP versus the no SpA group, although this difference was not statistically significant (p=0.06) (table 2).

Table 1. Characteristics of patients

	SpA n=444 (69%)	No SpA n=203 (31%)	P value
Age (years)	32.4 ± 8.6	34.8 ± 8.3	0.001
Male	223 (50%)	76 (37%)	0.01
Caucasoid	400 (90%)	159 (88%)	0.5
Back pain duration	1.0 ± 0.9	0.9 ± 8.4	0.03
HLA-B27 positive	368 (83%)	8 (4%)	<0.0001
Sacroiliitis on MRI	106 (52%)	0 (0%)	<0.0001
Sacroiliitis on X-Ray	107 (24%)	0 (0%)	<0.0001
CRP (mg/L)	3.9 (1–8.6)	2.6 (1–5)	<0.0001
hsCRP (mg/L)	2.8 (1.1–8.1)	1.6 (0.3–3.6)	<0.0001

Table 2. Serum levels of hs-CRP in patients with normal CRP values (<5 mg/L)

hsCRP	SpA (n=260)	No SpA (n=152)
<2	174 (66.9%)	110 (72.4%)
≥2–<3	41 (15.8%)	30 (19.7%)
≥3–<4	34 (13.1%)	11 (7.2%)
≥4–<5	7 (2.7%)	0
≥ 5	4 (1.5%)	1 (0.7%)

Finally, we investigated how many extra patients from the no SpA group (n=203) would be classified as SpA substituting the traditional CRP by hsCRP in the clinical arm (HLA-B27 arm) of the ASAS axial SpA criteria. Only 4 (2%) extra patients had 2 axial SpA features instead of only 1 feature (IBP) substituting hsCRP by CRP (195 vs 191 patients), but none of them was HLA-B27 positive. Consequently, none of the no SpA patients met ASAS criteria applying this modification.

Conclusion: In patients with a normal CRP, hsCRP is increased in axial SpA patients compared with patients without SpA. However, hsCRP measurement in patients with IBP may not add any extra value for early axial SpA diagnose compared with CRP measured by traditional method.

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1345

Validation of the Health Assessment Questionnaire for Spondyloarthritis in Patients with Non-Radiographic Axial Spondyloarthritis. Dennis Revicki[1], Wen-Hung Chen[1], Ying Jin[1], Sumati Rao[2], Philip Mease[3] and Mary Cifaldi[2]. [1]United Biosource Corporation, Bethesda, MD, [2]Abbott Laboratories, Abbott Park, IL, [3]Swedish Rheumatology Research Group, Seattle, WA

Background/Purpose: To evaluate the psychometric properties of the Health Assessment Questionnaire for Spondyloarthritis (HAQ-S) in patients with non-radiographic axial spondyloarthritis (nr-axSpA).

Methods: Data from 185 nr-axSpA patients receiving the human anti-TNF monoclonal antibody adalimumab (ABILITY-1-trial) were analyzed. Internal consistency and test–retest reliability were assessed using Cronbach's alpha and intraclass correlation coefficient (ICC), respectively. Convergent validity was assessed by correlating HAQ-S with Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), EQ-5D™, Patient and Clinical Global Assessment of Disease Activity Visual Analog Scales (PGA-VAS and CGA-VAS), and Patient's Global Assessment of Pain (PAIN-VAS). Known-groups validity and ability to detect changes were assessed based on Patient Acceptable Symptom State Questionnaire (PASS) and PGA-VAS using analysis of variance. PASS, PGA-VAS, and CGA-VAS were used as anchors to determine the minimally important difference (MID).

Results: The HAQ-S Global and Activity scores demonstrated internal consistency, with good Cronbach's alpha (0.95 and 0.78, respectively), but Cronbach's alpha was lower for Driving scores (0.63). The HAQ-S Global, Activity, Driving, and Stiffness scores all demonstrated test–retest reliability, with good ICCs (0.90, 0.82, 0.71, and 0.87, respectively). The HAQ-S Global, Activity, and Stiffness scores demonstrated good convergent validity, as indicated by the moderate to high correlations with BASFI, BASDAI, EQ-5D™, PGA-VAS, and PAIN-VAS at baseline (0.31–0.76) and week 12 (0.53–0.89). Correlations between the HAQ-S Driving score and the criterion measures were lower (0.24–0.46 at baseline; 0.41–0.63 at week 12). For known-groups validity, mean HAQ-S Global, Activity, Driving, and Stiffness

scores at week 12 were significantly different for patients with different PASS responses (P<0.001). The HAQ-S Global, Activity, and Stiffness scores were significantly different for patients with PGA-VAS scores below and above the sample median at baseline and at week 12 (P<0.001). The HAQ-S Global, Activity, Driving, and Stiffness scores demonstrated significantly larger changes for responders (PASS="Yes" at week 12) than for non-responders (PASS="No"), and for responders (PGA-VAS decreased ≥30% at week 12) than for non-responders (PGA-VAS decrease <30% or increased), indicating the ability to detect changes in clinical status. Using anchor-based methods (based on PASS, PGA-VAS, and CGA-VAS), MIDs ranged from −0.17 to −0.42 for HAQ-S Global score, −0.09 to −0.57 for HAQ-S Activity score, 0.10 to −0.29 for HAQ-S Driving score, and −8.8 to −32.7 for HAQ-S Stiffness score. The MID for the HAQ-S Global score should be 0.26 calculated as the average of the MIDs based on PGA-VAS and CGA-VAS anchors.

Conclusion: This study of the HAQ-S indicated that Global, Activity, and Stiffness scores were reliable and valid measures of functional ability in patients with nr-axSpA. The HAQ-S scores also demonstrated ability to detect change in clinical status.

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Comparison of Three Screening Tools in Psoriatic Arthritis: The Contest Study. Laura C. Coates[1], Tariq Aslam[1], A. D. Burden[2], Esther Burden-Teh[3], Anna R. Caperon[4], Rino Cerio[5], Chandra Chattopadhyay[6], Hector Chinoy[7], Mark J. D. Goodfield[8], Lesley Kay[9], Bruce W. Kirkham[10], Christopher R. Lovell[11], Helena Marzo-Ortega[12], Neil McHugh[13], Ruth Murphy[3], Costantino Pitzalis[14], NJ Reynolds[9], Catherine H. Smith[15], Elizabeth Stewart[6], Richard B. Warren[7], Hilary E. Wilson[16] and Philip S. Helliwell[17]. [1]Division of Rheumatology and Musculoskeletal Disease, LIMM, University of Leeds, Leeds, United Kingdom, [2]Western Infirmary, Dumbarton Road, United Kingdom, [3]Nottingham Independent Treatment Centre, Nottingham, United Kingdom, [4]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [5]Bart's and The London NHS Tust, United Kingdom, [6]Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, United Kingdom, [7]The University of Manchester, Manchester, United Kingdom, [8]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [9]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [10]4th Fl Thomas Guy House, London, United Kingdom, [11]Royal United Hospital, Bath, United Kingdom, [12]University of Leeds, Leeds, United Kingdom, [13]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [14]Barts and The London School of Medicine and Dentistry, London, United Kingdom, [15]London, [16]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom, [17]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Background/Purpose: The majority of patients with PsA have psoriasis prior to arthritis and there is evidence that a significant proportion of patients in dermatology clinics have undiagnosed PsA. Multiple screening questionnaires have been developed and tested for the early detection of PsA but there has been no direct comparison to identify which is the optimal screening questionnaire. The aim of this study was to compare three existing PsA screening questionnaires (PASE, PEST, TOPAS) in a head-to-head study in secondary care dermatology clinics using the CASPAR criteria as the gold standard.

Methods: This study recruited from 10 UK secondary care dermatology clinics. Patients with a diagnosis of psoriasis, not previously diagnosed as PsA, were given a pack containing study information, and all 3 questionnaires in a random order. The completed questionnaires were compiled and scored by a study co-ordinator and all patients who were positive on any of the questionnaires were invited for a rheumatological assessment where consent was obtained. This assessment included physical examination of joints, entheses, dactylitis, spine, skin and nails. Where available, rheumatoid factor positivity and radiographic reports were collected. Receiver operator characteristic (ROC) curves were used to compare the sensitivity, specificity and area under the curve (AUC) of the 3 questionnaires with their diagnosis according to CASPAR criteria.

Results: In total, 938 patients with psoriasis were invited to participate and given a screening pack. Of these, 657 (70%) patients returned the screening questionnaires. One or more questionnaires were positive in 314

patients (48%) and these were invited for rheumatological assessment. Of these positive patients, 119 (37%) declined to attend for examination, leaving 195 (63%) patients with positive questionnaires who were assessed. There were 47 patients diagnosed with PsA according to the CASPAR Criteria, equating to 24% of those with positive questionnaires who attended for examination. The proportion of patients found to have PsA increased with the number of positive questionnaires (1 questionnaire = 19.1%, 2 questionnaires = 34.0%, 3 questionnaires = 46.8%). Sensitivities and specificities for the three questionnaires are shown in the table below. A positive non-PsA diagnosis was made in 54 subjects: 40 of these had degenerative tendinopathy or osteoarthritis.

Questionnaire	Sensitivity	Specificity	AUC	P value
PASE	74.5	38.5	0.594	0.052
PEST	76.6	37.2	0.610	0.023
TOPAS	76.6	29.7	0.554	0.267

Conclusion: Both the PEST and TOPAS questionnaires performed slightly better than the PASE questionnaire at identifying PsA but discriminatory capacity overall was best for the PEST questionnaire. As patients scoring negative for the questionnaires were not examined these results are likely to overestimate the sensitivity and underestimate the specificity. Nevertheless, these screening tools do identify many cases of musculoskeletal disease other than PsA.

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Anti-TNFα Discontinuation in Psoriatic Arthritis: Is It Possible After Achieving Minimal Disease Activity? Amir Haddad, Arane Thavaneswaran, Vinod Chandran and Dafna D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Remission in Psoriatic Arthritis, defined as a period of at least 3 consecutive visits with no actively inflamed joints, occurs in about 17 percent of patients with PsA. Achieving a state of Minimal Disease Activity (MDA) can lead to reduction in joint damage progression. In clinical practice, we face a dilemma in terms of future management when a patient achieves MDA while being on anti-TNF therapy. The aim of this study was to identify and describe PsA patients who discontinued or reduced the dose of anti-TNF agent and continued to remain in a state of MDA.

Methods: Patients were identified from a large single centre psoriatic arthritis cohort. We included patients who achieved MDA (according to slightly modified criteria proposed by Coates et al) and discontinued their anti-TNF treatment or reduced the dose and continued to remain in MDA. No predetermined protocol was used for dose reduction and in most cases it was left to patient preference. MDA was defined when fulfilling at least 5 of the 7 following outcome measures: tender joint count ≤1; swollen joint count ≤1; psoriasis activity and severity index (PASI) ≤1 or body surface area ≤3; patient pain numerical rating scale (NRS) score of ≤ 2; patient global disease activity numerical rating scale (NRS) score of ≤2; Health Assessment Questionnaire (HAQ) score ≤0.5; and tender entheseal points ≤1. Baseline demographic and clinical characteristics at the first visit and before commencing anti-TNF therapy were collected including sex, age at diagnosis of psoriasis and PsA, disease manifestation (peripheral joint involvement, axial disease, the presence of enthesitis, dactylitis and tenosynovitis), previous disease-modifying anti-rheumatic drug use, the number of active and damaged joint counts, patient global assessment, C-reactive protein (CRP), ESR as well as the health assessment questionnaire (HAQ) and SF 36 PCS. Descriptive analyses were conducted.

Results: Of the 307 patients treated with anti-TNF agents in our cohort, 17 patients were identified who were able to reduce the dose of anti-TNF agents with a total of 22 observation periods and continued to be in MDA for a mean duration of 23.7 ± 18.6 months. 15 patients were on etanercept and 2 on adalimumab. Most patients were not treated concurrently with DMARDs at the time they reduced/stopped the dose of anti-TNF agent. 8 patients reduced their dose and did not flare for a mean duration of 38.7 ± 16.3

months, while 9 patients flared after a mean duration of 13.2 ± 11.2 months. Patients stopped the medications for the following reasons: 11 patients were in remission, 3 patients due to infection, 2 cases due to patient preference and one case due to non improvement in skin disease.

Conclusion: In this study, we identified a group of patients who have stopped or reduced the dose of anti-TNF medications after being in remission. Eight patients have reduced the dose with no evidence of disease exacerbation. The data support the need for randomized controlled trials to better define the duration of anti-TNF therapy in psoriatic arthritis.

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Diffuse Idiopathic Skeletal Hyperostosis (DISH) in Psoriatic Arthritis.
Amir Haddad[1], Arane Thavaneswaran[1], Sergio M.A. Toloza[2], Vinod Chandran[1] and Dafna D. Gladman[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Hospital San Juan Bautista, Catamarca, Argentina

Background/Purpose: Spondylitis in Psoriatic Arthritis (PsA) sometimes resembles DISH because of the presence of juxta-vertebral calcification that resemble syndesmophytes. Distinguishing spondylitis from DISH has therapeutic and prognostic implications. The purpose of this study was to determine the prevalence of DISH in PsA patients and to identify features associated with its occurrence.

Methods: PsA patients were recruited from a single centre prospective observational cohort initiated on 1978. All patients fulfilled the CASPAR criteria and were assessed every 6–12 months according to a standard protocol which included a detailed history, physical examination and laboratory evaluation. Radiographs of peripheral joints and spine were obtained every 2 years. DISH was defined as flowing bony bridges in at least 4 contiguous thoracic vertebrae irrespective of the presence of radiographic sacroiliitis on the last radiographic assessment. Each PsA patient with DISH was matched by sex to 3 PsA patients without DISH recruited to the clinic within a year. Demographics and disease characteristics were compared in both groups including age, disease duration, BMI, comorbidities (myocardial infarction, angina, diabetes, hypertension), uric acid levels, ESR and CRP. The radiographic features that were assessed included the presence of sacroiliitis, syndesmophytes at cervical, thoracic and lumbar spine, and calcaneal spurs. Descriptive analyses and comparisons were conducted using McNemar test, Fisher's exact test and Chi-squared test for categorical variables and paired t-test for continuous variables. Logistic regression analyses using univariate and multivariate models with stepwise regression were conducted.

Results: Of 938 PsA patients, DISH was observed in 78 patients with a prevalence of 8.3%. Patients with DISH were older (62.9 vs 49.3, P<0.0001), had a longer disease duration (15.1 vs 12.8 years, P<0.003), a higher BMI (32.9 vs 28.7, P<0.0001), had more diabetes (28% vs 9.8%, P<0.0001), hypertension (50% vs 24.9%, P<0.0001) and higher uric acid levels (16% vs 7%, P=0.02).The modified Steinbrocker score was also higher in patients with DISH (32.0 ± 39.8 vs. 19.5 ± 31.4, P=0.0001). The presence of inflammatory back pain, HLA-B*27 allele and sacroiliitis was similar in both groups. The difference in ESR and CRP was not clinically significant. However, patients with DISH had more syndesmophytes (38.5% vs 18.7%, P<0.0001) and calcaneal spurs (83.3% vs 60.9%, P<0.0001). Patients with DISH and syndesmophytes had more sacroiliitis (65% vs 38%, P=0.02) than patients with no syndesmophytes. Older age, higher BMI and the presence of radiographic damage to peripheral joints were associated with DISH in the multivariate analysis with an odds ratio of 1.13 95%CI(1.07–1.19), 1.19 95%CI(1.09–1.29) and 5.22 95%CI(1.35–20.13) respectively.

Conclusion: DISH was associated with known DISH related factors including older age and high BMI, as well as the presence of radiographic damage to peripheral joints. The diagnosis of DISH is possible in the presence of psoriatic spondylitis. The presence of sacroiliitis was similar but syndesmophytes were higher in patients with DISH.

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Trends in Incidence and Clinical Features of Ankylosing Spondylitis in Olmsted County (1980–2009): A Population Based Study.
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Background/Purpose: To determine trends in the incidence and clinical presentation of ankylosing spondylitis (AS) among residents of a geograph-ically defined area first diagnosed 1980–2009 and to describe survival among these patients.

Methods: A population-based inception cohort of patients with AS was assembled by screening all medical records of residents of a geographical area with any diagnosis consistent with AS. We identified residents aged 18 years or older first diagnosed between January 1, 1980 and December 31, 2009. Cases were included if they fulfilled the modified New York criteria for AS or the ASAS criteria for axial spondyloarthritis and the date at which the criteria was fulfilled was considered the date of diagnosis. Incidence rates were estimated and were age- and sex-adjusted to the 2000 US white population. All identified cases were followed until death, migration or December 31, 2011. Cases with psoriasis, inflammatory bowel disease (IBD) and reactive arthritis were identified. Survival was estimated using the Kaplan-Meier method and compared to expected survival for persons of the same age, sex and calendar year estimated using US population life tables.

Results: 95 patients were newly diagnosed with AS between 1980–2009 (25 women and 72 men) based on ASAS criteria for axial spondyloarthritis. 92 (97%) patients met modified New York criteria. The overall age and sex-adjusted incidence for AS was 3.9 per 100,000 population (95% CI 3.1, 4.6). The age- adjusted incidence in men was more than three times that of women: 6.0 (95% CI 4.6, 7.4) vs 1.8 (95% CI (1.0, 2.5) per 100,000 population. The mean age at diagnosis was 35 years (min: 18 max: 69). Patients diagnosed in the 1990s (mean 39 years) were older than those diagnosed in the 1980s (mean 32 years) or the 2000s (mean 34 years). The median interval between symptom onset and diagnosis was 4.0 years (min: 0, max: 36 years) with no significant difference over the study period (p = 0.539). The incidence of AS was highest in the 25–34 age group at 8.0 per 100,000. Of 75 patients tested for HLA-B27 antigen, 65 (87%) were positive. Inflammatory back pain was the most common presenting manifestation and was seen in 92% of patients. Twenty nine patients (32%) had peripheral arthritis at diagnosis which was more common in patients diagnosed in the 1990s (50%) compared to the 1980s (36%) or the 2000s (20%; p=0.034). Ten patients (11%) also had psoriasis and 10 (11%) had IBD. Uveitis was the most common extra-articular manifestation, seen in 31 patients (33%) with no significant change over the study period (p=0.22). Uveitis occurred more often in women (56% vs 25%; p=0.005). There were 3 deaths during a median follow up duration of 8.5 yrs. (total 998 person-years). This was consistent with the 4.4 expected deaths (standardized mortality ratio: 0.68; 95% CI 0.14, 2.00).

Conclusion: AS occurs in about 4 persons per 100,000 per year. Patients diagnosed in the 1990s had more peripheral arthritis and were slightly older at diagnosis than patients in any other decade. Clinical features, extra-articular manifestations and interval from symptom onset to diagnosis have remained constant in this population over the study period.

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Inflammatory Biomarkers in Psoriatic Arthritis.
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Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis that may progress rapidly and result in joint damage and disability. The aim of this study was to establish the frequency of raised inflammatory markers (ESR and CRP) in PsA and to investigate their association with disease activity and progression.

Methods: At the PsA Clinic patients are followed prospectively and are evaluated according to a standard protocol which includes a detailed clinical history, physical examination, laboratory and radiological assessments every 6–12 months.ESR levels are recorded as normal or raised (15 mm/hour for male patients, 20 mm/hour for female patients) as well as CRP as normal or raised (0–3). X-rays are done every two years. Patients followed between 2006 and 2011 were included.

ESR and CRP were measured at baseline in all patients included in this study, and correlated with other disease features at baseline. Pearson correlation coefficient was used for correlations between the continuous variables. We also constructed univariate and multivariate models based on information at baseline to detect the variables that associate with disease activity and severity. The covariates were age at onset of PsA, sex, duration of PsA, use of biologics, infection and BMI.

Results: A total of 253 patients with PsA (107 male and 146 female with mean duration of PsA 5.2±7.6 years) were included.ESR level ranged from 0 to 121 mm/hr at baseline. Mean ESR was 18.3±21.2 (median 11) and was

elevated in 28.1%. CRP level ranged from 3 to 132 mg/l. Mean CRP was 14.3±20.7 (median 5) mg/l and was elevated in 54.9%.

Correlation between ESR and CRP with the variables

	Active joint count		Damaged joint count		BASDAI		PASI	
	Correlation	P-value	Correlation	P-value	Correlation	P-value	Correlation	P-value
ESR	0.14	P=0.02	0.16	P=0.01	0.17	P=0.05	0.23	P=0.0004
CRP	0.07	P=0.26	0.03	P=0.63	0.23	P=0.008	0.31	P<0.0001

The association between ESR and CRP and different variables

	ESR		CRP	
variable	Univariate analysis p-value	Multivariate linear regression p-value	Univariate analysis p-value	Multivariate linear regression p-value
Active joints	0.02	0.006	0.26	0.67
Damage joints	0.01	0.07	0.63	0.32
PASI	0.0004	0.004	<0.0001	0.13
BASDI	0.05	0.28	0.008	0.30
Radiogical damage	0.12	0.68	0.04	0.16

Conclusion: Increased ESR was observed in 28.1% of PsA and was correlated with active and damaged joint count and PASI. Increased CRP was observed in 54.9% of PsA and was correlated with PASI. Inflammatory markers are associated with disease activity and progression.

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Ultrasonographic Entheseal Abnormalities Among Patients with Psoriatic Arthritis, Psoriasis Alone and Healthy Individuals and Their Correlation with Disease-Related Variables. Lihi Eder[1], Jai Jayakar[2], Arane Thavaneswaran[3], Amir Haddad[3], Daniel Pereira[3], Sutharshini Shanmugarajah[3], David Salonen[4], Cheryl Rosen[3], Vinod Chandran[3] and Dafna D. Gladman[3]. [1]Carmel Medical Center, Haifa, Israel, [2]University of Western Ontario, London, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON, [4]University Health Network, Toronto, ON

Background/Purpose: Enthesitis is an important manifestation of psoriatic arthritis (PsA). We aimed to compare the frequency of ultrasonographic (US) entheseal abnormalities between patients with PsA, psoriasis without arthritis (PsC) and healthy controls and to assess the correlation between disease-related variables and the extent of US enthesitis.

Methods: PsA and PsC patients who were part of two large prospective cohorts were recruited. PsC patients were assessed by a rheumatologist to exclude inflammatory arthritis. Healthy controls were recruited from hospital personnel. Ultrasound examinations were performed using a MyLab 70 XVG device equipped with 6–18 MHz linear transducer and Doppler frequency of 7.1–14.3 MHz. The following entheseal insertion sites were examined: patella (at insertions of the quadriceps and patellar tendons), tibial tuberosity, Achilles tendon and plantar fascia insertions to the calcaneous and triceps tendon insertion to the olecranon. Two scoring systems for US enthesitis (MAdrid Sonographic Enthesitis Index (MASEI) and Glasgow Enthesitis Scoring System (GUESS)) were used to generate scores that reflect the severity of entheseal abnormalities in each patient. Analysis of variance was used to compare GUESS and MASEI scores across the groups. Chi square test was used to compare the frequencies of entheseal abnormalities between the groups. The correlation between disease-related variables and enthesitis scores was assessed by Pearson correlation coefficients (r).

Results: A total of 59 PsA patients, 79 PsC patients and 60 healthy controls were assessed. The frequency of US entheseal abnormalities was high with 98.3% of PsA patients, 97.5% of PsC patients and 86.7% of healthy controls having at least one abnormality. However, the extent of US abnormalities showed a trend with the highest score found in PsA patients followed by PsC patients and lowest in the controls (GUESS 8.9±4.6, 5.6±3.5 and 4.4±3.9, respectively p<0.001, MASEI 18.5±13, 9.9±7.4 and 7.7±9.2, respectively p<0.001). GUESS and MASEI correlated significantly with age (p<0.001 for each score) and Body Mass Index (p<0.001 for each score) and after adjusting for these variables the difference in enthesitis scores across the groups were not significant. The frequency of individuals who had tendon hypoechogenicity (p<0.001) and thickening (p<0.001), bony erosions (p<0.001) and positive Doppler signal (p=0.04) at the entheses was highest in PsA patients compared to both PsC and healthy control. No

difference was observed in the frequency of individuals with calcifications or bursitis at the entheses. Among patients with PsA, C-reactive protein (CRP) and modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) correlated with GUESS (r=0.45, p=0.002 and r=0.44, p=0.004, respectively) and with MASEI (r=0.51, p=0.0007 and r=0.56, p=0.0005, respectively).

Conclusion: The prevalence of US entheseal abnormalities is high even among healthy individuals. However, their severity is highest in PsA patients followed by PsC and is lowest in healthy controls. Such abnormalities are associated with age, obesity, CRP and in PsA with the severity of radiographic axial damage.

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Adalimumab Significantly Reduces Recurrence Rate of Anterior Uveitis in Patients with Ankylosing Spondylitis. J. Christiaan van Denderen[1], Ingrid M. Visman[1], M. T. Nurmohamed[2], Maria S.A. Suttorp-Schulten[3] and Irene E. van der Horst-Bruinsma[4]. [1]Jan van Breemen Research Institute/Reade, Amsterdam, Netherlands, [2]VU University Medical Center/Jan van Bremen Research Institute, Amsterdam, Netherlands, [3]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands, [4]VU University Medical Centre, Department of Rheumatology, Amsterdam, Netherlands

Background/Purpose: A high percentage (30–40%) of patients with Ankylosing Spondylitis (AS) suffer from acute anterior uveitis (AAU) attacks. Local treatment with corticosteroids is a beneficial treatment, but not always sufficient. The objective of this study is to examine whether the use of adalimumab decreases the frequency of attacks of AAU in patients with AS, who receive this treatment for their spinal disease activity.

Methods: Consecutive AS patients, who were treated for at least 12 weeks with 40 mg of adalimumab every other week, were enrolled. The number of attacks of AAU in the year before start and during adalimumab treatment was assessed by ophthalmological controls at baseline and yearly thereafter. Follow-up ended at January First, 2012, or upon discontinuation of adalimumab treatment for any reason.

Results: In total 77 patients were enrolled of whom 67 (87%) were seen by the ophthalmologist at baseline and 44 (57%) during follow-up. The other data were retrieved from protocol visits to the research physician. Out of these 77 patients:

51 (66%) did not have attacks of uveitis in the year before (and during) treatment,

16 (21%) had uveitis before, but not during treatment,

10 (13%) had attacks of uveitis before and during treatment

No one developed uveitis for the first time during adalimumab treatment.

Figure 1 Uveitis before and after start adalimumab
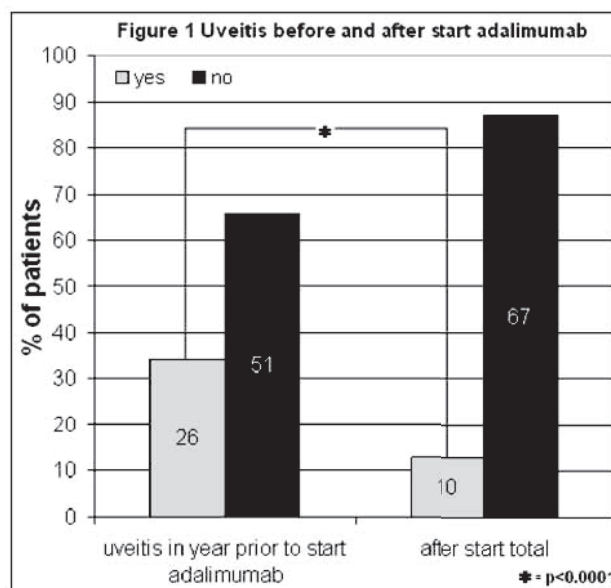
In total 26 patients (34%) suffered from recurrent flares of uveitis in the year before start of adalimumab treatment, with a median of 2.0 uveitis

attacks per year (IQR: 1.0–3.5). The median follow-up period of all patients was 1.74 years (IQR: 0.80–2.57). During follow-up only 10 patients (13%) had attacks of uveitis with a median of 0.56 uveitis attacks per year (IQR: 0.30–0.75). This constitutes a 62% drop in the number of patients with uveitis attacks. The number of patients with uveitis as well as the number of attacks/year dropped significantly (p<0.0001), compared with the year before adalimumab. Even the patient with a very high number of attacks of AAU (12 attacks/year) was completely free of uveitis attacks after start of adalimumab, during his entire 4 years of follow-up.

Conclusion: A significant and substantial reduction of recurrence rate of flares of anterior uveitis during adalimumab treatment was found, even in patients with a high recurrence rate of attacks. The majority (87%) of patients remained completely free of uveitis attacks for the entire follow-up period.

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Improvement in Physical Function, Health-Related Quality of Life, and Work Productivity with Adalimumab Treatment in Nonradiographic Axial Spa: Wk-52 Results From Ability-1. Désirée van der Heijde[1], Philip Mease[2], Aileen L. Pangan[3], Sumati Rao[4], Naijun Chen[4] and Mary A. Cifaldi[4]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Swedish Rheumatology Research Group, Seattle, WA, [3]Abbott, Abbott Park, IL, [4]Abbott Laboratories, Abbott Park, IL

Background/Purpose: To evaluate long-term effects of adalimumab (ADA) treatment on patient reported outcomes (PROs) in nonradiographic axial spondyloarthritis (nr-axSpA).

Methods: Ability-1 is an ongoing Phase III, multicenter, randomized, controlled trial of ADA vs. placebo (PBO) in patients with nr-axSpA (fulfilling ASAS axial SpA criteria but not modified New York criteria for AS). Following the 12-wk double-blind phase, all patients were switched to open-label (OL) ADA (represented by ADA/ADA and PBO/ADA groups) for 144 wks. This post hoc analysis evaluated physical function, health-related quality of life (HRQOL), and work productivity until Wk 52. Physical function was assessed using the disability index of the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) and HRQOL using the Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) score. Productivity was assessed using the overall work impairment domain of the Work Productivity and Activity Impairment Questionnaire. Changes from baseline to Wk 12 were compared between groups using ANCOVA with adjustment for baseline scores and with treatment as a factor. Analyses were conducted on the intent-to-treat (ITT) population excluding 7 subjects from a noncompliant site and the OL population (patients who had at least 1 dose of OL ADA).

Results: After 12 wks of therapy in the double-blind period, the ADA group experienced statistically significant improvements in HAQ-S (p<0.02) and SF-36 PCS (p<0.001) compared with PBO. A total of 179 patients entered the OL period (87/91 and 92/94 from the original ADA and PBO arms, respectively) and 150/151/81 patients completed the HAQ-S, SF-36 PCS, and work productivity questionnaires, respectively, at Wk 52 (**table**). At Wk 52, approximately 62% of the patients met the minimum important difference (MID) for HAQ-S of 0.26 and 77% met the MID for SF-36 PCS of 3.0. Nearly 65% of the patients also met the MID for work productivity of 7% at Wk 52. PBO patients who switched to OL ADA experienced improvements in HRQOL and work productivity levels comparable to patients who received ADA through Wk 52. By Wk 52, patients in both groups achieved SF-36 scores (42.8 and 44.1 for the PBO/ADA and ADA/ADA groups, respectively) that approached the US general population norm of 50.

Change From Baseline Through Wk 52 in Physical Function, HRQL, and Work Productivity in Patients With nr-axSpA.

	Wk 12 (ITT)	Wk 24 (OL Population)			Wk 52 (OL Population)	
	PBO	ADA[a]	PBO/ADA[a]	ADA/ADA	PBO/ADA	ADA/ADA
HAQ-S (mean ± SD)[b,c]	n = 90	n = 88	n = 89	n = 82	n = 78	n = 72
	−0.14 ± 0.43	−0.28 ± 0.50	−0.38 ± 0.56	−0.40 ± 0.39	−0.48 ± 0.52	−0.41 ± 0.45
SF-36 (PCS) (mean ± SD)[b,c]	n = 93	n = 91	n = 90	n = 87	n = 79	n = 72
	2.0 ± 7.04	5.5 ± 8.98	7.0 ± 9.42	7.4 ± 9.66	9.4 ± 10.42	9.9 ± 9.82
Work productivity (mean ± SD)[b,c]	n = 47	n = 49	n = 46	n = 49	n = 43	n = 38
	−5.7 ± 28.63	−12.1 ± 28.84	−20.8 ± 27.75	−18.5 ± 26.34	−21.0 ± 35.55	−24.7 ± 27.56

[a]Corresponds to 12 wks of ADA treatment.
[b]n = number of subjects with nonmissing values for both baseline and the respective visit. Baseline was defined as the last nonmissing value prior to the first dose of study drug.
[c]MID thresholds are −0.26, 3.0, and 7.0% for HAQ-S, SF-36 (PCS), and work productivity, respectively.

Conclusion: Patients who remained on ADA therapy for 52 wks had sustained improvement in PRO and productivity. Likewise, patients who received PBO and switched to ADA in the OL period showed improvement in physical function, HRQOL, and work productivity that was maintained through Wk 52.

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The Prevalence of Psoriatic Arthritis Based On Rheumatologists' Clinical Assessment Before and After Laboratory and Radiographic Tests in Psoriasis Patients in European/North American Dermatology Clinics. Dafna D. Gladman[1], Philip J. Mease[2], Rafat Y. Faraawi[3], Eustratios Bananis[4], Andrew S. Koenig[4], Robert Northington[4], Joanne Fuiman[4] and Daniel Alvarez[4]. [1]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [2]Swedish Medical Center, Seattle, WA, [3]McMaster University, Kitchener, ON, [4]Pfizer Inc., Collegeville, PA

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory disease with a heterogeneous presentation that is associated with impaired quality of life, joint damage, and limited ability to work.[1–3] Diagnosis of PsA is often challenging and may require close collaboration between dermatologists and rheumatologists. Reliance on laboratory and/or radiographic tests to diagnose PsA varies among rheumatologists. The PREPARE trial (NCT01147874) was conducted to estimate PsA prevalence as determined by rheumatologists' evaluation of psoriasis patients presenting to dermatologists' offices. The objective of the secondary analysis presented here was to estimate the prevalence of PsA in psoriasis patients based on clinical assessment by rheumatologists using medical history and physical examination before and after review of supplemental laboratory and radiographic tests.

Methods: Unselected, consecutive psoriasis patients, ≥18 years of age, were initially assessed for plaque psoriasis by dermatologists at 34 dermatology centers in 7 European and North American countries. After psoriasis was confirmed, patients were evaluated for PsA by rheumatologists based on medical history and physical examination alone. Rheumatologists reassessed their diagnoses after receiving laboratory test results (eg, C-reactive protein, erythrocyte sedimentation rate, or rheumatoid factor). In a patient subgroup undergoing radiographic evaluation of hands and feet, rheumatologists conducted a 2nd reassessment after x-rays were provided.

Results: In 949 psoriasis patients who were subsequently evaluated with the inclusion of laboratory tests, 281 (29.6%) were initially diagnosed with PsA based on medical history and physical examination alone (table). In comparison, 285 (30.0%) received clinical PsA diagnoses from rheumatologists based on medical history, physical examination, and laboratory results. In 183 psoriasis patients in the radiographic subgroup, 74 (40.4%) received a PsA diagnosis based on medical history, physical examination, and laboratory results, whereas 71 (38.8%) received this diagnosis based on medical history, physical examination, laboratory results, and radiographic findings.

Table. PsA prevalence based on different clinical assessment approaches in the PREPARE study

Clinical Assessments	Prevalence n (%) (95% CI)	Change in PsA Diagnosis n (%)	
		Negative to Positive	Positive to Negative
All Patients (N = 949)			
Medical history + physical examination	281 (29.6%) (26.7, 32.6)		
Medical history + physical examination + laboratory results	285 (30.0%) (27.1, 33.1)	8 (0.8)*	4 (0.4)*
Patients in Radiographic Subgroup (n = 183)			
Medical history + physical examination + laboratory results	74 (40.4%) (33.3, 47.9)		
Medical history + physical examination + laboratory results + radiographic results	71 (38.8%) (31.7, 46.3)	2 (1.1)†	5 (2.7)†

*Number (%) of patients whose diagnosis changed when laboratory tests were added to the initial clinical assessment based on medical history and physical examination.
†Number (%) of patients whose diagnosis changed when radiographic results were added to the clinical assessment based on medical history, physical examination, and laboratory results.

Conclusion: In this large, multinational prevalence study, approximately one-third of psoriasis patients had PsA based on rheumatologists' clinical assessment. This analysis confirms the ability of rheumatologists to diagnosis PsA based on medical history and physical examination alone. However, laboratory and radiographic results may assist in excluding and/or confirming the diagnosis in some patients.

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Hand Bone Loss Is Arrested in Early Psoriatic Arthritis but Not in Rheumatoid Arthritis Following Anti-Rheumatic Treatment Assessed by Digital X-Ray Radiogrammetry. Agnes Szentpetery[1], Muhammad Haroon[2], Phil Gallagher[3], Martina Cooney[1], Eric J. Heffernan[4] and Oliver M. FitzGerald[5]. [1]Department of Rheumatology, St. Vincent's University Hospital, Dublin, Ireland, [2]Dublin Academic Medical Center, St. Vincent's University Hospital, Dublin, Ireland, [3]Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [4]Department of Radiology, St. Vincent's University Hospital, Dublin, Ireland, [5]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Periarticular bone loss is an early feature of both psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Digital X-ray radiogrammetry (DXR) is a sensitive method for quantifying changes in periarticular bone mineral density (DXR-BMD) in the early phase of the disease. Only a few studies have examined the effect of anti-rheumatic drugs on hand bone loss as measured by DXR in RA and even less in PsA. To our knowledge there is no prospective study designed for capturing differences in hand bone loss between recent onset PsA and RA patients following intervention with anti-rheumatic treatments.

The aim of this study was to: (1) investigate DXR-BMD changes in early PsA and RA prior to and 3 and 12 months after introducing an anti-rheumatic drug; and (2) to explore associations between disease-related variables and DXR-BMD.

Methods: Recent-onset (<12 months), treatment naive PsA and RA patients with active disease were recruited. Hand BMD was assessed by DXR calculated from digitized radiographs (Sectra, Sweden) measuring the cortical thickness of the 2nd, 3rd and 4th metacarpal bones. Mean DXR-BMD (mg/cm^2) values and changes from baseline in DXR-BMD (mg/cm^2/month) were calculated and compared between the two groups at baseline, 3 and 12 months. Clinical parameters were correlated with DXR-BMD including ESR, CRP, TJC, SJC, DAS28-CRP4v and HAQ.

Results: 64 patients (31 PsA, 33 RA) were included with median age 43 years (18–71). 96.6% of the patients were commenced on a DMARD therapy (93.2% methotrexate) at baseline; 18.6% of the patients (12.1% of RA; 19% of PsA) were also started on a TNF inhibitor.

Mean DXR-BMD was significantly higher in PsA at 12 months compared to 3 months (p=0.0137). In contrast mean DXR-BMD was lower in RA at both 3 and 12 months compared to baseline (p=0.0347 and p=0.0302) and at 12 months compared to 3 months (p=0.0159). Highly elevated bone loss (>2.5 mg/cm^2/month) was only present in the RA cohort (6%). Changes from baseline and 3 months to 12 months were significantly less marked in PsA compared to RA (p=0.0084 and p=0.004). Similarly, comparing treatment responders only, changes from baseline to 12 months were less marked in the PsA responder group (p=0.0209). Disease activity scores were lower in PsA than in RA at all time points reaching significance at baseline and 3 months. ESR, CRP, TJC, SJC, DAS28-CRP4v and HAQ improved significantly in both diseases during the study. Mean DXR-BMD correlated with ESR at 3 months in PsA (r = −0.59; p= 0.013) and with CRP at baseline in RA (r = −0.448; p= 0.025). Similarly, significant inverse correlations were found between mean DXR-BMD and ESR and CRP at baseline in the entire group.

Conclusion: Hand bone loss is arrested by 12 months of intervention of appropriate DMARD therapy in PsA but not in RA. Higher disease activity is associated with accelerated cortical bone loss in both diseases. Changes in DXR-BMD were less marked in PsA supporting the hypothesis of different pathogenetic mechanisms being involved in hand bone resorption/formation balance in PsA.

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Gender Differences Among Spondylitis Associated with Psoriasis, Inflammatory Bowel Disease and Primary Ankylosing Spondylitis. Margarita Landi[1], Hernan Maldonado-Ficco[1], Jose A. Maldonado-Cocco[1], Gustavo Citera[2], Pablo Arturi[1], Percival Sampaio-Barros[3], Diana Flores[4], Ruben Burgos-Vargas[5], Helena Santos[6], Jose Chavez-Corrales[7], Daniel Palleiro[8], Miguel A. Gutierrez[9], Elsa Vieira-Sousa[10], Fernando Pimentel-Santos[11], Sergio O. Paira[12], Alberto Berman Sr.[13], Janitzia Vazquez-Mellado[14], Eduardo Collantes-Estevez[15] and On behalf of RESPONDIA Group[16]. [1]Instituto de Rehabilitacion Psicofisica and Fundacion Reumatologica Argentina, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica., Buenos Aires, Argentina, [3]University of Sao Paulo School of Medicine, Sao Paulo, Brazil, [4]Hospital Universitario "Dr. José Eleuterio González", Monterrey, Mexico, [5]Hospital General de Mexico, Mexico DF, Mexico, [6]Instituto Português de Reumatologia, Lisboa, Portugal, [7]Hospital Nacional E. Rebaglliti-ESSALUD, Lima, Peru, [8]Instituto Nacional de Reumatologia, Montevideo, Uruguay, [9]Pontificia Universidad Catolica de Chile, Santiago, Chile, [10]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [11]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [12]Hospital Jose Maria Cullen, Santa Fe SFE S3000BFP, Argentina, [13]Hospital Padilla, Tucuman, Argentina, [14]Hospital General de Mexico, Mexico city, Mexico, [15]IMIBIC-Reina Sofia Hospital, Cordoba 14012, Spain, [16]Buenos Aires

Background/Purpose: Differences regarding gender in primary Ankylosing Spondylitis are well known. However, there is less evidence regarding Spondylitis Associated with Psoriasis and that associated with Inflammatory Bowel Disease. To compare clinical manifestations, disease activity, functional capacity, spinal mobility and radiological findings among women and men from a multicenter, multiethnic cohort, of Ibero-American patients with Spondyloarthritis.

Methods: This observational cross-section study included 2044 consecutive spondyloarthritis (SpA) patients (ESSG criteria). Demographic, clinical, disease activity, functional ability, quality of life, work status and radiologic data were evaluated and collected by RESPONDIA members from different Ibero-American countries between June and December 2006. For this analysis patients were selected only if they met modified New York criteria for AS. Data was transmitted on-line and stored in the Spanish SpA Registry (REGISPONSER) website. Categorial data were compared by X^2 or Fisher's exact tests and continuous variables by ANOVA with post-hoc tests.

Results: Out of 2044 patients, 1264 met New York criteria; 73% were male, (mean age 43 years, SD=15.8), and 27% were female (mean age 45,8 years, SD=12.6). 1072 had primary Ankylosing Spondylitis (AS), 147 Spondylitis Associated to Psoriasis (PsSp) and 45 Spondilytis associated to Inflammatory Bowel Disease (IBDSp). Overall, male patients were significantly younger, had longer diagnostic delay, lower disease activity (BASDAI), less swollen joints, worse spinal mobility (BASMI), better quality of life although worse total BASRI. Frequency of dactylitis and enthesitis was significantly more common among women. Analysing only AS, there was marked male predominance (76.2%). Male patients were also significantly younger, had lower disease activity, worse BASMI, better quality of life and less frequence of dactylitis, yet worse total BASRI. When reading only BASRI in the spine, still it was significantly higher in male patients (mean 7.3 vs 5.8 p=0.000). However, among patients with PsSp male predominance was lower (57.8%), had significantly worse total BASRI and spinal BASRI and worse spinal mobility (BASMI). Among the 45 patients with IBDSp there was a slight female predominance (51.1%) and only differed in less lateral lumbar flexion in males (p=0.015). Regarding work disability in the total population, men had higher permanent work disability (13.2 vs. 6.9 p<0.05). These differences were maintained when subdividing patients according to primary AS but were no differences in PsSp. There were no patient with IBDSp and permanent work disability.

Conclusion: In this gender comparative analysis among Psoriatic, IBD and primary AS, male patients were significantly younger, had longer diagnostic delay, worse total BASRI, higher BASMI, strikingly lower disease activity (BASDAI) and better quality of life. In both primary AS and PsSp groups, women had better spinal mobility and less radiographic damage.

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Psoriatic Arthritis and Biologic Therapy: Treatment Response, Drug Survival and Outcome After Switching.

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Background/Purpose: Data on longer term efficacy and tolerance of biologic therapies in psoriatic arthritis (PsA) are emerging. Persistence with the first TNF inhibitor (TNFi) at one year is estimated at 70–87%. Data on the benefit of switching between TNFi are limited but persistence with a second agent at one year is reported as 74–81%. We aimed to investigate the treatment response, drug survival and outcome with the first and subsequent biologic agents in patients with PsA.

Methods: Data were collected from a prospective single-centre cohort of PsA patients who started a biologic agent between 1stJan 2003–1st Sept 2010.

Results: Seventy-one patients started a biologic agent of whom 96% had polyarticular disease. The median follow-up was 36 months, median age at start of biologic 47y and median disease duration 10y. The most frequently prescribed first biologic agent was etanercept (58%) followed by adalimumab (35%) and infliximab (7%).

Thirty-six percent started a biologic agent as monotherapy, 49% started in combination with one DMARD and 13% with two DMARDs. Ninety-six percent fulfilled the Psoriatic Arthritis Response Criteria (PsARC) where completed.

Persistence with the first biologic was 92% at 6 months, 87% at 12 months, 74% at 24 months and 70% at 36 months. Six patients (8.4%) stopped due to secondary inefficacy (after 12 weeks) and 16 (23%) stopped due to adverse event.

Nineteen patients switched to a second biologic agent (6 due to secondary inefficiency and 13 due to an adverse event). Persistence was 67% at 6 months and 53% at 12 months. One patient stopped due to primary inefficacy, 2 due to secondary inefficacy and 7 had an adverse event. Of the 6 patients who had switched to a second agent because of secondary inefficacy, one continued on the second agent, one switched again because of primary inefficacy, 2 switched again because of secondary inefficacy and 2 switched again because of an adverse event. Of the 13 patients who switched to a second agent because of an adverse event, 8 continued on the second agent, one stopped biologic therapy and 3 switched again because of an adverse event. One patient was pending switch to a third biologic at the time of analysis.

Eight patients switched to a third biologic. Six continued on the third agent (median follow up after switching 26 months). Two switched to a 4th agent (ustekinumab) because of secondary inefficacy and remained on the 4thagent at 4 and 11 months follow up respectively.

Median percentage improvements with the first biologic at 12 and 24 months respectively were 79% and 100% in swollen joint count, 77% and 83% in tender joint count, 50% and 56% in Health Assessment Questionnaire, 67% and 61% in Psoriasis Area and Severity Index, 89% and 100% in Dermatology Life Quality Index and 100% and 100% in the Bath Nail Score.

Conclusion: Persistence with the first biologic agent in this cohort was 87% at 12 months, 74% at 24 months and 70% at 36 months. The response to the first biologic agent was sustained at 24 months across joint, skin, nail and quality of life measures. Persistence with the second biologic agent was 53% at 12 months. Patients who switched to a second biologic agent because of adverse event were more likely to continue with the second agent than those who switched because of secondary inefficacy.

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Performance of Remission Criteria and Activity Indices in Psoriatic Arthritis.

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Background/Purpose: Remission criteria and activity indices used in rheumatoid arthritis (RA) are often applied in psoriatic arthritis (PsA). Although indices have been specifically developed for PsA: CPDAI (Composite Psoriatic Disease Activity Index), PASE (Psoriatic Arthritis Screening and Evaluation), DAPSA (Disease Activity index for Psoriatic Arthritis) and MDA (minimal disease activity criteria in Psoriatic Arthritis), few studies have compared their performance in PsA patients.

The Objective was to evaluate the performance of different remission criteria and activity indices in PsA.

Methods: 55 consecutive patients with PsA (CASPAR criteria) were included. At study entry visit, information necessary to complete the following indices was captured: CPDAI, DAPSA, PASE, MDA, DAS28, SDAI, CDAI, and ACR/EULAR Boolean RA remission criteria. The following assessments were also included: HAQ, BASDAI, BASFI and PASI (Psoriatic Assessment of Skin Index).

Results: Mean age was 53 years (SD=12), and 35 (63.6%) were males. Mean PsA disease duration was 5.9 (SD=8.5) years and mean psoriasis duration was 15.9 (SD= 12.6). Mean number of swollen and tender joint count was 2.4 (SD= 3) and 4.3 (SD=6) respectively. Mean PASI was 1.9 (SD=2.7). In 33 patients (60%) the treating rheumatologist indicated a change in treatment.

Table 1. Percentage of patients in remission and different levels of activity according to the different indices

Index	Percentage in remission (95% CI)	Low disease activity (95%CI)	Moderate disease activity (95% CI)	High disease activity (95% CI)
DAS28	33 (20–45)	11 (4–22)	43 (30–58)	13 (5–24)
SDAI	4 (0.4–14)	34 (21–49)	36 (23–51)	26 (15–40)
CDAI	9 (1–17)	36 (24–50)	35 (22–48)	20 (10–33)
CPDAI	0	78 (65–88)	20 (10–33)	2 (0.04–10)
ACR/EULAR (Boolean)	9 (1–17)	–	–	–
MDA	29 (18–43)	–	–	–

Table 2. Correlation coefficients between different indices (Pearson).

Index	DAS28	CDAI	SDAI	CPDAI	PASE	HAQ	BASDAI	BASFI
DAS28	1	0.83	0.75	0.58	0.75	0.71	0.68	0.66
CDAI	0.83	1	0.76	0.57	0.75	0.70	0.63	0.62
SDAI	0.75	0.76	1	0.42	0.61	0.61	0.52	0.64
CPDAI	0.60	0.57	0.42	1	0.44	0.53	0.38	0.39
PASE	0.75	0.75	0.61	0.44	1	0.84	0.84	0.72
HAQ	0.71	0.70	0.61	0.53	0.84	1	0.76	0.79
BASDAI	0.68	0.63	0.52	0.38	0.84	0.76	1	0.82
BASFI	0.66	0.62	0.64	0.39	0.72	0.79	0.82	1

Table 3. Comparison of mean indices values between patients with and without change in treatment.

Index	Not changing treatment (n=22)	Initiating/Changing treatment (n=33)	P value (Mann-Whitney)
Mean PASE (SD)	29.5 (8.5)	42.2 (14.1)	0.0004
Mean CPDAI (SD)	2 (0.9)	4.7 (3.6)	0.0013
Mean DAPSA (SD)	6 (4.5)	11.7 (6.1)	0.0008
Mean DAS28 (SD)	2.3 (0.9)	4.3 (1.2)	<0.0001
Mean SDAI (SD)	8.7 (8)	29.2 (24.6)	0.0005
Mean CDAI (SD)	5.3 (3.5)	19.4 (11.8)	<0.0001

All indices showed good discriminative power for a change in treatment in the ROC curve: PASE- AUC (area under curve) = 0.78 (95% CI:

0.65–0.9); CPDAI -AUC= 0.81 (95%CI: 0.7–0.9); DAPSA–AUC=0.78 (95% CI: 0.65–0.91).DAS28- AUC= 0.92 (95%CI: 0.89–1); CDAI-AUC= 0.93 (95%CI: 0.87–0.99); SDAI- AUC= 0.89 (95% CI: 0.79–0.99).

Conclusion: There were differences in the percentage of patients classified as in remission by the different remission criteria. Particularly, DAS28 and MDA seemed to be less stringent in PsA than the other indices. Of the specific indices studied CPDAI showed the poorest correlation with all the other activity measurements.

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Comparison of Sacroiliac MRI Evaluation Versus Sacroiliac x-Rays in Peripheral Psoriatic Arthritis: Evidence of Silent Disease and Lack of Association to HLA-B27. Jose Luis Fernandez-Sueiro[1], JA Pinto[1], S. Pertega-Diaz[1], E. Gonzalez[1] and Francisco J. Blanco[2]. [1]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain

Background/Purpose: Although there are no consensus on how to define spinal involvement in axial psoriatic artritis (axPsA), our data suggest that the presence of spinal symptoms (defined as a combination of inflammatory back pain plus back stiffness) can be sufficient. However x-ray evaluation of sacroiliac joints may be normal at the first stage of the disease. Objetive: to evaluate the negative predictive value of sacroiliac x-rays versus MRI to rule out the diagnosis of sacroiliitis in peripheral PsA.

Methods: cross sectional descriptive and observational study of PsA patients classified according to CASPAR criteria. All patients had peripheral arthritis not spinal back pain and normal or grade I sacroiliac involvement determined by x-rays. All patients were evaluated according to current standard care. HLA-B27 was determined in all patients. Sacroiliac MRI was performed with either a Tesla 1.5 Gyroscan Intera (Philips MS) or Tesla 1.5 Signa-Excite with the following coronal sequences T1-TSE, T2-TGE and STIR with slices of 4mm of thickness, criteria for lesions were as ASAS proposal. The negative predictive value of x-rays versus MRI was determined as well as the 95% CI. Patients' characteristics were compared according to MRI results, by means of Mann-Whitney U test, chi-squared test and Fisher's exact test.

Results: sacroiliac MRI was performed in 59 patients from a total of 97 PsA patients with peripheral arthritis. There were not significant differences in both groups of patients. MRI patients had a medium age of 49,2±12,9 years, a time of evolution of the disease of 9,4±7,6 years. 96,4% patients had a normal sacroiliac x-rays, 2 had grade I unilateral and bilateral sacroiliitis respectively. HLA-B27 was negative in 93,2%(n=55) patients. 20,3% (n=12) showed active inflammatory lesions (1 with x-rays grade I bilateral). All patients were HLA-B27 negative. There were not significant clinical differences between MRI positive/negative patients, the exception was the occiput to wall distance (p=0,032). The negative predictive value of sacroiliac x-rays versus sacroiliac MRI was of 79,7% (95%IC: 68,5%-90,8%)

Conclusion: Conventional x-rays versus MRI for the evaluation of sacroiliitis had a negative predictive value of 79,7%. In this study the sacroiliac involvement in PsA does not depend on the presence of spinal pain, HLA-B27 or radiological sacroiliitis.

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Spinal Involvement in Axial Psoriatic Artritis Is Not Determined by the Presence of HLA-B27. Is the HLA-B27 Arm of the Axial Spa Criteria Reliable for Classifying Axial Psoriatic Arthritis? Jose Luis Fernandez-Sueiro[1], JA Pinto[1], S. Pertega-Diaz[1], E. Gonzalez[1], Ignacio Rego-Perez[2], Francisco J. de Toro-Santos[3] and Francisco J. Blanco[4]. [1]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [2]INIBIC-Hospital Universitario A Coruña. Genomic Group. Rheumatology Division., A Coruña, Spain, [3]Complejo Hospitalario Universitario Juan Canalejo, Universidad de la Coruña, La Coruña, Spain, [4]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain

Background/Purpose: There is a debate whether axial psoriatic arthritis (axPsA) is an ankylosing spondylitis with psoriasis, however due to the fact that PsA has characteristic clinical features, this concept is debatable. On the other hand HLA-B27 is a key component of the clinical arm of the new ASAS criteria for axial SpA. Objective: to determine the prevalence of HLA-B27 in PsA and to analyze its prevalence according to the clinical forms

Methods: Cross-sectional prevalence study of HLA-B27. HLA-B27 was determined in the following populations: a) healthy controls (HC) (n= 308) and AS (n=106) (1), b) cutaneous psoriasis (n=113), c) PsA (n=172). axPsA was defined according to our previous definition (2,3). HLA-B27 was determined wit a commercial kit: Invitrogen®, Allset Gold B27 Low and High Res SSP. For each group of patients, HLA-B27 prevalence was determined, together with its 95% confidence interval. Using data from the Galician population as reference, prevalence ratio and odds ratio values were estimated from a logistic regression model. Comparisons among groups were performed by using the Mann-Whitney U, chi-squared and Fisher's exact tests.

Results: The prevalence of HLA-B27 was: HC 9,4%, AS 94,3% (p<0,001), cutaneous psoriasis 9,7% (p=0,921), PsA whole group 14,5% (p=0,099), peripheral PsA 8,2% (p=0,708), axPsA (mixed/"pure") (n=68) 23,5% (p=0,002), axPsA "mixed" (n=61) 18% (p=0,052), axPsA (pure) (n=7) 71,4% (p=<0,001),]. HLA-B27+ PsA patients had a diagnosis of the disease at an earlier age, 39,2±14,14 vs 45,3±13,52 years (p=0,036). Comparing axPsA (mixed/"pure") HLA-B27- (n=52) vs HLA-B27+ (n=16) there were no significant differences in the following: epidemiological, clinical, metrological, inflammatory, function and structural damage assessed by BASRI. The only exception was the occiput to wall distance (1,1 cm vs 4,7 cm; p=0,036)

Conclusion: The prevalence of HLA-B27 in PsA is similar to the general population. HLA-B27+ seemed to determine the age of presentation of PsA. There seems to be two populations with spinal involvement in axPsA, HLA-B27+/−, being the most prevalent the HLA-B27-. These data question the hypothesis that axPsA is a primary AS and question the reliability of HLA-B27 for classifying axPsA patients using the new ASAS criteria for axial SpA.

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Disease Burden Is Comparable in Patients with Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis. Joachim Sieper Male[1], Désirée van der Heijde[2], Dirk Elewaut[3], Aileen L. Pangan[4] and Jaclyn K. Anderson[4]. [1]Charité Universitätesmedizin Berlin, Berlin, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Ghent University Hospital, Ghent, Belgium, [4]Abbott Laboratories, Abbott Park, IL

Background/Purpose: Chronic back pain and functional impairment are disease characteristics common to all patients (pts) with axial spondyloarthritis (SpA), regardless of the presence of radiographic sacroiliitis in ankylosing spondylitis (AS) or its absence in non-radiographic axial SpA (nr-axSpA). This analysis compares baseline disease characteristics of pts with nr-axSpA and AS in registries and randomized clinical trials (RCT) with adalimumab (ADA).

Methods: Registry data in this analysis include the German SpA Inception Cohort (GESPIC)[1] that compared pts with AS by modified New York criteria (divided into >5 yrs and ≤5 yrs) and nr-axSpA (≤5 yrs) meeting modified ESSG criteria and a prospective cohort of TNF-naïve SpA pts meeting ASAS criteria for axial SpA.[2] ADA RCT data were derived from the ATLAS study[3] in AS pts, and the ABILITY-1[4] and Haibel[5] studies in nr-axSpA pts. Pts in RCTs were selected based on a pre-specified level of disease activity and inadequate response to non-steroidal anti-inflammatory drugs.

Results: Mean age was similar in nr-axSpA and AS pts, ranging from 36–42 yrs (table). A higher proportion of AS pts had elevated CRP as compared to nr-axSpA pts and gender differences were observed, with nr-axSpA pts being predominantly female and AS pts primarily male. Symptomatic pts with nr-axSpA and AS often went undiagnosed for years. Similar levels of disease activity as measured by the BASDAI, pain scores, and pt and physician global assessments of disease activity were seen between nr-axSpA and AS pts in registries and RCTs, with levels of disease activity generally higher in RCT pts due to minimum levels of baseline disease activity required for study eligibility.

Table. nr-axSpA and AS baseline disease characteristics

| | Registries | | | | | RCTs | | |
| | GESPIC | | | Kiltz | | ATLAS | ABILITY-1 | Haibel |
	All AS N=236	AS ≤5 yrs N=119	nr-axSpA ≤5 yrs N=226	AS N=56	nr-axSpA N=44	AS N=315	nr-axSpA N=185	nr-axSpA N=46
Age, yrs	35.6	36.1	36.1	41.2	39.1	42.2	38.0	37.5
Female, %	36.0	34.5	57.1	23.2	68.2	25.1	54.6	54.3
HLA-B27 +, %	88.2	73.1	74.7	89.1	86.4	78.7	75.1	67.4
Symptom duration, yrs	5.2	3.0	2.6	12.8	9.4	-	10.1	7.5
Duration since diagnosis, yrs	2.8	1.7	1.7	7.5	5.0	10.6	2.9	–
BASDAI, 0–10	4.0	4.0	3.9	4.2	3.6	6.3	6.5	6.3
Abnormal CRP, %	51.9	49.6	29.8	69.1	29.5	67.6	35.7	37.8
Total back pain, VAS 0–10	–	–	–	–	–	6.5	6.9	–
Total pain, VAS 0–10	5.0	4.8	4.8	4.7	4.0	–	6.8	7.2
PtGA of disease activity, VAS 0–10	5.0	5.0	4.9	4.6	4.0	6.3	6.8	6.6
PhGA of disease activity, VAS 0–10	4.5	4.4	3.6	3.5	2.7	5.7	5.7	5.9

Values are the mean unless otherwise indicated. AS, ankylosing spondylitis; BASDAI, Bath AS Disease Activity Index; CRP, C-reactive protein; nr-axSpA, non-radiographic axial spondyloarthritis; PhGA, physician global assessment; PtGA, patient global assessment; RCT, randomized clinical trial; VAS, visual analog scale.

Conclusion: Registry and clinical trial data demonstrate that both nr-axSpA and AS patients have comparable burden of disease. These findings suggest that all patients with axial spondyloarthritis can present with similar debilitating signs and symptoms requiring treatment regardless of the extent of radiographic damage.

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Evaluation of Spondyloarthritis activity by the Patients and the Physicians: ASDAS, Basdai, PASS and Flare.

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Background/Purpose: Objectives: to define thresholds of the ASDAS corresponding to the PASS (Pateint Acceptable Symptomatic State) and to the thresholds of activity of the disease through what the patients feel. Correlate these levels of activity to the presence of a depressive syndrome and determine a threshold ASDAS and BASDAI corresponding to a flare in spondyloarthritis (SpA).

Methods: A prospective study of SpA patients (ASAS criteria) from February 2011 until February 2012. Various scores (BASDAI, ASDAS, BASFI) as well as the evaluation of the PASS and the depressive syndrome were measured. Determination of ASDAS thresholds corresponding to the PASS, to the various thresholds of activity according to the patients, and to flare was performed using ROC curves. The Kappa coefficient was calculated to estimate the correlation between the physician's and the patient's evaluation of the flare.

Results: 200 SpA patients, mean age 44.4 ± 12.5 years (duration 12.9 ± 10.5 years) were included. The average scores were respectively 4.1 ± 2.2 for the BASDAI and of 2.4 ± 1 for the ASDAS-CRP and of 3.3 ± 2.7 for the BASFI. 58.9 % of the patients were considered in PASS. The PASS corresponded to a BASDAI ≤ 4.1 and to an ASDAS-CRP ≤2.3. Concerning the impression of the disease by the patients: a weakly active disease corresponded to a BASDAI ≤3.8 and to an ASDAS-CRP ≤2.3, and a strongly active disease in a BASDAI >5.2 and an ASDAS-CRP > 3.1. When the disease was considered as strongly active, 64.5 % of patients had a score of severe depressive syndrome on Beck's scale. A flare was considered by 36.9 % of the patients versus 28.3 % of the physicians. The threshold BASDAI "flare" was ≥5.2 and the threshold ASDAS-CRP "flare" was ≥2.3. The concordance between the evaluation of the flare according to the physician and the patient was good (Kappa: 0.61).

Conclusion: Our results report a significant link between the level of activity of the disease and the severity of the depressive syndrome. Our study confirms a good concordance between the BASDAI and the ASDAS. Thresholds of BASDAI and ASDAS are proposed for PASS and flare in SpA.

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Validation of the Self-Administered Comorbidity Questionnaire in Patients with Ankylosing Spondylitis.

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Background/Purpose: Comorbidities can importantly influence the results of clinical studies on functional outcomes as they may act as confounders or effect modifiers. The generic self-administered comorbidity questionnaire (SCQ) is a frequently used instrument to assess common comorbidities which might impact functioning but has never been validated for use in ankylosing spondylitis (AS). Objective was to measure the agreement between SCQ-responses and medical records diagnosis, and to assess construct- and concurrent validity of the SCQ in patients with AS.

Methods: The SCQ (range 0–45) asks about the presence, treatment and functional limitations of 12 common comorbidities and three additional non-specified medical problems. The SCQ, demographics and indices of disease activity (Bath AS Disease Activity Index [BASDAI]; AS Disease Activity Score- C-reactive protein); physical function (Bath AS Functional Index) and health-related quality of life (HR-QoL; Short form-36 [SF-36], Ankylosing Spondylitis Quality of Life [ASQoL], EuroQoL-VAS), were administered to 98 patients with AS who were followed in the Outcome in Ankylosing Spondylitis International Study (OASIS). The agreement between the SCQ-items and comorbidities retrieved from medical records was calculated by two independent extractors. Concurrent validity was assessed by the correlation with two other comorbidity indices: the Charlson index, a record-based comorbidity index which predicts mortality, and the Michaud/Wolfe index, which predicts functional outcomes. Construct validity was assessed by testing the hypothesis that a valid comorbidity index should correlate with age, function and overall HRQoL. An adapted version of the SCQ (adapted SCQ) was created and validated after removing items on rheumatic diseases (osteoarthritis, back pain, chronic rheumatic disease) because they were conceptually overlapping with the index disease.

Results: The median SCQ-score was 5 (range 0–19) and the median adapted-SCQ-score was 2 (range 0–13). Frequently reported non-rheumatic comorbidities were hypertension (27.6%), inflammatory bowel disease (10.2%) and depression (9.2%). Agreement between self-report and medical records was moderate to perfect for all diseases included in the SCQ (kappa 0.47–1.00), except for stomach disease, depression, and osteoarthritis (kappa

0.14–0.15). The correlations of the SCQ with the Michaud/Wolfe index and the Charlson index were 0.39 and 0.24 respectively, and of the adapted-SCQ with both indices 0.53 and 0.36 respectively. The SCQ correlated weakly with age (r=0.24) and disease activity (BASDAI r=0.27), and moderately with function (r=0.43) and HRQoL (SF-36 physical r=-0.45; AsQoL r=0.43). The adapted SCQ correlated weakly with age (r=0.28), and moderately with function (r=0.41) and HRQoL (SF-36 physical r=-0.41, ASQoL r=0.32), but not with measures of disease activity.

Conclusion: The SCQ can be used to measure comorbidities which have impact on functional outcomes in AS, but the rheumatic items showed low agreement. Exclusion of these items improved construct and concurrent validity.

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Development, Sensibility and Reliability of a New Case-Finding Questionnaire, the Toronto Axial Spondyloarthritis Questionnaire in Inflammatory Bowel Disease. Khalid A. Alnaqbi[1], Zahi Touma[1], Laura A. Passalent[1], Sindhu R. Johnson[1], George A. Tomlinson[2], Adele Carty[1] and R. D. Inman[1]. [1]Toronto Western Hospital, Toronto, ON, [2]Toronto General Hospital, Toronto, ON

Background/Purpose: Inflammatory bowel disease (IBD) encompasses Crohn's disease, ulcerative colitis, and indeterminate colitis. Articular involvement [(peripheral arthritis and axial spondyloarthritis (axSpA)] is the most common extra-intestinal manifestation. There is an unacceptable delay in diagnosis of axSpA by 8–11 years. Our aim was to develop a sensible and reliable questionnaire that identifies undetected axSpA among IBD patients and facilitates timely referral to rheumatologists.

Methods: Literature review facilitated identification of 3 domains:1) IBD, 2) inflammatory back symptoms, and 3) extra-axial features. Items of the Toronto Axial Spondyloarthritis Questionnaire (TASQ) were evaluated for sensibility among SpA team, 2 general rheumatologists, and axSpA patients. Sensibility assessment was related to purpose and framework (clinical function, clinical justification, clinical applicability), face validity, comprehensibility (oligovariability, transparency), replicability, content validity, and feasibility. For the test-retest reliability study, the final version of TASQ was mailed to 77 patients with established IBD and axSpA, who were followed at the Spondylitis clinic. Patients were instructed to complete the questionnaire on 2 occasions 1–2 weeks apart. Calculated sample size was 23 for reliability. Kappa statistics were calculated for the binary response options of each item.

Results: Item modification and reduction led to drafting version 4 of TASQ consisting of 16 items on a one-page double-sided document with a diagram of the back. Of the 77 patients, 34 responded to the TASQ. Responders and non-responders did not differ in terms of age, sex, level of education, types of IBD, BASDAI, BASFI, ESR and CRP levels. Kappa agreement coefficient ranged from 0.81 to 1.00 indicating almost perfect agreement. Absolute agreement of all items ranged from 91 to 100%.

Table 1.

Sensibility assessment	Pre-pilot testing n-9 (%)	Post-pilot testing n-9 (%)
Clinical function	9 (100)	9 (100)
Comprehensibility		
Oligo availability	7 (78)	9 (100)
Transparency		
Appropriateness of the number of response options	9 (100)	9 (100)
Weighting each item	0 (0)	8 (89)
Replicability	7 (78)	9 (100)
Face validity	6 (67)	9 (100)
Content validity		
Important omissions	2 (22)	0 (0)
Inappropriate inclusions	3 (33)	0 (0)
Feasibility		
Time so complesion, medium (range)	4 (3 5) minutes	4 (2 5) minutes
Acceptability	8 (89)	9 (100)
Readability		
Clarity of 1 questions	4 (44)	9 (100)
Flow of questions	7 (78)	9 (100)
Flesch reaching case scale*	72.2%	74.7%
Flesch Kineard grade level*	5.6	5.3
Absence of typographical errors	8 (89)	9 (100)
Usefulness of illustration(s)	5 (56)	9 (100)

Table 2.

Sensibility assessment	Stage I n-4 (%)	Stage II n-9 (%)	Stage III n-6 (%)
Comprehensibility			
Transparency approapearse response openss for each items	2 (50)	9 (100)	6 (100)
Replicability	4 (100)	9 (100)	6 (100)
Feasibility			
Complessor time, medium (range)	5 (3 5) minutes	4 (3 5) minutes	4 (3 5) minutes
Accepasability	4 (100)	9 (100)	6 (100)
Realabilaty			
Clarity of all questions	2 (50)	7 (78)	6 (100)
Flow of questions	4 (100)	9 (100)	6 (100)
Pase of reacability	3 (75)	7 (78)	6 (100)
Absence of typographical errors	4 (100)	8 (89)	6 (100)
Appropriate fent size	4 (100)	9 (100)	6 (100)
Usefulness of picture(s) edior cugram	4 (100)	6 (67)	6 (100)
Actions following each stages	Removal of 4 items. Modifications of 4 items	Removal of 2 items. Removal of dactylities picture Modification of 3 items	Minor modifications of few items

Conclusion: TASQ is a newly developed, sensible and reliable questionnaire to be administered to patients with IBD who have ever had chronic back pain or stiffness that lasted ≥ 3 months. TASQ should facilitate identification and referral of IBD patients to rheumatologists and should avoid delay in diagnosis of axSpA.

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Double-Blind, Placebo-Controlled, 28-Week Trial of Efficacy and Safety of Infliximab Plus Naproxen Vs Naproxen Alone: Results From the Infliximab As First Line Therapy in Patients with Early, Active Axial Spondyloarthritis Trial, Part I. Joachim Sieper[1], Jan Lenaerts[2], Jürgen Wollenhaupt[3], Vadim Mazurov[4], L. Myasoutova[5], Sung-Hwan Park[6], Yeong W. Song[7], Ruji Yao[8], Denesh Chitkara[8] and Nathan Vastesaeger[9]. [1]Charité, University Medicine Berlin, Berlin, Germany, [2]Reuma-instituut, Hasselt, Belgium, [3]Schön-Klinik, Hamburg, Germany, [4]St. Petersburg Medical Academy, St. Petersburg, Russia, [5]Kazan State Medical University, Kazan, Russia, [6]Catholic University of Korea, Seoul, South Korea, [7]Seoul National University, Seoul, South Korea, [8]Merck Sharp and Dohme, Kenilworth, NJ, [9]Merck Sharp and Dohme, Brussels, Belgium

Background/Purpose: Efficacy of anti–tumor necrosis factor (TNF) therapy in patients with axial spondyloarthritis (SpA) has been tested only in patients who are refractory to NSAIDs.

Objectives: To determine whether combination infliximab (IFX)+NSAID therapy is superior to NSAID monotherapy for achieving better clinical outcomes in patients with early, active axial SpA who were naïve to NSAIDs or had a submaximal dose of NSAIDs.

Methods: The INFAST trial was a double-blind, randomized controlled trial of IFX in biologic-naïve patients 18–48 years of age with early, active axial SpA (ASAS criteria, disease duration ≤3 years with chronic back pain and active inflammatory lesions of the sacroiliac [SI] joints on MRI). Patients naïve to NSAIDs or treated with a submaximal dose of NSAIDs were randomized (2:1) to receive 28 weeks of treatment with either IV IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24)+naproxen (NPX) 1000 mg/d or IV placebo (PBO)+NPX 1000 mg/d. The primary endpoint was the percentage of subjects meeting ASAS partial remission criteria at week 28. Treatment group differences were analyzed using Fisher exact tests or analysis of covariance.

Results: 106 patients were randomized to IFX+NPX and 52 to PBO+NPX. At baseline, mean BASDAI scores (100 mm VAS) were 64.4 (SD=15.37) mm and 63.0 (SD=15.43) mm and HLA-B27–positive statuses were 82.1% and 90.4% in the IFX+NPX and PBO+NPX groups, respectively. The primary endpoint, ASAS partial remission at week 28, was achieved by more patients treated with IFX+NPX (61.9%) than PBO+NPX (35.3%), P=0.0021. Partial remission rates increased steadily through weeks 2, 6, 16, and 28 in both the IFX+NPX group (28.6%, 41%, 51.4%, and 61.9%) and the PBO+NPX group (11.8%, 15.7%, 25.5%, 35.3%), with greater partial remission in the IFX+NPX group at each visit (all P <0.05). Improvements in BASDAI, ASDAS, and ESR were considerable and were significantly greater in the IFX+NPX group than the PBO+NPX group (**Table 1**). The observed CRP decrease was greater in the IFX+NPX group

than the PBO+NPX group, but did not reach statistical significance. A greater number of patients in the IFX+NPX group (51.4%) than the PBO+NPX group (19.6%), $P=0.0001$, achieved inactive disease, defined as ASDAS-CRP <1.3.

Table 1. Change in Efficacy Outcomes from Baseline to Week 28 by Treatment Group

Outcome	IFX+NPX (N=105)			PBO+NPX (N=51)			P Value
	Baseline, mean	Week 28, mean	Change, mean (SD)	Baseline, mean	Week 28, mean	Change, mean (SD)	
BASDAI (100 mm VAS)	64.4	18.0	−46.6 (22.38)	63.0	32.2	−30.2 (24.34)	0.0001
ASDAS	3.8	1.4	−2.4 (1.16)	3.9	2.4	−1.5 (1.13)	<0.0001
ESR (mm/hr)	23.0	7.1	−16.0 (16.11)	28.3	19.0	−9.4 (13.18)	<0.0001
CRP (mg/dL)	2.02	0.91	−1.24 (6.209)	1.65	1.15	−0.55 (1.315)	0.5943

Serious adverse events were reported in 5 (4.8%) patients in the IFX+NPX group (possibly related to study medication in 3 [2.9%] patients) and 3 (5.8%) patients in the PBO+NPX group (possibly related in 2 [3.8%] patients). No deaths occurred.

Conclusion: Patients with early, active axial SpA who were treated with IFX+NPX had greater rates of ASAS partial remission and were more likely to have lower or inactive disease (as measured by BASDAI and ASDAS) than those treated with PBO+NPX. Patients who were treated with PBO+NPX had good response but still had moderately active disease. The safety profile was consistent with that of other anti-TNF biologics.

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Golimumab Administered Subcutaneously Every 4 Weeks in Chinese Patients with Active Ankylosing Spondylitis: Week 24 Safety and Efficacy Results From a Randomized, Placebo - Controlled Study.

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Background/Purpose: This multicenter, randomized, placebo (PBO)-controlled study was conducted to evaluate the efficacy and safety of golimumab (GLM) in Chinese patients with active ankylosing spondylitis (AS).

Methods: Patients ≥18yrs of age with a diagnosis of active AS for ≥3 months prior to screening and symptoms of active disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] '4, and a visual analogue scale [VAS] for total back pain ≥4, each on a scale of 0 to 10cm) were eligible to be enrolled for study screening. Patients with prior exposure to biologic anti-tumor necrosis factor alpha (TNF) agents and patients with complete ankylosis of the spine were not permitted to be included in the study. Patients who passed study screening were randomized in 1:1 ratio to receive sub-cutaneous (SC) injections of GLM 50mg or PBO q4wks through wk20. At wk16, all patients randomized to PBO that met early escape criteria (<20% improvement from baseline in both total back pain and morning stiffness measures) began receiving GLM 50mg SC injections in a blinded fashion at wk16 and q4wks thereafter through wk48; all other patients still receiving placebo injections began receiving GLM 50 mg SC injection at wk24 and q4wks thereafter through wk48; all patients randomized to GLM continued receiving GLM 50 mg SC at wk24 and q4wk through wk48 regardless of the status of early escape.The primary efficacy endpoint was the proportion of patients with ≥ 20% improvement in the ASsessment in AS (ASAS) criteria at wk14.

Results: 213 patients were randomized to treatment; baseline demographics were comparable between groups with median age of 29yrs, median weight of 62.0kg, and 83.1% male. The primary endpoint and major secondary endpoints were achieved (Table). Adverse events through 24 wks were reported in 38.9% of GLM-treated and 34.3% of PBO-treated patients.

Serious adverse events were reported in 0.9% (1 ovarian epithelial cancer) and 0.0% of GLM and PBO-treated patients, respectively. Infections were reported in 22.2% and 19.0% of GLM and PBO-treated patients, respectively (primarily upper respiratory tract infections). No serious infections, TB or opportunistic infections, or deaths were reported. Antibodies to GLM were not detected in GLM-treated patients through wk24.

Table.

	Placebo	Golimumab 50 mg
Patients randomized	105	108
Baseline		
BASDAI	6.65 (5.16–7.54)	6.58 (5.74–7.40)
BASFI	4.82 (3.19–6.87)	5.26 (3.04–6.80)
BASMI	3.57 (2.38–4.62)	3.89 (2.40–5.36)
Week 14		
ASAS 20	26 (24.8%)	53 (49.1%)*
BASFI, change from baseline	0.18 (−0.94–1.20)	−0.80 (−2.62–0.29)*
BASMI, change from baseline	−0.17 (−0.66–0.22)	−0.33 (−0.93–0.00)**
Week 24		
ASAS 20	24 (22.9%)	54 (50.0%)*
ASAS 40	14 (13.3%)	36 (33.3%)*
ASAS 5/6	15 (14.3%)	49 (45.4%)*
ASAS partial remission†	3 (2.9%)	20 (18.5%)*
BASDAI 50	14 (13.3%)	36 (33.3%)*

Values are number of responders (%) or median (interquartile range) change from baseline
*p<0.001, **p<0.021;†ASAS partial remission=<2 (VAS 0–10) in each of 4 ASAS domains

Conclusion: GLM significantly improved, as compared to the placebo group, signs and symptoms and physical function in Chinese patients with active AS. GLM was well tolerated through 24wks of treatment.

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Clinical Features and Treatment Results of Japanese Patients with SAPHO (Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis) Syndrome.

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Background/Purpose: SAPHO syndrome is a disorder characterized by pustular skin lesions and osteoarticular lesions, which was proposed by Chamot et al. in 1987. Clinical studies based on the diagnostic criteria of SAPHO syndrome are mainly reported from Europe, and still limited in East-Asia.

Methods: We investigated the clinical features and treatment results in 31 Japanese patients with SAPHO syndrome (male 10, female 21) diagnosed and treated between 2003 and 2011. HLA-A and -B typing was performed in 30 patients, and their allele frequencies were compared with those in the healthy Japanese controls, using Fisher's exact test.

Results: The age at onset was ranged between 16 and 68 years old (y.o.) (average: 48.3), and the age at diagnosis from 16 to 74 y.o. (average: 53.8). The average follow-up period was 42 months. Sternocostoclavicular hyper-ostosis was the main manifestation and recognized in 29 cases (94%). Pustular dermatitis including palmoplantar pustulosis was seen in 26 cases (84%). As other manifestations, recurrent oral ulceration was seen in 6 cases (19%), and inflammatory bowel disease in 2 cases. Most patients had intermittent attacks of pain, therefore oral NSAIDs were needed in all cases and oral prednisolone (PSL) in 14 cases (45%). The oral NSAIDs and/or PSLwere effective for temporary pain relief. DMARDs (SSZ and/or MTX) were used in 14 cases (45%) with recurrent chronic pain. Pain relief more than 50% was seen in only 4 cases (29%) out of DMARDs users. In two refractory cases with severe spondylitis, adalimumab (ADA) was tried. Both cases showed immediate pain-relief and ADA was effective during at least one

year. HLA tests revealed that the allele frequencies of HLA-B27 and HLA-B51were respectively 0% and 12%, which were similar with those in healthy Japanese controls. On the other hand, the frequency of HLA-B61 was 27 % and significantly higher than that (12%) in healthy controls.

Conclusion: Mucosal lesions seem to be a rather frequent complication of SAPHO syndrome in our study. The efficacy of DMARDs (SSZ and/or MTX) was observed in a small number of patients. ADA was effective in two refractory cases with severe spondylitis. This study revealed that HLA-B61 was significantly increased in Japanese patients with SAPHO syndrome.

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Psoriatic Arthritis in South Asians- Comparison with Caucasians of European Descent. Vinod Chandran. Arane Thavaneswaran and Dafna D. Gladman Gladman, Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: The prevalence of psoriatic arthritis (PsA) varies substantially world-wideand is highest among Caucasians of European descent. Studies from India suggest that patients with PsA have a milder disease. Comparing disease phenotype across ethnicities can provide insight into mechanisms underlying disease severity. We aimed to determine whether demographic and disease characteristics differed in PsA patients of South Asian ethnicity compared to those of European ethnicity.

Methods: The study was conducted at a PsA clinic in a North American city with a diverse ethnic composition. Patients are assessed every 6–12 months according to a standard protocol. Prospectively collected data were retrieved from the clinic database. The distribution of ethnicities within the cohort was determined. The demographic and disease characteristics of those with South Asian ethnicity were compared to those of European ethnicity using chi-squared tests and unpaired t-test. Subsequently, each patient of South Asian ethnicity was matched by gender, age, duration of PsA and year of entry to clinic, to 3 patients of European ethnicity and the disease characteristics compared using McNemar and paired t-tests.

Results: The distribution of the 1184 patients in the cohort were as follows: European 1037 (88%), South Asian 59 (5%), Chinese 26 (2.2%), Black 12 (1%), Filipino 12 (1%), Hispanic 7 (0.6%), South-east Asian 4 (0.3%), Korean 2 (0.2%), Aboriginal 1 (0.1%) and other/mixed 24 (2%). Overall patients of South Asian descent had shorter duration of psoriasis, lower family history of psoriasis, lower family history of PsA, lower prevalence of obesity, lower exposure to biologic agents and NSAIDs as well as lower prevalence of nail psoriasis and severe radiographic damage (defined as grade 4 damage according to the Steinbrocker method) compared to patients of European descent. The summary of results of the matched analysis comparing patients of South Asian descent to those of European descent is presented in Table 1. Patients of South Asian descent had lower tender joint counts, less number of joints with severe damage, lower frequency of treatment with biologics, lower frequency of HLA*B27 and worse SF-36 MCS scores, compared to matched patients of European descent. Although they had lower prevalence of obesity, the prevalence of diabetes and hyperlipidemia was higher.

Table 1. Summary of the results of the matched-pair analyses between subjects of South Asian ethnicity and those of European ethnicity

Variable	South Asian (N=49)	Caucasian (N=147)	p-value
Active joint count	12.3 (12.8)	10.5 (8.0)	0.10
Tender joint count	10.2 (11.7)	7.5 (6.1)	0.01
Damaged joint count	4.3 (4.2)	6.0 (6.6)	0.06
No. of joints with grade 3 damage	9 (18.4%)	40 (27.2%)	0.09
No. of joints with grade 4 damage	1 (2.0%)	17 (11.6%)	0.003
HAQ	0.73 (0.75)	0.58 (0.59)	0.10
SF-36 MCS	43.9 (12.1)	46.4 (12.3)	0.03
Obesity	5 (17.9%)	34 (34.7%)	0.09
Diabetes	5 (11.1%)	7 (5.9%)	0.02
Hyperlipidemia	4 (9.3%)	3 (2.8%)	0.01
Biologics ever	8 (20.0%)	45 (40.9%)	0.0006
DMARDs ever	32 (72.7%)	78 (59.1%)	0.08
HLA-B*27	3 (8.6%)	23 (20.0%)	0.09

Conclusion: Although PsA patients of South Asian descent report higher HAQ scores, and have more tender joints, radiographic joint damage appears

to be less severe and they are less likely to be treated with biologic agents than patients of European descent. Although less likely to be obese, they have higher prevalence of diabetes and hyperlipidemia. Ethnic differences in disease manifestations may have an impact on long-term outcomes of patients with PsA.

Disclosure: V. Chandran, None; **A. Thavaneswaran**, None; **D. D. G. Gladman**, None.

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Severe Joint Damage in Psoriatic Arthritis: Mutilans and Ankylosis. Amir Haddad, Arane Thavaneswaran, Dafna D. Gladman Gladman and Vinod Chandran. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Patients with Psoriatic arthritis (PsA) who develop severe joint damage have severe functional disability and increased mortality risk. The most severe form of PsA is termed arthritis mutilans and is associated with severe erosions, osteolysis and pencil-in-cup change. Ankylosis is also a feature of severe PsA. The modified Steinbrocker method of scoring radiographic damage to peripheral joints in PsA recognizes grade 4 damage as severe damage, but does not explicitly distinguish between severe erosions, pencil-in-cup change, subluxation and ankylosis. We aimed to describe the prevalence and disease association of these features of severe joint damage in a cohort of patients with early PsA.

Methods: Patients presenting to a large PsA clinic with PsA duration of < 5years were identified. Patients are evaluated every 6–12 months and plain radiographs are obtained every 2 years. Radiographs are reviewed according to the modified Steinbrocker method by consensus of at least 2 rheumatologists. For this study radiographs that were scored as 4 were retrieved and rescored to indicate disorganization (4.0), subluxation (4.1), pencil-in-cup (4.2) and ankylosis (4.0). Subsequently, the clinical characteristics at first visit of patients who developed at least 1 joint with severe joint damage were compared to those without such damage.

Results: 664 patients who were enrolled within 5 years of diagnosis were the subjects of this study. 116/664 (17.5%) were observed to have at least one joint with 4.0, 4.1, 4.2 or 4.3 of the 42 scored. The demographic and disease characteristics at first visit of the patients who were observed to develop such damage compared to those who did not are reported in table 1. Patients with severe joint damage were older at diagnosis of psoriasis and had longer PsA duration, but shorter psoriasis duration. They had higher active and damaged joint counts and ESR. There was a trend towards higher prevalence of female sex, axial disease and HLA-B*27 in those with severe damage. Of the 116 patients observed to develop severe damage, 34 (29%), 63 (54%), 36 (31%), 58 (50%) patients were observed to have '4.0', '4.1', '4.2' and '4.3', respectively at baseline or during follow-up. The mean (sd) number of joints with '4.0', '4.1', '4.2' and '4.3', were 0.3 (0.7), 1.1 (2.1), 0.6 (2.0) and 0.7 (1.4), respectively. Only 15 (13%) patients were observed to have ankylosis without lysis. These patients had lower modified Steinbrocker score [mean, (sd) 31 (18) vs. 53 (43) p=0.001] compared to those with subluxation or pencil-in-cup change.

Table 1. Demographics and Disease Characteristics at baseline

Variable	Patients with severe joint damage N=116	Patients without severe joint damage N=548	p-value
Gender (Males)	58 (50.0%)	322 (58.8%)	0.08
Age	43.8 (13.9)	41.7(12.9)	0.11
Age at diagnosis of Psoriasis	33.9 (15.5)	29.0 (14.6)	0.002
Age at diagnosis of PsA	41.4 (14.1)	39.8 (13.0)	0.27
Duration of Psoriasis	9.9 (10.1)	12.7 (11.6)	0.02
Duration of PsA	2.3 (1.6)	1.9 (1.7)	0.02
ESR	30.2 (20.5)	20.9 (19.6)	<0.0001
PASI score	6.3 (9.1)	5.9 (8.4)	0.76
Active joint count	12.9 (10.5)	9.4 (8.7)	0.001
Swollen joint count	5.7 (5.7)	4.7 (5.1)	0.09
Damage joint count	5.8 (5.2)	3.1 (4.0)	0.0008
Axial disease	41 (35.3%)	148 (27.0%)	0.07
HLA B*27	21 (22.6%)	59 (14.0%)	0.06
Follow-up time (radiographic visits)	11.6 (9.3)	5.3 (7.4)	<0.0001

Conclusion: Patients with PsA who develop severe joint damage have higher disease activity at presentation. The most common form of severe joint

damage observed is subluxation. Only 13% have exclusive ankylosis. Further phenotypic characteristic of radiographic damage in PsA will facilitate genetic and mechanistic studies.

Disclosure: **A. Haddad**, None; **A. Thavaneswaran**, None; **D. D. G. Gladman**, None; **V. Chandran**, None.

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Clinical and Ultrasonographic Features of Nail Disease in Psoriasis and Psoriatic Arthritis. Amir Haddad, Arane Thavaneswaran, Vinod Chandran and Dafna D. Gladman Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: The purpose of this study was to investigate the association between clinical and unltrasonographic features of psoriatic nail disease and to identify specific nail features associated with psoriatic arthritis (PsA).
Methods: Patients with PsA and Psoriasis without arthritis (PsC) were recruited from prospective cohorts in a single centre. Healthy volunteers were also recruited. Subjects with co-existing OA or history of nail trauma were excluded. A detailed nail assessment according to the modified Nail Psoriasis Severity Index (mNAPSI) for the presence of onhycolysis, nail pitting, nail plate crumbling, leukonychia, splinter hemorrhages, nail bed hyperkeratosis and red spots in the lunula was completed for each participant. All participants underwent an ultrasound evaluation of the nail apparatus at each finger with detailed recording of loss of definition of the ventral or dorsal plates, thickness of the nail bed or matrix and the presence of increased vascularity in the nail bed or matrix using a 10-MHz linear array transducer. Doppler signal was standardized with a pulse repetition frequency of 400 Hz, a gain of 20 dB and a low wall filter. Descriptive analyses and comparisons were conducted using Kruskal Wallis for continuous variables and Fisher's exact test for categorical variables. Logistic regression analyses using GEE model was used to compare between the groups due to repeated observations for each patient.
Results: 10 patients were recruited into each group and the results are reported in the following tables:

Table 1. Demographic Characteristics (n=30) between Controls, PsC and PsA

Frequency (%) or Mean (sd)

Controls	Controls (n=10)	PsC (n=10)	PsA (n=10)	p-value
Gender (Males)	3 (30.0%)	9 (90.0%)	7 (77.8%)	0.02
Age	29.0 (4.4)	46.0 (16.1)	54.7 (12.6)	0.0006
Age at diagnosis of Psoriasis	–	33.0 (21.9)	33.4 (13.8)	0.60
Duration of Psoriasis	–	13.0 (13.9)	21.1 (11.7)	0.10
mNAPSI score	0	6.2 (5.8)	3.8 (4.6)	0.01

Table 2. Summary & Comparison of Fingers Affected by Nail Feature for the three groups

Nail Feature	Controls	PsC	PsA	p-value*	p-value**
Loss of definition of the ventral plate	6/100	24/100	29/100	<0.0001	0.42
Hyperechoioc focal involvement of the ventral plate	0/100	23/100	16/100	<0.0001	0.21
Thickening of both the and dorsal and ventral plates	0/100	8/100	2/100	0.005	0.052
Nail bed thickness (mm)	14.1 (1.2)	16.0 (2.9)	15.9 (3.0)	<0.0001	0.81
Nail matrix thickness (mm)	15.8 (0.92)	17.5 (2.9)	18.8 (3.0)	<0.0001	0.002
Nail bed vascularity	2/100	14/100	18/100	0.001	0.44
Nail matrix vascularity	16/100	30/100	34/100	0.01	0.54
Onycholysis and oil drop dyschromia (Some vs. none)	0/100	13/100	5/100	0.0005	0.048
Pitting Some vs. none	0/100	28/100	20/100	<0.0001	0.19
Nail bed crumbling (Some vs. none)	0/100	8/100	0/100	0.0003	0.004
Leukonychia	0/100	3/100	2/100	0.24	0.65
Splinter hemorrhage	0/100	0/100	0/100	NS	NS
Nail bed hyperkeratosis	0/100	0/100	0/100	NS	NS
Red spots in the lunula	0/100	0/100	1/100	0.37	0.32

P-value* is between the 3 groups, p-value** is between the PsC and PsA.

None of the nail's sonographic or clinical covariates were found to statistically different in between PsA and PsC groups after adjusting for repeated measurements.
Conclusion: This proof of concept study shows that ultrasounds can be used as a tool for assessment of psoriatic nail disease. Patients with psoriatic disease had increased nail bed and matrix thickness as well as vascularity compared to healthy controls. However, whether these microanatomical nail structures could be predictors for evolution of psoriatic arthritis is yet to be determined.

Disclosure: **A. Haddad**, None; **A. Thavaneswaran**, None; **V. Chandran**, Abbott Canada, 5; **D. D. G. Gladman**, Abbott Canada, 5.

1371

Predictors of Erosion-Free Psoriatic Arthritis. Zahi Touma, Arane Thavaneswaran, Vinod Chandran and D. D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: A number of patients with psoriatic arthritis (PsA) remain erosion-free despite years of disease. We aimed to determine the prevalence, characteristics and predictors of erosion-free patients (EFP) as compared to erosion-present patient (EPP) in PsA patients.
Methods: This is a retrospective analysis conducted on all PsA patients with at least a 10 year period of follow-up in single centre PsA cohort.
Radiographs at 1–2 year intervals were scored (modified Steinbrocker): 0-normal, 1-soft tissue swelling/osteopenia, 2-erosions (E), 3- E plus joint space narrowing and 4- total joint destruction. EPP was defined as any joint with ≥ grade 2 (EFP could not have erosions at any visit).
T-tests, Chi-squared and Fisher's exact test were used for comparison between groups. Baseline characteristics were used to predict the development of E with logistic regression models (reduced model using stepwise selection). The time to development of erosions was assessed with Kaplan-Meier estimator.
Results: Among 290 patients, 12.4% were EFP and 87.6% EPP. EFP were diagnosed with psoriasis at a younger age compared to EPP patients, 22.5±14.7 and 27.6±12.1 years respectively (p=0.02). Of the 243 EPP patients, 97 (39.9%) have no E at first visit and develop it later. The remaining 146 (60%) already had E at first visit. There was no statistically significant difference in ethnicities, gender, age at diagnosis of PsA and duration of psoriasis and PsA among groups.
At baseline, EPP displayed a greater number of actively inflamed joints (10.1±9.1) compared to EFP (4.8±5.3) (p=0.0007). 40.6% of EPP had damaged joints compared to 8.3% in EFP (p=0.0002). EPP had a higher BMI compared to EFP (p=0.03). More EPP were on NSAIDs and sulfasalazine; p=0.04 and p=0.02 respectively. EFP were all employed vs. 69.8% EPP (p=0.05). 93% of EPP had active joints as compared to 72% EFP (p<0.0001). Similar differences in characteristics among EPP and EFP were also present at the last follow-up visit. In particular EPP have a higher percentage of unemployment as compared to EFP; 25% vs. 52% respectively (p=0.02).
Univariate analyses showed that actively inflamed joint count (OR=1.12, p=0.001), damage joint count (OR=2.35, p=0.02) and use of DMARDs/NSAIDs (OR=2.73, p=0.02) were associated with the development of E. In the multivariate analysis actively inflamed joint count (OR=1.09, p=0.01) and damage joint count (OR=2.43, p=0.02) were predictive of the development of E whereas a longer duration of psoriasis at baseline decreased the odds of developing E (OR=0.96, p=0.03). The mean time to development of E was 2.96±5.23 years (Figure 1).
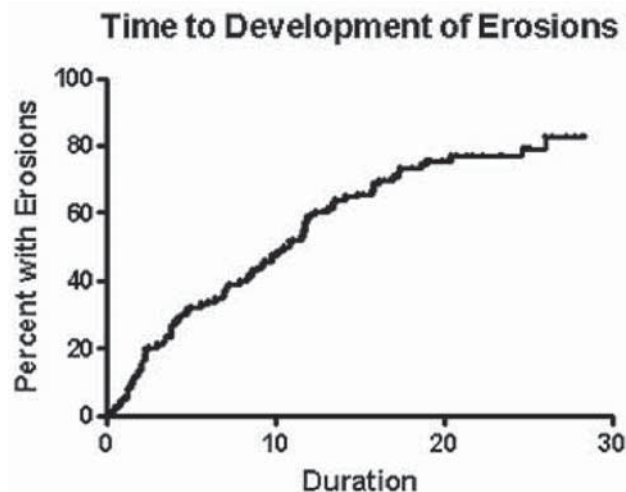
Figure 1. Time to Development of Erosions

Conclusion: Among patients with PsA followed for at least 10 years 12% never develop E.

Presence of actively inflamed and damaged joints at baseline increases the odds of development of E. A longer duration of psoriasis at baseline has a protective effect of development of E.

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Increased Participation in Daily Activities After 24 Weeks of Certolizumab Pegol Treatment of Axial Spondyloarthritis Patients, Including Patients with Ankylosing Spondylitis: Results of a Phase 3 Double-Blind Randomized Placebo-Controlled Study. Désirée van der Heijde[1], Jurgen Braun[2], Martin Rudwaleit[3], Oana Purcaru[4] and Arthur Kavanaugh[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Endokrinologikum Berlin, Berlin, Germany, [4]UCB Pharma, Braine, Belgium, [5]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Axial spondyloarthritis (axSpA) includes both ankylosing spondylitis (AS) and non-radiographic axial SpA (nr-axSpA). AS significantly affects patients' (pts) work productivity.[1] The impact of the entire spectrum of axSpA on work productivity is still poorly researched. RAPID-axSpA (NCT01087762) is the first report of the effect of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, on paid and household work productivity, and daily activities, in pts with axSpA.

Methods: Recruited pts had adult-onset active axSpA as defined by the ASAS criteria,[1] BASDAI ≥4, spinal pain ≥4 on a 10 point scale, CRP > upper limit of normal or sacroillitis on MRI. Pts must have failed ≥1 NSAID. Up to 40% of pts could have experienced secondary failure to 1 previous anti-TNF. The pt population reflected the broad axSpA population, including AS pts also meeting the modified New York criteria and nr-axSpA pts who met the ASAS MRI or clinical criteria. Pts were randomized 1:1:1 to PBO, or CZP 400mg at Week (Wk) 0, 2 and 4 (loading dose, LD) followed by either CZP 200mg every 2 wks (Q2W) or CZP 400mg every 4 wks (Q4W). Pts receiving PBO who failed to achieve an ASAS20 response at both Wks 14 and 16 were rescued and randomized at Wk16 to receive CZP 200mg Q2W or CZP 400mg Q4W following LD. The arthritis-specific Work Productivity Survey (WPS) assessed the impact of axSpA on workplace and household productivity. WPS was administered every 4 wks. WPS responses (last observation carried forward imputation) were compared between treatment arms using a non-parametric bootstrap-t method.

Results: 325 pts were randomized. 63.2%, 69.4%, and 74.8% of pts in the PBO, CZP 200mg Q2W, and CZP 400mg Q4W treatment groups were employed at study BL; 11%-13% of pts were unable to work due to axSpA; 4%-9% were students; 3%-8% were retired. Treatment groups were comparable at BL in terms of workplace and household productivity. At BL the burden of axSpA on absenteeism, presenteeism, household productivity and social activities was high (Table). Compared to PBO, pts employed in both CZP groups reported reduced absenteeism, presenteeism, and axSpA interference with work from Wk4 through to Wk24 (Table). CZP groups also reported greater reductions vs PBO in days lost of household work and of family/social/leisure activities per month, in days with reduced household productivity and in axSpA interference with household duties as early as Wk4 through to Wk 24 (Table).

Table. Work and household productivity in RAPID-axSpA study (FAS population, LOCF data)

WPS		PBO	CZP 200mg Q2W	CZP 400mg Q4W
Productivity at workplace[a]				
	BL	67	77	80
n	Wk4	68	78	79
	Wk24	66	80	81
	BL	2.4	2.3	1.4
Work days missed due to arthritis per month	Wk4	1.9	1.4	0.8*
	Wk24	2.0	1.1	0.6*
Days with work productivity reduced by ≥50% due to arthritis per month[b]	BL	5.3	5.8	4.7
	Wk4	3.2	2.7	3.2
	Wk24	4.4	2.4	2.7
	BL	4.8	4.5	4.6
Rate of arthritis interference with work productivity per month[c]	Wk3.9	3.1*	3.1*	
	Wk24	3.5	2.2*	2.0*

		All	107	111	107
Productivity at home and daily activities					
n	BL	6.9	5.8	4.7	
Household work days missed due to arthritis per month	Wk4	5.4	3*	3.2*	
	Wk24	5.6	2.3*	2.2*	
Household work days with productivity reduced by ≥50% due to arthritis per month[b]	BL	5.3	4.4	3.6	
	Wk4	6.5	5	4.9	
	Wk24	5.9	3.5*	3*	
Days missed of family, social, or leisure activities due to arthritis per month	BL	5.3	4.4	3.6	
	Wk4	4.1	2.3*	2.4*	
	Wk24	3.0	1.1*	1.9	
Days with outside help hired due to arthritis per month	BL	2.7	2	1.5	
	Wk4	2.2	1.6	1.1	
	Wk24	1.8	1.1	0.6*	
Rate of arthritis interference with household work productivity per month[c]	BL	5.0	5	4.6	
	Wk4	4.4	3.6*	3.3*	
	Wk24	4.2	2.4*	2.2*	

[a]Based only on employed pts; [b]Does not include work days missed counted in the previous question;
[c]0–10 scale, where 0 = no interference and 10 = complete interference; *p-value ≤0.05 vs PBO

Conclusion: CZP improved workplace productivity in pts with axSpA by reducing absenteeism, presenteeism and axSpA interference with work. CPZ also improved household productivity and increased participation in social and daily activities.

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Influence of Early Onset On the Clinical Characteristics and Prognosis of Ankylosing Spondylitis. Maria Aparicio[1], Jesús Rodríguez-Moreno[1], Paula Estrada[1], Irene Martín-Esteve[1], Laura López-Vives[1], Vicenç Torrente[2], Jordi Anton[3], Joan Miquel Nolla[1] and Xavier Juanola[1]. [1]Hospital Universitari de Bellvitge, Barcelona, Spain, [2]Hospital Sant Joan de Déu, Barcelona, Spain, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: To determine the influence of early onset (≤ 16 years) on the clinical characteristics and prognosis of ankylosing spondylitis (AS).

Methods: We revised patients diagnosed with AS according to the New York criteria included in our database. Age at symptom onset was taken from the patient's clinical history. Other data recorded were current: age, time of evolution, gender, form of onset, form of evolution, HLA B27, BASRI (cervical, lumbar column, sacroiliacs and hips), metrology (Schober test, modified Schober test, thoracic expansion and occipuci-wall distance), VSG and PCR (last measurements), uveitis development, surgery of the locomotive apparatus and treatment provided with special attention to the need for biological drugs in order to establish prognosis.

To ensure that the differences were no solely related to the time of evolution of the disease, we created a Control Group (CG) comprising, two randomly paired patients for each patient with early onset (EO), with an age of onset between 20 and 30 years and a time of evolution of the disease (± 5 years) similar to those with EO. The results were analyzed by means of the SPSS 15.0 statistical package. The differences between EO and CG were studied by means of χ^2 and ANOVA or Fisher's test depending on the characteristics of the variables.

Results: We revised 324 patients with EA; 35 (10.8%) had an age of onset ≤ 16 years. The chart shows the main characteristics of the patients from both groups. Significant differences in the development of uveitis and HLA B27 positivity were observed, as well as a tendency towards greater hip involvement and indication for hip prosthesis in the EO group.

	≤ 16 years (n= 35)	> 16 years (n = 66)	p		≤ 16 years (n = 35)	< 16 years (n = 66)	p
Age of onset (years)	14.9 ± 2.2	27.1 ± 9.1	<0.000	Form axial onset	77%	84%	ns
Male gender	89%	81%	ns	Form axial evolution	60%	72%	ns
Time of evolution (years)	34.6 ± 13.4	31 ± 12.7	ns	HLA B27 positive	100%	85%	< 0.05
Axial BASRI (cm)	6.4 ± 3.4	7 ± 3.3	ns	Uveitis	40%	17%	< 0.05
Hips BASRI (cm)	1.38	0.87	ns	Prosthesis indication	14%	5%	ns
Schober (cm)	2.7 ± 2.5	2.6 ± 1.6	ns	AINE use continuos	49%	49%	ns
Modified Schober (cm)	4.2 ± 2.1	3.8 ±3.1	ns	FAME use	29%	23%	ns
Thoracic expansion (cm)	4.7 ± 2	3.7 ± 1.6	ns	AntiTNF actual o pass use	29%	23%	ns
Occip-wall (cm)	5.2 ± 8.1	7.1 ± 7.6	ns				

Conclusion: AS patients with early onset were more likely to be positive for HLA B27 and to present more ocular involvement (uveitis). AS patients with EO also presented trend towards more serious radiological damage in the hips and a higher indication for hip prosthesis, although the differences were not significant.

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Value of C-Reactive Protein Level At Diagnosis of Psoriatic Arthritis in Predicting the Future Need for Treatment with Tumor Necrosis Factor-á Inhibitors. Yair Molad[1] and Shachaf Ofer-Shiber[2]. [1]Beilinson Hospital, Rabin Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Petah-Tikva, Israel, [2]Beilinson Hospital, Rabin Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel

Background/Purpose: To determine the value of acute-phase reactant levels at diagnosis of psoriatic arthritis in predicting the risk of failure of conventional treatment with disease-modifying anti-rheumatic drugs (DMARDs) and the–consequent need for biologic treatment with a tumor necrosis factor (TNF) inhibitor.

Methods: Clinical, laboratory, and treatment data were collected from the medical files of a real-life inception cohort of 71 consecutive patients diagnosed with psoriatic arthritis (CASPAR criteria) in 2000–2011 at the rheumatology clinic of a tertiary medical center. A logistic regression model was used to identify laboratory variables associated with TNF inhibitor use during the disease course.

Results: The cohort included 38 female (53.5%) and 33 male patients of mean age 41 ± 10.4 years; 66 (93%) Jewish and 5 (7%) Arabic. Mean disease duration was 11.56 ± 6.58 years. The most common clinical feature was symmetric polyarthritis (40.8%). All patients were treated with one or more DMARDs, mainly methotrexate (81.6%). Thirty-seven patients (52.11%) had an inadequate response and received at least one TNF inhibitor, at the discretion of the attending rheumatologist. C-reactive protein (CRP) level at diagnosis was positively correlated with need for a TNF inhibitor (p=0.009; hazard ratio = 1.8 95% CI 1.27–1.85). Patients with CRP >0.9 mg/dl at diagnosis started biologic treatment significantly earlier in the disease course than patients with a lower level (p=0.003, hazard ratio = 2.62 95% CI 0.393–2.5).

Conclusion: In patients with psoriatic arthritis, CRP ≥0.9mg/dl at diagnosis significantly predicts an inadequate response to conventional DMARDs and the probability that a TNF inhibitor will be needed to achieve disease control.

Disclosure: Y. Molad, None; **S. Ofer-Shiber**, None.

1375

Depression and Anxiety in Psoriatic Disease: Prevalence and Associated Factors. Emily McDonough[1], Arane Thavaneswaran[2], Adele Carty[3], Suthar-shini Shanmugarajah[2], Renise Ayearst[2], Lihi Eder[4], Vinod Chandran[5], Cheryl Rosen[2] and Dafna Gladman[2]. [1]University of Toronto, Ontario, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Toronto Western Hospital, Toronto, ON, [4]Carmel Medical Center, Haifa, Israel, [5]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Psoriatic arthritis (PsA) affects approximately 30% of patients with psoriasis and has the potential to cause severe joint damage. Research into the prevalence of depression and anxiety in PsA patients, and the contribution of joint disease to mental health in psoriatic disease, is limited. The objectives were: 1) To determine the prevalence of depression and anxiety in PsA patients and identify associated demographic and disease-related factors. 2) To determine if there is a difference between patients with PsA and those with psoriasis without PsA (PsC).

Methods: Consecutive patients attending PsA and PsC clinics were assessed for depression and anxiety using the Hospital Anxiety and Depression Scale (HADS). Patients with PsA satisfied CASPAR criteria and those with PsC had dermatologist confirmed psoriasis and PsA excluded by a rheumatologist. Patients underwent a clinical assessment according to a standard protocol and completed questionnaires assessing their health and quality of life. T-tests, ANOVA, univariate, and multivariate models were used to compare depression and anxiety prevalence between patient cohorts and determine factors associated with depression and anxiety.

Results: A total of 306 PsA and 135 PsC patients were assessed. The mean age of PsA and PsC patients was 53.8 and 52.4 years respectively. There were significantly more men in the PsA group (61.4% vs. 48% for PsC) and they were more likely to be unemployed (40% vs. 29.1%). The prevalence of both anxiety and depression was higher in PsA patients (36.6% and 22.2% respectively) compared to PsC (24.4% and 9.6%) (p = 0.012, 0.002). Factors associated with a higher likelihood of depression and/or anxiety included unemployment, female gender, and higher active joint count. Patient reported factors such as disability, pain, and fatigue were highly correlated with an increased likelihood of both depression and anxiety (p < 0.0001). In the univariate analyses, the protective factors for depression included having only PsC, drinking socially, and being employed. Factors associated with a higher odds ratio (OR) for depression included current smoking, a higher pain rating, higher patient reported physical disability, and a higher level of fatigue. In the multivariate reduced model, employment was protective for depression (OR 0.36) and a 1 unit increase on the fatigue severity scale (FSS) was associated with depression (OR 1.5).

Conclusion: The rate of depression and anxiety is significantly higher in PsA patients than in PsC patients. The factors most closely associated with higher rates of depression and anxiety are those in which patients express the negative effects PsA has on their quality of life, such as ratings of pain, disability and fatigue. The major limitation of this study is that it is not able to determine causation. Nonetheless, these results indicate the importance of addressing patients' perceptions of their own health and functioning, as well as objective measures of disease severity, when treating depression and anxiety in psoriatic disease. A deeper understanding of these factors is important for planning and evaluating future treatments.

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Development of A Health Index for Patients with Ankylosing Spondylitis - First Steps of A Global Initiative Based On the ICF Guided by ASAS. Uta Kiltz[1], Désirée van der Heijde[2], Annelies Boonen[3], Alarcos Cieza[4], Gerold Stucki[5], Muhammad Asim Khan[6], Walter P. Maksymowych[7], Helena Marzo-Ortega[8], John D. Reveille[9], William Taylor[10], Cristina Bostan[11] and Jügen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University Hospital Maastricht, Maastricht, Netherlands, [4]Munich, Germany, [5]University of Lucerne, Lucerne, Switzerland, [6]CASE at MetroHealth Med Center, Cleveland, OH, [7]University of Alberta, Edmonton, AB, [8]University of Leeds, Leeds, United Kingdom, [9]Univ of Texas Health Science Center at Houston, Houston, TX, [10]University of Otago, Wellington, New Zealand, [11]Paraplegic Research Unit, Nottwil, Switzerland

Background/Purpose: The burden of ankylosing spondylitis (AS) can be considerable. The patients suffer from pain, stiffness and fatigue, and they are limited in their activities and restricted in social participation. The International Classification of Functioning, Disability and Health (ICF), a model to systematically classify and describe functioning, disability and health in human beings, has been used by the Assessments of SpondyloArthritis international Society (ASAS) as a basis to define a core set of items that are typical and relevant for patients with AS. However, no ICF-based patient-reported outcome measure has been developed for AS patients. The objective is To develop a measure to assess the overall impact of AS on health based on the ICF Core Set for ankylosing spondylitis (add the ref) which can be

considered as the external standard of categories that are relevant and typical for AS and contains categories within the bio-medical as well as contextual part of the ICF model for health.

Methods: Development is being performed in five phases. *I* development of an item pool using categories of the ICF Core Set for AS as the domain structure; *II* Item exploration based on Rasch analyses for the items fitting the bio-medical categories and correlation analyses for the contextual factors; *III* - Agreement on item reduction; *IV* Validation of the draft version; *V* Agreement on a final version

Table 1. Phases of development for the ASAS Health Index

	Phase	Objectives	Methods
I	Preparatory	Development of a pool of items representing the categories of the Comprehensive ICF Core Set	Linkage of various assessment tools for functioning and health to ICF categories
II	1st postal patient survey	Item reduction	Factor Analysis, Rasch Analysis, Spearman rank correlation coefficient
III	Expert consultation	Agreement on item reduction	Nominal Consensus Process
IV	2nd postal patient survey	Validation of the draft version and further item reduction	Testing psychometric properties Rasch Analysis
V	Consensus Meeting	Agreement on a final version	Nominal Consensus Process

Results: Phase 1: The item pool contained 251 items in 44 categories. It was formed from various instruments (identified through literature search) which focus on symptoms and functioning in patients with AS. Phase 2: An international cross sectional study with 1915 AS patients (mean age 51.2±3.6, 53% male, BASDAI 5.5±2.4) was conducted in 4 continents. In 82 items of the *functioning* part a unidimensional scale, fit to the Rasch model and absence of Differential Item Function could be confirmed. 32 items of the *environmental factors* part showed a significant correlation between person score and ICF category (correlation coefficient between 0.04–0.45). Phase 3: Based on results of the analyses in step 2, an expert committee selected 50 functioning items and 16 environmental factor items using predefined selection criteria (clinimetric properties, ease of wording, coverage of the whole range of ability). Phase iV: The draft version are being tested in a 2nd cross sectional survey. Rasch analysis will help to choose those items which represents the full spectrum of functioning

Conclusion: The item pool has been successfully reduced to 66 items. In covering much of the ICF Core Set for AS, these items represent a whole range of abilities of patients with AS. This draft version will be tested in a second survey to create a first version of the ASAS Health Index. The final measure can be used in clinical trials and cohort studies as a new composite index that captures relevant information on the health status of the patients.

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Prevalence of Spondyloarthritis-Related Comorbidities, Osteoporosis and Fractures in Ankylosing Spondylitis: a Systematic Literature Review. Carmen Stolwijk[1], A.M. Van Tubergen[1], Jose Dionisio Castillo-Ortiz[2] and Annelies Boonen[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico

Background/Purpose: Comorbidities, both related and unrelated to the concept of spondyloarthritis (SpA), are common in patients with ankylosing spondylitis (AS) and may have substantial influence on health outcomes. However, data on the prevalence of these comorbidities in AS vary substantially. Objective of the study was to review the literature on the prevalence of SpA-related comorbidities uveitis, psoriasis and inflammatory bowel disease (IBD), as well as on prevalence of osteoporosis and vertebral fractures in patients with AS.

Methods: Medline, Embase and Cochrane were searched systematically up to November 2011, supplemented by a hand search of references. Specific MeSH headings and key words were used to identify all relevant studies without restriction of languages. Articles were eligible if reporting original data on the prevalence of one of the above mentioned comorbidities in studies on adult patients with AS. Study quality was assessed independently by 2 authors using a predefined criteria list. Demographic and prevalence data were extracted and studies were combined to express prevalence with 95% confidence intervals (CI) weighted for the number of patients included in the studies.

Results: Out of 7817 studies initially retrieved, 188 met the inclusion criteria. Additionally, 13 studies were found by hand search. The prevalence of uveitis, psoriasis, IBD, osteoporosis and vertebral fractures could be calculated in respectively 137 (40141 patients), 53 (25695 patients), 66 (30410 patients), 24 (2786 patients), and 17 articles (2285 patients). The overall (weighted) mean age was 43.9 (SD 6.9) years, mean disease duration 16.7 (SD 6.2) years and 63.7% were men. The weighted prevalence of uveitis was 30.3% (95% CI 30.2–30.4) for a mean disease duration of 16.4 (SD 6.4) years but increased with longer disease duration (from 19.4% for a disease duration of <10 years to 36.5% for a duration of >20 years). Prevalence of uveitis was also higher for studies using self-report compared to medical records (39.2% vs. 27.4%, p<0.001). Weighted prevalence of psoriasis was 11.3% (95% CI 11.2–11.4) for a mean disease duration of 18.0 (SD 6.3) years and prevalence of IBD was 7.2% (95% CI 7.1–7.2) for a mean disease duration of 17.8 (SD 6.4) years, without a clear relation to disease duration for both comorbidities. Prevalence of osteoporosis was 20.5% (19.4–21.6) in the lumbar spine, 10.9% (10.4–11.4) at the femoral neck and 29.2% (28.2–30.1) at both anatomical sites for a mean disease duration of 12.4 (SD 5.2) years in studies that screened for radiological evidence. The overall prevalence of osteoporosis increased with longer disease duration. Osteoporosis was diagnosed in 3.4% according to medical records data (936 patients). Vertebral fractures were present on 21.8% (21.0–22.4) of the radiographs for a mean disease duration of 19.5 (SD 6.1) years, and prevalence was 5.8% in studies using self-report (1071 patients).

Conclusion: SpA-related comorbidities, osteoporosis and vertebral fractures are very common in patients with AS but may vary with disease duration and method of investigation. Given the high prevalence, attention for comorbidities in relation to outcome in AS is recommended.

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Validity of Ankylosing Spondylitis Disease Activity Score (ASDAS) in Patients with Early Spondyloarthritis. Cruz Fernández-Espartero[1], Eugenio De Miguel[2], Milena Gobbo[3], Carmen Martínez[4], Miguel A. Descalzo[3], Estíbaliz Loza Sr.[5] and Esperanza Group[6]. [1]Hospital Universitario de Móstoles, Madrid, Spain, [2]Hospital Universitario La Paz, Madrid, Spain, [3]Spanish Society of Rheumatology, Madrid, Spain, [4]Sociedad Española de Reumatología, Madrid, Spain, [5]Research Unit. Sociedad Española de Reumatología, Madrid, Spain, [6]Madrid

Background/Purpose: Recently, a Working Group of the SpondyloArthritis International Society (ASAS) has proposed a composite disease activity score, the Ankylosing Spondylitis Disease Activity Score (ASDAS), for patients with ankylosing spondylitis (AS), for improved and feasible measures of disease activity and treatment response in patients with spondyloarthritis (SpA).

Objective: To evaluate the validity of the Ankylosing Spondylitis Disease Activity Score (ASDAS) as clinical tool for measurement of disease activity in early spondyloarthritis (SpA) in comparison with conventional clinical measures of disease activity. To assess the discriminative ability and correlation of the ASDAS and Bath Ankylosing Spondylitis Activity Disease Activity Index (BASDAI) with disease activity in early SpA.

Methods: Patients with early SpA were selected from ESPeranza database (n=676). To test concurrent validity of the indices, correlations of the two indices with activity variables were calculated in ESPeranza database. Patients were categorised into high and low disease activity states based on patient and physician global assessment scores and physician's decision to start on a disease-modifying anti-rheumatic drug or tumour necrosis factor blocker. Discriminatory ability of the indices was compared using the approach of standardised mean difference between subgroups of patients with high vs low disease activity.

Results: ASDAS-B and C showed good correlation with BASDAI (0.79, 0.74, p<0.001). Both scores correlated well with disease activity as reflected by the patient global assessment (BASDAI 0.71, ASDAS-B 0.70, ASDAS-C 0.70, p <0.001) and the physician global score (r=0.44 for BASDAI, r=0.46 for ASDAS-B, r=0.47 for ASDAS-C, p <0.001). CRP and ESR showed poor correlation with patient- and physician-derived disease activity scores.

ASDAS and BASDAI scores show good and moderate discriminative ability with different constructs of disease activity.

Conclusion: ASDAS is a disease activity index valid in early Spa. ASDAS and BASDAI scores show good and moderate discriminative ability and correlation with different constructs of disease activity. In early Spa, ASDAS showed a slight superiority to BASDAI in its ability to discriminate between high and low disease activity states.

1379

Ultrasonographic Is More Sensitive Than Traditional Clinical Evaluation in the Detection of Hands and Wrists Synovitis and Digital Soft Tissue Involvement in Early Psoriatic Arthritis. Francesca Bandinelli[1], Valentina Denaro[1], Francesca Prignano[2], Diletta Bonciani[2], Ledio Collaku[3] and Marco Matucci-Cerinic[1]. [1]University of Florence, Florence, Italy, [2]Florence, Italy, [3]University of Tirana, Tirana, Albania

Background/Purpose: Background: Clinical measures are widely used in established psoriatic arthritis (PsA) but in early phase of disease, often fail to identify the joint and tendons involvement. Purpose: To investigate the ultrasonography (US) abnormalities in hands and wrists of early PsA patients and to compare them with clinical evaluation

Methods: We performed a retrospective study on 112 early PsA (onset of inflammatory symptoms lower than one year) in the period 2008–2010, diagnosed with CASPAR criteria (1).

Data were carried out by the analysis of medical records of all patients, completed of demographic data, historical information, clinical (swollen joints and dactylitis count) and MyLab70 Xview (linear probe 15 MHz and PFR 1 Mhz) and US (Power doppler [PD] positive synovitis, erosions, tenosynovitis and PD in soft tissue around flexor finger tendons) hands and wrists assessment.

Results: Out of 224 wrists and 1120 MCP, 1120 PIP and 1120 DIP totally observed, synovitis was more frequently found on wrist (50/224; 22,3%) and US resulted more sensitive than clinical evaluation (swollen joints): in wrists 50/224 (22,3%) vs 42/224 (18,7%), in MCP 28/1220 (2,5%) vs 11/1120 (1%), in IPP 24/1120 (2,1%) vs 15/1120 (1,3%), in IPD 3/1120 (0,3%) vs 1/1120 (0,09%). Also erosions were present only in MCP (mostly II e III MCP) in 10/1120 joints (0,9%). At US, PD signal in soft tissue around tendons (68/1120, 6,1%) was more frequent than tenosynovitis of flexors (29/1120, 2,6%) and were both found also in patients without clinical dactilitis (55/68 PD [80,8] of soft tissue and 18/29 [62%] of tenosynovitis).

Conclusion: US showed more frequently synovitis of wrists but also erosions and PD signals in soft tissue are present in early phase of PsA. In all cases, US seemed more sensitive than clinical evaluation for synovitis and dactilytis.

Reference

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1380

A Spondyloarthritis Research Consortium of Canada Score Cut-off ≥3 As Best Match for the Assessment of Spondyloarthritis International Society Definition of a Positive MRI of the Sacroiliac Joints. Rosaline van den Berg, Manouk de Hooge, Victoria Navarro-Compán, Monique Reijnierse, Floris van Gaalen, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The definition of a 'positive' or 'negative' MRI of the sacroiliac joints (MRI-SIJ) according to ASAS is recommended for use in daily practice[1]. However, in several clinical trials the Spondyloarthritis Research Consortium of Canada (SPARCC)-score is used[2]. It would be useful to know which SPARCC-score is the best cut-off value as surrogate for the ASAS definition. Therefore, we investigated which SPARCC cut-off value best matches the ASAS definition for a positive MRI-SIJ.

Methods: All MRI-SIJs of two time points of patients included in the SPondyloArthritis Caught Early (SPACE)-cohort in the Leiden University Medical Center (LUMC) were scored independently by 3 readers. The readers, blinded to the time sequence, scored the MRI-SIJs according to the ASAS definition (ASAS-pos) and the SPARCC-score. An MRI-SIJ was marked ASAS-pos if 2/3 readers scored positive. In this analysis, mean SPARCC-scores of the readers that also scored ASAS-pos for that particular case were used. Cross-tabs were used to analyse agreement between several SPARCC-score cut-off values (≥1, ≥2, ≥3 and ≥4) and ASAS-pos, which served as external standard in this comparison.

Results: All available MRI-SIJs were used (n=238 in total; n=148 baseline MRI-SIJs; n=90 follow-up MRI-SIJs). The results of the different tested SPARCC cut-off values are presented in the table. A SPARCC cut-off value ≥1 resulted in 39 (16.4%) false-positive classifications and a cut-off value ≥2 resulted in 11 (4.6%) and both cut-off values had no false-negative classifications compared to ASAS-pos. A SPARCC cut-off value ≥3 resulted in 1 (0.4%) false-positive classification and 4 (1.7%) false-negative classifications, and a SPARCC cut-off value ≥4 resulted in 9 (3.8%) false-negative and 1 (0.4%) false-positive classifications. We found very similar results if baseline MRI-SIJs and follow-up MRI-SIJs were analysed separately.

	ASAS negative, n (%)	ASAS positive, n (%)
SPARCC <1, n (%)	143 (60.1)	0 (0.0)
SPARCC ≥1, n (%)	39 (16.4)	56 (23.5)
Agreement		**83.6%**
SPARCC <2, n (%)	171 (71.9)	0 (0.0)
SPARCC ≥2, n (%)	11 (4.6)	56 (23.5)
Agreement		**95.4%**
SPARCC <3, n (%)	181 (76.1)	4 (1.7)
SPARCC ≥3, n (%)	1 (0.4)	52 (21.8)
Agreement		**97.9%**
SPARCC <4, n (%)	181 (76.1)	9 (3.8)
SPARCC ≥4, n (%)	1 (0.4)	47 (19.7)
Agreement		**95.8%**

Conclusion: SPARCC cut-off values of ≥2, ≥3 or ≥4 have all high percentages of correctly classified patients (95.4%, 97.9% and 95.8%, respectively). A SPARCC cut-off value ≥3 shows the most balanced misclassification and the highest agreement with the ASAS definition for a positive MRI-SIJ.

References

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1381

Non-Radiographic Spondyloarthritis Has Greater Work Instability Than Other Spondyloarthritis Subtypes in a National Database. Sherry Rohekar[1], Robert D. Inman[2], Renise Ayearst[3], Proton Rahman[4], Walter P. Maksymowych[5] and Dafna D. Gladman[6]. [1]St. Joseph's Hospital, London, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON, [4]Memorial University, St. Johns, NF, [5]University of Alberta, Edmonton, AB, [6]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON

Background/Purpose: Clinical subsets of spondyloarthritis (SpA), such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA) can be associated with significant impact on work performance and attendance. Prior to becoming completely work disabled, patients' functional abilities do not match their work demands. This period of time is one of work instability (WI). The aim of this study was to determine the characteristics of WI in a large population of patients with SpA.

Methods: Patients were recruited from two large, well established cohorts of AS and PsA. WI was evaluated using a validated questionnaire, the AS-WIS, in which higher scores denote more WI, which may be stratified into low, medium and high risk of future job loss. Standard protocols were completed at the time of completion of the AS-WIS which included a detailed history, physical examination, physician-reported outcome measures and patient-reported outcome measures.

Results: 414 patients responded (222 PsA, 160 AS, 18 undifferentiated SpA [uSpa], 12 non-radiographic SpA [nr-axSpA] and 2 reactive arthritis [ReA]). Mean age was 47.2 (SD 14.4), 66.9% male. Mean duration of PsA was 17.4 years; AS was 11.9 years. Mean WIS scores were low in AS (8.0, SD 6.1), PsA (6.7, SD 6.0), ReA (7.5, SD 9.2) and uSpA (8.0, SD 6.9). However, those with nr-axSpA had significantly greater WIS scores than the other groups, placing them in the moderate risk category (mean 12.6, SD 6.6). Higher WIS scores were significantly correlated with female gender, lower education, lung disease, gastrointestinal (GI) disease, diabetes, peripheral joint involvement, NSAID use, tender joint count, fibromyalgia tender point count (FMTP), MD global assessment of disease activity, EQ5D, Dermatology Life Quality Index, pain, stiffness, Health Assessment Questionnaire, Fatigue Severity Score, Bath AS-Global, Bath AS Disease Activity Index, Bath AS Functional Index, AS Quality of Life, Functional Assessment of Chronic Illness Therapy, SF-Physical Component Scale, SF-Mental Component Scale, and patient global assessment of disease activity. Linear regression revealed that sex, lower education level, history of GI disease, diabetes, NSAID use and FMTP were significantly associated with higher WIS scores. Multinomial logistic regression was carried out on WIS risk level (low, medium or high) with low risk as the reference category. Medium WIS risk scores were significantly associated with education level, history of GI disease, diabetes, NSAID use and FMTP. High WIS risk scores were significantly associated with education level and history of GI disease.

Conclusion: WI was significantly higher in those with nr-axSpA than other types of SpA, suggesting that these patients have a greater mismatch between their functional abilities and job demands. Education level, history of GI disease, NSAID use and higher FMTP were associated with higher levels of WI. The highest risk of WI was associated with education level and history of GI disease.

1382

A Comparison of Three Methods of Measuring Intermalleolar Distance in Patients with Ankylosing Spondylitis. Buse Ozata[1], Burak Uyar[2], Dilek Solmaz[2], Ismail Sari[2], Servet Akar[3] and Nurullah Akkoc[4]. [1]Dokuz Eylul University School of Medicine, Izmir, [2]Dokuz Eylul University School of Medicine, Izmir, Turkey, [3]Dokuz Eylul University School of Medicine Department of Internal Medicine Division of Rheumatology, Izmir, Turkey, [4]Dokuz Eylul University School Of Medicine, Department Of Internal Medicine, Division Of Rheumatology, Izmir, Turkey

Background/Purpose: Involvement of the hips are relatively common in AS and associated with a higher degrees of disability and worse prognosis. The measurements of spinal mobility could be used for predicting clinical involvement and monitoring disease severity. In this regard, intermalleolar distance (IMD) < 100 cm suggests hip disease in AS. There are two reccommended methods of measuring IMD. First, distance between the two medial malleoli is measured, with the patient lying in a supine position with the hips fully abducted. Second, the patient stands and separates the legs as far as possible and the distance between the medial malleoli is measured. Alternatively, some physicians measure IMD in sitting position, while keeping knees and the legs straight in contact with the resting surface, patient is then asked to take legs as far apart as possible, and the distance between the medial malleoli is measured. Today, it is not known whether these three methods are in agreement with each other. In this study, we evaluated the agreement of IMD measurement methods performed during standing, sitting and supine positions.

Methods: In total of 61 consecutive AS patients (44.1±12.3 years; 35 male, and 26 female), were included in the study. Each patient was examined independently by two observers. Reproducibility of the methods and reliability of observers were evaluated by means of the single measures intraclass correlation coefficient (ICC) values. For the analysis of intra- and interobserver variability, ten randomly chosen patients were reexamined by the observers on two different occasions (2 weeks apart). An ICC value of > 0.75 indicated good agreement.

Results: The three measurement methods of IMD showed good agreement between each other (Table 1). The ICCs obtained by each observer were as follows: 1- measurements performed by the observer 1: 0.81 (95% CI= 0.73–0.88), and 2- measurements performed by observer 2: 0.81 (95%CI= 0.72–0.87). Both intra- and interobserver reliability of the observers also showed good agreement (Table 1).

Table 1. Comparison of agreement between three methods of IMD measurements and intra- and inter-observer reliability of the examiners.

	Observer 1	Observer 2
Comparison of agreement between three methods of IMD measurements	0.81 (0.73–0.88)	0.81 (0.72–0.87)
Intra-observer reliability of observers		
Supine	0.98 (0.91–0.99)	0.99 (0.97–0.99)
Standing	0.97 (0.88–0.99)	0.99 (0.97–0.99)
Sitting	0.88 (0.6–0.97)	0.98 (0.94–0.99)
Inter-observer reliability of observers		
Supine		0.96 (0.85–0.99)
Standing		0.99 (0.98–0.99)
Sitting		0.99 (0.97–0.99)

Conclusion: In this study we showed that IMD measurements (supine, standing and sitting) were in good agreement with each other. It is not of note that this finding obtained independently by both observers who had also good intra- and interobserver reliability. According to the results of our study investigators can reliably use any IMD measurement methods in their studies.

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The Burden of Ankylosing Spondylitis and the Cost-Effectiveness of Anti-Tumor Necrosis Factor α Agents in Romania. Ioan Ancuta[1], Catalin Codreanu[2], Ruxandra Ionescu[3], Magda Parvu[4] and Mihai Bojinca[1]. [1]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [2]"Dr. I. Stoia" Center for Rheumatic Diseases, Bucharest, Romania, [3]Clinic Hospital Sf. Maria, Bucharest, Romania, [4]"N.Gh. Lupu" Clinical Hospital, Bucharest, Romania

Background/Purpose: Ankylosing Spondylitis (AS) usually affects young males, severely impairing their quality of life. Chronic treatment of AS using anti-TNF α agents is costly and represents a main concern for the national health insurance system, currently covering costs for three drugs: Adalimumab (ADA), Etanercept (ETA) and Infliximab (INF). Limited budget prompted the need to find optimal therapeutic approach. We aimed to identify the best cost/efficiency ratio when comparing clinical outcomes of anti-TNF α agents ADA/ETA/INF and to develop future treatment guidelines.

Methods: In a longitudinal, population-based study we retrospectively investigated, as of June 2012, the clinical files of 320 patients treated with ADA (n=70, 40 mg/2 weeks), ETA (n=50, 50 mg/week) and INF (n=200, 5 mg/kg at week 0, 2 and 6 then at every 6 to 8 weeks), out of 1859 AS patients on record in database (2008–2012) of state health insurance system. Costs were calculated in local currency (RON), according to standard clinical practice prescribed doses and reimbursed drug list prices, no infusions or other additional costs were included. We used multiple analysis of variance (MANOVA) and chi-squared tests to analyze statistically significant differences (p<0.05) in treatment efficacy.

Results: Concomitant use of disease modifying therapy (DMARD) was similar in all groups. Treatment efficacy was assessed and compared using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), tender joints count (TJC) and swollen joints count (SJC), C Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). Assessments were made at 6 month intervals over a maximum period of 54 months after treatment initiation. In our nationally representative cohort, 266 (83.1%) patients were male. Overall, mean age was 37.4±9.8 years and average disease evolution 7.6±6.1 years. Sacroiliitis was present in 34 (10.6%) patients, calcaneum was affected in 45(14.1%), as confirmed on MRI scans, 27(8.4%) showed ophthalmic symptoms of auto-immune disease, 188 (58.8%) suffered from axial AS and 132 (41.2%) were diagnosed with mixed AS. Median baseline BASDAI values were 8.02±0.78, 8.07±0.92 and 8.13±0.82, in ADA, ETA and INF groups, respectively. We found statistical difference (p<0.0001) in CRP values at 6 months from baseline, but no difference at any other assessment. Similarly, there were no statistically significant differences between groups at any assessments for ESR, TJC and SJC. In contrast, drug cost analysis showed INF as the most expensive followed by ADA and by ETA.

anti-TNF α agent	Median price (RON)	Difference vs. most expensive (%)	Average price (RON)	Difference in average price (all patients) vs. average price per therapy (%)
INF	58.933	0	65.195	8.36
ADA	52.248	−12.80	52.248	−14.34
ETA	48.420	−21.71	48.420	−23.38

1 USD = 3.5766 RON

Conclusion: For the vast majority of endpoints, including BASDAI index, there were no statistically significant differences in treatment efficacy between the investigated groups at any assessment. Therefore, we suggest that treatment cost, rather than active compound, might be taken into consideration when choosing between these three anti-TNF α drugs for treatment of autoimmune AS.

Disclosure: I. Ancuta, None; **C. Codreanu**, None; **R. Ionescu**, None; **M. Parvu**, None; **M. Bojinca**, None.

1384

The Frequency of Non-Radiographic Axial Spondyloarthritis in Relation to Symptom Duration in Patients Referred Because of Chronic Back Pain: Results From the Berlin Early Spondyloarthritis Clinic. Denis Poddubnyy[1], Henning Brandt[1], Janis Vahldiek[1], Inge Spiller[1], In-Ho Song[1], Martin Rudwaleit[2] and Joachim Sieper[3]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Endokrinologikum Berlin, Berlin, Germany, [3]Charité Universitätesmedizin Berlin, Berlin, Germany

Background/Purpose: Non-radiographic axial spondyloarthritis (nr-axSpA) and radiographic axial SpA (=ankylosing spondylitis–AS) are considered currently as two stages of axial SpA. We reported recently that about 12% of the patients with non-radiographic axial SpA progress in AS over 2 years [1]. Although it can be expected that in the first years after back pain onset non-radiographic (without definite sacroiliitis on the x-ray) SpA is more likely to see than established AS, their frequencies and their ratio in relation to back pain duration at the referral time point is not known.

This study was aimed at investigating of the frequencies of non-radiographic axial SpA (nr-axSpA) and ankylosing spondylitis (AS) diagnoses and their ratios in relation to symptom duration in patients referred because of chronic back pain and suspicion of axial SpA.

Methods: In this monocenter study performed in Berlin [2] orthopaedists and primary care physicians were requested to refer patients with chronic low back pain (duration >3 months) and onset of back pain before <45 years of age to a SpA-specialized rheumatology outpatient clinic for further diagnostic investigation if at least one of the following screening parameters was present: 1) inflammatory back pain, 2) positive HLA-B27, and 3) sacroiliitis detected by imaging. The final diagnosis was made according to the opinion of rheumatologist.

Results: A diagnosis of definite axial SpA was made in 43.7% of the referred patients (n = 522). Axial SpA was diagnosed in a similar percentage of about 50% if back pain duration was <9 years but decreased to 36% if symptom duration was >9 years. Nr-axSpA represented the majority of patient (67.3%) only if duration of back pain was 1 year and less at the time of referral. Between 1 and 6 years of back pain duration the probability of nr-axSpA and AS was nearly equal (1–3 years: 52.5% and 47.5%, respectively; 3–6 years: 53.7% and 46.3%, respectively). In patients with back pain duration of 6–9 years, AS was more likely (61.1%) to be diagnosed than nr-axSpA (38.9%), and this increased further over time - figure.
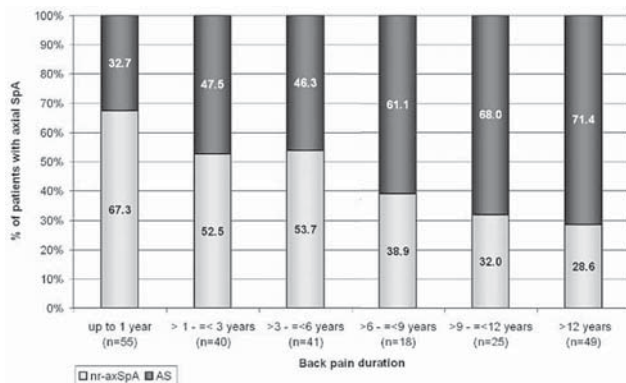
Figure. Ratio of nr-axSpA to AS among referred patients who were diagnosed with definite axial SpA.

Conclusion: Non-radiographic axial SpA represents an important diagnosis in the structure of reasons of back pain, especially in patients with recent symptom onset.

Reference
1. Ann Rheum Dis 2011;70:1369–74. 2. Ann Rheum Dis 2007;66:1479–84.

Disclosure: D. Poddubnyy, None; **H. Brandt**, None; **J. Vahldiek**, None; **I. Spiller**, None; **I. H. Song**, None; **M. Rudwaleit**, None; **J. Sieper**, None.

1385

Increased Body Mass Index in Ankylosing Spondylitis Is Associated with a Greater Burden of Symptoms and Poor Perceptions of the Benefits of Exercise. Laura J. Durcan[1], Fiona Wilson[2], Richard Conway[1], Gaye Cunnane[1] and Finbar (Barry) D. O'Shea[1]. [1]St James's Hospital, Dublin, Ireland, [2]Trinity College, Dublin, Ireland

Background/Purpose: In Ankylosing Spondylitis (AS) the effect of obesity on disease characteristics and exercise perceptions is unknown. Exercise is an essential component in the management of AS. This study was undertaken to assess the attitudes of our AS patients to exercise and to evaluate the effect an increased BMI has on symptoms and disease activity.

Methods: AS patients fulfilling the New York diagnostic criteria were recruited consecutively from our dedicated AS clinic. Demographic data and disease characteristics were collected. Disease activity, symptomatology and functional disability were examined using standard AS questionnaires. Body mass index (BMI) was calculated using standardised methods as kg/m^2. Co-morbidity was analysed using the Charlson co-morbidity index. Patient's attitudes towards exercise were assessed using the exercise benefits and barriers scale (EBBS). The total EBBS score was used to assess their overall perception of exercise and the barriers component was used to evaluate their conceptual barriers to exercise. We then compared the disease characteristics, perceptions regarding exercise and functional limitations in AS patients who were overweight to those who had a normal BMI. Continuous variables were compared using a t-test and categorical variables were assessed using chi squared testing.

Results: Forty six AS patients were included. The mean disease duration in the group was 12.8 years (SD 10.2), 76.1% (N=35) were male, and 69.6% (N=32) were taking biologic therapy. There were 37% (N=17) either current or ex-smokers in the group. The mean BMI was 27.4 kg/m^2(SD 4.0). 67.5% (N=32) were overweight or obese. There was a statistically significant difference between those who are overweight and those with a normal BMI regarding their perceptions of exercise (EBBS 124.7 Vs 136.6 (p=0.006)) indicating that those who are overweight have a worse perception of the benefits of exercise. With regards to those who were overweight versus those with a normal BMI there were significant differences in both BASFI and HAQ (BASFI 4.7 Vs 2.5 (p=0.009), HAQ 0.88 Vs 0.26, (p=0.002)). The disease activity in the groups were also significantly different (BASDAI 4.8 Vs 2.9 (p=0.007) and patient global score 5.0 Vs 2.7 (p=0.007)). There was no difference between the groups in terms of their co-morbid conditions as measured by the Charlson index (p=0.3), smoking (p=0.29), disease duration (p=0.78), gender (p=0.71), or treatment (p=0.89).

Conclusion: The majority of AS patients in this cohort are overweight. These overweight patients have a greater burden of symptoms, worse perceptions regarding the benefits of exercise and enhanced awareness of their barriers to exercising. This is of particular concern in a disease where exercise plays a crucial role.

Disclosure: L. J. Durcan, None; **F. Wilson**, None; **R. Conway**, Roche Pharmaceuticals, 2, UCB Pharma, 2, Merck Pharmaceuticals, 7; **G. Cunnane**, None; **F. D. O'Shea**, None.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus: Clinical Aspects
Monday, November 12, 2012, 9:00 AM–6:00 PM

1386

Genetic Variation and Coronary Atherosclerosis in Patients with Systemic Lupus Erythematosus. Cecilia P. Chung[1], Joseph F. Solus[1], Annette Oeser[1], Chun Li[1], Paolo Raggi[2], Jeffrey R. Smith[1] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]Emory University, Atlanta, GA

Background/Purpose: Premature coronary artery disease is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). However, this is not explained by traditional cardiovascular risk

factors or markers of inflammation. Little is known about the contribution of genetic variation to atherosclerosis in this patient population. Therefore, we examined the hypothesis that, in patients with SLE, candidate gene polymorphisms were associated with the presence of coronary atherosclerosis.

Methods: One hundred and twenty five patients with SLE, enrolled in an ongoing study to evaluate the prevalence and associated risk factors of coronary atherosclerosis in SLE, were studied. Patients fulfilled the 1997 American College of Rheumatology classification criteria for SLE and were 18 years or older. Coronary artery calcium (CAC), a non-invasive measurement of coronary atherosclerosis, was measured by electron beam computed tomography. Using the Illumina Goldengate platform, we determined the genotype of 714 single-nucleotide polymorphisms (SNPs) in 176 selected candidate genes. Candidate genes were selected because of their relevance to autoimmune or cardiovascular risk. The associations between the presence of CAC and individual SNPs were assessed with logistic regression, adjusted for age, gender, and race. To account for multiple comparisons, a false discovery rate (FDR) threshold of 20% was specified.

Results: Patients with SLE were 41 ± 12 years old, 91% were women and 64% were Caucasian. The presence of CAC was detected in 33 patients (26%). After adjustment for age, race, and sex, associations were detected for *CSF1, ADIPOQ, REST, VCAM1, MIF, TNFSF4, INS, IRF5, TH* and *HMOX1* (Table). However, none of these associations remained significant after FDR correction.

Table. Genetic Association with Coronary Atherosclerosis in Patients with SLE

SNP	Gene	Major, minor allele	Minor allele frequency	Odds ratio* (95% CI)	p-value
rs333947	*CSF1*	G,A	0.18	4.71 (1.93–11.53)	0.001
rs7649121	*ADIPOQ*	A,T	0.20	0.05 (0.01–0.30)	0.001
rs1862513	*REST*	C,G	0.31	2.94 (1.47–5.93)	0.002
rs3917009	*VCAM1*	C,T	0.07	3.75 (1.53–9.22)	0.004
rs875643	*MIF*	G,A	0.41	0.36 (0.17–0.74)	0.005
rs333970	*CSF1*	C,A	0.45	0.39 (0.20–0.77)	0.006
rs738806	*MIF*	A,G	0.25	3.24 (1.41–7.45)	0.006
rs34124816	*REST*	A,C	0.06	6.69 (1.51–29.72)	0.012
rs3850641	*TNFSF4*	A,G	0.14	3.15 (1.28–7.78)	0.013
rs3842748	*INS*	C,G	0.29	0.35 (0.15–0.80)	0.013
rs3745369	*REST*	G,C	0.41	2.49 (1.20–5.15)	0.014
rs1874328	*IRF5*	A,G	0.39	0.38 (0.17–0.83)	0.015
rs2070762	*TH*	A,G	0.44	2.43 (1.18–4.98)	0.015
rs333968	*CSF1*	C,T	0.26	0.41 (0.19–0.88)	0.022
rs11912889	*HMOX1*	G,A	0.15	0.32 (0.12–0.85)	0.022
rs3093037	*CSF1*	C,T	0.10	0.21 (0.06–0.81)	0.024

* Odds ratios for the comparison between minor and major allele.

Conclusion: Our results suggest that polymorphisms of genes coding CSF-1, adiponectin, resistin, VCAM-1, MIF, TNFSF-4, insulin, IRF-5, TH, and HMOX-1 may be associated with the presence of coronary atherosclerosis in patients with SLE. Studies in additional cohorts will be informative.

Disclosure: **C. P. Chung**, None; **J. F. Solus**, None; **A. Oeser**, None; **C. Li**, None; **P. Raggi**, None; **J. R. Smith**, None; **C. M. Stein**, None.

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Hospitalizations and Reasons for Admission in a Clinical SLE Cohort. Alaa Dekis[1], Kenjey Chan[1], Christian A. Pineau[2], Evelyne Vinet[2], Emil P. Nashi[2], Sasha Bernatsky[3] and Ann E. Clarke[3]. [1]McGill University, Montreal, QC, [2]McGill University Health Centre, Montreal, QC, [3]Research Institute of the McGill University Health Centre, Montreal, QC

Background/Purpose: Data published from several countries have suggested that patients affected by systemic lupus erythematous (SLE) may have high annual hospitalization rates. However, there is a lack of data regarding the incidence and causes of hospitalization in Canadian SLE patients. Our objective was to provide recent estimates for hospitalization rates, and reasons for admission, in a clinical systemic lupus (SLE) cohort.

Methods: We preformed a retrospective study of patients followed at the McGill University Health Center Lupus Clinic from the year 2000 till 2006. Each patient undergoes a yearly clinical assessment, which includes documentation of hospital admissions in the past year.

Results: Our SLE cohort consisted of 316 female patients and 27 males, with an average age of 46.3 years. Over the interval studied, there were 234 reported admissions. SLE-related causes accounted for the highest proportion of hospitalizations (29.5%), and infections were the next most common

reason for hospitalization (13.8%). Other categories included surgical and gynecological reasons for hospitalization (12.9% each), hospitalizations for cardiac and gastrointestinal causes (7.9% each) and other causes.

Conclusion: Canadian annual hospitalization rates are approximately 1.1 hospitalizations per 10,000 residents. Our results suggest much high hospitalization rates in SLE. Previous authors have emphasized disease flares and infections as common reasons for hospitalizations in SLE, and our data seems consistent with this. Further work is in progress, to provide more detailed comparisons with general population data.

Disclosure: **A. Dekis**, None; **K. Chan**, None; **C. A. Pineau**, None; **E. Vinet**, None; **E. P. Nashi**, None; **S. Bernatsky**, None; **A. E. Clarke**, None.

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Diagnostic Accuracy of Anti-dsDNA Antibodies in Unselected Patients with Recent Onset of Rheumatic Symptoms. Michele Compagno[1], Søren Jacobsen[2], Ole Petter Rekvig[3], Lennart Truedsson[4], Niels H. H. Heegaard[5], Johannes C. Nossent[6], Andreas Jönsen[1], Rasmus Sleimann Jacobsen[2], Gro Østli Eilertsen[6], Gunnar K. Sturfelt[1] and Anders Bengtsson[1]. [1]Lund University, Lund, Sweden, [2]Copenhagen University Hospital, Copenhagen, Denmark, [3]University Hospital, Tromsø, Norway, [4]Department of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund, Sweden, [5]Statens Serum Institut, Copenhagen S, Denmark, [6]University of Tromsø, Tromso, Norway

Background/Purpose: Anti-dsDNA antibodies are widely used in diagnostic settings when SLE is suspected. Crithidia Luciliae Immunofluorescence Test (CLIFT) and Enzyme Linked ImmunoSorbent Assay (ELISA) are commonly used assays to detect anti-dsDNA antibodies in clinical practice. The aim of the present study was to evaluate the diagnostic accuracy of CLIFT and ELISA in unselected patients with recent onset of rheumatic symptoms.

Methods: In the three participating centres, 1073 consecutive patients were locally screened for ANA. A total of 292 ANA positive patients and 292 matching ANA negative patients were selected. Anti-dsDNA antibodies were assessed at study entry by different laboratories with CLIFT (totally four times using two different commercial kits) and with ELISA (totally four times with three different commercial kits). The results of the laboratory tests were related to the clinical diagnosis formulated at study entry and verified after a long term follow-up period (median 4.8 years).

Results: Discrepant results were obtained from the different assessments regardless of the assay used, with kappa statistics value ranging between 0.25 and 0.75. At least one anti-dsDNA analysis was positive in 164 patients, but in only seven patients the positivity was confirmed by all the assessments. SLE diagnosis was initially made in 65 patients, of which 40 were anti-dsDNA positive. A wide spectrum of other diagnoses was observed among anti-dsDNA positive patients. Overall, about one third of anti-dsDNA positive patients were ANA negative. At follow-up after approximately 5 years, SLE diagnosis was unchanged in 63 patients (39 anti-dsDNA positive) and changed in only two (one anti-dsDNA positive). Among the 120 anti-dsDNA positive patients not diagnosed with SLE at study entry, only one developed SLE during the follow-up period.

Conclusion: Regardless of the assay used, assessment of anti-dsDNA antibodies was not reliable as diagnostic tool in our cohort of unselected patients with rheumatic symptoms. ANA showed poor reliability as screening test before anti-dsDNA analysis. Anti-dsDNA antibodies had surprisingly low positive predictive value for SLE diagnosis, despite their high specificity. For non SLE patients, being anti-dsDNA positive poses little risk of developing SLE within 5 years.

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Erythrocyte Sedimentation Rate Is a Predictor of Renal and Overall Systemic Lupus Erythematosus Disease Activity. George Stojan[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: To assess whether ESR levels correlate with the level of disease activity at each visit and whether a change in ESR could be useful in predicting changes in disease activity.

Methods: 34000 visits in a prospective SLE cohort were analyzed for the association of ESR and level of disease activity. Follow-up visits when patients had cancer, infection, pregnancy or were in renal failure were excluded.

Results: After adjusting for confounding factors, ESR correlated with the SELENA-SLEDAI, the physician global assessment (PGA), fatigue, renal, joint, rash, serositis, and hematologic visual analogue scales (VAS) and proteinuria (p<0.0001). A change in ESR between two visits was highly correlated with a concurrent change in physician global assessment (PGA), renal, fatigue and joint VAS (p<0.0001) (Table). There was no statistically significant correlation between change in ESR between two visits and a future change in disease activity.

Table. Mean change in disease activity between two consecutive clinic visits, per 1 standard deviation change (27 mm/hr) in ESR.

Change in Disease Activity Measure	Adjusted[1] Difference in mean activity level (95% CI)	P-value
SLEDAI	0.09 (0.00, 0.19)	0.043
PGA	0.05 (0.03, 0.07)	<0.0001
Fatigue VAS	0.016 (0.008, 0.024)	0.0001
Neuro VAS	−0.005 (−0.012, 0.002)	0.19
Rash VAS	0.006 (−0.006, 0.019)	0.33
Renal VAS	0.030 (0.018, 0.043)	<0.0001
Joints VAS	0.030 (0.013, 0.046)	0.0004
Pulmonary VAS	−0.001 (−0.004, 0.002)	0.65
Hematology VAS	0.001 (−0.007, 0.010)	0.79
Serositis VAS	0.005 (−0.002, 0.011)	0.16
Hematuria	−0.000 (−0.000, 0.000)	0.36
Proteinuria	0.009 (0.002, 0.016)	0.013

[1] Adjusted for age, race, sex, and changes in: weight, c3, c4, hematocrit, andti-dsDNA, prednisone use, plaquenil use, and immunosuppresant use.

Conclusion: ESR is associated with disease activity in SLE measured by the SELENA-SLEDAI, the physician global assessment (PGA), and with organ specific activity including serositis, rash, joint, renal and hematologic visual analogue scales. A change in ESR between two visits was highly correlated with a change in physician global assessment (PGA), renal, fatigue and joint visual analogue scale (VAS). However, change in ESR between two visits did not predict the disease activity at the next (third) visit. Until more specific biomarkers are validated, serial ESR does have utility in following disease activity, in particular renal, in SLE.

Disclosure: G. Stojan, None; **H. Fang**, None; **L. S. Magder**, None; **M. Petri**, None.

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Vitamin D Deficiency Is Not Associated with Nor Does It Predict Progression of Coronary Artery Calcium or Carotid Intima-Media Thickness in Systemic Lupus Erythematosus. Adnan Kiani[1], Hong Fang[1], Ehtisham Akhter[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: In the general population, vitamin D deficiency is associated with cardiovascular disease including myocardial infarction and stroke. In SLE, Vitamin D deficiency has been associated with carotid plaque. We investigated whether low vitamin D would predict change in subclinical measures of atherosclerosis over 2 years.

Methods: 167 SLE patients (93% female, 63% Caucasian, 32% African-American, mean age 45 yrs) had measurement of coronary artery calcium and carotid intima-media thickness IMT (IMT)) and vitamin D.

Results:

Table 1. shows the baseline characteristics by vitamin D status.

Variable	Number (%) with the characteristic Vitamin D <32 (n=133)	Vitamin D ≥32 (n=34)	p-value
Age			
18–30	14 (11%)	4 (12%)	0.80
31–49	75 (56%)	17 (50%)	
50+	44 (33%)	13 (38%)	
Ethnicity			
Caucasian	79 (59%)	27 (79%)	0.066
African-American	47 (35%)	5 (15%)	
Other	7 (5%)	2 (6%)	
Gender			
Female	124 (93%)	31 (91%)	0.68
Male	9 (7%)	3 (9%)	

Table 2. Changes in coronary artery calcium (CAC) and carotid intima-media thickness (IMT)

Measure	Mean at baseline	Mean after 2 years	Mean Change	p-value for change	Difference in change (95% CI)*	p-value for difference between groups**
Log$_e$(CAC score+1)						
Vitamin D <32	1.18	1.23	0.05	0.63	−0.14 (−0.58,0.30)	0.69
Vitamin D ≥32	1.11	1.30	0.19	0.25		
Carotid IMT						
Vitamin D <32	0.58	0.66	0.08	<0.0001	0.01 (−0.02,0.04)	0.59
Vitamin D ≥32	0.58	0.65	0.07	<0.0001		

This table is based on the 123 patients with vitamin D <32 and the 32 patients with vitamin D ≥32 for whom there were both baseline and follow-up measures.
* Difference in change: measure in vitamin D <32 group minus measure in vitamin D ≥32 group.
** Adjusted for ethnicity.

Conclusion: Vitamin D deficiency was not associated with any measure of subclinical atherosclerosis in SLE. Another study by Bruce et al (Rheumatology:2012) did not show an association of low Vitamin D in SLE with carotid IMT or plaque either. Vitamin D deficiency did not predict progression of subclinical atherosclerosis over 2 years. Future studies with larger sample size and longer follow up are needed to confirm our findings.

Disclosure: A. Kiani, None; **H. Fang**, None; **E. Akhter**, None; **L. S. Magder**, None; **M. Petri**, None.

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Anti-Ku Autoantibodies in Systemic Lupus Erythematosus Versus Autoimmune Myositis As Measured by a Novel Chemiluminescence Assay. Michael Mahler[1], Jason Wu[2], Magdalena Szmyrka-Kaczmarek[3], Andreas Swart[4], Marvin J. Fritzler[5], Jean-Luc Senécal[6] and John G. Hanly[7]. [1]INOVA Diagnostics, Inc., San Diego, CA, [2]INOVA Diagnostics, San Diego, [3]Wroclaw Medical University, Wroclaw, Poland, [4]Rheumatology clinic Neuss, Neuss, Germany, [5]University of Calgary, Calgary, AB, [6]Hôpital Notre-Dame du CHUM, Montréal, QC, [7]Dalhousie University and Capital Health, Halifax, NS

Background/Purpose: Autoantibodies targeting Ku, an abundant nuclear protein with DNA helicase activity, have been reported in patients with systemic autoimmune rheumatic diseases. Little is known about the clinical association of anti-Ku antibodies, especially when tested using novel technologies. The objective of the present study was to analyze the prevalence of anti-Ku antibodies in different pathologies using a novel chemiluminescence immunoassay (CIA) on the BIO-FLASH®, a fully random access automated immunoanalyzer.

Methods: Serum samples from adult patients with systemic lupus erythematosus (SLE, n=305) and autoimmune myositis patients (AIM, n=109) were used. **Results** were compared to disease controls (rheumatoid arthritis, n=30; infectious diseases, n=17) and healthy adults (HA, n=167). In addition, samples from patients referred to a rheumatology clinic submitted for routine autoantibody testing (n=1078) were studied. All samples were tested for anti-Ku antibodies by QUANTA Flash Ku (research use only, INOVA Diagnostics, San Diego, CA, USA) using recombinant Ku coupled to paramagnetic beads. SLE patient samples were also tested for other connective tissue disease associated autoantibodies using the respective QUANTA Lite® ELISAs (INOVA Diagnostics). Clinical data of anti-Ku positive patients (high titers) from the referral study were collected by retrospective chart review. Statistical analysis (Fisher exact test, receiver operating characteristics [ROC] analysis) was done with ANALYSE-IT version 2.03.

Results: At cut-off values of 10,000 or 15,000 relative light units (RLU), 43/305 (14.1%) or 30/305 (9.8%) SLE patients and 4/109 (3.7%) AIM patients were positive, respectively. The 4 positive AIM patients had myositis in overlap, including 2 patients with SLE and myositis. In the control cohorts, 4/167 (2.4%) or 2/167 (1.2%) HA (all low titer), respectively, 0/30 (0.0%) rheumatoid arthritis and 0/17 (0.0%) infectious disease patients were positive. The area under the curve values were: 0.65 for SLE vs. controls and 0.37 for AIM vs. controls. In three SLE patients, anti-Ku antibodies were the only detectable autoantibody. In the rheumatology clinic referral cohort, 12/1078 (1.1%) were positive for anti-Ku antibodies, 9 showing low and 3 high titers. The diagnoses of the 3 high positive anti-Ku positive patients were: suspected SLE, mixed connective tissue disease, and rheumatoid arthritis treated with anti-TNF in a patient with a positive ANA.

Conclusion: Anti-Ku antibodies detected by CIA are present in 14.1% or 9.8% of SLE, but in only 3.7% of AIM patients, 50% of whom have SLE.

This suggests that anti-Ku antibodies are associated with SLE rather than with AIM. This association may have been missed in previous studies due to the past use of indirect immunofluorescence screening assays or the high sensitivity of the current CIA assay.

Disclosure: **M. Mahler**, Inova Diagnostics, Inc., 3; **J. Wu**, Inova Diagnostics, Inc., 3; **M. Szmyrka-Kaczmarek**, None; **A. Swart**, None; **M. J. Fritzler**, Inova Diagnostics, Inc., 5; **J. L. Senécal**, None; **J. G. Hanly**, None.

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Clinical Correlation with Anti Double Stranded Deoxyribonucleic Acid Via Enzyme Linked Immunoassay Versus Multiplex Immunoassay.
Megan L. Krause, Melissa R. Snyder, Cynthia S. Crowson, Abigail B. Green and Kevin G. Moder. Mayo Clinic, Rochester, MN

Background/Purpose: In systemic lupus erythematosus (SLE), antibodies to double-stranded DNA (dsDNA) are utilized for disease classification and assessment of activity. Enzyme immunoassays (EIAs) and multiplex immunoassays (MIAs) are frequently used. However, anti-dsDNA antibody assays are not well-standardized with previously reported low concordance rates. In this study, clinical factors and laboratory data were evaluated for their association with anti-dsDNA antibody testing performed by EIA and MIA.

Methods: Patients from a single institution (n=102) underwent anti-dsDNA antibody testing by EIA (INOVA Diagnostics) and MIA (BioRad Laboratories). Clinical diagnoses, SLE disease activity index (SLEDAI), medication exposure, and laboratory data (serologies, complement values, and inflammatory markers) were abstracted. Qualitative concordance between the two methods was defined as both methods being classified as "negative" or "positive" according to the manufacturer's recommended reference ranges. Discordance was defined as one method having different categorization than the other, "positive," "borderline/indeterminate," or "negative."

Results: Within the total cohort, 35% and 44% of patients were positive for anti-dsDNA antibodies by EIA and MIA, respectively. Further, 54 had a diagnosis of definite, probable, or cutaneous SLE with 63% positive by MIA and 50% by EIA. In addition, only 6% of these patients had negative concordance, while 37% demonstrated positive concordance (p=0.02). Of those negative by both methods, none had lupus nephritis. In patients with lupus nephritis, 35% demonstrated positive concordance. The remaining demonstrated discordance with a higher qualitative value of MIA in 52% compared to 13% with EIA higher (p=0.14). The mean SLEDAI score calculated without the anti-dsDNA value was 3.3 in patients with negative concordance and 7.7 with positive concordance. In comparison, patients with discordant higher MIA had a mean SLEDAI score of 5.9 compared to 2.9 in patients with higher EIA (p=0.1). No patients with negative concordance had low complement values. In contrast, in patients who were positive by both methods, a low C3 or C4 was observed in 46% (p<0.01) and 62% (p=0.01), respectively. Of patients with positive concordance, 53% were positive for anti-SS-A antibodies and anti-RNP antibodies compared to 8% and 23% of patients with negative concordance, respectively. In patients with positive MIA, 80% were currently on at least one medication for SLE, compared to 37% with negative and 39% with borderline MIA results (p<0.01). In patients with positive MIA, they were more likely to have been treated with cyclophosphamide and hydroxychloroquine. In contrast, 73% of patients with positive EIA were currently on at least one medication for SLE compared to 43% and 63% of patients with negative or borderline results (p=0.09).

Conclusion: The association between clinical factors and anti-dsDNA antibodies may be determined, in part, by the specific methodology. Further clarification of these relationships could assist with interpretation of anti-dsDNA antibody results as well as choice of a method for a specific clinical scenario.

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Predictors of Panniculitis in Systemic Lupus Erythematosus.
Ashika Odhav[1], Michelle Petri[2] and Hong Fang[2]. [1]University of Missouri Kansas City School of Medicine, Kansas, MO, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Panniculitis is a rare, but devastating manifestation of SLE. We examined associates of panniculitis in a large SLE cohort.

Methods: 52 out of 2,149 SLE patients in the cohort had panniculitis (2.4%). The mean age at last assessment was 49 ± 15 years. The patients were 46% African-American, 46% Caucasian, and 96% female. Other SLE manifestations were determined at baseline by history, physical examination, and chart review; patients were then seen quarterly in follow-up.

Results: The table shows the association of demographics, SLE manifestations and serologies with panniculitis. Panniculitis was strongly associated with discoid lupus and leg ulcers. It was also associated with serositis, seizures, myositis, alopecia, and vasculitis. Proteinuria was significantly less frequent in those with panniculitis.

Association between Various Factors and Panniculitis in SLE

Characteristics/ Manifestations	Panniculitis (%, N=52)	No panniculitis (%, N=2097)	Odds Ratio (95% CI)	Adjusted P-value§
History of smoking	48.1	37.8	1.3 (0.7, 2.3)	0.34
Disability	40.4	21.8	2.1 (1.1, 3.7)	0.016
Malar rash	57.7	51.0	1.3 (0.7, 2.3)	0.41
Discoid	50.0	19.0	3.8 (2.1, 6.9)	<.0001
Photosensitivity	63.5	53.7	1.4 (0.8, 2.6)	0.22
Mouth ulcers	61.5	51.2	1.5 (0.9, 2.7)	0.15
Arthritis	80.8	73.5	1.2 (0.6, 2.5)	0.57
Serositis	67.3	48.9	2.0 (1.1, 3.7)	0.020
Proteinuria	28.9	44.3	0.4 (0.2, 0.8)	0.0062
Hematologic disorder	75.0	65.7	1.4 (0.8, 2.7)	0.27
ANA positivity	98.1	96.5	1.7 (0.2, 12.8)	0.59
Myositis	19.2	7.7	2.3 (1.1, 4.9)	0.023
Alopecia	73.1	53.1	2.0 (1.0, 3.8)	0.040
Vasculitis	28.9	14.2	2.2 (1.2, 4.2)	0.012
Leg ulcers	17.3	2.5	7.1 (3.2, 15.7)	<.0001
Seizure	19.2	9.5	2.4 (1.2, 4.8)	0.019
Peripheral Neuropathy	11.5	3.7	2.5 (1.0, 6.4)	0.046
Leukopenia	59.6	43.9	1.8 (1.0, 3.2)	0.044
Lupus Anticoagulant	26.0	27.2	0.9 (0.5, 1.7)	0.73
Low C3	46.2	55.6	0.6 (0.4, 1.1)	0.12
Low C4	36.5	48.3	0.6 (0.3, 1.1)	0.10
Increased ESR	82.7	74.9	1.4 (0.6, 3.0)	0.41
Anti- Sm	11.5	19.4	0.6 (0.2, 1.4)	0.20
Anti-DNA	63.5	63.0	1.0 (0.5, 1.7)	0.88
Anti-Ro	38.5	30.6	1.4 (0.8, 2.6)	0.21
Anti-La	15.4	12.9	1.3 (0.6, 2.8)	0.52

§ Adjusted for ethnicity, gender, age at last assessment, and duration of SLE at last assessment

Conclusion: In contrast to photosensitive cutaneous lupus, panniculitis is not associated with anti-Ro, anti-La, or smoking. It is strongly associated with discoid (discoid lesions often overlay panniculitis areas). It is not associated with any serologic test, and, in fact, is less frequent in those with renal lupus. The impact of panniculitis has been unrecognized, with 40% becoming disabled due to it.

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

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Health Status Burden and Impact of Fatigue On Patient Functioning in SLE Patients From a Phase 1b Study.
Michelle Petri[1], Ariane K. Kawata[2], Ancilla W. Fernandes[3], Kavita Gajria[3], Warren Greth[4] and Asha Hareendran[5]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]United Biosource Corporation, Bethesda, MD, [3]MedImmune LLC, Gaithersburg, MD, [4]MedImmune, LLC, Gaithersburg, MD, [5]United Biosource Corporation, London, United Kingdom

Background/Purpose: Systemic Lupus Erythematosus (SLE) has a significant impact on patient's quality of life. Fatigue is the most common symptom of SLE and affects between 50–80% of SLE patients (Cleanthous et al. 2012; Tench et al. 2000; Krupp et al. 1990). Our objective was to evaluate the health related quality of life burden in SLE in a clinical trial and to explore the relationship between fatigue and overall health status.

Methods: Pooled treatment group data from a Phase Ib dose-escalation clinical trial study of adult patients with moderate to severe SLE were analyzed. Clinical trial outcomes included clinician-reported global assessment of disease severity (MGDA) and PRO measures: Short Form 36-item Health Survey, Version 2 (SF-36v2), Fatigue Severity Scale (FSS), and patient numeric rating scale (NRS) global assessment. Descriptive analyses were conducted to characterize overall burden of SLE

compared to US general population. The relationship between fatigue and overall health status was evaluated by comparing SF-36v2, patient and physician global assessments changes at endpoint from baseline between fatigue responders and non-responders. A fatigue response was defined as FSS change score ≤-1.0.

Results: There were 161 patients, predominantly female (96%) and white (72%), with average age of 43±11 years (range: 18–71). Mean SF-36v2 subscale scores ranged from 34.5 (SD=9.6) for general health (GH) to 42.1 (SD=13.2) for mental health (MH); summary component scores reflected overall problems with physical (PCS; mean=35.2, SD=9.7) and mental health (MCS; mean=40.9, SD=12.9). SLE patients had worse health status on all SF-36v2 subscale domains than US general population and comparable age and gender norms (effect size [ES] = −0.51 to −2.15; Figure 1). A comparison of change scores between fatigue responders and non-responders showed that fatigue responders had greater improvement on SF-36v2 and patient and physician global assessments than non-responders. Fatigue responders had larger ES improvements than non-responders on SF-36v2 bodily pain (BP; ES=0.6 vs. 0.2), physical functioning (PF; ES=0.6 vs. 0.1), social functioning (SF; ES=0.6 vs. 0.0), and PCS (ES=0.7 vs. 0.1), patient global assessment NRS (ES=−0.7 vs. 0.0), and MDGA (ES=−1.6 vs. −0.7).
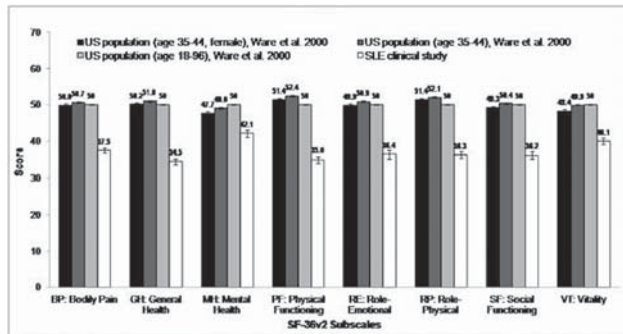
Figure 1. Comparison of Mean Baseline SF-36v2 Subscale Scores in the SLE Clinical Study to US Population Norms

Conclusion: SLE patients had poor HRQL in this study. All SF-36 domains including physical and mental health components were worse than general population averages. Improvement in fatigue was associated with improvements in the individual SF-36 domains as well as the physician's global assessment of disease activity.

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The Validation of a New Simple Disease Activity Tool in Systemic Lupus Erythematosus (SLE): The Lupus Activity Scoring Tool (LAST) As Compared to the Sledai Selena Modification. Majed M. Khraishi[1], Rana Aslanov[2] and Krista Fudge[3]. [1]Memorial University of Newfoundland, St Johns, NF, [2]Memorial University of Newfoundland, St.John's, NF, [3]Corner Brook, NF

Background/Purpose: SLE is a chronic autoimmune disease with variable manifestations. New developments in the understanding and treatment of SLE mandated closer monitoring of the disease activity and its response to treatment. Current disease activity indices (e.g. SLEDAI SELENA, BILAG & SLAM) have their own limitations. We designed a new disease activity evaluation tool: the Lupus Activity Scoring Tool (LAST) that simplifies the approach to quantify SLE activity while maintaining high sensitivity. We have also developed an easy to use electronic application of this tool.

Primary: To validate a SLE activity tool with it correlation to the SLEDAI SELENA modification. Secondary: To test the usability and the accuracy of electronic applications of the same tool in clinical settings.

Methods: The new disease activity tracking and evaluating tool included patient global assessment of disease activity (PGA), physician global assessment of disease activity (PHGA), and a formula incorporating the current immuno-modulating medication used as an indication of SLE activity. The LAST included C3, C4 and Anti-ds Anti-DNA titer abnormalities as activity indicators. Patients who met the SLE ACR 1997 criteria update were seen in a rheumatology clinic

within the last 12 months and had the laboratory investigations done within 2 weeks of their visit. The SLEDAI was calculated for each visit. Five different systems (algorithms) of weighting the different variables of disease activity were calculated. Apple iPad and Windows web-based applications were developed for the LAST and a clinical only LAST (without incorporating serological values). Descriptive statistics and correlation bivariates (Pearson's & Spearman's) were conducted. Each algorithm result and the disease activity of patients with multiple assessments were compared to the SLEDAI SELENA scores.

Results: Twenty three patients (91% females) with 43 assessments were included. Scores from 5 algorithms of the variables in addition to the SLEDAI SELENA scores were obtained at each visit. The mean (SD) age was 47.97 (14.61) years and the mean (SD) of disease duration was 12.26 (6.47) years. The mean (SD) SLEDAI score was 6.30 (4.01). The mean (SD) LAST (with C3, C4 and Anti-ds DNA) score was 39.85 (18.67). The correlation between the two new activity indices was very high: 0.920 with p<0.001. The SLEDAI scores were consistent with the LAST scores at the baseline and follow-up visits: SLEDAI scores 0–4 corresponded to the LAST scores of 0–30 while SLEDAI scores of 8 or higher corresponded to 50 and higher, respectively. The electronic applications of the LAST were easy to use and no errors were found with their results as compared to the manually obtained scores.

Conclusion: The Lupus Activity Scoring Tool (LAST) is a new disease activity index correlated well with the SLEDAI SELENA modification. The use of simple clinical variables as a measure of SLE activity seems to be valid. The development of easy to use electronic apps will make the use of these activity tracking tools easier to calculate and can be possibly utilized in non-specialist settings.

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Associates of a History of Thrombosis in Systemic Lupus Erythematosus. Melissa Nastacio[1], Hong Fang[1], Thomas Kickler[1], Jayesh Jani[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Thrombosis in SLE is highly associated with anti-phospholipid antibodies, yet the majority of those with antiphospholipid antibodies never have a thrombotic event. Plasma microparticles have been identified as a risk factor for atherosclerosis. D-dimers are elevated in the setting of deep venous thrombosis. Endogenous thrombin potential (ETP) measures the thrombin formation capacity of plasma and may be elevated in hypercoagulable states.

Methods: We measured plasma microparticles by their functional capacity to generate thrombin, ETP, and D-dimer levels in 986 SLE patients. The relationship between these biomarkers and history of thrombosis was estimated.

Results: The patients were 92% female, 37% African American, 55% Caucasian with mean age 48.1 ±13.1 years. Of the 986 patients, 258 had at least one thrombotic event, including deep venous thrombosis (113), stroke (75), myocardial infarction (26), other venous (21), and other arterial thrombosis (13). Elevated levels of D-dimer (> 0.88 mg/L) were not associated with thrombosis. Thrombin generated microparticles were associated with history of a thrombotic event (Table). In subanalyses, we found that this association was only found with respect to venous (but not arterial) events. Low ETP was associated with a higher likelihood of a history of thrombosis. However, controlling for antiocoagulant use, this association disappeared, suggesting that the association was due to the fact that those with a history of thrombosis were put on anticoagulants which reduced their ETP.

Table 1. Life-time rates of thrombotic events in SLE patients by biomarker levels

	Group	# events	# of person-years at risk	Rate per 1000 person years	Risk Ratio (95% Confidence Interval)	P-value	Adjusted[1] Risk Ratio (95% Confidence Interval)	P-value
Everyone		258	42,513	6.1				
Ddimer (High/Low)	<0.88	173	28,305	6.1	1.0 (Ref Group)	.91	1.0 (Ref Group)	.52
	0.88+	85	14,208	6.0	1.0 (0.8, 1.3)		0.9 (0.7, 1.2)	
Thrombin generated microparticles (High/Low)	<5	76	14,262	5.3	1.0 (Ref Group)	.044	1.0 (Ref. Group)	.0075
	5+	165	25,845	6.4	1.3 (1.0, 1.7)		1.5 (1.1, 1.9)	
ETP quartiles	<343	111	9,699	11.4	1.0 (Ref. Group)	<.0001	1.0 (Ref. Group)	.61
	343–.395	42	10,486	4.0	0.3 (0.2, 0.5)	<.0001	0.9 (0.6, 1.4)[2]	.81
	395–.436	36	10,030	3.6	0.3 (0.2, 0.4)	<.0001	0.9 (0.6,1.5)[2]	.50
	436+	52	10,545	4.9	0.4 (0.3, 0.6)		1.2 (0.8, 1.8)[2]	

[1] Adjusting for ever having a positive ACL or RVVT test unless specified
[2] Adjusting for ever having a positive ACL or RVVT test and use of anti-coagulants.

Conclusion: Thrombin generated plasma microparticles increase the risk of thrombosis at levels >5. These data indicated that hypercoagulability in SLE can be further characterized beyond antiphospholipid antibodies, allowing prophylactic therapy to be given to the subset at greatest risk.

Disclosure: **M. Nastacio**, None; **H. Fang**, None; **T. Kickler**, None; **J. Jani**, None; **L. S. Magder**, None; **M. Petri**, None.

1397

Risk Factors Associated with Early Central Nervous System Damage Detected Through Perfusion MRI in Patients with Systemic Lupus Erythematosus. Paola Tomietto[1], Federica Casagrande[2], Maja Ukmar[2], Luca Weis[2], Pia Morassi[1], Rita Moretti[3], Gianni Biolo[3], Carlo Giansante[3] and Maria Assunta Cova[2]. [1]AOU Ospedali Riuniti di Trieste, Trieste, Italy, [2]Radiology Department, University of Trieste, Trieste, Italy, [3]Internal Medicine Department, University of Trieste, Trieste, Italy

Background/Purpose: Antiphospholipid antibodies (aPL), hypertension and accumulated damage (SLICC-DI) have been associated to the severity of cerebral MRI lesions and to cognitive deficits in SLE. Perfusion weighted MRI (PWI) is a sensitive technique that assess the capillary microcirculation and might allow to detect an early vascular damage, eventually preceding the appearance of structural damage in conventional MRI. The aim of this study was to determine the main factors affecting CNS damage detected through perfusion MRI in SLE.

Methods: 20 consecutive SLE patients underwent a clinical evaluation to characterize central nervous system involvement (NPSLE) including the clinical history, a 45-minutes neuropsychological battery and the Hospital Anxiety and Depression Scale (HADS). All the patients underwent MRI examination performed on a 1.5T magnet. In all of them conventional (cMRI) and dynamic susceptibility contrast (DSC) sequences were performed. Cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) maps were reconstructed for 19 patients. Region of interest (ROI) were placed symmetrically on normal appearing white matter (NAWM) in 12 areas (frontal and parietal WM, amygdala, corpus callosum and middle cerebellar peduncles). ROI relevant to distinguish patients with NPSLE vs patients without were selected on the basis of the receiver operating characteristic (ROC) curve analysis. SLEDAI, SLICC-DI, generic cardiovascular risk factors, positivity for Raynaud's phenomenon, livaedo reticularis, cutaneous vasculitis, aPL, anti-RNP and anti-DNA were determined for all the patients and included as independent variables in several stepwise regression analysis to determine which of them affected changes in CBF, CBV MTT and TTP of NAWM.

Results: Measures of CBV of right frontal WM (sensitivity 83,3%, specificity 71,4%) and of MTT in left frontal (sensitivity 58,3%, specificity 100%) and parietal WM (sensitivity 66,6%, specificity 85,7%) showed moderate accuracy (AUC 0,72) in distinguishing patients with and without NPSLE, according to the clinical classification. Among generic cardiovascular risk factors, smoking resulted as an independent factor affecting CBF and CBV in frontal and parietal subcortical NAWM, while cholesterol and hypertension were independent variables associated to MTT respectively of the fronto-parietal NAWM and corpus callosum. Among SLE-related factors, aPL and livaedo reticularis were independent factors affecting MTT of corpus callosum. Finally SLICC-DI resulted as an independent factor affecting all the parameters of PWI in fronto-parietal NAWM and corpus callosum.

Conclusion: This preliminary analysis showed as some cardiovascular risk factors, (smoking, hypertension, cholesterol levels), and some SLE-related factors (aPL, SLICC-DI, livaedo reticularis), previously reported as related to NPSLE, are associated to early changes of cerebral perfusion in fronto-parietal subcortical normal appearing white matter and corpus callosum. These data, if confirmed, suggest the importance of a tight control of cardiovascular risk factors, aPL and of the disease activity to prevent early central nervous system damage in SLE.

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1398

Inflammatory Back Pain Is Increased in SLE and Associated with Anti-Sm Antibodies. Neslihan Yilmaz[1], Ayten Yazici[2], Sibel Z. Aydin[3] and Sule Yavuz[4]. [1]Marmara University, Faculty of Medicine, Istanbul, Turkey, [2]Sakarya Research and Training Hospital, Sakarya, Turkey, [3]Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey, [4]Marmara University, Istanbul, Turkey

Background/Purpose: Growing evidence suggest that autoantibodies may present in patients with ankylosing spondylitis. Here, we aim to determine the association of inflammatory back pain and autoantibodies in patients with systemic lupus erythematosus (SLE) which is a protype autoimmune disease.

Methods: One hundred thirty two SLE patients (130 females, 2 males) and 100 healthy controls (98 females,2 males) were questionnaired for having inflammatory low back pain (LBP). The SI joints of SLE patients with LBP were evaluated by conventional radiography followed by color and duplex Doppler ultrasonography (CDDUS) examination. X-Rays were scored according to the modified New York criteria. CDDUS evaluations included the presence of a vessel in and/or around the SI joints and measurement of the RI, which is expected to decrease by inflammation of the joint. The CDDUS results of 44 SLE patients (88 SI joints) were compared with 17 healthy controls (HC) (34 SI joints) without any low back pain.

Results: The incidence of LBP was 58/132 (43.9%) in SLE patients and 15/100 (15%) in HC (p<0.05). Forty four of SLE patients gave consent to participate the study. Within these patients 20/132 (15%) had inflammatory, 24/132 (18%) had noninflammatory LBP. None of the HC has inflammatory LBP. The mean age was 38.6±11.3 years and mean disease duration was 6.8±5.7 years. Mean SLEDAI was 1.94±1.94, BASDAI was 4.11±1.63. In SLE patients; Anti ds-DNA seropositivity was 17(38.6%), anti Sm was 6 (13.6%), anti RNP was 14 (31.8%), anti Ro was 9 (20.5%) and Anti La was 6 (13.6).Two of 16 (12.5%) HC had unilateral grade 1 sacroiliitis and 11/44 (25%) patients had unilateral, 2/44 (4.5%) patients had bilateral grade 1–2 sacroiliitis on X-ray of the SI joints. Vascularisation inside or around the SI joints was seen in 25/44 (56.8%) SLE patients with 41 of 88 SI joints (46.5%) and 12/17 (70.6%) HC with 18 of 34 SI joints (52.9%) (p>0.05). The mean RI of the SI joints was 0.66 ± 0.11 in SLE patients and 0.64 ± 0.07 in HC with no significant difference between the groups (p>0.05). Prevalence of sacroiliitis on X ray and power Doppler signal inside the SI joints on CDDUS examination had no correlation (Pearson: 0.06). Clinical features and autoantibody seropositivity were not related to sacroiliitis (p>0.05), except anti Sm antibodies (p=0.026).

Conclusion: Although a significant subset of SLE patients had inflammatory LBP, most patients had no severe radiological or CDDUS evidence of sacroiliitis implicating a mild axial disease. The association with anti-Sm antibodies needs further evaluation.

Disclosure: **N. Yilmaz**, None; **A. Yazici**, None; **S. Z. Aydin**, None; **S. Yavuz**, None.

1399

Regional Fat Distribution Is Independently Associated with Damage Accrual in Systemic Lupus Erythematosus Female Patients. Manuel F. Ugarte-Gil, Rocio V. Gamboa-Cardenas, Karim E. Diaz-Deza, Mariela Medina-Chinchon, J. Mariano Cucho-Venegas, Risto A. Perich-Campos, Jose L. Alfaro-Lozano, Alfredo A. Sanchez-Torres, Zoila Rodriguez-Bellido, Sheyla Rodriguez-Ulloa and Cesar A. Pastor-Asurza. Hospital Almenara, Lima, Peru

Background/Purpose: In general population, a higher trunk fat and the ratio of trunk fat to leg fat (trunk-leg ratio) increase the risk for a cardiovascular event, and a higher leg fat decreases this risk. The purpose of this study is to determine if level of disease cumulative damage in Systemic Lupus Erythematosus (SLE) as measured by the SLICC/ACR damage index (SDI) is independently associated with body fat distribution in female patients with SLE.

Methods: In a cross-sectional single center study, we evaluated 101 consecutives SLE female patients who were seen at the Rheumatology department of our hospital. SLE was defined using the ACR criteria; body composition analysis was assessed by dual energy X-ray absorptiometry (DXA). A chart review, clinical evaluation and laboratory exams were performed. We defined damage using SDI. Disease activity was measured using SLEDAI. Body fat percentage and fat distribution was reported as trunk fat percentage, leg fat percentage and trunk-to-leg fat ratio. For the univariate analysis we performed a simple linear regression model, after that, we performed a logistic regression model adjusted to disease activity, metabolic syndrome, body mass index, age, disease duration, time of exposure to prednisone and current dose of prednisone.

Results: One hundred and one SLE patients with an average age of 42.64 (SD: 12.77) years were evaluated. Almost all of them were mestizo, only one

was African Latin-American. Disease duration was 8.32 (SD: 7.20) years. Percent total body fat was 36.4% (SD: 7.0%), percent trunk fat 36.4% (SD: 8.1%), percent leg fat 37.8% (SD: 7.4%), trunk-to-leg ratio 1.72 (SD: 0.68). SDI was 0.86 (SD: 1.27), SLEDAI was 5.82 (SD: 4.26). Body mass index was 27.11 (SD: 5.20) kg/m2. Forty-four (43.6%) patients had metabolic syndrome. Current dose of prednisone was 8.43 (SD: 5.18) mg/d and the time of exposure to prednisone was 8.11 (SD: 6.79) years. SDI correlate with trunk-to-leg fat ratio (β: 0.41, p<0.001) and percent leg fat (β: −0.22, p: 0.03), but not with percent total body fat (β: −0.10, p: 0.31) or percent trunk fat (β: −0.04, p: 0.71). After adjustment for disease activity, metabolic syndrome, body mass index, age, disease duration, time of exposure to prednisone and current dose of prednisone, SDI remained associated with trunk-to-leg fat ratio (β: 0.50, p<0.001) and leg fat (β: −0.25, p:0.009).

Conclusion: In SLE female patients, a higher level of disease damage is associated with a higher trunk-to-leg fat ratio and a lower leg fat, independently of disease activity, metabolic syndrome, body mass index, age, disease duration, time of exposure to prednisone and current dose of prednisone.

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1400

Predictors of Obesity in Systemic Lupus Erythematosus. Michelle Petri, Sesha Adusumilli and Hong Fang. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Hypertension and obesity are the two most important traditional cardiovascular risk factors in the prediction of subclinical measures of atherosclerosis in SLE. Obesity is the most important associate of hsCRP in SLE, as well. We analyzed predictors of obesity in a longitudinal SLE cohort.

Methods: Body mass index (BMI) was calculated at baseline and at last visit in a longitudinal cohort. 2,016 SLE patients with 48,163 visits were analyzed. Obesity was defined as BMI > 30.

Results: The patients were 92.6% female, with average age on 1/1/12 of 47.6 years. 37.4% were African-American and 55.6% Caucasian. The average BMI at cohort entry was 27.5 ± 7.9 and at last visit 28.2 ± 8.1. At cohort entry 28.1% were obese and at cohort end 32.5% were obese. 8.7% became obese and 4.4% who were obese became not obese. The table shows prediction of new obesity over cohort follow-up in a multivariate model.

Factor	Coefficient	P-value
Prednisone (mgs)–maximum dose	−0.009	**0.0249**
African-American ethnicity	0.057	0.5696
Education (years)	−0.010	0.7680
Private Insurance	−0.064	0.5612
Age at Diagnosis	0.009	0.2484
Current smoker	0.228	**0.0401**
Current drug abuser	0.107	0.6532
Discoid lupus	0.086	0.4112
Alopecia	0.081	0.3826
Proteinuria	−0.043	0.6655
Anemia	−0.043	0.6909
Lupus anticoagulant (RVVT)	0.246	**0.0072**
Dry mouth	−0.171	0.2257
Cardiac murmur	0.193	**0.0371**
Anti-dsDNA positive	0.008	0.9402
Low C4	0.015	0.8798
ESR	0.293	**0.0301**
Hyperglycemia	0.020	0.8266

Conclusion: New obesity developed in 8.7% during follow-up. Surprisingly, both maximum and mean (data not shown) prednisone dose had negative coefficients. The lupus anticoagulant and ESR were both predictors of obesity. Demographic factors (African-American race, lack of private insurance, smoking) were all predictive of new obesity. These data suggest that demographic variables can identify the subsets most at risk, for preemptive dietitian consulting and lifestyle intervention. However, the reason why some laboratory tests (lupus anticoagulant and ESR) are predictors is unknown. Ironically, prednisone dose was NOT a positive predictor in the multivariate model.

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

1401

Characterization of Clinical Photosensitivity in Cutaneous Lupus Erythematosus. Kristen Foering[1], Aileen Y. Chang[2], Evan W. Piette[2], Joyce Okawa[3] and Victoria P. Werth[4]. [1]University of Pennsylvania, Philadelphia VAMC, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Perelman School of Medicine at the University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA, [4]University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA

Background/Purpose: Photosensitivity (PS) is one of the most common manifestations of systemic lupus erythematosus (SLE), and is 1 of only 11 criteria used to make the diagnosis of SLE. However, the definition of photosensitivity is vague and its pathophysiology is not well understood. There is a need to better define the clinical aspects of photosensitivity in lupus, to enhance further study of this difficult problem. The objective of this study was to characterize self-reported photosensitivity phenotypes among a primarily cutaneous lupus (CLE) population.

Methods: A novel photosensitivity questionnaire provided a framework for characterizing subjects' experience of sun sensitivity. The PS questionnaire was based on information gathered over a 9-month period of subject interviews pertaining to sun exposure. Recurring themes of self-reported photosensitivity relating to morphology, characteristics, and timing of reactions were identified and incorporated into a brief PS questionnaire. The PS questionnaire was used to classify subject responses into five PS phenotypes: sun-induced CLE exacerbation (directCLE); general worsening of CLE in summer (genCLE); PMLE-like reactions (genSkin); general pruritus/paresthesia (genRxn); and systemic symptoms, e.g. headache, arthralgia (genSys). 100 subjects with CLE alone or both CLE and SLE were interviewed.

Results: 83% of subjects ascribed to any and 66% reported more than one PS phenotype. 47% cited direct examples of sun-induced CLE [directCLE]. Other PS phenotypes were reported as follows: 22% genCLE, 38% genSkin, 36% genRxn, and 37% genSys. The genSys phenotype was reported by fewer discoid and subacute cutaneous LE compared with acute and tumid LE subjects, χ^2=13.0, p<0.05. Subjects with both CLE and SLE reported more paresthesias/pruritus (51% vs 23%) and systemic symptoms (50% vs 26%) compared to those without SLE, p<0.05. Subjects with PMLE-like reactions had lower CLE Disease Area and Severity Index (CLASI) activity scores compared to other PS phenotypes (6.4 ± 5.4 vs 11.5 ± 11.11, p=0.02).

Conclusion: Self-reported photosensitivity in lupus ranges from CLE-specific reactions to generalized cutaneous eruptions to systemic symptoms. Clinical PS phenotypes are associated with CLE subtype, SLE diagnosis, and CLASI activity scores. Recognition of various PS phenotypes in CLE will permit improved definitions of clinical photosensitivity and allow for more precise investigation into the pathophysiology of photosensitivity in lupus.

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1402

Anti-ApoA1 Antibodies Associate with Disease Activity in Lupus and Are Lower in Patients Taking Hydroxychloroquine: A Longitudinal Analysis of 398 Samples. Sara Croca, Ian Giles, David A. Isenberg, Yiannis Ioannou and Anisur Rahman. University College London, London, United Kingdom

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have a significantly increased risk of developing cardiovascular disease. The presence of chronic inflammation which characterizes SLE disease activity may contribute to this risk. Apolipoprotein A1 (ApoA1) plays a protective role against atherosclerosis. Anti-ApoA1 antibodies have been described in patients with coronary disease. Our previous cross-sectional studies showed that anti-apoA1 levels are raised in patients with current and persistent disease activity but there are few longitudinal data. This abstract describes the result of longitudinal studies of anti-ApoA1 levels and measures of disease activity, serological profile and treatment in patients with SLE.

Methods: Longitudinal serum samples (n= 398) were selected retrospectively from a cohort of 49 patients with SLE with a mean of 8 samples per patient (SD 2.16; min 3; max 14) and a mean follow-up of 89 months (SD 46; min 14; max 180). Serum from 40 healthy controls and 15 patients with rheumatoid arthritis (RA) was also tested. Anti-ApoA1 levels were measured using a direct ELISA. Using the British Isles Lupus Assessment Group (BILAG) index, we categorized the samples by disease activity as follows. Current activity was defined as high if global BILAG score was ≥5 and

low if it was <5). Disease activity over the most recent 4 assessments was characterized as persistently low (all systems BILAG C, D or E) or persistently moderate-high (A or ≥1 B in any BILAG system on at least 2/4 occasions). 90% of all samples fell into one of those two categories and the rest were excluded.

Anti-dsDNA was defined as high or normal based on a cut-off of 50IU/ml. C3 was defined as low or normal based on a cut-off of 0.9g/l.

Data on the treatment at the time of each individual sample were also obtained, considering prednisolone dose and whether either immunosuppressants (IS) or hydroxychloroquine (HCQ) were used.

Results: 42% of the samples tested were positive for anti-ApoA1 (greater than mean + 3SD of healthy controls). Patients with SLE had significantly higher anti-ApoA1 levels than healthy controls and patients with RA (p< 0.0001). No association between either sex or ethnicity and anti-ApoA1 levels was found. Higher anti-ApoA1 levels were significantly associated with the following factors:
- Low complement levels (p= 0.017).
- Persistent disease activity (p=0.04)
- Disease activity on date of sample (p=0.04)
- Not being on HCQ (p<0.0001)
- Prednisolone dose< 5mg/day (p= 0.0067)

We found no association between anti-ApoA1 and positivity for anti-dsDNA or ENA and no significant association with use of IS.

Conclusion: The presence of anti-ApoA1 antibodies has been shown in patients with SLE and may play a role in disturbing the normal lipid homeostasis which in turn may contribute to the increased cardiovascular risk associated with this disease. We have found that anti-ApoA1 levels are increased in patients with SLE compared to healthy controls and patients with RA. Anti-ApoA1 levels appear to be associated with both clinical and serological disease activity measures. The use of HCQ seems to be associated with lower anti-ApoA1 levels.

1403

Anti-Nucleosome Antibodies Are Associated with Disease Activity and Hydroxychloroquine Use in Patients with Lupus: A Longitudinal, Multivariate Analysis of 398 Samples. Sara Croca, Ian Giles, David A. Isenberg, Yiannis Ioannou and Anisur Rahman. University College London, London, United Kingdom

Background/Purpose: Impaired apoptotic clearance appears to play a pivotal role in the pathogenesis of SLE leading to the accumulation of nuclear debris, such as nucleosomes, ultimately stimulating the production of autoantibodies. Both nucleosomes and anti-nucleosome antibodies (AN) have been found in serum of patients with SLE and appear to correlate with disease activity. AN have been particularly associated with renal and skin disease. This abstract describes the result of longitudinal studies of AN levels, ethnicity, autoantibody profile, treatment and measures of disease activity in patients with SLE.

Methods: Longitudinal serum samples (n= 398) were selected retrospectively from a cohort of 49 patients with SLE with a mean of 8 samples per patient (SD 2.16; min 3; max 14) and a mean follow-up of 89 months (SD 46; min 14; max 180). Sera from 40 healthy controls were also tested. OD values were converted to standard absorbance units (AU) by comparison to a positive control serum sample loaded on every plate. AN levels were measured using a direct ELISA and a positive result was defined as mean + 3SD of the healthy controls (0.17). Using the British Isles Lupus Assessment Group (BILAG) index, we categorized the samples by disease activity as follows.

Current activity was defined as high if global BILAG score was ≥5 and low if it was <5. Disease activity over the most recent 4 assessments was characterized as persistently low activity (all systems BILAG C, D or E) or persistently moderate-high activity (A or ≥1 B in any BILAG system on at least 2/4 occasions). 90% of all samples fell into one of those two categories and the rest were excluded.

Anti-dsDNA was defined as high or normal based on a cut-off of 50IU/ml. C3 was defined as low or normal based on a cut-off of 0.9g/l.

Data on the treatment at the time of each individual sample were also obtained, considering prednisolone dose and whether either immunosuppressants (IS) or hydroxychloroquine (HCQ) were used.

Results: Table 1 shows that higher AN levels were significantly associated with low C3 and high anti-dsDNA levels as well as with higher

current or persistent disease activity defined by the BILAG index. We found no association between AN levels and ethnicity, ENA positivity or flares in individual organs. Patients who were taking HCQ and those on low dose steroids (≤5mg/day) had significantly lower AN levels (p< 0.0001). No differences were found with regards to presence or absence of IS.

	Number of samples (*n*)	Mean (SD) AN level	*p*-value (high vs. low)
Persistently moderate-high activity	209	59.1 (99.4)	0.0243
Persistently low activity	166	49.1 (84.0)	
BILAG< 5	166	49.1 (84.0)	0.0243
BILAG≥ 5	209	59.0 (99.4)	
Anti-dsDNA			
High (>50IU/ml)	177	37.5 (75.2)	<0.0001
Normal (≥50IU/ml)	170	78.5 (112.5)	
Complement (C3)			
Normal (≤0.9g/l)	209	50.1 (90.4)	0.04
Low (>0.9g/l)	138	68.9 (105.6)	
Hydroxychloroquine			
Yes	174	43.46 (76.9)	>0.0001
No	223	65.15 (105.4)	
Predisolone			
>5mg/day	209	40.2 (76.9)	>0.0001
≤5mg/day	188	72.8 (108.4)	

Conclusion: AN levels were significantly associated with disease activity assessed both by clinical and serological measures. In addition, it appears that the type of treatment used, namely the use of HCQ may influence the levels of AN.

1404

There Is an Association Between Disease Activity and Risk of Thromboembolism in SLE. Reem Jan, Emily E. Lewis, Ting Ting Lu, Emily Siegwald and W. Joseph McCune. University of Michigan, Ann Arbor, MI

Background/Purpose: Venous thromboembolism is a recognized complication of systemic lupus erythematosus (SLE). The role of antiphospholipid antibodies (aPL) in thrombogenesis is well documented; much less is known about the potential for an increased risk of thromboembolic disease in the absence of these markers. Inflammatory stimuli are prothrombotic, with apoptotic endothelial cells identified as a potential trigger through tissue-factor dependent pathways. We aim to determine whether venous thromboembolic events (VTE) in patients with SLE correlate with periods of enhanced disease activity.

Methods: A retrospective chart review was performed on 837 patients enrolled in the Michigan Lupus Cohort to identify patients diagnosed with VTE. Patients satisfied ≥4 ACR criteria for SLE. Diagnosis of VTE was defined as a positive venous doppler, CT scan of the thorax, or high probability VQ scan.

Risk factors for VTE were noted including: use of oral contraceptives within 3 months of the event, pregnancy/6 weeks postpartum, surgery within 3 months, smoking, inherited thrombophilia, malignancy, and the presence of nephrotic-range proteinuria. We also noted the presence of aPL positivity (defined by positive lupus anticoagulant or antibodies to cardiolipin or beta-2 glycoprotein-1 IgG, IgM or IgA at >99% percentile of assay).

Disease activity was measured by the Systemic Lupus Disease Activity Index (SLEDAI).

Markers of disease activity at the time of VTE were recorded using the closest SLEDAI score within 3 months before, or up to 1 month after the event. Comparisons were made between the SLEDAI score at the time of the event and a baseline SLEDAI collected up to 12 months prior to the event for each patient.

Results: 72 patients were identified as having sustained a VTE (8.6%). Of these patients, 36 had serial SLEDAI data available. The most frequently detected confounding risk factors were recent surgery (30.6%; p= 0.012) and the presence of aPL (25%; p= 0.033). If aPL positivity was required to be present on two separate occasions, this no longer became a statistically significant association.

There was a significant association between VTE and disease activity, with a mean increase in SLEDAI score of 1.72 at the time of event (p= 0.021; 95% CI 0.274–3.471).
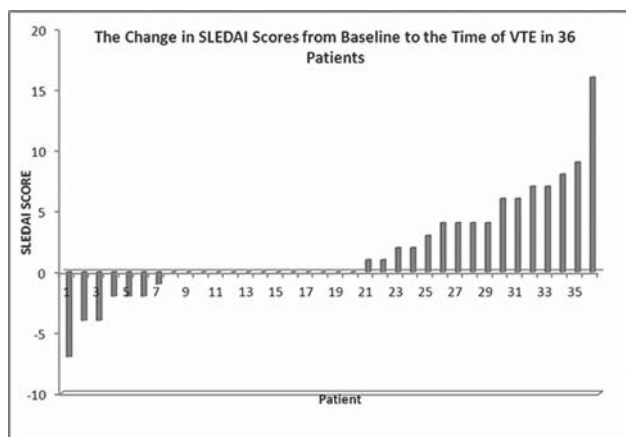
Figure 1. The difference for each patient between the SLEDAI score at the time of VTE compared with the score 4–12 months previously.

Conclusion: Our results show a statistically significant association between disease activity and VTE, independent of the presence of aPL. This has implications for the management of patients with active SLE, including decisions regarding the safety of estrogens for contraception and the threshold for anticoagulation in high-risk situations such as pregnancy. It may also lend clinical support to a growing body of basic science research that suggests an association between inflammation and thrombosis.

1405

Real World Experience Comparing Multiplex Immunobead Assay versus Immunoflorescence Assay for Anti-Nuclear Antibody Detection At a University Hospital. Neha Dang, Brock E. Harper, Emilio B. Gonzalez, Silvia S. Pierangeli, Trisha M. Parekh, Michael J. Loeffelholz and Kimberly K. Bufton. University of Texas Medical Branch, Galveston, TX

Background/Purpose: Anti-nuclear antibody (ANA) is considered a screening method for diagnosis of autoimmune disorders. Immunoflorescence ANA assay (IF) remains the gold standard for detection of ANA as per the 2011 ACR position statement. Many laboratories perform immunoassays for detection of ANA as it is less labor-intensive to perform.

Methods: We collected data prospectively on patients tested for ANA by multiplex immunobead assay MIA (BioPlex ANA screen, Bio-Rad Laboratories, Hercules, CA, USA) and IF assay (HEp-2000 (Immuno Concepts, Sacramento, CA, USA) from chart review of rheumatology patients from March 2011 to May 2012. Patients were separated into 4 groups based on positive and negative ANA by MIA and IF assay. Data were collected by individual chart review including age, gender, ethnicity, and indication for ANA testing. Sensitivity and specificity of the immuno assay were determined using the IF results as the "gold standard".

Results: One hundred and ten (110) patient samples were tested for both assays. Multiplex immunobead assay (MIA) were considered positive based on the manufacturer's instructions, and IF was considered positive at a titer $\geq 1{:}160$; 12 (10%) were positive by both assays and were considered true positives (TP), 74 (67%) were negative by both or true negatives (TN); 15 (14%) were positive by IF and negative by MIA and were false negatives (FN); 9 (8%) were positive by MIA and negative by IF, or false positives (FP) (Table 1). Indications for ANA testing in the false negative group included systemic sclerosis, polymyositis, rheumatoid arthritis on treatment with anti-TNF therapy, undifferentiated connective tissue disorders, and polyarthralgias (Table 2). Sensitivity and specificity for the multiplex immunoassay was 44%, and 89%, respectively.

Table 1. Comparison of ANA MIA and IF

	IF positive ($\geq 1{:}160$)	IF negative
Multiplex positive n (%)	12 (10%) TP	9 (8%) FP
Multiplex negative n (%)	15 (14%) FN	74 (67%) TN

Sample size 110

Table 2. Baseline Demographic comparison

	Multiplex +, IF+ (TP)	Multiplex −, IF − (TN)	Multiplex +, IF − (FP)	Multiplex −, IF + (FN)
Age (mean±SD)yrs	45±13	48±15	47±18	48±16
Females n (%)	11 (91%)	59 (79%)	8 (89%)	13 (86%)
Ethnicity*(%)	AA (16%) C (25%) H (50%)	AA (13%) C (70%) H (9%)	AA (33%) C (44%) H (11%)	AA (46%) C (46%)
Indication for testing/ Clinical diagnosis (n)				
SLE	5	1	1	-
Sjogren's	1	-	-	-
RA	1	9	1	2
Systemic sclerosis/PM/DM	-	-	-	2
Polyarthralgias	2	30	2	6
UCTD	2	-	-	3
Others	2	32	5	1

*AA African American, C Caucasian, H Hispanic

Conclusion: Our study reveals a low sensitivity with high rate of false negatives when MIA is used for ANA screening compared to IF in a real world rheumatology setting of patients presenting with a variety of autoimmune diseases. Patients misclassified by the MIA included patients with definite ANA-associated autoimmune diseases. These data suggest that screening with an immuno assay would result in misclassification and potential delay or missed diagnoses of certain systemic autoimmune diseases. Immunoflorescence assay should remain the preferred assay for ANA testing in patients with suspicion of autoimmune disorders until until high sensitivity platforms are developed.

1406

The Cost of Management of Adult Active Systemic Lupus Erythematosus in the UK. Munther A. Khamashta[1], Christina Donatti[2], Ian N. Bruce[3], Caroline Gordon[4], David A. Isenberg[5] and Ateka-Barrutia Oier[1]. [1]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [2]IMS Health, United Kingdom, [3]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [4]University of Birmingham, Birmingham, United Kingdom, [5]University College London, London, United Kingdom

Background/Purpose: Several international studies have shown that systemic lupus erythematosus (SLE) has a considerable financial burden on patients and the health-care economy. Little recent information is available in most European countries about the cost of SLE care (treatment strategies, healthcare pathways, medical resource utilization), especially for patients with moderate to severe disease to make valid comparison with other countries. The aim of this study was to evaluate the annual direct medical costs of the management of adult SLE with active disease in the UK.

Methods: A multi-centre retrospective chart review involving four specialist lupus centres in the UK recruited 86 SLE patients: 38 severe and 48 non severe patients. At inclusion, patients had to have: 1) at least one change (increase in dose and/or new treatment) in treatment related to current SLE activity, and/or a new manifestations and/or worsening of clinical symptoms of SLE; or, 2) presence of at least one biomarker of SLE activity and concurrently, the presence of at least one clinical and/or hematological feature of SLE. Two-year direct costs were obtained by summarizing all the health resource costs related to laboratory and imaging tests, medical treatment, visits to doctors, day hospitalization, day surgery, emergency room visits, inpatient stays and rehabilitation stays.

Results: Of the patients studied, 68 (94.4%) were female. The mean age was 45.5 ($\pm$13.9) years and the mean duration of SLE was 11.9 ($\pm$8.3) years. At baseline, 48/86 (55.8%) of patients had relapsing-remitting SLE and 29/86 (33.7%) had chronically active SLE; 73/86 (84.9%) of patients received corticosteroids, 63/86 (73.3%) antimalarials, 48/86 (55.8%) immunosuppressants and 17/86 (19.8%) NSAIDS. No biological drugs were prescribed at inclusion. The mean (SD) SELENA-SLEDAI score was 7.7 (5.7), and was statistically significantly greater in severe patients (9.6 vs 6.1, p=0.004). Organ damage was present in 34/86 (39.5%) of patients. Anti-dsDNA antibodies were tested in 83/86 (96.5%) at baseline; of which 53/83 (63.9%) were positive.

The median annual direct medical cost of management of adult SLE patients with active autoantibody positive disease on medication for SLE was £2855.87 (US$4389.02) (mean [SD]: £3230.65 [£2333.21] (US$4,964.98 [US$3585.77]). The minimum and maximum costs (min: £389.06 (US$597.92), max: £9701.52 (US$14909.66) respectively) showed the wide range of costs, associated with a wide spectrum of disease activity and complications needing intervention in these lupus patients. The mean annual direct medical cost was 2.2 times higher in severe than in non-severe SLE patients (p<0.001).

Conclusion: The trend in terms of direct costs for treating active SLE patients and the marked gradient associated with increasing disease severity are consistent with Sutcliffe et al (2001), which calculated direct costs at £2613 and higher disease activity was associated with increased costs. There are very few published studies attempting to calculate the direct costs of SLE and this study provides current and reliable source of cost data for active SLE patients in the UK and comparable healthcare systems.

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1407

The Effect of the Antiphospholipid Syndrome (APS) On Survival in Chinese Patients with SLE: A Prospective Study of 679 Patients. Chi Chiu Mok, Ling Yin Ho, Ka Lung Yu and Chi Hung To. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To study the effect of the antiphospholipid syndrome (APS) on survival in Chinese patients with SLE

Methods: A cohort of 679 southern Chinese patients who fulfill at least 4 of the ACR criteria for SLE from 1995 to 2011 was studied. The status of the patients at last clinical visits (alive or death) was evaluated. The cumulative survival rate over time was studied by Kaplan-Miere's plot. For those who died during the course of their disease, data were censored at the time of their deaths whereas data of other patients were censored at the time of last clinic visits. APS was defined by the modified Sydney criteria in 2006, ie. The presence of arterial or venous thrombosis, or miscarrages (recurrent abortion or intra-uterine death) plus any one of the following positive twice at least 12 weeks part: (1) lupus anticoagulant; (2) moderate to high titers of anticardiolipin antibodies (IgG or IgM); or (3) beta-2-glycoprotein-I. Comparison of the survival of patients with and without APS was made.

Results: 679 SLE patients (92% women; age of disease onset 32.5±14 years) were prospectively followed for 9.7±7.3 years. Sixty-eight (10%) patients died and 33 (4.9%) patients were lost to follow-up. The main contributing causes of death in these patients were: infection (53%), cardiovascular events (6%), cerebrovascular events (15%), and cancer (9%). Forty-four (6.5%) patients qualified the criteria for APS, manifested as: ischemic stroke (55%), deep venous thrombosis (32%), obstetric morbidity (14%), cardiovascular events (9%) and peripheral vascular disease (9%). Twenty-three (52%) patients developed APS after the diagnosis of SLE, 16 (36%) patients had concomitant APS diagnosed at the same time as SLE and 5 (11%) patients had APS preceding SLE diagnosis. Nine (20%) APS patients died, which was significantly more frequent than the non-APS SLE patients (59/635[9%]; p=0.02). Patients with the APS died at an older age than those without APS (54.0±11.4 vs 45.1±18.2; p=0.07). The duration of SLE at the time of death was also longer in patients with the APS than those without (13.9±10.4 vs 7.47±7.4 years; p=0.11). The cumulative mortality of patients with APS was 4.6% at 5 years, 7.8% at 10 years and 22.2% at 15 years, which was not significantly higher than that of non-APS patients (5.4% at 5 years, 9.2% at 10 years and 11.3% at 15 years; p=0.14). However, if only patients with APS caused by arterial thrombosis were considered, the presence of APS was significantly associated with mortality (HR 2.29 [1.13–4.64]; p=0.02).

Conclusion: The presence of APS increases the mortality risk of patients with SLE, which is mainly contributed by arterial thrombotic events that occur late in the disease course.

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1408

Monitoring Patients with Systemic Lupus Erythematosus in Clinical Practice: Have You Already Checked the Vaccination Status in Your Patients? Olga Malysheva, Jean-Philipp Ivanov, Sybille Arnold and Christoph G. Baerwald. University Hospital, Leipzig, Germany

Background/Purpose: Infection is one of the main causes of morbidity and increased mortality in patients with systemic lupus erythematodes (SLE). Information about vaccination history and updating vaccinations on a regular basis is an economical way to avoid complications of various infections. Ideally vaccinations should be done prior to starting immunosuppressive treatment. Influenza, pneumococcal and tetanus vaccines are safe and do not lead to SLE flares while the majority of patients develop protective antibodies. Recommendations for hepatitis B and varicella herpes zoster (VZV) vaccination have not yet been validated in SLE patients. The purpose of study was to assess the vaccination rates against common infections and to determine the incidence of hepatitis B and VZV infections in patients with SLE attending a rheumatology outpatient clinic.

Methods: Data collected included age, duration of disease and treatment (systemic corticosteroids, methotrexate, azathioprine, hydroxychloroquine). According to the recommendations for vaccination in patients with rheumatic diseases derived from The European League against Rheumatism (EULAR) and the German Robert Koch Institute for Infection Control vaccination history was taken for MMR (measles, mumps and rubella), poliomyelitis, pertussis, diphtheria, influenza, human papillomavirus, hepatitis A, hepatitis B, tetanus, meningococcal and pneumococcal vaccines. A simple questionnaire was designed and 68 SLE patients were asked to provide their vaccination records. Patients were also tested for hepatitis B (anti-HBc, anti-HBs) and VZV (IgG) status.

Results: 95.6 % of SLE patients presented a vaccination card. Of interest, 75 % patients did not receive the influenza vaccine in the previous year. Only 12 patients (19 %) in total and 30 % in the age group > 60 years have ever received the pneumococcal vaccination. The vaccination rate for tetanus (combined vaccination with diphtheria and pertussis) was 51 %. For the remaining vaccinations the following picture emerged: vaccination was complete for 66 % against poliomyelitis, 11.8 % for hepatitis A, 1.5 % for meningococcus, 2.6 % for MMR. Only 1.6 % of SLE patients were vaccinated against human papillomavirus (only 12.5 % of the patients < 27 years). Patients with SLE do not have an increased incidence of hepatitis B and we did not detect any patient with an active hepatitis B. Only 14.7 % patients with SLE had a vaccination against hepatitis B. 2 SLE patients (3.6%) exhibited an abnormal hepatitis serology (increase of anti-HBc + anti-HBs-Titre, or anti-HBc) and only one of them had a moderate increase of liver enzymes. 97% SLE patients were positive for VZV IgG and 23 SLE patients (33.8%) had a history of VZV infection with postherpetic neuralgia. Therefore, 60% of SLE patients may be considered for herpes zoster vaccination; however, no patient was vaccinated against VZV.

Conclusion: In SLE patients with stable disease the vaccination rate was low. More careful monitoring of SLE patients concerning vaccination is necessary. In particular with new therapies being directed against B-lymphocytes a timely update of the vaccination status is mandatory for every individual patient with SLE.

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1409

A Multicentre Clinical Study of Umbilical Cord Mesenchymal Stem Cells Transplantation in Active Systemic Lupus Erythematosus. Lingyun Sun[1], Dandan Wang[1], Jing Li[2], Miao Zhang[3], Yu Zhang[4] and Xia Li[1]. [1]Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Department of Rheumatology, Affiliated Hospital of Jiangsu University, Zhenjiang, China, [3]Department of Rheumatology, Jiangsu Provincial People's Hospital, Nanjing, China, [4]Department of Rheumatology, Subei People's Hospital of Jiangsu Province, Yangzhou, China

Background/Purpose: Umbilical cord (UC) derived mesenchymal stem cells (MSCs) have shown safety profile and therapeutic effect in severe and refractory systemic lupus erythematosus (SLE) in our single-centre pilot study. The present multicentre clinical trial was undertaken in China to assess the efficacy and safety of allogenic UC MSCs transplantation (MSCT) in active SLE patients.

Methods: Forty patients (aged ≥16 years) with active SLE (SLE Disease Activity Index >6) were enrolled from 4 clinical centres in China. All patients gave informed consents before transplantation, and allogenic UC MSCs were infused intravenously on days 0 and 7. Adverse event was monitored during and after MSCs transplantation. Primary efficacy endpoints were major clinical response (MCR), partial clinical response (PCR) and relapse at 6 and 12 months. Secondary endpoints were improvement in SLEDAI score, British Isles Lupus Assessment Group (BILAG) score, serum levels of creatinine, urea nitrogen, complements and albumin pre- and post-MSCT.

Results: Fourteen and fifteen patients achieved MCR (14/40, 35.0%) and PCR (15/40, 37.5%) at 6 months follow-up, respectively. Three and four patients experienced disease relapse at 9 (7.5%) and 12 (10%) months follow-up, respectively, after a prior clinical response. SLEDAI score significantly decreased at 3 (7.43±3.93), 6 (6.30±3.63), 9 (6.40±3.84) and 12 months (6.48±3.52) follow-up (P all <0.05 vs. baseline 10.83±4.63). Total BILAG score markedly decreased 3 months after MSCT, and continued to decrease in the following visit times. BILAG score for renal and hematopoietic system significantly improved. For those with lupus nephritis, 24-hour proteinuria declined after transplantation, with statistical differences at 9 (1.24±1.09 mg) and 12 months (1.41±1.33 mg, P<0.05 vs. baseline 2.24±1.43 mg). Serum creatinine and urea nitrogen decreased to the lowest level at 6 months, while slightly increased at 9 and 12 months due to the 7 relapsed cases. Additionally, Serum levels of albumin, complements 3 and 4 increased after MSCT, peaked at 6 months visit, then slight declined at 9 and 12 months. Serum anti-nuclear antibody (ANA) and anti-double strand DNA (dsDNA) antibody decreased after MSCT, with statistical differences at 3 months follow-up. Furthermore, hemoglobin and platelet counts increased after MSCT in those with hematopoietic involvement. UC-MSCT was well tolerated and no adverse event was observed.

Conclusion: Our findings indicate that UC MSCT results in satisfactory clinical responses in SLE. However, several cases experienced disease relapse after 6 months visit, which suggests the necessity for repeated MSCT after 6 months in some patients.

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1410

Relationship Between Individual Organ Damage and Mortality of Systemic Lupus Erythematosus (SLE): A Prospective Cohort Study of 679 Patients. Chi Chiu Mok, Ling Yin Ho and Ka Lung Yu. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To study the relationship between damage in different organ systems and mortality in patients with SLE.

Methods: 679 patients who fulfilled at least 4 of the ACR criteria for SLE between 1995 and 2011 were prospectively followed. The cumulative rate of survival was studied by Kaplan-Meier's plot. For those who died during the disease course, data were censored at the time of death. For other patients, including those who were lost follow-up, data were censored at the time of last clinic visits. Organ damage was assessed by the ACR SLICC damage scores (SDI). Cox regression models were established to study the association between damage in individual systems and mortality in this cohort of patients.

Results: 679 SLE patients were studied (623 women, 92%). All were ethnic Chinese. The mean age of onset of SLE was 32.5±13.6 years and the mean follow-up time of the entire cohort of patients was 117±89 months. 67 (9.9%) patients died during the course of illness and 33 (4.9%) patients were lost to follow-up. 23 (3.4%) patients developed end stage renal failure (ESRF). The main contributing causes of death were: infection (51%), cardiovascular events (12%), cerebrovascular events (16%), cancer (9%), suicide (3%) and others (8%). Infective complications were the commonest causes of death both in patients with disease duration of less (55%) and more than 5 years (47%). In patients with SLE for less than 5 years, 19% of all deaths were caused by vascular events, which was lower than those with disease for more than 5 years (36%). The cumulative survival rate of the patients was 94.8% at 5 years, 91.3% at 10 years and 88% at 15 years. 301 (44%) patients had organ damage (SDI score $\geq$1). Among patients who had organ damage, the frequency of damage in individual systems was, in decreasing order: neuropsychiatric (N=102, 15%), musculoskeletal (N=93, 14%), renal (N=78, 11%), ocular (N=46, 6.8%), cardiovascular (N=38, 5.6%), pulmonary (N=36, 5.3%), gonadal (N=32, 4.7%), endocrine (N=23, 3.4%), peripheral vascular (N=22, 3.2%), malignancy (N=19, 2.8%) and gastrointestinal (N=8, 1.1%). Within the first 5 years of onset of SLE, neuropsychiatric damage was most frequent (10%), followed by renal (7.9%) and dermatological (7%) damage. In patients with SLE duration of more than 5 years, the commonest cause of damage was in the musculoskeletal system (18.4%), followed by neuropsychiatric (17%) and renal damage (13.3%). The presence of any organ damage was strongly and significantly associated with mortality (HR 6.42[3.05–13.5]; p<0.001). Cox regression analysis revealed that damage in the neuropsychiatric system (HR 1.74[1.31–2.32]; p<0.001), renal (HR 1.97 [1.61–2.42]; p<0.001), cardiovascular (HR 1.75 [1.21–2.53]; p=0.03) and pulmonary (HR 2.63 [1.50–4.62]; p=0.001) systems was significantly associated with mortality.

Conclusion: In patients with SLE, organ damage predicts mortality, in particular damage in the renal, nervous, cardiovascular and pulmonary systems. Neuropsychiatric damage is most common in early disease while musculoskeletal damage is most frequent in long-standing disease. Prevention of infective and cardiovascular complications, and minimization of renal damage is important in improving the survival of SLE.

Disclosure: **C. C. Mok**, None; **L. Y. Ho**, None; **K. L. Yu**, None.

1411

Equivalence of Various Language Versions of Lupus Specific Patient Reported Outcomes Measure (LupusPRO). Meenakshi Jolly[1], Mark Kosinski[2], Sergio M.A. Toloza[3], Joel A. Block[1], Rachel A. Mikolaitis[1], Sergio Durán-Barragan[4], Ana M. Bertoli[5], Ivana Blazevic[6], Luis M. Vila[7], Dilrukshie Cooray[8], Emmanuel P. Katsaros[9], Karina Marianne D. Torralba[10], Ioana Moldovan[11], Arif Kaya[12], Berna Goker[12], Seminur Haznedaroglu[12], Mehmet E. Tezcan[12], Josiane Bourré-Tessier[13], Sasha Bernatsky[14], Ann E. Clarke[15], Michael H. Weisman[16], Sandra V. Navarra[17], Daniel J. Wallace[16] and Graciela S. Alarcon[18]. [1]Rush University Medical Center, Chicago, IL, [2]QualityMetric Inc, Lincoln, RI, [3]Hospital San Juan Bautista, Catamarca, Argentina, [4]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico, [5]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [6]University of Buenos Aires, Buenos Aries, Argentina, [7]University of PuertoRico Medical Sciences Campus, San Juan, PR, [8]Harbor UCLA Medical Center, Torrance, CA, [9]Loma Linda Univ, Loma Linda, CA, [10]USC Keck Schl of Medicine, Los Angeles, CA, [11]Loma Linda Univ Medical Center, Loma Linda, CA, [12]Gazi University Medical School, Ankara, Turkey, [13]McGill University, Montréal, QC, [14]Research Institute of the McGill University Health Ctre, Montreal, QC, [15]MUHC, Montreal, QC, [16]Cedars-Sinai Medical Center, Los Angeles, CA, [17]University of Santo Tomas Hospital, Manila, Philippines, [18]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Due to observed disparities in health outcomes in Systemic Lupus Erythematosus (SLE) across racial/ethnic groups, socioeconomic status, or health care systems, studies on group comparisons can highlight important contextual influences on health outcomes. However, comparative research requires the measurement tool used to quantitate such health outcomes to have similar measurement qualities across settings (Measurement Equivalence). This property focuses on the internal structure of multi-item instruments. Currently measurement equivalence data is not available on any of the SLE specific patient reported outcome tools. Herein, we present measurement equivalence properties of various language versions of the LupusPRO that were tested across nations.

Methods: Data from the SOUL study (Study of Outcomes in Lupus) collected during cross-cultural validation studies of the LupusPRO in various languages were utilized: English [USA (n=180), Canada (n=123), Philippines (n=100)], Spanish [USA (n=121), Mexico (n=34), Argentina (n=56)] and Turkish (Turkey n=102). Confirmatory factor analysis (CFA) was conducted with the LupusPRO ítem responses using a robust weighted least squares estimator. The goodness of fit parameters used were the Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI). In addition, item to factor loadings were tested. For measurement equivalence, a logistic regression approach was used to test for differential Item functioning (DIF) in each LupusPRO scale item across languages, while conditioning on the aggregate sum score for each LupusPRO score. The magnitude of DIF was quantified by a pseudo R^2 difference measure and $\geq$2 % variance was considered significant DIF across languages

Results: Results of the CFA lend empirical support for the conceptual framework of the LupusPRO across languages. The model fit for the hypothesized item to scale relationships was good (CFI=0.94–0.98, TLI=0.95–0.99). In addition, item to factor representing the hypothesized item to scale relationships were also satisfactory. In general, items loaded >0.6 with their respective factor. Of the 43 LupusPRO items, only 6 items showed a marginal DIF: (1) woke up feeling worn out, (2) worried about losing income, (3) lacked control over appearance, (4) ability to plan activities and schedule events, (5) received comfort/strength from spiritual/religious beliefs, and (6) doctor was accessible when I had questions. Some of these could be due to cultural differences.

Conclusion: Since the LupusPRO demonstrates measurement equivalence across languages, it can now be used for comparative research

studies to gain better insight into health outcomes disparities or effects of interventions across various groups of SLE patients in cross-national studies. Further evaluation and analysis of the items showing DIF are ongoing.

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1412

Vascular Cell Adhesion Molecule (VCAM-1) and Angiostatin in Systemic Lupus Erythematosus. Adnan Kiani[1], Hong Fang[1], Tianfu Wu[2], Chandra Mohan[3] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [3]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule, is involved in the progression of glomerular and tubulo-interstitial injury. High levels of VCAM-1 have been found in the urine of patients with active lupus nephritis. Angiostatin, due to its anti-inflammatory action, has been shown to improve kidney function in murine models. Over expression of angiostatin inhibits leukocyte and macrophage migration and recruitment. We investigated both VCAM-1 and angiostatin as potential biomarkers for lupus nephritis.

Methods: VCAM-1 and angiostatin were measured during 2 to 16 clinic visits in 17 SLE patients (82% female, 42% African-American, 45% Caucasian, and 13% others) for a total of 88 visits by ELISA (R&D). Mean age was 38 years. We analyzed the relationship between these potential urine biomarkers and the urine protein/creatinine ratio (urine Pr/Cr), the SLICC Renal Activity Score, SLEDAI renal descriptors and other clinical variables.

Results:

Table 1. Mean (SD) Log-transformed and Normalized (by urine creatinine) VCAM-1 and Angiostatin, by Clinical Variables at Each Visit

	Clinical Variables at Each Visit	VCAM-1		Angiostatin	
		Mean (SD)	P-value*	Mean (SD)	P-value*
Age, years	21–.44 (n=65)	9.1 (2.4)	0.99	5.1 (1.6)	0.019
	45–.70 (n=23)	9.2 (1.2)		6.1 (1.8)	
Sex	Female (n=72)	9.2 (2.3)	0.63	5.4 (1.6)	0.77
	Male (n=16)	8.9 (1.1)		5.5 (2.1)	
Ethnicity	Caucasian (n=40)	8.4 (2.7)	0.086	4.7 (1.5)	0.21
	African American (n=37)	9.7 (1.1)		6.0 (1.6)	
	Other (n=11)	9.9 (1.0)		5.8 (2.2)	
Physician's Global Assessment	≥1.5 (n=64)	9.7 (1.1)	0.0069	5.9 (1.6)	<0.0001
	<1.5 (n=24)	7.5 (3.2)		4.1 (1.3)	
Hematuria	Present (n=14)	9.2 (1.4)	0.12	5.0 (1.6)	0.65
	Absent (n=74)	9.1 (2.2)		5.5 (1.7)	
Proteinuria	Present (n=26)	9.9 (1.1)	0.089	6.2 (1.4)	0.012
	Absent (n=62)	8.8 (2.4)		5.0 (1.7)	
Pyuria	Present (n=10)	9.7 (1.4)	0.94	5.2 (1.4)	0.74
	Absent (n=78)	9.0 (2.2)		5.4 (1.8)	
Anti-dsDNA	Present (n=37)	9.9 (0.9)	0.088	5.6 (1.8)	0.31
	Absent (n=51)	8.6 (2.5)		5.2 (1.6)	
Low C3 or C4	Present (n=31)	10.1 (1.0)	0.059	5.6 (1.9)	0.12
	Absent (n=55)	8.6 (2.4)		5.3 (1.6)	
Urine Protein/ Creatinine Ratio	≥0.5 (n=64)	9.6 (1.2)	0.022	5.9 (1.6)	<0.0001
	<0.5 (n=22)	8.0 (2.9)		3.8 (1.0)	
Renal Failure	Ever (n=3)	7.8 (1.1)	0.28	4.6 (1.2)	0.12
	Never (n=85)	9.2 (2.1)		5.4 (1.7)	
Hydroxychloroquine	Yes (n=66)	8.9 (2.3)	0.22	5.4 (1.8)	0.41
	No (n=22)	9.8 (1.2)		5.5 (1.6)	
Diabetes mellitus	Present (n=9)	9.9 (1.1)	0.38	6.7 (1.3)	0.096
	Absent (n=79)	9.0 (2.2)		5.2 (1.7)	
Use of ACE/ARB inhibitor	Yes (n=64)	9.2 (2.1)	0.36	5.5 (1.7)	0.79
	No (n=24)	8.9 (2.3)		5.1 (1.7)	
SLICC Renal Activity Score	≥4 (n=51)	9.8 (1.1)	0.036	6.1 (1.6)	<0.0001
	<4 (n=29)	8.4 (2.7)		4.2 (1.3)	

*P-values are based on a mixed effects model to account for the fact that some patients contributed multiple observations.

Conclusion: Both urine VCAM-1 and angiostatin had a strong association with multiple renal activity descriptors. However, in contrast to a previous murine study which showed angiostatin may improve kidney function, our study showed the reverse (Am J Physiol Renal Physiol 2009:F145–152). Further studies of urinary VCAM-1 and angiostatin with larger sample size, and long-term renal outcomes ARE justified.

Disclosure: A. Kiani, None; **H. Fang**, None; **T. Wu**, None; **C. Mohan**, None; **M. Petri**, None.

1413

Clinical Presentation, Treatment and Outcome of Membranous Nephropathy in SLE: A Comparison with Proliferative Lupus Glomerulonephritis in 141 Patients. Chi Chiu Mok, Ling Yin Ho and Ka Lung Yu. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To study the presentation and outcome of membranous nephropathy in SLE in comparison with proliferative lupus glomerulonephritis.

Methods: Patients with biopsy firmed active lupus nephritis who were recruited in our randomized comparative trial of mycophenolate mofetil (MMF) vs tacrolimus (Tac) were studied. Participants were divided into 3 groups: group 1 (pure membranous lupus Gn: RPS/ISN class V); group 2 (mixed membranous and proliferative Gn: class V+III or IVS/IVG) and group 3 (proliferative lupus Gn: IVS/IVG). The clinical presentation, treatment response, outcome and complications were compared.

Results: 141 patients were studied (92% women; age 35.2±12.8 years; SLE duration 49.3±62 months at renal biopsy). There were 25 patients (18%), 31 patients (22%) and 85 patients (60%) in group 1, 2 and 3, respectively. At presentation, group 1/2 patients had significantly higher hemoglobin level (11.3±1.8 vs 9.9±1.7g/dL), creatinine clearance (CrCl) (90.0±31 vs 69.7±27ml/min), complement C3 level (0.62±0.27 vs 0.42±0.16g/L) but lower serum Cr (70.8±25 vs 91.5±33umol/L) and anti-dsDNA titer (166±116 vs 234±89IU/ml;p<0.001) than that of group 3 patients (p<0.001 in all). 18 (32%) patients in group 1/2 had normal range C3 or anti-dsDNA, compared to 3 (4%) patients in group 3 (p<0.001). Nephrotic syndrome was more common in group 1/2 than group 3 (46% vs 32%; p=0.08). Blood pressure and serum albumin level was similar among the 3 groups. SLE disease activity index (SLEDAI) score was significantly lower in group 1/2 than group 3 patients (13.5±4.9 vs 18.0±5.3 points; p<0.001). Extra-renal activity was less common in group 1/2 than group 3 patients, but the difference was only statistically significant for arthritis (25% vs 42%; p=0.04). All patients were treated with high-dose prednisolone and either MMF (N=72) or Tac (N=69), followed by low-dose prednisolone and azathioprine for maintenance. Complete response to induction treatment at 6 months, defined as urine P/Cr of <1.0, resolution of active urine sediments, improvement in lupus serology and stabilization of CrCl, was less common with group 1/2 than group 3 patients (45% vs 62%; p=0.10). After a mean of 48.5±21 months, the cumulative risk of loss in 30% of CrCl compared to baseline was 4.6% at year 1, 6.3% at year 3 and 18% at year 5. Group 1/2 patients did not differ significantly from group 3 patients in terms of decline in CrCl (HR 0.46[0.15–1.46];p=0.19, adjusted for age, sex, SLE duration, initial CrCl and treatment arms). There were 4 arterial events (2 acute coronary syndrome; 2 cerebrovascular accidents) and 1 venous event (deep vein thrombosis) - all occurred in group 1/2 patients (compared with group 3; p=0.01). Infections (major and minor) were numerically more common in group 1/2 than group 3 patients.

Conclusion: The presence of histological membranous component in lupus nephritis is associated with heavier proteinuria, better renal function but less active lupus serology or extra-renal activity such as arthritis. One-third of patients have either normal complements or anti-dsDNA. Renal function decline in membranous lupus nephropathy is no different from proliferative lupus nephritis at 5 years, but thrombotic complications are more frequent.

Disclosure: C. C. Mok, None; **L. Y. Ho**, None; **K. L. Yu**, None.

1414

Combination of Mycophenolate Mofetil and Tacrolimus for Refractory Lupus Nephritis: A 12-Month Open-Labeled Trial. Chi Chiu Mok, Pak To Chan, Ling Yin Ho and Ka Lung Yu. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To evaluate the efficacy and tolerability of a combination of mycophenolate mofetil (MMF) and tacrolimus (Tac) for refractory lupus nephritis

Methods: Patients with refractory lupus nephritis were recruited. Inclusion criteria: (1) Active nephritis documented by renal biopsy within 24

months; (2) Failure to respond to =2 regimens which consisted of high-dose corticosteroid combined with another non-corticosteroid immunosuppressive agent together with ACE inhibitors. Each regimen should be used for [3]4 months at the maximally tolerated dosages of drugs. Exclusion criteria: (1) Previous intolerance to either MMF/Tac; and (2) Scr >200umol/L. Treatment failure to previous regimens, defined as any one of the following: (1) Failure of proteinuria to improve to <3g/day or urine protein-to-creatinine (uP/Cr) ratio to <3.0; or <50% of pre-treatment values; (2) Deteriorating Scr by [3]20% or loss in creatinine clearance (CrCl) by [3]30% not accounted by causes other than active nephritis; (3) Persistently active urinary sediments (RBC, active cellular casts [3]5/HPF). While prednisolone (£10mg/day) and ACE inhibitors were continued, other immunosuppressive agents were replaced by combined MMF (1g/day) and Tac (4mg/day). Patients were followed 2-monthly for the primary end-point (clinical response) at 12 months and adverse events.

Results: 18 patients (17 women) were recruited. The mean age of these patients was 35.3±9.9 years and the mean SLE duration was 112±46 months. The distribution of the ISN/RPS histological classes of lupus nephritis were: class IV/III (33%), pure V (39%), V+III/IV (28%). Previous treatment regimens were: high-dose prednisolone (100%), CYC (pulse/oral) (39%), AZA (89%), MMF (89%), CSA (28%) and Tac (39%). The mean Scr, CrCl, uP/Cr, and serum albumin was 83.6±29umol/L, 83.9±30ml/min (56% <90ml/min), 3.00±1.3 and 29.4±5.7g/L, respectively. Twelve (67%) patients had active urinary sediments and 13 (72%) patients had active lupus serology. After 12 months, 7 (39%) patients had very good response (uP/Cr<0.5; return of lupus serology to baseline; improvement/stabilization of CrCl; and resolution of urinary sediments), 1 (6%) patient had good response (uP/Cr<1.0; improvement in lupus serology and urinary sediments; and stabilization of CrCl) and 3 (17%) patients had partial response (50% improvement in uP/Cr and to <3.0; improvement in serology and urinary sediments; and stabilization of CrCl). Seven (39%) did not respond to the protocol and required further salvage treatment. For those patients who responded to treatment, significantly improvement in uP/Cr, serum albumin and anti-dsDNA titer was observed. CrCl in these patients did not change significantly. 27 adverse events were reported: major infection (7%), minor infection including herpes zoster (41%), diarrhea (7%), dyspepsia/anorexia (7%), transient increase in serum Cr (7%), cramps (7%), alopecia (4%), facial twitching (4%), diabetes mellitus (4%) and others (11%). None of these had led to protocol withdrawal.

Conclusion: Combined MMF and Tac is a viable option for refractory lupus nephritis, with 61% patients improves after 12 months without significant adverse effects.

1415

Effect of Renal Disease On Survival of Patients with Systemic Lupus Erythematosus: A Prospective Cohort Study of 694 Patients.
Chi Chiu Mok[1], Raymond Kwok[2] and Paul Yip[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]University of Hong Kong, Hong Kong, Hong Kong

Background/Purpose: To study the effect of renal disease on survival and life expectancy of patients with systemic lupus erythematosus (SLE).

Methods: Patients who fulfilled >=4 ACR criteria for SLE who were prospectively followed in our unit from 1995 to 2011 were studied. The cumulative survival rate was calculated using Kaplan Miere's plot. The standardized mortality ratios (SMR) (adjusted for age and sex) compared to the general population within the same period of time was worked out. The effect of renal involvement, different histological classes, renal damage and end stage renal failure on survival of SLE was also evaluated by the Cox proportional hazard models, with adjustment for age, sex and use of various immunosuppressive drugs.

Results: 694 patients were studied (92% women; mean age of onset of SLE 32.9±13.4 years). 368 (53%) had evidence of renal disease according to the ACR definition (persistent proteinuria of >=0.5g/day; cellular casts or histological evidence). 285 (77%) patients had undergone renal biopsy for at least 1 time. The distribution of histological classes (ISN/RPS) was: class I (1%), class II (6%), class III (19%), class III+V (10%), class IV (47%), class V (16%) and others (1%). The mean follow-up time was 9.6±7.3 years, 79 (11%) had renal damage as assessed by the SLE damage index (SDI) and 24 (3%) patients developed end stage renal failure (ESRF). The cumulative 5, 10 and 15 year survival of patients with renal involvement was 92.3%, 88.8% and 84.3%, respectively (significantly lower than that of patients without renal disease [97.0%, 93.7% and 91.6%, respectively; log rank test p=0.004]). Cox regression demonstrated the age and sex adjusted hazard ratio (HR) of

mortality in patients with renal disease and renal damage compared with those without renal was 2.23 [1.29–3.85] (p=0.004) and 3.59 [2.20–5.87] (p<0.001), respectively. The corresponding HR ratio for mortality in patients who developed ESRF was 9.20 [4.92–17.2] (p<0.001). Patients with proliferative types of lupus nephritis (class III, IV±V) had significantly increased mortality (adjusted HR 2.28[1.22–4.24]; p=0.01). In contrast, pure membranous lupus nephropathy was not associated with increased mortality (adjusted HR 1.09 [0.38–3.14]; p=0.88). The age and sex adjusted SMRs of all SLE patients, SLE patients with renal disease, proliferative nephritis, pure membranous nephropathy, renal damage and renal failure compared to the general population were 7.3[5.7–9.3], 9.1[6.7–12.0], 9.8[6.5–14.1], 6.2[2.0–14.4], 13.9[9.1–20.4] and 63.1[33.6–108], respectively. All patients with proliferative or membranous lupus nephritis were treated with glucocorticoids, and the proportion of patients who had ever received other immunosuppressive agents in combination was: azathioprine (89%), cyclophosphamide (51%), MMF (50%), cyclosporin A (31%), tacrolimus (38%) and hydroxychloroquine (68%). Adjustment for the use of immunosuppressive regimens in the Cox regression models above did not materially affect the overall hazard ratios for mortality.

Conclusion: The presence of renal disease, in particular proliferative types of nephritis causing renal function impairment, significantly increases the mortality risk of patients with SLE.

1416

Tumor Necrosis Factor Alpha Is Associated with Mood Disorders in Patients with Systemic Lupus Erythematosus.
Mariana Postal[1], Aline T. Lapa[1], Nailu A. Sinicato[1], Karina Peliçari[1], Lilian Costallat[2] and Simone Appenzeller[3]. [1]State University of Campinas, Campinas, Brazil, [2]Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, Brazil, [3]State University of Campinas, São Paulo, Brazil

Background/Purpose: Elevated serum levels of tumor necrosis factor alpha (TNF-α) have been reported in patients with major depressive disorder and in patients with depression in multiple sclerosis. However, the association between activation of the immune system, levels of proinflammatory cytokines and mood disorders is still unknown in systemic lupus erythematosus (SLE).

Objective: To determine if increased serum levels of TNF-α are associated with mood disorders in SLE.

Methods: We included 153 SLE patients (women 148; mean age 32.16±14.49; range 10–67) and 41 healthy (women 32; mean age 31±12.04; range 12–59) age and sex matched controls. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory in all participants. The total score ranges from 0 to 63 for BDI and BAI. The cutoffs used for the BDI were: 0–13: no/minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression and for the BAI: 0–7: no/minimal level of anxiety; 8–15: mild anxiety; 16–25: moderate anxiety; 26–63: severe anxiety. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Serum samples were obtained from all participants in the absence of infections. TNF-α levels were measured by enzyme-linked immunosorbent assay using commercial kits from R&D Systems. Mann-Whitney Test was used to compare TNF-α concentrations between groups. Multivariate analysis was performed including sex, age, SLE duration, disease activity, and cumulative damage, severity of depression and anxiety and current drug exposures.

Results: Depression was identified in 70 (45.7%) SLE and in 10 (25%) controls (p<0.001). Anxiety was identified in 93 (60.7%) SLE and in 17 controls (41.5%) (p<0.001). Serum TNF-α levels were increased in individuals with depression (p<0.001) and with anxiety (p=0.037). A direct correlation between the severity of depression and serum TNF-α levels (r=0.15; p=0.023) was observed. TNF-α levels were significantly increased in patients with active disease (SLEDAI≥3) (p=0.007) and with current prednisone dosage (p<0.001). In addition, we observed a correlation between serum TNF-α levels and SLEDAI (r=0.23, p=0.004) and with current prednisone dosage (r=0.18; p=0.031). No association between TNF-α levels and other clinical, laboratory variable and SDI scores was observed. No difference in TNF-α levels was observed between patients with and without hydroxicloroquine or other immunosuppressants. In the multivariate analysis, serum TNF-α levels were independently associated with depression (OR=3.1; 95%CI 1.8–5.6) and with disease activity (OR=4.4; 95%CI 1.3–7.1).

Conclusion: Serum TNF-α levels are elevated in individuals with mood disorders. In SLE, serum TNF-α levels were independently associated with

depression and with disease activity. The etiology of mood disorders is still debated in SLE, but our findings suggest the presence of immunological basis for depression in SLE.

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1417

Favorable Response to Belimumab At Three Months. Katrina M. Shum[1], Jill P. Buyon[1], H. Michael Belmont[1], Andrew G. Franks[2], Richard Furie[3], Diane L. Kamen[4], Susan Manzi[5], Michelle Petri[6], Rosalind Ramsey-Goldman[7], Chung-E Tseng[1], Ronald F. van Vollenhoven[8], Daniel Wallace[9] and Anca Askanase[1]. [1]NYU School of Medicine, New York, NY, [2]New York University, New York, NY, [3]North Shore-LIJ Health System, Lake Success, NY, [4]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC, [5]West Penn Allegheny Health System, Pittsburgh, PA, [6]Johns Hopkins University School of Medicine, Baltimore, MD, [7]Northwestern University Feinberg School of Medicine, Chicago, IL, [8]The Karolinska Institute, Stockholm, Sweden, [9]Cedars-Sinai/UCLA, Los Angeles, CA

Background/Purpose: Belimumab (Benlysta) is a monoclonal antibody that inhibits soluble B-Lymphocyte Stimulator and improves SLE disease activity. This study was initiated to evaluate the use of Belimumab in academic SLE clinical practices.

Methods: An invitation to participate was sent to 16 physicians experienced in SLE Phase III clinical trials. All agreeing to participate completed a one page questionnaire for each patient prescribed Belimumab. The questionnaire contained demographic information on each patient (age, gender, race/ethnicity), SLE data (duration of disease, SELENA-SLEDAI, clinical manifestation(s) targeted, background medications), and Belimumab information (start date, clinical response, side effects). Clinical response was defined as the investigator's impression of a ≥50% improvement in the initial manifestation being treated and no worsening in other organ systems.

Results: Of 16 invitations sent, ten investigators accepted to participate in the study. Questionnaires on 83 treated patients were returned. The mean age was 43.9±11.2 years old, 94% were female, 65.1% White, 24.1% Black, 8.4% Asian, and 6.0% Hispanic. The average SLE disease duration was 11.1±8.4 years. All patients were ANA positive. Concomitant medications included: antimalarials in 74.7% immunosuppressants in 75.9% (Azathioprine 19.3%, Mycophenolate Mofetil 43.4%, Methotrexate 13.3%), and prednisone in 72.3% (average dose of 11.3±11.5 mg, 63.3% on ≥10 mg). Only 2.4% of patients were not on background SLE medications. The dominant clinical manifestation driving treatment was arthritis (74.7%) followed by rash (41.0%) and serositis (15.7%). Other SLE manifestations included renal (7.2%, 4 membranous, 2 proliferative), hematological (8.4%), and inability to taper steroids (8.4%). Approximately half of patients (55.4%) had two or more active manifestations. Forty-two patients were on Benlysta for at least 3 months. Of those, 23 (55%) patients clinically responded by 3 months with marked improvement in arthritis and/or rash. Twenty-three patients were on Benlysta for at least 6 months. Of those, 14 (60.9%) patients clinically responded with improvements in arthritis and/or rash. Of the 6 patients in whom Benlysta was discontinued, 2 had CNS lupus, 1 MI, 1 infection, 1 infusion reaction, and 1 elective surgery.

Conclusion: These early data support the use of Benlysta across all ethnic groups and efficacy similar to that reported in the Phase III trials. Relevant to physician and patient decision making, improvement was observed within 3 months.

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1418

Directed Intuitive Assessment of Lupus (the DIAL system for real world clinics) Correlates Well with BILAG and SLEDAI. Anca D. Askanase[1], Katrina M. Shum[1], Stan Kamp[2], Fredonna C. Carthen[2], Teresa J. Aberle[2] and J.T. Merrill[2]. [1]NYU School of Medicine, New York, NY, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Disease activity measures used in SLE clinical studies, including the SLEDAI (SLE Disease Activity Index) and BILAG (British Isles Lupus Assessment Group) index are challenging due to potential scoring pitfalls, and require extensive training and experience. This leaves a busy clinician with limited tools for tracking SLE patients to ensure quality care and documentation of treatment targets. The SLEDAI physician's global assessment (PGA) is simple to learn and efficient to use, but compresses assessment of moderate to severe disease into a small region of the scale, limiting the ability to evaluate change. Also, no organ specific evaluation is performed.

Directed Intuitive Assessment of Lupus (DIAL) is a pilot application composed of seven anchored visual analogue scores (0–100mm each) representing the most common organs affected by SLE: mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, renal, hematologic, or other (for more rare conditions). The physician selects the scale(s) for active organ(s) and rates disease severity using simple anchored landmarks based on the SLEDAI system: 0=no disease, 1=mild, 2=moderate, and 3=severe. Only features due to active SLE are rated. The total DIAL score is the sum of scores for active organs. This enables both organ-specific distinctions and a wider spectrum of change.

This study was initiated to compare BILAG, SLEDAI and DIAL scores.

Methods: A prospective real world clinic exercise was performed by evaluating 91 consecutive SLE patients in two rheumatology clinics. SLEDAI, BILAG, and DIAL scores were recorded. The level of agreement was determined by the strength of Spearman rank correlations.

Results: The study included 86 women and 5 men, mean age 42.1 years, 54% Caucasian, 31% African, 14% Asian, 24% Hispanic. 70(77%) patients were taking antimalarials, 53(58%) immunomodulators, and 40(44%) prednisone (11>10 mg). 17(19%) were rated as flaring at the time of the assessment. The median (range) SLEDAI was 4.0(0–28), BILAG 2004 score 8.0(0–32) representing a broad spectrum from minimal to severe disease. The median PGA (on 100mm scale) was 38(4–92) vs the total DIAL score 50(0–268). 33 patients were rated moderate-severe (≥1.5 on PGA) and their median PGA was 66(50–92) vs DIAL 100(50–268) confirming a wider distinction potential of comparative scores. The total DIAL score correlated well with the PGA, SLEDAI, and BILAG summary scores (correlation coefficients of 0.90, 0.82, and 0.93 respectively, p<0.0000002 for all). The DIAL scores for musculoskeletal and mucocutaneous domains correlated with the corresponding BILAG domain scores at 0.92 and 0.94 (p<0.0000002). The DIAL index took only a few seconds to score.

Conclusion: This simple, intuitive measurement of disease severity performed reliably at two clinics. The advantage over the PGA is ability to distinguish involvement of different systems and more range to assess change in moderate/severe disease. Community input, refinement and formal validation of the DIAL system is planned. The final product of this work (which could be amenable to paper or encrypted electronic applications) could improve treatment justification, documentation of progress and standard of care for lupus patients.

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1419

Infections Increase Risk of Arterial and Venous Thromboses in Systemic Lupus Erythematosus Patients: 4925 Patient Years of Follow-up. Renata Baronaite Hansen[1] and Søren Jacobsen[2]. [1]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [2]Copenhagen University Hospital, Copenhagen, Denmark

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at increased risk of developing coronary heart disease as well as infections. Acute infections have been recognized to be associated with the development of arterial coronary events and previous studies have also demonstrated an increased risk of deep venous thrombosis and pulmonary embolism following an infection in general population. Our aim was to determine if there is an association between infections and risk of arterial and venous thrombotic events in patients with SLE.

Methods: Based on both retrospectively and prospectively collected data on 571 adult SLE patients fulfilling the ACR classification criteria, we identified all cases of acute infections requiring hospitalization, cutaneous herpes zoster, as well as arterial and venous thrombotic events. For each patient, the start of follow-up was the date of SLE diagnosis, and the end of follow-up was date of death or most recent information recorded.

Patients were divided into 3 groups based on infection type: respiratory, cutaneous herpes zoster and other (urinary tract, cerebral, gastrointestinal, gynecological, cutaneous infections, bacteremia and bacterial endocarditis). Period of interest (POI) was defined as one year following an infection. Poisson regression analysis was used to estimate relative risks (RR) and their 95% confidence intervals (CI).

Results: Of the 571 enrolled patients 89% were female and the mean age at diagnosis was 36 ± 16 years. The mean length of follow-up was 8.9 ± 7.6 years. The total amount of patient years of follow-up was 4925 years. 271 infections (104 acute respiratory, 41 cutaneous herpes zoster and 126 other acute infections),

as well as 98 arterial and 61 venous thromboses were identified. The table presents number of infections, number of thromboses during and outside POI, RR and corresponding 95% CI for arterial and venous thromboses in patients with different infection types.

Table 1. Association between infections and thrombotic events in SLE patients

Type of infection	Infection, n	Arterial thromboses during POI, n/ Months at risk, n	Arterial thromboses outside POI, n/Months at risk, n	Arterial thromboses RR (95% CI)	Venous thromboses during POI, n/ Months at risk, n	Venous thromboses outside POI, n/ Months at risk, n	Venous thromboses RR (95% CI)
Respiratory	104	5/1078	93/60162	3.00 (1.22–.7.38)	6/1078	55/60162	6.09 (2.62–.14.1)
Other	126	5/1299	93/59941	2.48 (0.99–.6.21)	2/1299	59/59941	1.56 (0.37–.6.59)
Cutaneous herpes zoster	41	2/409	96/60831	3.10 (0.89–.12.9)	0/409	61/60831	Not calculated

Conclusion: Our data showed that SLE patients were at increased risk of developing an arterial thrombosis within 12 months following a respiratory infection, and similar risk was observed for cutaneous herpes zoster and other infections. For venous thrombosis, the risk was increased following respiratory infections, but not following cutaneous herpes zoster or other infections. These data suggest that the increased risk of thromboses observed in SLE patients may also be partly explained by infections. To our knowledge, this is the first study describing an association between infections and risk of thromboses in SLE patients.

1420

Ethnicity and B Cell Depletion Therapy in Systemic Lupus Erythematosus. A. Lois-Iglesias[1], J. Ishorari[2] and D.A. Isenberg[2]. [1]University Hospital Ramón y Cajal, Madrid, Spain. University College London, London, United Kingdom, [2]University College London, London, United Kingdom

Background/Purpose: The aim of this study was to determine if there is any relation between ethnicity and outcome in patients with SLE treated with B cell depletion therapy (BCDT).

Methods: Between June 2000 and December 2011, 102 SLE patients received BCDT in our centre. The mean age was 31 years old. 92,2% were female. 41.2 % of them (42) received at least two cycles. It was administered intravenously, each cycle consisting of: cyclophosphamide 750–1500 mg, methylprednisolone 125–250 mg and rituximab 1 g, on 2 occasions, 2 weeks apart.

In this observational study we reviewed the disease activity assessments at the time of BCDT and six and twelve months later using the British Isles Lupus Assessment Group (BILAG) activity index, and the serological markers C3 and anti-dsDNA antibody levels.

Complete remission (CR) was defined as the loss of all BILAG A or B scores (to a C or D score). Partial remission (PR) was a change from a BILAG A or B score to a C or D score in at least 1 system, but with the persistence of 1 or more A or B scores in another system. No improvement was defined as a BILAG A or B score that remained unchanged after treatment. Worsening was also noted (no improvement and worsening = other, see below).

Results: In our cohort at the time of the initial BCDT 46 patients (45.1%) were Caucasian (C), 28 (27.4%) Afrocaribbean (AC), 21 (20.6%) Asian (As) and 7 (6.8%) Oriental (O). In the second cycle 13 (31%) were C, 16 (38.1%) AC, 11 (26.1%) As and 2 (4.8%) O.

There were no statistically significant differences between the ethnic groups in terms of gender, mean age and mean BILAG total score at the time of BCDT.

For our analysis we excluded the Oriental patients because of their small number. We had sufficiently complete data on 80 patients for the analysis.

After the first and second cycle of BCDT the rates of complete remission, partial remission and other outcomes including worsening (CR/PR/other) were as follows:

	6 months after BCDT 1st cycle	12 months after BCDT 1st cycle	6 months after BCDT 2nd cycle	12 months after BCDT 2nd cycle
C	37.5%/22.5%/40%	37.8%/24.3%/37.8%	38.5%/7.7%/53.8%	33.3%/16.7%/50%
AC	38.1%/9.5%/52.4%	45%/5%/50%	28.6%/28.6%/42.9%	53.9%/7.7%/38.5%
As	36.8%/15.8%/47.4%	42.1%/15.8%/42.1%	33.3%/22.2%/44.4%	16.7%/33.3%/50%

These differences between the ethnicities were not statistically significant (p>0.05) and there were no significant differences between groups with respect to the number of patients who increased their C3 by 25% from baseline or decreased their anti-dsDNA antibody level by 50% or more.

Conclusion: Our data suggest that BCDT is equally effective in SLE patients of Caucasian, Afrocaribbean and Asian. However, a larger sample size is recommended to confirm this.

1421

Antimalarials Protect Systemic Lupus Erythematosus Patients From Damage Accrual During the First Five Years of the Disease. Ioana Ruiz-Arruza, D. D. Gladman, Dominique Ibanez and Murray B. Urowitz. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Studies in the last 20 years have demonstrated that antimalarials (AM) prevent flares, protect from damage accrual, reduce the risk of thrombosis and increase survival, making them one of the cornerstone treatments for lupus. The aim of this study was to examine whether damage accrual, measured with the SLICC/ACR DI, over a 5 year period is reduced with the previous use of AM.

Methods: The present study was designed as a nested case-control embedded in an inception cohort of patients with SLE from our Lupus Clinic database, a long term prospective observational cohort study. All subjects fulfilled 4 of the ACR classification criteria or 3 ACR criteria plus having a histological lesion indicative of SLE.

All patients who had SLICC/ACR DI of 0 at inception and developed first damage in the time between the initial and the last follow-up visit at 5 years were considered cases. Two controls, comprising lupus patients in whom damage did not develop, were identified for each case and matched for known confounders for the development of damage: age, sex and disease activity at enrolment measured by the SLEDAI-2K.

AM exposure was classified as *never* or *ever* if patients were on either chloroquine or hydroxychloroquine at any visit prior to the onset of damage or during the 5 year interval for the controls.

Comparisons between cases and controls were made using descriptive statistics. Time to presence of damage was compared using Kaplan-Meier curves and time-dependent covariate proportional hazard models.

Results: 719 patients constituted the inception cohort. 490 had the first SLICC/ACR DI measure available within the first year and equal to 0. From the 354 who had at least 5 year follow-up in the clinic, 77 developed damage during the study period and 75 could be matched to 150 controls with no damage.

At first clinic visit, there were 84% women in both groups, with a mean age of 38.5 years in both groups and a SLEDAI-2K of 10.9 in the cases and 9.5 in the controls.

In the univariate analysis AM use was associated with a protective effect for the development of damage (cases 49.3% vs controls 70.7% p=0.002).

Analyzing the damage free survival with Kaplan-Meier curve, AM prolonged the time to damage accrual.
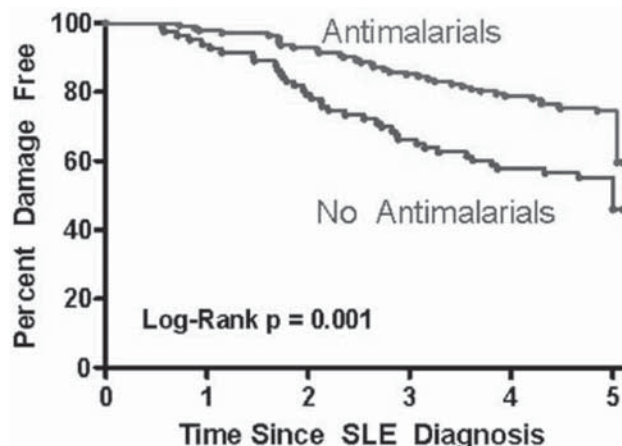
In the proportional hazard regression model, AM usage prior to the onset of damage reduced the probability for damage (HR 0.60 95%CI 0.38–0.95 p=0.03).

In further adjusting for potential risk factors (sex, age at diagnosis, disease duration, SLEDAI-2K) in the time-to-event regression analysis, AM was protective (HR 0.62 95%CI 0.39–0.99 p<0.05) and SLEDAI-2K at each visit increased the risk of damage (HR 1.05 95%CI 1.02–1.09 p<0.005).

Conclusion: AM is protective for damage accrual in SLE patients during the first five years of the disease, supporting their use at diagnosis of SLE.

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Clinical Associations of Anti-Smith Antibodies in Profile: A Multiethnic Lupus Cohort. Yesenia C. Santiago-Casas[1], Luis M. Vila[1], Gerald McGwin Jr.[2], Ryan S. Cantor[2], Michelle Petri[3], Rosalind Ramsey-Goldman[4], John D. Reveille[5], Robert P. Kimberly[2], Graciela S. Alarcon[2] and Elizabeth E. Brown[2]. [1]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Univ of Texas Health Science Center at Houston, Houston, TX

Background/Purpose: Anti-Smith (anti-Sm) antibodies are highly specific for systemic lupus erythematosus (SLE) and have an important value in the diagnosis of this disease. However, whether these autoantibodies are associated to a specific subset of clinical manifestations or if they convey a prognostic value in lupus remains controversial. The aim of this study was to determine the association between anti-Sm antibodies and clinical manifestations, comorbidities, and disease damage in a large multiethnic SLE cohort.

Methods: SLE patients (per ACR criteria), age $\geq$ 16 years, disease duration $\leq$ 10 years at enrollment, and defined ethnicity (African American, Hispanic or Caucasian), from a longitudinal cohort were studied. Socioeconomic-demographic features, cumulative clinical manifestations, comorbidities, and disease damage [as per the Systemic Lupus International Collaborating Clinics Damage Index (SDI)] were determined. The association of the anti-Sm antibodies with clinical features was examined using multivariable logistic regression adjusting for age, gender, race/ethnicity, disease duration, education, smoking, and type of medical insurance.

Results: A total of 2,322 SLE patients were studied. The mean (standard deviation, SD) age at diagnosis was 34.4 (12.8) years and the mean (SD) disease duration was 9.0 (7.9) years; 2,127 (91.6%) were women. Anti-Sm antibodies were present in 579 (24.9%) patients. In the multivariable analysis, SLE patients with anti-Sm antibodies were more likely to have serositis (odds ratio [OR] 1.51, 95% confidence interval [95% CI] 1.23–1.84), renal involvement (OR 1.33, 95% CI 1.08–1.64), neurologic involvement (OR 1.51, 95% CI 1.12–2.04), psychosis (OR 1.60, 95% CI 1.01–2.53), vasculitis (OR 1.50, 95% CI 1.17–1.94), Raynaud's phenomenon (OR 1.64, 95% CI 1.34–2.00), hemolytic anemia (OR 1.73, 95% CI 1.28–2.35), leukopenia (OR 1.56, 95% CI 1.28–1.91), lymphopenia (OR 1.76, 95% CI 1.43–2.16), and arterial hypertension (OR 1.32, 95% CI 1.07–1.62). No significant associations were found for mucocutaneous manifestations and damage accrual.

Conclusion: In this cohort of SLE patients, anti-Sm antibodies were associated with several clinical features including serious manifestations such as renal disease, neurologic involvement, hemolytic anemia and vasculitis.

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1423

Vascular Thrombosis and Pregnancy Morbidity in Patients with Systemic Lupus Erythematosus with Positive Antiphospholipid Profile and Thrombocytopenia. Amir Haddad, Murray B. Urowitz, Dominique Ibanez and D. D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: The trigger for a thrombotic in patients with antiphospholipid antibodies is unknown. Thrombocytopenia is among the most common clinical manifestations of the Antiphospholipid antibody syndrome (APS). The purpose of this study was to investigate whether patients with lupus and positive antiphospholipid profile with thrombocytopenia are at more risk to have obstetric or thrombotic events than patients with antiphospholipid but without thrombocytopenia.

Methods: Patients with SLE and positive antiphospholipid (aPL) profile (Lupus anticoagulant (LA), anticardiolipin (aCL) antibody of IgG and/or IgM isotype or anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype) and chronic thrombocytopenia (Platelet count<100,000) confirmed for 2 consecutive clinic visits followed at the prospective longitudinal lupus cohort since 1996 were recruited (study group). As controls a group of patients with SLE with positive aPL without thrombocytopenia were selected and matched by sex, age of SLE diagnosis, age at study start, disease duration and length of follow up period. Patients in the lupus cohort are followed at 2–6 month intervals according to a standard protocol which documented the presence of thrombotic events and obstetric morbidity as defined by the revised Sapporo

criteria of APS. Descriptive analysis was used to describe the patients. Kaplan-Meier (KM) curves was used to compare time to 1st event between study groups.

Results: The study group included 21 patients and 63 controls, 81% were females with a mean age of 39.8 $\pm$ 13.0 years and age of SLE diagnosis at 31.7 $\pm$ 14.7 years. The mean disease duration was 8.1 $\pm$ 7.8 years and they were followed for an average of 12.1 $\pm$ 9.3 years.

During the study period, the medication used by cases and controls respectively were: on steroids 86% vs 79% (p=.075); on antimalarials 43% vs 68% (p=0.07); on immunosuppressants 52% vs 43% (p=0.46); on ASA 20% vs 22% (p=1.00); and on anticoagulants 5% vs 10% (p=0.67).

16 events occurred in the study group compared to 43 events in the controls and included 6 Obstetrical morbidities in 2 patients in the study groups compared to 4 events in 2 patients in the controls (KM p=0.17), 9 arterial thrombosis in 4 patients in the study group compared to 24 events in 17 patients in the controls (KM p=0.19) and 1 event of venous thrombosis in 1 patient in the study group compared to 15 events in 10 patients in the controls (KM p=0.19).
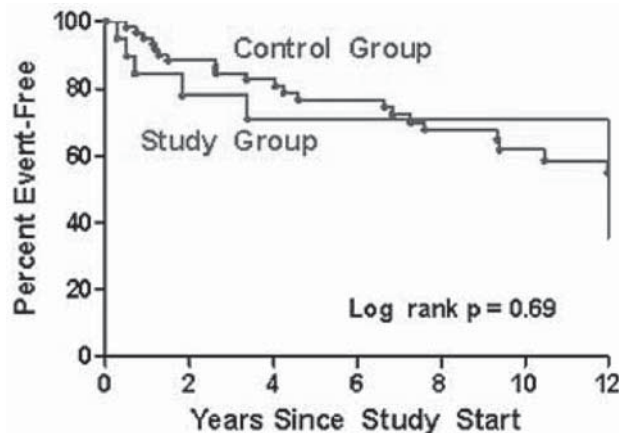
Figure 1. The Kaplan-Meier curve for time to 1st event after Study Start.

Conclusion: Thrombocytopenia in patients with antiphospholipid antibodies in SLE is not associated with increased thrombotic events.

Disclosure: **A. Haddad**, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **D. D. Gladman**, None.

1424

Prevalence and Clinical Significance of Severe Infection in Patients with Systemic Lupus Erythematosus: Preliminary Data From Relesser (Registry of lupus of the Spanish Society of Rheumatology). José M. Pego-Reigosa[1], Iñigo Rúa-Figueroa[2], Francisco J. López-Longo[3], María Galindo[4], Jaime Calvo-Alén[5], Alejandro Olivé[6], Loreto Horcada[7], Esther Uriarte[8], Eva Tomero[9], Ana Sánchez-Atrio[10], Carlos Montilla[11], José Rosas[12], Antonio Fernández-Nebro[13], Paloma Vela[14], Mercedes Freire[15], Lucía Silva[16], Elvira Díez-Álvarez[17], Carlos Marras[18], Antonio Zea[19], Javier Narváez[20], Jose Luis Marenco[21], Monica Fernández de Castro[22], Olaia Fernánde-Berrizbeitia[23], Marian Gantes[24] and Celia Erausquin[25]. [1]Hospital do Meixoeiro, Vigo, Spain, [2]Hospital Universitario Dr Negrín, Las Palmas de Gran Canaria, Spain, [3]Hospital Gregorio Marañón, Madrid, Spain, [4]Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain, [5]Hospital Sierrallana, Torrelavega, Spain, [6]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [7]Hospital de Navarra, Spain, [8]Hospital de Donosti, Donosti, Spain, [9]Hospital Universitario La Princesa, Madrid, Spain, [10]Hospital Príncipe de Asturias, Madrid, Spain, [11]Hospital Universitario de Salamanca, Salamanca, Spain, [12]Hospital de Marina Baixa, Alicante, Spain, [13]Hospital Carlos Haya, Malaga, Spain, [14]Hospital General de Alicante, Alicante, Spain, [15]Hospital Universitario Juan Canalejo, La Coruña, Spain, [16]Hospital de Guadalajara, Guadalajara, Spain, [17]Hospital de León, León, Spain, [18]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [19]Hospital Universitario Ramon y Cajal, Madrid, Spain, [20]Hospital de Bellvitge, Barcelona, Spain, [21]Hospital de Valme, Seville, Spain, [22]Hospital Puerta del Hierro-Majadahonda, Madrid, Spain, [23]Hospital de Basurto, Basurto, Spain, [24]Hospital Clinico de Tenerife, Spain, [25]Hospital de Gran Canaria Dr Negrin, Las Palmas GC, Spain

Background/Purpose: Infection is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). Immunosuppression, co-

morbidities, and the disease itself makes patients with SLE susceptible to severe infections (SInf) but the relative contribution each of this factors are not well known. We retrospectively assess the prevalence of SInf and potential differences between patients with or without SInf in a multicentric SLE cohort.

Methods: Patients with SLE on active follow up, with enough data about infection, from the first 684 patients registered on RELESSER. Cumulative clinical data were collected at the moment of the last assessment. SInf was defined by the need for hospitalization. Charlson index (ChI) was use to evaluate comorbidity, and SLICC/ACR/DI (SDI) and Katz index (ISK) to assess damage and SLE severity respectively. We analyzed the impact of infection on SLE mortality in the entire cohort.

Results: 583 SLE patients (92% ≥4 ACR criteria) were included; 88.3% females, mean age: 45.5 years, median SLE duration: 111 months (IQR: 47.8–188.4). 80 patients (14.5%) suffered ≥ 1 SInf (any time). Median SInf: 1(IQR: 1–2). First SInf localization: respiratory: 51.2%, urinary: 16.2% and bloodstream (8.7%), with a predominant bacterial aetiology (42.5%). However, we found an elevated rate of non-isolations (48.7%), likely related to the predominance of respiratory infections. Comparing with patients without SInf, patients with SLE and SInf were older: 50(39–61) [median (P25–75)] vs. 43(34–53) years, p <0.0001, had longer duration of SLE:170 (83–253) vs.103(42–174) months (p <0.0001), more ISK: 4(2–5) vs. 2(1–3), p <0.0001, more SDI:1(0–3) vs. 0(0–1), p <0.0001 and a higher ChI: 3(1–4) vs. 1(1–2), p <0.0001. Furthermore, ≥ 2 SInf also associated with more SDI (p= 0.003), more ISK (p=0.027) and more ChI (p<0.001) comparing with only 1 SInf. In addition, patients with InfG were more frequently hospitalized by SLE (excluding by infection): 80.0% vs. 45.0%, p <0.0001 and treated with corticosteroids (CE): 98.7% vs. 87.6%, p= 0.004, cyclophosphamide (CPM): 40.8% vs.17.3%, p<0.0001, or mycophenolate m. (MPM):33.8% vs. 17.1%, p =0.001(any time), without differences in antimalarials use. At the moment of the first infection, 41 patients (77.4%) were treated with CE, 25(48.1%) with immunosupressors, 5(20%) with CPM and 4(16.0%) with MPM, figures higher than the prevalence of these treatments in the last assessment available in RELESSER, i.e., GC: 51.8%, CPM: 1.1 % and MPM: 12.3%. Only 3 of 24 (12.5%) deceased patients, died by SInf. Excluding patients died by infection, the mortality was higher in SLE with history of SInf (9.6 vs. 1.7%, p<0.000; χ2 Pearson).

Conclusion: Despite being a low-severity cohort, the cumulative incidence of serious infection is high in our SLE patients. These data confirm the respiratory infection as the most common localization of SInf in SLE. An antecedent of severe infection seem to associate to more severe SLE, more mortality and increased comorbidity, although these associations could be related with a longer disease exposure y/or older age.

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1425

Circulating Free Protein S Levels May Be Linked to Cardiovascular Events and Venous Thrombosis in SLE.
Gregg J. Silverman[1], John Jung[1], Ehtisham Akhter[2], Michelle Petri[2] and Caroline Grönwall[1]. [1]NYU School of Medicine, New York, NY, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: SLE patients are at risk for diverse organ systems involvement, which increases the challenges for diagnosis and predictions for the development of specific clinical features. In recent studies we have compared traditional and novel serologic markers and identified profiles that correlate with levels of overall clinical disease activity, and for specific organ system involvement (1). In the current studies we extended our studies to surveys of levels of Protein S, a vitamin K dependent factor implicated both in the coagulation cascade and as a ligand for the TAM receptor tyrosine kinase family that regulates inflammatory responses and apoptotic cell clearance.

Methods: In cross-sectional surveys of 90 SLE patients, we assessed levels of free Protein S with a commercial immunoassay. All clinical and experimental data was imported into a customized database where multivariate methods were used to seek natural divisions in the sample set based on a panel of IgM and IgG lupus/apoptosis-associated natural autoantibodies and to relate them to various clinical parameters.

Results: Low Protein S levels correlated with a history of DVT/PE (N=12, Spearman, P<0.0007, R=0.41)(Sens. 0.92, Spec.0.56). These correlations had greater significance than for well known lab correlates, that include high levels of IgG anti-cardiolipin (P=0.007, R=−0.29), IgG anti-β2-GPI (P=0.03, r=−0.23), and RVVT (P=0.001, R=−0.34). Patients with a hx of MI/CVA also had significantly lower levels of free Protein S (N=17, P=0.001 R=−0.34) (Sens. 0.76, Spec.0.56). We found no correlations between protein S and overall SLE disease activity levels by SELENA-SLEDAI, physician's global assessment, or organ damage by the SLICC index, or for nephritis. Although the vitamin K antagonist, coumadin, is reported to affect Protein S levels, we found no significant difference in Protein S levels between those with and without coumadin. For MI/CVA affected patients not treated with coumadin, we found significantly lower levels of Protein S compared to clinically unaffected SLE pts (P<0.01).

Conclusion: Significantly lower levels of free Protein S were found in the subsets of SLE patients with clinical DVT/PE and for MI/CVA events. These findings support the hypothesis that disturbance in levels of the anti-coagulant Protein S may play roles in both venous thrombopathy and cardiovascular events.

Collectively, this study describes a potential biomarker, free Protein S, which identifies a specific SLE subgroup that may be at increased risk for pathogenic mechanisms responsible for thrombotic events and serious CV events. Further investigations of this topic may allow for the development of better diagnostic and prognostic tests and personalized therapies in patients afflicted by SLE.

Reference
(1) Grönwall et al. Clinical Immunology **2012** 142(3):390–8

Disclosure: **G. J. Silverman**, None; **J. Jung**, None; **E. Akhter**, None; **M. Petri**, None; **C. Grönwall**, None.

1426

The Clinical Relevance of a "False Negative" Enzyme Linked Immuno-assay: Which Antinuclear Antibody Screening Test Is Preferred by Rheumatologists in an Integrated Health System?
Rachita Bansal, David Bulbin, Alfred E. Denio, Sandi Kelsey and Harold Harrison. Geisinger Medical Center, Danville, PA

Background/Purpose: Historically, Immunofluorescence Assay (IFA) methodology has been the gold standard for ANA screening. Most clinical laboratories in recent years utilize the Enzyme Linked Immunoassay (ELISA) to screen for ANA rather than IFA as ELISA is automated and less expensive. Studies have suggested the sensitivity and specificity of the two methods are comparable but most of these studies were retrospective and not done in populations of patients referred to rheumatologists. There has been concern among rheumatologists that there may be a high "false negative" rate for ELISA when compared to IFA, potentially affecting a rheumatologist's ability to diagnose patients with connective tissue disorders. We studied the incidence and clinical relevance of a negative ANA by ELISA when the IFA is positive and when ordered by a rheumatologist.

Methods: We conducted a prospective study in a 12 person integrated health system rheumatology practice to determine the rate of "false negative" ANA by ELISA. 200 consecutive negative ELISA ANA's ordered by rheumatologists were subsequently reanalyzed with IFA. We reviewed medical records of these patients and surveyed their rheumatologists regarding the clinical relevance of the positive IFA ANA finding for each patient identified. After their experience with the "false negative" ELISA and after providing the rheumatologists with the lab's comparative costs of the 2 methodologies, their opinion about the most cost effective ANA screening strategy was solicited.

Results: Of 200 consecutive ELISA negative ANA's ordered by rheumatologists reanalyzed using IFA, 15% were positive by IFA. Six% had titers of 1:160 or greater. One was 1:10240. The rheumatologist survey demonstrated that of the 30 patients with false negative ANA by ELISA, the clinical suspicion of an underlying connective tissue disorder remained medium or high in 17 despite the negative ANA. In 8 patients, the clinical suspicion for a connective tissue disorder increased following the finding of a positive ANA by IFA and in 4 patients led to additional testing or start of treatment for a connective tissue disorder. The surveyed rheumatologists by a large majority felt that the abnormal ANA cut off titer should remain 1:160. After experience with each "false negative" ELISA patient and after being provided with cost differences for the IFA and ELISA methodologies, the rheumatologists by a slim majority (14 to 13) recommended continuation of the current lab's practice of screening all ANAs with ELISA rather than the option of

screening rheumatology ordered ANAs with IFA (added lab cost $3,323.50/yr.) No one felt the entire system's ANAs screening should be done by IFA (added cost to lab *$33,465.20/yr.*)

Conclusion: Use of IFA rather than ELISA as initial screening ANA test would rarely change a rheumatologist's patient management decisions. With knowledge of the "false negative" ELISA rate, the system's cost differences between the ELISA and IFA, and experience with their own patients who have had a "false negative", rheumatologists in an integrated health system prefer the ELISA methodology over IFA as initial ANA screen.

1427

Late Onset Systemic Lupus Erythematosus: Is It Actually A Milder Variant?

Juan G. Ovalles-Bonilla[1], Julia Martínez-Barrio[1], Javier Lopez-Longo[1], Inmaculada de la Torre[1], Carlos Gonzalez Fernandez[1], María Montoro Álvarez[1], Francisco Aramburu[1], Carolina Marin[1], Lina Martinez-Estupiñan[1], Juan C. Nieto[2], Michelle Hinojosa[1], Natalia Bello[1], Indalecio Monteagudo[1] and Luis Carreño[1]. [1]Gregorio Marañon Hospital, Madrid, Spain, [2]Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Classically, late onset Systemic Lupus Erythematosus (SLE) has been described as a milder variant of the disease. The objective of this study is to describe the clinical and immunological features, the damage accrual and mortality of late onset compared with adult onset SLE.

Methods: The data was obtained from a long term prospective cohort of 353 patients diagnosed with SLE in the Rheumatology Department of Gregorio Marañon Hospital in Madrid, Spain. Demographic, clinical, and laboratory data were collected at disease onset and during it's course from 1986 to 2006. Patients were divided into 2 groups: adult onset 19–49 years (n=276) and late onset ≥50 years (n=77). Organ damage was scored using the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) Damage Index. Damage accrual was defined as an SLICC/ACR score ≥1. The groups were compared using the chi-square, Fisher-Holton and t-student tests.

Results: A total of 353 patients were recruited, with a following mean time of 11 years. The female to male ratio differed significantly (p=0.005) between groups. At diagnosis, the late-onset group presented cutaneous manifestations less frequently (p<0.001). During follow-up, the late-onset group presented a lower incidence of arthritis (p=0.02), malar rash (p=0.001), photosensitivity (p=0.04), fever (p=0.03), low serum complement (p=0.001), hematologic (p=0.03) and renal (p=0.01) manifestations. The late-onset group had significantly more hypertension (p=0.03), neoplasms (p=0.02), damage accrual (p=0.007) and mortality (p=0.006). As for autoantibody profile, no statistically significant differences were found.

CHARACTERISTICS	Adult Onset 19–49 Years (n=276)	Late Onset ≥50 Years (n=77)	p
At Disease Onset			
DEMOGRAPHIC			
Female/Male Ratio	8.9 (248/28)	3.5 (60/13)	0.005
Age at diagnosis, (range)	31.9 (19–.50)	61.2 (51–.86)	<0.001
CLINICAL MANIFESTATIONS (%)			
Cutaneous	93 (33.7)	8 (10.4)	<0.001
During Follow-up			
CLINICAL MANIFESTATIONS (%)			
Arthritis	254 (92)	64 (83.1)	0.02
Malar Rash	130 (47.1)	17 (22.1)	<0.001
Photosensitivity	147 (53.3)	31 (40.3)	0.04
Fever	103 (37.3)	19 (24.7)	0.03
Hematologic Manifestations	228 (82.6)	55 (71.4)	0.03
Renal Manifestations	124 (44.9)	22 (28.6)	0.01
Hypertension	77 (27.9)	31 (40.3)	0.03
Neoplasms	13 (4.7)	9 (11.7)	0.02
SLICC/ACR (mean ± SD)	1.7 ± 2.1	2.5 ± 2.5	0.007
Mortality	17 (6.2)	13 (16.9)	0.006
Disease duration time (mean ± SD)	12.6 ± 8.6	9.9 ± 7.5	0.01
Low serum complement	220 (81.2)	40 (58)	<0.001

Conclusion: Late onset SLE is clinically different with less arthritis, fever, low serum complement, cutaneous, hematologic and renal manifestations, but with higher mortality and organ damage rates, compared with the adult onset group. The higher frequency of damage accrual, mortality and hypertension observed in the late-onset group can be affected by aging-related factors other than disease activity or duration.

1428

Long-Term Outcomes of Children Born to Women with Systemic Lupus Erythematosus.

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Background/Purpose: SLE can cause considerable morbidity during pregnancy. Although several studies have evaluated foetal outcome in lupus pregnancy, very few have examined the long-term outcome of children born to mothers with SLE. In a large population-based study, we aimed to determine if children born to women with SLE have an increased risk of major congenital anomalies, serious infections, and cardiac conduction disturbances compared to children born to women without SLE.

Methods: We identified all women who had ≥ 1 hospitalization for delivery after SLE diagnosis using Quebec's physician billing and hospitalization databases (1989–2009). Women were defined as SLE cases if they had any of the following: 1) ≥ 1 hospitalization with a diagnosis of SLE prior to the delivery, 2) a diagnosis of SLE recorded at the time of their hospitalization for delivery, or 3) ≥ 2 physician visits with a diagnosis of SLE, occurring 2–24 months apart, prior to the delivery. We randomly selected a general population control group, composed of women matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery.

We identified children born live to SLE cases and their matched controls, and ascertained major congenital anomalies (i.e. ≥ 1 hospitalization or physician visit for a major congenital anomaly < 12 months of life), serious infections (i.e. ≥ 1 hospitalization with a primary diagnosis of infection), and cardiac conduction disturbances (i.e. ≥ 1 hospitalization or 2 physician visits occurring 2–24 months apart) through to end of database follow-up.

We performed multivariate analyses to adjust for maternal demographics, sex and birth order of child, major maternal co-morbidities, obstetrical complications, and relevant maternal medication.

Results: 507 women with SLE had 721 children, while 5862 matched controls had 8561 children. Compared to controls, children born to women with SLE experienced slightly more major congenital anomalies [13.6% (95% CI 11.3, 16.3) vs 10.4% (95% CI 9.7, 11.1)], serious infections [31.5% (95% CI 28.2, 35.0) vs 26.0% (95% CI 25.1, 26.9)], and cardiac conduction disturbances [3.1% (95% CI 2.0, 4.6) vs 1.2% (95% CI 1.0, 1.4)]. Mean age at the time of serious infection was 1.8 (95% CI 1.6, 2.0) year for children born to women with SLE and 2.1 (95% CI 2.0, 2.2) years for controls, while mean age at the time of cardiac conduction disturbance was 0.2 (95% CI 0.17, 0.22) year for children born to women with SLE and 1.8 (95% CI 1.7, 1.8) year for controls.

In multivariate analyses, children born to women with SLE had substantially increased rates of serious infections (HR 1.76, 95% CI 1.21, 2.56) and cardiac conduction disturbances (HR 1.90, 95% CI 1.03, 3.52) compared to controls. There was also a trend for an increased risk of major congenital anomalies in children born to women with SLE compared to controls (OR 1.24, 95% CI 0.98, 1.58).

Conclusion: Compared to children from the general population, children born to women with SLE have increased rates of serious infections and cardiac conduction disturbances. Our findings suggest that children born to mothers with SLE might also be at slightly increased risk of major congenital anomalies and prompt further research to elucidate this issue.

1429

Women with Systemic Lupus Erythematosus (SLE) May Have Different Predictors of Risk for Progression of Aorta Calcium (AS) Than Women without SLE. Apinya Lertratanakul[1], Peggy W. Wu[1], Alan Dyer[1], William Pearce[1], George Kondos[2], Daniel Edmundowicz[3], James Carr[4] and Rosalind Ramsey-Goldman[4]. [1]Northwestern University, Chicago, IL, [2]University of Illinois at Chicago, Chicago, IL, [3]Temple University School of Medicine, Philadelphia, [4]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: Women with SLE have increased rates of subclinical atherosclerosis and cardiovascular (CV) events. We investigated which risk factors may be significant in the rate of subclinical atherosclerosis progression, as measured by AS, in women with (cases) and without (controls) SLE.

Methods: Baseline data were collected on cases and controls including demographics, self-reported and measured Framingham CV risk factors. SLE factors collected included the modified SLICC/ACR-DI Damage Index (SDI) (excluding CV outcomes). AS was measured by electron beam or multi-dimensional computed tomography at baseline and at 1 follow-up visit in the Study of Lupus Vascular and Bone Long-Term Endpoints (SOLVABLE). A high risk AS was defined as AS>100 and progression in AS at follow-up was defined as an AS>100 and an increase of >10% compared to baseline. A low risk AS was defined as AS<100. Univariate regression models of AS with risk factors were examined, and also adjusted for age. Presence of hypertension (HTN) was defined as systolic blood pressure (BP) ≥ 140 or diastolic BP ≥ 90 or on anti-HTN medication.

Results: At the baseline visit in 142 cases, their age was 43.3 ± 9.9 yrs, disease duration was 12.0 ± 8.4 yrs, SLEDAI was 3.8 ± 3.5, SDI was 1.5 ± 1.6 (mean ± SD). Imaging data with AS at baseline and follow-up were available on 106 cases; baseline AS scans were not performed in 36 cases. In 120 controls, their age was 46.7 ± 10.1 yrs (mean ± SD). Imaging data with AS at baseline and follow-up were available on 118 controls; 2 were missing baseline AS measurements. Mean ± SD follow-up time between imaging studies in 106 cases and 118 controls was 3.26 ± 0.35 yrs and 3.37 ± 0.41 yrs, respectively. Follow-up time was slightly different between cases and controls (p=0.05).

In 106 cases, 67 (63%) had low risk AS at baseline and at follow-up, 11 (10.4%) had low risk AS at baseline with progression at follow-up, 4 (3.8%) with high risk AS at baseline regressed to low risk at follow-up, and 0 with low risk AS at baseline progressed at follow-up.

In 118 controls, 87 (73%) had low risk AS at baseline and at follow-up, 7 (5.9%) had low risk AS at baseline with progression at follow-up, 2 (1.7%) with high risk AS at baseline regressed to low risk at follow-up, and 0 with high risk AS at baseline progressed at follow-up.

In the women with SLE, AS progression was univariately associated with HTN, current smoking, older age, and higher SDI. After adjustment, only increased SDI remained significant (OR 1.60, 95% CI 1.22–2.16). In controls, AS progression was univariately associated with HTN, current smoking status, older age, and higher BMI. After adjustment, only current smoking status remained significant (OR 6.65, 95% CI 1.55–31.29).

Conclusion: In cases and controls, traditional CV risk factors are univariately associated with the progression of subclinical atherosclerosis as measured by AS. In cases, SLE damage is significantly associated with progression. While aging mediates the effect of many traditional CV risk factors for AS progression in women with and without SLE, increased risk due to SLE damage is independent of age. Further investigation with multivariate models is needed.

1430

Women with Systemic Lupus Erythematosus (SLE) May Have Different Predictors of Risk for Progression of Coronary Artery Calcium (CA) Than Women without SLE. Apinya Lertratanakul[1], Peggy W. Wu[1], Alan Dyer[1], William Pearce[1], George Kondos[2], Daniel Edmundowicz[3], James Carr[4] and Rosalind Ramsey-Goldman[4]. [1]Northwestern University, Chicago, IL, [2]University of Illinois at Chicago, Chicago, IL, [3]Temple University School of Medicine, Philadelphia, [4]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: Women with SLE have increased rates of subclinical atherosclerosis and cardiovascular (CV) events. We sought to deter-mine which risk factors may be significant in the rate of subclinical atherosclerosis progression, as measured by coronary artery calcium score (CAC) in women with (cases) and without (controls) SLE.

Methods: Baseline data were collected on cases and controls including demographics, self-reported and measured traditional CV risk factors. SLE factors collected included modified SLICC/ACR-DI Damage Index (SDI) (excluding CV outcomes). CAC was measured by electron beam or multi-dimensional computed tomography at baseline and at 1 follow-up visit in the Study of Lupus Vascular and Bone Long-Term Endpoints (SOLVABLE). A high risk CAC was defined as CAC>10 and progression in CAC at follow-up was defined as a CAC>10 and an increase of >10% compared to baseline. Low risk CAC was defined as CAC<10. Univariate regression models of CAC with risk factors were examined. These models were further adjusted for age.

Results: At the baseline visit in 142 cases, the age was 43.3 ± 9.9 yrs, disease duration was 12.0 ± 8.4 yrs, SLEDAI was 3.8 ± 3.5, SDI was 1.5 ± 1.6 (mean ± SD). In 120 controls, the age was 46.7 ± 10.1 yrs (mean ± SD). Follow-up time between imaging studies in 142 cases and 120 controls was 3.25 ± 0.35 yrs and 3.37 ± 0.41 yrs (mean ± SD), respectively. Follow-up time was longer in controls than in cases (p=0.02).

In 142 cases, 103 (73%) had low risk CAC at baseline and at follow-up, 12 (8.5%) had low risk CAC at baseline with progression at follow-up, 2 (1.4%) with low risk CAC at baseline had regression to low risk at follow-up, and 21 (14.8%) with high risk CAC at baseline and progression at follow-up. Four (2.8%) had high risk CAC at baseline and follow-up without progression.

In 120 controls, 100 (83%) had low risk CAC at baseline and at follow-up, 7 (5.8%) had low risk CAC at baseline with progression at follow-up, 3 (2.5%) with high risk CAC at baseline had regression to low risk at follow-up, and 10 (8.3%) with high risk CAC at baseline and progression at follow-up.

In cases, progression in CAC was univariately associated with presence of diabetes, older age, and higher BMI. After adjustment for age, only SDI remained associated with CAC progression (Table 1). In controls, presence of hypertension and older age were univariately associated with CAC progression. After adjustment for age, no risk factors remained significant.

Table 1. Risk Factors Associated with Coronary Artery Calcium Progression in Cases and Controls, Adjusted for Age

Risk Factor	Cases OR (95% CI)	Controls OR (95% CI)
HTN*	1.06 (0.44–2.53)	0.93 (0.24–3.28)
Smoking	0.75 (0.15–2.79)	2.60 (0.46–12.69)
Diabetes	3.42 (0.912–12.88)	NA**
Total cholesterol	1.01 (0.63–1.60)	1.20 (0.67–2.16)
BMI	1.48 (1.00–2.22)	1.16 (0.64–2.07)
SDI	1.56 (1.21–2.05)	NA

*HTN = systolic blood pressure≥90 or on an anti-HTN medication **1 control subject noted having diabetes

Conclusion: In cases and controls, traditional CV risk factors are univariately associated with the progression of subclinical atherosclerosis as measured by CAC. In cases, SLE damage is significantly associated with progression. While aging mediates the effect of many traditional CV risk factors for CAC progression in women with and without SLE, increased risk due to SLE damage is independent of age. Further investigation with multivariate models is needed.

1431

Single Photon Emission Computed Tomography Contributes to Clinical Assessments in Neuropsychiatric Systemic Lupus Erythematosus Patients. Maasa Hama, Mitsuhiro Takeno, Atsushi Ihata, Daiga Kishimoto, Reikou Watanabe, Takeaki Uehara, Ryusuke Yoshimi, Yukiko Asami, Atsuhisa Ueda and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan

Background/Purpose: Because the clinical manifestations of NPSLE are diverse, multifaceted approaches are necessary to evaluate the disease activity

and therapeutic responses. We investigated contribution of various CNS examinations to clinical assessment in each subtype of NPSLE.

Methods: We retrospectively analyzed clinical features and the findings of CSF, EEG, CNS imaging modalities including MRI and SPECT in 41 patients (6 male, 35 female) who met ACR 1997 SLE classification criteria with neuropsychiatric symptoms from 2000 to 2011. The patients were categorized into 3 groups according to ACR-defined NPSLE syndromes at 1999; Patients with neurological symptoms (Group N), those with psychiatric symptoms (Group P), and those with the both (Group N+P).

Results: Median age at onset of SLE was 25 years old (range 5–63). About a half of the patients developed neuropsychiatric symptoms within a year from SLE onset. Based on the clinical symptoms such as cognitive dysfunction (37%), acute confusional state (32%), seizure (29%), headache (22%), aseptic meningitis (20%), and cerebrovascular disease (15%), the patients were classified into Group N (16 patients, 39%), Group P (13 patients, 32%), and Group N+P (12 patients, 29%). Pleocytosis and increased protein in CSF were the most frequently found in Group N, whereas increased protein with high IgG index was also observed in a part of patients in Group P. EEG abnormality, especially emergence of slow waves, was more prevalent in group P and N+P than group N. MRI showed any abnormalities in 85 %. Diffuse white matter (WM) high intensity signals in Group N, and cerebral parenchymal atrophy and focal WM high intensity signals in group P and N+P were common. SPECT revealed the hypoperfusion, particularly in the frontal and parietal lobes in all patients but one, even in those having normal MRI. Most patients received potent immunosuppressive therapies including steroid pulse and IVCY, leading to clinical improvement in 69% of Group N but 37.5% of Group P and N+P, irrespective of pre-therapeutic clinical parameters. In 19 patients having follow-up examinations of SPECT, brain perfusion was restored with clinical amelioration responding the therapy in 4 out of 5 patients of Group N. In contrast, hypoperfusion was unchanged or decreased in about 75%, 50% of Group P, N+P, respectively. In the two groups, there was a discrepancy between SPECT findings and clinical course in 5 of 14 patients.

follow-up SPECT
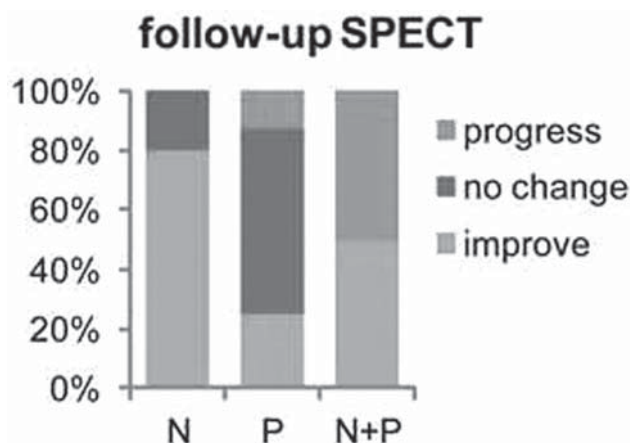
Conclusion: Cerebral hypoperfusion in SPECT was associated with NP lesions in SLE and the findings were closely correlated with disease activity especially in neurological deficits rather than psychiatric symptoms.

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1432

Safety and Efficacy of Etanercept in Systemic LUPUS Erythematosus.
Josefina Cortes-Hernandez[1], Natalia Egri[1], Miquel Vilardell-Tarres[1] and Josep Ordi-Ros[2]. [1]Hospital Universitari Vall dxHebron, Institut de Recerca (VHIR), Barcelona, Spain, [2]Vall De Hebron General Hospt, Barcelona, Spain

Background/Purpose: TNF is a strong mediator of inflammation with a controversial role in SLE. Whereas few open-label studies have shown efficacy of anti-TNFα agents in patients with SLE arthritis and renal disease, many others have reported its potential risk of autoantibody formation. The aim of the study was to evaluate the efficacy and safety of etanercept in patients with moderate active SLE without renal involvement.

Methods: In this open-label study, 42 SLE patients with cardiopulmonary and/or articular involvement (10 with serositis, 6 with shrinking lung syndrome (SLS) and 35 with arthritis) refractory to other therapies were given etanercept (50 mg/weekly) in addition to conventional immunosuppression therapy. Clinical response was categorized in complete response when a complete resolution of the symptoms and/or SLEDAI score <4 was achieved; partial response when there was a 50% clinical improvement and no response when there was no clinical improvement.

Results: Forty two lupus patients (34 female and 8 male, mean age 38.2 (18–60) were included and followed up prospectively for 24 months (3–6). Two of them withdrew from the study due to significant local reactions. Of the remaining patients, clinical improvement was observed in 38 of them (95%). Six patients had to be switched to adalimumab due to etanercept side-effects or lack of efficacy. Eight of the ten patients (90%) with pleuropericarditis achieved clinical remission in a mean period of 5.67±2.65 weeks. In four patients (80%) with SLS, FVC (%) rose from 43±12 to 58±16 (p<0.05) at the end of treatment. Thirty-five patients (92%) with joint involvement achieved remission of arthritis. Relapse was frequent after stopping medication and occurred 8–11 weeks after stopping treatment. The main adverse effects were local reactions (14%) and urinary tract infection (5%). Levels of ANA and/or anti-dsDNA rose in 6 patients (14%), but were not associated with lupus flare.

Conclusion: Anti-TNF agents are safe and efficacious in SLE and did not lead to an increase SLE activity. In view of their anti-inflammatory properties they can be a therapeutical alternative for refractory serositis and SLS.

Disclosure: **J. Cortes-Hernandez**, None; **N. Egri**, None; **M. Vilardell-Tarres**, None; **J. Ordi-Ros**, None.

1433

Persistent Dyslipidemia Is a Risk Factor of Progression to Chronic Kidney Disease in Patients with Lupus Nephritis.
Dong-Jin Park, Kyung-Eun Lee, Tae-Jong Kim, Yong-Wook Park and Shin-Seok Lee. Chonnam National University Medical School, Gwangju, South Korea

Background/Purpose: To investigate the effect of dyslipidemia at baseline and during follow-up period on the progression to chronic kidney disease (CKD) in patients with biopsy-proven lupus nephritis (LN).

Methods: We studied 68 patients who had kidney biopsy prior to the start of induction treatment, and who subsequently were treated with immunosuppressive drugs for at least 6 months. Sociodemographic, clinical, laboratory including lipid profile, and treatment-related data at the time of kidney biopsy and during follow-up were obtained by reviewing patients' charts. In addition, lipid profile data were collected at 6 months and 1 year of follow-up periods. Patients were divided into two groups based on mean levels of LDL cholesterol: the ≥100 mg/dl group with 25 patients and the < 100 mg/dl group with 43 patients. Cox- proportional regression analyses were performed to identify independent predictors of progression to CKD in these patients.

Results: The higher LDL cholesterol group had a significantly older age at onset of LN, had higher WBC counts, and excreted more 24-hour urine protein than the lower LDL cholesterol group (p=0.010, p=0.035, and p=0.048, respectively). The high LDL cholesterol levels during the follow-up period was a significant predictor of CKD in LN patients in unadjusted model (hazard ratio [HR] 3.997, 95% CI 1.193-13.388, p=0.025), and this association remained significant after adjustment for confounders including estimated glomerular filtration rate (HR 3.592, 95% CI 1.067-12.094, p=0.039).

Conclusion: Our findings suggested that persistent dyslipidemia during 1-year follow-up after the onset of LN was an independent risk factor to predict the development of CKD in LN patients. Therefore, lipid profile should be monitored regularly and dyslipidemia should be managed aggressively to prevent deterioration of kidney function in these patients.

Disclosure: **D. J. Park**, None; **K. E. Lee**, None; **T. J. Kim**, None; **Y. W. Park**, None; **S. S. Lee**, None.

1434

Cardiovascular Morbidity in a Long-Term Follow-up Cohort of Systemic Lupus Erythematosus Patients in Southern Sweden.
Ragnar Ingvarsson[1], Ola Nived[2], Gunnar Sturfelt[1], Anders Bengtsson[3] and Andreas Jönsen[4]. [1]Department of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [2]University Hospital - Lund, Lund, Sweden, [3]University Hospital Lund, Lund, Sweden, [4]Section of Rheumatology, Lund, Sweden

Background/Purpose: The main objective was to study the incidence of myocardial infarction in a cohort of patients with Systemic Lupus Erythem-

atosus (SLE) assembled prospectively over 25 years within a geographically defined area in Southern Sweden.

Methods: All SLE patients living within a defined geographical area in Southern Sweden between 1981–2006 were included in the study. The patients were observed prospectively within a structured follow-up program. Myocardial infarctions (AMI) were registered according to the definitions in the SLICC/ACR organ damage index during follow-up. The frequency of AMI was compared with the general population in the same area. Population data on AMI in the study period 1981–2006 were obtained through central databases (Socialstyrelsen). Data were stratified for age and sex.

Results: The health care district of Lund-Orup had a mean population during 1981–2006 of 176.460 persons (>15 yrs of age). One-hundred seventy-five new cases were diagnosed with SLE from 1981–2006. There were 148 women and 27 male patients that received the diagnosis of SLE, with a mean age of diagnosis at 44.3 years. Average follow-up time was 12,4 years from the time of diagnosis. There were 23 cardiovascular related deaths during the study period. Females between the ages 45–54 had an increased risk for acute AMI compared to healthy paired controls (SIR 12,4 (95%CI 1.4–45). In the other 10-year age groups, both for males and females, no significant differences were found.

Conclusion: Acute myocardial infarction is more prevalent in females between the ages 45–54 with SLE compared with the population in a geographically defined area in southern Sweden.

Disclosure: **R. Ingvarsson**, None; **O. Nived**, None; **G. Sturfelt**, None; **A. Bengtsson**, None; **A. Jönsen**, None.

1435

Identifying Systemic Lupus Erythematosus Patients At Higher Risk of Coronary Artery Disease. Dominique Ibanez, D. D. Gladman and Murray B. Urowitz. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: There is a high prevalence of premature atherosclerosis among patients with SLE. The traditional Framingham risk score (FRS) identifies few of the SLE patients who go on to develop coronary artery disease (CAD). This is particularly true among patients aged 30 to 70. It has been suggested that a modified Framingham risk score (mFRS) where each item is multiplied by 2 more accurately identifies patients at Moderate/High risk of CAD, and more accurately predicts subsequent CAD. Moreover FRS predicts outcomes at 10 years. In a clinic setting, FRS and mFRS can be assessed more than once over time. The aim of this study was to determine whether the mFRS more accurately identifies patients at higher risk of CAD then FRS when the Risk Scores are assessed repeatedly through time.

Methods: Patients aged 30 to 70, seen at a large lupus clinic with multiple clinic visits, and in whom all of the variables necessary for the evaluation of FRS and mFRS were available, were included. FRS and mFRS were assessed for each visit and subsequent development of CAD was determined. CAD was defined as presence of myocardial infarction or angina. Descriptive statistics were used to characterize the survey population. Time-dependent covariate proportional hazard models were used to evaluate the Hazard Ratio associated with FRS and with mFRS for the development of future CAD. Adjustments were made in the models for disease activity at each clinic visit using SLEDAI-2K.

Results: A total of 630 patients were seen for 8098 visits where FRS and mFRS were assessed. 575 (91.3%) were female and their age at SLE diagnosis was 31.4 ± 11.2 years. At first visit in the study, the mean age was 42.4 ± 11.2 with disease duration of 11.1 ± 9.1 years. FRS and mFRS were evaluated for an average of 12.9 ± 9.6 visits per patient. The mean time from study start to the development of CAD or last clinic visit is 12.3 ± 9.7 years. A total of 37 patients went on to develop CAD.

FRS was classified as Moderate/High for 1.2% of all visits and for 16.4% of all visits when using mFRS. 31 (4.9%) patients were classified as Moderate/High at least once in their follow-up compared to 221 (35.1%) for mFRS.

Table 1. Hazard Ratio for the prediction of CAD

	Risk Score: FRS HR (95% CI)	p value	Risk Score: mFRS HR	p value
Risk Score	2.66 (0.63,11.33)	0.18	3.10 (1.76,6.58)	0.0003
Models adjusting for Disease Activity				
Risk Score	2.96 (0.70,12.58)	0.14	3.50 (1.81,6.77)	0.0002
SLEDAI-2K	1.08 (1.02,1.15)	0.01	1.08 (1.02,1.15)	0.01

Conclusion: The Modified Framingham Risk Score can better identify patients with Moderate/High risk for CAD. Being applied over multiple visits through time, it better selects patients who are more likely to benefit from more intensive risk factors control.

Disclosure: **D. Ibanez**, None; **D. D. Gladman**, None; **M. B. Urowitz**, None.

1436

Application of European League Against Rheumatism Recommendations for the Management of Systemic Lupus Erythematosus Patients with Neuropsychiatric Involvement May Limit Unnecessary Diagnostic Testing and Curve Intensification of Immunosuppressive Therapy of Unclear Benefit. Cristina Pamfil[1], Antonios Fanouriakis[2], Argyro Repa[2], Maria Melissourgaki[2], Prodromos Sidiropoulos[2], Ileana Filipescu[3], Mirela Rinzis[3], Simona Rednic[3], George Bertsias[2] and Dimitrios Boumpas[4]. [1]University of Medicine and Pharmacy, Cluj, Romania, [2]University of Crete, Iraklion, Greece, [3]Emergency County Clinical Hospital Cluj Napoca, Cluj-Napoca, Romania, [4]Panepistimio Kritis, Rethymnon, Greece

Background/Purpose: Systemic lupus erythematosus (SLE) patients may experience a wide variety of neurological and psychiatric manifestations (neuropsychiatric [NP] SLE [NPSLE]), which pose diagnostic and therapeutic challenges to clinicians leading to significant heterogeneity in their management. We have recently published evidence and expert based recommendations on NPSLE. We sought to measure them against usual care by auditing the management in our centers prior to issuing these recommendations.

Methods: NPSLE events were reviewed in two lupus centers in Iraklio, Greece and Cluj, Romania. Non-SLE-related events were excluded. We compared the diagnostic and treatment decisions in our cohort with the recommendations issued by the European League Against Rheumatism (EULAR) for specific NPSLE manifestations.

Results: A total of 105 NP events attributed to SLE were recorded in 89 patients (89% female, mean age 41.1 years, mean time from SLE onset to NPSLE 5.2 years) by cxahrt review over the last decade (2001–11). Most common events included cerebrovascular disease (n=19, 18%), cognitive dysfunction (n=17, 16%), intractable headache (n=10, 9.5%), psychosis (n=10, 9.5%), and transverse myelitis (n=10, 9.5%). Overall, the concordance between clinical decisions and the recommendations was 74% for diagnostic work-up and 67% for treatment of NPSLE (**Table 1**). Regarding diagnosis, lower concordance rates were noted in cases of cognitive dysfunction with only 5/17 (29%) SLE patients undergoing the recommended neuropsychological testing, and also in mood disorder where 4/7 (57%) patients had brain neuroimaging despite limited evidence for its usefulness. In contrast, the diagnostic work-up of major NPSLE such as seizure disorders, cranial neuropathy, and peripheral neuropathy, was generally in accordance with the recommendations. In terms of treatment, 40% of patients with seizure disorder and 40% of patients with cerebrovascular disease underwent intensification of immunosuppressive therapy without clear evidence of generalized SLE activity, as the recommendations suggest. Antiplatelet or anticoagulant treatment was initiated in 34/39 (87%) of patients with NPSLE and positive antiphospholipid antibodies in accordance with EULAR recommendations. In contrast, the management of cognitive dysfunction did not include the recommended psycho-educational support in the majority of cases.

Table 1. Concordance of clinical practice with recommendations

	N	Diagnostic work-up	Treatment
Cardiovascular disease	19 (18%)	14/19 (74%)[a]	9/19 (47.3%)[b], 6/11 (55.5%)[d]
Cognitive disorder	17 (16%)	5/17 (29.4%)[f]	17/17 (100%)[g], 1/17 (6%)[h]
Psychosis	10 (9.5%)	7/10 (70%)[a]	8/8 (100%)[b]
Seizure disorder	9 (8.5%)	8/9 (88.9%)[c]	3/5 (60%)[b], 0/2 (0%)[d]
Mood disorder	7 (6.6%)	4/7 (57%)[a]	5/7 (71%)[b]
Transverse myelitis	10 (9.5%)	7/10 (70%), 8/10 (80%)[e]	6/10 (70%), 7/10 (80%)[b]
Cranial neuropathy	8 (7.5%)	2/2 (100%)[i]	2/2 (100%)[b]
Peripheral neuropathy	6 (5.7%)	6/6 (100%)[j]	5/6 (83%)[b]

Abbreviations: a, brain imaging; b, glucocorticoids and immunosuppressants; c, MRI and EEG; d, antiplatelet/anticoagulation; e, MRI and CSF; f, neuropsychological tests; g, disease and risk management; h, psycho-educational support. i: ophtalmological evaluation, j: electromyography and nerve conduction studies

Conclusion: The diagnostic and therapeutic decisions in NPSLE patients managed in two European centers were often not in concordance with the existing EULAR recommendations. Applications of these recommendations

may decrease unnecessary testing and curve intensifications of immunosuppressive therapy in cases no clear benefit has been documented. Longitudinal studies to further validate the impact of these recommendations in improving outcomes are needed.

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1437

Majority of Lupusqol Domains Are Negatively Correlated with Systemic Lupus Activity Questionnaire (SLAQ) Score. Wendy Marder[1], Martha Ganser[1], Margaret Hyzy[2] and Emily C. Somers[1]. [1]University of Michigan, Ann Arbor, MI, [2]Universitiy of Michigan, Ann Arbor, MI

Background/Purpose: Systemic lupus erythematosus (SLE) disease activity measures such as the SLEDAI and BILAG require real time physician and laboratory assessment of patients, making them difficult to use in large, epidemiologic studies. The Systemic Lupus Activity Questionnaire (SLAQ) is a self-administered tool developed specifically for screening purposes and epidemiologic studies, and takes a lupus patient < 5 minutes to complete. While the SLAQ is not intended for clinical management or in lieu of physician assessment for disease management purposes, it has been validated in a large community based cohort in response to other health indices such as SF12 and SF 36. We assessed correlations between these two self-administered SLE disease measures in a cohort of well characterized SLE patients at a large tertiary care outpatient setting.

Methods: SLE patients from the University of Michigan rheumatology clinics who met 4 or more ACR criteria and age 18 years or older were enrolled. Patients completed SLAQ and LupusQoL questionnaires, as well as sociodemographic data. The total SLAQ score is calculated on a scale of 0–47, with groups of symptoms aggregated and assigned different weights. LupusQOL consists of 34 items, grouped as 8 domains. Pearson's correlation was utilized to assess the strength of associations between overall disease activity and individual QOL domains.

Results: 100 adult SLE patients responded, including 89 females and 11 males. Mean age was 40 years (sd 13 range 18–71). Patients were 66% White, 21% Black, 11% Other, 2% not reported. Mean SLAQ score was 13.3 (SD 9.0, range 0 to 39). SLAQ score (0–47 scale) was negatively associated with all QOL domains except body image, including physical health, pain, planning, intimate relationships, burden to others, emotional health, and fatigue. Pearson correlation coefficients ranged between -0.39 and -0.70.

Conclusion: Using lupus-specific self-report measues, increased disease activity (by SLAQ) is associated with reduced QOL (by LupusQOL) in 7 of 8 domains. While QOL measures have been examined more thoroughly in the context of physician-measured disease activity measures, data are needed in relation to patient-reported lupus activity in order to provide the basis for more extensive evaluation of these concepts in the epidemiologic setting. The total SLAQ score is negatively associated with nearly all domains of the LupusQoL questionnaire, supporting its utility in self-report SLE disease assessment.

Disclosure: W. Marder, None; M. Ganser, None; M. Hyzy, None; E. C. Somers, None.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Animal Models
Monday, November 12, 2012, 9:00 AM–6:00 PM

1438

Development of Systemic Lupus Erythematosus (SLE) in NZM 2328 Mice in the Absence of Any Single BAFF Receptor. Chaim O. Jacob[1], Ning Yu[2], Shunhua Guo[2], Noam Jacob[2], William J. Quinn III[3], Michael P. Cancro[3], Beatrice Goilav[4], Chaim Putterman[5], Thi-Sau Migone[6] and William Stohl[2]. [1]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [2]University of Southern California Keck School of Medicine, Los Angeles, CA, [3]University of Pennsylvania School of Medicine, Philadelphia, PA, [4]Children's Hospital at Montefiore, Bronx, NY, [5]Albert Einstein College of Medicine, Bronx, NY, [6]Human Genome Sciences, Rockville, MD

Background/Purpose: To determine the necessity for any individual BAFF receptor in the development of SLE.

Methods: NZM 2328 wild-type (WT), NZM.$Bcma^{-/-}$, NZM.$Taci^{-/-}$, and NZM.$Br3^{-/-}$ mice were evaluated for lymphocyte phenotype and BAFF receptor expression by flow cytometry, for serum BAFF and total IgG and IgG anti-dsDNA levels by ELISA, for glomerular deposition of IgG and C3 by immunofluorescence, for renal histopathology, and for clinical disease.

Results: The phenotypes of NZM mice deficient in a single BAFF receptor were highly divergent. In comparison to WT mice, NZM.$Bcma^{-/-}$ and NZM.$Taci^{-/-}$ mice harbored increased spleen B cells, T cells, and plasma cells (PC), whereas serum total IgG and IgG anti-dsDNA levels were similar to WT levels. Although B cells were markedly reduced in NZM.$Br3^{-/-}$ mice, they nonetheless harbored increased T cells as well as WT-like numbers of PC and levels of IgG anti-dsDNA. Serum BAFF levels were increased in NZM.$Taci^{-/-}$ and NZM.$Br3^{-/-}$ mice but were decreased in NZM.$Bcma^{-/-}$ mice. Expression of TACI on B cells and of BCMA and TACI on bone marrow (BM) PC was reduced in NZM.$Br3^{-/-}$ mice, and expression of BR3 and TACI on BM PC was markedly diminished in NZM.$Taci^{-/-}$ mice. Despite their phenotypic differences, renal immunopathology in NZM.$Bcma^{-/-}$, NZM.$Taci^{-/-}$, and NZM.$Br3^{-/-}$ mice, including robust glomerular deposition of IgG and C3 and development of glomerular hypercellularity, glomerular crescents, mesangial matrix deposition, interstitial inflammation and fibrosis, tubular atrophy, and perivascular leukocyte infiltration, was at least as severe as in WT mice. Moreover, clinical disease was indistinguishable among the four cohorts of mice. Severe proteinuria began to develop in each of the cohorts at 4–5 months of age, and ₋90% of the mice in each cohort was affected by 12 months of age. Mortality in each of the cohorts was noted as early as 6–7 months of age, with ₋90% of the mice in each cohort being dead by 12 months of age.

Conclusion: Any single BAFF receptor, including BR3, is dispensable to development of full-blown clinical SLE in NZM mice. The development of disease in NZM.$Br3^{-/-}$ mice demonstrates that BAFF/BCMA and/or BAFF/TACI interactions importantly contribute to SLE. Moreover, development of disease in NZM.$Br3^{-/-}$ mice demonstrates that profound, chronic reduction in B cells does not equate with protection from SLE. As such, NZM.$Br3^{-/-}$ mice may serve as a useful model in elucidating why the efficacy of B cell-depletion therapy in human SLE is limited.

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CTL-Promoting Effects of IL-21 Results in B Cell Elimination and Disease Improvement in a Murine Model of Lupus. Vinh Nguyen[1], Daniel Veizaga-Udaeta[2], Horea Rus[3] and Violeta Rus[3]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]University of Maryland at Baltimore County, MD, [3]University of Maryland School of Medicine and Veteran Affairs Medical Center, Baltimore, MD

Background/Purpose: IL-21 is a member of the type I cytokine family with pleiotropic activities. IL-21 enhances CD8 T cells maturation into cytotoxic T lymphocytes (CTL), promotes the differentiation of T follicular helper (T_{FH}) and Th17 cells while downregulating Tregulatory (Treg) cells and regulates B-cell proliferation and survival, Ig production and class switching. In humans, an association of IL-21 and IL-21R polymorphisms with SLE were reported, while studies in murine models of lupus have indicated that IL-21 blockade was beneficial in MRL-Fas^{lpr}, BXSB-Yaa and chronic graft versus host disease (cGVHD) mice. Furthermore, we have shown that in the cGVHD model, IL-21 promotes the autoimmune phenotype by both B and CD4 T cell intrinsic mechanisms. The relative importance of IL-21R signaling in CD8 T cells on autoimmune parameters in murine lupus has not yet been assessed. In this study we set to determine whether the effect of IL-21 in promoting CD8 T cell differentiation into CTL, leads to the elimination of autoreactive B cells and subsequently the attenuation of autoimmune parameters in murine lupus.

Methods: To address this question we have used two established models of chronic and acute GVHD to dissect the effect on autoimmune parameters of IL-21R signaling in donor CD8 T cells. Specifically, IL-21R sufficient and deficient mice were used as donors in the B6-into-F1 model of acute (a)GVHD. In addition, the effect of exogenous IL-21 on autoimmune parameters was assessed in the DBA-into-F1 lupus-like model of cGVHD that is characterized by defective CTL activity resulting in the persistence of autoreactive B cells. In both models, parameters of acute and cGVHD including donor CD4 and CD8 T cell engraftment, host B cell number and

activation, anti-ssDNA autoAb production, in vivo donor anti-host CTL activity were assessed at two weeks after disease induction.

Results: Acute GVHD induced by injection of IL-21R$^{-/-}$ splenocytes on the B6 background into B6D2F1 hosts, resulted in the conversion of acute to chronic GVHD phenotype, as demonstrated by increased autoAb production, decreased host B cell elimination (57%±6 vs. 90%±0.3; p=0.03) and impaired in vivo CTL activity along with significant decrease in donor (d)CD4 and dCD8 cell expansion. In contrast, DBA-into-F1 cGVHD mice that received rmIL-21 exhibited attenuated autoimmune parameters with respect to host B cell expansion and activation, anti-ssDNA autoAb production along with enhanced donor CD8 expansion and donor anti-host CTL activity. In both models, IL-21/IL-21R interaction on donor CD8 cells resulted in their increased proliferation, expansion and differentiation into CTLs that expressed higher levels of granzyme B and IFNg levels, but nor perforin.

Conclusion: These results suggest that lack of IL-21/IL-21R interaction on CD8 T cells converts acute to chronic GVHD by impairing B cell elimination, while in cGVHD, IL-21 administration attenuates the humoral component by enhancing CTL generation and subsequently host B cells elimination. Therefore, IL-21R signaling on CD8 T cells attenuates disease phenotype in murine lupus, thus opposing the enhancing effects of IL-21R signaling on CD4 T cells and B cells.

Disclosure: V. Nguyen, None; **D. Veizaga-Udaeta**, None; **H. Rus**, None; **V. Rus**, None.

1440

Lupus-Prone Mice Demonstrate Enhanced Neutrophil Extracellular Trap Formation: Implications for Autoantibody Formation and Organ Damage.

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Background/Purpose: Recent evidence suggests that enhanced neutrophil extracellular trap (NET) formation—the programmed release of chromatin fibers decorated with granular antimicrobial peptides—is as an important activator of plasmacytoid dendritic cells in systemic lupus erythematosus (SLE). We have proposed that NETosis is also linked to skin, kidney, and premature vascular damage in human SLE. Understanding the role of NETosis in murine models of lupus will be crucial to further investigations of the pathogenic role of this process in autoimmune diseases.

Methods: The New Zealand Mixed (NZM) 2328 model of murine lupus was utilized, with BALB/c and C57BL/6 mice as non-autoimmune controls. Percentage of neutrophils undergoing NETosis was assayed both at baseline and upon exposure to NZM or control serum. Autoantibodies (autoAbs) to NET proteins were characterized by immunofluorescence, western blotting, and in-house ELISAs for Abs to the LL-37 mouse orthologue CRAMP and to NET proteins in general. Glomerular and skin NET-like material were detected by immunofluorescence analysis.

Results: NZM neutrophils demonstrated enhanced spontaneous NETosis (7.13% ± 1.16 vs. 1.83% ± 0.25; p=0.0008) as compared to control BALB/c neutrophils; further, incubation of control neutrophils with NZM serum increased NETosis percentage to levels observed in NZM neutrophils. The NET-stimulating effect of NZM serum was also robust in type I interferon receptor-knockout neutrophils, suggesting that serum factors other than these cytokines contribute to the phenotype. NZM mice develop anti-NET autoAbs. Immunofluorescence analysis using NZM serum as primary Ab demonstrated a granular pattern of reactivity with NETs, which in many places co-localized with anti-myeloperoxidase (MPO) and anti-neutrophil elastase (NE) staining. Using similar methodology, western blotting revealed NZM serum reactivity with specific proteins derived from NETs. By ELISA, NZM serum reacted more strongly with CRAMP (1.98 ± 0.19 vs. 1.00 ± 0.14; p=0.017) and NET proteins (1.85 ± 0.16 vs. 1.00 ± 0.090; p=0.014) than age-matched control serum. NET-like material—consisting of DNA, MPO, and NE—was detected in nephritic NZM kidneys and in non-affected NZM skin, but not in control mice.

Conclusion: The NZM2328 murine model of lupus replicates a number of the features of human SLE with regards to aberrant neutrophil function. These include enhanced NETosis, anti-NET autoAb formation, and the potential for organ damage attributable to NETs. Future studies should better dissect the role of NETosis both in driving lupus pathogenesis and in contributing to organ damage such as skin disease, nephritis, and accelerated atherosclerosis.

Disclosure: J. S. Knight, None; **A. A. O'Dell**, None; **W. Zhao**, None; **R. Khandpur**, None; **S. Yalavarthi**, None; **M. J. Kaplan**, None.

1441

Epstein Barr Virus CD40 Functional Mimic Latent Membrane Protein-1 Drives Cellular Molecular Mimicry in the Presence of Epstein Barr Virus Nuclear Antigen-1 in a Novel Murine Model of Lupus-Like Disease.

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Background/Purpose: Immune dysregulation underlies the complex pathogenesis of SLE. Infection with Epstein Barr Virus (EBV) and expression of latent protein Epstein Barr Virus Nuclear Antigen-1 (EBNA-1, a humoral molecular mimic with SLE associated autoantigens) has been linked with SLE. Acting in an enhanced and sustained manner, the Latent Membrane Protein-1 (LMP1, another major EBV latent protein) cytoplasmic tail is necessary and sufficient as a functional mimic of the TNF Receptor, B cell stimulatory molecule CD40. Mice were created expressing a transgene (Tg) for the chimeric molecule mCD40-LMP1 (containing the cytoplasmic tail of LMP1) and bred onto a CD40$^{-/-}$ background to remove endogenous CD40. The mCD40-LMP1 Tg mice have normal T-dependent antibody responses, spontaneous germinal center formation, and autoantibodies by 2–3 months of age. However, no overt autoimmune disease or early death develops in this model. This study evaluates the nature of the immune response to EBNA-1 in mCD40-LMP1 Tg mice and whether the addition of a molecular mimic in this model could accelerate lupus pathogenesis.

Methods: mCD40-LMP1 Tg, full length mCD40 Tg (Tg strain control), and congenic C57Bl/6 (B6) mice (8–12 weeks of age) were immunized (in CFA) and boosted (in IFA) with EBNA-1 over an 8-week course. Saline/adjuvant and naïve control mice were also employed. Draining lymph node cells were cultured in antigen-recall assays stimulated with EBNA-1, the EBNA-1 antigenic epitope PPPGRRP (GRR), the cross-reactive autoantigen Sm, or the Sm antigenic epitope PPPGMRPP (GMR). Proliferation was measured by ^{3}H-Thymidine incorporation and culture supernatant cytokines by xMAP multiplex assay. Serum antibodies to EBNA-1, autoantibodies, and BUN and creatinine levels were also assessed.

Results: Anti-EBNA-1 antibody levels are comparable in mCD40-LMP1 Tg, mCD40 Tg and B6 congenic mice. EBNA-1 specific proliferative and inflammatory cytokine responses, including IL-6, IL-17, IFN-γ, and TNF-α, are significantly enhanced ($p < 0.0001$) in mCD40-LMP1 Tg compared to mCD40 Tg, B6 mice, and adjuvant and naïve control mice. In addition, mCD40-LMP1 Tg mice immunized with EBNA-1 exhibit significantly enhanced cellular responses ($p < 0.0001$) to the EBNA-1 antigenic epitope GRR and cross-react to the autoantigen Sm, as well as its antigenic epitope GMR. The cross-reactive cellular response to GRR and Sm starts within 10 days post-immunization with EBNA-1 in mCD40-LMP1 Tg mice. Cross-reactivity to the Sm epitope GMR occurs within 4 weeks after initial immunization. Enhanced cellular immune dysregulation with EBNA-1 immunization in mCD40-LMP1 mice is accompanied by enhanced splenomegaly, increased serum BUN and creatinine levels, and elevated anti-dsDNA and ANA autoantibody levels (p <0.0001 compared to mCD40 Tg and B6 mice, $p < 0.01$ compared to adjuvant and naïve mCD40-LMP1 mice).

Conclusion: Mice Tg for mCD40-LMP1 exhibit enhanced cellular responses to EBNA-1. In the presence of LMP1, EBNA-1 induces cellular molecular mimicry to the SLE associated autoantigen Sm. These data suggest that expression of EBV latent proteins EBNA-1 and LMP1 may contribute to immune dysregulation that leads to pathogenic autoantigen-specific inflammation in lupus.

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IRF-1 Deficient Lupus-Prone MRL/Lpr Mice Show Reduced Glomerulonephritis but Develop Severe Interstitial Nephritis, Renal Vasculitis and Pulmonary Granulomas with Propensity for Th2 Polarity.

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Background/Purpose: The transcription factor interferon regulatory factor-4 (IRF-4) and -1 (IRF-1) are members of the IRF family of transcrip-

tion regulators and involved in the development of Th2/Th17 and Th1 cells, respectively. MRL/*lpr* mice, a murine model of human SLE, spontaneously develop lupus-like disease. At ACR 2011, we reported that *Irf4*$^{-/-}$ MRL/*lpr* mice, which lacked serum autoantibodies and Th17 cells, developed proliferative glomerulonephritis but minimal to no interstitial nephritis or renal vasculitis. *Irf4*$^{-/-}$ MRL/*lpr* mice also developed granulomas containing Langhans-type multinucleated giant cells (MGCs) in multiple organs with significantly increased numbers of IFN-γ producing CD4$^+$ T cells, suggesting autoreactive Th1 cell-mediated mechanisms for their pathogenesis. To further define the role of autoreactive CD4$^+$ T cells in murine lupus, we generated *Irf1*$^{-/-}$ MRL/*lpr* mice and assessed their disease.

Methods: *Irf1-KO* MRL/*lpr* mice were generated by backcrossing *Irf1-KO* C57BL/6 mice onto MRL/*lpr* background for 7 generations by using speed congenic strategy. Mice were sacrificed at 18 weeks of age and histopathological analysis in multiple organs was performed. Infiltration of CD4$^+$ T cells and CD68$^+$ macrophages/monocytes in tissues was detected by immunofluorescence or immunohistochemical staining. Splenic immune cell populations were analyzed by flow. To determine Th1/Th2/Th17 cell numbers, splenic CD4$^+$T cells were cultured with PMA/ionomycin, and IFN-γ, IL-4 or IL-17 production was detected by intracellular staining and flow analysis.

Results: Unlike WT or *Irf4*$^{-/-}$ MRL/*lpr* mice, *Irf1*$^{-/-}$ MRL/*lpr* mice showed severe inflammation in their renal intersititum and blood vessels characterized by predominant infiltration of CD4$^+$ T cells. In contrast, minimal to no inflammation was observed in their glomeruli, suggesting independent mechanisms for development of interstitial nephritis and renal vasculitis. *Irf1*$^{-/-}$ MRL/*lpr* mice also developed pulmonary granulomas characterized by predominant infiltration of CD68$^+$ macrophages/epithelioid cells with formation of foreign body-type and Langhans-type MGCs. No granuloma was observed in age-matched WT MRL/*lpr* or *Irf1*$^{-/-}$ C57BL/6 mice. Different appearances of renal disease and granulomas between *Irf4*$^{-/-}$ and *Irf1*$^{-/-}$ MRL/*lpr* mice are summarized in the table. Intracellular cytokine analysis showed that there was significantly increased population of IL-4-producing CD4$^+$ T cells in the spleens of *Irf1*$^{-/-}$ MRL/*lpr* and C57BL/6 mice than their WT controls.

Mouse	CD4$^+$ T cell polarity	Renal disease Glomerular change	Interstitial inflammation	Vasculitis	Granulomas Lung	Liver	Spleen	Lymph node
Irf4$^{-/-}$ MRL/*lpr*	Th1	±~++ (Proliferative GN)	–~±	None	CD4$^+$ T cell predominant infiltration with formation of Langhans-type MGCs	CD4$^+$ T cell predominant infiltration with formation of Langhans-type MGCs	CD4$^+$ T cell predominant infiltration with formation of few Langhans-type MGCs	CD4$^+$ T cell predominant infiltration with formation of few Langhans-type MGCs
Irf1$^{-/-}$ MRL/*lpr*	Th2	–~±	+++ CD4$^+$ T cell predominant infiltration	+++ CD4$^+$ T cell predominant infiltration	CD68$^+$ macrophages predominant infiltration with formation of foreign body-type and Langhans-type MGCs	Focal granulomatous lesions with formation of foreign body-type MGCs	No granulomas	No granulomas

Conclusion: Our results indicate that IRF-1 plays an important role in the regulation of Th2 polarity in MRL/*lpr* and C57BL/6 mice. Development of inflammatory renal disease and pulmonary granulomas not in *Irf1*$^{-/-}$ C57BL/6 mice but in lupus-prone *Irf1*$^{-/-}$ MRL/*lpr* mice with significantly increased numbers of IL-4 producing CD4$^+$ T cells suggests autoreactive Th2 cell-mediated mechanisms for their pathogenesis.

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Caspase-1 Modulates Endothelial Dysfunction and Vascular Repair in Murine Lupus. J. Michelle Kahlenberg, Wenpu Zhao, Srilakshmi Yalavarthi and Mariana J. Kaplan. University of Michigan, Ann Arbor, MI

Background/Purpose: Premature cardiovascular disease (CVD) represents a significant cause of morbidity and mortality in systemic lupus erythematosus (SLE). We recently proposed that type I interferon (IFN) modulation of the inflammasome and resultant IL-18 production contribute to dysfunction of endothelial progenitor cells (EPC) in SLE patients. This phenomenon may promote an imbalance of vascular damage and repair and increase CV risk. Thus, we hypothesize that activation of the inflammasome may play an important role in CVD development in SLE. In order to determine the role of caspase-1, the central enzyme of the inflammasome and activator of IL-18 and IL-1beta, in the enhanced risk of CVD in SLE, we utilized the type-I IFN dependent, pristane-induced model of murine lupus in wild type and caspase-1 deficient mice.

Methods: 8 week old C57Bl/6 (WT) mice or C57Bl/6 caspase-1 $-/-$ (KO) mice were injected intraperitoneally with 0.5 ml pristane or 0.5 ml PBS, and euthanized 6 months post injection. Aortic rings were assessed for relaxation following acetylcholine (Ach) exposure as a measure of endothelial function. Bone marrow EPCs were quantified by FACs and their capacity to differentiate into mature endothelial cells (ECs) was assessed by fluorescent microscopy. Lupus phenotype was also quantified.

Results: Aortas isolated from pristane-exposed wild type mice had dysfunctional relaxation, similar to what has been described in other lupus models and in SLE patients. In contrast, endothelial relaxation in caspase-1 KO mice exposed to pristane was significantly improved when compared to that observed in pristane treated wild-type mice. This suggests that caspase-1 is required for SLE mediated endothelial dysfunction. Bone marrow EPC numbers trended toward a reduction in numbers in pristane exposed wild type but not caspase-1 knockout mice. Additionally, the capacity of these cells to differentiate into mature ECs was significantly preserved in pristane treated caspase-1 KO mice compared to pristane treated WT mice. This indicates that caspase-1 contributes to lupus-induced aberrant EPC function in vivo. Lupus phenotype is currently being compared between the two groups.

Conclusion: In pristane-induced lupus, the absence of caspase-1 is protective against endothelial dysfunction and aberrant EPC function. This observation implicates inflammasome modulation by type I IFNs as an important contributor to cardiovascular damage in SLE.

Disclosure: J. M. Kahlenberg, None; **W. Zhao**, None; **S. Yalavarthi**, None; **M. J. Kaplan**, None.

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HLA-DR3 Controls Autoantibody Response to Sm in NZM2328. DR3+.AE0 Transgenic Mice. Vaidehi R. Chowdhary[1], Chao Dai[2], Shu Man Fu[2] and Chella S. David[1]. [1]Mayo Clinic, Rochester, MN, [2]University of Virginia Health System, Charlottesville, VA

Background/Purpose: Large genome wide scans have confirmed the strong association of HLA -DR3 with risk of developing SLE and antibody response to Sm which is specific to lupus. To understand the role of HLA-DR3 in pathogenesis of lupus and anti-Sm response, we generated NZM2328 mice transgenically expressing HLA-DR3 and devoid of endogenous mouse class II (AE0). Female NZM2328 spontaneously develop anti-dsDNA and severe glomerulonephritis whereas incidence of glomerulonephritis is less in male mice.

Methods: HLA DR3.AE0 transgenic mice were repeatedly backcrossed to NZM2328 mice for 6 generations. Mice were genotyped by PCR and Flow cytometry. Various cohorts of mice were followed monthly for proteinuria using Albustix and sera collected. Urinary protein greater than 300 mg/dL (3+ or more) was considered significant. Anti-Sm antibodies were determined by ELISA and immunoprecipitation.

Results: The overall incidence of proteinuria in female NZM2328. DR3+.AE0 and NZM2328 mice at 12 months was 58% and 62% respectively (p=0.38) whereas male mice, as expected, had low incidence of proteinuria namely 11% in NZM2328 and 19% in NZM2328.DR3+.AE0. No proteinuria was seen in DR3+.AE0 and AE0 mice. Both NZM2328 and NZM2328.DR3+.AE0 developed anti-dsDNA antibodies. NZM2328 males and females, AE0 and DR3+AE0 did not develop anti-Sm antibodies whereas both male and female NZM2328.DR3+.AE0 mice developed anti-Sm antibodies. Preliminary results from immunoprecipitation in few samples also confirm presence of anti-Sm antibody in NZM2328.DR3+.AE0 mice. These mice develop glomerulonephritis and kidney scores are shown in Table 1.

Table 1. Severity of glomerulonephritis in NZM2328 and NZM2328.DR3*.AE° mice

Group	Mesangial Expansion	Endocapillary Proliferation	Glomerular deposits	Extracapillary proliferation
NZM2328 Proteinuric	2.2 ± 0.75	1.8 ± 0.5	2 ± 0.9	0.16 ± 0.41
NZM.DR3+.AE0 Proteinuric	3 ± 0	2.8 ± 0.5	3.5 ± 0.6	0
NZM2328 Non-proteinuric	1.7 ± 0.9	1.6 ± 1.2	0	
NZM.DR3+.AE0 Non-proteinuric	2 ± 1.2	1.2 ± 1.3	1.5 ± 1.1	0.16 ± 0.4

Total number of spleen cells, CD4+, CD8+, B220+ and Mac1+ cells were enumerated in NZM2328, NZM2328.DR3+ AE0 mice and were not

significantly different. Similarly the total numbers of thymocytes, CD4, CD8 double negative, double positive, single positives were also not different in both the groups. Certain CD4+, CD8+ T cell Vβ families were increased in NZM2328 and NZM2328. DR3+.AE0 mice compared to DR3+AE0 mice.

Conclusion: These results strongly support that that HLA-DR3, in an autoimmune prone background, plays an important role in generating an immune response to Sm and development of glomerulonephritis.

Disclosure: **V. R. Chowdhary**, None; **C. Dai**, None; **S. M. Fu**, None; **C. S. David**, None.

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Shared and Unique Molecular Features of Nephritis in 3 Models of Murine SLE. Ramalingam Bethunaickan[1], Celine C. Berthier[2], Matthias Kretzler[3] and Anne Davidson[4]. [1]Feinstein Institute for Medical research, Manhasset, NY, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan, MI, [4]Feinstein Institute for Medical Research, Manhasset, NY

Background/Purpose: Mouse models are useful for studying the pathogenesis of SLE nephritis but it is not clear which model is the most appropriate for understanding human disease. The goal of this study was to understand both shared and unique features of SLE nephritis in mouse models of proliferative and glomerulosclerotic renal disease.

Methods: Perfused kidneys from NZB/W F1, NZW/BXSB and NZM2410 mice were harvested before and after nephritis onset. Affymetrix based expression profiles of whole kidney RNA were analyzed using Genomatix Pathway Systems and Ingenuity Pathway Analysis software. Fold-change ≥1.4 for the up-regulated genes and ≤ 0.7 for the down-regulated genes and q <0.001 were chosen as cut-off values. Only those genes with human orthologs were analyzed. Confirmation of gene expression patterns was performed using real-time PCR.

Results: 955, 1168 and 835 genes were regulated in the kidneys of nephritic NZB/W F1, NZW/BXSB and NZM2410 mice respectively. 263 genes were regulated in all three strains reflecting immune cell infiltration, endothelial cell activation, fibrinolysis, complement activation and cytokine signaling. STAT3 was the top transcription factor having a binding site in the regulated gene promoter and IL-6 signaling was a top pathway in the ingenuity analysis. Each strain also expressed a unique pattern of genes. NZB/W mice had dominant T cell and IL-1 signatures whereas NZW/BXSB mice had prominent integrin, complement signatures and p53 signatures. NZM2410 mice that have severe glomerulosclerosis and scant lymphocytic infiltrates had a dominant metabolic and mitochondrial dysfunction signature; part of this signature was shared with NZB/W mice. The two strains with proliferative disease NZB/W and NZW/BXSB shared a macrophage/DC infiltration and activation signature. Importantly, overlapping signatures with human SLE biopsies were observed for all three mouse strains.

Using real-time PCR we confirmed these gene expression profiles and showed significant differences in the inflammatory response between strains. For example regulatory T cells infiltrated the kidneys of NZB/W mice but not the other two strains. NZM2410 mice had features of renal macrophage activation but lacked dendritic cell infiltration and had less endothelial cell activation than the other two strains. Loss of nephrin, indicating podocyte death, was most marked in the NZM2410 strain and was not observed in NZW/BXSB mice. Robust markers of interstitial disease/remodeling and hypoxia were shared between nephritic mice of all three strains. IL1F6, a marker of tubular dysfunction was an earlier marker of proteinuria than Lcn2.

Conclusion: These findings among genetically related strains of SLE prone mice illustrate the heterogeneity of renal responses to immune complex deposition and inflammation and suggest that individualized targeting of effector mechanisms might need to be based on biopsy findings. These findings further suggest that the progression of renal impairment in SLE shares many common mechanisms with other non-immune–mediated renal diseases and that strategies currently being applied in other diseases to prevent tissue hypoxia and remodeling may also be useful in SLE.

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The Granulocyte Signature and Organ Inflammation in TLR7 Responsive Mice Is RNA and Type 1 Interferon Dependent. Xizhang Sun[1], Alice Wiedeman[2], Thomas H. Teal[2], Nalini Agrawal[2], Jeffrey Duggan[2], Matt B. Buechler[3], Jeffrey A. Ledbetter[2], Denny Liggitt[2], Jessica A. Hamerman[4] and Keith B. Elkon[2]. [1]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, WA, [2]University of Washington, Seattle, WA, [3]Benaroya Research Institute at Virginia Mason, Seattle, WA, Seattle, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA

Background/Purpose: Microarray expression analysis of blood taken from patients with Systemic Lupus Erythematosus (SLE) has revealed two characteristic signatures: one that reflects exposure to type 1 interferon (IFN) and the other reflective of immature circulating granulocytes. Whereas the IFN signature is thought to arise predominantly from the activation of TLR7 in plasmacytoid dendritic cells (pDC) by RNA containing nucleoprotein immune complexes (ICs), the generation of the granulocyte signature is uncertain. Mice that overexpress TLR7 (TLR7 transgenic (Tg) mice) not only develop a lupus-like syndrome, but also a myeloid expansion in the spleen.

Goals: A) To determine the relationship between the myeloid expansion and the pathology in TLR7 Tg mice. B) To determine whether the myeloid expansion and immunopathology is driven by the TLR7 ligand, RNA, and whether it is also IFN dependent.

Methods: Granulocytes (CD11bhigh Ly6Ghigh Ly6Chigh) and inflammatory monocytes (CD11bhigh Ly6Chigh Ly6Gnegative) were flow sorted from the spleen. Microarray analysis on RNA isolated from whole spleen was performed using Illumina's MouseWG-6 v2.0 Expression BeadChips. Chips were scanned on an Illumina HiScanSQ System and >2.0-fold changes in gene expression by TLR7 Tg compared with B6 were analyzed by Ingenuity software. To create TLR7 mice that either overexpressed RNase A or were deficient in the type 1 interferon receptor (IFNAR), TLR7 mice were crossed to RNase Tg or IFNAR deficient mice respectively. Parenchymal organs were examined by light microscopy, Mac2 staining and by other methods as appropriate.

Results: Transcript profiling of TLR7 Tg and B6 spleens (n=10 in each group) revealed a striking granulocyte signature in the TLR7 Tg spleen (e.g. proteinase 3, myeloperoxidase and elastase were expressed at 16 × wild type). Surprisingly, Q-PCR of flow sorted subpopulations revealed that it was the inflammatory monocytes rather than the granulocytes that expressed high levels of these genes. These myeloid populations from TLR7 Tg mice expressed 5–10-fold more TLR7 mRNA compared to B6 mice and the inflammatory monocytes from TLR7 Tg mice expressed more inflammatory cytokines in response to the TLR7 agonist gardiquimod. Pathologic studies of TLR7 Tg mice revealed only mild kidney disease whereas a striking inflammatory infiltrate predominantly of myeloid cells was observed in the liver. This infiltrate was associated with hepatic necrosis. The inflammatory infiltrate was markedly reduced in double mutant TLR7 Tg mice that either co-expressed RNase or that were deficient in IFNAR expression.

Conclusion: Our results indicate that TLR7 Tg mice express a granulocyte signature similar to that observed in humans with SLE. This signature was a consequence of high expression of neutrophil genes in inflammatory monocytes which is likely explained by increased numbers of immature cells released by the bone marrow suggestive of altered myelopoiesis. Attenuation of disease in the double mutant mice indicate that myelopoiesis and/or activation of myeloid cells is caused by exposure to RNA in an IFN dependent process. These results have important implications for therapy.

Disclosure: **X. Sun**, Resolve Therapeutics, 3; **A. Wiedeman**, None; **T. H. Teal**, ResolveTherpeutics, 3; **N. Agrawal**, None; **J. Duggan**, None; **M. B. Buechler**, None; **J. A. Ledbetter**, ResolveTherapeutics, 3; **D. Liggitt**, None; **J. A. Hamerman**, None; **K. B. Elkon**, Hoffman La Roche, 5, Resolve Therapeutics, 4.

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A Synthetic Triterpenoid CDDO-Me Prevents and Reverses Murine Lupus Nephritis. Tianfu Wu[1], Yujin Ye[1], Mei Yan[1], Xin J. Zhou[2], Michael Andreef[3] and Chandra Mohan[1]. [1]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [2]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [3]The University of Texas M. D. Anderson Cancer Center, Houston, TX

Background/Purpose: Current treatment options for lupus are far from optimal. Previously, we have reported that PI3K/AKT/mTOR, MEK1/Erk1,2, p38, STAT3, STAT5, NF-κB, multiple Bcl-2 family members, and various cell cycle molecules were overexpressed in splenic B-cells in an age-

dependent and gene-dose-dependent manner in mouse strains with spontaneous lupus. As the synthetic triterpenoid methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate (CDDO-Me) has been shown to inhibit AKT, MEK1/2, and NF-κB, and to induce caspase-mediated apoptosis, we proceeded to test the therapeutic potential of CDDO-Me on murine lupus.

Methods: In a preventive study, CDDO-Me or placebo were administered to 2 month old *B6.Sle1.Sle3* mice (n=10 per group) at a dose of 3mg/kg, 3 times a week for 2 months. In the treatment study, diseased NZM2410 (age = 7mo; n = 4–7 per group) were treated with CDDO-Me at a dose of 3mg/kg, 5 times a week for 2 months. Proteinuria, BUN, autoantibody levels, cellularity and renal disease were examined to determine the efficacy of this agent.

Results: Splenic cellularity was reduced after CDDO-me treatment. Particularly, the percentage of splenic CD4+ T cells was decreased (12.1 $\pm$ 0.35% vs 15.1 $\pm$ 1.2%, P = 0.021), while the percentage of CD8+ T cells was increased (9.73 $\pm$ 0.4% vs 6.8 $\pm$ 1.1%, P = 0.023) in the CDDO-Me treated group compared to the placebo group. In addition, CDDO-Me-treated mice exhibited significant reductions in serum autoantibody levels, including anti-dsDNA and anti-glomerular antibodies. Finally, CDDO-Me treatment attenuated renal disease in mice, as revealed by reduced 24-hour proteinuria, blood urea nitrogen, and glomerulonephritis. In order to confirm the therapeutic efficacy of CDDO-Me, we carried out a treatment study by administering CDDO-Me to a different lupus strain (NZM2410, age = 7mo; N = 4–7 per group) for a period of 2 months. These mice were already proteinuric at the beginning of the study. Once again, CDDO-Me was remarkably effective in improving survival, and reducing cellularity, circulating antibodies and proteinuria. Thus, we have established that CDDO-Me is therapeutically effective, even when administered after disease onset. In terms of the underlying molecular mechanisms, we demonstrated that CDDO-Me treatment dampened MEK1/2, ERK, and STAT3 signaling within lymphocytes. Importantly, the NF-E2-Related Factor 2 (Nrf2) pathway was activated after CDDO-Me treatment, indicating that CDDO-Me can attenuate renal damage in lupus via the inhibition of oxidative stress. Collectively, these findings underscore the importance of AKT/MEK1/2/NF-κB signaling in engendering murine lupus.

Conclusion: CDDO-me may effectively prevent the hematological, autoimmune and pathological manifestations of lupus via the blockade of multiple signaling nodes and oxidative stress.

Disclosure: **T. Wu**, None; **Y. Ye**, None; **M. Yan**, None; **X. J. Zhou**, None; **M. Andreef**, None; **C. Mohan**, None.

1448

Inhibition of Calcium/Calmodulin-Dependent Protein Kinase IV Suppresses the Autoimmunity in Lupus-Prone Mice. Kunihiro Ichinose[1], Atsushi Kawakami[1] and George C. Tsokos[2]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease associated with abnormal immune cell function.SLE T cells express high levels of calcium/calmodulin-dependent protein kinase IV (CaMKIV). We have shown previously that pharmacologic (Arthritis Rheum. 2011) or genetic silencing of Camkiv (J Immunol. 2011) suppresses lupus nephritis in lupus-prone mice. The purpose of this study was to determine whether pharmacologic inhibition of CaMKIV would improve immune function abnormalities.

Methods: We treated MRL/lpr mice with KN-93, a CaMKIV inhibitor. The agent was administered by intraperitoneal injections at a dosage of 2.67 ug/gm of body weight per mouse 3 times a week, starting at week 8 of age through week 16. We evaluated the presence of CD4+, CD8+, CD3+CD4-CD8- (double negative, DN) and CD62L low T cells and proinflammatory cytokine production. We also determined the effect of inhibition or silencing of CaMKIV on proinflammatory cytokine production by human T cells and macrophages.

Results: CaMKIV inhibition in MRL/lpr mice resulted in significant suppression of DN and CD62L low of T cells population and IFN-γ production by T cells. In human activated T cells and macrophages, pharmacologic inhibition of CaMKIV resulted in suppression of IFN-γ production and CD69 expression by T cells and IL-1β, IL-6 and TNF-α by macrophages. Silencing of CaMKIV in human activated T cells showed increased expression of FoxP3 mRNA level and decreased IL-17A mRNA level.
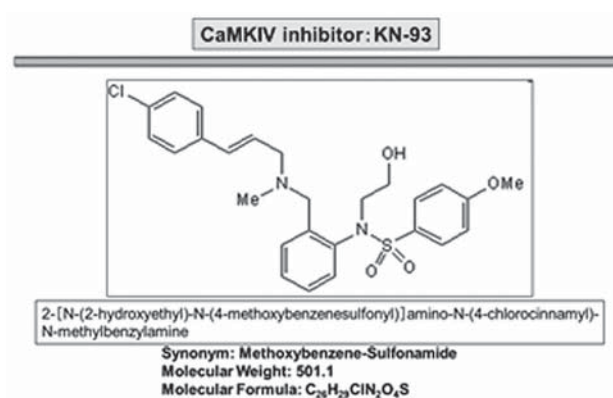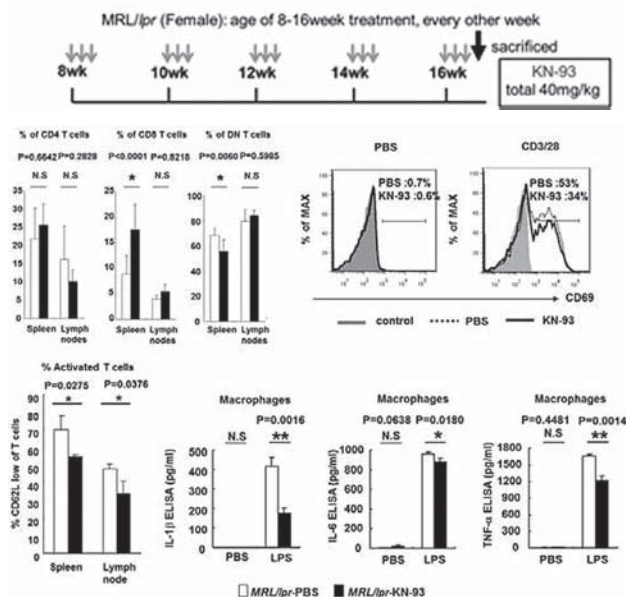
Conclusion: We conclude that pharmacologic inhibition of CaMKIV suppresses cell activation and cytokine production in lupus-prone mice. Our data justify the development of small-molecule CaMKIV inhibitors or silencing CaMKIV for the treatment of patients with SLE.

Disclosure: **K. Ichinose**, None; **A. Kawakami**, None; **G. C. Tsokos**, None.

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Numbers of Splenic Long-Lived Plasma Cells in Autoimmune and Pre-Autoimmune Lupus Mice Are Linked to a Hyper-Responsive Variant of the Thrombopoietin Receptor and Enhanced Megakaryopoiesis. Oliver Winter[1], Katrin Moser[2], Rudolf A. Manz[3] and Falk Hiepe[4]. [1]Charité - University Medicine Berlin, Berlin, Germany, [2]German Arthritis Research Center (DRFZ Berlin), Berlin, Germany, [3]University of Lübeck, Lübeck, Germany, [4]Charité University Hospital Berlin, Berlin, Germany

Background/Purpose: Autoantibodies contribute to the pathogenesis of the autoimmune disease Systemic Lupus Erythematosus (SLE) by stimulating the immune response. Further, deposits of immune complexes in the kidneys can lead to severe nephritis. The autoantibodies are secreted by short- and long-lived plasma cells located in the bone marrow and in the spleen. In NZB/W mice - a mouse model for SLE - both parental strains New Zealand Black (NZB) and New Zealand White (NZW) contribute different *sle-loci* to the formation of SLE. The NZB strain passes the *sle2c locus* in which the gene for the Thrombopoietin (TPO)-receptor (*c-mpl*) is located.

According to the relevance of megakaryocytes for the plasma cell niche and the correlation between plasma cell and megakaryocyte numbers, we wanted to elucidate whether c-Mpl and/or megakaryopoiesis is altered in auto-immune mice.

Methods: Therefore, we examined in wild type, NZB and NZW mice the amount of megakaryocytes and plasma cells in spleen and bone marrow, the occurrence of genetic variations for *c-mpl* and the degree of megakaryopoiesis upon TPO stimulation by histological survey, flow-cytometric and genetic analysis and by *in vitro* studies.

Results: We found, that in the spleen of NZB mice the number of long-lived plasma cells and megakaryocytes are 10-times higher than in wild type while in NZW mice the numbers are equal. We detected a missense mutation in the *c-mpl* gene of NZB mice leading to an amino acid replacement within the essential TPO-binding site. Upon TPO stimulation of splenocyte and bone marrow cultures NZB cultures responded significantly stronger resulting in the double amount of megakaryocytes compared to NZW cultures.

Conclusion: In summary, our data indicate that the mutated *c-mpl* gene located within the *sle2c-locus* is leading to an augmented megakaryopoiesis which enables the accumulation of a greater number of autoreactive plasma cells and thus is contributing to the development of SLE.

1450

MEDI-551 Depletes a Majority of Murine B Cells and Reduces Serum Titers of Autoantibodies in the SLE1-huCD19 TG Mice. Sandra Gallagher, Yue Wang, Isharat Yusuf, Thomas McCaughtry, Ronald Herbst and Laura Carter. MedImmune, Gaithersburg, MD

Background/Purpose: Systemic Lupus Erythematosus (SLE) is characterized by chronic inflammation that can affect various organs. Hyperactive B cells appear to be key drivers in SLE disease. Although some monoclonal antibody (MAb) therapies targeting B cells have shown positive therapeutic effect, these therapies do not effectively deplete plasma cells or autoantibodies. MEDI-551 is an antibody-dependent cellular cytotoxicity (ADCC)-enhanced, humanized, anti-CD19 MAb. Previous studies demonstrated that MEDI-551 can effectively deplete a broad range of tissue B cells in naïve mice. In immunized mice, MEDI-551 led to depletion of tissue plasma cells and a reduction of serum titers of responding antibodies. In this study, we examined the ability of MEDI-551 to deplete B cells in the SLE1-huCD19 TG mice and the impact on the autoimmune phenotype.

Methods: SLE1-huCD19 TG mice were given either a single IV dose of MEDI-551 or repeated doses biweekly for up to twelve weeks. The number of B cells in the blood, spleen and bone marrow (BM) were detected by flow cytometry staining. In the spleen and bone marrow, the number of antibody secreting cells (ASC) specific for total IgG and IgM as well as anti-dsDNA IgG and IgM were determined by ELIspot. Serum autoantibody and total immunoglobulin levels were determined by ELISA.

Results: Aged SLE1-huCD19 TG mice display classical autoimmune symptoms, including antibodies against self antigens and hyper-activation of B and T cells. A single dose of 10mg/kg MEDI-551 led to depletion of 90% of B cells in spleen, BM, and blood at day 7 post injection. Spleen germinal center B cells and plasma cells (PC) were largely sensitive to MEDI-551, and their numbers were reduced by 72%. BM PC, with numbers 80% less than spleen PC, were not significantly affected. In a follow-up longitudinal study, the SLE1-huCD19 TG mice were given biweekly dosing of MEDI-551 or PBS for up to twelve weeks. Repeated dosing of MEDI-551 resulted in significant (>90%) and sustained B cell depletion throughout the duration of the experiment. At week 12, spleen ASC were reduced by ≥90%; whereas, only dsDNA IgM BM ASC were reduced (70%). This reduction in spleen PC was correlated with a 40–80% reduction in autoantibodies specific for dsDNA, histone, and ANA. Total serum immunoglobulins were reduced ~50% compared to control by 12 weeks.

Conclusion: In the autoimmune SLE1-huCD19 TG model, MEDI-551 is able to eliminate naïve as well as activated germinal center B cells and PC in spleen, but spared a majority of BM PC. MEDI-551 dosing resulted in a robust reduction of autoantibodies, whereas total Ig was moderately reduced. Thus, MEDI-551's novel ability to remove a broad range of B cells and eliminate most disease-driving autoantibodies in an SLE model warrants continued research.

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Estrogen Receptor Alpha Deficiency Protects Against Cognitive Defects in Murine Lupus. Melissa A. Cunningham[1], Osama S. Naga[2], Heather A. Boger[2], Ann-Charlotte E. Granholm-Bentley[2] and Gary S. Gilkeson[3]. [1]MUSC, Charleston, SC, [2]Medical University of SC, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC

Background/Purpose: Up to 80% of SLE patients have cognitive defects or affective disorders. The mechanism of CNS injury responsible for cognitive impairment is unknown. Anti-dsDNA antibodies cross-reacting with NMDA receptors in the brain mediate excitotoxic cell death, causing behavioral changes in lupus–prone mice. A breach in the blood-brain barrier (BBB) is required for these effects. Data suggest that BBB breakdown, pathogenic autoantibodies, and subsequent neuronal damage in key areas are critical to the development of neuropsychiatric SLE. We previously showed that estrogen receptor alpha (ERa) deficiency significantly reduced renal disease and increased survival in murine lupus. We hypothesized that ERa also plays a role in modulating BBB integrity and/or neuroinflammation leading to CNS dysfunction in lupus prone MRL/lpr mice.

Methods: MRL/lpr lupus mice (n=28) were ovariectomized at 4wks, received 90d-release estradiol pellets at 6wks, and underwent behavioral testing beginning at 8wks with radial arm water maze (RAWM) and novel object recognition (NOR). Mice were sacrificed at 12wks, or after re-testing at 20wks. Hippocampus, pre-frontal cortex, ventral striatum and parietal cortex were dissected. Western blotting and IHC were used to evaluate tight junction proteins, BBB and inflammatory mediators.

Results: MRL/lpr ERa−/− mice (n=9) performed significantly better in RAWM testing than WT MRL/lpr mice (n=11). There was a significant reduction in working memory errors (2.33 vs. 5.64, p=0.041), reference memory errors (8.22 vs. 12.73, p=0.033) and start arm errors (1.67 vs. 5.18, p=0.048) in ERa−/− mice at 8–10wks. There were no significant differences in NOR testing in discrimination index or latency to novel object, but ERa−/− mice spent significantly more time with both objects compared to WT MRL/lpr. Eight of 20 brains were processed and analyzed to date, with no significant differences seen in tight junction proteins (Zo-1 or occludin), however there is a trend towards reduced Zo-1 in hippocampus and cortex from ERa−/− mice. GFAP (astrogliosis marker) was not significantly different between groups, but there was a trend towards reduced Iba1 (microgliosis marker) in hippocampus.
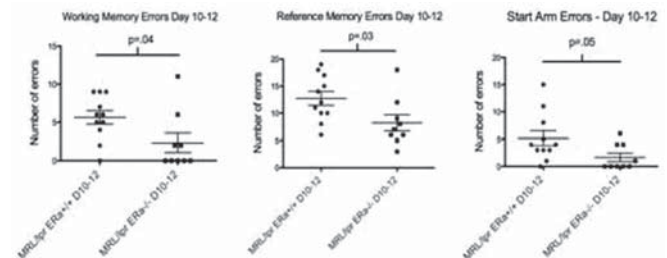
Conclusion: Preliminary data suggest a trend towards reduced microgliosis as a marker of inflammation in the hippocampus of ERa−/− mice. Most notably, ERa deficiency provides profound protection against cognitive deficits in MRL/lpr mice as early as 8wks of age.

1452

Inherent Strain-Based Differences in Qualitative CD4 T Cell Responses Determine Lupus Severity. Kateryna Soloviova, Maksym Puliaiev and Charles S. Via. Uniformed Services University of Health Sciences, Bethesda, MD

Background/Purpose: A lupus-like disease can be induced in B6D2F1 mice by the transfer of parental DBA/2 splenocytes (DBA->F1). Transfer of splenocytes from the other parent (B6->F1) results in B6 anti-F1 CD8 cytotoxic T lymphocytes (CTL) that abort lupus by eliminating host lymphocytes, particularly B cells (acute graft-vs.-host disease)(GVHD). In DBA-

>F1 mice, donor anti-host CTL fail to develop allowing donor CD4 T cell help to B cells and autoantibody production to proceed unchecked (chronic GVHD). Depletion of donor CD8 T cells (i.e. transfer of purified CD4 T cells) from either parent results in lupus although renal disease is milder with B6 CD4 T cells.

Methods: To determine whether CD4 T cells exhibit strain-based differences in lupus inducing capacity, disease was induced in B6D2F1 mice following transfer of equal numbers of purified parental CD4 T cells. B10.D2 splenocytes (which behave like B6 splenocytes) were substituted for B6 donors to ensure that both donor populations recognized H-2[b]. Because the F1 strain is constant, differences in disease expression can be ascribed to the donor strain.

Results: Long term, DBA CD4->F1 mice exhibited more severe lupus renal disease (histology, proteinuria, mortality) and significantly greater T follicular helper cells (donor and host) and IL-21 gene expression vs. B6 CD4->F1. Short term (< 2 weeks), B6 CD4->F1 mice exhibited greater donor CD4 intracellular IFN-g and TNF and greater host CD8a+ DC expansion vs. DBA CD4->F1 mice however, DBA CD4->F1 mice exhibited significantly greater expansion of plasmacytoid DC and IL-21 gene expression. To address the mechanism of defective DBA CD8 CTL maturation, purified CD4 and CD8 T cells from both donors were matched or mixed prior to transfer. For matched injections, both B10.D2 CD4 +B10.D2 CD8 (D2+D2->F1) mice and DBA+DBA->F1 mice exhibited the expected acute and chronic GVHD phenotype respectively at 2 weeks. For mixed subsets, D2+ DBA->F1 exhibited a phenotype not significantly different from control acute GVHD indicating that normal (D2) CD4 T cell help could correct intrinsic DBA CD8 CTL defects e.g., poor KRLG-1 upregulation. By contrast, DBA+D2->F1 mice exhibited an intermediate phenotype significantly different from either control group indicating that normal D2 CD8 CTL maturation was significantly impaired with DBA CD4 help. Long term, only DBA+DBA->F1 and DBA+D2->F1 mice exhibited significant lupus autoantibodies or renal disease.

Conclusion: Following an experimental loss of tolerance, B10.D2 CD4 T cells skew towards a strong Th1 cell mediated immune response that mitigates lupus expression whereas DBA CD4 T cells exhibit weak Th1 skewing but are strongly lupus prone by virtue of: 1) greater help for autoreactive B cells, 2) greater pDC and IL-21 expression, and 3) poorer help for down regulatory CD8 CTL. These data indicate that inherent strain differences in qualitative CD4 T cell responses to the same F1 alloantigens determine lupus expression in this model. Similar qualitative differences in CD4 T cell responses to a lupus trigger in humans could also contribute to disease expression.

Disclosure: **K. Soloviova**, None; **M. Puliaiev**, None; **C. S. Via**, None.

1453

Estrogen Receptor Alpha Impacts Th17 Expansion in Murine Lupus.
Melissa A. Cunningham[1], Osama S. Naga[2], Jackie G. Eudaly[2] and Gary S. Gilkeson[3]. [1]MUSC, Charleston, SC, [2]Medical University of SC, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC

Background/Purpose: Systemic lupus erythematosus is a disease that disproportionately affects females. The mechanisms underlying the female predominance in this disease are largely unknown. We previously showed that estrogen receptor alpha (ERα) deficiency resulted in significantly reduced renal disease and increased survival in murine lupus. More recently we showed a role for ERα in TLR induction of the IL-23/IL-17 inflammatory pathway. TLR7 and TLR9 agonists induced significant increases in IL-1β and IL-23 expression in dendritic cells derived from ERα+/+, but not ERα-/- mice. Additionally, TLR7 and TLR9 stimulation upregulated IL-23R, which is critical for the stabilization of the Th17 cell phenotype, but this effect could not be demonstrated in the absence of ERα. We hypothesized that the capacity to expand/stabilize Th17 cells is partially regulated by ERα.

Methods: NZM2410 lupus-prone mice (n=19) were sacrificed at 17–19wks and spleens were harvested. T cells were isolated and analyzed prior to and after 4–5d Th17 polarizing conditions (stimulated with CD3/CD28 beads, +TGFβ, +IL-6, +anti-IFNγ, +anti-IL-4; +IL-23 on d3). Flow cytometry, ELISA and RT-PCR were used to evaluate IL-17/CD4 positivity, and IL-21, ICOS, IL-23R message levels, respectively.

Results: Consistent with previous experiments that demonstrated reduced IL-17-producing *ex vivo* spleen cells from ERα deficient mice, we

now show that T cells isolated from NZM2410 ERα-/- mice also produce less IL-17 and have reduced IL-21, ICOS, and IL23R mRNA levels compared with WT NZM2410. In addition, under Th17 polarizing conditions, fewer Th17 (IL17+/CD4+) cells were attained from NZM2410 ERα-/- mice.

Conclusion: T cells from lupus-prone ERα-/- mice express less IL-17 and other markers of Th17 development and stabilization. Taken together, our previous and current data suggest that ERα impacts the IL-23/IL-17 inflammatory pathway. A reduction in Th17 cells may partially explain the decrease in inflammatory renal damage and increased survival in ERα deficient animals.

Disclosure: **M. A. Cunningham**, None; **O. S. Naga**, None; **J. G. Eudaly**, None; **G. S. Gilkeson**, None.

1454

Characterization of Renal Mononuclear Phagocyte Populations in Murine SLE Nephritis.
Ranjit Sahu[1], Ramalingam Bethunaickan[2] and Anne Davidson[1]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Feinstein Institute for Medical research, Manhasset, NY

Background/Purpose: Macrophages and dendritic cells contribute to renal damage in chronic renal diseases including lupus nephritis. However owing to their multiple phenotypic and functional variations, the role of these cells in organ pathology is still not defined. The present work examines the phenotype and functional characteristics of renal macrophages and dendritic cells in two murine lupus nephritis models.

Methods: A bead based enrichment step followed by cell sorting was used to isolate populations of interest. Cells were cultured in M-CSF or GM-CSF +/- LPS/IFN¥ and analyzed by microscopy and for arginase activity and nitrite production. Antigen presentation capability was measured in mixed lymphocyte reactions. Flow cytometry was performed using multiple phenotypic markers. Gene expression was performed using real-time PCR.

Results: We identified two populations of macrophages and three populations of dendritic cells in both SLE models, with a large increase in the number of cells belonging to two of these five populations during active nephritis. F4/80[hi] monocyte derived macrophages, that are normally resident in the kidneys and increase in number during nephritis, do not differentiate into either M1 or M2 macrophages upon cytokine stimulation and acquire a mixed pro and anti-inflammatory functional phenotype during nephritis in both SLE strains that resembles the constitutively activated phenotype of gut F4/80^{hi} macrophages. F4/80^{lo} macrophages are infrequent in the kidneys of both strains and do not alter their phenotype during nephritis. CD11c^{hi}/CD103^{-} DCs accumulate in large numbers during nephritis. These cells have a myeloid DC phenotype and can easily be distinguished from resident renal CD103+ DCs on the basis of morphology, motility and cell surface phenotype. Patterns of TLR expression and chemokine receptors differ between subsets.

Conclusion: This study highlights the heterogeneity of the macrophage/DC infiltrate in chronic SLE nephritis and provides an initial phenotypic and functional analysis of the different cellular components that can now be used to define the role of each subset in nephritis progression or amelioration.

Disclosure: **R. Sahu**, None; **R. Bethunaickan**, None; **A. Davidson**, None.

1455

Mitochondrial Dysfunction in the Liver of Lupus-Prone MRL/Lpr Mice Prior to Disease Onset.
Zachary A. Oaks[1], Tiffany Telarico[2] and Andras Perl[3]. [1]SUNY, Syracuse, NY, [2]SUNY Upstate Medical University, Syracuse, NY, [3]Upstate Medical University, Syracuse, NY

Background/Purpose: Liver dysfunction, characterized by serum elevation of liver enzymes, is detectable in 20% of patients with systemic lupus erythematosus (SLE.) Males had a higher prevalence of liver dysfunction (12/33: 36%) than females (65/387; 18%; p=0.014; Yu and Perl submitted). Patients with SLE have mitochondrial dysfunction with increased mitochondrial mass and transmembrane potential, yet the biochemical consequences of mitochondrial accumulation in SLE have yet

to be determined. ATP generation is reduced in SLE, a process which is regulated by O_2 consumption through the electron transport chain (ETC) of mitochondria. Here, we characterize utilization of O_2 through the ETC and the generation of oxidative stress in pre-disease lupus-prone MRL/lpr mice to determine whether mitochondrial dysfunction precedes onset of SLE.

Methods: Mitochondrial ETC activity of isolated liver mitochondria was assessed in 4-week-old MRL/lpr lupus-prone mice as well as C57BL/6, MRL/MpJ, and Black 6/lpr age and gender-matched controls mice. ETC was measured O_2 with a Clark electrode. State IV respiration, a measurement of O_2 consumption through complex II, was measured by addition of succinate, ADP, and inorganic phosphate to isolated mitochondria. Hydrogen peroxide (DCF-DA), superoxide (HE), peroxynitrite (DAR-4M), nitric oxide (DAF-FM), mitochondrial potential (JC-1, TMRM), and mitochondrial mass (NAO) were measured by flow cytometry of isolated liver mitochondria. Statistical analysis of data was done by paired t-tests and Pearson's correlation analysis using GraphPad 5.0 software, with a cutoff of $p < 0.05$ considered significant.

Results: 4 week old male MRL/lpr mice exhibited increased mitochondrial respiratory capacity, measured by complex II respiration, in comparison to C57BL/6 (25.8%, p=.03) and Black 6/lpr (11.4%, p=.004) control strains. Mitochondrial mass was increased in male MRL/lpr mice in comparison to C57BL/6 (+26.5%, p=.04) and Black 6/lpr (+55.5%, p=.001). Male MRL/lpr mitochondria also had increased mitochondrial potential (+64.2%, p=.006), production of hydrogen peroxide (+60.0%, p=.02), superoxide (+72.4%, p=.03), nitric oxide (56.1%, p=.0004), and peroxynitrite (107.9%, p=.0005) relative to Black 6/lpr controls. Mitochondrial potential positively correlated with production of hydrogen peroxide (r= 0.883, p=0.047), superoxide (r= 0.881, p=0.049), and peroxynitrite (r= 0.912, p=0.031). MRL/lpr females had increased complex II state 4 respiration (+51.2%, p=0.02) relative to Black 6 controls.

Conclusion: Mitochondrial dysfunction, characterized by increased respiratory capacity and increased mitochondrial mass, precedes disease onset in lupus-prone MRL/lpr mice. We show these changes correlate with increased production of reactive oxygen and nitrogen intermediates, which cause oxidative stress in SLE. Mitochondrial dysfunction in MRL/lpr was more robust in males than females that may account for a higher prevalence of liver disease in men than women with SLE.

Disclosure: **Z. A. Oaks**, None; **T. Telarico**, None; **A. Perl**, None.

1456

A Tolerogenic Peptide Down-Regulates the Expression of Interferon-a in Murine and Human Systemic Lupus Erythematosus. Zev M. Sthoeger[1], Heidy Zinger[2], Amir Sharabi[2], Ilan Asher[1] and Edna Mozes[2]. [1]Kaplan Hospital, Rehovot, Israel, [2]The Weizmann institute of Science, Rehovot, Israel

Background/Purpose: The tolerogenic peptide, designated hCDR1, was shown to ameliorate manifestations of systemic lupus erythematosus (SLE) via down-regulation of pro-inflammatory cytokines, up-regulation of immunosuppressive cytokines and molecules and the induction of regulatory T cells. Because type I interferon (IFN-a) has been implicated to play a major role in the pathogenesis of SLE, in the present studies we investigated the effects of hCDR1 on IFN-a in a murine model of SLE and in human lupus.

Methods: (NZBxNZW)F1 female mice with established SLE manifestations were treated with hCDR1 (10 weekly subcutaneously injections) or with the vehicle alone. The effects on anti-dsDNA antibody levels, proteinuria and kidney immunohistology were assessed. Splenocytes were obtained for gene expression studies. Peripheral blood lymphocytes (PBL) of lupus patients (10), primary anti-phospholipid syndrome (APS) patients (5) and healthy controls (5) were incubated in vitro for 48 hours with hCDR1 or medium prior to gene expression assays. Lupus patients were treated for 26 weeks with hCDR1 (5) or placebo (4) in a Phase II clinical trial by weekly subcutaneous injections. Disease activity was assessed using SLEDAI-2K and BILAG scores [1]. Blood samples were collected, before and after treatment, in PAXgene tubes and frozen until mRNA isolation. Gene expression of IFN-a was determined by real-time RT-PCR.

Results: Treatment of (NZBxNZW)F1 SLE afflicted mice with hCDR1 down-regulated significantly IFN-a gene expression (73% inhibition compared to vehicle, p= 0.002). The latter was associated with diminished anti-dsDNA titers as well as proteinuria and glomerular

immune complex deposit levels. Further, hCDR1 reduced, in vitro, the IFN-a gene expression in PBL of lupus patients (74% inhibition compared to medium, p=0.002). hCDR1 had no significant effects on the expression levels of IFN-a in PBL of primary APS patients or of healthy controls. Moreover, a significant reduction in IFN-a was determined in PBL of lupus patients that were treated with hCDR1 for 26 weeks (64.4% inhibition compared to pretreatment expression levels, p=0.015). No inhibition of IFN-a expression was observed in PBL of placebo treated patients. In agreement, as previously reported, treatment with hCDR1, but not with placebo, resulted in a significant decrease of disease activity as determined by the BILAG and SLEDAI-2K scores [1].

Conclusion: Treatment with hCDR1 resulted in a significant amelioration of lupus manifestations in murine models. Studies of a limited number of lupus patients indicated beneficial effects in hCDR1 treated patients. We reported previously that hCDR1 affected various cell types and immune pathways involved in the pathogenesis of SLE. The present studies demonstrate that hCDR1 is also capable of down-regulating significantly (and specifically to lupus) IFN-a that has been recently considered as a target for SLE therapy. Thus, hCDR1 has a potential role as a novel, disease specific treatment for human lupus.

[1] Journal of Autoimmunity, 33 (2009) 77–82.

Disclosure: **Z. M. Sthoeger**, None; **H. Zinger**, None; **A. Sharabi**, None; **I. Asher**, None; **E. Mozes**, None.

1457

A Novel Small Molecular Anti-Rheumatic Drug, T-614, Ameliorates Lupus-Like Disease in MRL/Lpr Mice by Suppressing B Cell Functions. Qingran Yan, Fang Du and Chunde Bao. Renji Hospital, Shanghai, China

Background/Purpose: T-614 is a small molecular drug that has multiple immunomodulatory effects and has been used for treating rheumatoid arthritis. Previous work has revealed this agent may have inhibitory effects on B cells. Since excessive B cell activation is a characteristic of systemic lupus erythematosus (SLE), here we investigated efficacy of T-614 on lupus-like disease and its potential mechanism in MRL/lpr mouse, a classic lupus model.

Methods: Female MRL/lpr mice were randomly given T-614 (30mg/kgμd), vehicle solution or cyclophosphamide (CTX, 20mg/kg w) as controls before their disease onset. 24-hour-urine and blood samples were collected regularly. Kidney and spleen samples of each mouse were collected at the end point of observation. Urine protein concentrations were measured by bicinchoninic acid protein assay, serum C3 and immunoglobulin were detected by ELISA, anti double strand DNA (dsDNA) antibody titers were quantified by radioimmunoassay and serum alanine transaminase (ALT), creatinine and blood cell counts were analyzed by auto analyzer. Expressions of B cell related cytokines by splenic cells were determined by real-time polymerase chain reaction, CD20+ B cell invasions in kidney were detected by immunohistochemistry, immune complex deposition in kidney was determined by immunofluorescence, and kidney injury was blindly scored by a renal pathologist.

Results: T-614 ameliorated lupus-like disease activity in MRL/lpr mice. Mice in T-614 group had lower frequency of severe proteinuria (over 20mg/24h, Figure A), lower serum creatinine (15.53 ±0.5845 vs 19.19 ±0.9184 μmol/L, P=0.025) and higher levels of serum C3 (2.027 ±0.1807 vs 1.296 ±0.0866 g/L, P=0.026) than vehicle controls. Kineys from T-614 treated mice had less lymphocyte invasions, creasants, casts in tubula and vasculitis changes than those from controls. Glomerular injury scores showed statistically significant difference (median: 1.46, QR 1.35–3.745 vs median: 3.37, QR 2.17–4.0, P=0.0381) between these two groups. Immunofluorescence also showed less immune complex depositions in kidneys from T-614 group. For B cells, T-614 remarkably reduced serum immunoglobulin (Figure B), anti-dsDNA antibody titers (Figure C) and B cell related cytokine (Figure D) expressions in splenic cells. Notably, effects of T-614 on immunoglobulin and B cell cytokines were comparable to CTX. Furthermore, mice from T-614 group had less CD20+ B cell invasions in their kidneys than vehicle group (mdian: 1.0, QR 0.875–2.0 vs mdian: 2.0,QR 2.0–3.0, P=0.0157). Lastly, overt adverse effects, including infection, elevated serum ALT or abnormal peripheral blood cell counts, were not observed.

*P<0.05, ** P<0.01, ***P<0.001
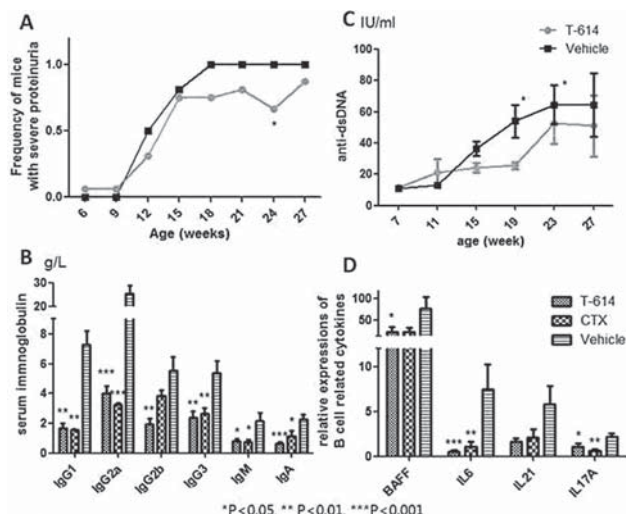
Conclusion: T-614 can ameliorate lupus-like disease in MRL/lpr mice mostlikely through B cell suppression without overt toxicity. Our results suggest that T-614 has potential for the therapy of SLE.

Disclosure: Q. Yan, None; F. Du, None; C. Bao, None.

ACR/ARHP Poster Session B
Systemic Sclerosis, Fibrosing Syndromes, and
Raynaud's – Clinical Aspects and Therapeutics
Monday, November 12, 2012, 9:00 AM–6:00 PM

1458

Left Ventricular Diastolic Dysfunction May Play a Role in Pathophysiology and Poor Prognosis of Pulmonary Arterial Hypertension Associated with Systemic Sclerosis. Sumiaki Tanaka[1], Eisuke Ogawa[1], Tatsuhiko Wada[1], Tatsuo Nagai[1], Jun Okada[2] and Shunsei Hirohata[1]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Kitasato University, Sagamihara, Japan

Background/Purpose: Cardio-pulmonary involvements of systemic sclerosis (SSc), including cardiomyopathy, interstitial lung disease, and pulmonary arterial hypertension (PAH) are leading causes of SSc-related deaths. Several potent effective PAH-specific therapies have recently been recently available, improving survival of patients with overall PAH. However, the survival of patients with PAH associated with SSc (SSc-PAH) is still poorer than that of patients with PAH associate with other connective tissue diseases (CTDs). To explore the characteristics relevant to poor survival of SSc-PAH patients, we analyzed hemodynamics data.

Methods: We analyzed 157 right heart catheter data obtained from 66 patients with PAH associated with CTDs, including 30 patients with SSc, and 36 non-SSc-CTD patients (17 patients with SLE,13 patients with MCTD and 6 patients with other CTDs), who had been followed between January 1980 and April 2012 in our hospital. We compared mean pulmonary artery pressure (mPAP), cardiac output (CO), pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR) between SSc-PAH patients and non-SSc-PAH patients. Survival from the date of the initial diagnosis of PAH was measured, and analyzed using Cox's proportional hazard model.

Results: The values (mean $\pm$ SD) of mPAP, CO, PCWP, and PVR at the initial diagnosis of PAH were 37.7 $\pm$ 11.3 mmHg, 4.6 $\pm$ 1.2 L/min, 7.7 $\pm$ 3.5 mmHg, and 6.9 $\pm$ 3.8 Wood's units, respectively. Thirty-six of the 66 patients died. Cox's proportional hazard model estimated that lower CO, higher PVR and higher PCWP, but not mPAP in hemodynamics at the initial diagnosis of PAH appeared to be risk factors for death (**Table**). Of the 36 patients who died, 20 were SSc-PAH patients. Moreover, PCWP measured throughout the course of PAH was significantly higher in SSc-PAH patients than that in non-SSc-PAH patients (8.66 $\pm$ 3.93 mmHg, 6.79 $\pm$ 2.73 mmHg, respectively; p=0.0354) (**figure**).

Table. Hazard ratios for death in hemodynamics at the initial diagnosis of PAH in patients with CTDs estimated by Cox's proportional hazard model

Covariant	HR for death	95%CI	p
mPAP (mmHg)	1.011	0.979 - 1.043	0.4817
PCWP (mmHg)	1.122	0.984 - 1.258	0.0840
CO (L/min)	0.580	0.396 - 0.815	0.0012
PVR (Wood's unit)	1.151	1.045 - 1.265	0.0051

| P value | 0.6294 | 0.0354 | 0.2227 | 0.8826 |
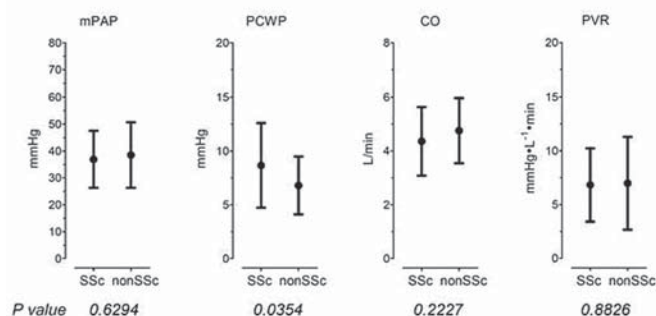
Figure. Hemodynamics data obtained from 157 right heart catheter test from 30 SSc-PAH patients and 36 non SSC-PAH patients.

Conclusion: These results demonstrate that the presence of left ventricular diastolic dysfunction as evidenced by the elevation of PCWP plays a role in pathophysiology and poor prognosis of SSc-PAH. The data therefore suggest the importance of care for left ventricular diastolic dysfunction under management using PAH-specific therapies in order to improve prognosis in SSc patients.

Disclosure: S. Tanaka, None; E. Ogawa, None; T. Wada, None; T. Nagai, None; J. Okada, None; S. Hirohata, None.

1459

Limited Utility of Pulmonary Function Tests and B-Type Natriuretic Peptide As Screening Tools for Pre-Capillary Pulmonary Hypertension in Patients with Systemic Sclerosis. Yuichiro Shirai[1], Yuichi Tamura[1], Hidekata Yasuoka[1], Tsutomu Takeuchi[1], Toru Satoh[2] and Masataka Kuwana[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Kyorin University School of Medicine, Tokyo, Japan

Background/Purpose: A series of recent studies indicate that early detection of pulmonary hypertension (PH) improves a survival in patients with systemic sclerosis (SSc). Thus, annual screening based on echocardiography combined with Doppler procedure is recommended in SSc patients. On the other hand, pulmonary function test (PFT) and B-type natriuretic peptide (BNP) are also reported to be useful for identifying patients with PH, but roles of these tests in routine PH screening remain unclear. We evaluated if PFT parameters and BNP, in combination with or without echocardiography, are useful as screening tools for PH in patients with SSc.

Methods: This single-center observational study enrolled 94 consecutive SSc patients who visited our center between January 2008 and June 2012, and underwent PFTs, serum BNP measurement, and echocardiography for PH screening. Our routine screening program consists of two steps: i) selection of patients suspected to have PH based on dyspnea symptoms and echocardiography that assesses morphology and estimated systolic pulmonary arterial pressure (esPAP) calculated from tricuspid regurgitation velocity and presumptive right atrial pressure (5 mmHg), and ii) diagnostic confirmation by right heart catheterization (RHC) in patients with esPAP >50 mmHg, esPAP 37–50 mmHg with echocardiographic variables suggestive of PH, or unexplained dyspnea. Patients with mean pulmonary arterial pressure $\geq$25 mmHg at rest and pulmonary capillary wedge pressure <15 mmHg were diagnosed as having pre-capillary PH (pre-PH). We also enrolled 14 incident SSc cases with pre-PH. PFT variables recorded were %FVC, %DLCO, %DLCO/VA, and a ratio of %FVC and %DLCO or %DLCO/VA. Receiver-operating characteristic (ROC) curve analysis was performed to obtain area under the curve (AUC) and optimal cut-off values.

Results: Of 94 patients screened, 19 underwent RHC, resulting in diagnosis of pre-PH in 5 patients. Individual screening parameters were compared between 89 patients without pre-PH and 19 with pre-PH consisting of 14 incident and 5 newly identified cases. There were significant differences in %DLCO, %DLCO/VA, %FVC/%DLCO ratio, %FVC/%DLCO/VA ratio,

and serum BNP between PH and non-PH groups (P <0.01 for all comparisons). ROC analysis revealed that %FVC/%DLCO was the best PFT parameter that discriminated PH and non-PH cases (AUC 0.76), while BNP and esPAP gave the higher AUC (0.93 and 0.98, respectively). The %FVC/%DLCO ratio provided sensitivity of 79% and specificity of 76% when cut-off was set at 2.45, while BNP gave sensitivity of 84% and specificity of 91% with the cut-off of 86 pg/mL. Diagnostic utility of these two tests was apparently inferior to esPAP, which provided sensitivity of 100% and specificity of 93% with the cut-off of 45 mmHg. When %FVC/%DLCO ratio and BNP were combined with esPAP, the specificity was increased from 93% to 96% without decrease of sensitivity.

Conclusion: Our results clearly indicate PFT or BNP alone was inappropriate for PH screening in SSc. Simultaneous measurement of PFT and BNP with echocardiography slightly improves diagnostic accuracy, indicating limited utility of these tests in current echocardiography-based screening program.

Disclosure: Y. Shirai, None; **Y. Tamura**, None; **H. Yasuoka**, None; **T. Takeuchi**, None; **T. Satoh**, None; **M. Kuwana**, None.

1460

Unmasking Latent Pulmonary Arterial Hypertension by Fluid Challenge in Patients with Systemic Sclerosis. Amee Sonigra[1], Melanie Hurford[2], Patricia Lewis[3], David Kilpatrick[1], Nathan Dwyer[1] and Jane Zochling[3]. [1]Royal Hobart Hospital, Hobart, Australia, [2]Menzies Research Institute, Hobart, Australia, [3]Menzies Research Institute Tasmania, Hobart, Australia

Background/Purpose: Pulmonary arterial hypertension (PAH) is associated with high morbidity and mortality in Systemic Sclerosis. Early diagnosis and treatment leads to substantial improvements in quality of life, prognosis and mortality. Right heart catheterization remains the only test that can diagnose PAH and differentiate it from pulmonary venous hypertension or diastolic dysfunction. Controversies exist in unmasking PAH with exercise or fluid challenge during right heart catheterization. However, there are no studies so far to identify them as one of the means of early diagnosis.

Methods: Our study includes 173 Systemic sclerosis patients enrolled in the Tasmanian Systemic Sclerosis Epidemiology (TASSIE) study, recruited from rheumatologists, physicians, cardiologists, general practitioners and other health professionals across Tasmania since 2007. Echocardiogram and pulmonary function tests were routinely performed on each patient at screening and at annual follow up. Right heart catheter was performed when clinically indicated. A proportion of symptomatic patients underwent right heart catheterization with fluid challenge based on clinical suspicion of PAH or diastolic dysfunction. Treatment for PAH was initiated in all patients who qualified under current regulations. Treatment effects on their six minute walk test (6MWT) and quality of life were studied at the end of two years.

Results: Seventy-eight of the cohort (45.1%) were diagnosed with PAH. Thirty-seven (21.4%) were diagnosed by standard RHC and 41 (23.7%) had latent PAH unmasked by the fluid challenge on RHC. Patients with PAH showed female predominance, and those who had diagnosis on fluid challenge were younger than those who were diagnosed without fluid challenge (57.5–vs-59.8, p < 0.05). More patients with limited SSc than diffuse disease had PAH (51-vs-27). Improvements in 6MWT were observed in both groups at 6 months and 12 months after treatment commencement for PAH (Table).

	PAH on RHC	PAH on fluid challenge	Any form of PAH
Total	37 (21.4%)	41 (23.7%)	78 (45.1%)
Sex (M:F)	8:29	4:37	12:66
Age (Mean yrs)	59.8	57.5	59
Diffuse	16	11	27
Limited	21	30	51
Mean % improvement from baseline in 6MWT at 6 months	14.34%	11.33%	13.33%
Mean % improvement from baseline in 6MWT at 12 months	12.96%	15.84%	14.4%

Conclusion: Fluid challenge is a sensitive measure of early diagnosis of pulmonary arterial hypertension secondary to systemic sclerosis. Early diagnosis has led to improved treatment outcome in our small cohort.

Disclosure: A. Sonigra, None; **M. Hurford**, None; **P. Lewis**, None; **D. Kilpatrick**, None; **N. Dwyer**, None; **J. Zochling**, None.

1461

Clinical Outcomes of Scleroderma Patients At High Risk for Pulmonary Hypertension. Analysis of the Pulmonary Hyparternsion Assessment and Recognition of Outcomes in Scleroderma Registry. Avram Z. Goldberg[1], Vivien M. Hsu[2] and Virginia D. Steen[3]. [1]North Shore-LIJ Health System, Lake Success, NY, [2]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [3]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Pulmonary hypertension (PH) is the most frequent cause of death in Systemic Sclerosis (SSc). It is critical to identify patients early to begin treatment before onset of irreversible heart failure. The PHAROS registry is a prospective observational longitudinal cohort study to better understand the natural history of this problem. This analysis looks at outcomes of patients at high risk for developing PH, the Pre PAH group.

Methods: Pre-PAH is defined by one of the following entry criteria: echocardiogram systolic pulmonary arterial pressure (sPAP) of ≥40mmHg, or DLCO<55% predicted or FVC%/DLCO% ratio >1.6. PFTs, 6 minute walk test (6MW), and sPAP were performed yearly. If PH was clinically suspected, a right heart catheterization was performed. A mean pulmonary artery pressure (MPAP) ≥25 mmHg on right-heart catheterization (RHC) was required for the diagnosis of PH. Descriptive statistics, changes in baseline studies, such as PFTs and 6MWT, at the time of diagnosis of PH, Kaplan-Meier estimate of the time to PH diagnosis and survival of the Pre PAH group were studied.

Results: 253 patients were enrolled in the Pre-PAH group: 35 developed PH at follow-up (New PH), 21 PAH (Group 1), 11 pulmonary venous hypertension (WHO Group 2) and 3 PH secondary to interstitial fibrosis (WHO Group 3). By 4 years, PH developed in 24% of these high risk patients. There was no difference in the age, sex, disease duration or SSc subgroup in patients with New PH and those with no PH. All patients had long disease duration (mean 11.7 years of Raynaud's) and 64% had limited SSc. The baseline DLCO was low in both groups (46.66 in New PH group vs 51.3 in the no-PH group) but there was not a further significant decrease in those who had a repeat DLCO at the time of diagnosis of PH. there was no difference in 6MW distance at baseline, but patients with New PH had a significant decrease in the mean 6MW distance of 60.27 meters at the time of the diagnosis of PH, compared to the no PH group (−13m) (p<0.01) Those that progressed to PH also exhibited significant oxygen desaturation during 6MW (saturation < 92%) both at baseline and at time of diagnosis of PH which was not experienced by the no PAH group (p<0.01). There were 22 deaths in the pre PAH group: 3 year survival was 92%. Three of the 35 New PH patients died of PH, 6 pre-PAH died of interstitial lung disease, 6 had multisystem SSc deaths, and 7 others were either non SSc or unknown. Patients who died had lower DLCO at baseline than those who were still living, 35% vs 51% (p<0.01)

Conclusion: We show that 24% of the prePAH SSc patients developed PH by 4 years. In addition to the known high risk features of long standing limited scleroderma and a low DLCO, patients had a decreasing 6MW distance and significant 02 desaturation prior to the diagnosis of PH by RHC. Overall, 3 year survival of these patients at 92% was fair, but deaths in these high risk patients were associated with a very low DLCO. Our study shows the usefulness of the serial 6MW distance and exercise induced hypoxia to determine patients that may progress to PH. We hope that early identification and treatment of SSc -PH will significantly alter the long-term outcome of these patients.

Disclosure: A. Z. Goldberg, None; **V. M. Hsu**, None; **V. D. Steen**, Gilead Science, 2, Actelion Pharmaceuticals US, 2, United Therapeutics, 2, Roche Pharmaceuticals, 2.

1462

Expert Consensus for Performing Right Heart Catheterization in Suspicion of Pulmonary Arterial Hypertension Associated with Systemic Sclerosis: A Delphi Consensus Study with Cluster Analysis From the Eposs Group. Jerome Avouac[1], Dörte Huscher[2], Daniel E. Furst[3], Oliver Distler[4] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [2]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [3]UCLA Medical School, Los Angeles, CA, [4]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Pulmonary hypertension (PH) has emerged as a critical cause of death in systemic sclerosis (SSc). Recent data have highlighted the poorer outcomes of SSc associated PAH as compared to the idiopathic forms. Therefore, the management of SSc patients at risk of PAH risk must be improved to allow early diagnosis. However, there is presently no guideline regarding the parameters that should lead the physician to perform right heart catheterization, the only tool unequivocally establishing

the correct diagnosis. Our aim was, by consensus, to identify the most appropriate indications for RHC in patients with SSc.

Methods: A three-stage Delphi exercise involving worldwide PH experts was designed to answer the following question: "based on which parameters, performed on the basis of an annual screening of SSc patients in clinical practice, do you decide to refer patients for RHC?". The Delphi exercise was performed between March 2011 and December 2011.

The aim of the first stage was to obtain a comprehensive list of domains and tools to be considered before referring a SSc patient for RHC. This list combined evidence-based indications extracted from published reports on SSc-PH and expert opinions. For the second stage, experts were asked to rate each item proposed in the list, using a 5-point scale (1 indicates "not important/appropriate at all" and 5 indicates "very important/appropriate"). For the third stage, experts were asked to rate the items accepted after the second round, using the same 5-point scale. After each of stages 2 and 3, the number of domains and tools was reduced according to a cluster analysis. The number of clusters was generated by an automatic cluster algorithm using Bayes information criterion.

Results: 77 experts were contacted by e-mail to participate in this Delphi procedure. 47 (61%) participated in stage 1, 50 (65% of the 77) in stage 2, and 48 (62% of the 77) in stage 3. The list obtained after the first stage consisted on 7 domains (clinical, biomarkers, pulmonary function tests, echocardiography, cardiopulmonary exercise, imaging and EKG) containing a total of 142 tools. Cluster analysis performed after the second stage allowed discarding of 63 of the 142 initial tools. Cluster analysis performed after stage 3 reduced the EPOSS instrument to 3 domains containing 8 items (see table).

Domains	Tools	Mean ratings (5-point scale)
Clinical tools	*Progressive dyspnea over the last 3 months	4.4
	*Unexplained dyspnea	4.3
	*Worsening in WHO dyspnea functional class	4.4
	*Any finding on physical examination suggestive of elevated right heart pressures (Jugular venous distension, accentuated S2, TR murmur, etc)	4.4
	*Any sign of right heart failure	4.8
Echocardiography	*sPAP>45 mmHg	4.3
	* Dilation of right ventricle	4.3
Pulmonary function tests	*DLCO<50% without pulmonary fibrosis	4.4

Conclusion: Among experts in PH-SSc, a core set of indications for clinical practice has been defined to refer SSc patients to RHC in case of PH suspicion. This EPOSS instrument is the first expert guidelines for PH detection that is based on validated consensus methods. Although these indications are recommended by this expert group, it is an interim tool. It will be necessary to formally validate and extend the EPOSS instrument in further studies, both for clinical practice and in terms of additional research.

1463

Pulmonary Hypertension and Interstitial Lung Disease within Pharos: Impact of Extent of Fibrosis and Pulmonary Physiology On Cardiac Hemodynamic Parameters. Aryeh Fischer[1], Stephen C. Mathai[2], Marcy B. Bolster[3], Lorinda Chung[4], Mary Ellen Csuka[5], Robyn T. Domsic[6], Tracy M. Frech[7], Monique E. Hinchcliff[8], Vivien M. Hsu[9], Laura K. Hummers[2], Jason R. Kolfenbach[10], Mardi Gomberg-Maitland[11], Aida Manu[12], Robert W. Simms[13] and Virginia D. Steen[14]. [1]National Jewish Health, Denver, CO, [2]Johns Hopkins University, Baltimore, MD, [3]Medical Univ of South Carolina, Charleston, SC, [4]Stanford Univ Medical Center, Palo Alto, CA, [5]Medical College of Wisconsin, Milwaukee, WI, [6]University of Pittsburgh, Pittsburgh, PA, [7]University of Utah School of Medicine, SLC, UT, [8]Northwestern Univ Med School, Chicago, IL, [9]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [10]Univ of Colorado School of Med, Aurora, CO, [11]University of Chicago, Chicago, [12]Rheumatology, Georgetown University Medical Center, Disrict of Columbia, [13]Boston University School of Medicine, Boston, MA, [14]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are the leading causes of mortality in systemic sclerosis (SSc). Many SSc patients have both pulmonary hypertension (PH) and ILD and it can be difficult to distinguish PAH from PH secondary to chronic ILD (PH-ILD). In addition, it is not known to what degree the extent of ILD or pulmonary physiology impact cardiac hemodynamic parameters of PAH. The purpose of this study was to determine the impact that extent of ILD and degree of pulmonary physiologic restriction have on specific cardiac hemodynamic parameters within a subset of the PHAROS cohort.

Methods: We identified PHAROS subjects with right-heart catheter-proven PH that had a forced vital capacity (FVC) < 70% predicted or that had ILD reported on computed tomography (CT) scans. Subjects with pulmonary venous hypertension (wedge pressure >15mmHg) were excluded. Baseline CT scans were scored by the investigator at each site by a standardized system that graded severity of ILD as none (0), mild (1), moderate (2), or severe (3) at 5 specific zones distributed throughout the lungs. A cumulative score based on summation of the score for all 5 zones was generated from each CT scan and defined as none-mild (sum=0–5), moderate (sum=6–10), or severe (sum=11–15).

Results: Sixty subjects met the inclusion criteria and had CT scoring performed: 19 had none-mild, 26 had moderate, and 15 had severe ILD. There were no differences between groups with respect to age (mean 57+/−11) or SSc type (43% diffuse). None-mild ILD was associated with higher mean pulmonary artery pressures (mPAP) (41.8+/−10.7) than moderate (32.7+/−8.4; p=0.002) and severe ILD (mPAP 34.3+/−8.1; p=0.03) or the combination of moderate and severe ILD (33.3+/−8.2; p=0.001). None-mild ILD was also associated with higher pulmonary vascular resistance (PVR) (623+/−340) than seen with combined moderate and severe ILD (361+/−227; p=0.001). There were no differences in mPAP or PVR between moderate and severe ILD or between the combinations of none-mild-moderate ILD compared with severe ILD. In contrast, when stratified by FVC, no differences in mean PAP or PVR were identified. FVC was not a reliable predictor of the extent of ILD in this cohort: 29% of those with FVC% less than 70 had none-mild ILD, and in those with FVC% greater than 70, 54% had moderate and 16% had severe ILD.

Conclusion: Within this PHAROS subset, significant differences in cardiac hemodynamics were associated with varied extent of ILD but not with degree of restriction estimated by FVC. Furthermore, FVC was not a reliable predictor of degree of ILD. Further studies, incorporating CT extent of ILD along with pulmonary physiology, are needed to help determine ways to distinguish PAH from PH-ILD.

1464

Comparison of Baseline Characteristics of the Combined Response Index for Systemic Sclerosis (CRISS) Cohort to Patients Enrolled in Clinical Trials of Diffuse Systemic Sclerosis. Heather Gladue[1], De Furst[2], Veronica Berrocal[1], James R. Seibold[3], Peter A. Merkel[4], Maureen D. Mayes[5], Kristine Phillips[6], Robert W. Simms[7], Shervin Assassi[8], Philip J. Clements[9], Paul Maranian[10] and Dinesh Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]University of California at Los Angeles, Los Angeles, CA, [3]Scleroderma Research Consultants LLC, Avon, CT, [4]University of Pennsylvania, Philadelphia, PA, [5]University of Texas Health Science Center at Houston, Houston, TX, [6]University of Michigan Medical School, Ann Arbor, MI, [7]Boston University School of Medicine, Boston, MA, [8]Univ of Texas Health Science Houston, Houston, TX, [9]UCLA School of Medicine, Los Angeles, CA, [10]UCLA Medical School, Los Angeles, CA

Background/Purpose: Randomized clinical trials (RCTs) of treatment of diffuse systemic sclerosis (dcSSc) would benefit from a composite index that predicted efficacy better than current standard measures that are based on single organ systems. As a first step to achieve the goal of a validated composite index, a longitudinal observational registry was launched in the U.S.: the combined response index for SSc (CRISS) cohort. We aim to compare the baseline characteristics of the 200 patient CRISS cohort with those of 3 large dSSc clinical trials to ascertain whether the CRISS patients are representative of the patients in dSSc clinical trials.

Methods: We compared the baseline clinical characteristics of the 200 patients enrolled in the CRISS cohort to patients who participated in 3 large RCTs in dcSSc: the Oral Collagen, the D-Penicillamine, and the Relaxin trials. Patients were enrolled into the CRISS cohort from 4 scleroderma

centers and all study patients have early dcSSc (< 5 years from first non-Raynaud's sign or symptom).

Results: The Table provides comparison between CRISS and the 3 RCTs. The CRISS cohort is similar across all 3 trials for most of the 15 selected measures. The CRISS cohort is similar to the Oral Collagen trial being statistically not different for 13 of 15 measures; it is similar to the D-Pen cohort for 11 of 15 measures and similar to the Relaxin cohort for 9 of 15 measures. While statistical differences existed for age, gender, BMI, tender joints, DLCO and MD global in some comparisons, majority were not clinically meaningful.

Table. Baseline data for study subjects in the CRISS cohort and comparison clinical trials

	CRISS (n=200)	Collagen (n=165)	D-Pen (n=134)	Relaxin (n=196)
Age (years), mean (SD)	50 (12)	51 (12)	44 (12)*	47 (10)*
Female, n (%)	149 (75)	132 (80)	104 (78)	167 (85)*
Race: Caucasian, n (%)	141 (71)	116 (70)	91 (68)	145 (74)
BMI, mean (SD)	25.4 (5.7)	29.1 (6.9)*	25.4 (4.7)	25.3 (4.7)
Disease duration[a], mean (SD)	32.4 (17.8)	41.9 (32.8)	9.5 (4.1)*	26.4 (16.4)*
MRSS, mean (SD)	20.6(10.3)	26.3 (7.7)*	21.0 (8.0)	27.3 (6.9)*
Tender joints count, mean (SD)	2.8(4.2)	NA	1.5 (2.4)*	1.2 (1.9)*
Active digital ulcers (present), mean (SD)	0.2 (0.7)	NA	0.1 (0.3)	NA
MD global assessment (0–100), mean (SD)	43.0 (21.7)	43.7 (22.6)	NA	49.4, (20.4)*
Pt global assessment (0–100), mean (SD)	39.6(26.9)	38.6(29.3)	NA	50.7 (23.4)*
HAQ-DI (0–3), mean (SD)	1.2 (0.8)	1.3 (0.7)	1.0 (0.7)	1.2 (0.7)
FVC predicted %, mean (SD)	82.4 (18.4)	85.1 (18.2)	83.6 (16.9)	84.9 (15.7)
DLCO predicted %, mean (SD)	66.3 (21.3)	67.9 (20.8)	75.3 (18.4)*	69.3 (21.3)
Serum CPK (U/L), mean (SD)	167 (403)	132 (245)	82 (124)	132 (193)
Serum Creatinine (md/dl), mean (SD)	0.90 (0.95)	0.78 (0.36)	0.90 (0.19)	0.67 (0.22)*

D-Pen=D-Penicillamine; MRSS=Modified Rodnan skin score; Pt=patient; NA=data not available
*Time since first non-Raynaud's symptoms/signs (months)
*p<0.05 for difference between CRISS cohort and the 3 RCTs

Conclusion: The CRISS cohort is generally representative of patients enrolled in large multicenter RCTs of dcSSc and will be fit for the purpose of developing a composite response index. The CRISS cohort will also be a valuable resource for studying the clinical characteristics of patients with early dsSSc followed at major academic centers and treated according to the current standards of care.

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World Health Organization Classification of Pulmonary Hypertension and Survival in Systemic Sclerosis Patients in the Pharos Cohort. Jessica K. Gordon[1], Lorinda Chung[2], Robyn T. Domsic[3], Wei-Ti Huang[4], Stephen L. Lyman[1], Evelyn M. Horn[5], Virginia D. Steen[6] and PHAROS Investigators[7]. [1]Hospital for Special Surgery, New York, NY, [2]Stanford Univ Medical Center, Palo Alto, CA, [3]University of Pittsburgh, Pittsburgh, PA, [4]Hospital for Special Surgery, New York, [5]New York Presbyterian Hospital/Weill Cornell Medical College, New York, NY, [6]Georgetown Univ Medical Center, Washington, DC, [7]Washington, DC

Background/Purpose: Pulmonary hypertension (PH) is a leading cause of death in patients (pts) with Systemic Sclerosis (SSc). The World Health Organization (WHO) classifies PH into groups: pulmonary arterial hypertension (PAH - Group 1); PH secondary to left heart dysfunction or pulmonary venous hypertension (PVH - Group 2); and PH secondary to pulmonary disease (PH-ILD - Group 3). Our objective was to compare the clinical features and survival among the 3 PH groups.

Methods: Pts in the PHAROS database with PH, defined by a mean PAP≥25 mmHg on initial right heart catheterization (RHC), were categorized by WHO criteria. A pulmonary capillary wedge pressure (PCWP) <15 mmHg differentiated Group 1 and 2. Pts with ILD with a forced vital capacity (FVC) <65% predicted or significant fibrosis on chest CT with a normal PCWP were included in group 3. Statistical analysis was carried out using ANOVA, logistic regression, and Kaplan-Meier estimates.

Results: There are 248 pts with PH in the PHAROS database: PAH − 160, PVH − 49, and PH-ILD Π39. Demographic and clinical differences are summarized in the table below. PAH pts are slightly older, more likely to be anti-centromere (ACA) positive, and to have limited SSc. Pts with PVH are more likely to be African-American (AA).

Pts have been observed for up to 6.5 yrs. The median period of observation is: PAH 5.02, PVH 1.86, and PH-ILD 2.82 yrs. The 1-year survivals were as follows: PAH 91.8%, PVH 95.2%, and PH-ILD 81.3%, and the 3-year survivals were: PAH 79.4%, PVH 79.1%, and PH-ILD 61.3%. Although the PH-ILD had only a 61% 3 year survival, Kaplan-Meier analysis did not show a significant difference in time to death between the groups, p=0.28, and Cox regression analysis did not show a difference between the groups with respect to survival. Using univariate logistic regression, we assessed the following baseline features as predictors of death: age, gender, race, antibody, disease duration, SSc subtype, RHC parameters, and pericardial effusion. Diffuse subtype was a predictor of death with OR of 1.9 (95% CI 1.008, 3.82), p =0.047. Higher mPAP on RHC was statistically significant with an OR 1.03 (1.005, 1.064) p =0.026. The presence of an effusion missed statistical significance (OR 1.93 (0.977, 3.796), p=0.058).

Survival Analysis stratified by PH_TYPE

Variable	WHO 1	WHO 2	WHO 3	p-value (overall)	p-value (1 v 2)	p-value (1 v3)	p-value (2 v 3)
Age (years)	60.4 (10.3)	54.4 (12.5)	56.2 (11.7)	0.027	0.0048	0.1023	0.7489
% female	85.2	77.3	69.4	0.0702	Overall Insignificant		
% white	81.2	59.1	75.0	0.0357	0.0428	0.268	0.1998
% AA	11.0	27.2	17.1				
Antibody	37.6	13.3	8.33	0.0004	0.024	<0.001	0.672
%aca	8.1	22.2	30.6				
%scl70	22.8	24.4	13.9				
% nuc ANA							
%limited	70.5	51	43.6	0.0109	0.0418	0.0064	0.7812
Disease Duration (yrs)	10.7 (9.2)	7.7 (5.5)	10.2 (8.6)	0.1134	Overall Insignificant		
Right Heart Catheterization Parameters							
mPAP	37.3 (10.5)	34.4 (9.6)	33.8 (10.6)	0.0693	Overall Insignificant		
pulmonary capillary wedge pressure	10.0 (3.3)	20.6 (4.1)	10.0 (4.4)	<0.001	<0.001	0.9987	<0.001
cardiac output	5.0 (1.5)	5.7 (1.8)	5.3 (1.8)	0.0419	0.0365	0.5566	0.5407
pulmonary vascular resistance	506.7 (365.6)	249.7 (183.4)	338.8 (272.2)	<0.001	<0.001	0.1119	0.1222
Pulmonary Function Test Parameters							
FVC % predicted	81.8 (16.1)	66.0 (18.8)	54.1 (13.9)	<0.001	<0.001	<0.001	0.0029
DLCO % predicted	42.2 (16.9)	40.0 (17.1)	28.6 (10.3)	<0.001	0.721	<0.001	0.0052
TLC % predicted	80.5 (16.2)	70.4 (20.1)	60.0 (16.1)	<0.001	0.0053	<0.001	0.0173
FVC:DLCO ratio	2.2 (0.9)	1.8 (0.6)	2.1 (0.7)	0.0249	0.0193	0.6179	0.3977

Conclusion: Overall survival in the PH patients enrolled in PHAROS is better in this observational cohort than in other recent studies, but WHO Group classification did not affect survival over the present period of observation. How these categorizations affect the prognosis of PH pts will continue to be studied in the long-term follow-up of the PHAROS cohort.

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Patients with Systemic Sclerosis Are Dying of Non-Systemic Sclerosis Related Causes, However Interstitial Lung Disease Remains the Predominant Systemic Sclerosis Related Cause of Death. Rebecca L. Batten and Bridget Griffiths. Freeman Hospital, Newcastle Upon Tyne, United Kingdom

Background/Purpose: Studies suggest that despite aggressive treatment of interstitial lung disease (ILD) secondary to systemic sclerosis with

cyclophosphamide, over one third of patients will experience a decline in lung function, death or require a lung transplant. The objective of this retrospective cohort is to document the causes of mortality in a UK based population with systemic sclerosis based in a tertiary centre in the North East of England over a period of seven years, and to review the causes of death in those patients treated aggressively with cyclophosphamide.

Methods: All patients attending a North East of England Tertiary Medical Centre with a diagnosis of systemic sclerosis were identified using the departmental database. From this group, all patients who died between 2003 and 2010 were identified. Medical records were reviewed and government death certificates were obtained for these patients. Patients were excluded from the study if either of these resources were not available.

Results: Of the twenty patients identified, five were male and fifteen were female. Four patients had a diagnosis of diffuse systemic sclerosis. Sixteen had a diagnosis of limited disease.

	Cause of death	Diffuse	%	Limited	%
NSR	Cancer	2	50	3	18.8
	Infection	1	25	2	12.5
	Other	1	25	3	18.8
SR	Multiorgan	0	0	1	6.25
	ILD	0	0	6	37.5
	PH	0	0	1	6.25

More patients died of non-systemic sclerosis related (NSR) causes (55%) than systemic sclerosis related (SR) causes. These included cancer (not related to cyclophosphamide) (25%), infection (15%), and other chronic disease (15%). Of the eleven patients treated with cyclophosphamide therapy, nine (82%) died of their underlying lung disease. The leading scleroderma related cause of death in our cohort was ILD (30% of all deaths), followed by pulmonary hypertension (10% of all deaths).

Conclusion: This highlights the importance of screening for organ complications of systemic sclerosis. Patients are, however more likely to die of non-systemic sclerosis related diseases. Physicians should therefore also remain vigilant for NSR disease such as malignancy, which accounted for 25% of deaths.

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Association of Gastroesophageal Factors and Progression of Interstitial Lung Disease in the Canadian Scleroderma Research Group, a Large, Multicenter Database.

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Background/Purpose: Interstitial lung disease (ILD) is a common complication of systemic sclerosis (SSc) and is a leading contributor to mortality in SSc patients. Once lung fibrosis occurs, lung function disease course may become stable or progressively decline. While some demographic and SSc-related factors have been associated with development of ILD, little is known about what contributes to progression. We studied the clinical manifestations of SSc-gastroesophageal (GE) involvement in relation to ILD status to determine associations between GE involvement and ILD progression in SSc. Our objective was to determine if GE reflux and dysphagia are associated with progressive ILD as measured by PFTs over three years.

Methods: Canadian Scleroderma Research Group (CSRG), a multi-center database of adult SSc patients, annually evaluates and collects patient information including demographics, skin manifestations, internal organ involvement and function assessment data. Using indicators of GE involvement and annual pulmonary function test results from the CSRG database, comparisons were made between no ILD, stable ILD and progressive ILD groups based on FVC% predicted. Univariate and multivariate analysis were used to determine association between GE factors and ILD development and progression.

Results: The study included data of 1043 SSc patients with mean age of 55.7 years and mean disease duration of 10.8 years. Among the variables of interest, physician indicators such as esophageal dysmotility (P=0.009) and post-esophageal dilatation (P=0.041) along with patient indicators such as difficulty swallowing (P=0.016), waking up choking (P=0.026) appeared to significantly increase risk of developing ILD. In comparing progressive vs. stable ILD patients, early satiety (p=0.018) a combination term composed of post-dilatation*choking (p=0.042) increased risk of ILD progression.

Table 1. Logistic regression models for dysphagia and GERD indicators

Moderate/Severe ILD vs. No/mild ILD			Single Effects					Interaction Effects	
COVARIATES	Model 1 Dilatation	Model 2 Dysmotility	Model 3 Difficulty Swallowing	Model 4 Choking	Model 5 Heartburn	Model 6 Food/Acid	Model 7 Early Satiety	Model 8 Dilatation* Difficulty Swallowing	Model 9 Dilatation* Choking
ESR	1.014 (.007)	1.016 (.003)	1.019 (.001)	1.007 (.002)	1.019 (.001)	1.019 (.001)	1.019 (.001)	1.019 (.001)	1.018 (.002)
ACA	0.497 (.024)	.500 (.026)	0.470 (.017)	0.480 (.020)	0.505 (.029)	.501 (.028)	.485 (.022)	0.448 (.012)	0.462 (.015)
Digital Ulcers	1.925 (.016)	1.843 (.025)	1.649 (.072)	1.716 (.051)	1.742 (.044)	1.759 (0.41)	1.792 (.035)	1.649 (.072)	1.667 (.067)
Pulmonary Hypertension	2.317 (.005)	2.420 (.003)	2.436 (.004)	2.704 (.001)	2.602 (.002)	2.538 (.002)	2.452 (.003)	2.509 (.003)	2.658 (.002)
GI variable of interest	1.937 (.041)	6.742 (.009)	1.993 (.016)	1.962 (.026)	1.334 (.327)	1.133 (.652)	1.538 (.119)	1.871 (.476)	0.607 (.468)

Progressive vs. Stable			Single Effects					Interaction Effects	
COVARIATES	Model 1 Dilatation	Model 2 Dysmotility	Model 3 Difficulty Swallowing	Model 4 Choking	Model 5 Heartburn	Model 6 Food/Acid	Model 7 Early Satiety	Model 8 Dilatation* Difficulty Swallowing	Model 9 Dilatation* Choking
Age	1.066 (.014)	1.068 (.0110	1.069 (.013)	1.067 (.013)	1.062 (.021)	1.071 (.011)	1.072 (.010)	1.069 (.012)	1.075 (.011)
Telangiectasia	0.124 (.036)	.126 (.033)	0.122 (.028)	0.127 (0.34)	0.138 (.044)	.124 (.040)	.073 (0.17)	0.142 (.052)	0.095 (.028)
GI variable of interest	2.150 (.263)	-	2.045 (.248)	1.325 (.653)	2.680 (.098)	3.009 (.072)	4.573 (.018)	0.367 (.677)	29.075 (.042)

Results are **OR (P-value). GI variable of interest is what each model studied (listed under each Model). Covariates with P<0.1 from univariate logistic regression were included for each comparison. Odds ratio are indicated as OR (p-value). P<0.05 was considered to be significant. (−) indicates that multivariate analysis could not be performed. Pulmonary arterial hypertension (PAH)=physician answering yes to 'Has the patient ever had pulmonary hypertension? * indicates interaction term between indicated variables.**

Conclusion: Indicators of esophageal dysmotility and GERD studied appear to be associated with ILD in SSc, with some factors specifically related to progressive ILD. Further, the strong association of an interaction term of both dysmotility and GERD with progressive ILD illustrates a potential dose-response phenomenon. These results hold important implications for management of ILD in SSc.

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Patient Perspective Informs Core Sets, Constructs of Metrics and Communication Tools for Patients with Connective Tissue Disease Related Interstitial Lung Disease.

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Background/Purpose: Limited information on the patient experience exists in CTD-ILD. Herein supports that the patients' perspective is essential to informing clinical practice and in developing optimal outcome measures for CTD-ILD.

Methods: Focus groups were dedicated to patients with each of the following ILD subtypes: rheumatoid arthritis, idiopathic inflammatory myositis, systemic sclerosis, and various CTD subtypes. Focus groups were followed with patient questionnaires and/or patient interview. Institutional review board approval was attained at all participating institutions.

Included were English speaking adults with a diagnosis of ILD by either histologic or computed tomography (CT) evidence with either a) symptoms of cough and/or dyspnea or b) restrictive pulmonary physiology or c) resting or exertion-related peripheral oxygen desaturation. CTD diagnoses were by rheumatologists based on accepted criteria. Patients with pulmonary hypertension or hypersensitivity pneumonitis made were excluded.

The script included 2 questions ("How have you experienced your disease since the diagnosis of ILD?", "How has the disease changed?"), with the WHO-100 domains as back-up to insure comprehensiveness. Data were analyzed through inductive development. The thematic structures of 5 independent analysts were triangulated, including 1 patient for each transcript.

Results: Six focus groups of 6–9 (total 45) participants per group across 5centres (University of Manitoba, University of Toronto, Louisiana State University, Johns Hopkins University, Massachusetts General/Brigham and Womens) and two countries (Canada and USA) were conducted; the following themes that emerged from preliminary findings from a subset analysis.

I. Biophysiologic Sphere:
   A. Cough:
      i. Universal and relevant patient experience
      ii. Patients described types of coughs and its triggers
   B. Dyspnea:
      i. Reference to breath/breathing rarely used
      ii. Often described within context of functional limitation or loss of pleasurable activity and/or connectedness (eg. reading to children)
II. Psychological Sphere:
   A. Living with Uncertainty:
      i. Perpetuated by inadequate physician communication
      ii. Unknown and unpredictable disease course in the immediate and long-term (death)
      iii. Conflicts in management between CTD and ILD
   B. Struggle Over the New Self:
      i. Maintaining an autonomy
      ii. Parenting and grand-parenting roles were a central concern
   C. Development Of Resilience Through Coping (Self-Efficacy)

Conclusion: Patient experts have informed our understanding around communication and promising, relevant outcome measures in CTD-ILD. Medical expert consensus identified 5 domains in CTD-ILD for outcome measures. While dyspnea remained a core outcome measure for both patient and medical experts, cough was relevant to patients but not medical experts. A discordant language related to dyspnea exists between clinicians and patients and may impact performance of current and potential metrics related to dyspnea.

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Heterogeneity of Autoantibodies in Systemic Sclerosis: Reconsidering Current Paradigms. Sonal Mehra[1], Murray Baron[2], Mat Stephenson[1], Marie Hudson[3], Janet E. Pope[4], Canadian Scleroderma Research Group[5] and Marvin J. Fritzler[1]. [1]University of Calgary, Calgary, AB, [2]Jewish General Hospital, Montreal, QC, [3]McGill University, Montreal, QC, [4]St. Joseph's Health Care London, London, ON, [5]Montreal

Background/Purpose: One of the hallmarks of systemic sclerosis (SSc) is the presence of disease specific autoantibodies (aab): anti-centromere (CENP), anti-topoisomerase I (TopoI), anti-RNA polymerase III (RNAP), and anti-fibrillarin (Fib). Current paradigms suggest that SSc aab profiles are relatively monospecific and that SSc-specific aab are mutually exclusive. We undertook a study using array technologies to evaluate the spectrum and interrelations of aab in SSc

Methods: Sera from 805 SSc patients enrolled in the a multi-centre cohort biobanked at −80C were used for this study. Aab to Topo I, CENP, RNAP, Fib, NOR90, Th/To, Pm100, Pm75, Ku, platelet derived growth factor (PDGFR), and Ro-52/TRIM21 were detected by line immunoassay (LIA). Addressable laser bead immunoassay (ALBIA) was used to detect other antibodies to Extractable Nuclear Antigens Jo-1, Sm, UI1RNP, SSA/Ro60, SSB/La, Rib P. The frequency of each aab occurring individually or associated with other aab was calculated, tabulated and plotted as a heat map derived from an Excel database.

Results: In order of decreasing overall frequency, anti-CENP was positive in 38.5%, anti-RNAP 23.2%, anti-Topo I 21.4% and anti-Fib 7.2%. In contrast to current paradigms, the SSc-related aab overlapped with other SSc-specific aab: anti-CENP 8.9%; anti-Topo I 4.7%; anti-RNAP 9.8%; anti-Fib 6.6%. SSc-specific aab also overlapped with the broader spectrum of aab: anti-CENP 73%, anti-Topo I 60%, anti-RNAP 63% and anti-Fib 88%. Accordingly, 'monospecific' aab (i.e. no other detectable aab) to

CENP, RNAP, U1RNP, Topo-I, and Fib, I were detected in 26.7%, 36.8%, 18%, and 39.3%, 13.8% and 12%, respectively. Likewise, the majority of sera with aab to Ku, Th/To, Sm and SSB/La also overlapped with other aab. Aab to PM-Scl 75/100, NOR-90, SSA and Fib were observed in 12%, 77 9.5%, 8.5%, 7.2%, respectively. Anti-U1RNP and Ku (both 5.4%), anti-PDGFR (2%), anti-Jo-1 (0.5%) were the least common. Of note, 8.6% of the SSc sera did not have any aab detectable by LIA or ALBIA.

Conclusion: Our study indicates that the majority of SSc sera have multiple aab and independent segregation of the SSc-specific or SSc-related autoantibodies is not as clear-cut as current literature suggests. Furthermore, studies of clinical correlations with certain aab in SSc should be reconsidered in light of the complexity of the serological profiles of individual patients.

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Clinical Features Associated with Anti-Th/to in Non-Scleroderma Patients - Sine Scleroderma? Ann D. Chauffe, Minoru Satoh, Angela Ceribelli, Edward K.L. Chan, Yi Li, Eric S. Sobel, Westley H. Reeves and Michael R. Bubb. University of Florida, Gainesville, FL

Background/Purpose: Autoantibodies in scleroderma (systemic sclerosis, SSc) such as anti-topoisomerase I (Scl-70), RNA polymerase III, centromere, U3RNP/fibrillarin, and Th/To are associated with a unique subset of the disease and useful biomarkers in diagnosis and management. Among these, anti-Th/To is found in 4–13% of SSc patients and believed to be relatively specific for SSc, however, some reports show the detection of anti-Th/To in patients without SSc or some specific features such as interstitial lung disease (ILD). We sought to further characterize the clinical significance of anti-Th/To by focusing on non-SSc patients in an unselected cohort of rheumatology patients.

Methods: Patients enrolled in the registry from 2000 to 2012 were studied. All sera collected at the initial visit of each patient were tested by immunoprecipitation of ^{35}S-methionine-labeled K562 cell extracts. In addition, 132 SSc and 45 non-SSc sera that had predominant nucleolar staining reported from diagnostic laboratories were tested by urea-PAGE and silver staining for RNA component analysis. Anti-Th/To was defined based on detection of 7–2 and 8–2 RNA in the immunoprecipitates. The clinical information of anti-Th/To positive patients were collected from the database and analyzed.

Results: Overall, 16 patients were found to have anti-Th/To; 7 had sclerodermatous skin changes (SSc group) while 9 patients had neither sclerodermatous skin changes nor a diagnosis of SSc (non-SSc group). All except one in the non-SSc group were female and 7/7 SSc and 7/9 non-SSc were Caucasians (2 in non-SSc were African Americans). In the SSc group, 5 had limited cutaneous (lcSSc) disease and 2 had the diffuse cutaneous (dcSSc) variant. In the non-SSc group, there was 1 SLE with Sjogren's (SjS), 1 with polymyositis (PM) and 2 with primary SjS. Other patients had a diagnosis based on organ involvement or symptoms, such as ILD, pulmonary hypertension (PH), and/or Raynaud's phenomenon (RP). Most non-SSc group patients had features typically associated with SSc: 5/9 RP, 2/9 pitting scars, 3/9 telangiectasias, 3/9 ILD, 2/9 PH. No SSc patients had ILD or PH. 4/9 patients in the non-SSc group may be considered sine scleroderma; 2 with ILD and RP (one also with PH) and 1 with PH and telangiectasias. Another patient had SjS, Hashimoto's thyroiditis and ILD complicated by diffuse alveolar hemorrhage that resulted in his death.

	Scleroderma (n = 7)	No scleroderma (n = 9)
Female, Caucasian	7/7, 7/7	8/9, 7/9
Age (mean)	48	48
Raynaud's	86% (6/7)	56% (5/9)
Pitting scars	0% (0/7)	22% (2/9)
Telangiectasia	71% (5/7)	33% (3/9)
Interstitial Lung Disease	0% (0/7)	33% (3/9)
Pulmonary Hypertension	0% (0/7)	22% (2/9)
Esophageal Dysmotility	43% (3/7)	0% (0/9)
Pericardial effusion	14% (1/7)	22% (2/9)

Conclusion: A significant number of patients with anti-Th/To did not have a diagnosis of SSc. However, most of these patients were found to have other features associated with SSc, many of which may be considered the sine

scleroderma variant. In particular, non-SSc patients with anti-Th/To were found to be enriched for ILD and PH when compared to SSc patients with anti-Th/To. It may be worth testing for anti-Th/To in patients with ILD or PH and anti-nucleolar antibodies. Further studies on the clinical significance of anti-Th/To in non-SSc patients are warranted.

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Differential Expression of Hepatocyte Growth Factor (HGF) in Patients with Systemic Sclerosis-Associated Pulmonary Arterial Hypertension.

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Background/Purpose: Pulmonary arterial hypertension (PAH) is one of the leading causes of death in patients with systemic sclerosis (SSc). Non-invasive biomarkers are needed to identify patients with early PAH who may benefit from early intervention. We sought to identify novel cytokines that differentiate patients with incident right heart catheterization (RHC)-confirmed SSc-PAH from SSc patients who are at high risk for PAH.

Methods: The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry is a registry of SSc patients at high risk for or with incident RHC-confirmed PAH that includes 23 centers throughout the US. Pre-PAH patients fulfill at least one of the following criteria: pulmonary artery systolic pressure (PASP) $\geq$ 40 mmHg on transthoracic echocardiogram (TTE), diffusing capacity of carbon monoxide (DLCO) $<$ 55% predicted, or forced vital capacity (FVC)/DLCO ratio $>$ 1.6. Patients with definite incident PAH have a mean pulmonary artery pressure $\geq$ 25 mmHg and a pulmonary capillary wedge pressure $\leq$ 15 mmHg (without significant interstitial lung disease) on RHC performed $\leq$ 6 months from enrollment. Cytokine and chemokine profiling of 17 cytokines/chemokines measured by Bio-Plex™ bead arrays was performed comparing serum samples from 10 pre-PAH patients to 9 definite PAH patients. Significance Analysis of Microarrays (SAM) was used to identify statistical differences in cytokines/chemokines between the groups with a false discovery rate (q) $<$0.1%. We also evaluated for longitudinal changes in cytokine profiles from 3 pre-PAH patients who subsequently developed definite PAH during follow-up.

Results: All patients were female with a mean age of 52 ± 12 years and disease duration from first Raynaud's symptom of 13 ± 10 years. Two-thirds of patients had limited cutaneous disease, 37% were anti-centromere antibody positive, 32% had a nucleolar ANA, and 16% were anti-U1RNP antibody positive. Mean FVC and DLCO were 82 ± 20% and 45 ± 13% predicted, respectively. Clinical features in the pre- vs. definite PAH groups were not significantly different except with respect to PASP on TTE (34 ± 7 vs. 45 ± 8 mmHg, p=0.006) and 6 minute walk distance (508 ± 115 vs. 393 ± 70 m, p=0.02). Profiling of the pre-PAH vs. definite PAH group identified only one cytokine whose expression levels significantly differed between the groups—hepatocyte growth factor (HGF) levels were significantly higher in the definite PAH group (q$<$0.1%). Evaluation of cytokine profiling from longitudinal samples of pre- to definite-PAH patients did not identify any cytokines with significant changes in expression levels over time.

Conclusion: We found that patients with definite incident PAH from the PHAROS registry expressed higher levels of HGF than patients at high risk for PAH. HGF is a potent pro-angiogenic and anti-fibrotic factor, and has been shown to correlate significantly with right ventricular systolic pressure on echocardiogram as well as a diagnosis of PAH based on RHC. Our findings suggest that HGF expression levels may provide predictive information regarding the risk for PAH in patients with SSc in addition to clinical parameters such as DLCO and PASP on TTE.

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Enhanced Liver Fibrosis Test: A Further Step Toward Depiction of Fibrotic Process in Very Early Diagnosis of Systemic Sclerosis.

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Background/Purpose: Enhanced Liver Fibrosis (ELF) test is derived from an algorithm of 3 serum biomarkers of fibrosis (*i.e.* tissue inhibitors of matrix metalloproteinases, hyaluronic acid and aminoterminal propeptide of type III procollagen), it has been suggested as a sensitive/predictive tool for liver fibrosis. Aim of the study was to evaluate whether ELF may help in differentiating primary Raynaud's phenomenon (Rp) from very early Systemic Sclerosis (SSc) in a cross-sectional multi-center study.

Methods: 110 consecutive adult subjects with "isolated" Rp (*i.e.* without any symptoms/signs suggesting a connective tissue disease) referring to 3 Italian Rheumatology Centers in approximately 6 months time were enrolled. Patients underwent as first screening nailfold capillaroscopy (NC) and were tested for anti-nuclear antibodies (ANA) by IFF and blotting and classified as primary Rp (pRp) (*i.e.* NC and ANA negative), very early SSc (*i.e.* ANA and NC positive), or Rp with NC or ANA positive. Patients with any other fibrosing disorder and treated with interferon were excluded. 15 limited cutaneous (lc)-SSc and 15 diffuse cutaneous (dc)-SSc with disease duration $<$5 years were also studied. ELF score was determined blindly by an independent commercial service (iQur, UK). Statistical analysis was performed by regression modelling this score as a function of the diagnosis and age. The discriminant performance was evaluate by ROC curve analysis adjusting for age.

Results: 60 subjects had pRp (mean age 43.1 yrs), 35 had Rp with positive ANA only (mean age 43.6 yrs), 4 had Rp with NC scleroderma pattern only (mean age 38.2 yrs) and 10 had a diagnosis of very early SSc (mean age 59.7 yrs). There were significantly differences between ELF scores in subjects with pRp (mean 7.84) vs patients with very early SSc (mean 8.44), lc-SSc (mean 8.68) and dc-SSc (mean 9.00) (p 0.03, 0.001 and $<$0.0001 respectively). ELF score in pRp and Rp with positive ANA or NC scleroderma pattern only was not statistically different, although a progressive increase was observed (mean 7.84, 7.90 and 7.95 respectively). Considering patients with and without SSc, the area under the ROC curve was 0.7465 (CI 95%: 0.6578–0.8351). When adjusting for age the AUC for youngest patients was 0.77 and it significantly decreased for the older patients. A correlation was observed between ELF score and age.

Conclusion: ELF score shows unbalanced fibrosis biomarkers in very early SSc; it may represent useful potential tool in identifying Rp associated with a scleroderma signature.

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Sub-Analysis of ELF Score Biomarkers Components Indicates a Specific Correlation with Different Organ Involvement in Systemic Sclerosis.

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Background/Purpose: A recent large multicenter study has identified an algorithm, known as Enhanced Liver Fibrosis (ELF), by combining the serum concentrations of amino-terminal propeptide of procollagen type III (PIIINP), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and hyaluronic acid (HA) in a weighted average developed to match liver fibrosis pathology scoring The algorithm has been shown to predict liver related outcomes in patients with chronic liver diseases and recently it has been shown to correlate with several measures of fibrosis in SSc including modified Rodnan Skin

Score, presence of ILD, DLCO as well as age, disease activity and different aspects of disease severity. The aim of this study was to compare the performance of ELF with its single components in correlating with the different clinical and instrumental variables in SSc, to determine whether any of the three biomarkers could have a specific predictive value as surrogate outcome measure in SSc.

Methods: The serum concentrations of the three biomarkers were analysed in 129 SSc patients employing the same platform used to calculate the ELF score (siemens, advia centaur). All patients were investigated for clinical and serological subset, disease duration, skin and internal organ involvement, HAQ-DI, disease severity and activity. Correlations were calculated using Spearman correlation test. Mann-Whitney test was used to perform comparison between groups. Statistical analysis was performed using GraphPrism software.

Results: Median, correlation coefficient and statistical significance of ELF and its single analytes are summarised in table 1. All three components of ELF showed a similar strong correlation with mRSS and HAQ-DI, confirming a strong predictive value on skin involvement. Interestingly, the concentration of HA was the only parameter correlating with Age, muscle severity and Heart severity, whereas it did not correlate with DLCO% or lung severity. In this regard the biomarker with better performance on Lung involvement was TIMP-1, which showed a strong correlation with DLCO and lung Severity. Furthermore SSc patients with interstitial lung disease (ILD) showed significant higher levels of TIMP-1 (P=0.0136) and TIMP-1 was the only biomarker to correlate with the EScSG-Activity Index. On the contrary, PIIINP was the only one to correlate with Joint and kidney severity.

Coefficient correlation (rho) between ELF score and single serum markers with clinical parameters in 129 SSc patients

	ELF score	PIIINP (ng/mL)	TIMP-1 (ng/mL)	HA (ng/mL)
Serum values (median, range)	8.84, 6.49–.10.84 rho	6.25, 2.63–.33.06 rho	215.3, 88.5–.531.2 rho	41.53, 4.69–.236.4 rho
Age	0.34***	0.05	0.11	0.42***
mRSS	0.26**	0.30***	0.33***	0.19*
DLCO, absolute value	−0.26**	−0.1	−0.28**	−0.20*
DLCO %	−0.06	−0.05	−0.20*	0.02
Skin_sev	0.34***	0.34***	0.37***	0.20*
Join/tendon_sev	0.26**	0.25**	0.13	0.11
Muscle_sev	0.34***	0.17	0.08	0.26**
GI_sev	0.17*	0.15	0.03	0.09
Lung_sev	−0.01	−0.01	0.18*	−0.11
Heart_sev	0.16	0.08	0.09	0.21*
Kidney_sev	0.16	0.23**	−0.001	0.05
EScSG-AI	0.15	0.09	0.20*	0.08
HAQ-DI	0.32***	0.25**	0.31***	0.22*

*P<0.05; **P<0.01; ***P<0.001

Conclusion: Subanalysis of the single serum markers included in the ELF score algorithm suggests that the different biomarkers may function as surrogate outcome measure of specific organ involvement in SSc. In this regard, longitudinal studies confirming the predictive value and sensitivity to change over time of the single biomarkers may pave the way to develop specific algorithms tailored to carry the maximum predictive value on specific organ involvement in SSc.

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Interferon-Inducible Chemokines Correlate with Disease Severity in Systemic Sclerosis.
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Background/Purpose: The most prominent gene expression profile in the peripheral blood of patients with systemic sclerosis (SSc) is an interferon (IFN) inducible signature. A large scale correlation of this signature with disease subtypes and features has not been performed due to scarcity of RNA samples. Herein, we identify plasma chemokines that correlate strongly with the IFN gene signature and investigate their correlation with disease features in a large early SSc cohort.

Methods: We examined the correlation of IFNγ-inducible protein-10 (IP-10/CXCL10), IFN-inducible T cell alpha chemoattractant (I-TAC/CXCL11), and monocyte chemoattractant protein-1 (MCP-1/CCL2) with the IFN gene expression signature. We generated an IFN-inducible chemokine score with the correlated chemokines, IP-10 and I-TAC, and compared it in 266 patients enrolled in the GENISOS cohort (disease duration<5 years, 59% diffuse cutaneous involvement) to that of 97 matched controls. Subsequently, the correlation between the baseline chemokine score and markers of disease severity was assessed. Finally, the course of chemokine score over time was examined in 63 follow-up plasma samples prospectively.

Results: The plasma IFN-inducible chemokine score highly correlated with the IFN-inducible gene expression signature (r_s=0.612, p=0.0015) and was significantly higher in SSc patients than matched controls (p<0.001). When the chemokine level was dichotomized based on the 95th percentile level in unaffected controls, 39.2% of patients had a positive chemokine score, which is more prevalent than any SSc-related autoantibody. Furthermore, the chemokine score was associated with the presence of anti–U1 ribonucleoprotein antibodies (RNP) (p<0.001) and absence of anti–RNA polymerase III antibodies (p=0.002), but not disease duration, disease type, or other autoantibodies. As shown in Table 1, the chemokine score correlated with the concomitantly obtained muscle, skin and lung components of the Medsger Severity Index, as well as, FVC, DLco, creatine kinase independent of anti-RNP or other potential confounders (age, gender, ethnicity, disease duration, and treatment with immunosuppressive agents). Finally, there were no significant changes in the chemokine scores over time while their baseline levels correlated significantly with those on the follow-up visits (r=0.39, p=0.002). This indicates that the chemokine score is a stable marker of disease severity and does not fluctuate in a consistent time-dependent manner.

Table 1. Correlation of plasma IFN-inducible chemokines with disease severity

	IFN-inducible chemokine score				
	r	p	pm†	β	95CI
FVC	−0.17	0.013	0.024	−4.02	−7.57, −0.47
DLCO	−0.18	0.008	0.001	−5.92	−9.38, −2.46
CK	0.21	0.002	0.004	70.30	21.21, 119.39
mRSS	0.1	0.125	0.161	0.96	−0.78, 2.71
Skin*	0.12	0.073	0.043	0.11	−0.01, 0.24
Muscle*	0.18	0.006	0.011	0.08	0.02, 0.15
GI*	0.06	0.38	0.270	0.06	−0.03, 0.16
Lung*	0.15	0.021	0.009	0.23	0.07, 0.40
Heart*	0.04	0.565	0.377	0.07	−0.04, 0.18
Kidney*	0.01	0.878	0.876	−0.004	−0.07, 0.06
Joints*	0.10	0.106	0.117	0.15	−0.04, 0.33

* Components of Medsger Severity Index. † Multivariable model after adjustment for age at enrollment, gender, ethnicity, disease duration, and treatment with immunosuppressive agents. Abbreviations: Percent predicted forced vital capacity; DLco: Percent predicted diffusing capacity; mRSS: modified Rodnan Skin Score; CK: Creatine Kinase. r: Correlation coefficient; β = regression coefficient.

Conclusion: The IFN-inducible chemokine score is a stable marker of more severe subtype of SSc. This composite score may be useful for risk stratification regardless of disease type, serology or duration. It also might identify the subgroup of patients that benefit from treatments targeting IFN pathways.

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Does Skin Gene Expression Profile Predict Response to Imatinib?
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Background/Purpose: Imatinib is a potent inhibitor of TGF-β signaling. Furthermore, a subgroup of SSc patients shows a prominent TGF-β gene expression signature in skin biopsy samples. We examined whether baseline TGF-β skin gene expression signature or other previously described signatures differentiate responders from non-responders to imatinib treatment.

Methods: Patients with SSc were enrolled in a 1-year open-label pilot study of imatinib (Khanna D, A&R 2011). All patients had active interstitial lung disease defined as forced vital capacity (FVC) < 85% predicted, dyspnea on exertion, and presence of a ground glass opacity on HRCT. Percent changes in the modified Rodnan Skin Score (mRSS) and % predicted FVC were calculated based on the baseline and last measurement in the study.

Baseline skin biopsies were available in five patients (3 diffuse and 2 limited cutaneous involvement) who completed a 12 month course of treatment. Additional 3 patients had 3 month data available who stopped due to adverse events. Percent change in mRSS ranged from 53% worsening to 33% improvement while percent change in FVC ranged from 9% worsening to 5% improvement. Global gene expression profiling was performed on Illumina HumanHT-12 arrays in the baseline patient samples and 36 unaffected controls. All patient and control samples were processed according to the same procedures and the microarrays were performed in one batch. Previously described TGF-β, IL-13, and diffuse proliferative gene signatures (Milano et al. PLoS ONE 2008) were examined. We also developed an IFN-α gene signature using control fibroblasts treated with IFNa. Unsupervised hierarchical clustering was performed after selecting genes that were present in the above gene signatures in separate analyses. The goal of our analysis was to examine whether clustering based on these gene lists separate responders from non-responders.

Results: As shown in Figure 1, these five patients clustered separately from the majority of control samples when the transcript list was filtered based on TGF-β responsive genes. However, there was no clear separation between responders and non-responders in regard to skin (Figure 1) or lung disease. Similarly, patients clustered separately from the majority of control samples when the transcript list was selected based on IL-13, diffuse proliferative, or IFN-α gene signatures. However, there was again no clear separation between responders and non-responders to treatment with imatinib. The findings were similar when additional 3 patients with 3 month data were included in the analysis.

Unsupervised hierarchical clustering of patient and control samples –
Numbers indicate percent change in mRSS after treatment
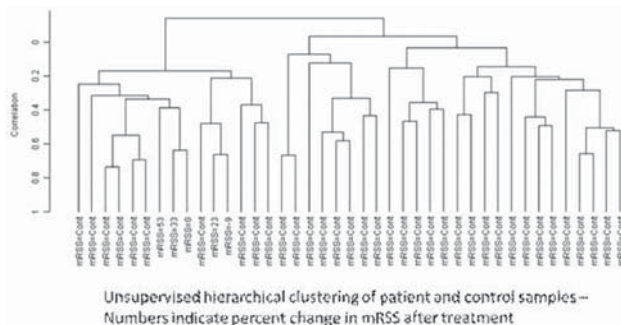
Figure 1.

Conclusion: This pilot study confirms presence of distinct gene signatures in skin biopsy samples of patients with SSc. However, neither the TGF-β signature nor the other investigated transcript signatures were able to predict response to imatinib.

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Caveolin-1 Deficiency May Play a Role in the Predisposition of African Americans to SSc ILD. Elena Tourkina[1], Charles Reese[2], Beth Perry[2], Shanice Dyer[2], Michael Bonner[2], Richard P. Visconti[2], Jing Zhang[2], Richard M. Silver[3] and Stanley Hoffman[3]. [1]Medical University of South Carolina, Charleston, SC, [2]Medical University of SC, Charleston, SC, [3]Medical University of SC, Charleston

Background/Purpose: Scleroderma-associated Interstitial Lung Disease (SSc-ILD) is more prevalent and more severe in African Americans (AA) than in Caucasian (C) patients, but little is known of the factors underlying this health disparity. In the course of studies comparing caveolin-1 function in SSc and healthy blood monocytes, we made the striking observation that healthy AA monocytes share abnormalities with SSc monocytes including low caveolin-1 levels. The aim of this study was to determine the consequences of low caveolin-1 expression in AA and SSc monocytes,

Methods: The study was approved by the university's IRB for Human Subject Research. Monocytes were isolated from the blood of SSc-ILD patients and healthy donors using negative selection. SSc patients fulfilled the ACR criteria for the classification of systemic sclerosis. Monocyte migration was assayed in Multiwell Chemotaxis Chambers, with or without treatment with caveolin-1 scaffolding domain (CSD) peptide and control peptides. CD14, CXCR4, alpha-smooth muscle actin (ASMA), and caveolin-1 levels were determined by Western blot analysis and immunostaining. For fibrocyte differentiation, peripheral blood mononuclear cells (PBMC) isolated from 40 ml of blood were incubated for 14 days in 20 ml DMEM/20 % FBS on fibronectin-coated plates with or without treatment with CSD.

Results: Like SSc-ILD monocytes, healthy AA monocytes differ from healthy C monocytes in signaling and in function. Healthy AA monocytes contained only 49 % as much caveolin-1 as healthy C monocytes (n = 7). The percentage of AA monocytes that migrated in response to the CXCR-4 ligand, CXCL12, was almost three-fold enhanced (19 ± 2.5 vs 57 ± 4.3) compared to C monocytes (n = 10). Like SSc monocytes, when healthy AA monocytes were treated with CSD to restore caveolin-1 function, migration in response to CXCL12 was inhibited by at least 70%. When we compared the ability of healthy C monocytes, healthy AA monocytes, and SSc monocytes to differentiate into fibrocytes, we observed a three-fold increase (quantified in terms of number of spindle-shaped cells per high-power field) in both the SSc and healthy AA samples compared to the healthy C samples (C = 6.4 ± 2.1, AA = 17.3 ± 3.8, SSc = 16.5 ± 4.0; n = 12). In all three cell types, CSD treatment inhibited fibrocyte differentiation by >50%. Although fibrocyte differentiation is enhanced in both healthy AA and SSc, there are phenotypic differences between these two groups. When the CD14- population is isolated by FACS from each source, then cultured on fibronectin-coated coverslips, the level of collagen I and caveolin-1 is similar for all three groups, CXCR4 was upregulated in both the AA and SSc fibrocytes, and ASMA was upregulated only in the SSc fibrocytes.

Conclusion: Our results support the notion that low caveolin-1 levels may play a role in the predisposition of the AA population to SSc-ILD through effects both on the migration of fibrocytes and fibrocyte precursors into damaged tissue and on fibrocyte differentiation.

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Skin Autofluorescence As a Measure of Oxidative Stress in Systemic Sclerosis Is Not Affected by Skin Thickness, Erythema or Melanin. Andrea Murray[1], T. Moore[1], J. Manning[2], Christopher E.M Griffiths[3] and Ariane Herrick[1]. [1]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom, [2]Department of Clinical Rheumatology, Salford Royal NHS Foundation Trust, Salford, United Kingdom, [3]Dermatology Centre, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom

Background/Purpose: Skin autofluorescence (AF) has been suggested as a non-invasive measure of oxidative stress in patients with diabetes and other diseases. We have previously shown that skin AF is also increased in patients with systemic sclerosis (SSc). As part of the disease process, patients with SSc undergo fundamental changes in their skin properties including skin thickening, alteration in perfusion secondary to microvascular dysfunction, and altered pigmentation. There are concerns that these might influence AF. The aim of this study was to determine whether skin AF is altered by these changes and thus to assess whether skin AF is a valid non-invasive technique to measure oxidative stress in SSc. This is a key question given the increasing evidence implicating oxidative stress in pathophysiology.

Methods: Twenty healthy controls (HC [2 males, median 45 (interquartile range 39–52) years]), 20 patients with limited cutaneous (LcSSc, [2 males, 55 (50–67) years]) and 20 with diffuse cutaneous SSc (DcSSc, [6 males, 56 (52–66) years]) participated. Skin AF, induced by ultra-violet light was measured at 10 body sites (distal and proximal digit (dorsal aspect), dorsum of hand, lower and upper arm (dorsal aspect), forehead, anterior chest and abdomen, calf and foot (dorsal aspect)). Each of the following assessments was also made: 1) dermal (skin) thickness, by high frequency ultrasound, 2) erythema index (EI, an indirect measure of blood flow) and 3) melanin index (MI, a measure of pigmentation). EI and MI were both calculated from white light reflection measurements with a spectrometer. Linear regression was used to assess the relationships between AF, skin thickness, EI and MI and SSc subtype.

Results: Linear regression confirmed previous findings that fluorescence is increased in patients with SSc as compared to controls. Patients with DcSSc showed a higher increase in AF than patients with LcSSc; data shown for one exemplar (forearm) in Table 1. Linear regression showed no associations between skin fluorescence and skin thickness, EI or MI (as shown on the last row of Table 1). No consistent differences for values of EI or MI were found between groups.

Table 1. Data for forearm for HC, LcSSc and DcSSc: mean (inter-quartile range); and linear regression at the forearm.

Group/Method	AF (intensity, arbitrary units)	Skin thickness (micrometers)	EI (arbitrary units)	MI (arbitrary units)
HC	0.034 (0.030–0.048)	88 (82–103)	10.36 (7.02–11.16)	59.21 (55.32–63.23)
LcSSc	0.040 (0.030–0.051)	81 (62–99)	9.82 (7.77–14.05)	63.96 (55.25–66.28)
DcSSc	0.045 (0.034–0.060)	109 (76–126)	10.73 (9.20–14.33)	58.23 (53.40–64.80)
Linear regression: Difference from AF (95% confidence intervals); p-value	n/a	-3.95×10^{-05} (-2.30×10^{-04} to 1.51×10^{-04}); 0.680	7.95×10^{-04} (-3.84×10^{-04} to 1.97×10^{-03}); 0.182	-5.11×10^{-04} (-1.05×10^{-03} to 2.57×10^{-05}); 0.062

Conclusion: The skin changes observed in patients with SSc, as measured by high frequency ultrasound and white light reflection, do not appear to influence skin AF measurements, i.e. skin AF is independent of skin thickness, EI and MI and should therefore be a valid technique for use in the assessment of oxidative stress in SSc.

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Gender-Associated Differences in Disease Characteristics and Outcome in Systemic Sclerosis. Svetlana I. Nihtyanova[1], Voon H. Ong[2] and Christopher P. Denton[3]. [1]Royal Free Hospital, Medical School, London, England, [2]UCL Medical School, London, England, [3]UCL, London, United Kingdom

Background/Purpose: Although significant female gender predominance is seen in majority of large systemic sclerosis (SSc) cohorts, multiple studies have suggested that male gender generally associates with more severe disease and worse outcome. We explore disease characteristics, morbidity and mortality in male and female patients with SSc from a large single centre cohort.

Methods: We analysed a cohort of incident cases of SSc that developed over a period of 5 years and were followed up over a decade. Basic demographic, clinical and serological characteristics were recorded and comparison of survival and cumulative incidence of clinically-significant organ complications was made between male and female patients.

Results: A total of 398 SSc patients were included. Of those 54 (14%) were male. Age at onset was very similar in both male (mean±SD 50±13 years) and female (mean±SD 48±13 years) patients. A higher proportion of men had diffuse cutaneous (dc) subset of SSc compared to women − 48% (n=26) v 35% (n=120), although the difference showed only a trend towards statistical significance (p=0.069). Duration of Raynaud's phenomenon (RP) with relation to onset of first non-RP symptom of SSc was significantly shorter in male patients with mean (range) of 40 (−12 to 576) months compared to 85 (−29 to 744) months in females (p=0.004). Comparison between frequencies of autoantibodies demonstrated significant differences only in anti-centromere antibody (ACA) positivity, which was twice as common among women – 28% (n=96) compared to 15% (n=8) in men (p=0.046).

There was a significantly higher proportion of male patients with some degree of pulmonary fibrosis (PF) confirmed on HRCT compared to females − 72% (n=39) v 49% (n=168), p=0.002. Analysis of cumulative incidence of clinically significant PF also demonstrated significantly higher frequencies among men. At 5 and 10 years from disease onset 32% and 43% of men had developed significant PF compared to 21% and 26% of women (p=0.017). There were no differences in incidence of pulmonary hypertension (PH), cardiac involvement or scleroderma renal crisis (SRC) between genders. At 5 years 6% of men and 4% of women had developed PH, 2% of men and 3% of women – cardiac SSc and 4% of men and 6% of women – SRC while at 10 years PH was found in 16% of men and 13% of women, SRC in 4% of men and 7% of women and there were no new cases of cardiac SSc in either group.

There was also no difference in survival between genders with 91% of both male and female patients being alive at 5 years. Mortality rate among men increased slightly between 5 and 10 years compared to women, although

the difference did not reach statistical significance and at 10 years survival was 79% in women and 70% in men. There was also no difference in survival from development of significant organ complications between the genders.

Conclusion: Although male patients have significantly higher incidence of PF, reflected by the lower frequency of ACA and show a trend towards greater frequency of diffuse SSc subset compared to females, there was no significant increase in overall mortality.

Disclosure: S. I. Nihtyanova, None; **V. H. Ong**, None; **C. P. Denton**, None.

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Early Versus Late Onset Systemic Sclerosis: Analysis of 1037 Patients From Rescle Registry. Marco A. Alba[1], Juan Carlos Mejia[2], Gerard Espinosa[3], María-Victoria Egurbide[4], Carles Tolosa[5], Luis Trapiella[6], Carmen Pilar Simeon[7], Vicent Fonollosa[8] and And RESCLE investigators[9]. [1]Vasculitis Research Unit. Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [2]Hospital Clinic University Barcelona, Barcelona, Spain, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Hospital de Cruces, UPV/EHU, Barakaldo, Spain, Barakaldo, Spain, [5]Corporación Sanitaria Universitaria Parc Taulí, Barcelona, Spain, [6]Hospital Universitario Central de Asturias, Asturias, Spain, [7]Hospital Valle de Hebron, Barcelona, Spain, [8]Hospital Vall dxHebron, Barcelona, Spain, [9]RESCLE, Barcelona, Spain

Background/Purpose: Systemic sclerosis (SSc) is characterized by extensive fibrosis, vascular dysfunction and the presence of several autoantibodies. As in other autoimmune diseases, age at disease onset seems to modify initial and cumulative clinical manifestations. The aim of this study was to determine if the age at disease onset may modulate the clinical characteristics and evolution of patients with SSc.

Methods: The Spanish Network for Systemic Sclerosis recruited 1037 patients with a mean follow-up of 5.2±6.8 years. Based on the mean ± 1SD of age at disease onset (45±16 years), patients were classified in 3 groups; Group 1: age equal or below 30 years (early onset); Group 2: age between 31 and 58 years, and Group 3: age equal or older than 59 years (late onset). We compared the initial clinical presentation, capillaroscopy pattern, immunological features, cumulative clinical manifestations and death rates between the three groups.

Results: One hundred and ninety five patients belonged to group 1, 651 to group 2 and 191 to group 3. Female distribution was similar between the three groups (91%, 86%, and 88%). Interestingly, time from disease onset to diagnosis was significantly higher in patients with early onset (group 1) (12±13, 5.8±6.7, and 2.4±3.6 years; p<0.001). Raynaud's phenomenon was the most frequent initial manifestation without differences between the three groups (88%, 84%, and 78%; p=0.134). Patients with early onset SSc had higher prevalence of myositis (11%, 7.2%, and 2.9%; p=0.009), esophageal involvement (72%, 67%, and 56%; p=0.004) and lower prevalence of centromeric antibodies (33%, 46%, and 47%; p=0.007). In contrast, patients with late onset SSc was characterized by lower prevalence of digital ulcers (54%, 41%, and 34%; p<0.001) but higher rates of heart conduction system alterations (8.7%, 13%, and 21%; p=0.004), and pulmonary hypertension (12%, 19%, and 25%; p=0.048). Mortality tended to be higher in late onset patients (9.7%, 15%, and 18%; p=0.053) and the Kaplan-Meier survival curves were significantly different (p<0.0001) for the three groups of patients.

Conclusion: Age at disease onset is associated with differences in clinical presentation and outcome in patients with SSc.

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The 15% Rule in Scleroderma: A Systematic Review of the Frequency of Organ Complications in Systemic Sclerosis. Chayawee Muangchan[1], Murray Baron[2], Janet E. Pope[3] and Canadian Scleroderma Research Group[4]. [1]Mahidol University, Siriraj Hospital, Bangkok, Thailand, [2]Jewish General Hospital, Montreal, QC, [3]St. Joseph Health Care London, London, ON, [4]Montreal, QC

Background/Purpose: The prevalence of each organ complication in scleroderma (SSc) varies by definition used. However, it is important to be aware of several complications that can be detected and treated. A simple rule of prevalence of organ complications in SSc can be helpful for clinicians. This study was done to determine the frequency of several SSc features including

organ involvement (lung, heart, digital ulcers {DU}, scleroderma renal crisis {SRC}, pulmonary arterial hypertensions {PAH}).

Methods: A comprehensive literature search of the Medline-OVID/ EMBASE, Pub Med, and Scopus databases from 1980 to November 30th, 2011 was conducted to identify relevant articles with at least 50 SSc patients. Search words were within organ systems such as lung, heart, pulmonary artery, kidney, digital ulcers, arthritis, myopathy and secondary Sjogren's. Study quality was assessed using the STROBE checklist. Prevalence of each organ complication was extracted from studies. Pooled prevalence and odds ratios (ORs) were calculated using the random effects method, and between-study heterogeneity was quantified using the I-squared statistic.

Results: 5916 articles were identified (913 from Embase, 1009 from PubMed and 3994 from Scopus). 5665 were excluded of which 4912 were irrelevant, 237 did not report organ prevalence, 183 were case reports, 193 were reviews, 111 had less than 50 patients,24 were not in English and 5 were not obtained; leaving 251 articles for full text review with 80 included in the meta-analysis. Where available, frequencies were also included from the Canadian Scleroderma Research Group (a database with more than 1000 SSc patients). There were no GI complications at a prevalence of 15% (GERD and dysphagia are far higher) and RP is nearly 100%. Xray ILD was common but significant restrictive ILD on PFTs occurred in approximately 15%.

SSc Feature	# of studies	# of patients total	Frequency	95% CI
Cardiac (CHF, low LEVF, pericarditis)	2	1024	15%	6–24%
Arrhythmia from SSc	11	15790	16%	13–18%
Diastolic dysfunction	5	15134	15%	14–16%
SRC in SSc	21	23103	3%	2–4%
SRC in dcSSc	6	2848	12%	5–19%
PAH by R heart catheter or echo	15	7426	14%	10–17%
PAH by R heart catheter	7	6571	14%	8–20%
ILD				
FVC<80%	5	1070	17%	13–22%
FVC<70%	4	2774	13%	10–16%
FVC<55%	3	1427	14%	7–21%
Myopathy	14	4419	13%	10–16%
Arthritis	7	19834	14%	11–16%
Digital ulcer prevalent	10	6895	17%	12–21%
Complications DU	4	1756	12%	8–16%
Sjogren's	5	2036	13%	11–16%

Conclusion: Many complications in SSc occur 15% of the time including low FVC, PAH, diastolic dysfunction, clinical and echo cardiac changes, arrhythmias, inflammatory arthritis, myopathy, Sjogren's and digital ulcers. 15% of digital ulcers have complications. SRC is uncommon but occurs in almost 15% of dcSSc. This is a helpful rule for frequency of organ involvement in SSc.

Disclosure: C. Muangchan, None; **M. Baron**, None; **J. E. Pope**, None;

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A Double-Blind Placebo-Controlled Crossover Trial of the Alpha-$_{2C}$ Adrenoceptor Antagonist Orm-12741 for Prevention of Cold-Induced Vasospasm in Patients with Systemic Sclerosis. Ariane Herrick[1], Andrea Murray[1], Angela Ruck[2], Juha Rouru[3], Tonia Moore[1], John Whiteside[2], Pasi Hakulinen[3], Fredrick M. Wigley[4] and Amir Snapir[3]. [1]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom, [2]Orion Pharma UK, Research & Development, Nottingham, United Kingdom, [3]Orion Corporation Orion Pharma, Turku, Finland, [4]Johns Hopkins University, Baltimore, MD

Background/Purpose: The alpha-$_{2C}$ adrenoceptor is thought to play a key role in mediating cold-induced vasospasm in the digits. A previous study suggested that in patients with systemic sclerosis (SSc), treatment with the alpha-$_{2C}$ adrenoceptor antagonist OPC-23826 improved recovery of finger skin perfusion following a cold challenge. Our primary purpose was to evaluate the efficacy of the high potency alpha-$_{2C}$adrenoceptor antagonist ORM-12741 in the attenuation of a cold-induced reduction in finger blood flow and temperature in patients with Raynaud's phenomenon secondary to SSc. Secondary objectives were to assess safety and tolerability.

Methods: This was a phase IIa, randomised, double-blind, crossover, single-dose placebo-controlled, single-centre study. Patients attended 5 times: screen, treatment visits 1–3 (each at least one week apart), and an end of study visit 1–2 weeks after the last treatment. At each treatment visit, each subject

after acclimatisation received a single oral dose of 30mg or 100mg of ORM-12741 or placebo. 30 minutes later s/he underwent a cold challenge (the hand was placed in a cold chamber cooled to −18°C until the finger temperature reached 12°C or until the subject could no longer tolerate the cold). Blood flow to the fingers was assessed by 3 methods (temperature by probe, laser Doppler imaging [LDI] and infrared thermography) performed before, during and after the cold challenge, until 70% of the drop in skin temperature had been recovered (but no longer than 45 minutes).

Results: 12 patients (10 female, mean age 58 years) were included. Recovery from cold challenge was faster after placebo treatment than with either dose of ORM-12741 as measured by temperature probe and LDI (Table 1). In 10 out of 12 subjects the area under the time-LDI curve was greater with placebo than with either ORM-12741 dose. Overall ORM-12741 was well tolerated. Headache was the most common adverse effect with 8 events (3 placebo, 5 active treatment) in 4 patients.

1. P= 0.045 versus placebo
2. P = 0.023 versus placebo

Table 1. Mean (standard deviation) blood flow results by the 3 different methods

	Placebo	ORM-12741 30mg	ORM-12741 100mg
Time to 70% temperature recovery (by probe) (minutes)	21.4 (12.4)	25.7 (12.2)	26.9 (13.9)
LDI (Area under the curve, right index finger) (arbitrary flux units × time)	20.5 (13.7)	11.2 (10.6)[1]	9.6 (7.0)[2]
Thermography (area under the curve) (°C × time)	288.4 (172.2)	280.0 (108.8)	305.8 (136.3)

Conclusion: ORM-12741 did not expedite recovery from a cold challenge in the fingers of patients with SSc.

Disclosure: A. Herrick, Orion Pharma, 5; **A. Murray**, None; **A. Ruck**, Orion Pharma, 3; **J. Rouru**, Orion Pharma, 3; **T. Moore**, None; **J. Whiteside**, Orion Pharma, 3; **P. Hakulinen**, Orion Pharma, 3; **F. M. Wigley**, Orion Pharma, 5; **A. Snapir**, Orion Pharma, 3.

1482

Laser Speckle Contrast Imaging May Help in the Differential Diagnosis of Raynaud's Phenomenon. Alessandra Della Rossa[1], Massimiliano Cazzato[1], Walter Bencivelli[1], Anna d'Ascanio[2], Marta Mosca[1] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy

Background/Purpose: to investigate blood flow and microvascular reactivity by laser speckle perfusion imager (Perimed, Jarfalla) in consecutive patients affected by Raynaud's phenomenon at baseline and following dynamic stimulations.

Methods: skin blood flow in the dorsum of the hand was measured at baseline and after cold test and post-occlusive hyperemia test in 56 consecutive subjects affected by Raynaud's phenomenon who attended the Rheumatology clinic of the university of Pisa between June 2011 and May 2012. 20 Healthy subjects (HS) were studied as controls. The protocol was approved by local ethic committee. All the subjects signed informed consent prior to the study. Statistical analysis was performed by ANOVA and logistic regression, both univariate and multivariate (SPSS). In view of the high number of comparisons inolved, Bonferroni correction was applied.

Results: Raynaud's subjects were divided into two cathegories: 20 primary Raynaud's phenomenon (PRP) defined according to LeRoy criteria and 36 Raynaud's secondary to Systemic sclerosis (SSc-RP). 28 SSc patients fulfilled American college of rheumatology criteria for diagnosis of SSc (4 diffuse cutaneous subset and 24 limited cutaneous subset) and 8 were classified according to very early diagnosis criteria for SSc (VEDOSS). After cold test SSc RP had a significant reduction of blood flow (−58%) as compared to HS (−19%) (p= 0.01). Time to rescue of the basal value was significantly higher in SSc-RP (58 minutes) as compared to HS (18 minutes) and PRP (19 minutes) (p=0.002). Peak flow after ischemic test was significant reduced in SSc-RP (+237%) and in HS (+258%) as compared to PRP (+485%) (p=0.03, p=0.008). Post-ischemic AUC flow showed a significant difference between SSc-RP (+79%) and PRP (+167%) (p=0.01). Patchy pattern of flux distribution was significantly different between HS (5%), PRP (20%), and SSc-RP (84%) (p< 0.0001). Differences between groups sorted out by univariate analysis were entered in a multivariate model

to outline items that independently discriminated between groups. Peak flow after ischemic test and patchy pattern of flux distribution independently discriminated between HS and PRP and SSc-RP.Within SSc patients, a significant difference in peak flow after ischemic test (543% vs 150% p=0.002), in the post-occlusive hyperemic response (158 vs 58 % p=0.005) and in duration of hyperemic response after ischemic test (711 seconds vs 171 seconds p=0.02) was shown between patients with very early SSc (VEDOSS) versus patients with definite SSc. No difference in the dynamic of microcirculation was noticed between diffuse and limited disease.

Conclusion: our preliminary results indicate a clearcut alteration in the dynamic of microcirculation in SSc-RP as compared to PRP and HS. Within SSc patients, early disease seem to have a different pattern of microvascular reactivity as compared to estabilished disease.

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1483

Predictors of Digital Ulcers in Systemic Sclerosis: Correlation Between Clinical and Hemodynamic Features, Capillaroscopy, Endothelium Dysfunction and Angiogenesis Biomarkers. Ivone Silva[1], Isabel Almeida[1], António Marinho[2] and Carlos Vasconcelos[3]. [1]Raynaud Clinics, Porto, Portugal, [2]Unidade de Imunologia Clínica, Porto, Portugal, [3]Hospital Geral Santo Antonio, Porto, Portugal

Background/Purpose: Digital Ulcers (DU) are a major disabling complication of Systemic Sclerosis (SSc) interfering with personal and professional life of our patients. The aim of our study was to analyze functional dysfunction of endothelium, capillaroscopy and angiogenesis biomarkers in patients with SSc, with or without peripheral microvascular complications, in order to try to predict the development of digital ulcers in these patients.

Methods: This is a prospective study of a cohort of Systemic Sclerosis (SSc) and primary Raynaud Phenomenon (RP) patients attending our Raynaud's Clinic (n= 108). Demographic and epidemiological data, autoimmune serological screening, inflammatory protein screening, Flow mediated dilation (FMD) and end diastolic volume (EDV), capillaroscopy, Endothelin-1 (ET-1), ADMA, VEGF and Endoglin were analyzed and compared to a control group (n=31). Statistical calculations were performed using SPSS (v 20.0). Comparison and distribution between groups were performed using Kruskal-Wallis test. The Mann-Witney test was used to compare continuous variables wit nominal variables. A p value ≤ 0.05 was considered significant.

Results: Flow mediated dilation (FMD) was reduced in patients with digital ulcers. The brachial artery diameter at 60 s after cuff deflation had statistical differences (P<0.001) between SSc patients with digital ulcers compared to SSc patients without DU or primary Raynaud phenomenon (RP). End diastolic volume was significantly different between groups (P<0.001) suggesting an increase in peripheral resistance in patients with DU. FMD was more reduced in patients with late pattern (Cutolo's classification) in capillaroscopy and a statistical differences (P<0.001) between early and late pattern (P<0.007) was found. Endothelin-1 and ADMA were increased in patients with DU (P<0.001) which might explain an excessive vasoconstrictor tone in these patients in association with occlusion of distal digital circulation (avascular areas incapillaroscopy) leading to the reduced FMD in patients with DU. VEGF was increased in SSc patients without DU, we found no difference with primary RP (P<0.168). A statistical differences (P<0.002) between patients with DU and SSc patients with no DU or with primary RP was found in VEGF. Endoglin was increased in patients with DU (p<0,001). Patients with Cutolo's late pattern in capillaroscopy had a increase in the angiostatic biomarker endoglin in comparison with the other groups (p<0,005).

Conclusion: In our cohort, we identified patients at risk of developing DUs: Ssc 70 positive, decreased FMD and low EDV, late pattern of Cutolo's classification, increased ET-1, ADMA and endoglin and a reduced VEGF. Microvascular lesions and an increase in the peripheral resistance associated to endothelial dysfunction and a impaired angiogenesis with an imbalance in favor of increased angiostatic biomarkers may be behind the underling mechanism of DU. These data may help us identify patients with high risk of developing digital ulcers and defining a correct target therapy at an early stage.

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1484

Investigating Determinants of Subjective and Objective Assessments of Peripheral Vascular Function in Primary Raynaud's Phenomenon and Systemic Sclerosis. John D. Pauling, Jacqueline A. Shipley, Nigel Harris and Neil McHugh. Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom

Background/Purpose: The Raynaud's condition score (RCS) diary is recommended for use in clinical trials of Raynaud's phenomenon (RP) and systemic sclerosis (SSc). We report the findings of a cross-sectional study exploring determinants of the RCS diary in patients with primary RP and SSc. We report associations between the RCS diary and objective assessment of digital vascular function using infrared thermography (IRT) and laser speckle contrast imaging (LSCI).

Methods: Patients with primary RP and SSc were recruited between December 2010 and February 2012. All patients underwent a standardized local cold challenge (15°C for 60s) with simultaneous assessment of digital vascular perfusion using IRT and LSCI. Patients with SSc completed a Scleroderma Health Assessment Questionnaire (SHAQ) and had disease characteristics documented. Baseline demographics and medication usage were recorded for all subjects. Patients received training on the completion of a 2-week RCS diary enabling calculation of the mean daily frequency, duration and impact (10-point RCS score) of RP attacks.

Results: Twenty-five patients with SSc and 18 patients with primary RP took part. Four (9.3%) patients failed to adequately complete the RCS diary. A similar number of patients were recruited between October-March (n=21) compared with April-September and the distribution of primary RP vs. SSc was similar in each group. There was a high correlation between individual components of the RCS diary (Spearman's Rho 0.62–0.78, p<0.001 for all comparisons). The RCS score was higher in patients taking vasodilator therapy (median 2.14 vs. 1.57, p=0.058). There was moderate correlation between the RCS and the HAQ-Disability Index (Rho 0.51, p=0.013). There was moderate to high correlation between components of the RCS diary and the SHAQ RP Visual Analogue Scale (VAS, Rho 0.54–0.83, p<0.05). There were no associations between RCS diary endpoints and a history of digital ulceration (DU) or the SHAQ DU VAS (Rho 0.26–0.46) in patients with SSc. The daily frequency of RP attacks was significantly higher in females (median 1.93 vs. 0.82, p=0.031). The RCS score was significantly higher in October-March compared with April-September (median 2.29 vs.1.57, p=0.024). There were moderate to high correlations between IRT and LSCI (Spearman's Rho 0.577–0.837, p<0.01 for all comparisons). There was no correlation between individual components of the RCS diary and objective non-invasive microvascular imaging, using either IRT or LSCI. Perfusion of the digits was significantly lower in females for all IRT assessments and the majority of assessments using LSCI. Temperature of the palmer aspect of the digits was higher during April-September (p<0.05). LSCI and IRT assessment of perfusion at other regions of the fingers was not influenced by season.

Conclusion: Subjective and objective assessment tools provide differing information on digital vascular function and impact of disease in RP and SSc. This is the first study to demonstrate the influence of gender and seasonal variation on both patient self-report and objective non-invasive microvascular imaging assessment of RP. These findings must be considered when using such tools as outcome measures in clinical trials of RP and SSc.

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1485

Patients with Very Early Diagnosis of Systemic Sclerosis (VEDOSS) Present Esophageal and Anorectal Involvement: Data From a Single Centre. Gemma Lepri[1], Silvia Bellando-Randone[2]. Serena Guiducci[1], Iacopo Giani[3], Cosimo Bruni[1], Giulia Carnesecchi[4], Jelena Blagojevic[2], Alessandra Radicati[2], Filippo Pucciani[5] and Marco Matucci Cerinic[1], [1]Department of Biomedicine, Division of Rheumatology AOUC, Excellence Centre for Research, Florence, Italy, [2]University of Florence, Florence, Italy, [3]General Surgery, ASL 8, Arezzo, Italy, Arezzo, Italy, [4]Department of Internal Medicine, Rheumatology Section, University of Florence, Florence, Italy, [5]General and Urgency Surgery, University of Florence, Florence, Italy, Florence, Italy

Background/Purpose: Systemic Sclerosis (SSc) affects gastrointestinal tract in more than 80% of patients. Esophageal involvement is the most common manifestation with a prevalence ranging between 50–90%, followed by anorectal involvement (prevalence of 50–70%) that had a high impact on

patients quality of life. Objectives of the study: evaluation of esophageal and anorectal involvement and of their correlations in very early SSc patients.

Methods: 56 VEDOSS patients (55 females), mean age 49,2 ± 14, were evaluated with esophageal and anorectal manometry. The demographic data, esophageal and anorectal symptoms (dysphagia, typical GERD symptoms and fecal incontinence and constipation), Raynaud phenomenon (presence/absence, duration) autoantibodies profile (anticentromere antibodies [ACA], antinuclear antibodies [ANA], anti-Scl70 [Scl70]), videocapillaroscopy patterns (Normal, Early, Active, Late), puffy fingers, digital ulcers were recorded for all patients.

Results: Esophageal body dysmotility (absence of peristalsis or abnormal mean pressure of peristalsis) was present in 49 patients (94,2%) and it was associated with an hypotensive lower esophageal sphincter (LES) in 26 (53,1%). Anorectal manometry was abnormal in 85% of patients and in all these patients an esophageal involvement was found (absence of peristalsis in 29% of patients and an abnormal peristalsis in 67,7% of patients). Esophageal symptoms were present in 26 patients (50%). 22 patients (42,3%) showed puffy fingers that were associated with a smaller area of LES (p-value: 0,011). Only five patients (12,5%) complained anorectal symptoms. In 4 patients esophageal manometry was not performed because of scarce tolerance of the procedure and in 16 patients anorectal manometry was not performed for the same reason.

Conclusion: In VEDOSS patients esophageal and anorectal disorders are frequently detected even in asymptomatic patients. Our data showed that VEDOSS is characterized by simultaneous esophageal and anorectal involvement. Esophageal disorders seem to correlate with the presence of puffy fingers.

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1486

Poor Outcome in Patients with Systemic Sclerosis and Myocardial Involvement: A Combined Approach Based On Clinical and Laboratory Findings, EKG-Holter and Cardiac Magnetic Resonance. Silvia Laura Bosello, Giacomo De Luca, Antonella Laria, Giorgia Berardi and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: Cardiac involvement is a relevant prognostic determinant in Systemic Sclerosis (SSc), but the diagnosis is often delayed due to the lack of a specific diagnostic algorithm. Objective of the present study is to define the role of a combined approach, based on evaluation of clinical symptoms, laboratory findings, EKG-holter and cardiac magnetic resonance (CMR), to characterize cardiac involvement in SSc-patients.

Methods: Twenty-five SSc-patients with symptoms of cardiac involvement (dyspnea, palpitation) or signs of cardiac failure and elevation of cardiac enzymes (MB-CK and/or troponin T) underwent EKG-holter and cardiac magnetic resonance (CMR). Median follow-up was 24±0.2 months.

Results: Major EKG-holter modifications were present in 45% of patients. CMR study demonstrated T2 hyperintensity in 2 patients while none of the patients presented early gadolinium enhancement and 16 (64.0%) patients presented late gadolinium enhancement (LGE). We identified 3 different patterns of distribution of LGE: subepicardial, midwall and subedocardial. Sixteen (64.0%) patients presented almost one pattern of distribution, while 9 patients presented more than one: 81.3% of patients presented a midwall distribution of LGE, 50% of patients presented a subepicardial LGE with a linear distribution pattern and 37.5% presented a subendocardial LGE distribution. 28% of patients showed hypokinetic area and only one patient an akinetic area. The ejection fraction (EF), corrected for the age, was decreased in 7 patients (28%). The mean EF of left ventricle was 60.2±11.1%, and of right ventricle was 55.1±10.2%. Hypokinetic and akinetic area corresponded with the LGE area. The subepicardial distribution pattern was more frequent in patients with an early disease, while patients with diffuse skin involvement presented more frequently with the subendocardial pattern. This latest distribution pattern was also associated with a reduction of EF and with major-EKG abnormalities. The extension of LGE on CMR was evaluated according to a standardized left-ventricular segmentation (Cerqueira et al; Circulation 2002, 105:539–542). Patients with major abnormalities on EKG-holter presented a higher number of myocardial segments involved on CMR (4.8±2.3) with respect to the patients without EKG-abnormalities(2.7±0.9) (p=0.041). A weak correlation was found between NYHA-dyspnea class and the number of involved myocardial segments on CMR (R=0.5, p=0.02). After a mean follow-up of 24±0.2 months, 4

patients(16%) died for arrhythmias or heart failure. All patients who died at follow-up had severe dyspnea, elevated cardiac enzymes, myosytis, major EKG-holter abnormalities, reduction of EF and LGE on CMR at baseline; 75% of patients who died had a subendocardial distribution pattern of LGE on CMR.

Conclusion: Our study suggests that a combined approach, based on clinical presentation, laboratory findings, EKG-holter examination and study of distribution of LGE on CMR, is useful to characterize the extension of myocardial damage and to identify patients with a poor outcome related to heart involvement in SSc.

Disclosure: **S. L. Bosello**, None; **G. De Luca**, None; **A. Laria**, None; **G. Berardi**, None; **G. Ferraccioli**, None.

1487

Incidence of Fibromyalgia Syndrome in Systemic Sclerosis and Rheumatoid Arthritis. Comparative Results According to Clinical Diagnosis, Screening Test with Fibromyalgia Rapid Screening Tool, Diagnosis with ACR1990 and ACR 2010 Criteria. Serge Perrot[1], Mariana Peixoto[2], Philippe Dieude[3], Eric Hachulla[4], Sébastien Ottaviani[5] and Yannick Allanore[6]. [1]Hopital Hotel Dieu, Paris, France, [2]Cochin Hospital, Paris, France, [3]APHP, Hopital Bichat, Paris, France, [4]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [5]APHP, Paris, France, [6]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France

Background/Purpose: Fibromyalgia (FMS) is a chronic widespread pain condition that may be associated with inflammatory chronic disorders like rheumatoid arthritis (RA) and systemic sclerosis (SSc). In these latter, it is important to detect associated FMS since it may interfere with disease specific assessment. Moreover, in some studies, associated FMS could be related with the occurence of Secondary Sjogren's Syndrome (SSS). FMS diagnosis is frequently established by clinical analysis, although there are newly validated screening tools (Fibromyalgia Rapid Screening Tool (FiRST)) and diagnostic criteria (ACR 2010 criteria) that may confirm clinical impression.

The aims of the study was i) to estimate the incidence rate of FMS in RA and SSc, ii) to compare these rates according to clinical diagnosis, screening tool (FiRST), diagnostic criteria (ACR 1990 and 2010), iii) to test if FMS was associated with the occurrence of SSS.

Methods: Consecutive adult patients with confirmed RA or SSc (international classification criteria), visiting 4 university hospitals were included. Demographic characteristics were collected and FMS diagnosis was established by several consecutive methods: (i) FMS clinical impression, (ii) FMS screening by FiRST questionnaire, (iii) FMS diagnosis by ACR 1990 classification criteria and ACR 2010 diagnostic criteria. Cohen's Kappa correlation coefficient (K) was calculated for inter-agreement between diagnostic tools.

Results: In total, 274 patients were recruited: FMS was diagnosed (ACR2010) in 22.4% of the cases, without significant difference between RA and SSc (p=0.11). In global and each group, FMS occurrence was not associated with a SSS.

-In the RA group, 172 patients (12.2 % men, 54.4 ± 15.11 years old) were recruited.

FMS clinical diagnosis was proposed in 32.5%, detected by the FiRST in 22.6%, confirmed with ACR 1990 criteria in 22.1% and with ACR 2010 criteria in 19.1% of the RA patients.

In RA, considering ACR 2010 criteria as the current gold standard, K was: 0.66 with clinical diagnosis, 0.47 with FiRST and 0.41 with ACR 1990 classification criteria.

-In the SSc group, 122 patients (13.9% men, 58.2 ± 12.1 years old) were recruited: 54 with limited SSc and 66 with diffuse SSc. Clinical diagnosis of FMS was proposed in 39.3%, detected by the FiRST in 27.9%, confirmed with ACR 1990 criteria in 30.3% and with ACR 2010 criteria in 27.0% of the SSc patients.

In SSc, considering ACR 2010 criteria as the gold standard, K was 0.64 with clinical diagnosis, 0.63 with FiRST questionnaire, 0.50 with ACR 1990 classification criteria.

Conclusion: Our results reveal an unknown high prevalence of SSc associated FMS, which will need to be taken into account in the assessment of the patients who often report a heavy burden of pain. Both in SSc and RA, occurrence of FMS is not related to SSS. In both groups, there was a good correlation between FiRST and ACR FMS 2010 criteria. FiRST may represent a simple method to detect FMS in various rheumatological conditions. Further studies are needed to analyze FMS association with specific RA and SSc phenotypes.

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Prevalence and Risk Factors of Low Bone Mineral Density in Chinese Patients with Systemic Sclerosis: A Case-Control Study. Chi Chiu Mok, Pak To Chan, Kar Li Chan, Ling Yin Ho and Chi Hung To. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To study the prevalence and risk factors of low bone mineral density (BMD) in patients with systemic sclerosis (SSc).

Methods: Consecutive patients who fulfilled the ACR criteria for SSc were screened for BMD and BC (fat and lean mass) by DXA scan. An equal number of age and gender matched healthy controls were also recruited for the same measurements. Data on risk factors for osteoporosis were also compared between patients and controls. In SSc patients, the extent of skin involvement was assessed by the modified Rodnan skin score (mRSS) and organ damage was evaluated by the Medsger SSc severity index. Risk factors for low BMD in SSc patients were studied by linear regression analyses.

Results: 84 patients with SSc were studied (89% women; age 49.4 ± 11.3 years; disease duration 7.8 ± 6.4 years). Eighteen (21%) patients had diffuse cutaneous SSc while the other 66 (79%) patients had limited cutaneous SSc according to the LeRoy classification. Nineteen(23%) SSc patients had been treated with glucocorticoids. The mean$\pm$SD and median (IQR) mRSS score of the SSc patients was 11.2 ± 9.8 (range 0–40) and 8 (IQR 4–14), respectively. The highest mean Medsger severity score was observed for involvement of skin (1.33 ± 0.83), followed by joint/tendon (0.89 ± 1.44), peripheral vascular system (0.86 ± 1.00), lung (0.68 ± 1.04), heart (0.23 ± 0.68) and the kidney (0.14 ± 0.60). Four (5%) SSc patients required aids for walking and 4(5%) other patients were chair-bound. Except for significantly lower body mass index (BMI) and body weight in SSc patients, the frequency of osteoporosis risk factors was similar to that of controls. The BMD of the lumbar spine, total hip, femoral neck and whole body was significantly lower in SSc patients than controls after adjustment for age, sex, BMI and menopausal status. Fourteen (17%) patients with SSc had low BMD of the lumbar spine expected for their age (Z score < -2.0) and 5 (6%) patients had a total hip Z score of < -2.0. Osteopenia of the lumbar spine, total hip and femoral neck, defined as a Z score of between -1.0 and -2.0, occurred in 37%, 45% and 40% of the SSc patients, respectively. Four (7%) patients reported a personal history of fracture (all non-vertebral; two arose from low impact injury). The proportion of patients with osteopenia of the hip, femoral neck and lumbar spine was significantly higher in SSc patients than controls. Linear regression analyses revealed that increasing age was an independent risk factor for lower BMD in all sites. Low BMI was independently associated with low BMD of the total hip and femoral neck, whereas menopause was an independent associated factor of low BMD at the lumbar spine. Other covariates such as the subtype of SSc (diffuse vs limited SSc), parity, smoking, drinking, female sex, disease duration, menopause, ever use of glucocorticoids and family history of fractures were not significantly associated with lower BMD at these sites. The skin score and disease severity scores in any organs were not significantly associated with the BMD values.

Conclusion: BMD of the spine and hip is significantly lower in SSc patients than healthy subjects, which is independent of age, sex, menopause, low BMI and altered body composition.

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Peripheral Neuropathy: A Complication of Systemic Sclerosis. Melissa Reily[1], Tracy M. Frech[2], Maureen Murtaugh[2], Jason Penrod[3] and Barry M. Stults[4]. [1]University of Utah, Salt Lake City, UT, [2]University of Utah School of Medicine, SLC, UT, [3]University of Utah, Salt Lake City, [4]Salt Lake City Veterans Affairs Medical Center and University of Utah, Salt Lake City, UT

Background/Purpose: We performed bedside testing for peripheral neuropathy in our Systemic Sclerosis (SSc) population to determine whether foot care guidelines should be developed for SSc.

Methods: Twenty consecutive SSc patients and 20 healthy control patients were evaluated for peripheral neuropathy in both feet using the 10-g Semmes-Weinstein monofilament examination [SWME] three times on four sites bilaterally and vibration sensation using the on-off method on the dorsum of the 1st toe just below the nail with 128-Hz tuning fork eight times. Independent blinded evaluations were performed on each subject by two investigators who had completed a training session to standardize each exam. Abnormal SWME testing was defined as at least one pedal site failing three monofilament assessments twice. Abnormal vibratory sensation was defined

as inability to determine pressure from vibration, or as having 5 of 8 tests abnormal on the on-off methodology. Statistics were performed on SAS 9.3. We examined the inter-rater variability using Cohen's Kappa. We compared SWME and vibratory sensation in SSc to healthy controls using Fischer's exact. T-test was used look at duration of disease and modified Rodnan skin score (mRSS) for those with abnormal SWME and vibratory sensation.

Results: Mean age was 56.2 years for the SSc population and 49.4 years for the healthy control population (p: 0.7). Disease distribution included 8 diffuse and 12 limited cutaneous SSc patients. Two of 20 SSc patients reported sensory foot symptoms consistent with peripheral neuropathy, prior to the examination. Inter-rater agreement of SWME and vibration sensation was strong (kappa: 0.72 and 0.83, respectively). Two healthy controls and 12 SSc patients demonstrated abnormal vibration sense (one-sided Fishers' exact, $p < 0.002$). No healthy controls and 4 of the SSc had abnormal monofilament exam (one-sided Fishers exact, $p = 0.053$). The mRSS and duration of SSc did not differ between those with peripheral neuropathy as those without as diagnosed by these modalities (p: 0.07).

Conclusion: Patients with SSc have a high prevalence of pedal peripheral neuropathy, which may be asymptomatic and place them at risk for neuropathic complications. Similar to persons with diabetes, SSc patients should be screened annually for peripheral neuropathy. Those with significant abnormalities should be referred for routine podiatry care.

Disclosure: M. Reily, None; **T. M. Frech**, None; **M. Murtaugh**, None; **J. Penrod**, None; **B. M. Stults**, None.

ACR/ARHP Poster Session B
Systemic Sclerosis, Fibrosing Syndromes and
Raynaud's – Pathogenesis, Animal Models and Genetics
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Dysregulation of Angiogenic Homeostasis in Systemic Sclerosis. Naglaa Y. Assaf[1], Hanan M. Farouk[2] and Iman M. Aly[1]. [1]Faculty of Medicine, Ain-Shams University, Cairo, Egypt, [2]Ain-Shams University, Cairo, Egypt

Background/Purpose: systemic sclerosis (SSc) is a connective tissue disorder characterized by tissue hypoxia and excessive fibrosis of skin and internal organs. The present study was planned to evaluate the possible role of angiogenesis imbalance in the pathogenesis of SSc.

Methods: 25 SSc patients, 20 age and sex matched healthy controls were included. Assay of serum vascular endothelial growth factor (VEGF) and endostatin was done for all patients and controls using ELISA. Patients were subjected to modified Rodnan skin score (mRss), pulmonary function tests (PFTS), and skin biopsies for histopathological skin thickness score assessment.

Results: There was significant increase in the mean levels of serum VEGF and endostatin in SSc patients compared to controls (t=4.07, p<0.001), mean values of serum endostatin is significantly increased in late compared to early stage of disease (t=6.65, p<0.01). A significant positive correlation was found between serum levels of endostatin, mRss and histopathological skin thickness score (r=0.99, 0.94 respectively p<0.01). SSc patients with ischemic manifestations had significantly higher levels of serum endostatin compared to those without ischemic manifestations (t=6.27, p<0.001). SSc patients with restricted PFTS had significantly higher levels of serum endostatin compared to those without pulmonary affection (t=4.3, p<0.001).

Conclusion: Angiogenic inhibitor (endostatin) is induced and outweighs angiogenic inducer (VEGF) in late stage of SSc. Increased serum endostatin is associated with skin sclerosis severity and pulmonary fibrosis and favors SSc disease progression.

Disclosure: N. Y. Assaf, None; **H. M. Farouk**, None; **I. M. Aly**, None.

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Systemic Sclerosis – Effects of Agonistic Autoantibodies Directed Against the Angiotensin Receptor Type 1 and the Endothelin Receptor Type A On Effector Cells. Jeannine Guenther[1], Angela Kill[2], Mike O. Becker[3] and Gabriela Riemekasten[4]. [1]Charite University Hosptial, Berlin, Germany, [2]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [3]Charité University Hospital, Berlin, Germany, [4]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany

Background/Purpose: Autoimmunity, vasculopathy and fibrosis are features of systemic sclerosis (SSc). The functional link between these three pathophysiological components is still missing. Research suggests an involvement of endothelin-1 and angiotensin II, and of the activation of their receptors by the natural ligands as well as by agonistic autoantibodies against these receptors in SSc–associated vasculopathy and fibrosis [1]. Autoantibodies against the angiotensin receptor type 1 (AT1R) and the endothelin receptor type A (ETAR) are present in the majority of SSc patients and high levels of the antibodies are associated with severe organ manifestations [1]. AT1R and ETAR are expressed in various cell types such as endothelial cells, fibroblasts, as well as cells of the adaptive and innate immune system. The aim of the present study was to identify the effects of these antibodies on those effector cells and establish a link to SSc pathogenesis.

Methods: Human microvascular endothelial cells, fibroblast, and peripheral blood mononuclear cells (PBMCs) from healthy donors were stimulated in vitro by affinity-purified IgG from sera of SSc patients containing anti-AT1R and anti-ETAR antibodies as well as by affinity-purified IgG from sera of healthy donors. Effects of the antibodies were measured by ELISA, migration assay, and PCR. To To prove that the IgG effects are specifically due to AT1R and ETAR activation, specific receptor blockers were used. Cytokine expression was correlated with clinical data from the IgG donors.

Results: In endothelial cells, anti-AT1R and anti-ETAR ab induced adhesion molecules and IL-8 expression as well as further pro-fibrotic and inflammatory cytokines. IL-8 levels in the supernatants correlated with the antibody levels in the IgG fractions. In fibroblasts, collagen-I expression was induced. At a molecular level, c-Jun expression, known to play a role in SSc, was upregulated. The antibodies increased the migration of neutrophils as well as of PBMC. Stimulation of PBMCs by IgG from SSc patients resulted in a significantly increased expression and secretion of IL-8 and, in most cultures, of CCL18 compared to the stimulation by IgG of healthy donors. All the effects were significantly reduced or completely blocked by commercial AT1R and ETAR antagonists. Correlation analyses with clinical data of the SSc IgG donors revealed correlations between cytokine expression, induced by the antibodies, and clinical findings.

Conclusion: As shown in vitro, anti-AT1R and anti-ETAR antibodies exhibit effects on inflammation, immune regulation, migration of cells, and on fibrosis. Based on the broad expression of the receptors on various effector cell types, the antibodies may link the adaptive and innate immune system as well as resident cells in order to produce the typical features vasculopathy, fibrosis, and autoimmunity.

Reference

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Disclosure: **J. Guenther**, None; **A. Kill**, None; **M. O. Becker**, None; **G. Riemekasten**, CellTrend, 7.

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IL-13 Receptors and Signaling in the Dermal Fibroblasts From Patients with Systemic Sclerosis.
Yuko Ota[1], Yasushi Kawaguchi[1], Atsushi Kitani[2], Kae Takagi[1], Hisae Ichida[1], Yasuhiro Katsumata[1], Takahisa Gono[1], Masanori Hanaoka[1], Yuko Okamoto[1] and Hisashi Yamanaka[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Mucosal Immunity Section, NIAID/NIH, Bethesda, MD

Background/Purpose: Interleukin (IL)-13 is a pleiotropic cytokine involved in T helper type 2 cell immune response and in the development of fibrotic conditions such as liver cirrhosis, and pulmonary fibrosis and also implicated in systemic sclerosis (SSc). Although elevated serum levels of IL-13 has been reported in SSc and recently CD8 T cells was found as a producing subset of IL-13, IL-13 effect of effector phase in the skin fibroblasts has not been well characterized in SSc. The aim of the present study was to investigate the fibrotic effects of IL-13 on the collagen production by skin fibroblasts from patients with SSc. We also evaluated the signal transduction of IL-13 in the cultured skin fibroblasts.

Methods: We examined the expression of IL-13Rα1 and IL-13Rα2 on skin fibroblasts by flow cytometry and Western blot analyses. Skin fibroblasts from patients with diffuse cutaneous SSc were cultured with indicated concentrations of IL-13 and TNFα for various periods. Procollagen type I C-peptide and TGF-β1 levels were then measured using commercial ELISA kits. mRNA expression of COlA1, ColA2, TGF-b1, CTGF were also measured by standard real-time qPCR. The phosphorylation of STAT6 and various MAPK and Akt pathways have been evaluated by Phospho-Kinase Arrays. Various specific inhibitors for STAT6-mediated pathways, U0126 (Erk1/2 inhibitor), LY294002 (PI3K inhibitor), JAK inhibitor, and Tyk inhibitor (RO495) were used for evaluation of IL-13-mediated signaling.

Results: With the flow cytometric analysis, we revealed the expression of IL-13Ra2, but did't detect IL-13 Ra1 with confirmation of the same Ra1 mAb detecting neutrophil expression of IL-13 Ra1. We also found that IL-13Rα2 expression was increased by TNF-α stimulation (13% vs 20%). On the contrary, Western blot analysis revealed both expression of IL-13 Ra1 and Ra2. With IL-13 stimulation, the phosphorylation of STAT6 and Akt was induced, and IL-13 plus Jak/Tyk inhibitor(s) suppressed the phosphorylation of STAT6, suggesting IL-13Rα1 was functional, though flow cytometry pattern does not show positive. Treatment with U0126 (Erk1/2 inhibitor) or LY294002 (PI3K inhibitor) did not suppress the phosphorylation of STAT6. We observed IL-13 increased collagen production in 72 hours (p = 0.009) compared to no stimuli. On the contrary, TNF-a decreased COLA1, COL A2, and CTGF mRNA compared to no stimuli.

Conclusion: Our results suggest that IL-13 may be a potent stimulator of collagen production in skin fibroblast derived from patients with SSc and IL-13 signaling pathway would be a potential target for the new treatment of SSc. TNF-a may have inhibitory effect on fibrotic development and the use of TNF blocking biological reagents in SSc would not be recommended in SSc.

Disclosure: **Y. Ota**, None; **Y. Kawaguchi**, None; **A. Kitani**, None; **K. Takagi**, None; **H. Ichida**, None; **Y. Katsumata**, None; **T. Gono**, None; **M. Hanaoka**, None; **Y. Okamoto**, None; **H. Yamanaka**, None.

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Transforming Growth Factor-β and Endothelin-1 Induce Endothelial-to-Mesenchymal Transition in Cultured Human Endothelial Cells.
Stefano Soldano[1], Paola Montagna[1], Renata Brizzolara[1], Barbara Villaggio[2], Alberto Sulli[1] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, Genova, Italy, [2]Research Laboratory of Nephrology, Department of Internal Medicine, University of Genova, Genova, Italy

Background/Purpose: The endothelial/microvascular injury and the myofibroblast activation are crucial events that seem to contribute to the development of fibrosis in connective tissue diseases such as systemic sclerosis (SSc), which is characterized by increased local transforming growth factor-β (TGF-β) and endothelin-1 (ET-1) levels (1,2). Recently it was shown that myofibroblast activation from altered microvasculature may arise through the transition of endothelial to mesenchymal cells (EndoMT), thus expressing α-smooth muscle actin (α-SMA), vimentin and fibrillar collagens (3).

To investigate the possible involvement of TGF-β and ET-1 in the early step of EndoMT in cultures of human endothelial cells.

Methods: Human umbilical vein endothelial cells (HUVEC) were cultured in collagen-coated dishes with EGM-2 medium and used between the third and fifth passages. The cells were treated with ET-1 (100 nM) or TGF-β (10 ng/ml) for 1, 3 and 6 days. Untreated endothelial cells were used as controls (cnt). Cell proliferation was evaluated by methyl-tetrazolium salt test (MTT) after 1 day. The expression of α-SMA as marker of myofibroblast phenotype, and platelet endothelial cell adhesion molecule (PECAM-1 or CD31), as marker of endothelial phenotype, was evaluated after 3 and 6 days of treatment by immunofluorescence (IF) and western blot analysis (WB) according to recent evidences (4). Data were obtained by eight different experiments and statistical analysis was carried out by a non-parametric Friedman test.

Results: After 6 days of treatment, TGF-β induced the α-SMA expression in cultured human endothelial cells, which maintain their capability to express CD31.

Interestingly, also ET-1 was able to stimulate the endothelial cells to express α-SMA after 6 days of treatment. The data were obtained by IF and confirmed by WB analysis.

In addition, MTT test showed that both TGF-β and ET-1 induced a statistically significant increase of proliferation of human endothelial cells vs. cnt (p<0.001).

Conclusion: These preliminary results show that both ET-1 and TGF-β seem to share similar effects in inducing the α-SMA expression and cell proliferation in human endothelial cells thus supporting a possible direct involvement in promoting the transition from endothelial to myofibroblast phenotype (2, 4–6). The implications in the fibrotic process that characterize SSc are matter of further evaluations.

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Disclosure: S. Soldano, None; **P. Montagna**, None; **R. Brizzolara**, None; **B. Villaggio**, None; **A. Sulli**, None; **M. Cutolo**, None.

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CD40 Signaling Results in Microvascular Endothelial Dysfunction: A Possible Clue to the Pathogenesis of Scleroderma Vasculopathy. Bashar Kahaleh and Yongqing Wang. University of Toledo, Toledo, OH

Background/Purpose: Increased expression of CD40 in SSc- Microvascular Endothelial Cells (MVEC) was noted on a gene expression array and increased concentrations of soluble CD40 ligand (sCD40L) was reported in scleroderma. In this study we investigated the effect of CD40 ligation on MVEC apoptosis, activation and dysfunction.

Methods: MVEC were isolated from involved SSc skin and from matched healthy control subjects. MVEC apoptosis was assessed by flow cytometry, caspases3/7 activity and cell viability. MVEC genes expression was determined by real-time-PCR and results were confirmed by western blot analysis. Endothelial permeability was assessed by FITC-Dextran permeability assay.

Results: Significant increase in CD40 expression of was noted in SSc-MVEC (3.2 folds $\pm$ 0.3 in SSc vs. control MVEC). Similar increase in expression level was noted in SS skin biopsies (2.4 folds $\pm$ 0.3 in SSc skin vs. control skin biopsies, n=3 each).

The addition of CD40 ligand to MVEC resulted in the following observations:

1. Reduction in nitric oxide synthase (*NOS3*) expression (80%$\pm$6 reduction in control-MVEC and 82%$\pm$ 8 in SSc-MVEC, mean 4 cell lines $\pm$SD) and in prostacyclin synthase (*PTGS1*), 64% $\pm$ 3.0 reduction in control-MVEC and 79% $\pm$ 4.5 reduction in SSc-MVEC, mean 4 cell lines $\pm$SD). While Endothelin 1 expression was significantly increased by 2.2$\pm$ 0.12 folds in control MVEC and by 2.8 $\pm$0.31 folds in SSc MVEC.
2. Increase EC *p*ermeability (2.2$\pm$ 0.3 in control-MVEC and 2.8 $\pm$ 0.34 in SSc-MVEC, folds$\pm$SD)
3. Significant Increase expression of the CC and CXC chemokines including CCL2, interleukin-8, CXCL3, 5, 6 and 9.
4. Increase expression of IL1B, hepatocyte growth factor and adhesion molecules particularly ICAM1.
5. Significant down regulation of c-fos induced growth factor (FGIF, vascular endothelial growth factor D), epidermal growth factor, Insulin-like growth factor 1 and metallopeptidase inhibitor TIMP2.
6. The addition of CD40L to MVEC cultured in 0.5% serum resulted in a dose dependent apoptosis of MVEC. SSc-MVEC were more susceptible to apoptosis than control MVEC, thus at 10 μg concentration of CD40L, MVEC apoptosis was 45% $\pm$ 5 and 20% $\pm$ 3 in SSc vs. control MVEC respectively (mean $\pm$ SD of 4 cell lines). Apoptosis was confirmed by increase caspase 3/7 activity 2.2 folds in control and 3.0 folds in SSc-MVEC.

Conclusion: The study demonstrates increase expression of CD40 in SSc skin and in SSc-MVEC. CD40 ligation led to reduce expression of vasodilatory and increase expression of vasoconstrictive genes. Moreover, addition of CD40L increased endothelial permeability and the acquisition of an activated/dysfunctional phenotype in association with increase MVEC apoptosis. In all instances, SSc MVEC were more *susceptible* to CD40 signaling effects than control MVEC. The results suggest that the blockade of CD40/CD40 ligand interaction could be an effective therapeutic strategy in SSc.

Disclosure: B. Kahaleh, None; **Y. Wang**, None.

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Platelet Aggregability, Eicosanoid Biosynthesis and Oxidative Stress in Primary Raynaud's Phenomenon and Systemic Sclerosis. John D. Pauling and Neil McHugh. Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom

Background/Purpose: Increased platelet activation, endothelial dysfunction and oxidative stress are all thought to contribute to the pathogenesis of Raynaud's phenomenon (RP), particularly in the context of systemic sclerosis (SSc). We report the findings of a cross-sectional study evaluating platelet function, endothelial production of prostacyclin and a novel biomarker of oxidative stress in patients with primary RP and SSc.

Methods: Patients with primary RP and SSc who were not taking anti-platelet or non-steroidal anti-inflammatory drugs were included in the study. All patients had their disease characteristics and medication use documented. Platelet number and structure (mean platelet volume, platelet distribution width and plateletcrit) were assessed using automated haematology analysis. Platelet function was assessed using light transmission aggregometry (maximum % aggregation over 5 minutes and maximum gradient of aggregation) to adenosine diphosphate (ADP, 1.25–10μl/L) and arachidonic acid (AA, 0.82–1.64mmol/L). Fasting levels of the major urinary metabolite of thromboxane (11-dehydro-TxB2), prostacyclin (2,3-dinor-6-keto-PGF1α) and non-enzymatic markers of lipid peroxidation and oxidative stress (F2-isoprostanes) were assessed using Gas Chromatography/Mass Spectrometry (GC/MS) analysis.

Results: Seventeen patients with primary RP and 17 with systemic sclerosis were recruited to the study. Age, gender, smoking status and use of vasodilator therapy were similar in each group (p>0.05). Platelet number and structure did not differ between groups. Maximum % aggregation to low concentration ADP (0.125–0.5μl/L) was significantly greater in SSc compared to primary RP (p<0.05 for all comparisons). Percent aggregation to high concentration ADP (10μl/L) and AA (1.64 and 0.82mmol/L) did not differ between groups, possibly representing a ceiling effect. The maximum gradient of aggregation was significantly greater for 1.64mmol/L AA in SSc compared with primary RP. Urinary metabolites of thromboxane (medians 425 vs. 382 pg/mg creatinine [Cr]), prostacyclin (160 vs. 122 pg/mg Cr) and F2-isoprostanes (1.00 vs. 1.12 ng/ml Cr) did not differ between SSc and primary RP (p>0.05 for all comparisons). There were moderate correlations between urinary 11-dehydro-TxB2 and both 2,3-dinor-6-keto-PGF1α and F2-isoprostanes (Spearman's Rho 0.537 and 0.612 respectively, p≤0.001). A history of digital ulceration was associated with increased aggregation to 5μl/L ADP in SSc. There were no associations between disease characteristics and eicosanoid biosynthesis in SSc.

Conclusion: This pilot study has identified increased *ex vivo* platelet reactivity in SSc compared with primary RP. *In vivo* lipid biomarkers of platelet activation, endothelial function and oxidative stress did not differ between groups. Biosynthesis of thromboxane (a potent vasoconstrictor) is associated with increased oxidative stress and increased synthesis of prostacyclin (a potent vasodilator) in RP. Additional work evaluating the clinical associations of platelet function and eicosanoid biosynthesis in a larger cohort of patients with primary RP and SSc may help guide the use of anti-platelet therapy in these patient groups.

Disclosure: J. D. Pauling, None; **N. McHugh**, None.

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Downregulated Expression of Metallothionein Genes in Response to the Gadolinium Contrast Agent Omniscan in Normal Human Differentiated Macrophages and Dermal Fibroblasts. Peter J. Wermuth[1], Francesco Del Galdo[2], Sankar Addya[3], Paolo Fortina[3] and Sergio A. Jimenez[1]. [1]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center,Thomas Jefferson University, Philadelphia, PA, [2]University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [3]Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background/Purpose: Metallothioneins bind heavy metals with high affinity and can serve as storage proteins for labile Zn^{2+} which in turn can regulate immune system activity through interactions with Toll-like receptor (TLR) signal transduction. Nephrogenic Systemic Fibrosis (NSF) is a generalized progressive fibrotic disorder described in some patients with renal insufficiency exposed to various gadolinium based contrast agents (GdBCA). The GdBCA Omniscan activates expression and production of several proinflammatory and profibrotic cytokines and growth factors in normal differentiated human macrophages via TLR4 and TLR7.signaling. Since some GdBCA are capable of inducing transmetallation by displacing Zn^{2+} from proteins the effect of GdBCA on expression levels of metallothionein genes in normal human macrophages and fibroblasts was examined in this study.

Methods: Terminally differentiated macrophages generated from two normal buffy coats were exposed for 24 hour to either 50 mM Omnisan or saline. Total RNA was isolated, labeled and hybridized to Affymetrix human U133 2.0 Plus microarrays. Volcano plots were used to identify differentially expressed genes between Omniscan treated and saline treated cells employing parametric testing assuming equal variances. Differential gene expression was confirmed by real-time PCR on the same RNA samples. Validation experi-

ments utilizing 3 additional differentiated macrophage isolates and two early passage (<6) normal human dermal fibroblasts examined the effect 1 mM Omniscan on the expression of metallothionein genes.

Results: Microarray analyses showed marked downregulation (~1.5 to 4 fold) of expression of multiple metallothionein genes (MT1E, MT1F, MT1G, MT1H, MT1M, MT1X and MT2A) in cells treated with 50 mM Omniscan compared to saline treated controls. These results were confirmed by real time-PCR analysis. Lower doses (1 mM) of Omniscan also downregulated the expression of these same genes as well as MT3 and MT4 whereas the expression of MT1A and MT1B was upregulated in normal human differentiated macrophages as well as in normal human dermal fibroblasts.

Conclusion: Global gene expression microarrays and real-time PCR analysis showed that exposure of terminally differentiated normal human macrophages to 50 mM Omniscan downregulated expression of multiple metallothionein genes in comparison to saline treated controls. Exposure of differentiated macrophages and normal human dermal fibroblasts to 1 mM Omniscan also decreased expression of these genes but increased expression of MT1A and MT1B suggesting that changes in metallothionein expression following GdBCA exposure in macrophages and dermal fibroblasts may play a role in the pathogenesis of the severe fibrotic process of NSF pathogenesis.

Disclosure: **P. J. Wermuth**, None; **F. Del Galdo**, None; **S. Addya**, None; **P. Fortina**, None; **S. A. Jimenez**, None.

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Activation of Sirt1 Attenuates Bleomycin Induced Scleroderma Through Inhibiting Mammalian Target of Rapamycin Activation. Xiaoxia Zhu[1], Jianhua Qiu[2], Qiong Liu[3], Minrui Liang[4] and Hejian Zou[5]. [1]Huashan Hospital, Fudan University, Shanghai, China, [2]Neuroscience Center, Massachusetts General Hospital, Harvard Medical School, Massachusetts, USA, Boston, MA, [3]Institute of Rheumatology, Immunology and Allergy,Shanghai Medical College, Fudan University, Shanghai, China, [4]Huashan Hospital,Fudan University, Shanghai, Shanghai, China, [5]Huashan Hospital, Shanghai, China

Background/Purpose: Scleroderma is an autoimmune disease, characterized by progressive fibrosis of skin and internal organs. Inflammation is one of the main manifestations of scleroderma, especially at the early stage. Inflammation is also an important initiating agent of fibrosis, suppression of inflammation may be a promising resolution to attenuate scleroderma. Sirt1 (a NAD^{+} dependent deacetylase) and its potent activator, resveratrol, both have been shown to have important role in regulation of inflammation.

Methods: In this study, we investigated the anti-inflammation role of Sirt1 and resveratrol in TNF-α treated fibroblasts and bleomycin induced mice experimental scleroderma, and further explore the anti-inflammatory mechanisms of Sirt1 and resveratrol in fibroblasts.

Results: Upregulation of matrix metalloproteinases 9 (MMP9), interleukin-1beta (IL-1β), IL-6 and inducible nitric oxide synthase (iNOS) were observed in the 3T3/NIH fibroblasts after being treated by TNF-α. Resveratrol suppressed the upregulation of inflammatory factors induced by TNF-α in a dose-dependent manner. And the suppression was significantly decreased if resveratrol was applied after the inflammation being induced. In the scleroderma mice model, bleomycin induced significant inflammation and fibrosis in the skin where infiltrated inflammatory cells, increased fiber bundles, upregulated collagen deposition were examined by HE staining and Masson's trichrome staining. But the pathological changes in were then notably attenuated by resveratrol treatment in time and dose dependent manner. The bleomycin induced upregulation of inflammatory factors were also inhibited by resveratrol treatment in the mice skin. We further explored the potential anti-inflammatory mechanisms of resveratrol in vitro. We blocked Sirt1 expression by Sirt1 siRNA transfection in 3T3/NIH fibroblasts, and investigated that knockdown of Sirt1 caused cell sensitizing to TNF-α stimulation and diminished the inflammatory inhibition of resveratrol. Furthermore, in this study, we also found that resveratrol inhibited the phosphorylation of both mammalian target of rapamycin (mTOR) and S6 ribosomal protein (S6RP) while ameliorating the inflammation in TNF-α treated fibroblasts. And rapamycin, the specific inhibitor of mTOR, attenuated the TNF-α induced inflammation in the fibroblasts.

Conclusion: The results suggest that Sirt1 is an efficient target for suppression of inflammation and fibrosis in scleroderma. As a Sirt1 activator, resveratrol may be used for therapy in scleroderma. Suppression of mTOR/S6RP phosphorylation may be involved in the mechanisms. This study provides a novel insight or treatment of scleroderma and other inflammation-related diseases.

Disclosure: **X. Zhu**, None; **J. Qiu**, None; **Q. Liu**, None; **M. Liang**, None; **H. Zou**, None.

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Wisp-1 Neutralization Reduces Gvhd-Induced Skin Fibrosis by Altering TSLP-OX40L Axis-Dependent Th2 Responses. Raphael Lemaire, Tim Burwell, Rachel Griffin, Julie Bakken, Joseph Madary, Lynne Murray, Ronald Herbst and Jane Connor. MedImmune LLC, Gaithersburg, MD

Background/Purpose: There is accumulating evidence for a role of Wnt-signaling pathway activation in connective tissue disorders, including dermal and lung fibrosis. In particular, expression of WNT1-inducible signaling protein–1 (WISP1) is increased in human scleroderma skin and idiopathic pulmonary fibrosis (IPF) lung. A recent study showed that WISP-1 mediates lung fibrosis in mice. In the current study, we investigated the function of WISP-1 in dermal fibrosis.

Methods: There is accumulating evidence for a role of Wnt-signaling pathway activation in connective tissue disorders, including dermal and lung fibrosis. In particular, expression of WNT1-inducible signaling protein–1 (WISP1) is increased in human scleroderma skin and idiopathic pulmonary fibrosis (IPF) lung. A recent study showed that WISP-1 mediates lung fibrosis in mice. In the current study, we investigated the function of WISP-1 in dermal fibrosis.

Results: Anti-WISP-1 mAb treatment reduced skin fibrosis in the GVHD model, as documented by reduction of hydroxyproline content and Masson's trichrome staining in skin at week 4 post-graft. Gene expression analysis showed a concomitant reduction of GVHD-associated Th2 responses in skin, including cytokine/receptor (IL-13, IL-4Rα) and chemokines (CCL2, CCL17 and CCL22). This Th2 profile reduction was associated with a broad-based reduction of the pro-Th2 TSLP-OX40L axis (TSLP, TSLPR, IL-7R, OX40L), suggesting that the TSLP/OX40L pathway may in part mediate the effect of WISP-1 on the Th2 response in GVHD. This view was supported with data generated from a separate study showing that anti-TSLP mAb treatment in GVHD-induced fibrosis reduces levels of Th2 (IL-13, IL-4) but not Th1 (IFN-γ) cytokines in skin and blood. TSLP neutralization also fully reduced GVHD-induced WISP-1 expression, further substantiating a functional link between WISP-1 and the TSLP/OX40L axis in fibrosis.

Conclusion: Consistent with the role of Wnt signaling pathways in fibrosis, WISP-1 neutralization reduces GVHD-induced skin fibrosis in part by affecting TSLP-OX40L-based Th2 responses. Interestingly, scleroderma shows increased dermal TSLP level and OX40L polymorphisms, suggesting that targeting WISP-1 may offer a valuable therapeutic strategy for the treatment of scleroderma and other skin fibrosis disorders.

Disclosure: **R. Lemaire**, None; **T. Burwell**, None; **R. Griffin**, None; **J. Bakken**, None; **J. Madary**, None; **L. Murray**, None; **R. Herbst**, None; **J. Connor**, None.

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The Soluble Guanylate Cyclase Mediates Its Anti-Fibrotic Effects by Inhibiting TGF-β Signaling. Christian Beyer[1], Sonia C. Schindler[2], Alfiya Distler[1], Clara Dees[1], Helena Reichert[2], Hümeyra Akan[2], Peter Sandner[3], Oliver Distler[4], Georg Schett[5] and Joerg HW Distler[6]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Bayer Health Care, Global Drug Discovery – Common Mechanism Research, Wuppertal, Germany, [4]University Hospital Zurich, Zurich, Switzerland, [5]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [6]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: We have recently demonstrated that stimulation of the soluble guanylate cyclase (sGC) has potent anti-fibrotic activity in different models of fibrosis. sGC stimulation increases levels of cGMP, which acts as a second messenger to induce various cellular effects. The molecular mechanisms, however, by which sGC stimulation exerts its anti-fibrotic effects have not been characterized yet. In the present work, we investigated interactions between sGC signaling and the TGF-β pathway.

Methods: Normal and SSc fibroblasts as well as sGC-knockout fibroblasts were pre-treated with the sGC stimulator BAY41–2272 or 8-Bromo-cGMP and stimulated with TGF-β. sGC-knockout fibroblasts were generated by isolation of dermal fibroblasts from sGCI^{fl/fl} mice and recombination induced by Cre-adenovirus. In vivo, we studied anti-fibrotic effects of BAY41–2272 in mice challenged with either bleomycin or an adenovirus expressing a constitutively active TGFβI receptor (TBR model).

Results: sGC stimulation by BAY41–2272 effectively inhibited TGFβ-dependent collagen release (mRNA and protein levels) from normal and SSc

dermal fibroblasts. In sGC-knockout fibroblasts, pre-treatment with the sGC stimulator BAY41–2272 did not reduce collagen release, demonstrating that the anti-fibrotic effects of BAY41–2272 are indeed mediated exclusively via sGC. To demonstrate that the second messenger cGMP is the central mediator of the sGC effects, we used the stable cGMP analogon 8-Bromo-cGMP. 8-Bromo-cGMP was effective in reducing TGFβ-dependent increase of collagen mRNA levels and collagen release in normal and SSc fibroblasts as well as in sGC-knockout fibroblasts. To further elucidate the novel link between sGC- and TGFβ-signaling, we studied nuclear p-smad2/3 levels: BAY41–2272 or 8-Bromo-cGMP prevented the TGFβ-induced increase in nuclear p-smad2/3 in normal and SSc fibroblasts. In sGC-knockout fibroblasts, only 8-Bromo-cGMP reduced p-smad2/3 levels, while BAY41–2272 had no effects. In vivo, we examined the antifibrotic effects of sGC stimulation in TGFβ-dependent, experimental dermal fibrosis (TBR model). BAY41–2272 dose-dependently reduced dermal thickening, hydroxyproline content and myofibroblast counts as well as p-smad2/3 levels, suggesting that sGC stimulation inhibited fibrogenesis via blocking TGFβ-signaling. We confirmed these findings in the more general disease model of bleomycin-induced dermal fibrosis, in which TGFβ is one of several important pro-fibrotic mediators.

Conclusion: We elucidated the molecular mechanisms underlying the anti-fibrotic effects of sGC signaling. Stimulation of sGC increases cGMP levels, which inhibits smad phosphorylation and results in decreased fibroblast activation and collagen release. Importantly, sGC stimulators have vasodilatory and anti-remodeling effects and are in phase 3 clinical trials for pulmonary arterial hypertension (PAH). Thus, sGC stimulators may soon become available for clinical trials and may provide simultaneous treatment of vascular disease and fibrosis in SSc.

1500

Activation of Pregnane X Receptor Induces Regression of Experimental Dermal Fibrosis. Christian Beyer[1], Alla Skapenko[2], Alfiya Distler[1], Clara Dees[1], Helena Reichert[3], Louis E. Munoz[3], Jan Leipe[4], Hendrik Schulze-Koops[2], Oliver Distler[5], Georg Schett[6] and Joerg HW Distler[7]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Munich, Munich, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]Division of Rheumatology and Clinical Immunology, Munich, Germany, [5]University Hospital Zurich, Zurich, Switzerland, [6]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [7]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Pregnane-X-receptor (PXR) belongs to a super-family of nuclear receptors that function as ligand-activated transcriptional factors. Although endogenous ligands have not yet been identified, PXR is a well-established master regulator of endobiotic metabolism as well as glucose and lipid homeostasis. Herein, we studied the role of PXR in experimental dermal fibrosis.

Methods: Mice were challenged with subcutaneous bleomycin injections and treated with 5-Pregnen-3β-ol-20-one-16α-carbonitrile (PCN) to activate PXR (i.p. once daily, conc. 25 mg/kg). After treatment, murine skin samples were analyzed for skin thickness, hydroxyproline content, α-smooth muscle actin (α-SMA)-positive myofibroblast counts, and phosphorylated smad2/3 (p-smad2/3) levels. Interleukin (IL)-13 was measured by multiplex bead array technology in murine skin. In vitro, murine fibroblasts were treated with PCN prior to stimulation with TGFβ to determine direct effects of PXR on collagen release. To study the release of the Th$_2$ cytokines IL-4 and IL-13 from murine CD4$^+$ T cells, murine T cells were isolated from FVB mice, kept in Th$_0$ and Th$_2$ conditions, and treated with PCN.

Results: We found that PXR activation effectively prevented bleomycin-induced dermal fibrosis as shown by reduced skin thickening (by 85.9 ± 7.5 %; $p = 0.002$), hydroxyproline content (by 50.5 ± 6.4 %; $p = 0.002$) and myofibroblast counts (by 77.0 ± 12.0 %; $p = 0.005$). Apart from preventing fibrosis, PXR stimulation induced regression of established bleomycin-induced dermal fibrosis in a modified treatment model with significant reductions of skin thickening, hydroxyproline content and myofibroblast

counts below pre-treatment levels. When elucidating the molecular mechanisms of the anti-fibrotic activity of PXR, we found that PXR activation reduced p-smad2/3 levels by 62.5 ± 9.2 % ($p = 0.010$) in the skin of bleomycin-challenged mice, suggesting that PXR activity inhibited pro-fibrotic canonical TGF-β signaling. Although PXR was expressed in low levels in dermal fibroblasts, PCN treatment did not change TGF-β-induced collagen release in vitro. This suggested indirect anti-fibrotic effects of PXR on the collagen release from fibroblasts. We therefore examined the effects of PXR stimulation on the release of Th$_2$ cytokines from murine CD4$^+$-positive lymphocytes, which are well-established pro-fibrotic mediators in fibrotic disease. We found that PXR activation reduced the expression of pro-fibrotic T$_{H2}$ cytokine IL-13 by 60.0 ± 13.1 % ($p = 0.010$ for 100 μM PCN). Of note, we could confirm these results in vivo since PXR stimulation significantly reduced IL-13 levels by 166 ± 17.3 % ($p = 0.001$) in the skin from mice challenged with bleomycin.

Conclusion: In summary, we are the first to establish potent anti-fibrotic effects of the nuclear receptor PXR. Pharmacological activation of PXR interferes with IL-13 release from T$_{H2}$ cells, which leads to inhibition of pro-fibrotic TGF-β signaling and results in decreased fibroblast activation and collagen release. These findings suggest that activation of PXR might be a novel anti-fibrotic approach in particular for early, inflammatory stages of SSc and other fibrotic diseases.

1501

Increased Periostin Levels in Patients with Systemic Sclerosis. Yukie Yamaguchi[1], Junya Ono[2], Miho Masuoka[3], Shoichiro Ohta[4], Kenji Izuhara[3], Zenro Ikezawa[5], Michiko Aihara[1] and Kazuo Takahashi[1]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Shino-Test Corporation, Sagamihara, Japan, [3]Saga Medical School, Saga, Japan, [4]Saga medical School, Saga, Japan, [5]International University of Health and Welfare Atami Hospital, Atami, Japan

Background/Purpose: Systemic sclerosis (SSc) results in significant morbidity and mortality due to organ fibrosis characterized by increased deposition of extracellular matrix (ECM). Periostin is one of the matricellular proteins, a class of ECM-related molecules defined by their ability to modulate cell–matrix interactions. Recent studies revealed that periostin serves as a critical regulator of wound healing, epithelial mesenchymal transition, and fibrosis. However, the role of periostin in the pathogenesis of SSc is unknown. In this study, we determined periostin levels in association with clinical characteristics, including severity of skin sclerosis and disease duration in patients with SSc.

Methods: Expression of periostin was examined in primary fibroblasts and the skin obtained from SSc patients using immunoblotting and immunohistochemistry respectively. Enzyme-linked immunosorbent assay was performed to evaluate serum periostin levels in association with clinical characteristics in 56 patients with SSc (diffuse cutaneous SSc (dSSc); n=16, limited cutaneous SSc (lSSc); n=40) and 66 healthy controls. In addition, the sensitivity and specificity of serum periostin levels for detecting SSc were analyzed using a receiver operating characteristic (ROC) curve.

Results: Periostin was strongly expressed in the affected dermis and primary fibroblasts obtained from SSc patients. Serum levels of periostin in dSSc patients were markedly elevated compared to those in lSSc patients and control subjects. Patients with lSSc had increased periostin levels compared with healthy controls. In addition, significantly higher levels of periostin were observed in dSSc patients with disease duration £5 years compared with those with disease duration >5 years. No significant difference was found in serum periostin levels between SSc patients with interstitial lung disease (ILD) and those without ILD. Furthermore, the modified Rodnan total skin thickness score (MRSS) was positively correlated with periostin levels in SSc patients. Serial analysis revealed the relevance of MRSS and periostin levels in some dSSc patients during their course of the disease. Finally, ROC analysis demonstrated that measurement of serum periostin by ELISA would be useful to distinguish SSc patients from healthy controls.

Conclusion: An elevated periostin level in SSc patients was correlated with severity of skin sclerosis. Periostin may be a potential biomarker reflecting for disease severity in patients with SSc.

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1502

Hedgehog Signaling in Murine Chronic Sclerodermatous Graft-Versus-Host Disease.
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Background/Purpose: Sclerodermatous chronic graft-versus-host disease (cGvHD) is a prognosis limiting complication of allogeneic bone marrow transplantation. cGVHD can manifest on virtually every organ system. However, the skin is most commonly affected with progressive skin fibrosis resembling the findings in systemic sclerosis (SSc). The hedgehog pathway plays a critical role in cellular differentiation during embryogenesis, but also for tissue homeostasis in adult. The prominent role of hedgehog signaling in various tumors prompted the development of small molecule inhibitors, some of which have already been successfully tested in clinical trials.

Methods: Sublethally irradiated recipient mice received miHAg-mismatched bone marrow to induce sclerodermatous cGvHD. Activation of sonic hedgehog (Shh) pathway in cGvHD was analyzed by immunohistochemistry for Shh and its downstream transcription factors Gli-1 and Gli-2 in human and murine skin. Smoothened (Smo) inhibitor LDE223 was used to investigate the efficacy of hedgehog inhibition for prevention and treatment of murine cGvHD. Skin samples were analyzed for dermal thickness, myofibroblast counts and hydroxyproline content. The effect of Shh on cultured fibroblasts was analyzed by quantification of stress fibers formation, real time PCR for Col1a2 and the collagen content in supernatants.

Results: Hedgehog signaling was activated in human and murine cGvHD with increased expression of Shh, Gli-1 and Gli-2. Inhibition of coreceptor Smo with LDE223 was well tolerated without evidence of toxicity. LDE223 effectively reduced cGvHD in both preventive and therapeutic regime without decreasing the desired graft versus leukemia effect. Treatment with LDE223 initiated either before disease onset or after first clinical signs of cGvHD, significantly reduced clinical signs such as weight loss, alopecia and skin ulcers. Moreover, inhibition of Smo effectively ameliorated the histological changes of cGvHD. Preventive as well as therapeutic regime of LDE223 significantly decreased the dermal thickness, the number of myofibroblasts and the hydroxyproline content compared to control mice. Of note, therapeutic regime of LDE223 did not only stop progression, but induced histological regression of cGvHD. While LDE223 did not ameliorate leukocyte infiltration, B- or T cell activation, incubation of human dermal fibroblasts with Shh induced fibroblast activation with increased release of collagen and myofibroblast differentiation, suggesting a direct inhibitory effect on fibroblasts as mechanism of action.

Conclusion: This is the first study on the role of hedgehog signaling in sclerodermatous cGvHD. We demonstrate that hedgehog signaling is activated in cGvHD and stimulates progression of cGvHD by activating resident fibroblasts. Considering the potent therapeutic effects of Smo inhibition in preventive as well as therapeutic settings, good tolerance and lack of interference with the desired GVL and the availability of Smo inhibitors for clinical trials, our findings might have direct translational implications and stimulate clinical trials with Smo inhibitors in cGvHD and other fibrotic diseases such as SSc.

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1503

Effect of Thiol Antioxidants On the Profibrotic Phenotype of Scleroderma Dermal Fibroblasts.
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Background/Purpose: Systemic sclerosis (Scleroderma, SSc) is a connective tissue disease characterized by vasculopathy and fibrosis of the skin and organs. Increase in superoxide production and platelet-derived growth factor receptor (PDGFR) activation promote collagen I (Col I) production, leading to fibrosis in SSc. Protein tyrosine phosphatases (PTPs), which are responsible for terminating the PDGFR pathway, are oxidatively inactivated in SSc dermal fibroblasts. In addition, these cells exhibit myofibroblast characteristics with increased α-smooth muscle actin (αSMA) expression. The goal of this study is to determine the effect of two thiol antioxidants, N-acetylcysteine (NAC) and dihydrolipoic acid (DHLA), on the phenotype of SSc fibroblasts, namely PDGFR stimulation, Col I synthesis, superoxide levels, phosphatase activities, αSMA expression, and matrix metalloproteinase 1 (MMP-1) production.

Methods: Punch biopsies (4 mm) from distal skin were obtained from patients with SSc (n=5). Normal (NL) skin tissue was obtained from the tissue procurement service of the University of Michigan. Superoxide levels were measured using dihydroethidium. PDGFR phosphorylation was determined by immunoprecipitation and Western blotting. Quantitative PCR was performed with primers for Col I and β-actin. Immunofluorescence was performed to probe for Col I and αSMA. An enzyme linked immunosorbent assay was completed to detect MMP-1. Phosphatase activities were measured using the amount of phosphate released as an end point.

Results: Addition of NAC decreased superoxide in SSc dermal fibroblasts while DHLA did not. Both NAC and DHLA decreased PDGFR phosphorylation in SSc fibroblasts. Col I mRNA was increased in SSc fibroblasts compared to normal (NL) at basal level, while NAC and DHLA decreased both Col I mRNA and protein levels. SSc fibroblasts produced lower levels of MMP-1 compared to NL, but the levels increased after NAC or DHLA incubation. DHLA not only decreased the expression of αSMA in SSc dermal fibroblasts, but also restored the activities of phosphatases that inactivate the PDGFR, including PTP1B, SHP-2, and DEP-1. Almost as effective was NAC which restored PTP1B and DEP-1 activity, but not SHP-2.

Conclusion: Our results show that thiol antioxidants are beneficial for SSc dermal fibroblasts due to their ability to reverse the profibrotic phenotype of these cells. Thiol antioxidants decrease PDGFR activation, possibly by restoring the activities of phosphatases, and hence decrease Col I production. In addition, they increase MMP-1 production, which degrades Col I. Moreover, DHLA lowered the expression of αSMA, suggesting that it could reverse the myofibroblast phenotype of SSc dermal fibroblasts. Hence thiol antioxidants could prove to be an effective treatment in SSc.

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1504

A Possible Contribution of Visfatin to the Resolution of Skin Sclerosis in Patients with Diffuse Cutaneous Systemic Sclerosis Via a Direct Anti-Fibrotic Effect On Dermal Fibroblasts and Th1 Polarization of the Immune Response.
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Background/Purpose: Our latest studies have demonstrated that adipocytokines, including adiponectin, apelin, and retinol-binding protein-4, are potentially involved in the development of complicated clinical symptoms associated with systemic sclerosis (SSc). Visfatin is another member of adipocytokines with pro-fibrotic, pro-inflammatory, and immunomodulating properties, having been implicated in the pathogenesis of certain fibrotic and inflammatory autoimmune diseases. As an initial step of a series of studies regarding the role of visfatin in the pathogenesis of SSc, we herein investigated the clinical significance of serum visfatin levels and its contribution to the developmental process in this disorder.

Methods: Serum visfatin levels were determined by a specific ELISA in 57 SSc patients and 19 healthy controls. The effects of visfatin on the mRNA

levels of a2(I) collagen (COL1A2) and matrix metalloproteinase-1 (MMP-1) genes were examined in normal and SSc dermal fibroblasts by reverse-transcript real-time PCR. The levels of IL-12p70 produced by THP-1 cells differentiated with IFN-g plus LPS in the presence or absence of visfatin were measured by a specific ELISA.

Results: Serum visfatin levels were comparable among total SSc, diffuse cutaneous SSc, limited cutaneous SSc, and healthy controls. The only finding in a series of analyses regarding the correlation of serum visfatin levels with clinical symptoms and laboratory data was the significantly longer disease duration in dcSSc with elevated serum visfatin levels than in those with normal levels. Consistently, serum visfatin levels were significantly elevated in late stage dcSSc (disease duration of > 6 years), but not in early and mid-stage dcSSc, compared with healthy controls, suggesting the possible contribution of visfatin to the resolution of skin sclerosis in late stage dcSSc. To assess this hypothesis, two sets of *in vitro* experiments were carried out using dermal fibroblasts and THP-1 cells. Visfatin suppressed the mRNA levels of COL1A2 gene, while increasing the mRNA levels of MMP-1 gene, in a dose-dependent manner in SSc dermal fibroblasts, whereas the mRNA levels of these genes were not affected by visfatin at all in normal dermal fibroblasts, indicating the direct anti-fibrotic effect of visfatin on SSc dermal fibroblasts. Furthermore, visfatin increased the production of IL-12p70 in THP-1 cells differentiated with IFN-g plus LPS in a dose-dependent manner, suggesting the promotion of Th1 immune responses by visfatin.

Conclusion: Visfatin may contribute to the resolution of skin sclerosis in late stage dcSSc via the direct anti-fibrotic effect on dermal fibroblasts and Th1 polarization of the immune response.

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1505

Inactivation of Tankyrases Ameliorates Canonical Wnt Signaling and Prevents Experimental Fibrosis. Alfiya Distler[1], Lisa Deloch[2], Jingang Huang[2], Clara Dees[1], Neng Yu Lin[2], Christian Beyer[1], Oliver Distler[3], Georg A. Schett[4] and Joerg HW Distler[4]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]University Hospital Zurich, Zurich, Switzerland, [4]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Systemic sclerosis (SSc) is characterized by aberrant activation of fibroblasts with increased release of extracellular matrix components. Canonical Wnt signaling has recently emerged as a key mediator of fibroblasts activation and tissue fibrosis in SSc. However, targeting of canonical Wnt signaling has so far been complicated by the lack of pathway components that are amenable to pharmacological inhibition. However, tankyrases have recently demonstrated to regulate Wnt signalling by stimulating the proteasomal degradation of axin. In the present study, we evaluated the tankyrases as a potential novel target for the treatment of fibrosis in SSc.

Methods: The anti-fibrotic effects of the selective tankyrase inhibitor XAV-939 or of siRNA mediated knockdown of tankyrases were evaluated in the mouse models of bleomycin-induced dermal fibrosis and in experimental fibrosis induced by adenoviral overexpression of a constitutively active TGF-β receptor I (adTBR). Dermal thickness, α-smooth muscle actin (αSMA) and hydroxyproline content were determined by haematoxylin-eosin and trichrome stainings, by immunohistostaining for αSMA and by hydroxyproline assay respectively. Activation of canonical Wnt signaling was assessed by quantification of nuclear β-catenin and analyses of the target gene c-myc.

Results: Inactivation of tankyrases either by XAV-939 or by siRNA mediated knockdown of tankyrases prevented the activation of canonical Wnt signaling in experimental fibrosis and reduced the nuclear accumulation of β-catenin and the mRNA levels of the target gene c-myc. Pharmacologic inhibition of tankyrases was well tolerated without any clinical signs of toxicity. Treatment with XAV-939 potently reduced bleomycin-induced dermal thickening by 50 % compared to sham-treated mice (p = 0.0007). XAV-939 also significantly reduced the differentiation of resting fibroblasts into myofibroblasts and accumulation of collagen. XAV-939 also exerted potent anti-fibrotic effects in adTBR driven skin fibrosis with reduced dermal thickening, decreased myofibroblast counts and reduced accumulation of collagen compared to sham-treated mice. siRNA mediated knockdown of

tankyrases in the skin also exerted potent anti-fibrotic effects confirming that the anti-fibrotic effects of XAV-939 were not due to off-target effects.

Conclusion: Inactivation of tankyrases abrogated the activation of canonical Wnt signaling and demonstrated potent anti-fibrotic effects in different preclinical models of SSc without evidence of toxicity. Considering the great medical need, the potent anti-fibrotic effects, the good tolerability and first clinical trials with tankyrase inhibitors, tankyrases might be potential candidates for targeted therapies in SSc and other fibrotic diseases.

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1506

Primary Human Scleroderma Dermal Endothelial Cells Exhibit Defective Angiogenesis. Pei-Suen Tsou[1], Bradley J. Rabquer[1], Beatrix Balogh[1], Ann Kendzicky[1], Bashar Kahaleh[2], Elena Schiopu[1], Dinesh Khanna[1] and Alisa E. Koch[1]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Toledo, Toledo, OH

Background/Purpose: Angiogenesis, the formation of new blood vessels, plays a critical role in a number of pathological processes including systemic sclerosis (scleroderma, SSc). SSc is a multifactoral disorder that is characterized by early inflammation, excessive extracellular matrix deposition, and vascular abnormalities. In this study we determined if the endothelial cells (ECs) isolated from SSc skin mount a proangiogenic response towards angiogenic chemokines, including growth-regulated protein-γ (Gro-γ/CXCL3), granulocyte chemotactic protein-2 (GCP-2/CXCL6), and CXCL16. The expression of transcription factors inhibitor of DNA-binding protein 1 and 3 (Id-1 and 3), which are required for ECs to mount an angiogenic response, were also examined.

Methods: Skin biopsies from the distal forearm (more involved) were obtained from patients with SSc. Normal (NL) skin tissue was obtained from the tissue procurement service of the University of Michigan. ECs were isolated from skin biopsies via magnetic selection. Immunofluorescence staining of EC markers such as CD31 and von Willebrand factor (vWF), as well as fibroblast markers such as collagen I and α-smooth muscle actin (αSMA) was performed. To determine if chemokines mediate specific angiogenic events in SSc ECs, chemotaxis assays were performed. ECs were stimulated with chemokines to determine which signaling pathways were activated. The expression of Id-1 and 3 were quantified by quantitative PCR.

Results: Both NL and SSc ECs stained positive for EC markers while they did not stain for fibroblast markers. SSc ECs migrated toward phorbol-12-myristate-13-acetate (PMA) but not to basic fibroblast growth factor (bFGF) compared to their corresponding controls, dimethyl sulfoxide (DMSO) or phosphate buffered saline (PBS). GCP-2/CXCL6 dose dependently induced both NL and SSc EC migration. In contrast, the ability of Gro-γ/CXCL3 and CXCL16 to promote cell migration was hampered in SSc ECs compared to NL ECs. GCP-2/CXCL6 stimulated the phosphorylation of Akt, cJun, Erk1/2, NFkB p65, and p38 kinases in a dose dependent manner in NL ECs, while only cJun, Erk1/2, and p38 kinases in SSc ECs. CXCL16 stimulated Akt, Erk1/2, NFkB p65, and p38 kinases phosphorylation in NL ECs, while only cJun, Erk1/2, and p38 kinases in SSc ECs. The mRNA levels of Id-1 and Id-3 in SSc ECs were 2.5 and 2.1 fold lower compared to NLs (n=3).

Conclusion: Our results show that Gro-γ/CXCL3 and CXCL16 induce anigogenic activity in NL but not SSc ECs. This might be due to the differences in the signaling pathways activated by these chemokines in NL vs. SSc ECs. In addition, the lower expression of transcription factors Id-1 and Id-3 might also decrease the angiogenic response in these cells. The inability of proangiogenic chemokines to promote EC migration provides an additional mechanism for the impaired angiogenesis that characterizes SSc.

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1507

Propylthiouracil Reduces Fibrosis in Chronic Oxidant Stress Mouse Model of Scleroderma.

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Background/Purpose: Systemic sclerosis (SSc) is characterized by fibrosis of skin and visceral organs; vascular damage and resultant ischemia; and immunological dysregulation manifested by autoantibodies. Hypothyroidism, induced by either propylthiouracil (PTU) or thyroidectomy, has been shown to induce regression of pulmonary hypertension in the sumatinib/hypoxia rat model involving blockade of vascular endothelial growth factor (VEGF). The aim of this study was therefore to evaluate the effect of PTU in another murine model closer to human SSc, a mouse model of diffuse SSc reported to cause the development of anti-topoisomerase antibodies.

Methods: SSc was induced in BALB/c mice by daily subcutaneous injections of HOCl as an oxidant stress for 6 weeks (Batteux F, Kavian N, Servettaz A. New insights on chemically induced animal models of systemic sclerosis.Curr Opin Rheumatol. 2011 Nov;23(6):511–8). Mice (n=25) were randomized in three arms to treatment with either HOCl (n=10); HOCl plus PTU (n=10); or vehicle alone (n=5). PTU treatment was initiated 30 minutes after HOCl subcutaneous injection (12 mg/kg) continuing daily for the 6 weeks. Skin and lung fibrosis were evaluated by histological methods. The severity of fibrosis was assessed using ordinal or nominal scales in both tissues and the results compared nonparametrically.

Results: Injections of HOCl induced both cutaneous and lung fibrosis in BALB/c mice, as reported in the model. Concomitant PTU treatment reduced skin thickness by 77% (images not shown) and reduced pulmonary fibrosis below the level of histological detectability, in effect preventing it entirely in this model. Pulmonary concentrations of VEGF were significantly higher in mice exposed to HOCl (p<0.001) and were reduced by concomitant treatment with PTU (p<0.001). Its downstream mediator ERK (extracellular signal-related kinase) followed the same pattern (images not shown).

healthy control | disease control (scleroderma model) | scleroderma + propylthiouracil

VEGF
Beta-actin

* p< 0.001
# p< 0.001
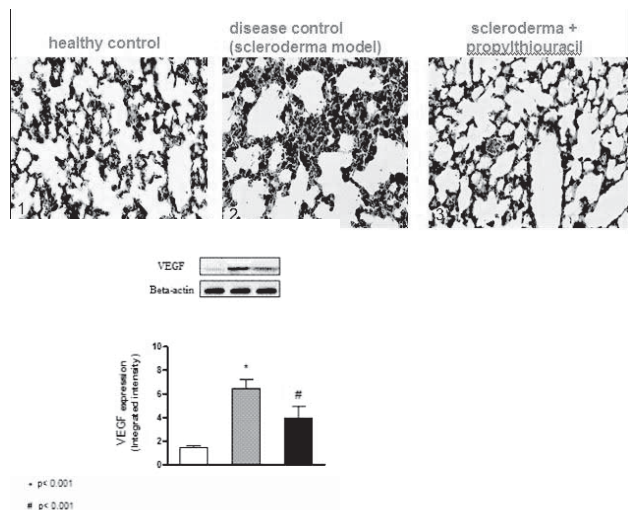
Conclusion: PTU-induced hypothyroidism (or the PTU itself, via another mechanism of action not related to hypothyroidism, such as antioxidant effect) reduced significantly the development of fibrosis in the HOCl mouse model of SSc. No confirmatory thyroidectomy experiments were performed in this model, in contrast to those reported in the previous rat model. Further studies are therefore needed to investigate both the roles of thyroid function and reactive oxygen species in scleroderma pathogenesis, including analysis of any direct antioxidant effect of PTU, independent of its effect upon thyroid status.

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1508

Simvastatin Attenuates Pulmonary Fibrosis in a Murine Model of Systemic Sclerosis.

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Background/Purpose: Simvastatin is best known for its antilipidemic action due to its inhibition of 3-hydroxy-3-methylglutaryl CoenzymeA (HMG CoA) reductase. Inhibition of biological precursors in this pathway also enables pleiotrophic immunomodulatory and anti-inflammatory capabilities. The antifibrotic effect of simvastatin has been shown in human lung fibroblasts. This study aimed to measure beneficial effects of simvastatin, and to explore mechanisms of, development of pulmonary fibrosis and skin thickening in a murine model of systemic sclerosis.

Methods: Chronic oxidant stress SSc was induced in BALB/c mice by daily subcutaneous injections of HOCl for 6 weeks as characterized in detail as the Cochin chronic oxidant stress model of SSc (Batteux F, Kavian N, Servettaz A. New insights on chemically induced animal models of systemic sclerosis.Curr Opin Rheumatol. 2011 Nov;23(6):511–8). Mice (n=24) were randomized in three arms: treatment with either simvastatin plus HOCl (n=9): vehicle plus HOCl (n=10), or vehicle alone (n=5). Statin treatment (40 mg/kg) was initiated 30 minutes after HOCl subcutaneous injection and continued daily for the 6 weeks. Skin and lung fibrosis were evaluated by histological methods. The severity of fibrosis was assessed using ordinal or nominal scales in both tissues and the results compared nonparametrically

Results: Injections of HOCl induced cutaneous and lung fibrosis in BALB/c mice as demonstrated by routine histological analysis. Simvastatin treatment both reduced skin thickness by 55% (upper row of 3 representative photomicrographs) and attenuated the histopathological change of HOCl-induced pulmonary fibrosis as shown in the lower series.

S1=normal healthy control | SH_3 = HOCl disease model without intervention | ss9 = HOCl + simvastatin

healthy control | disease control (scleroderma model) | scleroderma + simvastatin
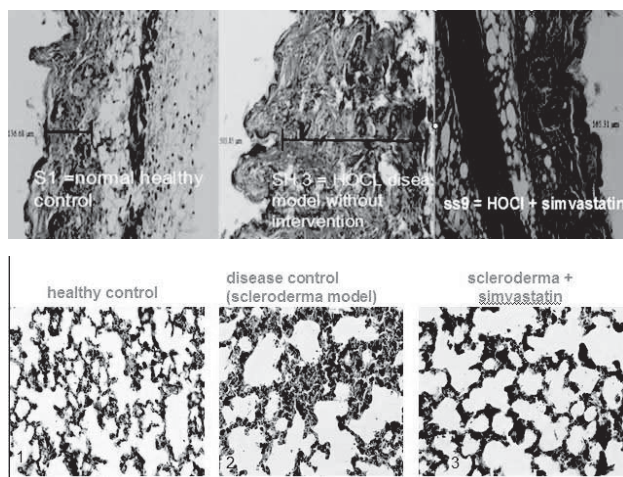
Conclusion: Simvastatin reduces the development of pulmonary fibrosis potentially modulating adverse lung parenchymal remodeling as shown by the reduced deposition of collagen in alveolar septae in this murine model. Simvastatin also reduces skin thickness in the model. The histological evidence from these experiments suggests that—given the low, 1 per million death rate from statin prescriptions and the morbidity and mortality of SSC pulmonary disease—consideration of human trials is warranted to determine the potential safety and efficacy of simvastatin for treatment of pulmonary fibrosis.

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1509

Correlates of Skin Gene Expression Profile in Systemic Sclerosis.

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Background/Purpose: Skin global gene expression profiling indicates presence of distinct gene expression signatures in patients with systemic sclerosis (SSc). We examine the correlation of the skin gene expression profiles with clinical subsets of disease in a large sample of SSc patients.

Methods: In this study, 61 SSc patients (61% diffuse disease, mean disease duration: 7.7 years) and 36 gender, ethnicity, and age matched controls were examined. All skin biopsies were obtained from subjects' arm and processed according to the same procedures. In 40 SSc patients, the skin was affected at the biopsy site. Global gene expression profiling was performed by Illumina HumanHT-12 arrays in one batch. Only 1 biopsy per subject was analyzed. Differentially expressed (DE) genes were detected in multivariable analysis with False Discovery Rate of 10% at the confidence level of 80%. Involved Canonical Pathways were identified by Ingenuity Pathway Analysis. Unsupervised hierarchical clustering was performed with all expressed genes and after filtering the gene list with the previously published TGF-β, IL-13, and diffuse proliferative (Milano et al. 2008) signatures. We also generated an interferon-α (IFN-α) inducible gene signature using control fibroblast treated with IFNa.

Results: The transcriptome of the majority of SSc patients differed from controls. Specifically, 2525 DE genes were identified, belonging to fibrotic, leukocyte extravasation, and oxidative phosphorylation pathways. However, there was significant heterogeneity among the SSc samples. We examined whether the observed heterogeneity correlated with known clinical subtypes of SSc. However, we could not identify any significant differential expression when patients were subgrouped by disease type (limited versus diffuse), antibody subtypes, treatment status (immunosuppression versus no immunosuppression), or disease duration. The presence of anti-RNP antibodies was the exception. Comparison of anti-RNP positive to the anti-RNP negative patients resulted in 188 DE genes, belonging mainly to IFN pathways. However, we detected prominent gene expression differences among SSc patients who have affected vs. unaffected skin at the biopsy site. This comparison resulted in 378 DE expressed genes, belonging to fibrotic and leukocyte extravasation pathways. This was further underscored by the fact that comparison of SSc affected skin to controls resulted in 3458 genes while comparing patients wit unaffected skin to controls resulted in only 38 DE genes. We next filtered our gene list by TGF-β, IL-13, diffuse proliferative, and IFN-α gene signatures in separate unsupervised clustering analyses. While these gene signatures were helpful in separating the majority of patients from controls, they did not correspond to known clinical subtypes of SSc including disease type and treatment status.

Conclusion: The majority of SSc patients have distinct (but heterogeneous) global gene expression profile when compared to controls. Within SSc group, the status of skin at the biopsy site is a major source of variability (affected versus unaffected skin). The observed heterogeneity in SSc transcriptomes does not correspond to the known clinical subtypes of disease.

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1510

Critical Role of the Adhesion Receptor Dnax Accessory Molecule-1 (DNAM-1) in the Development of Inflammation-Driven Dermal Fibrosis in Mouse Model of Systemic Sclerosis.
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Background/Purpose: DNAX accessory molecule 1 (DNAM-1) is an adhesion factor involved in the adhesion and co-stimulation of T cells. DNAM-1 has been recently identified as a genetic susceptibility factor to systemic sclerosis (SSc) and also to other autoimmune diseases. Our aim was to investigate the contribution of DNAM-1 in the development of dermal fibrosis upon gene inactivation and targeted molecular strategies.

Methods: Human skin expression of DNAM-1 was determined by immunohistochemistry. Mice deficient for DNAM-1 (dnam1$^{-/-}$) and wild-type controls (dnam1$^{+/+}$) were injected with bleomycin or NaCl. Infiltrating leukocytes, T cells, B cells and monocytes were quantified respectively on hematoxylin and eosin stained sections and by immunohistochemistry for CD3, CD22 and CD68. Inflammatory cytokines were measured in lesional skin of dnam1$^{-/-}$ and dnam1$^{+/+}$ mice by flow cytometry. The anti-fibrotic potential of a DNAM-1 neutralizing monoclonal antibody (mAb) was also evaluated in the mouse model of bleomycin-induced dermal fibrosis.

Results: Overexpression of DNAM-1 was detected in the lesional skin of SSc patients, especially in perivascular inflammatory cells. Dnam1$^{-/-}$ mice were protected from bleomycin-induced dermal fibrosis with reduced dermal thickening ($75\pm5\%$ reduction, p=0.02), hydroxyproline content ($46\pm8\%$ decrease, p=0.02) and myofibroblast counts ($39\pm5\%$ reduction, p=0.04). The numbers infiltrating T cells were decreased in lesional skin of dnam1$^{-/-}$ mice by $69\pm15\%$ (p=0.009). The number of B cells and monocytes was not significantly different in dnam1$^{-/-}$ and dnam1$^{+/+}$ mice upon bleomycin challenge. Moreover, dnam1$^{-/-}$ mice displayed in lesional skin decreased levels of inflammatory cytokines, such as IL-6 ($59\pm12\%$, p=0.001 decrease), and TNFα ($60\pm15\%$, p=0.03). Treatment with anti-DNAM-1 mAb significantly reduced dermal thickening by $64\pm6\%$ (p=0.01), hydroxyproline content by $61\pm8\%$ (p=0.001), and myofibroblast counts by $83\pm12\%$ (P=0.03). These results were similar to those observed in DNAM-1 deficient mice.

Conclusion: We demonstrate with two complementary approaches that inhibition of DNAM-1 significantly ameliorates dermal inflammation-driven fibrosis. DNAM-1 displays profibrotic effects by promoting the infiltration of T cells, into lesional skin and by stimulating the release of inflammatory cytokines. In addition, molecular targeting strategy using a DNAM-1 neutralizing mAb confirmed potent antifibrotic properties of DNAM-1 inhibition. Our findings might have direct translational implications and inhibition of DNAM-1 might be a promising new approach for the treatment of SSc and potentially other fibrotic diseases.

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1511

Low Circulating Endothelial Progenitor Cell Levels and High VEGF Serum Levels Are Associated with the Late Nailfold Capillaroscopic Pattern in Systemic Sclerosis.
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Background/Purpose: To assess whether nailfold videocapillaroscopy (NVC) changes are associated with peripheral blood or serum levels of angiogenic biomarkers in systemic sclerosis (SSc).

Methods: Endothelial markers were assessed in a cohort of 60 SSc patients consecutively recruited. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting, as previously described (1). Serum levels of vascular endothelial growth factor (VEGF), placenta growth factor (PlGF), soluble vascular adhesion molecule (sVCAM), endothelin-1 (ET1), angiopoietin-2, endoglin, endostatin and Tie-2, were measured by quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique (Quantikine kits, R&D systems). Capillaroscopy was performed on 8 fingers, at $200\times$ magnification, by a single examiner (JA), on two consecutive fields extending over 1 mm, in the middle of the nailfold. Images were analysed anonymously by four investigators (VS, AS, CP and MC), blinded for the clinical and serum status of SSc patients and classified as early, active and late pattern (2).

Results: The mean $\pm$ standard deviation (SD) age of the 60 patients (46 women) was 56 ± 13 year old and the mean $\pm$ SD disease duration was 9 ± 8 years at baseline. Thirty-six patients had the diffuse cutaneous subset, and 24 the limited. Fourteen patients had an early, 22 an active, and 24 a late NVC pattern. By univariate analysis focused on biomarkers, patients with late NVC pattern exhibited significantly lower EPC levels

and higher VEGF serum levels than patients with early and active patterns (p=0.001 and p=0.01, respectively). Endothelin serum levels were significantly higher in the active pattern compared to early and late patterns (p=0.02). In multivariate multiple regression analysis, lower EPC and higher VEGF levels were independently associated with the late capillaroscopic pattern (p=0.007 and p=0.0008 respectively). In an alternate model including these 2 biomarkers and SSc-related disease characteristics, lower EPC counts, higher VEGF levels, and a modified Rodnan skin (mRSS) score >14, were independently associated, in multiple regression analysis, with the late capillaroscopic pattern (p=0.02, p=0.0001 and p=0.0003, respectively).

Conclusion: Our data revealed decreased EPC counts in patients with the late capillaroscopic pattern, suggesting that deficient vasculogenesis may contribute to the severe loss of capillaries observed in this pattern. VEGF upregulation in the late pattern may appear as a compensatory mechanism to stimulate this deficient vasculogenesis and could be implicated in the altered vessel morphology observed in this pattern. In addition, a mRSS>14 was independently associated with the late NVC pattern, highlighting from the clinical side the fibrotic component of this pattern. Further studies are now needed to determine the predictive value of capillaroscopy, in combination with these biomarkers, for the development of the vascular complications of SSc.

References

(1) Avouac et al, Ann Rheum Dis 2008,
(2) Cutolo M et al. J Rheumatol. 2000

Disclosure: J. Avouac, None; **M. Vallucci**, None; **V. Smith**, None; **B. Ruiz**, None; **A. Sulli**, None; **C. Pizzorni**, None; **G. Chiocchia**, None; **M. Cutolo**, None; **Y. Allanore**, None.

1512

Bleomycin Delivery by Osmotic Pump: A Superior Model for Human ILD. Rebecca Lee, Michael Bonner, Charles Reese, Elena Tourkina, Zoltan Hajdu, Jing Zhang, Richard Visconti and Stanley Hoffman. Medical University of South Carolina, Charleston, SC

Background/Purpose: Interstitial lung disease (ILD) represents a group of chronic, progressive, irreversible diseases associated with pulmonary fibrosis, including systemic sclerosis and idiopathic pulmonary fibrosis. In ILD, pulmonary fibrosis is accompanied by alveolar epithelia cell injury, inflammatory cell accumulation, fibroblast and myofibroblast proliferation, loss of the master regulatory protein caveolin-1 from fibroblasts and inflammatory cells, and excessive deposition of extracellular matrix (ECM) resulting in impairment of pulmonary function. Fibrosis in ILD is predominantly localized in the subpleural region of the lung. ILD is modeled in rodents by bleomycin treatment. In most studies, bleomycin has been delivered directly into the lungs by intratracheal or intraoral administration; however, bleomycin has also been delivered using subcutaneous osmotic pumps. Here we have compared the effects in mice of bleomycin delivered by "Pump" or by the "Direct" route to determine which is a better model for human ILD.

Methods: Male CD1 mice (ten weeks old) are treated with bleomycin either by the "Direct" route (a single intraoral administration of 2 U/kg) and sacrificed on day 14, or by "Pump" (the pump delivers 100 U/kg continuously over 7 days, then is removed) and sacrificed on day 35. Tissue sections are stained histochemically and immunohistochemically for caveolin-1, inflammatory cell markers, several ECM proteins, and proteins associated with fibrosis. Other methods are used to analyze the progression of inflammation and fibrosis including Western blotting, gelatin zymography, collection of BAL fluid, and flow cytometry. The role of the loss of caveolin-1 in the progression of inflammation and fibrosis is determined by using the caveolin-1 scaffolding domain peptide to restore caveolin-1 function.

Results: The Pump model provides a much higher level of subpleural fibrosis than the Direct model as evaluated by Masson's Trichrome stain and immunohistochemistry for the ECM proteins collagen I, tenascin-C, and periostin, and the collagen chaperone HSP47 (Figs. 1 and 2). Conversely, there is a much higher level of inflammatory cell accumulation, weight loss, and death in the Direct model. There is a striking absence of caveolin-1 from the HSP47-positive cells in the Pump model. Experiments are underway to determine the effects of replacing caveolin-1 function in the Pump model.
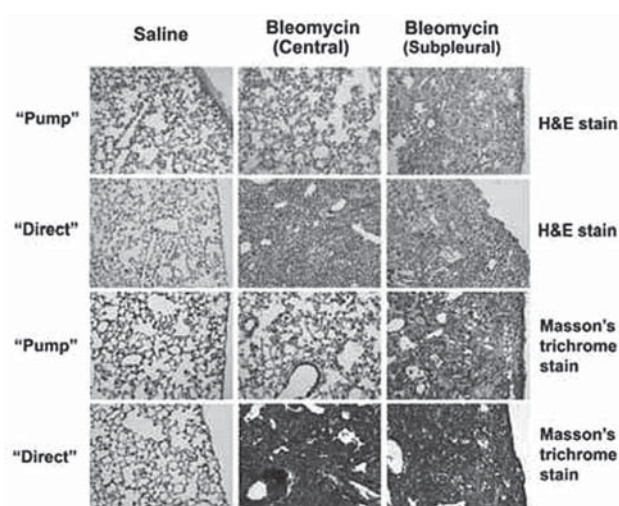
Figure 1. Comparison of tissue morphology in mice treated wih bleomycin by the "Direct" and "Pump" methods. Sections are stained with H&E or Masson's trichrome stain. Images are all 20X.
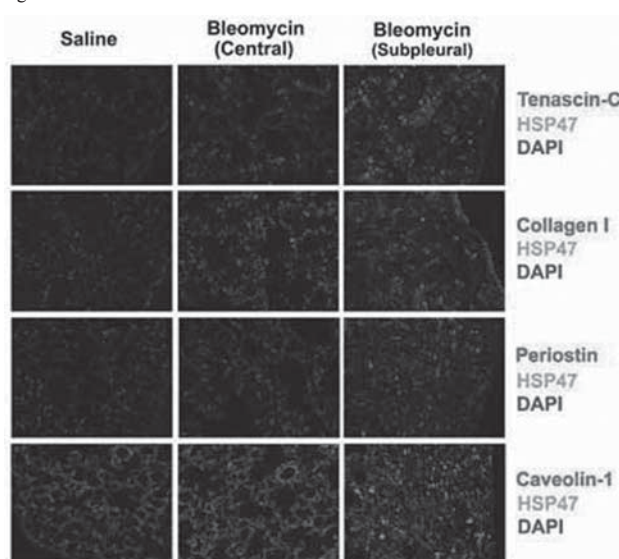
Figure 2. Immunofluorescent staining in lung tissue sections from mice treated with bleomycin by "Pump" methods. Images are all 20X.

Conclusion: The Pump model is superior to the Direct model because: 1) The resulting disease more accurately recapitulates human ILD, and 2) It is more convenient because there is less animal weight loss and death.

Disclosure: R. Lee, None; **M. Bonner**, None; **C. Reese**, None; **E. Tourkina**, None; **Z. Hajdu**, None; **J. Zhang**, None; **R. Visconti**, None; **S. Hoffman**, None.

1513

TSLP Receptor Deficiency Reduces IL-13 Expression and Prevents Fibrosis in Experimental Scleroderma. Alicia Usategui[1], Vanessa Miranda[1], Gabriel Criado[1], Manuel J. Del Rey[1], Elena Izquierdo[1], Warren J. Leonard[2] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by progressive fibrosis of the skin and internal organs. Although SSc shares pathogenetic features with other autoimmune diseases, the participation of profibrotic Th2 cytokines is unique to SSc. However, the reasons for Th2 cytokine skewing are unknown. Thymic Stromal Lymphopoietin (TSLP) is a pivotal cytokine in induction of Th2 responses in allergic skin and lung inflammation. We have previously observed TSLP overexpres-

sion in human and experimental scleroderma (Arthritis Rheum 2011; 63: S904). To understand its function in this context, we have analyzed the contribution of TSLP to Th2 cytokine expression and fibrosis in a mouse model of scleroderma.

Methods: Skin fibrosis was induced in 6 week old female C57BL/6 TSLP receptor (TSLPR) deficient and wild type (WT) mice by subcutaneous injections of bleomycin (1mg/ml) into the shaved back skin daily for 4 weeks. Treated skin was harvested and histological examination and collagen content were determined by Masson's trichrome staining and total hydroxyproline content. Analysis of cytokines mRNA and protein expression in the skin was performed by quantitative RT-PCR, immunohistochemistry and ELISA. Quantitative data were compared by Mann-Whitney U-test and p-value<0.05 was considered significant.

Results: Bleomycin induced dermal fibrosis and an increase in the collagen content of the skin in both TSLPR deficient and WT mice. The fractional collagen area of the dermis and the total collagen protein content of the skin were significantly reduced in TSLPR deficient mice compared to WT mice. A significant increase in the expression of IL-13 and IL-17 but no IL-4 and IFN-γ mRNA in the skin was observed in bleomycin- injected compared to saline-injected WT mice. Expression of IL-13 and IL-17 mRNA in fibrotic skin was significantly reduced in TSLPR deficient mice compared to WT mice. An increase in the number of IL-13-positive cells by IHC was observed in bleomycin-injected skin compared to saline-injected controls. This response was significantly reduced in TSLPR deficient compared to WT mice. Bleomycin did not increase IL-17 protein expression in either group of mice.

Conclusion: These data provide the first evidence of TSLP contribution to a non-allergic fibrotic process. TSLP profibrotic role is potentially medidated by specific changes in the local cytokine milieu. Thus, modulating TSLP may have anti-fibrotic therapeutic implications.

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1514

Differences in the Activation Levels and Expression Patterns of the Molecular Targets of Tyrosine Kinase Inhibitors May Account for the Heterogeneous Treatment Responses. Britta Maurer[1], Alfiya Akhmetshina[2], Renate E. Gay[1], Beat A. Michel[1], Steffen Gay[3], Joerg HW Distler[2] and Oliver Distler[1]. [1]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, Zurich, Switzerland

Background/Purpose: In SSc, treatment responses to tyrosine kinase inhibitors (TKI) are less distinct compared to animal models. Therefore, we assessed whether the heterogeneous therapeutic effects could be related to differences in the activation level of the TKI targets c-abl and PDGFRβ.

Methods: Skin sections of bleomycin treated (n=10), Fra-2 transgenic (tg) (n=6), non-bleomycin treated (n=10) and wt mice (n=6), of diffuse (n=10) and limited (n=28) SSc patients and healthy controls (n=8) were analyzed by Masson's trichrome stain and immunohistochemistry (IHC) using antibodies against p-PDGFRβ and p-c-abl. Subgroups of bleomycin treated (n=8) and Fra-2 tg mice (n=6) were treated with nilotinib. The bleomycin model reflects early pro-inflammatory stages, whereas the Fra-2 model displays features of vasculopathy-induced fibrosis. Parametric non-related data were expressed as mean$\pm$SEM, nonparametric non-related data as median$_{(Q1,Q3)}$.

Results: In bleomycin treated mice compared to non-bleomycin controls, the dermal expression of both activated PDGFRβ ($10.4_{(10,11)}$ vs. $3.1_{(2,5)}$% cells/HPF) and c-abl ($9.1_{(9,10)}$ vs. $1.5_{(1,2)}$% cells/HPF) was strongly upregulated (p<0.05), whereas in Fra-2 tg compared to wt mice, the expression of p-PDGFRβ ($8.2_{(6,12)}$ vs. $5.4_{(4,7)}$% cells/HPF) and p-c-abl ($2.3_{(1,6)}$ vs. $5.0_{(4,7)}$% cells/HPF) was not significantly increased (p=0.1). In accordance with the strong activation of PDGFRβ and c-abl in the bleomycin model, nilotinib was effective by reducing the increased dermal thickness ($293.5\pm13.3\mu$m) back ($226.4\pm20.6\mu$m) to non-bleomycin levels ($224.3\pm9.3\mu$m, p<0.05). In Fra-2 tg mice, in accordance with the moderate expression of p-PDGFRβ and p-c-abl, nilotinib did not decrease dermal thickness. Given the correlation of activation level and treatment response in the animal models, we examined potential differences in the dermal activation status in subsets of SSc patients and healthy controls. Compared to healthy controls, in limited SSc, there was no significantly increased expression of p-PDGFRβ (3.1 ± 0.2 vs. 7.0 ± 1.2% cells/HPF, p=0.08) and p-c-abl (1.3 ± 0.3 vs. 1.3 ± 0.3% cells/HPF, p=0.9).

Interestingly, in diffuse SSc compared to healthy controls and limited SSc, the activation status of both PDGFRβ (8.0 ± 0.9% cells/HPF) and c-abl (3.9 ± 1.2% cells/HPF) was significantly increased (p<0.05). Whereas in the bleomycin model activated PDGFRβ and c-abl were ubiquitously expressed, particularly in skin fibroblasts, in Fra-2 tg mice there was a vascular predominance which might explain the lacking effect of nilotinib on skin fibrosis. In SSc patients, double staining showed that p-PDGFRβ and p-c-abl were most abundantly expressed in vascular smooth muscle cells (SM22α+) and endothelial cells (vWF+), but only occasionally in scattered dermal fibroblasts(prolylhydroxylase+).

Conclusion: Our study suggests that the activation level and the cellular expression pattern of target molecules are able to predict treatment responses in animal models of fibrosis. The predominant vascular expression of TKI targets in SSc patients might account for the minor anti-fibrotic effects of imatinib in clinical SSc trials.

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1515

Pharmacological Blockade of Adenosine A2A Receptors (A$_{2A}$R) Prevents Radiation-Induced Dermal Injury. Miguel Perez Aso[1], Yee C. Low[2], Obinna Ezeamuzie[2], Jamie Levine[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]New York Univ Medical Center, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Ionizing radiation is a commonly used therapeutic modality and following irradiation dermal changes, including fibrosis and atrophy, may lead to such problems as contractures. The molecular basis for radiation fibrosis is not well understood. We have previously found that adenosine, acting at adenosine A$_{2A}$ receptors (A$_{2A}$R), stimulates collagen production by human dermal fibroblasts and plays a central role in the development of dermal fibrosis in a murine model of scleroderma (bleomycin-induced dermal fibrosis). We therefore tested the hypothesis that A$_{2A}$R play a role in radiation-induced fibrosis and studied the effect of adenosine A$_{2A}$R blockade on development of radiation-induced changes of the skin.

Methods: After targeted irradiation (40Gy) to the skin on the dorsum of each mouse, the A$_{2A}$R antagonist ZM241385 (2.5mg/ml in Carboxymethylcellulose 3%) was applied daily for 28 days. To determine the effect of irradiation on skin we measured skin, dermal and epithelial thickness, collagen alignment with SiriusRed stain, collagen deposition with the hydroxyproline assay and myofibroblast content by immunostaining for α-SMA.

Results: When compared to non-irradiated skin, irradiation induced an increase of the epidermal thickness (33.9 ± 9.8 vs $94.2\pm13.3\mu$m; p<0.01 N=4) but did not affect the skin fold or dermal thickness. In contrast, high dose ZM241385 (2.5mg/ml) completely prevented radiation-induced epidermal thickening ($42.7\pm7.8\mu$m; p<0.001 vs vehicle N=8). Direct measurement of collagen content (hydroxyproline) shows that the collagen increase after the radiation insult (control: 15.2 ± 1.3 vs radiation: 21.6 ± 1.4 μg/ml; p<0.05 N=5) is partially prevented by ZM241385 application (18.7 ± 1.5 μg/mg N=8). Collagen alignment and packaging analysis by SiriusRed stain reveals that irradiation promotes a dramatic increase in loose packed collagen fibrils (421 ± 104% of Control: p<0.05 N=9), which is significantly diminished by ZM241385 application (75 ± 21% of Control; p<0.01 vs vehicle N=7). After irradiation-induced fibrosis, we detected an increase on myofibroblasts (α-SMA$^+$ cells; 34 ± 3 vs 83 ± 10 cells per field; p<0.01 N=5) which was again prevented by ZM241385 application (57 ± 5 cells per field; p<0.05 vs vehicle N=8).

Conclusion: Taken together, these data indicate that pharmacological blockade of A$_{2A}$R prevents skin thickening in a murine model of irradiation-induced fibrosis, and suggests that topical application of an A$_{2A}$R antagonist may be useful in the prevention or amelioration of radiation changes in the skin.

Disclosure: **M. Perez Aso**, None; **Y. C. Low**, None; **O. Ezeamuzie**, None; **J. Levine**, None; **B. N. Cronstein**, Canfite BioPharma, 1, NIH, URL Pharma, OSI, 2, Bristol-Myers Squibb, Novartis, URL, Regeneron, Gismo Therapeutics, 5, Arthritis Foundation, SLE Foundation, 6, Patents on use of adenosine receptor antagonists to treat or prevent fibrosis. Multiple other patents.

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TSLP Upregulation in Human SSc Skin and Induction of Overlapping Profibrotic Genes and Intracellular Signaling with IL-13 and TGFb.
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Background/Purpose: to investigate the expression of Thymic Stromal Lymphopoietin (TSLP) in diffuse cutaneous systemic sclerosis (dcSSc) patients and explore its effects in vivo and in vitro comparing with IL-13 and TGF-beta stimulations.

Methods: Skin biopsies [dcSSc; n=13 and healthy controls (HC); n=12] were used for immunohistochemistry (IHC) and immunofluorescence studies using TSLP, $CD4^+$, $CD8^+$, $CD31^+$, and $CD163^+$ markers. Wild type (WT) and IL4Ra1-deficient mice (IL4Ra1-ko) were treated with TGF-beta, IL-13, Poly(I:C), or TSLP. Human fibroblasts and peripheral blood mononuclear cells (PBMCs) were stimulated with the same cytokines. Gene expression (microarray and rt-PCR) and protein levels of phospho-Smad2 were tested.

Results: TSLP was highly expressed in skin of dcSSc patients, stronger in perivascular areas, where we observed inflammatory cell infiltrates, and in interstitial cells. TSLP expression was co-localized with immune cells, such as $CD4^+$, $CD8^+$, although mainly produced by $CD163^+$ cells. Skin of TSLP-treated mice showed upregulated clusters of genes that overlapped with IL-13 and TGFb-treated mice. In addition, a specific TSLP-cluster showed upregulation of CXCL9, proteasomes, and other interferon-regulated genes. In PBMCs, TSLP alone upregulated mannose-receptor-1 (MRC1), an alternatively-activated macrophage marker, to a similar degree as after IL-13 stimulation. MRC1 was also highly expressed in dcSSc skin compared to controls. TSLP kinetics, along 24 hours of stimulation in PBMCs, showed an early induction of TNF, MX1, and INFg, followed by an induction of CXCL9 and MRC1 gene-expression. Human fibroblasts and skin of mice-treated with TSLP showed TGF-beta-canonical pathway activation with phosphorylation of Smad2. The lack of IL4Ra1 in TSLP-treated mice promotes similar cutaneous inflammation and upregulation of profibrotic markers (PAI-1 and CXCL5). Poly(I:C)-treated mice, a SSc-like murine model, showed high levels of TSLP in similar areas as seen in the skin of dcSSc patients and also mainly in infiltrating immune cells, shown by IHC.

Conclusion: TSLP is highly expressed in skin of dcSSc patients, mainly produced by macrophages, and regulates similar genes as other profibrotic cytokines (TGF-beta and IL-13), strongly suggesting that it promotes SSc fibrosis directly or by stimulating production or activation of these cytokines. TSLP also promotes a proinflammmatory effect, which might explain this dual finding in SSc patients.

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TLR9 Signaling in Fibroblasts Promotes Pro-Fibrotic Responses Via TGF-Beta.
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Background/Purpose: Systemic sclerosis (SSc) is associated with progressive fibrosis and transforming growth factor β (TGF-β) is implicated in its pathogenesis. Toll-like receptors (TLR) respond to microbial pathogens or injury-associated endogenous danger signals, and aberrant TLR9 signaling is implicated in chronic inflammation, autoimmunity and pulmonary fibrosis. However, the role of TLR9 in fibrogenesis, and the underlying mechanism of action are still unknown.

Methods: TLR9 expression in explanted fibroblasts and mouse skin biopsies was determined. Regulation of fibrotic gene expression and TGF-β signaling by the TLR9 ligand CpG was examined by real-time PCR, Western blot, transient transfection and immunofluorescence assays. Inhibitors of TLR9 were used to examine the antifibrotic response in vitro.

Results: TLR9 was detected in explanted normal and scleroderma skin fibroblasts, and the skin from mice with bleomycin-induced scleroderma. The TLR9 ligand CpG caused dose-dependent stimulation of collagen and α-smooth muscle actin (ASMA) gene expression along with inflammatory genes. Induction of fibrotic responses was blocked by the TLR9 antagonist iCpG. Moreover, CpG stimulated TGF-β production, TGF-β-mediated responses and canonical Smad signaling, and a neutralizing antibody to TGF-β abolished CpG-induced fibrotic responses. The proteasome inhibitor Bort-

ezomib abrogated CpG-induced stimulation of collagen and ASMA gene expression by disrupting intracellular TLR9 trafficking.

Conclusion: TLR9 activation in fibroblasts is associated with TGF-β-mediated fibrotic responses. Novel small molecule inhibitors of TLR9 already in clinical trial for lupus are sufficient to abrogate these responses, suggesting a potential therapeutic strategy for blocking TLR9 in fibrosis.

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Damage-Associated Endogenous TLR4 Ligand Fibronectin-EDA Is Overexpressed in Scleroderma and Drives Persistent Fibrosis Via TLR4 and Inhibition of TLR4 Prevents and Reverses Experimental Dermal Fibrosis: Novel Target for Scleroderma Therapy.
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Background/Purpose: Recent studies implicate innate immune signaling and Toll like receptor-4 (TLR4) in fibrogenesis. We hypothesized that injury in scleroderma leads to tissue accumulation of damage-associated molecules such as fibronectin-EDA (Fn-EDA), which serve as endogenous ligands for TLR4. We sought to characterize the expression, mechanism of action and potential fibrogenic role of Fn-EDA. We further investigated the effect of pharmacological inhibition of TLR4 signaling on fibrogenesis.

Methods: TLR4 expression and Fn-EDA production and accumulation were evaluated in scleroderma skin biopsies and sera, in explanted normal and scleroderma skin fibroblasts, and in mouse models of scleroderma. The fibrogenic effect of Fn-EDA-TLR4 signaling was evaluated in explanted normal and scleroderma skin fibroblasts and in human organotypic skin raft cultures. The role of Fn-EDA in fibrogenesis was further evaluated using Fn-EDA-null mice. The effect of pharmacological inhibition of TLR4 signaling was evaluated in experimental models of dermal fibrosis and in explanted scleroderma fibroblasts.

Results: Fn-EDA was markedly elevated in scleroderma serum and skin biopsies, and in lesional tissues from mice with bleomycin-induced scleroderma. Microarray analysis showed elevated Fn-EDA mRNA levels in skin biopsies from patients with diffuse cutaneous scleroderma. Explanted scleroderma fibroblasts in organotypic skin raft cultures produced elevated Fn-EDA and deposited it into the matrix. Fn-EDA stimulated collagen synthesis and myofibroblasts differentiation in vitro, and induced dermal sclerosis in the skin equivalent. The profibrotic effects of Fn-EDA were TLR4-dependent and mediated via the microRNA miR29. Pharmacological TLR4 disruption using a novel small molecule inhibitor, or genetic deletion of Fn-EDA, protected mice from the development of skin fibrosis.

Conclusion: Together, these complementary in vitro and in vivo experiments firmly implicate TLR4-mediated innate immune signaling and aberrant Fn-EDA production and accumulation in driving persistent fibroblast activation and progressive fibrogenesis. Disrupting the TLR4-Fn-EDA axis by either preventing Fn-EDA accumulation, or blocking TLR4 signaling using selective small molecule inhibitors, represent appealing novel strategies for treating scleroderma.

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Heterogeneous Nuclear RNP-K Is a Novel Cold-Related Autoantigen in Patients with Raynaud's Phenomenon.
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Background/Purpose: Raynaud's phenomenon (RP) is a vasospastic disorder and shows discoloration of the fingers, toes, and occasionally other areas. RP affects 3–9% of the general population, but more frequently of patients with connective tissue diseases. In particular, more than 90% of systemic sclerosis (SSc) patients suffer from RP. While a variety of stress

including cold and emotional stress have been reported to influence both cellular and humoral immune function, the pathogenesis of the RP is not fully understood. The aim of study was to identify a novel autoantigen related to cold-induced RP.

Methods: Cold-induced surface proteome alterations in human normal dermal microvascular endothelial cells (dHMVECs) were identified by iTRAQ (isobaric tag for relative and absolute quantitation) analysis. Autoantigens were screened by serological proteome analysis (SERPA) using the sera from patients with SSc-associated RP.

Results: By proteomic analyses combining iTRAQ and SERPA approach, heterogeneous nuclear RNP-K (hnRNP-K) was identified as a candidate autoantigen for patients with SSc-associated RP. Cold-induced translocation of hnRNP-K to cell surface was verified by western blot (WB) and flow cytometric analysis. The presence of anti-hnRNP-K autoantibody in patients' sera with SSc-associated RP was confirmed by WB. ELISA analysis revealed that the prevalence of anti-hnRNP-K autoantibody in patients with SSc-associated RP was 30.70% (35 of 114), which was significantly higher than that of SSc patients without RP (7.14%, 2 of 28, P = 0.0027) and healthy controls (0%, 0 of 27, P = 0.0001).

Conclusion: Autoantibody against hnRNP-K is a potential marker for detecting a subset of SSc-associated RP. Cold stimulation may exacerbate RP by revealing autoantigens including hnRNP-K and inducing autoimmune reaction in vascular endothelia.

Disclosure: **S. Serada**, None; **M. Fujimoto**, None; **T. Naka**, None.

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Role of 12/15-Lipoxygenase(LOX) in Patients with Systemic Sclerosis.
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Background/Purpose: Recently 12/15-lipoxygenase (LOX) and it's metabolites have a prominent anti-fibrotic role during dermal fibrosis in scleroderma experimental model using 12/15-LOX deficient mice were reported (Ann Rheum Dis. 2012,71,1081). To evaluate the role of 12/15-lipoxygenase (LOX) in patients with systemic sclerosis(SSc) we measured 12/15-LOX and these enzyme metabolites.

Methods: SSc 32 patients:age57±10.3years old, disease duration 6.4±4.9years. dcSSc: lcSSc 20:12. control:RA 20 patients, normal healthy subjects 20. We measured the level of 12-LOX, 15-LOX mRNA in peripheral blood mononuclear cells(PBMC)of patients with SSc by real time quantitative PCR. 12-LOX and 15-LOX metabolites 12-(S)-Hydroxytetraenoic acid (HETE), 15-(S)-HETE and lipoin A_4(LXA$_4$)were measured by ELISA in plasma and bronchoalveolar lavage fluid (BALF) of patients with SSc. 15-LOX/12-LOX expression was measured by immunohistological analysis in biopsy specimens of dermal and interstitial pneumonia of patients with SSc.

Results: Level of plasma 12-(S)-HETE of SSc was significantly higher than that of RA and normal subjects(SSc10.76±3.22, RA 4.08±1.22, Control 3.77±1.26 ng/ml, P<0.01). Level of plasma lipoxin A_4 of SSc was also higher than that of RA and control (SSc, 3.39±1.79, RA 0.75±0.35, normal 0.77±0.30 ng/ml). On the other hand level of plasma 15-(S)-HETE in SSc was lower than that of control (SSc2.07±1.18,RA3.76±1.82, normal2.39±0.98ng/ml). Plasma 12-(S)-HETE, LXA$_4$ levels in dcSSc patients were higher than that of lcSSc (dcSSc 4.1±1.6, lcSSc 1.86±0.85 ng/ml). Expression of 12-LOXmRNA in PBMC of patients with SSc was higher than normal (SSc 4.7, control 1). Expression of 15LOX was not higher than SSc. BALF LXA$_4$ and 15-LOX in lung biopsy specimens were lower than that of other interstitial pneumonia.

Conclusion: Expression of platelet type 12-LOX was correlated with the progression of fibrotic lesion in patients with SSc. These data suggested that platelet type 12-LOX and 12-(S)-HETE may be increased for the negative feedback mechanisms for fibrosis because these enzymes and metabolites had anti-fibrotic effects. 12/15-LOX systems may contribute a new therapeutic approach in skin and organ involvement in patients with SSc.

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A Possible Contribution of Decreased Cathepsin V Expression to the Development of Dermal Fibrosis, Proliferative Vasculopathy, and Altered Keratinocyte Phenotype in Systemic Sclerosis.
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Background/Purpose: Cathepsin V (CTSV) is a proteolytic enzyme potentially modulating angiogenic processes, collagen degradation, and keratinocyte differentiation. Although our latest paper demonstrated that cathepsin B, another member of cathepsin family, is potentially involved in the developmental process of dermal fibrosis and vasculopathy in systemic sclerosis (SSc), the role of cathepsin V, to the best of our knowledge, has not been well studies so far in this disorder. Therefore, we herein investigated the clinical correlation of serum CTSV levels and the expression levels of CTSV in skin sections among SSc patients.

Methods: Serum CTSV levels were determined by enzyme-linked immunosorbent assay in 51 SSc patients and 18 normal controls. The expression levels of CTSV protein in normal and SSc skin were evaluated by immunohistochemistry. The contribution of transcription factor Friend leukemia virus integration 1 (Fli1), whose deficiency is associated with the developmental process of SSc, to the altered expression of CTSV in SSc skin was examined in cultured dermal fibroblasts, dermal microvascular endothelial cells, and keratinocytes by reverse-transcript real-time PCR.

Results: Serum CTSV levels were significantly lower in diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) patients than in healthy controls. In early-stage dcSSc, serum CTSV levels were remarkably and uniformly decreased compared with healthy controls. The decrease in serum CTSV levels in mid- and late-stage dcSSc and in lcSSc was linked to the development of proliferative obliterative vasculopathy. In immunohistochemistry, CTSV expression was decreased in microvascular endothelial cells, pericytes/vascular smooth muscle cells, and keratinocytes of dcSSc and lcSSc skin and in dermal fibroblasts of dcSSc skin compared with control skin. Consistently, mRNA levels of CTSV gene were decreased in cultured dermal fibroblasts from early-stage dcSSc and in normal dermal fibroblasts treated with TGF-β1. Furthermore, Fli1 gene silencing by siRNA, which potentially reproduces SSc phenotype in microvascular endothelial cells and keratinocytes, reduced the mRNA levels of CTSV gene in human dermal microvascular endothelial cells and normal human keratinocytes.

Conclusion: Loss of CTSV expression may contribute to the specific phenotype of fibroblasts, endothelial cells, and keratinocytes in SSc, suggesting the possible involvement of decreased CTSV expression to the developmental process of this disorder.

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Differential Response to Endoplasmic Reticulum Stress Between Alveolar Epithelial Cells and Lung Fibroblasts in Systemic Sclerosis.
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Background/Purpose: Interstitial lung disease is a prevalent and worrisome complication of systemic sclerosis (SSc), which is now the leading cause of death in SSc. There is growing recognition that endoplasmic reticulum (ER) stress plays a pathogenic role in SSc-associated interstitial lung disease (SSc-ILD) and in other interstitial lung diseases. However, the nature of the response during ER stress in alveolar epithelial cells (AEC) and lung fibroblasts, two key players in pulmonary fibrosis, remains unknown. Here we demonstrate that differential ER stress response in these two cell types depends upon the expression of the pro-apoptotic C/EBP homologous protein or "CHOP", an important ER stress marker.

Methods: Lung tissues were collected postmortem from control subjects and from SSc patients who fulfilled the ACR preliminary criteria for SSc and had evidence of lung involvement. SSc-ILD was confirmed by histological examination of postmortem lung tissue. Additionally, lung tissues were obtained from mice with bleomycin-induced pulmonary fibrosis and from control animals. AEC and lung fibroblasts were isolated using standard

procedures. Lung tissues were analyzed by immunohistochemistry. Protein expression in AEC and lung fibroblasts was determined by immunoblotting; apoptosis was measured by enzyme-linked immunosorbent assay; *chop* promoter activity was analyzed by luciferase assay.

Results: We demonstrate for the first time that CHOP expression is profoundly increased in AEC surrounded by fibrotic tissues in SSc-ILD patients, but not in normal lung tissues. We observed staining for CHOP exclusively in AEC surrounded by fibrotic tissues. CHOP expression was also noted to be localized to thickened alveolar septae in SSc-ILD patients and in bleomycin-treated mice, but not in normal lung tissues from human or murine controls. In contrast, myofibroblasts (positively stained for α-SMA) show no significant immunoreactivity for CHOP. Thrombin, known to be elevated in SSc-ILD patients and in the bleomycin murine model of ILD, had no observable effect on CHOP expression in lung fibroblasts. However, thrombin was noted to upregulate CHOP expression in primary AEC and in A549 cells via an Ets1-dependent pathway. Importantly, we demonstrate that lung myofibroblasts from SSc-ILD patients and from mice treated with bleomycin, which are resistant to apoptosis, lose the resistance to apoptosis when transfected with CHOP.

Conclusion: AEC and lung myofibroblasts in SSc-ILD exhibit a differential response to ER stress, which may confer the differential fate of these two cell types, i.e., the susceptibility to apoptosis of AEC and the resistance to apoptosis of lung myofibroblasts. The ER stress marker CHOP is involved in regulating apoptotic mechanisms in fibrotic lung tissue downstream of two key mediators, thrombin and TGF-β, making CHOP a possible novel target for the treatment of SSc-ILD.

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ACR/ARHP Poster Session B
Vasculitis
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Systemic Vasculitis and Pregnancy: a Multicenter Study On Maternal and Neonatal Outcome of 43 Prospectively Followed Pregnancies.
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Background/Purpose: Systemic Vasculitis (SV) are rare diseases that may affect females during childbearing age. Quite a few data are available in literature, and mostly from case reports. Aim of our study is to evaluate the maternal/neonatal outcome, the activity of maternal disease before, during and after pregnancy in patients with diagnosis of SV followed in five Italian Institutions.

Methods: Our study is a retrospective analysis of 43 pregnancies (prospectively followed by a multispecialistic team, with a least 1 documented visit each trimester) in 33 patients with diagnosis of SV, according to Chapel Hill Consensus Conference and/or ACR Criteria for SV. We collected: Takayasu Arteritis (TA) (6pregnancies in 4 patients), Churg-Strauss Syndrome (CS) (6 in 6 pt), Polyarteritis Nodosa (PA) (3 in 2 pt), Behcet's Disease (BD) (20 in 16 pt), Wegener Granulomatosis (WG) (3 in 3 pt), Henoch-Schönlein (HS) (2 in 1 pt) and ANCA associated-neuropathy (3 in 1 pt). Data regarding the duration of disease, serological and clinical features, pregnancy outcome, neonatal and maternal complications and therapy during pregnancy were collected from clinical charts.

Results: The mean age of the patients at the onset of the disease was 24.7yrs (with standard deviation (SD) of 6.9 yrs) and at the diagnosis was 26yrs (SD6.1yrs); our patients were Caucasians (28), afro-americans (2), Asians (2) and African (1). The mean duration of SV before pregnancy was 6,5 yrs (SD 5yrs). 5 patients were ANCA positive. 11 patients had been treated with cytotoxic or embriotoxic drugs but none of the pregnancies were exposed to such drugs. 1 out the 3 patients previously treated with cyclofosphamide had primary ovarian failure (POF). Five pregnancies were obtained by in vitro fertilization (all because of female infertility), one by oocyte donation in the patient with POF. During the 43 pregnancies, 6 flares of SV occurred during the first trimester (13.9%), 7 (20%) occurred in the 35 evaluable in the second trimester and 3 in 33 (9%) whose data are available in the third trimester. The onset of BD at 10°week of gestation was reported in one patient. Pregnancy-related complications occurred in 14 pregnancies, among which 4 cases of gestational diabetes. The mean week of delivery was 37.7 (SD 3 weeks) with 5 preterm delivery (before the 34°week). The pregnancy outcome was 33 live births (2 twins pregnancy), 8 miscarriages (1in a twin pregnancy), 1 fetal death. 2 pregnancies are still ongoing. 6 newborns had neonatal complications. Data about the postpartum period were available for 34 pregnancies:11 flares (32.3%) occurred.

Conclusion: Our data show that a strict multidisciplinary monitoring does not prevent maternal/neonatal complications in patients with Systemic Vasculitis. In addition puerperium should be regarded as a risk period for vasculitis flares, similarly to other systemic autoimmune diseases.

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The Use of the International Classification of Function, Disability and Health As a Conceptual Framework for Comparison of the Content of Core Outcome Instruments with the Patient Perspective in Vasculitis.
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Background/Purpose: The International Classification of Functioning, Disability and Health (ICF) is a general health model endorsed by the World Health Organization. It describes health along 4 domains: body functions, body structures, activities and participation, and environmental factors. There is interest in applying ICF to human disease states to determine what domains of health are captured by current disease assessment tools.

In 2010 the OMERACT (Outcome Measures in Rheumatology Clinical Trials) initiative endorsed the Core Set of outcome measures for ANCA-associated vasculitis (AAV). The Core Set includes a choice of 3 disease activity measures (Birmingham Vasculitis Activity Score (BVAS), BVASv.3, BVAS for Wegener's Granulomatosis), 1 damage measure (Vasculitis Damage Index (VDI)), 1 patient-reported outcome (Short Form-36 (SF36)), and death. This study examined the extent to which the AAV Core Set captures the impact of AAV relevant to patients, using the ICF classification.

Methods: Outcome measures included in the OMERACT Core Set for AAV were linked to the corresponding ICF categories according to the previously established ICF linkage rules.

Two focus groups involving 9 patients were conducted. Patients identified aspects of disease that have an important impact on their lives. Focus group transcripts were analyzed according to standard qualitative analytic techniques. Identified concepts were linked to ICF categories. Coverage of various ICF domains by the Core Set tools was compared to coverage by the items identified by patients.

Results: All items of the Core Set's measures of disease activity and damage linked to categories of the ICF domains 'body functions' and 'body structures'. In contrast, the majority of items of SF36 linked to categories of the ICF domain 'activities and participation', with the remaining smaller number of items linking to categories of 'body functions' domain.

AAV Core Set instruments and patients focus on different aspects of the domain 'body functions'. The Core Set covers specific organ functions (e.g. hearing) while patients focus on sensations associated with these functions (e.g. ear fullness); similarly, the Core Set covers pain in specific body parts, while patients identify generalized and multifocal pain as most relevant. Sleep, temperament and personality, and exercise tolerance were areas in the 'body functions' domain identified by patients as important but not measured by any of the Core Set tools.

One broad area in the domain 'activities and participation' that was identified as crucial by patients but not covered by the Core Set is "interpersonal interactions and relationships". Similarly, environmental factors are not part of the AAV Core Set, while for patients a number of such factors are relevant in establishing the impact of AAV (various products and technology, support and relationships, attitudes, and services).

Conclusion: The ICF model is useful for identifying areas of health important for capturing the impact of AAV from patients' perspective but not covered by the currently utilized AAV outcome tools. These observations support the ongoing initiatives to expand the scope of outcome assessment in AAV, especially to include patient-reported outcomes.

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Determinants of Poor Quality of Life in ANCA Associated Vasculitis (AAV). Neil Basu[1], Andrew McClean[2], Raashid Luqmani[3], Lorraine Harper[2], Oliver Flossmann[4], David Jayne[5], Mark Little[6], Esther N. Amft[7], Neeraj Dhaun[8], John McLaren[9], Vinod Kumar[10], Lars Erwig[1], Gareth T. Jones[1], David M. Reid[1] and Gary J. Macfarlane[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]University of Birmingham, Birmingham, United Kingdom, [3]University of Oxford, Oxford, United Kingdom, [4]Royal Berkshire Hospital, Reading, United Kingdom, [5]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [6]Trinity College Dublin, Dublin, Ireland, [7]Western General Hospital, Edinburgh, United Kingdom, [8]Edinburgh Royal Infirmary, Edinburgh, United Kingdom, [9]NHS Fife, Whyteman's Brae Hospital, Kirkcaldy, United Kingdom, [10]Ninewells Hospital, Dundee, United Kingdom

Background/Purpose: Patients with ANCA associated vasculitis (AAV) report significantly reduced quality of life (QOL), however the precise causes of such impairments are poorly understood.

This large study aimed to identify the determinants of poor QOL amongst AAV patients with view to informing future interventions designed to modify this crucial outcome.

Methods: A cross-sectional study was conducted. AAV cases were recruited from rheumatology and renal departments across the UK according to consecutive clinic attendance and classified using the EMEA vasculitis algorithm. Participants completed a questionnaire which determined physical- and mental-health related QOL (SF36 physical and mental component summary scores; PCS and MCS, respectively). In addition, data on putative psychosocial determinants of poor QOL was collected, including depression, anxiety (Hospital and Anxiety Depression Scale), fatigue (Chalder Fatigue Scale), sleep disturbance (Estimation of sleep problems questionnaire), coping (Brief Cope) and pain (body manikins). Concurrently, putative clinical determinants were measured, including assessments of disease activity (Birmingham Vasculitis Activity Score 3, BVAS), disease damage (Vasculitis Damage Index), co-morbidity (Charlson index), immunosuppressant exposure, laboratory tests (ANCA, haemoglobin, albumin, renal function, CRP) and system involvement. Measures were categorised and 2 multivariable explanatory models of poor PCS and MCS (defined as scores below general population mean) were developed using forward stepwise logistic regression. The relative importance, in population terms, of the identified associations was further quantified using population attributable risks.

Results: Of 486 invited patients, 410 participated (86%): 49% male, median age 63.5 years (Inter-quartile range 51.8–72.4 years), 19.3% recording active disease (BVAS>0). The final multivariable models identified a number of clinical and psychosocial factors found to be independently and significantly associated with poor PCS and MCS (Table). Fatigue was the only factor to be independently associated with both PCS and MCS and was also, by far, the greatest contributor to poor QOL in population terms across both models.

Table. Multivariable explanatory models of poor Quality of Life (QOL) amongst AAV patients

	Odds Ratio (95% CI)	Population attributable risk
Poor Physical related QOL (PCS) model		
High Fatigue (CFS)	3.2 (1.5–6.9)	24.6%
High Sleep Distrubance (ESQ)	5.3 (2.3–12.1)	13.1%
Pain	3.6 (1.7–7.8)	11.5%
High current PRED do se (>5mg)	3.8 (1.5–9.7)	5.3%
Old Aged (>69 years)	3.5 (1.4–8.9)	5%
Raised CRP	4.1 (1.6–10.6)	5%
Nervous system involvement (ever)	2.2 (0.6–7.2)	1.2%
Poor Mental related QOL (MCS) model		
High Fatigue (CFS)	4.0 (1.8–8.9)	47.4%
Self distraction (BC)	3.2 (1.6–6.6)	19.3%
Low Positive reframing (BC)	3.0 (1.5–6.3)	16.1%
Hypoalbuminemia	2.9 (1.3–6.6)	15.0%
Self blame (BC)	4.3 (1.8–10.4)	8.0%
Anxiety (HADS)	5.7 (2.1–15.0)	7.3%
Depression (HADS)	5.6 (2.0–15.8)	6.3%
Behavioural disengagement (BC)	2.1 (0.9–4.6)	5.5%
Unemployment	8.1 (2.2–30.3)	5.5%
Substance dependence (BC)	2.1 (0.9–4.6)	3.2%

*Dichotomised at general population mean; CFS Chalder Fatigue Scale; HADS Hospital Anxiety and Depression scale; BC Brief Cope; ESQ Estimation of Sleep Problems Questionnaire; PCS SF 36 Physical Component Summary; MCS SF36 Mental Component Summary

Conclusion: Poor QOL amongst AAV patients is determined by multiple clinical and psychosocial factors, however, fatigue appears to be the most important. Clinically, optimal control of underlying inflammation and neurological manifestations are likely to improve aspects of QOL, however multidisciplinary interventions targeting psychosocial determinants may offer even greater gains. Further work is required to develop treatment strategies specific to alleviating fatigue.

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Patient Reported Outcomes in ANCA-Associated Vasculitis. A Prospective Comparison Between Birmingham Vasculitis Activity Score and Routine Assessment of Patient Index Data 3. Osama ElSallabi, Joel A. Block and Antoine Sreih. Rush University Medical Center, Chicago, IL

Background/Purpose: ANCA-associated vasculitis (AAV) is a rare group of diseases comprising Granulomatosis with polyangiitis (Wegener's; GPA), Microscopic Polyangiitis (MPA), and Churg-Strauss Syndrome (CSS). These diseases often result in severe morbidity and frequent relapses. The Birmingham Vasculitis Activity Score v3 (BVAS) is a well-established and validated tool to measure AAV activity. However, current tools do not include patient-reported outcomes to assess for disease activity. The Multi-Dimensional Health Assessment Questionnaire (MDHAQ) has been documented to be effective in many rheumatic diseases. Therefore, we compared BVAS scores to a patient-only index termed the "Routine Assessment of Patient Index Data 3" (RAPID3) on an MDHAQ.

Methods: Patients with AAV treated by one rheumatologist at Rush University Medical Center in Chicago, IL from Jan 2010 to May 2012 were asked to participate and given MDHAQ to complete for 4 consecutive visits approximately every 6 months. An independent investigator scored RAPID3, which comprises 3 Core Data Set measures on the MDHAQ for function, pain, and patient global assessment (PATGL) and takes 5 seconds to score; scores range from 0 to 30, with higher scores being worse. BVAS was calculated at each patient visit; scores range from 0 to 63, with worse disease being higher. Both scores were compared using Spearman non-parametric correlations. BVAS was also compared to PATGL, which is a visual analogue scale from 0 to 10 and is one of the Core Data Set measures in RAPID3. Linear regression was used to adjust for age, sex, ethnicity, RAPID3 version language, type of the disease, duration of the disease, years of schooling and type of insurance. $P \leq 0.5$ was considered significant. The institutional Review Board approved the study.

Results: Twenty-nine patients with AAV consented and were included in the study, 22 had GPA, 5 MPA and 2 CSS. The mean age was 54.1 years, 77% were females, 69% Caucasians, 23% Hispanics, and 8% African-Americans. The mean duration of disease was 4.3 years. The mean BVAS at first visit was 6.1 ± 0.9 (range: 0–17), RAPID3 was 8 ± 1.3 (range: 0–22.7), and PTGA was 3.6 ± 0.5. RAPID3 correlated with BVAS at each visit (rho $= 0.45, 0.75, 0.73, 0.54$ with p values of 0.02, <0.0001, 0.002, and 0.05 for visits 1 to 4, respectively) and PATGL correlated with BVAS at 3 out of 4 visits, independently of RAPID3 (rho$= 0.24, 0.75, 0.64, 0.59$ with p values of 0.23, <0.0001, 0.01, 0.01 for visits 1 to 4, respectively).

Conclusion: RAPID3, a patient-only index, is correlated significantly with the BVAS. RAPID3 can be calculated in 5 seconds and does not require physician input, laboratory or imaging information. PATGL, a one simple measure of patient global assessment, may also reflect disease activity. As patient-relevant outcomes become increasingly important to insurers and to society, it is critical to identify valid patient-reported markers of vasculitis activity; RAPID3 permit longitudinal assessments of disease activity at any medical facility by any physician or even away from physician's offices. In the face of increased expenses and busy practices, such instruments may help document patient status and add to clinical decisions.

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Patient Global Assessments for Disease Activity Are Predictive of Future Flare in Granulomatosis with Polyangiitis (Wegener's). Gunnar Tomasson[1], John C. Davis Jr.[2], Gary S. Hoffman[3], W. Joseph McCune[4], Ulrich Specks[5], Robert F. Spiera[6], E. William St. Clair[7], John H. Stone[8] and Peter A. Merkel[9]. [1]University of Iceland, Reykjavik, Iceland, [2]Genentech, Inc, South San Francisco, CA, [3]Cleveland Clinic, Cleveland, OH, [4]University of Michigan, Ann Arbor, MI, [5]Mayo Clinic, Rochester, MN, [6]Hospital for Special Surgery, New York, NY, [7]Duke University Medical Center, Durham, NC, [8]Massachusetts General Hospital, Boston, MA, [9]University of Pennsylvania, Philadelphia, PA

Background/Purpose: In granulomatosis with polyangiitis GPA), disease activity is assessed by physician-based measures. In some other rheumatic diseases, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), the patient global assessment for disease activity (PtGA) contributes to composite disease activity scores such as the DAS28 (RA) and ASDAS (AS). The purpose of this study was i) to describe distribution of PtGA scores in patients with GPA enrolled in a clinical trial, ii) explore discordance between PtGA and physician global assessments for disease activity (MDglobal), and iii) determine if PtGA during disease remission is associated with future disease relapse.

Methods: Subjects were participants in a therapeutic clinical trial. Patients had active disease at enrollment, with study visits occurring at baseline, 6 weeks and every 3 months thereafter. PtgA was assessed on a visual analog scale (0–100) with the question: *"Please mark the line below indicating how active you believe your Wegener's granulomatosis has been in the past 28 days. Consider only how much your Wegener's (the disease itself) is causing you problems. Do not count the effects of other medical problems or side effects of medications".* Disease activity was assessed with the Birmingham Vasculitis Activity Sore for WG (BVAS/WG). Remission was defined as BVAS/WG=0 and disease relapse was defined as BVAS/WG>0 after remission was achieved. MDglobal was assessed on a visual analog scale (0–100mm). PtGA-MDglobal discordance was defined as difference of 20 millimeters (mm) between PtGA and MDglobal scores. Logistic regression was used to explore association of PtGA-MDglobal discordance with demographic and disease associated factors. Mixed linear models were used to explore difference in PtGA scores between study visits during remission, but immediately prior to overt relapse, and other study visits during remission.

Results: Data from 180 subjects seen for total of 1719 study visits were used. At baseline mean PtGA was 64.2 (sd=27.4) and mean MDglobal was 55.5 (sd=23.4). At baseline, there was modest, but significant, correlation between PtGA and MDglobal scores (r=0.30, p<0.001); 54.4% of patients had a $\geq$20mm PtGA-MDglobal discordance. PtGA-MDglobal discordance at baseline was associated with relapsing (vs. new-onset) disease at baseline (OR 2.70, 95%CI: 1.47–1.96) but not associated with age, sex, or presence of renal or pulmonary disease. During follow-up, subjects were in disease remission during 1058 study visits, of which 103 immediately preceded disease relapse. At remission visits immediately preceding relapse the mean PtGA was 20.4 and at visits not followed by disease relapse the mean PtGA was 15.9, a difference of 4.5 (95% CI 0.66–8.4, p=0.02).

Conclusion: In GPA, patient and physician assessments are frequently discordant. Higher PtGA during apparent remission is associated with future overt disease relapse. These data imply that PtGA captures aspects of disease activity missed by physician-based measures. PtGA could contribute to a composite measure of disease activity in GPA.

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Assessing Fatigue in Systemic Vasculitis From the Patient's Perspective. Peter C. Grayson[1], Naomi Amudala[1], Carol McAlear[2], Renée Leduc[3], Denise Shereff[3], Rachel Richesson[3], Liana Fraenkel[4] and Peter A. Merkel[5]. [1]Boston University Medical Center, Boston, MA, [2]Vasculitis Clinical Research Consortium, University of Pennsylvania, Philadelphia, [3]University of South Florida, Tampa, FL, [4]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [5]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Fatigue is considered an important disease burden by patients with vasculitis, yet mechanisms underlying fatigue are poorly understood. *Physician-derived* measures of vasculitis disease activity do not correlate with fatigue. The aim was to determine if fatigue is associated with *patient-reported* measures of disease activity and/or illness perceptions, defined as the cognitive beliefs that patients have about their illness.

Methods: Participants were recruited from an online patient contact registry in vasculitis. Disease activity (remission vs active), disease extent (presence of a defined severe manifestation), disease duration, remission duration, and clinical variables (age, sex, race, depression, sleep disturbance) were assessed per patient-report. Fatigue was measured using the general subscale of the Multidimensional Fatigue Inventory (MFI) with scores $\geq$13 indicating severe fatigue. Illness perceptions were assessed using the revised Illness Perception Questionnaire (IPQ-R). The IPQ-R measures illness perceptions in specific dimensions: *identity, timeline, timeline-cyclical, consequences, personal* and *treatment control, emotional representations, and coherence* [see **Table** for definitions]. Disease status, clinical variables, and IPQ-R dimensions were assessed in relation to MFI scores using linear regression in 3 sequential, additive models with model-fit comparisons.

Results: 692 people with 9 different forms of vasculitis completed the IPQ-R. Disease status characteristics included current disease remission (45%), severe disease manifestation (54%), median disease duration (7.4 years), and remission duration $\geq$ 1 year (27%). Mean MFI score was 15.0 ($\pm$3.9). Disease activity, remission duration, age, race, depression, sleep disturbance, and all IPQ-R dimensions except timeline were significantly associated with MFI scores (**Table**). Sequential models demonstrated that IPQ-R dimensions explained an additional 18% of variability in fatigue scores after accounting for disease status and clinical variables. 56% of variability in fatigue scores remained unexplained in the full model.

Table. Association of fatigue scores with disease status, clinical variables, and IPQ-R dimensions in three sequential, additive linear models.

Step One: Disease Status		Step Two: Add Clinical Variables		Step Three: Add IPQ-R Dimensions	
Disease Activity *(active vs remission)*	$\beta = 1.01$**	Age *(per year)*	$\beta = 0.01$**	Identity	$\beta = 0.07$*
Disease Extent *(severe vs not)*	$\beta = 0.33$	Sex *(female vs male)*	$\beta = -0.43$	Timeline	$\beta = 0.23$
Disease Duration *(continuous)*	$\beta = -0.03$	Race *(white vs other)*	$\beta = -2.28$*	Timeline-cyclical	$\beta = 0.43$ *
Remission Duration	$\beta = -1.03$**	Depression *(yes vs. no)*	$\beta = 1.63$**	Consequences	$\beta = 1.23$**
(0, <1 year, $\geq$1 year)		Sleep Disturbed *(yes vs. no)*	$\beta = 0.81$ *	Personal control	$\beta = -0.42$*
				Treatment control	$\beta = -0.73$*
				Emotional Representations	$\beta = 0.38$*
				Coherence	$\beta = 0.40$*
F = 24.16** Adjusted R^2 = 0.18		F = 15.03** Adjusted R^2 = 0.26 R^2 change = 0.08		F = 16.03** Adjusted R^2 = 0.44 R^2 change = 0.18	

*p<0.05 **p<0.0001.
Outcome=MFI score (continuous, higher scores indicate greater fatigue). High scores on the identity, timeline, cyclical, consequences, and emotional dimensions represent strongly held beliefs about the number of symptoms attributed to the illness, the chronicity of the condition, the cyclical nature of the condition, the negative consequences of the illness, and the negative emotional impact of disease. High scores on the personal control, treatment control and coherence dimensions represent positive beliefs about the controllability of the illness and personal understanding of the condition.

Conclusion: Patient-reported measures of disease activity and remission duration are associated with fatigue, suggesting that patients consider fatigue a manifestation of active vasculitis. Illness perceptions significantly explain differences in fatigue scores beyond what can be explained by measures of disease status and depression. These data suggest that in vasculitis i) fatigue is a major domain of illness only partially related to disease activity as currently assessed; ii) illness perceptions may have a causal role in fatigue; and iii) the mechanisms underlying fatigue are complex and multifactorial. These findings have important implications for the incorporation of fatigue measures into overall outcome assessment in vasculitis.

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Upper Airway Gene Expression Profiling in Granulomatosis with Polyangiitis. Peter C. Grayson[1], Katrina Steiling[1], Paul A. Monach[2], Ji Xiao[3], Xiaohui Zhang[1], Yuriy Alekseyev[1], Stephano Monti[3], Avrum Spira[1] and Peter A. Merkel[4]. [1]Boston University Medical Center, Boston, MA, [2]Boston University, Boston, MA, [3]Boston University Medial Center, Boston, MA, [4]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Nasal disease occurs in the majority of patients with granulomatosis with polyangiitis (Wegener's, GPA) and is often a presenting symptom of the disease. The objectives of this study were to use gene expression profiling techniques to gain insight into the biology of upper airway disease in GPA and explore the potential utility of genome-wide gene expression signatures as measures of nasal disease activity.

Methods: Nasal brushings of the inferior turbinate were obtained from 32 subjects with GPA (n=10 active nasal disease, n=13 prior nasal disease, n=9 never nasal disease) and 35 comparator subjects with and without inflammatory nasal disease (n=12 healthy, n=15 sarcoidosis, n=8 allergic rhinitis). RNA extracted from the brushings was processed and hybridized to Affymetrix Human Gene 1.0 ST Arrays. Gene expression changes associated with nasal disease activity were identified with a linear mixed effects model controlling for microarray batch, use of prednisone, and use of other immunosuppressant medication. Significant differences were defined at a threshold of false discovery rate (FDR) <0.1 and fold change > 1.5. Functional enrichment of biologic pathways among the gene expression profiles associated with nasal disease activity was determined using Gene Set Enrichment Analysis (GSEA) (FDR$_{GSEA}$ <0.25). The relationship of nasal gene expression profiles to peripheral blood mononuclear and neutrophil gene expression levels associated with GPA (*Cheadle et al A&R 2010*) was determined using GSEA.

Results: The expression levels of 452 genes were associated with active nasal disease, 309 with prior nasal disease, and 20 never nasal disease in subjects with GPA. GSEA revealed enrichment of several biologic pathways among genes associated with nasal disease activity. The 20 most significantly enriched pathways among subjects with active nasal disease were also significantly enriched among subjects with prior nasal disease and included pathways related to immune response (eg HSA04679 Leukocyte Transendothelial Migration) and thrombosis (eg HSA04610 Complement And Coagulation Cascade). There was no overlap between biologic pathways enriched in subjects with never nasal disease, and pathways enriched among subjects with active or prior nasal disease. Peripheral blood neutrophil and mononuclear gene expression levels associated with GPA were similarly altered in the nasal gene expression profiles of subjects with active or prior nasal disease, but were not significantly enriched in subjects with never nasal disease.

Conclusion: Nasal gene expression profiles are associated with nasal disease activity in subjects with GPA. Pathways analysis suggests that the biologic functions of genes altered in subjects with active nasal disease are similar to subjects with prior nasal disease, and distinct from subjects with never nasal disease. Upper airway gene expression profiles in subjects with active and prior nasal disease were similar to patterns of gene expression changes derived from fractionated peripheral blood in GPA, suggesting that nasal gene expression profiles in GPA may reflect systemic disease activity.

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Plasma Cell Analysis As a Biomarker for Disease Activity in Patients with Granulomatosis with Polyangiitis. Bimba F. Hoyer[1], Adriano Taddeo[2], Maika Rothkegel[2], Gerd R. Burmester[3], Andreas H. Radbruch[2] and Falk Hiepe[4]. [1]Charite University Hospital, Berlin, Germany, [2]Deutsches Rheumaforschungszentrum, Berlin, Germany, [3]Charité – University Medicine Berlin, Berlin, Germany, [4]Charité University Hospital Berlin, Berlin, Germany

Background/Purpose: B cells are thought to play an important role in granulomatosis with polyangiitis (GPA) due to the presence of autoantibodies reacting with specific neutrophil granular enzymes (ANCA) in a vast majority of patients as well as the success of B cell depleting therapies in GPA. Renal manifestations in GPA are considered to be directly ANCA –mediated (Flak, RJ, 2002) whereas the granulomatous inflammation appears to be mediated by CD4 T cells.

Onto better understand the possible role of B cells in ANCA-associated vasculitis we analyzed the B cell subsets in the peripheral blood of patients with GPA and found marked changes correlating with disease activity as measured by the BVAS (Birmingham vasculitis activity score) as well as ANCA-levels.

Methods: 14 patients with GPA (7 with active disease, 7 with inactive disease) were analyzed by flow cytometry as compared to 17 healthy donors. Staining for CD27, Cd20, CD19, MHCII, CD3, 4 and 8 was analyzed using flowjo software. Statistical analysis was performed using graph pad prism, and p-values of < 0,05 were considered as significant. The ethics committee of the Charité approved the study, and all patients had signed informed consent.

Results: Marked differences (p=0,0018) could be observed in plasma cell counts as well as frequencies in GPA patients with a BVAS-score > 0 as compared to those with a BVAS-score =0 (2,52± 1,6/μl) or healthy persons (2,27±1,15/μl). Plasma cell numbers as well as the frequency of plasma cells within all B cells correlated with the BVAS (r= 0,9135, p<0,0001) as well as the ANCA-level in the serum (r= 0,8316, p=0,0013). No significant differences could be observed for naive and memory B cells or the overall B cell numbers as compared to healthy donors.

Regarding T cells, there was a significant reduction of CD3 (p=0,01) and CD4 T (p=0,012) cells in patients with active GPA as compared to patients in remission, whereas CD8 T cells did not show any significant changes.

Conclusion: Plasma cell counts are increased in patients with active GPA which implies a role for plasma cell mediated effects in active GPA. This is probably due to B cell hyperactivity in GPA. Presumably, their main role is the production of autoantibodies, but also cytokine production. Independent of their direct contribution to the disease, they may serve as a biomarker of disease activity as they highly correlate with the BVAS.

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Comparative Proteomic Analysis of Neutrophils Between Microscopic Polyangiitis and Granulomatosis with Polyangiitis. Teisuke Uchida[1], Kouhei Nagai[2], Toshiyuki Sato[1], Mitsumi Arito[1], Nobuko Iizuka, Manae Kurokawa[1], Naoya Suematsu[2], Kazuki Okamoto[2], Shoichi Ozaki[4] and Tomohiro Kato[2]. [1]Clinical Proteomics and Molecular Medicine, St. Marianna University Graduate School of Medicine,, Kawasaki, Japan, [2]St. Mariannna University Graduate School of Medicine., Kawasaki, Japan, [3]St. Marianna University School of Medicine., Kawasaki, Japan

Background/Purpose: Both microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) belong to ANCA-associated vasculitis (AAV), in which dysfunction of polymorphonuclear cells (PMN) is thought to be involved in their pathology. Clinically, it is often difficult to distinguish MPA from GPA. In this study, proteomic profiles of PMN of MPA and GPA patients and healthy controls (HC) were analyzed using two-dimensional difference gel electrophoresis (2D-DIGE), in order to know whether the profiles are useful to discriminate between AAV and HC, or MPA and GPA.

Methods: Proteins extracted from PMN obtained from 11 MPA patients, 9 GPA patients, and 10 HC were separated by 2D-DIGE. Differentially expressed protein spots were identified by MALDI-TOF MS. Then the obtained protein profiles were subjected to the multivariate data analysis by SIMCA-P+® containing principal component analysis (PCA) and orthogonal partial-least-squares-discriminate analysis (OPLS-DA).

Results: In all the 864 protein spots detected, intensity of 55 spots were found to be significantly different ($p < 0.05$) among the three groups by an ANOVA analysis. 31 out of the 55 spots were identified by mass spectrom-

etry. The protein spots whose intensity as higher in MPA than in GPA included cytoskeletal proteins, while the proteins whose intensity as higher in GPA than MPA included protein inhibitors and anti-microbial proteins. The OPLS-DA analysis revealed that the expression profile of the 55 protein spots discriminated completely the AAV group from the HC group with a sufficiently high R^2 (0.903) and Q^2 (0.445) values, and also discriminated completely the MPA group from the GPA group with a sufficiently high R^2 (0.947) and Q^2 (0.626) values.

Conclusion: These results indicated that the profile of PMN proteins may be used as a biomarker that can discriminate AAV from HC, and MPA from GPA.

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Serum Angiopoietin-2 Level Reflects the Disease Activity and Renal Function in Antineutrophilic Cytoplasmic Antibody-Associated Vasculitis. Yoko Wada[1], Hiroe Sato[1], Takeshi Nakatsue[1], Shuichi Murakami[1], Takeshi Kuroda[2], Masaaki Nakano[3] and Ichiei Narita[1]. [1]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Niigata University, Niigata, Japan, [3]School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan

Background/Purpose: Angiopoietin-2 (Ang-2) has emerged as a key mediator of endothelial cell activation. Ang-1 and Ang-2 are antagonistic ligands which bind with similar affinity to the extracellular domain of the tyrosine kinase with Ig-like and epidermal growth factor-like domains 2 (Tie-2) receptor, which is almost exclusively expressed by endothelial cells. Ang-1/Tie-2 signalling maintains vessel integrity, inhibits vascular leakage, suppresses inflammatory gene expression and prevents recruitment and transmigration of leukocytes. In contrast, binding of Ang-2 disrupts protective Ang-1/Tie-2 signalling and facilitates endothelial inflammation. Recently, serum Ang-2 levels have been reported to be elevated in autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and ANCA-associated vasculitis (AAV). The purpose of this study is to examine the serum Ang-2 levels in patients with AAV, and investigate the relationship with the clinical and laboratory findings.

Methods: Fifty-nine patients with AAV (microscopic polyangitis (MPA, n=27), granulomatosis with polyangiitis (GPA, n=15), Churg-Strauss syndrome (CSS, n=14), others (n=3)), who had been referred to Niigata University Medical and Dental Hospital between 2000 and 2011, were enrolled in this study. Written informed consent was obtained from each participant. The patients were divided into 2 groups according to their disease activities using *Birmingham* vasculitis activity score (BVAS) (active disease group (AD group, n=45) and remission disease group (RD group, n=14)) Serum Ang-2 levels and laboratory findings were examined in each subject, and the data were compared between these 2 groups. The data from all subjects were analyzed using Spearman's rank correlation coefficient to determine the relationship with serum Ang-2 levels. Next, the patients with AD group were divided into 2 groups in accordance with their stages of chronic kidney diseases (CKD) (CKD<3 group, n=19, and CKD≥3 group, n=26), and the data were compared to examine the impact of renal function in this study.

Results: The serum Ang-2 level, C-reactive protein (CRP), white blood cell count, and urinary protein excretion were significantly higher in AD group compared with those in RD group. In Spearman's rank correlation coefficient analysis using data from all subjects, the serum Ang-2 level was positively correlated with BVAS (r=0.62, p < 0.0001), CRP (r=0.47, p=0.0003), serum creatinine (Cr) (r=0.38, p=0.005), and urinary protein excretion (UP) (r=0.55, p < 0.0001), and negatively correlated with estimated glomerular filtration rate (r=−0.37, p=0.005). In the next analysis, patients in CKD≥3 were significantly elder and BVAS was significantly higher compared to those with patients in CKD<3 group. Ang-2 was elevated in CKD≥3 group without statistical significance. In Spearman's rank correlation coefficient analysis, Ang-2 was positively correlated with CRP and BVAS in CKD<3 group, while it was correlated with UP, e-GFR, Cr, and CRP in CKD≥3 group.

Conclusion: Serum Ang-2 level was strongly correlated with the disease activity and renal function in AAV. These results indicated the possible role of Ang-2 in the development of AAV through endothelial injuries.

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Increased *FoxP3*^{+} T-Cells in Patients with Granulomatosis with Polyangiitis Are Attributed to an Increase in the Non-Suppressor FoxP3^{Low} CD45RO$^+$ T$_{Reg}$ Cell Subpopulation. Wayel H. Abdulahad[1], Coen A. Stegeman[1], Minke G. Huitema[1], Abraham Rutgers[1], Peter Heeringa[2], Pieter C. Limburg[1] and Cees G.M. Kallenberg[1]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Netherlands

Background/Purpose: Human *FoxP3*^{+}T-cells are functionally heterogeneous, and can be classified into three phenotypically distinct subpopulations based on the expression levels of *FoxP3* and the memory T-cell marker CD45RO. These three subpopulations can be defined as: activated suppressor T$_{Regs}$ (*FoxP3*^{High}CD45RO$^+$; $_{AS}$T$_{Reg}$), resting suppressor T$_{Regs}$ (*FoxP3*^{Low}CD45RO$^-$; $_{RS}$T$_{Reg}$), and cytokine-secreting non-suppressor T$_{Regs}$ (*FoxP3*^{Low}CD45RO$^+$; $_{NON}$T$_{Reg}$).

This study aimed to evaluate the identity of the elevated frequency of *FoxP3*^{+}T-cells in patients with granulomatosis with polyangiitis (GPA).

Methods: Peripheral blood mononuclear cells were isolated from 46 GPA-patients (27 ANCA-positief and 19 ANCA-negative at the time of inclusion) in remission and from 22 age- and sex-matched HCs. Expression of CD4, CD45RO, and *FoxP3* was determined by flow cytometric analysis. The expression levels of *FoxP3* and CD45RO were used for distinction between $_{AS}$T$_{Reg}$, $_{RS}$T$_{Reg}$, and $_{NON}$T$_{Reg}$ *FoxP3*^{+}T-cells. Next, frequencies of intracellular production of IL-17 within the FoxP3^{+} cell subpopulations were analyzed by flow cytometry in peripheral blood of ANCA-positive (n=10) and ANCA-negatieve (n=9) GPA-patients and matched HCs (n=12) upon ex vivo stimulation with *phorbol-myristate-acetate and calcium ionophore in the presence of brefeldin A.*

Results: A significant increase in the frequency of *FoxP3*^{+}T$_{Reg}$ cells was observed in GPA-patients as compared with HCs. No differences were detected in $_{RS}$T$_{Reg}$- and $_{AS}$T$_{Reg}$ cells between GPA-patients and HCs, whereas the $_{NON}$T$_{Reg}$ cells were significantly increased in GPA-patients. The distribution of $_{RS}$T$_{Reg}$- and $_{NON}$T$_{Reg}$ cells did not differ between ANCA-negative and ANCA-positive patients, whereas lower percentages of $_{AS}$T$_{Reg}$ cells were observed in ANCA-positive patients as compared to ANCA-negative patients and HCs. In addition, *frequencies of IL-17^{+} T-cells were significantly increased within the $_{NON}$T$_{Reg}$ subset from ANCA-positive patients in comparison with ANCA-negative patients and HCs, whereas no such difference was found between ANCA-negative patients and HCs.*

Conclusion: Increased *FoxP3* expression in CD4^{+}T-cells from GPA-patients is related to an increase in a subset of non-suppressive T-cells that produce higher levels of IL-17 and display low expression of *FoxP3*. Plasticity of CD4^{+}T-cells in GPA points towards FoxP3^{+}IL-17^{+} effector cells and decrease in suppressive T$_{Reg}$ cells in relation to ANCA production.

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IgG4 Plasma Cell Infiltration in Granulomatosis with Polyangiitis (formerly Wegener's) Lung Biopsies. Mollie Carruthers, Shweta Shinagare, Arezou Khosroshahi, Vikram Deshpande and John H. Stone. Massachusetts General Hospital, Boston, MA

Background/Purpose: Granulomatosis with polyangiitis (GPA) and IgG4-related disease (IgG4-RD) are both immune-mediated conditions that can involve multiple organ systems. In GPA, IgG4-positive plasma cell infiltration has been reported in the kidneys and upper respiratory tract, leading to potential confusion between these two disorders. We sought to determine the degree of IgG4-positive plasma cell infiltration within lung biopsies from patients with ANCA-positive and ANCA-negative GPA, and compared the histopathological and immunohistochemical findings in GPA to biopsies from patients with IgG4-related pulmonary disease.

Methods: Patients with GPA (n=154) were identified by searching the pathology database of the Massachusetts General Hospital (MGH) for search terms "lung" and "Wegener's". Nine ANCA-positive and 4 ANCA-negative patients with wedge biopsy samples of the lung were selected for further analysis. Their clinical, radiologic, and pathologic data were compared to those of 5 patients with IgG4-related pulmonary disease. Hematoxylin and eosin (H&E) stained slides were reviewed in a blinded manner. Immunohistochemistry was performed using antibodies to IgG4 and IgG and subsequently counted by averaging 3 high-power fields (hpf). The histopathologic features were compared using Fisher's exact test and IgG4+ plasma cells counts by unpaired t-tests.

Results: The mean number of IgG4+ plasma cells in lung biopsy samples was higher among the IgG4-RD patients compared to those with GPA. The mean

for the IgG4-RD biopsies was 101 IgG4+ plasma cells/hpf (range: 13–240 IgG4+ cells), compared with 25 cells (range: 0–135) for the GPA patients (P=0.035). IgG4+ plasma cells were numerically higher among GPA patients who were ANCA-positive as opposed to ANCA-negative (40 vs. 11 cells, respectively). Three of the 9 ANCA-positive GPA patients had IgG4+ plasma cell infiltrates that exceeded the minimum number considered characteristic of IgG4-RD in the lung (>50 IgG4+ plasma cells/hpf).

Comparisons of the histopathologic features between GPA and IgG4-RD are shown in Table 1. Two sets of findings were critical in distinguishing the pulmonary pathology of ANCA-positive GPA and IgG4-RD: 1) Obliterative phlebitis, present in 80% of the IgG4-RD biopsies, was not observed in any GPA cases; and, 2) Features of granulomatous inflammation – histiocytes, granulomas, and multi-nucleated giant cells – were absent in IgG4-RD.

Table 1. Lung Histopathologic Features: Granulomatosis with polyangiitis (GPA) versus IgG4-related disease (IgG4-RD)

Pathology Features	GPA	IgG4-RD	P-Value
GPA			
Neutrophilic Abscesses	6/9 (67%)	0/5 (0)	0.03*
Histiocytes	8/9 (89%)	0/5 (0)	0.003*
Giant cells	8/9 (89%)	0/5 (0)	0.003*
Granulomas	8/9 (89%)	0/5 (0)	0.003*
Necrotizing granulomas	2/9 (22%)	0/5 (0)	NS
Vasculitis	3/9 (33%)	0/5 (0)	NS
Hemorrhage	5/9 (56%)	0/5 (0)	NS
IgG4-RD			
Lymphoplasmacytic infiltrate	8/9 (89%)	5/5 (100%)	NS
Tissue eosinophilia	3/9 (33%)	3/5 (60%)	NS
Storiform fibrosis	3/9 (33%)	5/5 (100%)	0.03*
Obliterative phlebitis	0 (0)	4/5 (80%)	0.005*

Conclusion: Lung biopsies from both IgG4-RD and GPA patients are characterized by lymphoplasmacytic infiltrates and IgG4+ plasma cells. Histopathological features, particularly the finding of obliterative phlebitis in IgG4-RD and the absence of granulomatous inflammation, are essential in distinguishing between these conditions.

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1535

Genetic Background of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in a Japanese Population: Association of *STAT4* with Myeloperoxidase Antineutrophil Cytoplasmic Antibody-Positive Vasculitis. Aya Kawasaki[1], Naoya Inoue[1], Chihiro Ajimi[1], Ikue Ito[1], Ken-ei Sada[2], Shigeto Kobayashi[3], Hidehiro Yamada[4], Hiroshi Furukawa[5], Makoto Tomita[6], Takayuki Sumida[1], Shigeto Tohma[5], Nobuyuki Miyasaka[6], Shoichi Ozaki[4], Hiroshi Hashimoto[7], Hiroshi Makino[2], Masayoshi Harigai[6] and Naoyuki Tsuchiya[1]. [1]University of Tsukuba, Tsukuba, Japan, [2]Okayama University, Okayama, Japan, [3]Juntendo University Koshigaya Hospital, Tokyo, Japan, [4]St. Marianna University, Kawasaki, Japan, [5]Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan, [6]Tokyo Medical and Dental University, Tokyo, Japan, [7]Juntendo University School of Medicine, Tokyo, Japan

Background/Purpose: In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), geographic difference in the type of vasculitis is well known. While granulomatosis with polyangiitis (GPA) is the most common form of AAV in northern European populations, microscopic polyangiitis (MPA) accounts for the majority of AAV in Japan, suggesting that the genetic background may play a role in the occurrence of these diseases. Due to low prevalence in European populations, little is known on the genetics of MPA or myeloperoxidase (MPO)-ANCA positive vasculitis. We started a multicenter collaborative study on the genetics of AAV in a Japanese population in 1999. Thus far, we reported a significant association of *HLA-DRB1*09:01* with MPA. *HLA-DRB1*09:01*, one of the most common *HLA-DRB1* alleles in the Asian but rare in the Caucasian populations, has been shown to be associated with multiple autoimmune diseases in Japan.

We have also demonstrated that *STAT4*, *IRF5* and *BLK* were associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc) in a Japanese population, indicating that these genes are shared susceptibility genes to multiple autoimmune diseases. Thus far, association between these genes and MPA or MPO-ANCA positive vasculitis has not been reported. In this study, we examined association of these genes with Japanese AAV, mainly consisting of MPO-ANCA positive vasculitis.

Methods: Association of *STAT4* rs7574865, *IRF5* rs2280714 and *BLK* rs13277113, all previously shown to be associated with other autoimmune diseases in a Japanese population, was examined in 177 Japanese patients with AAV including 127 MPA, 31 GPA and 14 eosinophilic granulomatosis with

polyangiitis (EGPA), as well as in 511 healthy individuals. Among the patients, 155 were positive for MPO-ANCA. The genotypes were determined using TaqMan genotyping assay and direct sequencing.

Results: The frequency of *STAT4* rs7574865 T/T genotype, the risk genotype for SLE, RA and SSc, was significantly increased in MPO-ANCA positive patients (18.7%) as compared with healthy controls (10.4%, P=0.0058, odds ratio [OR] 1.98, 95% condidence interval [CI] 1.22–3.23). A tendency toward association was also observed in MPA (16.5%, P=0.053, OR 1.71, 95%CI 0.99–2.94), GPA (P=0.12, OR 2.07, 95%CI 0.83–5.18) and EGPA (P=0.013, OR 4.79, 95%CI 1.71–13.4).

With respect to *IRF5*, rs2280714 A allele showed a tendency toward decrease in MPA, although the difference did not reach statistical significance (A allele frequency in MPA: 49.2%, controls: 55.5%, P=0.072, OR 0.78, 95%CI 0.59–1.02). No evidence for association of *BLK* was detected.

Conclusion: *STAT4* rs7574865 T/T was associated with MPO-ANCA positive vasculitis. Our observations suggested that *STAT4* is a shared susceptibility gene for SLE, RA, SSc and AAV.

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Clinical Features of Patients with Anti-Neutrophil Cytoplasmic Autoantibodies Targeting Native Myeloperoxidase Antigen. Yuji Yamanishi[1], Toshiko Ito-Ihara[2], Shigeto Kobayashi[3], Peter Y. Shane[4], Gary S. Firestein[5], Hiroshi Hashimoto[6] and Kazuo Suzuki[7]. [1]Hiroshima Rheumatology Clinic, Hiroshima, Japan, [2]Kyoto University Hospital, Kyoto, Japan, [3]Juntendo University Koshigaya Hospital, Tokyo, Japan, [4]Tokyo Medical and Dental University, Tokyo, Japan, [5]UCSD School of Medicine, La Jolla, CA, [6]Juntendo Tokyo Koto Geriatric Center, Tokyo, Japan, [7]National Institute of Infectious Diseases, Tokyo, Japan

Background/Purpose: ANCA is a useful diagnostic marker in systemic vasculitic disorders with small-vessel involvement, but depending on the particular test the myeloperoxidase (MPO)-ANCA results are variable. Unfortunately, the exact origins of the antigens used in most commercial assays are confidential. In the present study, we performed a comparative analysis between a novel MPO-ANCA assay that targets the native MPO (nMPO) antigen and commercially available assays using sera of patients with clinical features of ANCA-associated vasculitis (AAV).

Methods: Serum samples from 24 patients strongly suspected of having AAV were tested for the presence of MPO-ANCAs by the novel nMPO-ANCA assay and by other commercial-based MPO-ANCA assays. These results were correlated to indirect immunofluorescence microscopy staining patterns and patient clinical parameters.

Results: Eighteen out of 24 patients (75%) were positive for nMPO-ANCA compared to 13 out of 24 patients (54%) by one of the most frequently used commercial-based MPO-ANCA ELISA assays in Japan. Interestingly, the patients that tested positive with our nMPO-ANCA assay alone showed clinical features of AAV marked by prolonged fever, polyarthritis, and mild nephritis. The titers of nMPO-ANCA decreased in association with clinical improvement after treatment.

Conclusion: Our data suggest that a positive nMPO-ANCA result, which identifies antibodies to human native MPO antigen, identifies patients with a subset of patients with AAV and a distinct clinical profile. In addition, the titer appeared to correlate with AAV disease activity. While additional studies in larger patient populations will be needed, the nMPO-ANCA test could have clinical utility in detecting AAV-affected patients who have tested negative using commercially available assays.

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Pathogenesis of Atherosclerosis in Granulomatosis Polyangiitis. Rula Hajj-Ali[1], Roy L. Silverstein[2], Gary S. Hoffman[3] and Carol A. Langford[4]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Medical College of Wisconsin, Milwaukee, WI, [3]Cleveland Clinic Found A50, Cleveland, OH, [4]Cleveland Clinic, Cleveland, OH

Background/Purpose: Previous studies from our group suggested that the inflammatory events that occur during relapses in patients with Granulo-

matosis with Polyangiitis (GPA, Wegener's) may have a direct role in the pathogenesis of atherosclerosis. We also showed that circulating microparticle (MPs) levels were elevated during relapse and correlated with platelet reactivity. We further elucidated possible mechanisms by which MPs act at the interface between inflammation and atherosclerosis in GPA.

Methods: Human dermal microvascular endothelial cells (huDMVEC, Clonetics CAMBREX) were cultured in EGm-2MV media from Lonza. MPs isolated from plasma from GPA patients, healthy controls or derived from THP-1 human monocytic cells in vitro, were added at various ratios to the huDMVEC and incubated for timed periods. Cells were then detached, washed, and re-suspended in buffer and analyzed by immunofluorescence flow cytometry with anti-ICAM-1 IgG to detect endothelial cell activation. An isotope-matched control IgG was used as control. In addition, fluorescent tagged normal human platelets were incubated with GPA patient-derived MPs (MP/platelet ratio of 10:1) and platelet activation was detected by flow cytometry with PAC-1, an antibody to the activated form of the $\alpha2b\beta3$ integrin.

Results: GPA patient-derived MPs, when incubated for 4h with huDMVEC, induced surface expression of ICAM-1. MP depleted plasma was used as a control and did not influence ICAM-1 expression. ICAM-1 induction by MPs was blocked by cycloheximide indicating a requirement for new protein synthesis and showing that the ICAM-1 was not transferred to the cells by the MPs. MPs isolated from control subjects or from cultured THP-1 cells exerted a similar activating effect on huDMVEC, suggesting that the effect of MP on EC activation was a general feature of MPs. Platelet surface expression of activated $\alpha2b\beta3$ integrin was also significantly enhanced when platelets from healthy donors were pre-incubated with patient-derived MPs and then exposed to low doses of ADP (1μM).

Conclusion: Our findings demonstrate that MPs isolated from plasma of GPA patients can activate platelets and vascular endothelial cells. These findings suggest possible roles for MPs as an interface between inflammation and athero-thrombosis in GPA.

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ANCA-Associated Vasculitis in Hispanic Americans: An Unrecognized Severity. Ranadeep Mandhadi[1], Fadi Aldaghlawi[2], Asad Khan[2], Vajiha Irshad[3], Joel A. Block[2] and Antoine Sreih[2]. [1]Mount Sinai Hospital, Chicago, IL, [2]Rush University Medical Center, Chicago, IL, [3]Stroger Hospital of Cook County, Chicago, IL

Background/Purpose: ANCA-associated vasculitis, once a disease thought to predominate in Caucasians, is now increasingly recognized in diverse ethnic populations. However, there has been little systematic analysis of ANCA-associated vasculitis among minorities in the United States, particularly among Hispanics. We have observed anecdotally that Hispanics appeared to present with systemic disease and severe renal involvement. Here, we describe the clinical severity and disease outcome in a group of Hispanic patients with ANCA-associated vasculitides, and we test the hypothesis that Hispanics have more severe disease relative to an age- and gender-matched Caucasian population living in the same geographical area.

Methods: We identified 21 Hispanic and 25 Caucasian patients treated for ANCA-associated vasculitis at Stroger Hospital of Cook County and Rush University Medical Center in Chicago, IL from January 2006 to December 2011. Ethnicity was determined by self-report. The definition and diagnosis of Granulomatosis with Polyangiitis (Wegener's; GPA), Microscopic Polyangiitis (MPA), and Churg-Strauss Syndrome (CSS) followed the American College of Rheumatology criteria and the 1992 Chapel Hill Consensus Conference criteria. Patient demographics, laboratory data, Birmingham Vasculitis Activity Score (BVAS), and Vasculitis Damage Index (VDI) were analyzed. The presence of renal involvement was defined by: elevated serum creatinine, hematuria >10RBC/hpf, RBC casts, and/or proteinuria> 1+. Student's t-test and chi-square tests were employed, p<=0.05 was considered significant.

Results: Of the 46 patients, 27 had GPA, 11 had MPA, 7 had CSS, and 1 renal-limited vasculitis. There was no difference between Hispanics and Caucasians in the median age at diagnosis (49.5 years in Hispanics and 50.3 years in Caucasians, p=0.36), time to diagnosis (263 days in Hispanics and 288 days in Caucasians, p=0.72), nor in the gender distribution (47.6% females among Hispanics versus 64% among Caucasians, p=0.37). As opposed to Caucasians, Hispanics had a higher mean BVAS at presentation (16.75 ± 7.7 versus 12.4 ± 6.7, p=0.03), a higher mean VDI at presentation (2.9 ± 1.5 versus 1.9 ± 1.2, p=0.03) and a cumulative mean VDI (3.9 ± 1.7 versus 2.5 ± 1.9, p=0.01) in Hispanics versus Caucasians respectively. In addition, there was a trend towards higher prevalence of renal involvement in Hispanics (89% of Hispanics vs. 56%

of Caucasians, p=0.06). Seventy percent of Hispanics had acute renal failure (Mean highest creatinine= 4.01 ± 3.01 mg/dl) of whom half required dialysis, versus 29% of Caucasians (Mean highest creatinine= 1.98 ± 1.67 mg/dl, p=0.05) and only two patients requiring dialysis. Two Hispanic patients died shortly after presentation. There were no deaths among Caucasians.

Conclusion: In contrast to Caucasians, who tended to have a limited form of vasculitis at presentation, Hispanics with ANCA-associated vasculitis presented with more systemic and severe disease with higher damage indices. Whether these differences are due to genetic, socio-economic, or healthcare access disparities is yet to be studied. Early detection and intervention in these patients may alter the course of the disease and reduce morbidity and mortality.

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Microscopic Polyangiitis: A Large Single Center Series. Leslie D. Wilke[1], Guy P. Fiocco[2] and Marilyn Prince-Fiocco[3]. [1]Scott & White Memorial Center, Temple, TX, [2]Scott & White Clinic, Temple, TX, [3]Temple, TX

Background/Purpose: Microscopic polyangiitis (MPA) is a rare systemic, ANCA (anti-neutrophil cytoplasmic antibody)-associated vasculitis of unclear etiology, characterized by necrotizing small vessel involvement with few or no immune complex deposits. Necrotizing glomerulonephritis is common. Pulmonary capillaritis causing alveolar hemorrhage and hemoptysis is well-recognized, but most case series are reported in the nephrology literature and emphasize renal considerations (1). We present a single center 10-year retrospective review of 40 patients meeting the Chapel Hill Consensus Conference case definition of MPA, with specific p-ANCA and MPO (myeloperoxidase) positivity, with emphasis on initial and subsequent pulmonary manifestations.

Methods: We searched the electronic data base as well as separate databases in our laboratory within our large integrated clinic-hospital system and reviewed charts of all patients with related ICD-9 codes for "vasculitis" in the last 10 years. Patients included in the study were both p-ANCA and MPO positive and met clinical and pathologic criteria for MPA. Patients with only c-ANCA disease or significant granulomata on pathologic evaluation were excluded. Several variables were reviewed (Table 1).

Characteristic	N = 40
Mean Age at Diagnosis	58.9 years *(range:14–83 years)*
Gender	
Male	37.5% (15)
Female	62.5% (25)
Male:Female ratio	1:1.6
Race	
White	73% (29)
Black	5% (2)
Hispanic	20% (8)
Other	2.5% (1)
Vital status as of 2011	
Alive	60% (24)
Deceased	30% (12)
Unknown	10% (4)
Smoking history prior to diagnosis	50% (20)
Patients who underwent pulmonary function testing	42.5% (17)
FEV1/FVC >70	70.5% (12 of 17)
Pulmonary involvement only	5% (2)
Renal involvement only	12.5% (5)
Pulmonary and renal involvement	75% (30)
Hemoptysis	40% (16)
Concomitant Medical History	
Positive ANA	18 (45%)
Hypertension	57.5% (23)
Diabetes mellitus	20% (8)
Cr >1.5 at time of diagnosis	62.5% (25)
Progression to hemodialysis	27.5% (11)
Diagnostic modalities	
Bronchoscopy	60% (24)
Renal Biopsy	60% (24)
Lung Biopsy	12.5% (5)
Other Biopsy	10% (4)
Clinical Diagnosis	15% (6)
Treatment	
Cyclophosphamide + Corticosteroids	60% (24)
Corticosteroids Alone	10% (4)
Azathioprine Alone	5% (2)
Azathioprine + Corticosteroids	10 (4)
Rituximab	5% (2)
Mycophenolate mofetil	12.5% (5)
Cyclophosphamide + Corticosteroids + Plasmapheresis	5% (2)
Corticosteroids + Rituximab + Mycophenolate + Plasmapheresis	2.5% (1)
No Treatment	2.5% (1)

Results: Onset of illness was usually abrupt and included respiratory symptoms. Most common presenting complaint was cough. Hemoptysis occurred during the course of illness in 40%.

Pulmonary evaluation included bronchoscopy in 60% and surgical lung biopsy in 12%, usually related to pulmonary hemorrhage.

Treatment doses and duration were quite variable but included combination corticosteroids and cytotoxic therapy in 60%. Therapy was directed by nephrology in 52.5%. Rheumatology and Pulmonary directed therapy in 22.5% patients each. One patient did not undergo therapy.

The course of illness was variable, with few significant pulmonary relapses. Hemodialysis occurred in 28%. Known deaths occurred in twelve, with none directly attributable to the disease process.

Conclusion:

1) Pulmonary involvement is much more frequent than the current literature report of 25–50% when features in addition to hemorrhage are recorded. (1,2)

2) MPA at onset usually includes respiratory symptoms. Demographic and medical variables failed to identify predisposing factors.

3) No clear guidelines direct the evaluation and management of MPA patients. Consistent communication between pulmonary, nephrology, and rheumatology services could improve our understanding of the disease process.

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Practice Patterns in the Treatment of ANCA-Associated Vasculitis: Exploring Differences Among Subspecialties At a Single Academic Medical Center. Lindsy J. Forbess[1], Kenneth W. Griffin[2] and Robert F. Spiera[3]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Weill Cornell Medical College, New York, NY, [3]Hospital for Special Surgery, New York, NY

Background/Purpose: Randomized controlled trial evidence helps guide physician treatment choices for ANCA-Associated Vasculitis (AAV). Data for remission maintenance therapy following rituximab (RTX) in generalized disease, as well as the use of RTX in limited disease, however, is currently lacking. In the absence of such data, treatment choices are largely driven by physician preferences. Our aim was to examine AAV treatment preferences to determine if patient gender and age and physician subspecialty affect treatment choices.

Methods: We invited rheumatologists, nephrologists and pulmonologists from an academic medical center to participate in a web-based survey. Three scenarios (remission induction in generalized disease; remission maintenance in generalized disease; remission induction in limited disease) were presented for 4 patient profiles (28 and 68 year old female/male). Physician treatment choices and reasons for these choices (efficacy, toxicity, cost/availability, comfort with use) were obtained. Differences between groups were analyzed using Chi-Square and Fisher's exact tests.

Results: Of 117 surveys sent, 46 were completed by 29 rheumatologists (63%), 8 pulmonologists (17%) and 9 nephrologists (19%).

For remission induction in generalized disease, 52% of physicians selected RTX, 42% CTX, 3% mycophenolate mofetil, and 3% no preference. Physicians were significantly more likely to choose RTX for young females compared with young males (p=0.039), older males (p<0.001), and older females (p<0.001). Toxicity was the most common reason for this choice. There was a trend toward rheumatologists choosing RTX over CTX compared with the other subspecialties.

Most physicians switched to a less toxic agent for remission maintenance (Table 1), but there was little agreement as to choice of maintenance therapy among subspecialties. It did appear, however, that pulmonologists were significantly less likely to choose azathioprine (AZA) (p=0.002) and nephrologists methotrexate (MTX) (p=0.007) than the other subspecialties.

Table 1. Physician Treatment Preferences for Remission Maintenance Therapy in Generalized ANCA-Associated Vasculitis

	AZA*, N (%)	Follow Expectantly, N (%)	MTX*, N (%)	MMF*, N (%)	RTX*, N (%)	CTX*, N (%)	TMP/SMX*, N (%)	LFN*, N (%)	No Preference, N (%)
After All Induction (N=128)	45 (35)	27 (21)	20 (16)	12 (9)	9 (7)	5 (4)	4 (3)	0 (0)	6 (5)
After CTX* Induction (N=56)	13 (23)	9 (16)	16 (29)	8 (14)	3 (5)	5 (9)	0 (0)	0 (0)	2 (4)
After RTX* Induction (N=64)	29 (46)	20 (31)	4 (6)	1 (2)	4 (6)	0 (0)	4 (6)	0 (0)	2 (3)

*AZA=azathioprine, MTX=methotrexate, MMF=mycophenolate mofetil, RTX=rituximab, CTX= cyclophosphamide, LFN=leflunomide, TMP/SMX= trimethoprim/sulfamethoxazole

For remission induction in limited disease, most chose RTX (36%), particularly for young females, followed by CTX (26%), MTX (24%), AZA (6%), trimethoprim/sulfamethoxazole (4%) and 4% no preference. Efficacy was the most common reason for selecting RTX. Rheumatologists chose RTX (34%) and MTX (31%) about equally, whereas pulmonologists chose RTX (67%) and nephrologists chose CTX (40%) most often.

Conclusion: Most physicians favor RTX for remission induction in young females with generalized disease because of toxicity issues, with a trend toward rheumatologists prescribing RTX more frequently than other subspecialties in this setting. Surprisingly, most physicians preferred RTX for remission induction even for limited disease, despite lack of clinical trial data supporting its use in this context. There was less agreement as to choice of remission maintenance therapy among subspecialties.

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Does Leflunomide Have a Place As Remission Maintenance Therapy in ANCA-Associated Vasculitis? A Bayesian Network Meta-Analysis with Hypothesis Driven Sensitivity Analyses to Adjust for Potential Biases. Glen S. Hazlewood[1], Claudia Metzler[2], George A. Tomlinson[1], Wolfgang L. Gross[3], Brian M. Feldman[4], Loic Guillevin[5] and Christian Pagnoux[6]. [1]University of Toronto, Toronto, ON, [2]University of Lubeck, Bad Branstedy, Germany, [3]Medical University at Lubeck, Lubeck, Germany, [4]The Hospital for Sick Children, Toronto, ON, [5]Cochin University Hospital, Paris, France, [6]Mount Sinai Hospital, Toronto, ON

Background/Purpose: *Primary:* To determine the relative treatment effects of maintenance therapy in adult patients with ANCA-associated vasculitis who have achieved remission, using a Bayesian network meta-analysis of randomized controlled trials (RCT). *Secondary:* To model the impact of *a priori* hypotheses about potential biases in a RCT comparing leflunomide (LEF) to methotrexate (MTX) on the relative treatment effects.

Methods: *Study selection:* RCTs identified from an existing systematic review and updated PUBMED and MEDLINE searches comparing at least 2 of the following maintenance agents: MTX, LEF, azathioprine (AZA) or mycophenolate mofetil (MMF). *Population:* Adult patients (age>18) with ANCA-associated vasculitis who have achieved clinical remission. *Outcome:* Relapse-free survival. *Data analysis:* A Bayesian arms-based fixed-effects network meta-analysis was performed using hazard ratio data. Sensitivity analyses were performed by down-weighting the effect of LEF in the LEF-MTX RCT because of the early trial termination (using a published meta-analysis of the impact of early termination) and by modeling the removal of early methotrexate relapses, as the initial dose titration of MTX in this trial was slow.

Results: Three trials were available (LEF-MTX; MTX-AZA; AZA-MMF). In the primary analysis, LEF was superior to MMF (HR:0.26 [0.08, 0.87]) and showed a trend towards superiority to AZA (HR:0.43 [0.14, 1.36]) and MTX (HR:0.47 [0.18, 1.22]). The probability that each treatment was the best was: LEF 90%, AZA 6%, MTX 4% and MMF <1%. The probability that LEF was the best decreased to 74% after the treatment effect for LEF/MTX was down-weighted for early trial termination in the LEF-MTX RCT. LEF remained the highest ranked treatment unless >6/13 of the initial MTX relapses (all relapses within the first 7 months) were censored.

Conclusion: Based on indirect evidence, there is a high probability that LEF is an effective maintenance therapy for ANCA-associated vasculitis after adjusting for potential study biases. Further RCTs of LEF should be considered to provide direct evidence.

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The Efficacy of Rituximab Vs Cyclophosphamide for Treatment of Renal Disease in ANCA-Associated Vasculitis: The RAVE Trial Geetha D, Fervenza FC for the RAVE-Itn Research Group. Duvuru Geetha[1] and Fernando Fervenza[2]. [1]Johns Hopkins University, Baltimore, MD, [2]Mayo Clinic, Rochester, MN

Background/Purpose: Rituximab (RTX) is non-inferior to cyclophosphamide (CYC) followed by azathioprine (AZA) for remission-induction in severe ANCA associated vasculitis (AAV) but details of outcomes among patients with renal involvement have not been reported. We present the long-term outcomes of patients who had renal involvement at baseline in the RAVE trial.

Methods: Patients with renal involvement defined by a Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) renal item score ≥ 3 at baseline were included. Glomerular filtration rate was estimated (e-GFR) by Cockcroft-Gault formula. Complete remission (CR) was defined by BVAS/WG $= 0$, off prednisone; Renal flare by renal BVAS/WG ≥ 3. Remission rates, slopes of eGFR and renal flares were compared between treatment groups.

Results: 102 of the 197 (52%) patients had renal involvement at entry (GPA: 68; MPA: 34; PR3-ANCA: 58; MPO-ANCA: 44; new diagnosis: 58; relapsing disease: 44). The mean age was 55 years, 52% were males. 51 patients each received RTX or CYC/AZA. Except for lower mean baseline e-GFR in the RTX group (53 ml/min vs 69ml/min p=0.01), there were no clinical differences between the treatment groups. 60.8 % patients treated with RTX and 62.7 % patients treated with CYC/AZA achieved CR by 6 months, and 74.5 % and 76.5% at any time on the originally assigned treatment, respectively. Median times to CR were similar in both groups. The mean e-GFR increased in parallel in the two groups during the 18 months. The number of renal flares did not differ between the two groups at 6, 12, or 18 months. When stratified by ANCA or AAV type or new vs relapsing disease, there were no differences in remission rates or slopes of e-GFR increase at 18 months. Four MPA patients treated with RTX without maintenance therapy had a total of 5 renal flares by month 18 vs none treated with CYC/AZA (p=0.04).

Conclusion: A single course of RTX is as effective as 18 months of therapy with CYC/AZA for induction and maintenance of remission in patients with AAV with renal disease. MPA patients treated with RTX and no maintenance therapy may be more likely to experience a renal flare following B cell reconstitution.

Disclosure: **D. Geetha**, Genentech and Biogen IDEC Inc., 9; **F. Fervenza**, Genentech and Biogen IDEC Inc., 2.

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Rituximab for ANCA-Associated Vasculitis: A Meta-Analysis of Randomized Trials. Carolina Mejia[1] and Carlos J. Lozada[2]. [1]Mount Sinai Medical Center, Miami, FL, [2]University of Miami Miller School of Medicine, Miami, FL

Background/Purpose: Over the past 40 years, cyclophosphamide/glucocorticoids combination therapy has been the standard regimen for remission induction in ANCA-associated vasculitis. Although a major advance in the treatment of these entities and a superior regimen to the glucocorticoid monotherapy regimens that preceeded it, non-responders and the potential for significant adverse effects have been major drawbacks.

The search for new therapeutic options has led to the investigation of anti-B cell therapies. Rituximab, an anti-CD20 monoclonal antibody, has compared favorably to cyclophosphamide-based regimens in remission induction in clinical trials, leading to formal approval by the Food and Drug Administration for this indication. It has also been able to maintain remission for many months of follow up without the need for medication-based maintenance regimens such as azathioprine which is standard in cyclophosphamide-based regimens.

Methods: All randomized controlled trials of rituximab on patients with ANCA-associated vasculitis were sought in PubMed, EMBASE, and Cochrane databases during June 2012. Significant non-randomized controlled trials were also reviewed for a separate analysis. Data was extracted by 2 reviewers and analyzed with RevMan 5 software.

Results: Three randomized controlled trials were found. In all, rituximab was demonstrated more efficacious in achieving remission, preventing relapse and decreasing ANCA titers (Figures 1A, 1B, 1C). There was also a trend favoring rituximab in achieving remission in nine non-randomized studies that were analyzed separately (Figure 2A).

Figure 1A: Clinical remission up to 6 months (Events: patients with flares)

Figure 1B: Clinical relapse up to 6 months (Events: patients who remained free of flares)

Figure 1C: Decrease in ANCA titers with 6 months. (Events: ANCA levels remained high despite treatment)

Figure 2A: Clinical remission up to 6 months (Data from non-randomized studies) (Events: patients with flares)
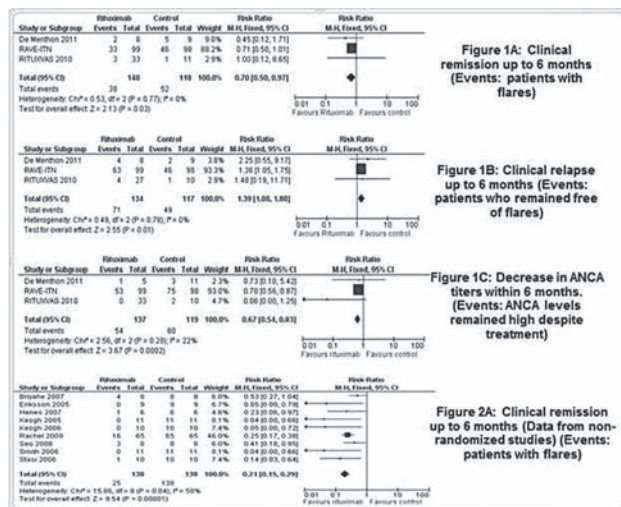
Conclusion: Rituximab has been shown a new and effective alternative for achieving remission in ANCA-associated vasculitides when compared to standard cyclophosphamide-based treatment.

Disclosure: **C. Mejia**, None; **C. J. Lozada**, None.

1544

Long-Term Outcome of Patients with Granulomatosis with Polyangiitis (Wegener's) Treated with Rituximab. Lama Azar, Jason Springer, Meng Xu, Tiffany M. Clark, Carol A. Langford and Gary S. Hoffman. Cleveland Clinic Foundation, Cleveland, OH

Background/Purpose: Rituximab (RTX) is an efficacious alternative to cyclophosphamide for treatment of granulomatosis with polyangiitis (GPA). However, relapses have been observed, long-term efficacy is not known and strategies to reduce risk of relapses after RTX-induced remission are just beginning to be explored. This study was performed to evaluate long-term efficacy and risks of RTX when used alone or in conjunction with another immunosuppressive agent other than steroids.

Methods: Single center retrospective review: patients (pts) with GPA who fulfilled 1990 ACR criteria and were treated with at least 1 course of RTX. Subset analysis included the effect of receiving a 2nd immunosuppressive agent, other than steroids. Remission defined as BVAS/WG=0.

Results: Total of 110 pts, 56 F, 54 M, received 211 courses of RTX. In 77% of cases, 2 infusions of 1gm were given 2 weeks apart. Mean age at 1st RTX (RTX1) was 50 yrs. Indications for RTX1 were: new onset (5), relapsing (85), persistent disease (15) and remission maintenance (5). At the time of RTX1, median BVAS/WG was 4 (range 1–11). Median follow up after RTX1 was 23 months (mo) (range 1–137). Apart from 3 pts with worsening or persistent lung involvement, complete remission was achieved in 99/102 pts with active disease and available information. 45 pts (42%) received only 1 course of RTX and remained in remission during follow up (median 10mo); 66% of these pts were on 2nd agent after RTX1. Among 21 pts followed >2 years after RTX1, 38% sustained long-lasting remissions, for up to 6 yrs. Fifty pts experienced 79 relapses after RTX1. Median time to 1st relapse was 13mo (range 2.5–66). Median dose of prednisone at time of relapse vs without relapse was 5 mg (range 0–30) vs 3.5 mg (range 0–25), respectively. The incidence of relapse over time after RTX1 was lower in patients who received a 2nd agent (figure; p=0.006). Among pts who received a 2nd agent (52), 42% relapsed vs.

65% of those who did not receive a 2nd agent (43). The 2nd agents used were: AZA (29), MTX (15) and MMF (8). Median follow up in the 2 groups was 13 and 11mo and median time to relapse was 16mo vs 11mo, respectively. Of pts who relapsed while on a 2nd agent, 27% had at least 1 major organ involved per BVAS/WG vs 39% of pts who were not on a 2nd agent. Serious adverse events did not differ between groups. Serious infections occurred after RTX1 in 7.6% (2nd agent subset) and 6.9% (no 2nd agent subset), respectively. At the time of relapse, 42.2% of pts were peripheral blood B cell depleted (data for 45 relapses in 31 pts).
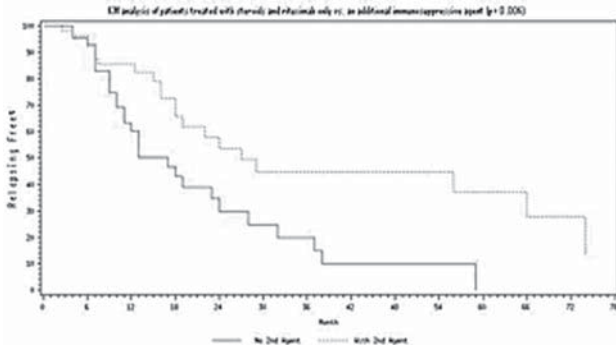
Conclusion: RTX is a very effective remission-inducing agent for GPA. 97% of treated pts achieved remission. Within a subset treated once and followed for > 2 yrs, remissions endured for 2–6 yrs in 38%. While 46% of pts had ≥1 relapses, use of a 2nd immunosuppressive agent diminished likelihood of relapse. A 2nd agent did not result in a greater number of serious adverse events.

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1545

Long-Term Follow-up of 118 Polyarteritis Nodosa and Microscopic Polyangiitis without Poor-Prognosis Factors. Maxime Samson[1], Xavier Puechal[2], Hervé Devilliers[3], Camillo Ribi[4], Pascal Cohen[5], Boris Bienvenu[6], Christian Pagnoux[7], Luc Mouthon[8], Loic Guillevin[9] and French Vasculitis Study Group FVSG[5]. [1]Hôpital Cochin, University Paris Descartes, Paris, France, [2]Hôpital Cochin, Paris, France, [3]CHU Dijon, Dijon, France, [4]Hôpital Universitaire Cantonal de Genève, Geneve, Switzerland, [5]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France, [6]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, France, [7]Mount Sinai Hospital, Toronto, ON, [8]Hopital Cochim, Paris, France, [9]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France

Background/Purpose: Polyarteritis nodosa (PAN) and microscopic polyangiitis (MPA) are 2 vasculitides characterized by necrotizing inflammation of the vessel wall. They share several clinical features and may be treated similarly. Nonsevere manifestations, as defined by the Five-Factor Score (FFS), respond to corticosteroids (CS) alone. This study aimed to describe the long-term follow-up of PAN and MPA patients without poor-prognosis factors.

Methods: Data from patients included in a prospective trial[1] were updated in 2012. New Chapel Hill criteria were applied to classify PAN and MPA. The following definitions were used: relapses, the recurrence and/or new appearance of ≥1 vasculitis manifestation(s) after remission lasting ≥3 months; major relapses, the emergence of major organ involvement (FFS≥1, 30% creatinine-level rise, pulmonary hemorrhage, threatened vision, new multifocal neurological lesions or mononeuritis multiplex, gastrointestinal hemorrhage or perforation and/or gangrene); failure, the absence of clinical remission with the assigned treatment. Times to relapse and/or death were calculated from that of treatment onset. Time to first event (failure, minor or major relapse and/or death) defined the disease-free survival.

Results: Among the 124 patients screened, 6 were excluded (2 FFS≥1, 4 other vasculitides). Mean±SD overall follow-up was 98.2±41.9 months. For the 118 patients (61 MPA and 57 PAN), mean age at diagnosis was 55.6±16.5 years, mean Birmingham Vasculitis Activity Score 2003 11.8±5.5; ANCA-positivity: 3 (5.3%) PAN (cANCA⁺, anti-proteinase-3 and

-myeloperoxidase negative) and 31 (50.8%) MPA (pANCA⁺, 77.4% myeloperoxidase-specific). After CS alone, 97/118 (82.2%, 49 MPA and 48 PAN) achieved remission; 21/118 (17.8%, 12 MPA, 9 PAN) failed on CS and received a second- or third-line therapy with immunosuppressant(s) (IS) that achieved remission in 19 cases (11 MPA, 8 PAN), and 2 patients (1.7%, 1 PAN, 1 MPA) died before remission. After remission, 61/116 (52.6%, 35 MPA, 26 PAN) patients relapsed 25.6±27.9 months after starting treatment, 30 (25.9%, 20 MPA, 10 PAN) experiencing ≥1 major relapse after 47.8±36.2 months of follow-up. The respective 5-, 7- and 8-year overall survival rates were 92%, 85% and 81%, with no significant difference between PAN and MPA patients (p=0.289). Relapse-free survival and major relapse-free survival tended to be shorter for MPA than PAN patients (p=0.174 and 0.06, respectively). Disease-free survival was significantly shorter for MPA than PAN patients (p=0.021). Throughout follow-up, 46.6% of patients required ≥1 IS. At the last follow-up visit, 44% were still taking CS, 15% an IS and the mean vasculitis damage index score was 1.9±1.9, with the most frequent sequelae being peripheral neuropathy, hypertension and osteoporosis.

Conclusion: For PAN or MPA patients with FFS=0 at diagnosis, overall survival at 120 months was good, with first-line CS alone able to achieve remission in >80% of them. However, relapses remained frequent, especially of MPA, meaning that 46.6% of the patients required immunosuppressant(s).

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Rhinosinusits and Nasal Polyps in the Diagnosis and Follow up of Patients with Eosinophilic Granulomatosis with Polyangitis (ex-Churg Strauss Syndrome). Chiara Baldini[1], Veronica Seccia[2], Manuela Latorre[3], Paolo Iannicelli[2], Daniela Martini[1], Francesco Ferro[1], Nicoletta Luciano[1], Antonio Tavoni[1], Stefano Sellari Franceschini[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Unit of Otorhinolaryngology, Department of Neuroscience, University of Pisa, Pisa, Italy, Pisa, Italy, [3]Pneumology Unit, Italy

Background/Purpose: Chronic rhinosinusitis with nasal polyposis (CRSwP) is a common manifestation of granulomatosis with polyangiitis (EGPA), and may represent an invalidating feature of the disease, causing nasal blockage and loss of smell. The aim of this study was to determine the frequency of CRSwP in a series of patients with EGPA and the impact of sino-nasal involvement on the patients' quality of life.

Methods: Consecutive patients with EGPA (ACR criteria) were prospectively enrolled in this observational cross-sectional study. Patients' cumulative clinical and serological features were collected including: ANCA status, blood eosinophilia, total IgE, IL-2, IL-4, IL-5 and eosinophil cationic protein levels (ECP). Nasal polyps were graded according to the Lund nasal endoscopy scoring system. To evaluate the impact of the sino-nasal symptoms on the quality of life (QOL), the short form (SF)-36 and the Sino-Nasal Outcome Test (SNOT-22) were used. Correlations between the different variables were analyzed using linear regression and the Spearman coefficient (p < 0.05).

Results: Twenty-six EGPA patients (12F:14M, 57±15yrs, mean follow-up =6±5yrs) were enrolled in the study. About one third of the patients (32%) was allergic to one or more common aero-allergen and high levels of IgE were found in 10/26 EGPA patients; 3/26 patients referred aspirin hypersensitivity and 3/26 patients were current smokers. Endoscopic intranasal evaluation identified: CRSwP in 14/26 cases, chronic rhinosinusitis (CRS) in 5/26, non-allergic rhinitis (NAR) in 4/26 and allergic rhinitis (AR) in 2/26 patients. One patient had a normal nasal endoscopy examination. The diagnosis of sino-nasal involvement preceded the diagnosis of EGPA of a mean period of 23±21 yrs. Surgery was needed in 13/26 cases, with 5/13 patients undergoing polypectomy, 2/13 septoplasty and 6/13 functional endoscopic sinus surgery. Polyps recurred in 9/13 EGPA patients over the follow-up. No correlation was found among CRSwP or Lund scores and ANCA status, blood eosinophilia, total IgE, IL-2, IL-4, IL-5 and ECP. Significant correlations were observed among CRSwP, LUND score and chronic use of nasal corticosteroids and between SNOT-22 and SF-36 questionnaire. There was no correlation between Lund and SNOT-22 scores.

Conclusion: Nasal polyps may represent the initial feature of EGPA, and may have a great impact on the patients' quality of life. The Lund score correlates well with CRSwP severity and chronic use of nasal corticosteroids but measures a different aspect of disease to "subjective" symptom scores.

This demonstrates the strengths and limitations of a commonly used staging system in EGPA and CRSwP.

Disclosure: **C. Baldini**, None; **V. Seccia**, None; **M. Latorre**, None; **P. Iannicelli**, None; **D. Martini**, None; **F. Ferro**, None; **N. Luciano**, None; **A. Tavoni**, None; **S. Sellari Franceschini**, None; **S. Bombardieri**, None.

1547

A 4 Plus 2 Infusion Protocol of Rituximab Provides Long-Term Beneficial Effects in Patients with HCV-Associated Mixed Cryoglobulinemia with Membranoproliferative Nephritis and Severe Polyneuropathy.
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Background/Purpose: Mixed cryoglobulinemia syndrome (MCs) is a systemic vasculitis characterized by multiple organ involvement due to the vascular deposition of immune-complexes, mainly the cryoglobulins. B cells expansion frequently triggered by HCV infection plays a central role in MCs. The long term effects of B-cells depletion in MCs are still on debate

Methods: Twenty seven patients, (mean age 60.2 [range 35–78] years, HCV infection in 96% of cases) with symptomatic type-II MCs with systemic manifestations, including renal involvement (diffuse membranoproliferative glomerulonephritis in 15 cases), peripheral neuropathy (26 cases) and large skin ulcers (9 case, in 7 necrotizing) were considered eligible for Rituximab (RTX) therapy. RTX was administered at a dose of 375 mg/m^2 on days 1, 8, 15 and 22. Two more doses were administered 1 and 2 months later. No other immunosuppressive drugs were added. Response was evaluated by assessing the changes in clinical signs, symptoms, laboratory parameters and electromyographic indices for a very long term follow-up (mean 54.3 months [12–96])

Results: Complete remission of pre-treatment active manifestations was observed in all the cases of skin purpuric lesions and non-healing vasculitic leg ulcers, and in 80% of the peripheral neuropathy, mainly paresthesias. A significant improvement in the clinical neuropathy disability score was observed. Electromyography examination revealed that the amplitude of compound motor action potential had increased. Cryoglobulinemic nephropathy, observed in 15 patients, significantly improved during the follow-up starting from the second month after RTX (serum creatinine from 2.2 ± 1.9SD to 1.6 ± 1.2SD mg/dl, $p\leq.05$; 24-hour proteinuria from 2.3 ± 2.1SD to 0.9 ± 1.9SD g/24h, $p\leq.05$). Improvement of cryoglobulinemic serological hallmarks, such as cryocrit and low complement C4, were reported. The safety of RTX was confirmed by the absence of side effects recorded during the mean 54-month follow-up. Re-induction was performed in 9 relapsed cases (after a mean of 31.1 months, range 12–54) with resolutive beneficial effects

Conclusion: In this open prospective study, RTX appeared to be effective and safe in the treatment of patients with MCs-associated neuropathy and membranoproliferative nephritis

Disclosure: **D. Roccatello**, None; **S. Sciascia**, None; **S. Baldovino**, None; **D. Rossi**, None.

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Cutaneous Vasculitis as a Paraneoplastic Syndrome.
Javier Loricera, Vanesa Calvo-Rio, Francisco Ortiz Sanjuan, Marcos Antonio Gonzalez-Lopez, Hector Fernandez-Llaca, Javier Rueda-Gotor, Carmen Gonzalez-Vela, Cristina Mata-Arnaiz, Miguel A. Gonzalez-Gay and Ricardo Blanco. Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain

Background/Purpose: Cutaneous Leukocytoclastic Vasculitis (CLV) may be associated with malignancies, and sometimes it behaves as a paraneoplastic syndrome. This association has been reported in a variable proportion of CLV patients (from 0 to 8 %) depending on population selection. Our aim was to assess the frequency and features of CLV associated to neoplasia in a wide and unselected series of CLV.

Methods: Study of CV associated to neoplasia in a series of 877 patients diagnosed as having CLV in the Rheumatology and Dermatology Divisions from a University Hospital.

Results: 16 out of 877 patients (1.82 %) presenting with CLV were finally diagnosed as having an underlying malignancy. There were 9 hematological and 7 solid malignacies. In all of them, skin lesions were the first clinical manifestation

and the median interval to the diagnosis of the malignancy from the onset of CLV was 17 days (range 8 –50 days). The most frequent skin lesions were palpable purpura (13 patients), legs ulcers (2 patients), urticaria (2 patient) and erythema (1 patient). Other manifestations were constitutional syndrome (10 patients) and arthralgias and/or arthritis (6 cases). There was no serious visceral vasculitic involvement. Cytopenia was frequently observed in the full blood cell count (11 cases), especially in those cases of vasculitis associated to hematological malignancies. Immature peripheral blood cells were observed in 9 cases. Immunological testing (ANA, Rheumatoid factor, C3, C4, and ANCA) were negative or within normal range in all cases. 10 patients died due to the malignancy and 6 patients recovered following malignancy therapy.

Case	Age/sex	Main clinical features	Peripheral blood smear	Skin biopsy	Diagnosis
1	40/F	Urticarial lesions, fever, polyarthritis	Anemia, immature cells	Leukocytoclastic Vasculitis	Megakaryocytic leukemia
2	52/F	Palpable purpura, constitutional symptoms	Pancytopenia, immature cells	Leukocytoclastic Vasculitis	Myelodysplastic Syndrome
3	56/M	Palpable purpura, constitutional symptoms, fever	Anemia, leukopenia, immature cells	Leukocytoclastic Vasculitis	Myelodysplastic Syndrome
4	70/M	Palpable purpura, constitutional symptoms,, polyarthritis	anemia, leukopenia, immature cells	Leukocytoclastic Vasculitis	Non- Hodgkin Lymphoma
5	78/M	Palpable purpura, constitutional symptoms, fever, arthralgias, abdominal pain	Anemia	Leukocytoclastic Vasculitis	Waldestrom's Macroglobulinemia
6	83/M	Palpable purpura, necrotic ulcer, constitutional symptoms	Anemia, leukopenia	Leukocytoclastic Vasculitis	Myelodysplastic Syndrome
7	61/F	Palpable purpura, hematuria, polyneuopathy	Anemia	Leukocytoclastic Vasculitis	Waldestrom's Macroglobulinemia
8	76/M	Palpable purpura, urticarial lesions, constitutional syptoms, fever	Pancytopenia, immature cells	Leukocytoclastic Vasculitis	Hairy cell leukemia
9	81/F	Palpable purpura, erythema, constitutional symptoms, fever	Anemia, immature cells	Leukocytoclastic Vasculitis	Mantle cell lymphoma
10	82/M	Palpable purpura, abdominal pain, fecal occult blood, hematuria	Normal	Leukocytoclastic Vasculitis	Oropharyngeal Squamous cell Carcinoma
11	49/F	Palpable purpura, constitutional symptoms, fever	Anemia	Leukocytoclastic Vasculitis	Infiltrating Breast Carcinoma
12	80/M	Palpable purpura, constitutional symptoms	Anemia	Leukocytoclastic Vasculitis	Lung Adenocarcinoma
13	85/F	Palpable purpura, ulcers	Normal	Leukocytoclastic Vasculitis	Breast Carcinoma
14	53/M	Palpable purpura, arthralgias	Normal	Leukocytoclastic Vasculitis	Pyriform sinus squamous cell carcinoma
15	71/M	Palpable purpura, constitutional syptoms	Normal	Leukocytoclastic Vasculitis	Bladder carcinoma
16	70/M	Palpable purpura	Normal	Leukocytoclastic Vasculitis	Glottic squamous cell carcinoma

Conclusion: CLV presenting as a paraneoplastic syndrome is a rare condition. The most common underlying malignancy is generally hematological. The prognosis depends on the underlying neplasia.

Disclosure: **J. Loricera**, None; **V. Calvo-Rio**, None; **F. Ortiz Sanjuan**, None; **M. A. Gonzalez-Lopez**, None; **H. Fernandez-Llaca**, None; **J. Rueda-Gotor**, None; **C. Gonzalez-Vela**, None; **C. Mata-Arnaiz**, None; **M. A. Gonzalez-Gay**, None; **R. Blanco**, None.

1549

Sibling Relative Risk and Heritability of Kawasaki Disease: A Nationwide Population Study in Taiwan.
I-Jun Chou[1], Chang-Fu Kuo[2], Jing-Long Huang[1], Chang-Teng Wu[1], Shao-Hsuan Hsia[1] and Hsiao-Chun Chang[1]. [1]Chang Gung Memorial Hospital, Taoyuan, Taiwan, [2]University of Nottingham, Nottingham, United Kingdom

Background/Purpose: Kawasaki disease (KD) is an autoimmune disease involving primarily medium-sized vessels and is the leading cause of acquired cardiac disease in children. The pathogenesis is still unknown and the

evidence for familial aggregation in Kawasaki disease is rare. The aims of this study was to estimate sibling relative risk (RR) and heritability of KD.

Methods: Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of 2,683,174 males and 2,483,901 females who were younger than 20 years in 2010. KD was defined as children < 20 years of age hospitalised with a primary or secondary diagnosis of KD between 1996 and 2010. We identified individuals with a full sibling affected by KD and compared the prevalence of the disease between individuals with and without an affected sibling. The identification of sibling of each individual was determined using the NIHRD registry for beneficiaries, which specifies relationships between the insured person who paid the insurance fee and his/her dependents and allows first-degree relatives (father, mother, son, daughter, brother, sister, twin) to be identified directly. Full siblings were identified as individuals who shared the same parents. The marginal Cox proportional hazard model with an equal follow-up time for all subjects was used to estimate RR and the 95% confidence interval (CI). This model was used to account for shared environment and case clustering within families with robust variance, and to adjust for age, place of residence, income levels and occupation. The RR was estimated for different first-degree relative categories and for the number of first-degree relatives affected by gout. Heritability (h2) was estimated using the multifactorial polygenic model.

Results: There were 7,443 male and 4,558 female individuals who had KD between 1996 and 2010. Individuals with an affected sibling with KD had a higher prevalence of KD (1.53%) than those without (0.23%). The risk of KD in individuals with an affected sibling was 6.39 (95% CI, 4.63–8.83) times greater than that in individuals without an affect sibling. The sibling RR (95% CI) was slightly higher among female individuals with affected siblings (6.79, 4.50–10.27) than male ones (6.11, 4.19–8.90). The heritability of KD was 0.45 (95% CI, 0.36–0.55).

Conclusion: The present study provides population-based estimate for sibling RR and demonstrates familial aggregation of KD. The results suggest a significant genetic contribution to the KD susceptibility.

Disclosure: **I. J. Chou**, None; **C. F. Kuo**, None; **J. L. Huang**, None; **C. T. Wu**, None; **S. H. Hsia**, None; **H. C. Chang**, None.

1550

Long-Term Outcomes of Patients with Reversible Cerebral Vasoconstriction Syndromes (RCVS). Seby John, Leonard H. Calabrese, Stewart Tepper, Mark Stillman, Ken Uchino and Rula Hajj-Ali. Cleveland Clinic Foundation, Cleveland, OH

Background/Purpose: RCVS is a syndrome characterized by acute onset of severe headaches, with or without neurologic deficit with evidence of reversible cerebral vasoconstriction. Natural history and long term outcome of RCVS has not been thoroughly investigated. To date, three main series of RCVS have been reported and long term outcomes were not readily available.

Objectives: i) To assess long term neurologic outcome of patients with RCVS using validated outcome measures for stroke and headache ii) To determine the impact of RCVS on patient's health related quality of life (QoL).

Methods: After approval from the institutional review board, prospective cohort analysis of patients recruited from our RCVS database registry was conducted. Validated questionnaires were mailed to the patients on a one-time-basis. The forms included: Headache screening questionnaire, Headache Impact Test-6 (HIT-6), Barthel index (BI), Patient Health Questionnaire (PHQ-9) and European QoL Questionnaire (EQ-5D-5L).

Results: A total of 57 patients were present in the RCVS registry. Of these patients, 3 refused to participate in the study, 26 were inaccessible or lost to follow-up, 11 agreed to participate but never returned the forms, and 17 returned the questionnaires (5 incomplete). Mean follow-up time from diagnosis to answering questionnaires was 112 months (range 10–254 months). Of the 17 patients, 8 (47%) continued to have headaches, but majority (88%) reported improvement in the character of headaches with only 1 patient having worsening. 3 (38%) patients reported that the headaches were similar to the initial headache during onset of RCVS. Headache impact on life as measured by the HIT-6 showed that only 2 patients (17%) had a severe impact (HIT score > 60), while 3 patients each (25%) reported substantial impact (56–59) or some impact (50–55); and 4 (33%) reported no impact (<50). The mean MIDAS score was 11.83 and only 2 (17%) had severe disabling headaches (MIDAS score > 21). 13(93%) patients were independent per BI scores > 85 (8 patients scored 100). EQ-5D-5L measurements showed that 9 (69%), 11 (85%)

and 9(69%) patients had no problems with mobility, self-care and leisure respectively. However, 10 (77%) and 7(54%) patients had slight to severe problems with pain and anxiety respectively. Scoring per the PHQ-9 questionnaire revealed that only 1 (7%) patient had severe depression (PHQ score 20–27), while 7(50%), 3(21%), 1(7%) and 3(21%) patients had no/minimal (0–4), mild (5–9), moderate (10–14) and moderately severe (15–19) depression.

Conclusion: This is the first study looking at the long term outcomes of patients with RCVS. Although limited by small numbers, preliminary data suggests that patients with RCVS have favorable outcomes both in terms of headaches and stroke. Although close to half (47%) of patients continued to have chronic headaches, most had improved in character with only 17% reporting severe headache by MIDAS and HIT-6 scoring. Majority of patients were also independent (93%) and had no problems with mobility or self-care, but pain and anxiety decreased the QoL. Severe and moderately-severe depression was present in 28% of patients. Additional studies are needed to determine if similar results are observed in other RCVS patients.

Disclosure: **S. John**, None; **L. H. Calabrese**, None; **S. Tepper**, Allergan, ATI, BristolMyerSquibb, DepoMed, GSK, MAP, Merck, NuPathe, and Zogenix, 2, ATI, 1; **M. Stillman**, None; **K. Uchino**, None; **R. Hajj-Ali**, None.

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Primary Angiitis of the Central Nervous System: Description of the First 52 Adult Patients Enrolled in the French COVAC' Cohort. Hubert de Boysson[1], Mathieu Zuber[2], Olivier Naggara[3], Jean-Philippe Neau[4], Françoise Gray[5], Marie-Germaine Bousser[6], Isabelle Crassard[6], Emmanuel Touze[7], Pierre-Olivier Couraud[8], Philippe Kerschen[9], Catherine Oppenheim[3], Olivier Detante[10], Anthony Faivre[11], Nicolas Gaillard[12], Caroline Arquizan[13], Boris Bienvenu[14], Antoine Neel[15], Loic Guillevin[1], Christian Pagnoux[16] and French Vasculitis Study Group and NeuroVascular Society[17]. [1]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [2]Department of Neurology, Groupe Hospitalier Saint-Joseph, Université Paris Descartes, Paris, France, [3]Department of Neuroradiology, Hôpital Sainte-Anne, Paris, France, [4]Department of Neurology, Centre Hospitalier Universitaire La Milétrie, Poitiers, France, [5]Department of Pathology, APHP Hôpital Lariboisière, Université Paris Diderot, Paris, France, [6]Department of Neurology, APHP Hôpital Lariboisière, Université Paris Diderot, Paris, France, [7]Department of Neurology, Hôpital Sainte-Anne, Université Paris Descartes, Paris, France, [8]Department of Cellular Biology, Institut Cochin, Paris, France, [9]Department of Neurology, Centre Hospitalier Universitaire Henri Mondor, Créteil, France, [10]Department of Neurology, Centre Hospitalier Universitaire de Grenoble, Grenoble, France, [11]Department of Neurology, Hôpital d'Instruction des Armées Saint-Anne, Toulon, France, [12]Department of Neurology, Centre Hospitalier de Perpignan, Perpignan, France, [13]Department of Neurology, Hôpital Gui de Chauliac, Université Montpellier, Montpellier, France, [14]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, France, [15]Department of Internal Medicine, Centre Hospitalier Universitaire de Nantes, Nantes, France, [16]Mount Sinai Hospital, Toronto, ON, [17]Paris, France

Background/Purpose: Primary angiitis of the central nervous system (PACNS) is rare and only 1 pediatric and 1 adult large cohorts including >30 PACNS patients have been published, both from North America. The French Vasculitis Study Group, in collaboration with the French NeuroVascular Society and Internal Medicine Society, initiated a multicenter cohort study to describe a new and large adult PACNS population.

Methods: Patients with PACNS, diagnosed recently or within the past 20 years, with follow-up >6 months after diagnosis (unless they died earlier) and negative diagnostic work-ups for alternative diagnoses or secondary CNS vasculitis, were eligible for inclusion. A multidisciplinary committee (internists, neuroradiologists, neurologists and pathologists) systematically analyzed all medical charts to validate patients' diagnoses, characteristics and outcomes. Poor outcomes were defined as no disease control and/or PACNS relapse or death.

Results: Eighteen months after cohort initiation, 52 patients (30 M/22 F; median age at diagnosis, 43.5 [18–79] yr) from 21 French hospitals have been included. Thirty-one (60%) underwent brain biopsy, which showed vasculitis features in 19 (37% biopsy-proven PACNS). All 12 patients with normal or non-contributive biopsies and the remaining 21 without brain biopsies, had persistent (>6 months) conventional cerebral angiography suggesting PACNS (33 [63%] angiography-diagnosed

PACNS). The most frequent initial manifestations were focal neurological deficits (83%), headaches (54%), cognitive impairment (35%), aphasia (35%) and/or seizures (33%). Compared to biopsy-proven PACNS, angiography-diagnosed PACNS patients had more frequent focal neurological deficits (p=0.004) and bilateral infarctions on MRI (p=0.04) but less frequent encephalitic manifestations, like seizures or cognitive disorders (p=0.003 and 0.04, respectively). Twenty-two (52%) of the 42 MRI with gadolinium injection showed enhanced-parenchymatous/meningeal (22/10) lesions. All but 1 patient received corticosteroids (CS) and 44 cyclophosphamide (CYC). At the time of this analysis (median follow-up, 35 [6–148] mo), 3 (6%) patients had died; 20 (51%) of the 49 survivors had poor outcomes (13 [27%] relapsed, 7 [13%] had no disease control) and 40 (77%) had some persistent neurological damage. Patients with gadolinium leptomeningeal enhancement responded promptly to therapy but relapsed more often (80%) than those without (14%; p<0.0001). Multivariable analysis retained only intraparenchymatous and meningeal gadolinium uptakes at diagnosis as independent predictors of poor prognosis or relapse (HR=2.45 [95% CI, 0.99–6.08] and 1.88 [95% CI, 0.80–4.46], respectively).

Conclusion: In this PACNS cohort, more than half the patients responded to CS–CYC and had good outcomes at 3 yr, but neurological damage was frequent. Leptomeningeal and intraparenchymatous enhancements on MRI were associated with a poorer outcome. Comparisons of the different ongoing cohorts should help identify subgroups with poorer outcomes.

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Clinical Correlates, Treatment Outcomes and Predictors of Vasculitis Associated with Rheumatoid Arthritis in the 'Biologic Era': A Case-Control Study. Ashima Makol, Cynthia S. Crowson, Eric L. Matteson and Kenneth J. Warrington. Mayo Clinic, Rochester, MN

Background/Purpose: 1.To determine the clinical presentation, treatment and outcomes of vasculitis (RV) associated with rheumatoid arthritis (RA) in the era of biologic use. 2. To identify risk factors associated with the development of RV.

Methods: A retrospective cohort of patients with RV evaluated at Mayo Clinic Rochester in 2000–2009 was identified. RV was defined as histopathological evidence of and/or a definitive clinical or radiological diagnosis of vasculitis made by a rheumatologist in a patient meeting the 1987 ACR classification criteria for RA. In a case-control study to identify risk factors for RV, RV cases were compared in a 1:2 ratio to controls (RA without RV).

Results: Eighty-six patients (58% women, 88% white) with RV were identified. All met the 1984 Scott and Bacon criteria for systemic RV. Histopathological confirmation was available for 58%. RV manifestations included cutaneous vasculitis (65%), vasculitic neuropathy (35%), CNS vasculitis (8%), mesenteric vasculitis (2%), scleritis/episcleritis (2%), pulmonary angiitis (1%) and necrotizing glomerulonephritis (1%). Median age at RV diagnosis was 63 y (IQR 51–71 y) and median duration of RA was 10.8 y (IQR 2.7–21 y). 29% were current smokers at RV diagnosis. Majority had a positive rheumatoid factor (84%), anti-CCP antibody (67%), elevated ESR (66%) and CRP (69%). For treatment, 99% received corticosteroids, 29% cyclophosphamide, 55% other DMARDs and 28% biologic response modifiers (BRM). At 6 months, 38% patients achieved complete remission, 52% had partial improvement, while 10% noted no clinical improvement. Median follow up was 16 months (IQR 2.4 –59) during which 21% patients died and 30% had a relapse of RV. Predictors of relapse included smoking at RV diagnosis, lower mean ESR at presentation, and cyclophosphamide use. Among RV patients, those treated with a BRM for their RA were younger (56 vs 65 y, p=0.004) and had a lower incidence of vasculitic neuropathy (21% vs 47%, p = 0.015) than those treated without a BRM. In none of the 34 patients treated with a BRM prior to RV, was the BRM conclusively implicated to be a trigger for RV.

The 86 RV cases were compared to 172 RA controls. After adjusting for age and disease duration, increased RV risk was associated with male sex, current smoking at RA diagnosis, coexistent peripheral vascular disease (PVD) and cerebrovascular disease. Patients with high disease severity characterized by a composite index of erosions, nodulosis and 1 or more joint surgery had a significantly higher risk of RV (Odds ratio 2.0, 95% CI 1.1–3.7). Biologic use also increased the odds for RV while use of hydroxychloroquine (OR 0.54, p=0.03) and low dose aspirin for cardioprotection (OR 0.42, p=0.02) were associated with lower odds of developing RV.

Conclusion: In this large series of patients with RV, the predominant clinical manifestations were cutaneous vasculitis and vasculitic neuropathy. Male sex, smoking, RA severity, PVD and cerebrovascular disease increased the odds of developing RV. Among patients with RV, use of BRM was associated with a lower frequency of vasculitic neuropathy. Even in the 'biologic era', RV remains a serious complication of RA and is associated with significant mortality.

Disclosure: A. Makol, None; **C. S. Crowson**, None; **E. L. Matteson**, Centocor, Inc./Johnson and Johnson, 2, Genentech and Biogen IDEC Inc., 2, Hoffmann-La Roche, Inc., 2, Human Genome Sciences, Inc., 2, Pfizer Inc, 2, Novartis Pharmaceutical Corporation, 2, Roche Pharmaceuticals, 2, UCB Group, 2, Centocor, Inc., 5, Horizon Pharma, 5, Novartis Pharmaceutical Corporation, 5; **K. J. Warrington**, None.

ACR/ARHP Poster Session B
Clinical Practice/Patient Care
Monday, November 12, 2012, 9:00 AM–6:00 PM

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The Effect of Knee Replacement On Participation Outcomes: The Multicenter Osteoarthritis Study and Osteoarthritis Initiative. Jessica L. Maxwell[1], Jingbo Niu[2], Julie J. Keysor[1], Tuhina Neogi[2], Tianzhong Yang[2], Michael C. Nevitt[3], Jasvinder A. Singh[4], Laura Frey-Law[5] and David T. Felson[2]. [1]Boston Univ Sargent College, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]University of California-San Francisco, San Francisco, CA, [4]University of Alabama at Birmingham, Birmingham, AL, [5]University of Iowa, Iowa City, IA

Background/Purpose: Little research has explored participation outcomes, defined as involvement in life situations, among persons following knee replacement (KR). We recently reported (OARSI 2012) that persons undergoing KR did not necessarily show improvement in participation after surgery. These findings, however, could be due to confounding by indication, thus we sought to examine whether participation restriction differed among persons following KR compared to similarly matched group with symptomatic knee osteoarthritis (OA).

Methods: Subjects were selected from the Multicenter Osteoarthritis (MOST) Study and the Osteoarthritis Initiative (OAI). We took the pre-KR pain and physical function WOMAC scores of MOST and OAI subjects who were at least one year after KR and matched each of these by quartiles to 1–2 subjects with symptomatic knee OA, (defined as radiographic evidence of knee OA and frequent knee pain over the last 30 days). Participation was measured using the Late Life Disability Instrument (LLDI) at the 60 month visit in MOST and at 48 months in OAI; restriction was defined using a previously established cut-point of < 69/100 on the Instrumental Limitation subscale of the LLDI (LLDI-IL). Data on covariates was collected at the pre-KR/index visit.

We compared the proportion of subjects with participation restrictions for each group overall and stratified by sex, race, age (< 65, 65–74, ≥75 years), # of comorbidities (> 1), and depressive symptoms (> 16 on CES-D) using chi square analyses. We evaluated the association between KR status and participation restrictions while adjusting for the above covariates, as well as body mass index, educational level, and presence of lower limb or back pain, using conditional logistic regression.

Results: Participation restriction was assessed on average 3 years post-KR and was common in both the post-KR group (45%) and in those with SxOA who had comparable pain/function (43%). There were no statistical differences in the proportion of participation restriction among subjects in each KR group overall or after stratification. The SxOA group had more younger subjects, fewer Whites and more with other lower limb pain (Table 1). After adjusting for these differences in groups, there was no difference in the odds of participation restriction among subjects with KR compared to those with SxOA (OR 1.0 (0.6, 1.6). Other factors independently associated with participation restrictions included male sex and increased depressive symptoms (Table 2).

Table 1. Demographic and clinical status of study subjects at pre-KR visit

Independent Variable	Knee Replacement Group	Symptomatic Osteoarthritis Group	p-value
Total, n	277	552	
Sex: Women, %	66	64	.5
Race: White, %	86	76	.0007
Age: <65 years, %	46	55	.01
65–74 years, %	45	35	.006
75+ years, %	9	10	0.8
Body Mass Index, mean (SD)	32.2 (6.4)	32.4 (6.6)	.99
Comorbidities: > 1, %	43	43	0.9
Depressive Symptoms: > 16, %	15	17	0.3
Education: < High School, %	5	6	0.6
Pain in lower limbs/back, %	75	83	.01
WOMAC physical function, mean (SD), range 0–68	26.2 (11.7)*	26.1 (11.8)*	0.8
WOMAC pain, mean (SD), range 0–20	8.1 (3.8)*	8.1 (3.8)*	0.9

* Knee replacement and symptomatic OA group matched on these variables

Table 2. Effect of Demographic and Clinical Factors on Participation Restrictions

Independent Variable	Unadjusted OR (95%CI)	Adjusted OR (95% CI)**
Knee Replacement Status (ref=SxOA)	0.9 (0.6, 1.4)	1.0 (0.6, 1.6)
Sex (ref=male)	0.7 (0.4, 1.1)	0.6 (0.4, 1.0)
Race (ref= White)	1.3 (1.2, 1.3)	0.9 (0.5, 1.8)
Age at KR: (ref= <65)	ref	ref
65–74	1.5 (1.0, 2.3)	1.4 (0.9, 2.3)
75+	0.4 (0.2, 1.0)	0.8 (0.3, 1.9)
Educational status (ref < High school)	1.2 (0.5, 2.9)	1.1 (0.4, 2.6)
Number of Comorbidities (ref ≤ 1)	1.7 (1.1, 2.7)	1.5 (0.9, 2.5)
Body Mass Index (ref <30)	1.8 (1.1, 2.7)	1.6 (0.9, 2.6)
Depressive Symptoms (ref'16)	2.9 (1.5, 5.3)	2.3 (1.2, 4.5)
Lower Limb and Back Pain	1.4 (0.8, 2.5)	1.3 (0.7, 2.5)

**Adjusted for KR group, sex, race, age category, educational status, # of comorbidities, bmi, depressive symptoms, lower limb and back pain

Conclusion: Despite prior evidence of improvements in pain and function after knee replacement, the current study demonstrates that after KR, there is no clear difference between those who underwent KR and those who still have SxOA in terms of participation in life activities. Other factors such as sex and depressive symptoms may play more of a role in one's involvement in life situations.

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Clusters of Fatigue—a Comparison Between Persons with Systemic Lupus Erythematosus and Age and Gender Matched Controls. Susanne Pettersson[1], Karin Eriksson[2], Carina Boström[2], Elisabet Svenungsson[3], Iva Gunnarsson[3] and Elisabet MB Welin Henriksson[4]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Division of Physiotherapy, Karolinska Institutet Huddinge, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institutet Rheum, Stockholm, Sweden

Background/Purpose: The aim (1) of this study was to explore fatigue in patients with SLE with age and gender match controls using cluster analysis and (2) analyze the clusters concerning health related quality of life (HRQoL), anxiety, depression and life-style habits.

Methods: This cross-sectional study included patients with SLE and paired controls (age and gender). The respondents answered self-assessment of fatigue: Fatigue severity scale (FSS), Vitality (VT) from SF-36 and Multidimensional Assessment of Fatigue scale (MAF). All three questionnaires were answered by 616 persons (mean age 47 years, SD 14.6, range 18–84) and hierarchic cluster analysis were used to form homogeneous groups of fatigue. Further the Medical Short Form-36 (SF-36) were used to collect data on HRQoL and The Hospital Anxiety and Depression Scale (HADS) with the two sub-scales, anxiety (HADS-A) and depression (HADS-D).

Results: Patients with SLE had higher levels of fatigue than the controls on all three fatigue questionnaires as well as all dimensions of HRQoL and depression. The hierarchic cluster analysis identified three divergent clusters of fatigue with significantly different levels of fatigue. The clusters were denominated by their levels of fatigue. The persons in the High fatigue cluster (n=221) were dominated by patients (80%) and most affected by depression

and anxiety, had lowest levels of HRQoL. This cluster had the lowest proportion of persons working ≥ 50% and they lived more often without a partner. The Low fatigue cluster (n= 240) was dominated by the controls (78%) and included persons with highest perceived HRQoL, lowest distribution of anxiety and no detected depression (p < 0.001). They represented the lowest proportion of smoker (13% vs 20%, both High and Intermediate). Persons in the Intermediate fatigue cluster (n=155) had smoking habits similar to the High fatigue cluster, and sleeping habits towards the Low fatigue cluster. The intermediate fatigue cluster had the most equal distribution at 48% patients and 52% controls, their level of fatigue were more moderate. There were no differences in gender distribution, age or sedentary behavior between the three clusters.

Comparing patients in the three clusters no significant difference was found regarding the number of ACR criteria, disease duration, or organ damage (SLICC/ACR). However, patients in the High fatigue cluster had more disease activity (SLAM) (mean 9.0, CI 8.3–9.7) than both the Low fatigue cluster (mean 4.2, CI 3.3–5.2, p < 0.001) and the Intermediate fatigue cluster (mean 5.3, CI 4.7–6.0, p < 0.001). However, there was no difference in disease activity between the Low fatigue cluster and the Intermediate fatigue cluster.

Conclusion: The analysis confirmed that a high number of patients with SLE are affected by fatigue but also that non-SLE persons were clustered together with the patients (6%) in the High fatigue cluster. Notable is that in this cross-sectional study a minority (7%) of patients with SLE report low levels of fatigue, high wellbeing and healthier life-style habits e.g interestingly less smoker.

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Minimal Clinically Important Difference for Seven Measures of Fatigue in Patients with Systemic Lupus Erythematosus – Results From a Swedish Setting. Susanne Pettersson[1], Ingrid E. Lundberg[2] and Elisabet MB Welin Henriksson[3]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet Rheum, Stockholm, Sweden

Background/Purpose: The objective of this study was to estimate the minimal clinically important difference (MCID) of seven self-administered measures assessing fatigue in persons with systemic lupus erythematosus (SLE).

Methods: The respondents (n=51, women 98%, age 52.8 ± 12.1 years, disease duration 18.7 ± 13.6 years) met in groups sessions with six to nine participants. After initial self-assessment with the seven fatigue questionnaires (Chalder Fatigue Scale, Vitality from SF-36, Fatigue Severity Scale, Multidimensional Assessment of Fatigue, Multidimensional Fatigue Inventory, Functional Assessment of Chronic Illness Therapy–Fatigue, and a single numeric rating scale), each respondent had a minimum of five face-to-face discussions, all followed by an individual comparative assessment of his or her own level of fatigue (7-grade scale: Much More, Somewhat More, Little More, About the Same, Little Less, Somewhat less, Much Less). This method resulted in 260 contrasting assessments; MCIDs were first calculated using paired differences and then established by a regression approach. Patients were offered the opportunity to provide additional free comments regarding the questionnaires.

Results: In total seven group sessions was hold with the 51 respondents (98% women). Correlations with the raw fatigue score for the seven questionnaires and patients' assessment of disease activity varied between 0.421 (p < 0.01) and 0.641 (p < 0.001). The self-reported disease activity and fatigue correlations of the patients varied between 0.504 and 0.562 (p<0.001 for all). No correlations were found between fatigue and age (r = −0.134–0.059) or fatigue and disease duration (r = −0.113–0.01).

The result was divided into contrast groups, based on the individual comparative assessment (the 7-grade scale). For most instruments, the mean paired difference followed a slope where the contrast groups represented a reasonable and increasing level of fatigue, compared to the neighboring contrast group. The mean paired difference for the patients scoring "about the same fatigue" ranged from 1.4 for Chalder Fatigue Scale fatigue scale to 3.4 for Functional Assessment of Chronic Illness Therapy – Fatigue. The means for the "about the same" groups were used to standardise the estimates. Except for the Chalder Fatigue Scale, the estimates for the MCID relative to "little *less* fatigue" tended to be smaller than those for "little *more* fatigue". The paired approach (contrast group: "Little more fatigue") varied from 4.6 to 17.0, and the regression approach varied from 4.45 to 10.75. Estimates in the regression approach were

consistently higher than in the paired model. The MCID estimates were least favorable for the single numeric rating scale. In the free comments section fewer respondents supported the use of the single-question measure compared to the other questionnaires.

Conclusion: Based on our results, all seven instruments are adequate for detecting clinically important differences of fatigue in patients with SLE. However, the use of a single-question measure was not supported by the MCID estimates or by comments from the respondents.

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The Effect of Ginger Therapy On Symptoms of Osteoarthritis: An Open Pilot Study. Tessa Therkleson. Edith Cowan University, Perth, Australia

Background/Purpose: Osteoarthritis (OA) is a painful, progressive disease of synovial joints characterised by deterioration of cartilage and bone and inflammation. Osteoarthritis of the knee and hip joints is common and a major cause of musculoskeletal pain and disability in older adults. In addition to conventional pharmacological management, people with OA often use complementary and alternative treatments. In vitro studies find ginger extract inhibits the inflammatory enzymes COX-2 and 5-lipoxygenase. Ginger seems to be absorbed after topical application by a compress that provides heat and relaxation therapy. European hospitals specialising in traditional therapies routinely use ginger compresses applied to the lower back for treatment of inflammatory conditions. In order for topical ginger treatments to be used more widely, a pre-packaged ginger patch was developed. This pilot study assessed the effects of the ginger compress and standardised ginger patch and the potential effect size of the treatments.

Methods: Twenty adult volunteers with osteoarthritis aged 35 – 90 years, recruited from medical centres and the community, were randomly assigned using a block size of 4, to ginger treatment with ginger compress (GC) or ginger patch (GP). Both treatments were provided daily for seven consecutive days at medical centres by trained nurses. While lying supine either a warm GC or GP was secured on the mid back for 45 minutes. All participants were offered a supply of the GP for self-treatment at home for the following 24 weeks. The 5-item modified Health Assessment Questionnaire (MHAQ) was used to assess pain, global effect, fatigue, functional status and health satisfaction. The MHAQ was completed once a week for 3 weeks and 4 weekly for 24 weeks.

Results: Participants (mean age 64 years, 80% female) had a mean pain score at baseline of 2.1, with 3 being the most extreme pain. Most participants had OA of the hips and/or knees (17/20, 85%). All participants had a reduction in pain one week after ginger therapy, with a mean pain score 1.1. A comparison of MHAQ scores for the GC and GP groups show a strong co-relation, with p = 0.98 at baseline and p = 0.97 at 7 days. After seven days of ginger treatment the MHAQ mean total scores for all participants for pain, fatigue, global effect and functional status were reduced by 48%, 49%, 40% and 31% respectively, with scores progressively declining over the following 24 weeks. Pain, fatigue, global effect and functional status were all statistically significantly reduced from baseline to 7 days, 12 weeks and 24 weeks after therapy (p < 0.001). Health status satisfaction improved for both GC and GP, with 80% dissatisfied 7 days before therapy to 70% satisfied 7 days after therapy and 82% satisfied 24 weeks after therapy.

Conclusion: This pilot study suggests ginger therapy using both the ginger compress and ginger patch has the potential to relieve symptoms and increase independence for people with osteoarthritis. These data will be utilised in the design of a randomised placebo-controlled trial of the ginger patch.

1557

What Percentage of Postmenopausal Women Younger Than Age 65 Years Have Low Bone Mineral Density At a Family Health Center? Marvin Vaishnani and Feyrouz T. Al-Ashkar. Cleveland Clinic,Lorain Institute, Lorain, OH

Background/Purpose: Many younger women, < 65 years of age may have low bone mineral density (BMD) that remains undetected in clinical practice due to following Medicare age guidelines of 65 years and older for BMD test and other factors. Prevalence of low BMD is a growing public health issue in the population but these have not been well quantified in this younger age group of women. This study aims to describe prevalence of low

BMD at a family health center in postmenopausal women younger than 65 years and identifying common risk factors noted in this age group.

Methods: Retrospective chart review was done of patients who had dual-energy x-ray absorptiometry (DXA) scan performed at family health center between Jan 2010 to May 2012, on Hologic® DXA machine. Postmenopausal women less than 65 years of age were included (amenorrhea ≥ 12 months). Patients who have been on osteoporosis medication therapy and used estrogen postmenopausal were also included in this study. The data of risk factors was collected from patient questionnaire present in medical charts. Patients were grouped into those with low T-score < −1.0, T-score ≤ −2.0, and T-score ≤ −2.5. T-scores of the spine (following the International Society for Clinical Densitometry guidelines), femoral neck, total hip, one-third radius (when available) was reviewed and from these the lowest T-score was used in the results.

Results: A total of 702 patient charts were reviewed. The age ranges from 30 to 64 years and average age of patients was 56.74 years. We found 71.93% of patients have T-score < −1.0, 35.47% of patients have T-score ≤ −2.0, and 17.52% of patients have T-score ≤ −2.5. The risk factors noted among T-score < −1.0 are summarized in figure-2 below and 88.51% were found to have at least 1 or more risk factors out of five.
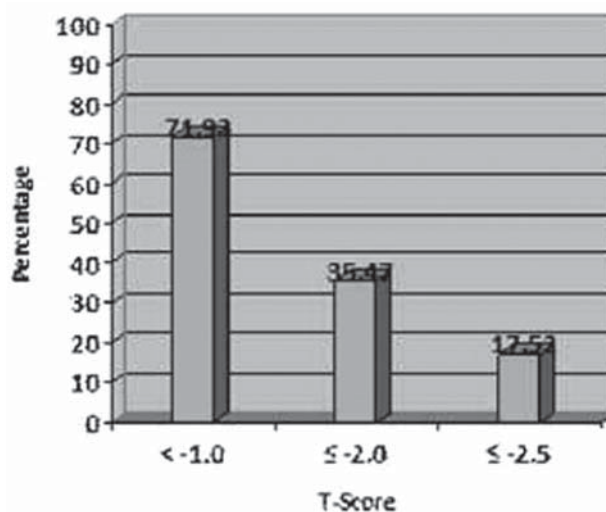
Figure 1. This figure represents percentage of patients in a T-score group. (n=702).
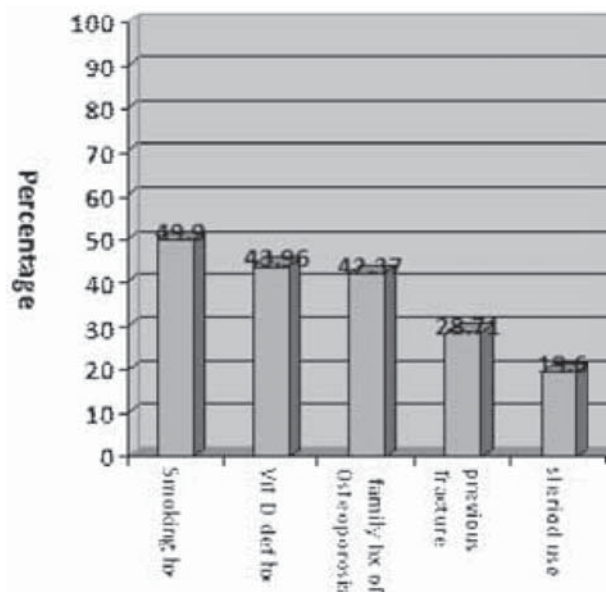
Figure 2. This figure represents percentage of patients among T-score <−1.0 have this risk factors.(n=505)

Conclusion: The results show high prevalence of low BMD in postmenopausal women younger than age 65 years at this family health center. Although population prevalence cannot be calculated from this study, findings

suggest that low BMD is fairly prevalent in this age group. A larger study would be needed to further evaluate low BMD in postmenopausal women younger than 65 years of age. If confirmed this should alarm clinicians to obtain BMD testing in women earlier than age 65 years and especially so in those who have the identified risk factors and to identify the younger age group women with undiagnosed osteoporosis.

Disclosure: **M. Vaishnani**, None; **F. T. Al-Ashkar**, None.

1558

"It Gets Me Down Every Single Day": Are Men with Rheumatoid Arthritis Getting the Support They Need? Caroline A. Flurey[1], Marianne Morris[1], Jon Pollock[1], Rodney A. Hughes[2], Pamela Richards[3] and Sarah Hewlett[1]. [1]University of the West of England, Bristol, United Kingdom, [2]St. Peters Hospital, Chertsey Surrey, United Kingdom, [3]University of Bristol, Bristol, United Kingdom

Background/Purpose: Daily life with RA has been explained as unpredictable and full of uncertainty. However, most research about daily life with RA was conducted before current more aggressive medications, and in women. The purpose is to explore daily life on modern therapies.

Methods: Q-Methodology: 30 RA patients sorted 39 statements (generated from previous qualitative interviews) about daily life with RA across a forced distribution, in ranked order of agreement. Data were analysed using centroid factor analysis with varimax rotation (i.e. the participants and not the items are the variables). Demographic and clinical data were collected and patients completed comments booklets about their rationale for sorting the statements.

Results: Three factors were generated, which explained 33% of the study variance and accounted for 23 of the 30 participants. None of the Q-sorts were confounded (loading on more than one factor). A participant loading of 0.41 reached significance at $p<.01$. Factor A (Taking Control: "Just a fact of life") and Factor B (Keeping RA in its place: "It's a very small part of you") were predominately female participants (86%, 100%) and have been reported previously.

Factor C: Struggling Through: "It gets me down every single day" comprised 8 participants, 63% male: mean disease duration 15.3yrs (SD 14.3), age 55.5yrs (SD 7.1), HAQ score 1.3 (SD 0.9), patient global 4.8 (SD 2.5), 50% on biologic therapies. These predominantly male patients are never symptom free, experiencing pain and fatigue daily: *"It's like feeling ill all the time"*, they describe fatigue as *"the worst symptom"*. They worry and get angry and frustrated about their RA: *"I get very frustrated with it, the problem is then I get irritated and take it out on the wife"*. This group report being unable to effectively manage their symptoms, some *"don't know what to avoid"*, whilst others use unadvisable methods: *"I find cocaine numbs the pain"*. They report being unable to be spontaneous or to exercise and they struggle to explain their experience to their family. These patients feel their body has let them down, life is unfair: *"Why me? Why now?"* and the idea that they are lucky in comparison to others is *"ridiculous"*.

We re-examined the preceding qualitative interviews that generated these Q-statements, and this clarified these men's views further. Having RA means men's traditional masculine coping strategies have to be adapted: *"you can't go and thump a wall because you end up with a flare and you can't go and kick a football around or anything like that, so you need to find an outlet and talking is the outlet I suppose"*. At the same time, they reject those traditional, more female-gendered RA support mechanisms: *"The self help groups don't confront it enough, it might be all lovey dovey [sweet and gentle] but sometimes you have got to be quite hard about it"*.

Conclusion: Whilst some patients cope well with their RA, others struggle to accept and adapt to their condition; the majority of these being male. These findings indicate a need to address the unique support needs of men with RA and to consider providing support that is acceptable to their masculine identities.

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Treatment Outcomes From a Nurse-Led Rheumatology Clinic in Monitoring of anti-TNF Therapy – a Randomised Controlled Trial. Ingrid Larsson[1], Bengt Fridlund[1], Barbro Arvidsson[2], Annika Teleman[3] and Stefan Bergman[4]. [1]School of Health Sciences, Jönköping University, Jönköping, Sweden, [2]School of Social and Health Sciences, Halmstad University, Halmstad, Sweden, [3]Spenshults Hosp of Rheum Dis, Oskarstrom, Sweden, [4]R&D Center, Spenshult Hospital, Oskarström, Sweden

Background/Purpose: Patients with chronic inflammatory arthritis (CIA) treated with anti-TNF therapy are usually followed up by rheumatologists. Nurse-led rheumatology clinics have been proposed for patients with low disease activity or in remission. The purpose of this trial was to compare treatment outcomes from a nurse-led rheumatology clinic and a rheumatologist clinic for patients undergoing anti-TNF therapy with low disease activity or in remission.

Methods: A randomized controlled trial (RCT) with a 12-month follow-up was conducted with 107 patients randomised into two groups with a 6-month follow up to a nurse-led rheumatology clinic based on a person-centred care (intervention group; n=53) or to a rheumatologist-led clinic (control group; n=54). The intention of the interventional trial was to replace one of the two annual rheumatologist monitoring visits by a nurse-led rheumatology monitoring visit for patients undergoing anti-TNF therapy. Inclusion criteria were patients undergoing anti-TNF therapy and Disease Activity Score 28 (DAS28) ≤3.2. The hypothesis was that the outcomes from nurse-led clinic will not be inferior to those obtained by rheumatologist-led clinic at 12-month follow-up. Primary outcome was disease activity measured by DAS28.

Results: After 12 months 47 patients in the intervention group and 50 patients in the control group completed the trial and there were no differences (p=0.66) in mean change of DAS28 between the intervention or control group. There were no differences (p>0.05) in mean change in Visual Analogue Scales (VAS) for pain, Health Assessment Questionnaire (HAQ), satisfaction or security with the rheumatology care between the two groups, see table.

Table. Mean difference of changes after 12 months between intervention group (Nurse-led rheumatology clinic) (n=47) and control group (Rheumatologist-led clinic) (n=50)

	Nurse-led rheumatology clinic-Rheumatologist-led clinic Mean difference of changes (Std Error Difference)	*p*
DAS28(mean)	−0.06 (0.14)	0.66
ESR (mm/h)	−1.05 (1.47)	0.47
Swollen joints(28)	0.13 (0.24)	0.60
Tender joints(28)	0.33 (0.40)	0.42
Global Health VAS(mm)	4.29 (3.46)	0.22
HAQ	0.02 (0.06)	0.79
Pain VAS(mm)	−0.24 (3.85)	0.95

student t-test

Conclusion: In monitoring of anti-TNF therapy treatment outcomes for patients at a nurse-led rheumatology clinic are not inferior to those obtained by rheumatologist-led clinic at 12-month follow-up. The follow-up care of anti-TNF therapy may advantageously be performed by a nurse-led clinic based on a person-centred care. The results from this trial demonstrated that patients with CIA undergoing anti-TNF therapy, with low disease activity or in remission, could be monitored by a nurse-led rheumatology clinic without any differences in outcome as measured by DAS28.

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1560

What Will Determine Adherence to Pharmaceutical Treatment for Rheumatoid Arthritis? A Systematic Review. Annelieke Pasma[1], Adriaan van 't Spijker[2], Jan van Busschbach[2], Johanna M.W. Hazes[3] and Jolanda J. Luime[2]. [1]Erasmus MC University Medical Centre, Rotterdam, Netherlands, [2]Erasmus MC - University Medical Center, Rotterdam, Netherlands, [3]Erasmus Medical Center, Rotterdam, Netherlands

Background/Purpose: In the early stages of Rheumatoid Arthritis (RA), adherence to the prescribed treatment is important to prevent irreversible joint damage. However, medication adherence rates in RA patients can be improved. To explain the suboptimal adherence, factors that influence adherence should be elucidated. These factors were last reviewed in 1982. Since then, treatment strategies for RA have changed, which means that nowadays different factors might play a role. Our aim is therefore to review adherence rates reported in the literature, to identify factors associated with adherence, to review the strength of the association between these factors and adherence and to cluster the identified factors according to the Health Belief Model (HBM) (Figure 1).
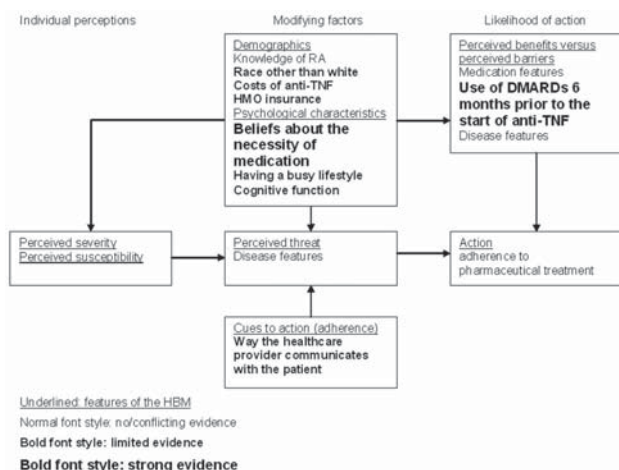
Figure 1. Health Belief Model

Methods: PubMed, PsycINFO, EMbase and CINAHL databases were systematically searched from inception to February 2011. Articles were included if they addressed medication adherence, used a reproducible definition, determinants and its statistical relationship. Methodological quality was assessed using a quality assessment list for observational studies derived from recommendations from Sanderson, Tatt and Higgins (2007). The strength of evidence for factors associated with adherence was assessed by defining 5 levels of evidence. Resulting factors were interpreted using the HBM.

Results: 18 out of the 1479 identified studies remained. Adherence rates ranged between 49.5% and 98.5%. 64 factors were identified and grouped according the HBM into demographic and psychosocial characteristics, cues to action and perceived benefits versus perceived barriers. The belief that the medication is necessary and DMARD use prior to the use of anti-TNF had strong evidence for a positive association with adherence. There is limited evidence for positive associations between adherence and race other than White, general cognition, satisfactory contact with the healthcare provider and the provision of adequate information from the healthcare provider. There is limited evidence for negative associations between adherence and having HMO insurance, weekly costs of TNF-I, having a busy lifestyle, receiving contradictory information or delivered information in an insensitive way by the rheumatologist. 18 factors were unrelated to adherence. The results are presented in figure 1.

Conclusion: The strongest relation with adherence is found for prior use of DMARDs before using anti-TNF and beliefs about medication. Because the last one is modifiable, this provides hope to improve medication adherence. Since research on factors influencing adherence has mostly focussed on demographic and disease futures, future studies should use a theoretical framework to explore the role of interpersonal and other relevant factors.

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1561

Factors Influencing Implementation of Intensive Treatment Strategies for Early Rheumatoid Arthritis. Sabrina Meyfroidt[1], Diederik De Cock[1], Kristien Van der Elst[1], Laura van Hulst[2], Marlies Hulscher[2], Johan Joly[1], Rene Westhovens[1] and Patrick Verschueren[1]. [1]University Hospitals KU Leuven, Leuven, Belgium, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Despite the availability and demonstrated effectiveness of intensive treatment strategies for early rheumatoid arthritis (RA), a discrepancy seems to exist between theoretical acceptance and practical implementation. Limited studies have looked at factors influencing the implementation of intensive treatment strategies for early RA in daily practice. The purpose of this study was to explore and identify these factors across different healthcare settings in Flanders.

Methods: This study involved rheumatologists, nurses and patients participating in the CareRA trial, a multicentre RCT comparing different intensive treatment strategies for early RA based on the original Cobra step down schedule with conventional DMARDs (MTX+Sulphasalazine, MTX+Leflunomide, MTX monotherapy) plus step-down glucocorticoids.

Two qualitative research methods were used, including semi-structured interviews and observations at outpatient clinics. Each interview was recorded, transcribed literally and analyzed thematically.

Results: We interviewed 26 rheumatologists, 6 nurses and 24 RA patients and observed interactions between 5 rheumatologists and their patients at consultation. Greatest facilitators reported by rheumatologists and nurses included available scientific evidence, personal faith in treatment strategy, colleague support and low cost of medication. For patients, trust in caregiver was a facilitator, as well as faith in the treatment strategy. Rheumatologists had no doubts about the value of MTX but some questioned the combination strategy, others the effectiveness or/and the dosage of individual compounds. Patients were only in doubt of glucocorticoids and MTX. Additional barriers for rheumatologists included fear for patients' preconceptions, concerns of applicability to the individual patient, break in routine, interference with organizational structures and processes, time constraints and lack of financial support.

Conclusion: The factors emerging from our study highlight the complexity of implementing intensive treatment strategies for early RA in daily clinical practice. Future improvement strategies should capitalize on the facilitators identified while at the same time addressing the barriers. The generalizability of these findings to other health care systems needs further examination.

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1562

Benign Joint Hypermobility Syndrome More Common Than Expected, Both in Controls and in SLE Patients. Pia Malcus-Johnsson[1], Lotta Köhlin[1], Gunnar K. Sturfelt[2] and Ola Nived[3]. [1]Department of Rheumatology, University Hospital, Lund, Sweden, [2]Lund University, Lund, Sweden, [3]University Hospital - Lund, Lund, Sweden

Background/Purpose: Benign joint hypermobility syndrome (BJHS) in connection to rheumatic disease is sparsely investigated. It has been postulated that BJHS is more frequent in SLE than in the healthy population. The aim of this study was to investigate the frequency of BJHS in SLE patients.

Methods: Seventy-one female individuals with SLE, age 18–65, were consecutively according to age groups, enrolled to the study and were matched by healthy female controls of the same age. The study required one visit to the clinic. All individuals were examined by physician (ON/GS) for Brighton criteria and medical symptoms, by physical therapist (LK) and occupational therapist (PMJ) for Beighton scores and manifestations in body structures and body functions.

Results: Thirty-nine (55 %) individuals in SLE group and 22 (31%) in the control group satisfied Brighton criteria for BJHS (p<.004), most commonly satisfying one major and two minor criterias, whereas 16 (23%) individuals with SLE and 19 (27%) healthy controls had Beighton score ≥4 (ns). Brighton criteria to show significant differences between the groups were arthralgia major n 44/9 (p<.000), soft tissue leasions n 35/7 (p<.000), eye signs n 17/32 (p<.008), and in addition depression n 15/6 p<.033. Six individuals in the SLE group and seven in the control group had Beighton score of four or more, but did not satisfy Brighton criteria.

Within the SLE group differences between satisfying Brighton criteria or not consisted of significant differences in arthralgia major (p<.000), soft tissue rheumatism (p<.000), abnormal skin (p<.041), eye signs (p<.000) and varicose veins or prolapse (p<.005). There was in addition a significant difference in disease activity (p<.009) and in pelvic pain (p<.035). No significant differences were found in Beighton scores or other factors constituting Brighton criteria.

In physical therapist protocol, within SLE-group, significant differences were detected in being clumsy or stumble (p<.003), standing still for a while (p<.033), jaw luxation (p<.002) and experiencing problems in shoulders (p<.009), knee (p<.001), foot (p<.033) and back (p<.033).

In occupational therapist protocol, within SLE-group, significant differences were found in estimating hand function on VAS (right p<.014, left p<.029), grip force (right p<.001, left p<.002), pinch force (right p<.000, left p<.000) and in right hand dexterity (p<.005) and estimating hand pain at work on VAS (p<.025). No differences were found in deformities of the hand.

According to age, within SLE-group, there was no significant difference in satisfying Brighton criteria but a significant difference (p<.019) in ≥ 4 Beighton score with higher scores in younger individuals, cut off point 45 years. Older individuals had significantly higher rates of Beighton 1,2,3

(p<.005), arthralgia minor (p<.014) and in addition symptoms from bowel (p<.008).

Conclusion: From this study no certain conclusion can be drawn whether SLE and BJHS are related, but for both cases and controls BJHS was much more common than in other published age matched Caucasian series from Sweden.

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1563

Is Automated DATA Capture As Reliable As Manual DATA Entry in Survey Based Research? Rachel A. Mikolaitis, Jessica Cornejo, Chris Alonzo, Joel A. Block and Meenakshi Jolly. Rush University Medical Center, Chicago, IL

Background/Purpose: The collection of patient reported outcomes requires accruing survey data from patients during routine medical visits. Many of these are paper-based and require manual data-entry for adequate analysis. However, entering surveys by hand is tedious, time consuming, and may result in entry-errors. Teleform data capture technology automates paper-based processes especially in high volume settings, decreases processing time and cuts personnel and material costs, but the accuracy of automated data capture has not been well documented in clinical settings.

Aims: To test the reliability of teleform captured data against traditional hand entered patient health outcomes data.

Methods: As a quality improvement initiative, we populated survey data from 50 patients using both methods in parallel. The survey had 43 multiple choice questions on health outcomes using a Likert scale. This scale was entered into the teleform program for each question. We programmed the teleform to ensure that each question had a response, and to alert the user for each missing response. We calculated internal consistency reliability by Cronbach alpha using a two-way random method to test for absolute agreement in item responses using the two methods. This analysis was repeated for each of the 43 items.

Results: The Internal consistency reliability estimates for 43 items ranged from 0.98 to 1.0. In the 7% of the items where the responses were not in 100% agreement, the discrepancy occurred by misclassification of the Likert category response by one point (0 and 1) in three different questions and subjects. This occurred due to human error in data entry by hand, or the scanner recognizing a small mark in the "0" response boxes.

Conclusion: Teleforms data-capturing for data entry is reliable and feasible for patient driven research in Rheumatology. This program has good reliability concerning correct data entry and is a faster way for data managers to capture large amounts of data in a shorter period.

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1564

Misperceptions of FMS Patients about Their Disease. Robert S. Katz[1], Hannah Bond[2], Jessica L. Polyak[2], Lauren Kwan[2] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates, Chicago, IL

Background/Purpose: What do fibromyalgia patients think causes their illness. We asked fibromyalgia syndrome patients to respond to a questionnaire which asked about potential etiologic factors.

Methods: 21 FMS office patients (18 women and 3 men) completed a questionnaire about the causes and nature of their disease.

Results: The following percentages of FMS patients agreed with the following statements about FMS: my illness is caused by allergies, 4.8%; my illness is caused by a bacteria or virus, 0%; my illness is caused by antibodies in my blood that are directed against my body chemistry, 23.8%; my immune system is attacking me, 23.8%; my illness is caused by stress, 47.6%; my illness is caused by a traumatic event, 42.9%; my illness is caused by food products, 14.3%; my illness is caused by environmental toxins, 9.5%; my illness involves a strong genetic component, 9.5%; the cause of my illness is unknown, 47.6%; none of the above are causes of FMS, 14.3%; my illness is commonly progressive, 33.3%; my illness is frequently fatal, 0%; my illness occurs with flares and remissions, 81.0%; I will have to take steroids to control my illness, 23.8%; my illness is diagnosed based solely on lab test results, 4.8%; my illness is diagnosed based on lab test results and my symptoms, 76.2%; medications to treat my illness have serious side effects that include cancer, 19.0%.

Conclusion: Fibromyalgia patients commonly think their illness is related to stress, previous trauma or the cause is unknown. However, some believe fibromyalgia is an autoimmune disease. About one third of patients think that fibromyalgia is a progressive illness. Some patients have other misconceptions based on the questionnaire.Further education from practitioners needs to be given to some fibromyalgia patients to disabuse them of certain incorrect assumptions regarding the etiology and the likely course of their illness

Disclosure: **R. S. Katz**, None; **H. Bond**, None; **J. L. Polyak**, None; **L. Kwan**, None; **S. Shott**, None.

1565

How FMS Patients Become Workaholics. Robert S. Katz[1], Hannah Bond[2], Jessica L. Polyak[2], Lauren Kwan[2] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates, Chicago, IL

Background/Purpose: Many patients with the fibromyalgia syndrome (FMS) bring in disability forms for the practitioner to fill out or have Social Security Disability applications requesting medical records mailed to the office. We asked a group of patients with fibromyalgia whether they were capable of working full-time or part-time and what strategies they use to continue working, if they are able to.

Methods: 76 office patients with FMS (68 women and 8 men; mean age 50 ± 13) completed a questionnaire about the impact of FMS on their ability to work.

Results: 48.7% were not working, 38.2% were working full-time, and 13.2% were working part-time. The reasons for not working were: FMS, 51.4%; medical problems other than FMS, 43.2%; choice, 21.6%; retired, 16.2%; childcare or other homecare responsibilities, 5.4%. The reasons for working part-time instead of full-time were: choice, 70.0%; FMS, 30.0%; medical problems other than FMS, 10.0%. Non-working respondents who were asked how FMS affected their ability to work provided the following responses: so much pain that it limited their ability to work, 54.1%; so fatigued that they couldn't work the required number of hours, 48.6%; difficulty focusing or concentrating, 45.9%; frequently late to work or miss too much work, 13.5%; employers not sensitive to FMS impairments, 13.5%. Working respondents who were asked how they were able to work with FMS provided the following responses: not giving in to FMS, 64.1%; staying busy, 53.8%; keeping a positive attitude, 48.7%; exercise, 38.5%; eating well, 38.5%; getting enough sleep, 33.3%; pacing themselves or taking breaks, 30.8%; listening to their bodies, 30.8%; medications, 28.2%; taking one thing at a time, 28.2%; relaxing, 25.6%; trying alternative therapies, 25.6%; understanding FMS, 23.1%; and setting goals, 20.5%.

Conclusion: Pain, fatigue and cognitive dysfunction seriously limited the ability of fibromyalgia patients to work. Patients who were able to continue working utilized tactics including not giving up, staying busy, maintaining a positive attitude, exercise, eating well, getting enough sleep and other strategies. Those who are disabled generally felt they were incapable of successfully using those strategies.

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Fibromyalgia's Impact On Relationships. Robert S. Katz[1], Alexandra Small[2], Sharon M. Ferbert[3] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois Medical School, [3]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL

Background/Purpose: The Fibromyalgia Syndrome (FMS) can place a strain on patients' personal relationships. Having a close support network is helpful in coping with illnesses, but chronic pain, fatigue, and other invisible symptoms associated with FMS can damage connections with family, friends, and co-workers. In this study, we asked FMS patients about the nature of their ties to their families, friends, and co-workers.

Methods: As a part of an Internet survey administered by the volunteer community fibromyalgia organization, AFFTER (Advocates for Fibromyalgia Funding, Treatment, Education and Research), 763 female respondents with self-described FMS responded to questions on how FMS has affected their relationships with family, friends, and co-workers. Only women's

responses were analyzed to eliminate confounding by gender. The McNemar test was done to compare percentages, using a 0.05 significance level.

Results: The mean FMS respondent age was 50.2 ± 10.8 years. Only 12.5% of the FMS group reported that co-workers were supportive, and only 18.1% reported that in-laws were supportive. Support was better among other groups: spouses/significant others (59.1%), children (41.8%), close friends (44.8%), and parents (38.0%) ($p < 0.001$). Only 9.0% of FMS patients reported that co-workers understood their limitations, and just 12.6% of patients responded that their in-laws understood the limitations imposed by the illness, compared to higher percentages in spouses/significant others (52.0%), children (36.9%), and close friends (35.1%), Only 29.7% of parents ($p < 0.001$) had an understanding of the limitations imposed by fibromyalgia. FMS patients reported that they sometimes had seriously damaged relationships with spouses/significant others (14.6%) and close friends (11.6%).

Conclusion: Except for spousal understanding (59.1%), patients perceived that less than 50% of other groups were supportive. While some FMS patients viewed spouses/significant others and close friends as strong sources of support, others reported a significant strain on those relationships. Very frequently, FMS patients reported that co-workers, in-laws, and parents were not sympathetic or kind.

These results indicate that the perceived strain on relationships as a result of having FMS can be severe, especially among coworkers, in-laws, and parents of patients. The strain on relationships could partially be due to the fact that the symptoms of FMS are invisible and therefore are often underestimated among friends and relatives of FMS patients. Better education of the public about FMS and counseling for patients may help in repairing some of these broken relationships.

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Sleep Study with Armband Device in Fibromyalgia Patients: Fibromyalgia Patients Don't Rest Their Weary Muscles. Robert S. Katz[1], Alexandra Small[2], Ben J. Small[3] and Jessica L. Polyak[4]. [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois Medical School, [3]Rush University Medical School, Chicago, IL, [4]Rheumatology Associates, Chicago, IL

Background/Purpose: Patients with the fibromyalgia syndrome (FMS) have frequent awakenings and poor sleep efficiency. The purpose of this study is to evaluate sleep patterns in fibromyalgia patients using an armband monitoring device, so patients could monitor sleep at home.

Methods: 16 patients with fibromyalgia and 3 normal controls were given an armband sleep device manufactured by SenseWear. Patients wore the sleep monitor for at least 4 consecutive nights. We assessed duration of sleep, sleep efficiency, and the number of awakenings reported by the device and compared those with patient self-reported sleep patterns on a VAS scale of 1–10, with 10 being sleep problems that interfere completely with daily activities.

Results: Fibromyalgia patients consisted of 10 females and 6 males.

Table 1. Summary of the sleep study changes in the patients with fibromyalgia

Controls

# of hours lying down (mean)	# of hours sleeping (mean)	# of awakenings (mean)	Sleep Efficiency (mean)
6.24	5.35	4.67	86.30%

Fibromyalgia

# of hours lying down (mean)	# of hours sleeping (mean)	# of awakenings (mean)	Sleep Efficiency (mean)
7.68	5.73	11	75.70%

Conclusion: Fibromyalgia patients wearing a sleep monitor at home exhibit many awakenings and poor sleep efficiency compared with controls. Fibromyalgia patients moved around a lot at night, possibly preventing adequate rest of their painful muscles. Ambulatory sleep monitoring to evaluate sleep efficiency, including the number of awakenings and nocturnal movement, may be helpful in understanding the pathophysiology of the myalgias of FMS. Patients can easily monitor their number of awakenings and their sleep efficiency without spending an evening in a sleep lab, and sleep evaluations might help in assessing the effectiveness of therapies for fibromyalgia.

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A Survey Study of Methotrexate Use by Rheumatologists and Their Patients with Rheumatoid Arthritis. Peter Nash[1] and Dave Nicholls[2]. [1]University of Queensland, Brisbane, Australia, [2]Coast Joint Care, Maroochydore, Australia

Background/Purpose: Methotrexate (MTX) is the anchor medication for the management of rheumatoid arthritis (RA); however there is limited patient-focused data available on the use of MTX, which could be used to improve RA outcomes. The primary objective of this study, termed MATRIX (Mapping Australian Treatment Reality Involving MTX), was to assess the use and perceptions of MTX by patients with RA. Secondary objectives included the assessment of patient-reported adverse events, the use of alcohol, folic acid, and biologic agents, and the perceptions of rheumatologists. Here we highlight tolerability to MTX, the perceptions of rheumatologists, and the use of biologic agents.

Methods: Rheumatologists ($N = 46$ of 50 completed surveys) and their patients with RA ($N = 1,313$ of 1,500 completed surveys; consecutively sampled; mean age 58.5 years, 72% female) completed pre-tested, voluntary, anonymous, self-administered questionnaires about their experience with MTX.

Results: Generally, patients reported taking oral MTX regularly (78% currently taking MTX, 92% orally, 70% $\geq$ 10 mg/week) and followed prescription instructions (91% took folic acid; 46% abstained from alcohol). However, 17% of patients had discontinued from MTX (13% within 1 to 2 years), mostly because of adverse events (12%). For patients taking MTX, adverse events (including nausea, headache, mouth ulcers, light-headedness, and diarrhea) were noted by 60% of patients, but events were experienced regularly (92%) and some were continual (13%). Most patients (72%) reported never missing a dose of MTX, but 6% miss at least 1 dose every 2 months and 8% intentionally and regularly 'take a break' from MTX, despite regular attendance at the clinic. Although rheumatologists were aware of tolerability to MTX, they generally underestimated the positive attitude that patients had towards their MTX therapy; for example 35% of patients would prefer to discontinue MTX but rheumatologists estimated 47% of patients would prefer to discontinue MTX. Rheumatologists also underestimated the proportion of patients who reported taking biologic agent 'monotherapy' (ie, without MTX; $\leq$ 20%); 29% of patients were on biologic agents, and of these, 29% were taking biologic agent 'monotherapy' and 70% were taking biologic agents in combination with MTX. The most common biologic agents were adalimumab, etanercept, and tocilizumab; tocilizumab use was higher with biologic agent 'monotherapy'. Of note, compared with all patients a greater proportion of patients taking biologic agents would prefer to discontinue MTX (43%).

Conclusion: MTX was well-used and positively perceived by patients with RA. However, our study highlights the need for rheumatologists to monitor patient use of RA medication with the aim of ensuring patients continue with, and maximize, their use of MTX therapy, particularly in combination with biologic agents.

Disclosure: **P. Nash**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5; **D. Nicholls**, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 5.

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Optimizing Care for Patients with Rheumatoid Arthritis Newly Treated with Biologics by Evaluating Health Status with AIMS-2. Mie Fusama[1], Hideko Nakahara[2], Keisuke Kawamoto[2], Satoko Nozato[2], Midori Taguchi[2], Kohji Nishioka[2], Shinji Higa[2], Eiji Takeuchi[2], Kayoko Higashi[2], Masao Yukioka[3], Tsuyoshi Igarashi[2], Taro Kuritani[2], Keiji Maeda[2] and Yasushi Miura[1]. [1]Kobe University, Kobe, Japan, [2]NTT West Osaka Hospital, Osaka, Japan, [3]Yukioka Hospital, Osaka, Japan

Background/Purpose: Biologics significantly improve disease activity of rheumatoid arthritis (RA), however, patient global assessment (PGA) is not always improved in parallel with disease activity scores. Though the 2011 ACR/EULAR definitions of remission criteria for RA adopt Boolean-based definition, there are few reports analyzing health status and patient satisfaction in the view of PGA for patients with RA treated with biologics.

To assess the correlation between each component of health status including patient satisfaction and Boolean-based definition of PGA remission for RA, patients newly treated with biologics were investigated for 24 weeks.

Methods: Patients with RA treated with 8 mg/kg of tocilizumab (TCZ) every 4 weeks, 3mg/kg of infliximab (IFX) at 0, 2, 6 weeks and thereafter every 8 weeks, 25mg of etanercept (ETN) twice a week were participated in this study. Health status with Arthritis Impact Measurement Scale 2 (AIMS-2), disease activity scores (tender joint count (TJC), swollen joint count (SJC),

PGA and evaluator global assessment (EGA) on visual analogue scale (VAS), DAS28-CRP, SDAI, and CDAI) were assessed at week 0 and week 24. Comparison analysis of health status was performed between the patients who achieved the remission criteria of PGA (PGA=<1cm) and those who did not. The data analysis was performed utilizing Wilcoxon rank sum test.

Results: Sixty-six patients newly treated with biologics (TCZ: 39, IFX: 16, ETN: 11) were participated. Baseline characteristics were as follows: mean±SD of age (54.6±11.7 years), duration (6.7±7.2 years), SJC (10.9±7.5), TJC (10.8±6.1), PGA (5.4±2.4cm), EGA (5.5±2.1cm), CRP (2.4±2.6mg/dl), DAS28-CRP (5.3±1.3), SDAI (35.0±15.9), and CDAI (33.0±14.7), respectively. Twenty-seven of 66 patients (40.9%) achieved PGA remission. At baseline, there were no significant differences in age, duration, SJC, TJC, PGA, EGA, CRP, DAS28, SDAI, CDAI, or components of AIMS-2 between PGA remission and non-remission groups. At week 24, SJC, TJC, EGA, DAS28-CRP, SDAI, and CDAI were significantly lower in PGA remission group. At week 24, among health status, physical function, symptom, and role of AIMS-2 were significantly improved in PGA remission group compared with non-remission group. At week 24, patient satisfactory scores were significantly improved in PGA remission group except social interaction. Only the patient satisfactory scores for household and role (work) were significantly higher in PGA remission group compared with non-remission group at baseline.

Conclusion: For the patients with lower satisfactory scores in household and role (work) of health status at baseline, it is considered difficult to achieve PGA remission even when treated with biologics. Social interaction is not improved even when PGA remission is achieved. Therefore, nurses caring patients with RA are expected to assist patients to understand the importance of early treatment, support social activity, and set proper goal of treatment by evaluating health status.

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Discrepancies Between Disease Activity and Disease Burden. Margot J.M. Walter[1], Adriaan van 't Spijker[1], Annelieke Pasma[2], Johanna M.W. Hazes[3] and Jolanda J. Luime[1]. [1]Erasmus MC - University Medical Center, Rotterdam, Netherlands, [2]Erasmus MC University Medical Centre, Rotterdam, Netherlands, [3]Erasmus Medical Center, Rotterdam, Netherlands

Background/Purpose: In a longitudinal study aiming to use patient self-reported disease activity measured by three domains: functional ability (HAQ), disease activity (RADAI) and fatigue (VAS) to predict change in the subsequent physician assessed DAS28 we failed to demonstrate a sufficient association between both measures. This led to the question to why there is a difference between the self-reported measures and the DAS 28.

Objectives: The aim of this study was to explore the patient's perspective on the discrepancy between patient self-reported disease activity and physician assessed disease activity.

Methods: An exploratory qualitative methodology using focus groups was applied using a semi-structured interview scheme. Patients were recruited from the RAPPORT study (RA patients from one outpatient clinic in Rotterdam). Four focus groups were convened with 29 participants.

Results: Five themes were identified: balance, mental stress, medication use, feeling of being misunderstood and lack of physical fitness. Balance (1) between activity and rest was reported to easily affect the observed discrepancy. To manage activities patients used planning, adapting, avoiding, but also ignoring of symptoms. Ignoring could results in "off days", and a number of patients accepted high levels of self-reported disease activity as they did not wish to reduce their level of activities. Mental stress (2) was regarded especially affecting levels of fatigue. Medication intake (3) was felt to have a negative influence on the self-reported measures that was not picked up by the physician measure of disease activity, although some patients mentioned that the relationship between disease and use of medication was difficult to disentangle. Feeling misunderstood (4) by others impacted on well being, maybe not directly affecting levels of self-reported disease activity, but via emotional and cognitive appreciation of the already existing symptoms. Chronicity of the disease (e.g. remarks by family and friends such as "are you still suffering from RA?"), appearing not being ill and pain and fatigue ignored by doctors were discussed. Lack of physical fitness (5) was perceived as having a negative impact on pain and fatigue both in mental and a physical way. Although patients were well aware of the potential positive impact of physical exercise, stress reducing techniques and finding the right balance in activities and rest, for many it was also hard to implement these strategies effectively into daily life.

Conclusion: Discrepancies between self-reported disease activity and physician reported disease activity in patients with low levels of DAS28 could be themed in mental stress, lack of physical fitness, difficulty in finding balance between rest and activity, feeling misunderstood by others and medication use. Patients highlighted that the reasons of the high disease burden are difficult to explain, and different combination of factors affecting self-reported disease activity hold for individual patients.

Stress management, finding the right balance and tailored physical exercise may help to improve general well being in these patients enabling them to cope better with their rheumatoid arthritis.

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"Pain and Fatigue in Adult Patients with Rheumatoid Arthritis - Associations with Demographic Factors, Disease Related Factors, Body Awareness, Emotional and Psychosocial Factors". Helena Lööf[1], Fredrik Saboonchi[2], Elisabet Welin Henriksson[3], Staffan Lindblad[4] and Unn-Britt Johansson[1]. [1]Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Stockholm, Sweden, [2]Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Medicine, Stockholm, Sweden, [3]Karolinska Institutet, Department of Neurobiology, Care Sciences and Society., Stockholm, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden

Background/Purpose: Patient's with Rheumatoid arthritis highlight fatigue as a major concern, as well as pain as a priority for improvement. Previous study has found that significant fatigue occurs in up to 70 percent of patients with Rheumatoid arthritis, and 82 percent of Rheumatoid arthritis patients (who consider their disease to be "somewhat to completely controlled") continue to report moderate to severe pain. Variables that are found to be related to fatigue are illness-related aspects, physical functioning, cognitive/emotional functioning and social environmental aspects. Pain affects quality of life, and the psychological well-being of the individual living with Rheumatoid arthritis is significantly affected by the fundamental life changes and the complexity of the disease process. Emotions have been pointed out as having a key role in the adjustment among people with Rheumatoid arthritis, and in the context of chronic pain in general. Furthermore, the tendency to focus attention on bodily sensations and internal stimuli, i.e. body awareness, has been associated with amplification of both somatic and emotional distress. Negatively toned self-focused bodily attention has been linked to less effective decision making strategies and worse adherence. The purpose of this study was to examine perceptions of fatigue and pain in adult patients with Rheumatoid arthritis and to investigate association with demographic factors, disease related factors, body awareness, emotional and psychosocial factors.

Methods: Data were collected from a convenience sample of patients with Rheumatoid arthritis recruited from a Rheumatology clinic. Eligible for inclusion were patients between 20–80 years diagnosed with Rheumatoid arthritis for at least a period of six months, according to American College of Rheumatology criteria for Rheumatoid arthritis. The patients filled out questionnaires, fatigue was measured by using the Multidimensional Assessment of Fatigue (MAF) scale, and the Visual Analogue Scale (VAS) was used to assess components of pain. To evaluate factors related to fatigue and pain, multiple stepwise linear regression analysis were performed. In the first step a univariate ANOVA was performed for all relevant independent factors. In the next step a backwards stepwise regression was performed. When the final model was found, the model assumptions was evaluated based on the residual diagnosis.

Results: 120 patients with Rheumatoid arthritis participated in the study (female 86%, $<$ 45 years 22.5%, 46–65 years 42.5%, $>$ 65 years 35 %). Fatigue in Rheumatoid arthritis associate significant with no smoking, (p=0.021), disease activity, DAS 28 (p=0.049), body awareness, BAQ (p=0.006) and PANAS, positive affect (p=0.008). The pain in Rheumatoid arthritis was significantly associated with health related quality of life, EQ-5D (p=0.008) and disease activity, DAS 28 (p=0.001). The final models for fatigue and pain were considered acceptable. Adjusted R-square were 28.6 % for fatigue and 50.0 % for pain.

Conclusion: This study identifies that in patients with Rheumatoid arthritis fatigue and pain appears to be associated with disease related factors. Furthermore, fatigue was related to body awareness and emotional factors.

Disclosure: **H. Lööf**, None; **F. Saboonchi**, None; **E. Welin Henriksson**, None; **S. Lindblad**, None; **U. B. Johansson**, None.

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Developing a Health Literacy Universal Precautions Toolkit for Rheumatology. Leigh F. Callahan[1], Victoria Hawk[2], Kimberly A. Broucksou[2], Betsy Hackney[2], Deb MacDonald[3], Lindsay Penny Prizer[1], Beth L. Jonas[2], Thomas K. Bauer[4], Rima E. Rudd[5], Cindy Brach[6] and Darren Dewalt[2]. [1]University of North Carolina, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, [4]Winston Salem, NC, [5]Harvard School of Public Health, Boston, MA, [6]Agency for Health Care Research and Quality, Rockville, MD

Background/Purpose: Research supports that health disparities exist between those with limited versus adequate literacy skills. Limited health literacy is associated with medication errors, increased healthcare costs, and inadequate care for chronic health conditions. In 2010, our team developed and tested a Health Literacy Universal Precautions Toolkit (HLUPTK) for use in primary care practices. Studies in rheumatology have demonstrated a significant number of patients have low literacy. The purpose of this project was to adapt the HLUPTK for use in rheumatology practices (HLUPTK-R).

Methods: We reviewed the HLUPTK and its 20 tools to determine areas for adaptation, expansion and discipline specific customization. An environmental scan was conducted to identify and assess existing health literacy tools, resources and well-designed education materials for use in the rheumatology setting. Gaps in rheumatology specific materials were also identified. A discipline specific toolkit was developed and tested in 4 rheumatology practices of various size and locations (urban vs. rural). A study team member visited all practices prior to testing. Over the 2-month testing period, practice staff reviewed the toolkit, conducted a health literacy assessment, and selected and tested a small-scale implementation of 2 or more tools. Practices completed questionnaires and participated in conference calls with the study team pre- and post- testing. They also completed Plan-Do-Study-Act (PDSA) worksheets for tested tools. Based on practice feedback and the testing results, the toolkit was revised.

Results: A new toolkit, HLUPTK-R, has been developed. Rheumatology specific resources have been added including a teachback video focusing on a patient with rheumatoid arthritis, a rheumatology-specific plain language guide, medication aides and education materials designed for rheumatic diseases. Based on feedback from the practices, the tools were shortened and reformatted. In addition, 2 new tools were developed and included: one for communicating care to other physicians and another for planning small changes in the practice setting. Furthermore based on key changes adopted by our practices, two new Quick Start guides were developed – one focused on patient encounters and the other on the practice setting. The Quick Start guides are designed to introduce the practice to the concepts of health literacy and making small changes without the need for coaching that the more comprehensive HLUPTK-R appears to require.

Conclusion: This new toolkit offers clinicians and staff in rheumatology practices a step-by-step approach to improving healthcare for patients of all literacy levels using discipline specific examples and tools. HLUPTK-R and quick start guides are now available for broader use and testing.

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Baseline Screening Recommendations for Rheumatoid Arthritis Patients Treated with Disease Modifying Anti-Rheumatic Drugs: Does an Educational Intervention Change Practice in an Outpatient Clinic? Debra C. Lloyd[1], John N. Mecchella[2] and Daniel Albert[3]. [1]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [2]Dartmouth Hitchcock Medical Center, Lebanon, NH, [3]Dartmouth-Hitchcock Medical Center, Geisel School of Medicine, Lebanon, NH

Background/Purpose: In 2008, the American College of Rheumatology (ACR) developed recommendations for use of non-biologic and biologic DMARDs in the treatment of rheumatoid arthritis (RA). The purpose of this study was to assess change in baseline screening practices following completion of an educational intervention reflecting the ACR recommendations.

Methods: An educational intervention designed to update providers in and new recommendations from the ACR was completed in an outpatient rheumatology clinic in September 2009.

Staff education activities included: 1) individual review of the ACR 2008 Recommendations for the Use of Non-biologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis (DMARD); 2) development and review of "DMARD reference" sheets; 3) formal presentation of key points from the journal article to clinic staff.

Retrospective chart reviews were completed on new RA patients seen in a hospital-based outpatient clinic for a six month period immediately before and after review of the guidelines. Documentation of recommended baseline screening test results (laboratory studies, imaging and tuberculosis testing) for DMARD was assessed.

Inclusion criteria: 1) New patient to rheumatology between 04/01/2009 and 03/31/2012 (NPW); 2), rheumatoid arthritis, inflammatory arthritis (ICD 9 codes 714.0 and 714.9); 3) DMARD (methotrexate or leflunomide) therapy planned.

Exclusion criteria: 1) Alternate diagnosis after initial or subsequent evaluation; 2) no DMARD (methotrexate or leflunomide) treatment; 3) follow up appointment(s) cancelled or not attended; 4) not a new patient to rheumatology clinic; 5) current therapy with DMARD (prescribed at alternate site).

Baseline screening data for DMARDs and biologic agents was consistently identifiable in the patient record.

A file for all patients with diagnosis code of 714.0 and 714.9, seen anywhere in the hospital/clinic system between 10/2007 and 12/2010, arriving as an NPW in rheumatology was reviewed. There were 256 patients seen between 04/01/2009 and 03/31/2010. 184 records were reviewed. Data for 144 records were excluded and data from 40 records (n= 20 pre-intervention; n= 20 post-intervention) were included.

Results: Comparison of the results (CBC, LFTS, CREA, ALB, HEP B, HEP C, and CXR) for the two groups was completed using a χ^2 analysis and Fisher's exact test and there was no significant difference between pre and post scores.

Baseline screening for DMARD therapy was completed in $\geq$ 90% of the baseline for CBC, LFTs, CREA and ALB in both the pre and post intervention periods. Hepatitis B and C screening was completed in $\leq$ 25% of the pre and post intervention screenings. CXR was completed in 20% of the pre-intervention baseline screenings and 50% of the post-intervention screenings but this difference did not achieve statistical significance.

Conclusion: Completion of recommended baseline screening testing for patients receiving DMARD treatment did not increase after the educational intervention. This is constant with other failed attempts to change clinician behavior through short term educational interventions. This suggests that incorporating work flow redesign into the electronic medical record is likely to be more effective.

Disclosure: **D. C. Lloyd**, None; **J. N. Mecchella**, None; **D. Albert**, None.

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The Correlation of Disease Activity, Functional Status and Quality of Life with Sleep Disturbance and Balance Status in Ankylosing Spondylitis (AS). Mehmet Tuncay Duruoz, Zuhre Sari Surmeli and Esra Topcu. Celal Bayar University Medical School, Manisa, Turkey

Background/Purpose: To assess the correlation of disease activity, functional and metrological status and quality of life with sleep quality and balance status in AS.

Methods: Subjects with Ankylosing Spondylitis (AS) according to Modified New York criteria were recruited into the study. Disease activity was assessed with BASDAI. Functional status (BASFI), quality of life (ASQoL) and metrological score (BASMI) were assessed. Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), Leeds Assessment Scale of Handicap (Leeds Scale) were managed. Berg Balance Scale, Tinetti Balance Assessment Tool and VAS-fear of falling were used to asses patients' balance.

Results: Forty two AS patients (36 male) with mean age 38,38 (SD=11,28) years were recruited. The disease duration was 139,06 (SD=100,37) months. There were significant correlations between BASDAI and Beck Depression Inventory (p=0,01), Pittsburgh Sleep Quality Index (p=0,01). BASDAI scores were not correlated with Tinetti Balance Assessment Tool (p=0,107), VAS-Fear of Falling (p=0,111), Leeds Scale (p=0,072) and Berg Balance Scale (p=0,164). BASFI had significant correlations with Beck Depression Inventory (p=0,01), Pittsburg Sleep Quality Index (p<0,001), Tinetti Balance Assessment Tool

(p=0,028), Leeds Scale (p<0,001) and Berg Balance Scale (p=0,001). BASMI had significant correlation with Beck Depression Inventory (p=0,007), VAS-fear of falling (p=0,011), Leeds Scale (p=0,005) and Berg Balance Scale (p<0,001). BASMI was not correlated with Pittsburg Sleep Quality Index (p= 0,124) and Tinetti Balance Assessment Tool (p=0,342). ASQoL had significant correlation with Beck Depression Inventory (p<0,001), Pittsburgh Sleep Quality Index (p= 0,005), Tinetti Balance Assessment Tool (p= 0,042), Leeds Scale (p=0,001) and Berg Balance Scale (p=0,023).

Conclusion: Although disease activity had good correlation with depression and sleep disturbances it had not significant correlation with patients' balance status. The functional level which shows disease severity had significant correlation with sleep disturbances and balance status in AS. Quality of life was worse in patients with sleep disturbance and low balance status.

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The Impact of Targeted Exercise Intervention On Health Outcomes in Rheumatoid Arthritis. Laura J. Durcan[1], Fiona Wilson[2], Finbar (Barry) D. O'Shea[1] and Gaye Cunnane[1]. [1]St James's Hospital, Dublin, Ireland, [2]Trinity College, Dublin, Ireland

Background/Purpose: Increased morbidity and mortality are recognized consequences of rheumatoid arthritis (RA). In addition to chronic inflammation, reduced physical activity may contribute to adverse outcomes in these patients. This study was undertaken to assess the impact of a targeted, exercise intervention on health outcomes in RA.

Methods: Patients with established, well-controlled RA were recruited. Baseline assessments relating to cardiovascular risk factors, body composition, disability, sleep quality and physical activity were ascertained using standardized measures. Exercise was then prescribed in order to a) target individual functional limitations as identified by the Health Assessment Questionnaire (HAQ) and b) increase each patients' physical activity according to the American College of Sports Medicine recommendations.

Patients were assessed every 3 weeks for 12 weeks by a rheumatologist and physical therapist. Compliance was aided by the provision of an exercise diary and a pedometer. All parameters were re-measured at the completion of the 12 week program. Ethical approval was obtained from the St James's Hospital Ethics Committee. Statistical analysis was undertaken using SPSS 18.

Results: Forty patients with RA (mean age 46 years) (SD8.0) and mean disease duration of 15.6 years (SD 10.9) were included. Thirty (75%) were seropositive and 38 (95%) had evidence of erosive disease. All fulfilled the ACR diagnostic criteria for RA. Twenty nine (72.5%) were current/ex-smokers. All (100%) were taking disease-modifying treatment; 10 (25%) were on biologic agents. Mean body mass index was 27.1 (SD 5.2). At baseline, only 2 (5%) were involved in any form of exercise.

	Pre-intervention	Post intervention	Significance
HAQ	0.81 (SD 0.38)	0.53 (SD 0.54)	0.000
Grip (lbs pressure) (R)	28.87 (SD 18.29)	33.87 (SD 18.19)	0.000
Grip (lbs pressure) (L)	25.15 (SD 15.83)	28.23 (SD 19.54)	0.000
Pain (VAS)	28.66 (SD 21.79)	20.83 (SD18.03)	0.000
Stiffness (VAS)	31.71 (SD 22.77)	23.83 (SD 23.82)	0.000
EBBS (range 43–172)	125.9 (SD 5.5)	131.5 (SD 9.4)	0.000
PSQI (range 0–21)	7.21 (SD 4.45)	6.22 (SD 3.58)	0.000
FSS (range 1–81)	37.89 (SD 25.58)	26.64 (SD 21.88)	0.000
FFM (kg)	44.76 (SD 9.38)	45.40 (SD 9.22)	0.005
BMI (kg/m^2)	27.15 (SD 5.23)	26.97 (SD 4.93)	0.316
Total cholesterol(mmol/L)	4.86(SD 0.83)	4.72 (SD 0.68)	0.018
LDL- cholesterol (mmol/L)	2.78 (SD 0.72)	2.65 (SD 0.59)	0.018
HDL- cholesterol (mmol/L)	1.44 (SD 0.33)	1.42 (SD 0.34)	0.571

EBBS: Exercise barriers and benefits scale, PSQI: Pittsburgh Sleep Quality Index, FFS: Fatigue Severity Scale, FFM: Fat Free Mass

Conclusion: A 12 week targeted exercise program yielded significant improvements in strength, pain, joint stiffness, sleep, fatigue and lipid profile, impacting on both health and quality of life in patients with RA. Although fat free mass measurements improved significantly, there was no major change in BMI suggesting that dietary adjustments may be a necessary accompaniment to a sustained exercise program in order to effect weight loss in overweight patients with RA.

Disclosure: **L. J. Durcan**, None; **F. Wilson**, None; **F. D. O'Shea**, None; **G. Cunnane**, None.

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Identifying Subgroups of Rheumatoid Arthritis Patients Based On Levels of Pain, Disability, and Depression. Taylor Draper[1], Sarah R. Ormseth[1], M. Custodio[2], M.H. Weisman[3], M.R. Irwin[2] and Perry M. Nicassio[2]. [1]Loma Linda University, Loma Linda, CA, [2]UCLA, Los Angeles, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA

Background/Purpose: Pain, disability, and depression are present in various degrees in patients with Rheumatoid Arthritis (RA). In spite of meeting the same diagnostic criteria, some patients with RA report much less pain, disability, and little or no psychological distress than others. The current study seeks to ascertain potential subgroups of patients in a RA sample based on levels of pain, disability, and depression and to identify factors associated with patient clustering.

Methods: The sample included 100 patients with confirmed RA participated in an assessment of their disease activity, pain, depression during an evaluation prior to participating in a randomized controlled trial. Self-report measures included the Rapid Assessment of Disease Activity in Rheumatology (RADAR), the SF-36 social functioning Scale, the Helplessness and Internality Subscales of the Arthritis Helplessness Index (AHI), the Active and Passive Pain Coping Scales of the Pain Management Inventory (PMI), the Center for Epidemiological Studies Depression Scale (CES-D), the Pittsburgh Sleep Quality Index (PSQI), Perceived Stress Scale (PSS), and the Health Assessment Questionnaire (HAQ). Cluster analysis was used in this research to ascertain the existence of subgroups of patients in a Rheumatoid Arthritis sample based on these variables.

Results: Two clusters were defined: a low-functioning group characterized by high levels of pain, disability, and depression (n = 73) and a high-functioning group characterized by low levels of pain, disability, and depression (n = 27). Analysis of Variance (ANOVA) confirmed differences between clusters on these health status factors, except disability. A second series of ANOVAs revealed that the high-functioning subgroup had greater social functioning, better sleep quality, and less passive coping and perceived stress than the low-functioning group. Hierarchical multiple regressions indicated that the best discriminators of subgroup membership were sleep quality and perceived stress.

Conclusion: These results indicate significant heterogeneity in RA patients. The data also suggest that different approaches to patient management, particularly intervention strategies aimed at reducing perceived stress and improving sleep quality, may be beneficial for patients who are functioning poorly in the face of this condition.

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Barriers to Recruit Unaffected Family Members of Patients with Rheumatoid Arthritis. Axel Finckh[1], A. Debost-Legrand[2], Martin Soubrier[3], I. von Muehlenen[4], I. Creveaux[2], JJ Dubost[3], MH Papon[2], H. Ayadi[5], P. Migliorini[6], E. Petit-Teixeira[7], F. Cornélis[2] and Eprac[8]. [1]Geneva University Hospitals, Geneva 14, Switzerland, [2]GenHotel-Auvergne, Clermon-Ferrand, France, [3]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [4]Universitäts-Poliklinik, Felix-Platter Spital, Basel, Switzerland, [5]Sfax university, Sfax, Tunisia, [6]Pisa university hospital, Pisa, Italy, [7]GenHotel-Evry-EA3886, Evry, France, [8]Clermont-Ferrand, France

Background/Purpose: Prospective studies are needed to answer key questions on rheumatoid arthritis (RA) screening in at risk populations: (1) How accurately does risk factor assessment identify persons who will later develop RA? (2) Does screening and subsequent early treatment improve long-term outcomes in RA? Such studies could focus on first degree relatives of RA patients (FDR-RA), as they have up to a 10 fold increase of RA incidence compared to the general population. The number of potential FDR per RA patient has been measured to be 6.9 per RA patient (J Rheumatol 2008;35:790–6).

The aim of this report is to describe the barriers encountered recruiting healthy FDRs-RA, without clinical evidence of synovitis at inclusion, in a prospective cohort study of individuals at increased risk of developing RA.

Methods: The initial recruitment strategy for this prospective cohort of individuals at increased risk of developing RA relied on the diseased relatives with RA. Patients with RA were informed of the possibility of a free screening test of RA susceptibility for their unaffected family members. We report the rate of FDR-RA enrollment into the study resulting from direct promotional efforts targeted to RA patients.

All participants are assessed for the absence of active synovitis (physical exam and/or questionnaire), for risk factors for RA and for biomarkers of RA susceptibility at inclusion. Participants are followed prospectively until they develop (or not) RA. In case of new symptoms suggesting incident synovitis, clinical assessment is performed by a Rheumatologist.

Results: In 2010–11, the new screening study was advertised massively amongst RA patients in Switzerland and France per mail, patient conferences, health fares and articles in patient journals. The 6000 RA patients in the Swiss cohort of RA patients and 5300 RA patients of the French patient association (AFP) were directly incited to invite their FDR to participate in this screening study. After ~2 years of various promotional efforts to RA patients, we counted that less than 30 FDRs-RA enrolled via their diseased parent. Based on discussion with participants and RA patients, we hypothesize that RA patients are unwilling to promote strongly a screening study to their FDRs, which underscores the hereditary risk associated with this diagnosis and may arise to feelings of guilt related to the possibility of transmitting RA.

To date, a total of 977 RA-FDRs have been included: 560 in Switzerland and 317 in France, mainly through direct advertisement to unaffected FDRs in pharmacies. At inclusion, mean age is 45 years (SD 15), 74% are female and 95% are Caucasian. On average, these individuals have 1.2 direct relatives with RA.

Conclusion: We have observed an unexpected low inclusion rate of FDRs in response to promotional efforts targeted towards the diseased relative with RA. Informal investigation strongly suggests that the main explanation is the lack of transmission of information from the RA patients to their unaffected FDR, which appears to be linked to a feeling of guilt in relation with a hereditary disease. More investigation is needed on the transmission of information within RA affected families in order to enhance future preventive strategies.

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How Disease Activity Trajectories Affect the Willingness to Change Treatment. Paul Falzer[1] and Liana Fraenkel[2]. [1]VA Connecticut Healthcare System, New Haven, CT, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT

Background/Purpose: Disease activity (DA) can change markedly over a short period, for a variety of reasons. The changes influence clinical practice and affect the willingness of patients to change their current treatment (WCT). However, impact cannot be examined in a cross-sectional study and is difficult to explore when DA is measured at only two points. This study measured DA at multiple points, distinguished observation-level DA from its patient-level trajectory, and examined the influence of both on WCT.

Methods: RA patients who were taking at least one DMARD and currently experiencing at least moderate pain were recruited from community-based rheumatology practices. They participated in four interviews over a six month period. DA was measured at each interview, using the Rapid-4. Scores were rounded up to single points. Patient-level trajectories were created, consistent with the rules described in Table 1, and each trajectory was coded as a nominal category. WCT was measured at each interview on a 10-point scale. Patient-level trajectory and observation-level Rapid-4 were examined by linear mixed models and were compared using AIC, a lower-is-better goodness of fit test.

Trajectory	Rule	N	Percent
Stable	All scores are within 1 full point on the Rapid-4	65	46
Better	>1 point difference between highest and lowest score; low score occurs later	28	20
Worse	>1 point difference between highest and lowest score; high score occurs later	24	17
Fluctuating	First and last scores are within 1 point; interim scores are >1 higher or lower	25	18

Results: N=142 patients participated. Their mean age was 59, mean duration of RA was 12.8 years; 86% were female and were 81% were Caucasian. As the table indicates, 46% of patients were stable, 20% were getting better, 17% were getting worse, and 18% were fluctuating. Observation-level Rapid-4 was significantly associated with WCT (F=5.42, df= 3/433, p=.001). Its interaction with the patient-level trajectory was also significant (F=2.55, df=15/354, p=.001) and offered the best fit (AIC is about 2% lower). Trajectory alone was non-significant and provided the worst fit of the 3 models. The figure shows estimated WCT at each Rapid-4 category for the stable and fluctuating trajectories. One exhibits a small

variation from mild to moderate; the other increases markedly at mild, then levels out.
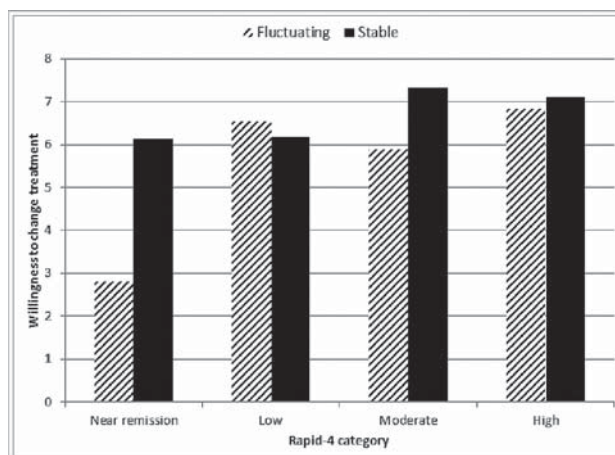
Conclusion: Patient- and observation-level DA have a combined influence on WCT. Despite marked differences, stable and fluctuating trajectories would not be distinguished if DA were assessed at only two points.

Disclosure: P. Falzer, None; **L. Fraenkel**, None.

ACR/ARHP Poster Session B
Rehabilitation Sciences
Monday, November 12, 2012, 9:00 AM–6:00 PM

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Why Do We Need to Pilot Interventions? Essential Refinements Identified During Pilots of a Fatigue Intervention. Emma Dures[1], Nicholas Ambler[2], Debbie Fletcher[3], Denise Pope[3], Frances Robinson[4], Royston Rooke[4] and Sarah Hewlett[1]. [1]University of the West of England, Bristol, United Kingdom, [2]Frenchay Hospital, Bristol, United Kingdom, [3]University Hospitals Bristol, United Kingdom, [4]University of Bristol, Bristol, United Kingdom

Background/Purpose: An RCT showed a 6 week group cognitive-behavioural (CB) intervention for RA fatigue self-management was effective, when delivered by a clinical psychologist.[1] Few rheumatology teams have clinical psychologists; therefore the intervention was re-formatted for delivery by the rheumatology team, in preparation for a multi-centre RCT. We piloted the feasibility of the materials, training, and support for clinicians, plus the acceptability of the intervention for patients.

Methods: The clinical psychologist from the original intervention worked with researchers, patient partners and clinicians to re-format a clinician-led version. A clinician's programme manual was developed with timetables, session aims, example scripts and patient handouts. A 2-day training for the rheumatology nurse and occupational therapist was developed, focusing on CB approaches (eg Socratic questioning, goal setting), managing groups, and using the session tools (eg activity diaries). They then co-delivered the intervention to 2 patient cohorts, first supervised by the clinical psychologist, then independently with supervised debriefing. On-going refinements were made, based on a cycle of feedback, review and de-briefing during all stages of the piloting.

Results: Materials for non-CB specialists: Some material has been re-written to be more suitable for non-CB specialists to deliver (eg 'sabotage' re-written as 'self-defeating behaviours'); links between sessions, explaining how they build on each other and relate to CB theory, have been made more explicit.

Training: Clinicians expressed anxiety about using new CB skills, and the need to respond rapidly to differences in session discussions that inevitably occur between different patient groups. Thus training will be increased to 4 days, with more focus on CB theory (eg formulating helpful questions) and more practice delivering sessions (eg explaining metaphors).

Support: An increased emphasis on the use of supervised debrief/reflection emerged; thus a guide to debriefing has been added to the manual, and extra time allocated. Proposed clinical supervision/quality control has

been increased by adding supervision of any sessions that clinicians find challenging in their second pilot.

Acceptability: Feedback from the 10 patients was positive. Mean scores on rating scales (0–10, higher scores representing greater acceptability) were: satisfaction 8.8, encouragement from clinicians 9.0, sessions well-run 9.0, helpfulness of handouts 8.4, and recommendation of the intervention to other patients 8.8.

Conclusion: Piloting interventions prior to RCT is recommended but there is little evidence about how it influences development. Iterative feedback during piloting led to essential refinements, particularly in training and support, when re-formatting the CBT intervention for delivery by non-CB specialists. It is now ready for formal testing in an RCT.

[1]Hewlett et al, Ann Rheum Dis 2011;70:1060–7.

1580

The Relationship Between Perceived Cognitive Dysfunction and Objective Neuropsychological Performance in Persons with Rheumatoid Arthritis. So Young Shin, Patricia P. Katz and Laura J. Julian. University of California San Francisco, San Francisco, CA

Background/Purpose: There is an increased appreciation of the burden of cognitive impairment in persons with rheumatoid arthritis (RA). Research shows a gap between perceived cognitive dysfunction and objective neuropsychological performance in persons with chronic diseases. This study explored this relationship in persons with RA.

Methods: Individuals from a longitudinal cohort study of RA participated in a study visit that included physical, psychosocial, and biological metrics. Subjective cognitive dysfunction was assessed using the Perceived Deficits Questionnaire (PDQ; range 0–20, higher score=greater impairment). Objective cognitive impairment was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices. On each test, subjects were classified as 'impaired' if they performed 1 SD below age-based population norms. A total cognitive impairment score (range 0–16) was calculated by summing the transformed scores (higher score=worst impairment). Multiple regression analyses controlling for gender, race, marital status, income, education, disease duration, disease severity, depression, and fatigue were conducted to identify the relationship between objective and subjective cognitive measures.

Results: 120 subjects with mean ($\pm SD$) age of 58.5 (± 11.0) years were included. Sixty four percent were female, 82% were white, and 7% met criteria for major depressive disorder. Mean educational level was 15.3 (± 2.2) years and disease duration was 19.9 (± 11.1) years. Mean total cognitive impairment score was 2.5 (± 2.2, range 0–10). The proportion of persons classified as cognitively impaired on each test ranged from 8% (semantic fluency test) to 28% (design fluency test). Mean PDQ score was 5.8 (± 3.8, range 0–16). In the multivariate analysis, there was no significant relationship between PDQ score and total cognitive impairment score. However, depression and fatigue ($\beta=0.31$, $p<0.001$; $\beta=0.32$, $p=0.001$) were significantly associated with the PDQ score.

Conclusion: There was no significant relationship between perceived cognitive dysfunction and objective neuropsychological performance in this cohort. Depression and fatigue were significantly associated with perceived cognitive dysfunction. Findings emphasize the gap between subjective and objective measures of cognitive impairment and the importance of considering psychological factors in the context of cognitive complaints in clinical settings.

1581

The Association Between Symptoms, Pain Coping Strategies, and Physical Activity Among People with Symptomatic Knee and Hip Osteoarthritis. Susan L. Murphy[1], Anna Kratz[1], David A. Williams[2] and Michael E. Geisser[1]. [1]University of Michigan, Ann Arbor, MI, [2]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: Effective use of coping strategies by people with chronic pain conditions is associated with better functioning and adjustment to chronic disease. Although the effects of coping on pain have been well studied, less is known about how specific coping strategies relate to actual physical activity patterns in daily life. The purpose of this study was to evaluate the effects of different coping strategies on symptoms and physical activity patterns in a sample of adults with knee and hip osteoarthritis (N = 44).

Methods: Physical activity was assessed by wrist-worn accelerometry; coping strategy use was assessed by the Chronic Pain Coping Inventory. We hypothesized that the use of coping strategies that reflect approach behaviors (e.g., Task Persistence), would be associated with higher average levels of physical activity, whereas avoidance coping behaviors (e.g., Resting, Asking for Assistance, Guarding) and Pacing would be associated with lower average levels of physical activity. We also evaluated whether coping strategies moderated the association between momentary symptoms (pain and fatigue) and activity. We hypothesized that higher levels of approach coping would be associated with a *weaker* association between symptoms and activity compared to lower levels of this type of coping. Multilevel modeling was used to analyze the momentary association between coping and physical activity.

Results: We found that higher body mass index, fatigue, and the use of Guarding were significantly related to lower activity levels, whereas Asking for Assistance was significantly related to higher activity levels. Only Resting moderated the association between pain and activity. Guarding, Resting, Task Persistence, and Pacing moderated the association between fatigue and activity.

Conclusion: This study provides an initial understanding of how people with osteoarthritis cope with symptoms as they engage in daily life activities using ecological momentary assessment and objective physical activity measurement.

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Long Term Costs and Cost-Effectiveness of an Integrated Rehabilitation Programme for Chronic Knee Pain. Mike Hurley[1] and Dr Nicola E. Walsh[2]. [1]St George's University of London, London, United Kingdom, [2]University of the West of England Bristol, Bristol, United Kingdom

Background/Purpose: Management of chronic knee pain incurs enormous direct and indirect healthcare costs. Enabling Self-management and Coping with Arthritic knee Pain through Exercise (ESCAPE-knee pain) is an integrated rehabilitation programme that, in the short term at least, is more clinically and cost-effectiveness than usual primary care. Unfortunately, the long term costs and cost-effectiveness of the programme is unknown and need to be evaluated. We continued to follow ESCAPE-knee pain participants for 2½ years after completing the programme, to establish the long term knee pain-related costs and cost-effectiveness of the programme.

Methods: 418 participants were randomised to remain on usual primary care or receive the ESCAPE-knee pain programme (individually or groups of 8 participants). Physical function (using WOMAC function sub-score) and knee pain-related health and personal costs (using Client Services Resources Inventory) were assessed at regular time points for 2½ years after completing the programme.

Missing data were imputed using multiple imputation. Mean differences in total cost (95% confidence interval) were obtained from non-parametric bootstrapped linear regression (1000 replications). Costs were estimated from a health and social care perspective in 2003/2004 prices. Costs were discounted at 3.5%.

Cost-effectiveness acceptability curves (CEAC) estimated the probability ESCAPE-knee pain had of greater net monetary benefit compared with usual care, over a range of monetary values a healthcare provider might be prepared to pay for a sustained, clinically meaningful, improvement in function (defined as ≥15% increase from baseline WOMAC-function score) after 2½ years.

Results: 250 participants (60%) were followed-up for 2½ years. Participating on ESCAPE-knee pain cost £224/person (£184-£262). Compared to those who remained on usual care, 2½ years after completing the ESCAPE-knee pain programme a significantly higher proportion (+14%) of participants maintained clinically meaningful improvement in function, and lower health and social care costs. CEAC showed there was a high probability (80–100%) ESCAPE-knee pain was more cost-effective than usual care in producing sustained clinically meaningful improvement in function.

Conclusion: ESCAPE-knee pain is a low-cost intervention with sustained clinical and economic benefits compared to than usual primary care. These conclusions need to be considered given the trial's high attrition rate and low power. Attrition rates are always high in trials with long term follow-up, and economic outcomes are rarely, if ever, used to power studies. Moreover, given

that large-scale, long-term trials are very expensive and complex, few similar studies will be performed and will suffer similar limitations. These results, therefore, are a good estimation of long term clinical and economic outcomes, and contribute to the pool of data from other trials of this chronic condition.

Disclosure: M. Hurley, None; D. N. E. Walsh, None.

1583

Therapist and Patient Perspectives On Exercise Adherence: Are We On the Same Page? Jill R. Blitz[1], Talitha Cox[2] and Amber Richards[3]. [1]Children's Hospital Los Angeles, Los Angeles, CA, [2]Children's Hospital of Los Angeles, Los Angeles, CA, [3]Children's Hospital, Los Angeles California, Los Angeles, CA

Background/Purpose: Exercise is essential to the health and function of children with chronic diseases. Patient adherence to home exercise programs has long been an obstacle for physical and occupational therapists.

Objectives: 1.To compare the perceptions of patient adherence to home exercise programs between therapists and patients. 2. To compare differences between the perceptions of rheumatology patients and patients with other diagnoses. 3. To gain a better understanding of the barriers to exercise and tools used to overcome these barriers in a pediatric physical and occupational therapy setting.

Methods: A survey was administered to physical and occupational therapists who work at a pediatric tertiary care facility. A similar survey was given to outpatients receiving physical and/or occupational therapy at the same facility, and patients seen in the Rheumatology clinic. The surveys included demographic information, frequency of exercise and a list of barriers and facilitators to choose from. Fisher's exact statistical analysis was used to compare responses of rheumatology patients versus non-rheumatology patients.

Results: 70 patients were surveyed; 36 from the outpatient physical and occupational therapy department and 34 from the Rheumatology clinic. The average age was 13.5(SD 3.8). 31 therapists completed the survey.

67% of therapists recommend that patients do their exercises every day, 20% 5x/week and 10% 3x/week. 40% of patients reported being noncompliant, 30% reported doing their exercises 5–7x/week, 20% reported 3–4x/week and 10% 1–2x/week.

The top cited barriers that therapists reported were patients' lack of interest, forgetting to do their exercises and lack of family support. Top cited barriers for patients included pain, forgetting to do their exercises and boredom. For facilitators, therapists felt that making age and developmentally appropriate exercises, a written home exercise program and family/community based activities were most helpful. Patients chose participating in sports or dance, integrating exercise into daily life and exercising with family as the most important facilitators of adherence.

There were no statistically significant differences in responses between rheumatology and non-rheumatology patients (p> 0.05).

Conclusion: Therapists and patients have different perspectives on adherence to exercise, but also agree on some aspects. The reasons for adherence or non-adherence were not dependent on diagnosis. Consideration of patients' perceived barriers and facilitators when planning home exercise programs may improve patients' adherence.

Disclosure: J. R. Blitz, None; T. Cox, None; A. Richards, None.

1584

Validity of the Nurses Health Study II Physical Activity Questionnaire (NHSPAQ) in Estimating Physical Activity in Adults with Rheumatoid Arthritis (RA). Maura D. Iversen[1], Thomas Quinn[2] and Michelle A. Frits[3]. [1]Northeastern University, Department of Physical Therapy, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [2]Northeastern University, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA

Background/Purpose: An accurate assessment of physical activity (PA) is critical to manage rheumatoid arthritis (RA). Accelerometry is an objective measure of PA but is not widely used clinically. The Nurses Health Study Physical Activity Questionnaire (NHSPAQ) is a brief, simple self-report measure used extensively to assess PA in adults with cancer and other chronic illnesses. Validity of the NHSPAQ has not been determined for estimation of PA in RA. This study examines the validity of the NHSPAQ for adults with RA when compared to accelerometry estimates and data from performance tests.

Methods: 32 adults with RA were sampled from a large tertiary care hospital-based arthritis clinic registry, consented and participated in a 1 week accelerometry trial. Medical and demographic data were collected including: age, gender, disease duration, disease activity (RADAI and DAS-CRP3), education, medications, and co-morbidities. At intake, participants completed the NHSPAQ, performed a self-paced 20-m Walk Test and Timed Step Test. Subjects were given an accelerometer to wear for 7 consecutive days and completed a second NHSPAQ at the end of the week. Descriptive statistics characterized the sample. Metabolic equivalents (METs) were derived from the NHSPAQ, accelerometers and the Timed Step Test using standardized algorithms. NHSPAQ validity was assessed by correlating NHSPAQ METs, accelerometer METs and METs derived from performance tests. Bland-Altman plots compared METs derived from the NHSPAQ and accelerometers. Posthoc power calculations were conducted

Results: 78% of subjects were female (mean age=62.1 years (SD=11.2). The mean disease duration of 21 years (SD=10). On average, RA disease was moderately active at intake (mean RADAI = 2.6 (SD=2) and 74% of subjects were taking biologics. The mean timed walk was 16.2 s (SD=3.9) and Timed Step Test METs was 4.7 (SD=0.9). Average weekly physical activity as determined by accelerometer was 33.3 METs (SD=23). A moderate correlation existed between NHSPAQ METs at one week and accelerometer METs (r =.67, p =.0001). Timed Step Test METs had a low correlation with self-reported physical activity levels (NHSPAQ METs) at one week (r =.42, p =.03). No significant correlation was found between disease activity, step test performance and NHSPAQ METs at intake. Bland-altman plots revealed METs derived from the NHSPAQ are more reliable among subjects with moderate to high physical activity levels. Posthoc power calculations suggested the study was appropriately powered

Conclusion: In this sample of adults with long standing relatively well controlled RA, the NHSPAQ appears to be a valid, simple and cost effective method of assessing PA. General fitness measures had a low correlation with weekly self-reported physical activity. Performance of the NHSPAQ appeared less stable among persons with low levels of physical activity. The NHSPAQ appears to be a valid method of assessing physical activity in adults with RA. However, the NHSPAQ may be less useful among persons engaged in low levels of physical activity

Disclosure: M. D. Iversen, None; T. Quinn, None; M. A. Frits, None.

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Physical Activity and Timing of Discharge From Physical Therapy Following Total Knee Replacement. Carol A. Oatis[1], Wenjun Li[2], Milagros Rosal[2], David Ayers[2] and Patricia D. Franklin[2]. [1]Arcadia University, Glenside, PA, [2]University of Massachusetts Medical School, Worcester, MA

Background/Purpose: In 2009 over 620,000 total knee replacement (TKR) surgeries were performed. That number is expected to increase to 3.5 million annually by 2030. Post-operative functional gain is variable. On average physical activity and functional ability remain diminished one year post TKR when compared to age matched controls. The purpose of this study was to examine the recovery pattern of physical activity from TKR to 6 months post surgery and its relation to the timing of physical therapy (PT) service received.

Methods: Subjects were 179 participants in an NIH funded RCT of telephone support interventions following unilateral, primary TKR. We requested the PT records from the first 102 participants who completed their TKR rehabilitation in outpatient PT and the first 40 participants who completed their PT rehabilitation in homecare and used no outpatient PT services. We received 90 outpatient and 27 homecare PT records. Participants were asked to wear an accelerometer (Step Activity Monitor™) at the ankle for four consecutive days (2 weekday and 2 weekend) before surgery and at 8 weeks and 6 months after surgery. Valid wear days required a minimum of 10 hours of wear time. Time from surgery to discharge from PT was extracted from PT records.

Results: Participants included 68% female, with a mean (SD) age of 65.1 (8.61). Mean (SD) age was 64 (8.4) and 66 (7.7) years for those completing rehabilitation in outpatient and home care respectively. All participants wore the accelerometer preoperatively with a mean of 3.3 days worn. 174, 163 and 168 participants had at least one valid wear day at baseline, 8 weeks and 6 months after surgery respectively. Mean (SD) steps/day were 7472 (3156), 6658 (3074) and 8295 (3531) at baseline, 8 weeks and 6 months respectively (Figure). Average

and median (5970) daily step counts at 8 weeks were approximately 1000 steps fewer than preoperative levels. Mean (SD) and median change in daily steps at 6 months were 738 (2591) and 354 respectively. 30% of participants had completed their rehabilitation by 8 weeks post surgery and 40% had completed it by 9 weeks. All but one participant who completed rehabilitation in home care had completed it by 8 weeks.
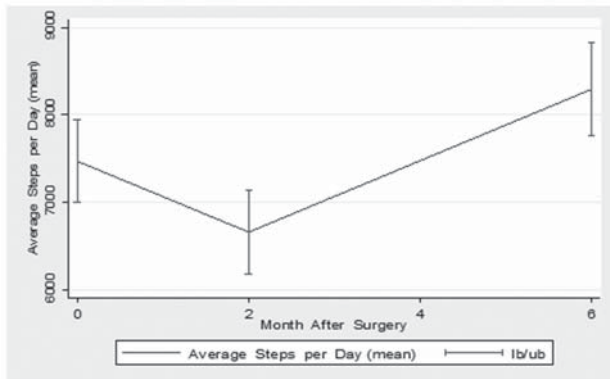
Conclusion: Although average physical activity at 8 weeks post TKR as measured by daily step counts was lower than pre-operative levels, almost one-third of patients had stopped receiving post TKR rehabilitation by that time. Increased functional ability and physical activity are frequent goals of TKR surgery. Our data show that many patients discontinue post TKR rehabilitation when their physical activity is still below pre-operative levels. Further research is needed to understand the association between recovery of physical activity and the timing of PT services post TKR.

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1586

Resistance Exercise Training for Fibromyalgia: A Systematic Review.
Angela J. Busch[1], Sandra Webber[1], Rachel Richards[2], Julia Bidonde[1], Candice Schachter[1], Laurel Schafer[3], Adrienne Danyliw[4], Anuradha Sawant[5], Vanina Dal Bello Haas[6] and Tamara Rader[7]. [1]University of Saskatchewan, Saskatoon, SK, [2]North Vancouver, BC, [3]Central Avenue Physiotherapy, Swift Current, SK, [4]Health Quality Council, SK, [5]London Health Sciences Center, ON, [6]McMaster University, Hamilton, ON, [7]University of Ottawa, Ottawa, ON

Background/Purpose: This systematic review investigated the effects of resistance exercise training on signs and symptoms, and physical fitness in people with fibromyalgia. Fibromyalgia, a condition of chronic pain, is frequently associated with poor physical fitness and low levels participation in physical activity.

Methods: We searched 8 electronic data bases (eg, Medline, CINAHL, EMBASE) to 01/2012. Inclusion criteria were randomized controlled trials, adults a fibromyalgia diagnosis based on published criteria, and between group data comparing resistance exercise to a control or other intervention. Study screening and data extraction were done by two independent reviewers. We extracted and analyzed data on symptoms, global rating of disease, health-related quality of life, physical function, psychological health, and adverse effects using Cochrane collaboration procedures. Studies were evaluated for risk of bias and congruence with the American College of Sports Medicine guidelines. We used the GRADE approach to evaluate the body of evidence.

Results: After removing duplicate entries, we found 1661 citations – only four studies met the selection criteria and were included in the review. The studies fell into two categories in which resistance exercise training was compared to: a) a control group (2 studies), and b) to other exercise interventions (one aerobic, one flexibility exercise). A total of 61 participants (all were women) were assigned to resistance training. The two randomized trials in the first category were 21 week moderate to high intensity progressive resistance interventions using isokinetic exercise equipment. In the second category, 8 weeks of progressive treadmill walking was compared to low to moderate intensity progressive free weight or body weight resistance exercise, and 12 weeks of flexibility exercise was compared to low intensity resistance training using light hand weights and elastic tubing. Large differences were found in pain, patient rated global, tender points, depression, fatigue, muscle strength and muscle power favoring the resistance training group when compared to the control group. Few significant differences were found when resistance exercise was compared to aerobic exercise: large effects were found in pain and sleep quality favoring the aerobics group. When compared to flexibility exercise, large differences were found in fatigue and sleep resistance training favoring the resistance training group. No injuries were observed in any of the studies.

Conclusion: There is moderate evidence that 21 weeks of medium to vigorous intensity resistance training exercise improves muscle strength, pain, and patient rated global well-being in women with fibromyalgia. There is moderate evidence that eight weeks of aerobic exercise is superior to moderate intensity resistance exercise training for reducing pain and improving sleep. There is low quality evidence that 12 weeks of low intensity resistance training is superior to flexibility exercise in women with fibromyalgia for reducing pain and fatigue and improving sleep. Furthermore, it appears that women with fibromyalgia perform resistance exercise training without adverse effects.

Disclosure: A. J. Busch, None; S. Webber, None; R. Richards, None; J. Bidonde, None; C. Schachter, None; L. Schafer, None; A. Danyliw, None; A. Sawant, None; V. Dal Bello Haas, None; T. Rader, None.

1587

Despite Low Disease Activity Patients with Poly- and Dermatomyositis Perceive Activity Limitation, Reduced Grip Force and Quality of Life Longitudinally. Malin Regardt[1], Marie-Louise Schult[2], Ingrid E. Lundberg[3] and Elisabet MB Welin Henriksson[4]. [1]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [2]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet., Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institutet Rheum, Stockholm, Sweden

Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are characterized by proximal muscle weakness. A recent study has shown that patients with PM and DM have reduced grip force compared to reference values. Although patients with PM/DM respond with clinical improvement to treatment several develop a sustained disability. Clinical data from most of the patients with PM and DM in Sweden are registered annually in the Swedish Myositis Network (SWEMYONET) registry. The aim of this study was to investigate how grip force, activity limitation and health related quality of life (HRQoL) change over time in a cohort of patients with PM/DM.

Methods: A multi-center longitudinal registry study following patients from disease onset and to 1, 2, 3, 4, 5, and 6 years follow-ups. Data were collected from the SWEMYONET registry on patients with PM/DM that had values on either grip force using Grippit, activity limitation measured by Myositis Activities Profile (MAP) or HRQoL measured with Short Form-36 (SF-36) on at least one time-point between disease onset and the 6 years follow-up during the years 2003–2012. A total of 88 patients were included (53 with PM (33 women and 20 men) and 35 with DM (19 women and 16 men)). Median age for the cohort at disease onset was 59.5 years. Disease activity was measured by Physician Global Assessment of disease activity (PGA). Patients were treated with conventional immunosuppressive treatment according to the choice of the treating physician.

Results: Both women and men had reduced grip force from disease onset and over time (compared to reference values), women up to 4 years follow-up from disease onset in right and left hand ($p < 0.02$) and men up to 4 years follow-up in the right hand and 3 years in the left hand ($p < 0.05$). At disease onset, both women and men rated their activities as moderately difficult to perform. Over time women improved at some time-points from disease onset and at the most to 3 years in all except two sub-groups of MAP (avoid overexertion and work/school). Men improved in four out of eight of MAP's sub-groups (movement, moving around, personal care and leisure) at some time-points from disease onset and at the most to 3 years The women had lower values on HRQoL in all eight dimensions of SF-36 compared to reference values from the Swedish population ($0.001 < p < 0.04$). In five of the eight dimensions of SF-36 the difference was present up to 6 years follow-up for women. Men also rated their HRQoL less than the reference values in all dimensions of SF-36 ($0.001 < p < 0.047$), but the difference was most frequent at disease onset.

Disease activity measured by PGA was lower for both women and men with PM/DM compared to disease onset and at alll time-points up to 6 years (p<0.05).

Conclusion: Even though disease activity decreases over time, patients with PM/DM still have reduced grip force and HRQoL compared to reference values. They also perceive activity limitation over time. The women with PM/DM seem to be more affected over time by the disease than men in grip force, activity limitation and HRQoL.

Disclosure: M. Regardt, None; **M. L. Schult**, None; **I. E. Lundberg**, None; **E. M. Welin Henriksson**, None.

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Relationship Over Time Between Beliefs, Motivation, and Worries about Physical Activity and Physical Activity Participation in Persons with Knee Osteoarthritis.

Linda S. Ehrlich-Jones[1], Jungwha Lee[2], Dorothy D. Dunlop[2], Pamela A. Semanik[2], Min-Woong Sohn[2], Jing Song[2] and Rowland W. Chang[2]. [1]Rehabilitation Institute Chicago, Chicago, IL, [2]Northwestern University, Chicago, IL

Background/Purpose: To determine the relationship over time between beliefs, motivation, and worries about physical activity and physical activity participation in persons with knee osteoarthritis (KOA).

Methods: Longitudinal data from 155 adults with KOA enrolled in a randomized clinical trial to assess the effectiveness of a behavioral intervention to promote physical activity were analyzed. Data included participant self-reported beliefs that physical activity can be beneficial for their disease, motivation for physical activity participation, worries about physical activity participation, and objective average daily accelerometer counts over a week's time at baseline, 3 months, 6 months, and 12 months. The relationships of physical activity with beliefs, motivation and worries about physical activity were examined by multiple regression models using general estimating equations adjusting for age, gender, body mass index, disease activity, and treatment group.

Results: Results from the adjusted analyses showed a strong significant concurrent relationship between beliefs and physical activity, as well as between motivation and physical activity (Figure 1). The predictive relationships of beliefs, motivation, and worries with subsequent physical activity were each not significant.

Figure 1. Adjusted[a] average daily activity counts for dynamic variables[b] (N=155)
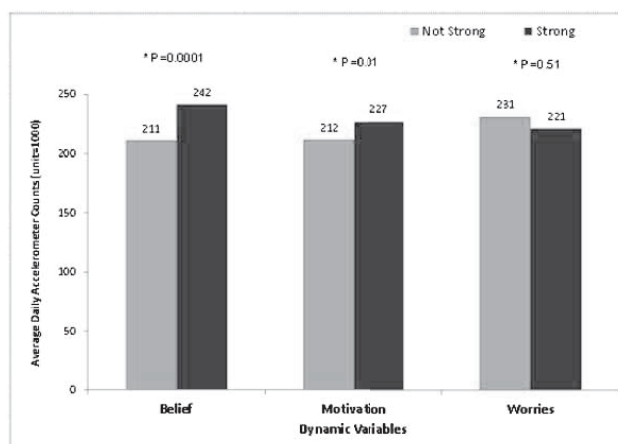
[a]Modeling average daily activity counts on concurrent dynamic variables adjusted for age, gender, body mass index, disease activity, and treatment group.
[b]Belief score: not strong 0~21, strong 22~33; Motivation score: not strong 6~20, strong 21~24; Worry score: not strong −7~0, strong 1~7.
* P-value comparing not strong versus strong.

Conclusion:
• Higher levels of physical activity participation in persons with KOA were concurrently related to stronger beliefs that physical activity can be helpful for managing disease and to greater motivation for being active.
• Prior beliefs, motivation, and worries did not predict subsequent physical activity.

• These findings suggest that persistent attention to motivation and beliefs are needed to sustain higher levels of physical activity.

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Obesity and Rehabilitation Outcomes After Lower Extremity Arthroplasty.

Soham Al Snih, Amol Karmarkar, Timothy A. Reistetter, Jinhyung Lee, Amit Kumar, James E. Graham and Kenneth J. Ottenbacher. University of Texas Medical Branch, Galveston, TX

Background/Purpose: To examine the effect of obesity on inpatient rehabilitation outcomes after lower extremity arthroplasty procedures (hip and knee) among Medicare Beneficiaries aged 65 years and older.

Methods: We conducted a retrospective analysis in a cohort of 103,445 Medicare Part A Beneficiaries with osteoarthritis who underwent primary total hip arthroplasty (THA) (N=32,671) or total knee arthroplasty (TKA) (N=70,774) between 2007 and 2009. Patients were identified using a combination of International Classification of Diseases, Ninth Revision and diagnosis related groups codes for primary THA or TKA, osteoarthritis, overweight/obesity, and morbid obesity. Data for rehabilitation outcomes were obtained using the Inpatient Rehabilitation Facilities Patient-Assessment Instrument file. Patients were grouped in three categories (normal weight, overweight/obesity, and morbid obesity). Rehabilitation outcomes included: Functional status information (FIM scores at admission and discharge, and FIM score change) and length of stay (LOS).

Results: The prevalence of overweight/obesity and morbid obesity was 11.4% vs. 4.7% among patients with THA, and 16.8% vs. 8.1% among patients with TKA. LOS was higher among morbid obesity for both THA and TKA [4.2, (Standard Deviation=2.7) vs. 4.2 (2.7)]. Mean FIM total score change was 29.4 (1.5) vs. 29.5 (12.3) for overweight/obesity and morbid obesity among those with THA, and 30.1 (11.5) vs. 31.3 (12.2) among those with TKA. Multivariable analysis for LOS controlled for age, gender, race/ethnicity, year of discharge, and discharge destination showed that LOS in morbid obesity in both THA and TKA was higher than those with normal weight or overweight/obesity (β = 0.18, p-value 0.0037 vs. 0.20, p-value < 0.0001). Multivariable analysis for FIM total score change showed that the highest change was observed among morbid obesity with TKA (β = 2.28, p-value < 0.0001) followed by morbid obesity with THA (β = 0.91, p-value = 0.0018), overweight/obesity with TKA (β = 0.89, p-value < 0.0001), and overweight/obesity with THA (β = 0.43, p-value = 0.0236) when compared with normal weight.

Conclusion: Patients with overweight/obesity and morbid obesity experience functional gains during inpatient rehabilitation, with those in the morbid obesity group experiencing the greatest gains. LOS for those with morbid obesity was greater than the other groups, providing support to the Center for Medicare and Medicaid Services tier comorbidity system for inpatient rehabilitation following THA or TKA. Our results suggest that obesity has an impact on LOS and functional status gains during rehabilitation. Future research is needed to explore the tier-based comorbidity reimbursement system and examine the impact of obesity on other rehabilitation impairment groups.

Disclosure: S. Al Snih, None; **A. Karmarkar**, None; **T. A. Reistetter**, None; **J. Lee**, None; **A. Kumar**, None; **J. E. Graham**, None; **K. J. Ottenbacher**, None.

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Post-Operative Rehabilitation Provides Unmet Need for Better Patient Support and Advice Following Lumbar Spinal Fusion.

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Background/Purpose: In the absence of evidence-based post-operative rehabilitation, following fusion surgery for severe persistent low back pain, people receive advice to rest for 3 months then progressively resume normal function. Such unclear, generic advice is unhelpful, and post-operative recovery may be delayed or suboptimal. We introduced a structured post-operative rehabilitation program of individualised progressive exercise and self-management advice for people who had undergone

lumbar fusion. We wanted to evaluate how helpful participants found the program.

Methods: 15 patients attending follow-up appointments were asked about their concerns, experiences, perceptions and needs. 4 patients on the program (small group, once a week for 10 weeks) were asked if and how the program helped them. The main themes that emerged were documented.

Results: Patients primarily reported concerns about musculoskeletal or psychosocial issues rather than technical surgical problems, e.g. residual pain and disability, how to reduce analgesia, when to resume certain activities, etc, but complained of a *lack of advice and support*. The program enabled access to a healthcare professional who could fully address people's concerns "... my GP said to ask my consultant but I never get to see him, so it is great that I can ask you ..."

Four areas raised most concerns:

Residual symptoms: People didn't know what to expect and presence of residual symptoms concerned them "... if the operation was a success why do I still have pain ..."

Prognosis: They wanted to know what would happen "... will this metalwork wear out ... will it have to come out ...". The program allowed them to ask questions and learn from others "... I am glad to hear that exercise will not cause my spine to wear out. The others in the class have helped me see that I can get better ..."

Physical function: People were keen to return to more normal physical function but were unsure what to do, how and when "... they told me to gradually increase my activity, but which activity and when ..."

Co-morbidity: People were unclear how co-morbidity might affect outcome "... how does my diabetes affect exercise ..." "... my neck hurts as well ..." but advice was lacking, unhelpful or impractical. The program gave individuals specific advice and they experienced benefits first-hand "... the consultant just kept telling me to walk, but my knee hurt and I was scared. It is so helpful that you can help me manage all of these problems ..."

Conclusion: There is a need for better support to answer concerns that cause distress, anxiety and may impede post-operative recovery. Surgeons are primarily concerned about infection, implant failure, etc. Our post-operative rehabilitation program improved access to healthcare professionals who gave advice and support that might improve outcome. The program warrants more thorough evaluation.

Disclosure: **M. V. Hurley**, None; **J. Greenwood**, None; **D. N. E. Walsh**, None.

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Efficacy of Neoprene Wrist Supports for Patients with Rheumatoid Arthritis. Kinue Matsuo[1], Koji Tateishi[2], Natsuko Nakagawa[2] and Yasushi Miura[1]. [1]Kobe University Graduate School of Health Sciences, Kobe, Japan, [2]Konan Kakogawa Hospital, Kakogawa, Japan

Background/Purpose: Wrist joints are frequently damaged by rheumatoid arthritis (RA). Wrist supports are often used to reduce pain and strain on wrists when patients with RA engage in hand-related activities, however, evidences for the efficacy of wrist supports are quite a few. Though wrist supports are made of either elastic or hard materials, elastic materials such as neoprene are preferred by patients with RA in Japan because wrist movement is tolerated. In this study, we investigated the efficacy of neoprene wrist supports on pain, hand function, activities of daily living (ADL), and instrumental activities of daily living (IADL) for patients with RA.

Methods: Patients with consistent wrist pain for at least a week and treated without changes of biologics or disease modifying antirheumatic drugs for at least 12 weeks were participated in this study. Patients with severe deformities of the fingers affecting hand function or a history of wrist surgery were excluded. Custom wrist supports (2mm thick, 8cm width, and 75cm length) are made of neoprene rubber laminated with knit fabric on both surfaces by occupational therapists (OT) to wrap three times on midcarpal joint, radiocarpal joint, and distal radioulnar joint. The participants were instructed to wear as long as possible when engaging in hand-related activities for 12 weeks. Wrist pain by 100mm visual analog scale (VAS), active range of motion (AROM) [dorsal, volar, pronation, and supination], grip strength, pinch strength (pulp pinch and key pinch), Disabilities of the Arm Shoulder and Hand (DASH), and Assessment of Motor and Process Skills (AMPS) were assessed at baseline, 1–2, 4, 8, and 12-week of wrist supports use. AROM, grip strength, and pinch strength were measured with or without wrist supports. The same AMPS task was performed for each evaluation. Data were analyzed with Wilcoxon signed rank test.

Results: Eight wrists of six female patients (age: 64.7±16.7 (33–79) years, disease duration: 15.2±9.9 (0.5–28) years, modified health assessment questionnaire (mHAQ) score: 1.6±0.4(1.13–2.25), Steinblocker's class: II; 2 and III; 4, stage I; 1, IV; 5, Larsen's classification of wrist: grade I; 1, II; 1, III; 2, IV; 4) were participated. Neoprene wrist supports significantly reduced wrist pain and improved ADL motor ability measures during the follow-up period. Grip strength was significantly increased only when wearing wrist supports. No significant changes were observed in AROM, DASH score, and key pinch strength.

Conclusion: Neoprene wrist supports reduce wrist pain, increase grip strength immediately, and improve ADL motor ability measures without limiting range of motion of wrist joints. Thus, neoprene wrist supports may be recommended for patients with RA when carrying out daily tasks.

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A Novel Approach to the Early Detection of Axial Spondyloarthritis in Patients with Inflammatory Bowel Disease: The Implementation of an Advanced Practice Physiotherapist Led Screening Program. Laura A. Passalent[1], Rebecca Morton[1], Khalid A. Alnaqbi[2], Nigil Haroon[3], Stephen Wolman[4], Mark Silverberg[5], A. Hillary Steinhart[5] and Robert D. Inman[3]. [1]Allied Health, Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [4]Toronto General Hospital, Toronto, ON, [5]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto, ON

Background/Purpose: The prevalence of SpA in patients with inflammatory bowel disease (IBD) ranges from 3.1 – 10%, compared to <1% in the general population, defining IBD patients as high risk for developing SpA. Traditional referral pathways to rheumatologists are associated with lengthy wait times for patients with suspected inflammatory arthritis. In order to address the need to improve access to care, there has been interest in traditional role expansion using non-physician models of care. One such model has been to train advanced practice physiotherapists (APPs) in the assessment/treatment of patients with inflammatory arthritis. The purpose of this study was to implement and evaluate a unique screening program for IBD patients with suspected SpA, led by an APP. The objectives were to: measure wait times from the day of referral to the day of screening; measure a) the clinical agreement for screening results and b) agreed recommendation of MRI for further assessment between the APP and three rheumatologists with expertise in SpA, and, compare the confidence of clinical judgment between the APP and rheumatologists.

Methods: Patients attending gastroenterology clinics with a diagnosis of IBD and ≥ 3 months of back pain were referred to the program. Patients who demonstrated signs and symptoms indicative of inflammatory back pain (i.e. positive screen) were referred to the Rheumatology Clinic for diagnosis. Patients who screened negative, were provided with education on appropriate back care. Descriptive statistics described clinical characteristics and wait times. Kappa coefficient (k) measured interobserver agreement and Pearson's Correlation compared confidence of the screening results of the APP and the rheumatologists. Bivariate analyses were based on "paper patients" reviewed by the rheumatologists that included clinical and investigative results of patients previously screened by the APP.

Results: A total of 20 patients were referred to the screening program. Most patients were men (55%), and the mean age was 40.9 years ±11.8. The average duration of back pain was 9.8 years; 65% reported insidious onset. The mean Oswestry disability index was 20.3 ±13.5, indicating minimal disability resulting from back pain. The median wait time was 13 days. The APP agreed with the rheumatologists' screening results on an average of 71.4% (k=0.5; CI: 0.07–0.87) of patients. The APP agreed with the rheumatologists to recommend MRI for further assessment on an average of 66.7% (k=0.6; CI: 0.23–0.94) of patients screened. Comparison of confidence of screening results was 6.8/10 (higher values indicating higher level of confidence) for the APP versus an average confidence level of 6.4/10 for the three rheumatologists (Pearson's = 0.3).

Conclusion: The utilization of the APP to screen for inflammatory back pain in patients with IBD demonstrates clinical judgement that is aligned with that of rheumatologists with expertise in SpA. The level of

confidence of the APP was similar to the rheumatologists'. Wait times to be screened by the APP are shorter than traditional referral pathways. This screening strategy has the potential to improve access to care and act as a model of care for patients at high risk for SpA.

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ACR Plenary Session II:
Discovery 2012
Monday, November 12, 2012, 11:00 AM–12:30 PM

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The Risk of Lymphoma in Patients Receiving Anti-Tumor Necrosis Factor Therapy for Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register - Rheumatoid Arthritis.
Louise K. Mercer[1], Mark Lunt[1], Audrey S. Low[1], James B. Galloway[1], Kath Watson[1], William G. Dixon[1], BSRBR Control Centre Consortium[2], Deborah P. Symmons[1], Kimme L. Hyrich[3] and On behalf of the BSRBR[4]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [4]British Society for Rheumatology, London, United Kingdom

Background/Purpose: The risk of lymphoma is increased in people with RA compared to the general population and is greatest in severe RA. Anti-TNF therapy is now widely used to treat RA, especially severe RA. The aim of this study was to determine whether anti-TNF influences the risk of lymphoma when used in routine UK clinical practice.
Methods: The analysis was conducted in the BSRBR-RA, a national cohort study. Patients with RA starting treatment with the TNF inhibitors etanercept (ETA), infliximab (INF) or adalimumab (ADA) and a biologic-naïve comparison cohort exposed to non-biologic therapy (nbDMARD) were recruited between 2001–2009. Subjects were followed until 09/30/2010, first lymphoma or death, whichever came first. Subjects with a history of lymphoproliferative malignancy prior to registration were excluded. Incident cancers were identified in 3 ways; lifelong flagging with national cancer agencies; 6 monthly patient and physician questionnaires for 3 years and annual physician questionnaires thereafter. Only first lymphoma per subject, confirmed by histology or cancer agency, was analysed. The rates of lymphoma and non-Hodgkin lymphoma (NHL) in the nbDMARD cohort and in patients ever exposed to anti-TNF were compared using Cox proportional hazards models adjusted using deciles of propensity score (DP) which included baseline age, gender, DAS score, HAQ, disease duration, use of steroids, current/previous cyclophosphamide, smoking and registration date. The first 6 months of follow-up were excluded. There were too few Hodgkin lymphoma (HL) to compare rates.
Results: 84 incident lymphomas were confirmed: 20 in 3465 nbDMARD-treated subjects and 64 in 11987 anti-TNF (152 versus 96 per 100000 person-years (pyrs); Table). After adjusting using DP there was no difference in risk of lymphoma between the cohorts; hazard ratio (HR) for anti-TNF 1.13 (95% CI 0.55, 2.31). There were 5 (22%) HL in the nbDMARD cohort and 9 (13%) in anti-TNF. Among 71 NHL, the most frequent subtype was diffuse large B cell lymphoma; 8 (50% of NHL) in nbDMARD and 25 (45%) anti-TNF. There was no significant difference in risk of NHL between the cohorts (table).

	nbDMARD N=3465	Anti-TNF N=11987
Follow-up (pyrs)	13186	66353
Median follow-up (pyrs; IQR)	4.5 (2.6, 5.9)	6.4 (4.8, 7.4)
Age: (years) Mean (SD)	60 (12)	56 (12)
Gender: N(%) female	2545 (73)	9145 (76)
RA disease duration: (years) Median (IQR)	6 (1, 15)	11 (6, 19)
DAS28 score: mean (SD)	5.3 (1.1)	6.6 (1.0)
HAQ: mean (SD)	1.5 (0.7)	2.0 (0.6)
Lymphoma: N	20	64
Lymphoma: Rate per 100000 pyrs (95% CI)	152 (93, 234)	96 (74, 123)
Lymphoma: Age and gender adjusted HR (95% CI)	Referent	0.71 (0.43, 1.20)
Lymphoma: DP adjusted HR (95% CI)	Referent	1.13 (0.55, 2.31)
Hodgkin lymphoma: N	4	9
Hodgkin lymphoma: Rate per 100000 pyrs (95% CI)	30 (8, 78)	14 (6, 26)
Non-Hodgkin lymphoma: N	16	55
NHL: Rate per 100000 pyrs (95% CI)	121 (69, 197)	83 (62, 108)
NHL: Age and gender adjusted HR (95% CI)	Referent	0.79 (0.44, 1.40)
NHL: DP adjusted HR (95% CI)	Referent	1.26 (0.58, 2.72)

Conclusion: There is no evidence that anti-TNF increases the risk of lymphoma over the background risk associated with RA, but further follow up is needed to establish if the picture changes with time.

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Clinical and Radiological Outcomes After One Year of Remission Steered Combination Treatment in Patients with Early Rheumatoid and Undifferentiated Arthritis.
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Background/Purpose: To evaluate the 1 year clinical and radiological outcomes of remission steered therapy in early arthritis patients treated aiming at remission (DAS<1.6).
Methods: In the IMPROVED study 610 patients were included with early rheumatoid or undifferentiated arthritis (RA or UA). All patients started with methotrexate (MTX) 25mg/wk and prednisone 60mg/day tapered to 7.5mg/day in 7 weeks. Patients in remission (DAS<1.6) after 4 months (early remission) tapered prednisone to zero and, when in remission at 8 months, tapered MTX. Patients not in early remission were randomized either to a combination of MTX 25mg/wk, hydroxychloroquine 400mg/day, sulphasalazine 2000mg/day and prednisone 7.5mg/day (arm 1) or to adalimumab (ADA) 40mg/2weeks with MTX 25mg/wk (arm 2). If not in remission after 8 months, patients in arm 1 switched to ADA+MTX and patients in arm 2 increased ADA to 40mg/week. Proportions of remission and radiological progression measured by Sharp-van der Heijde scoring method after one year follow up were compared between the different treatment strategies.
Results: After 4 months 375 patients (61%) achieved early remission and 221 (36%) did not, of which 161 patients were randomized, 83 to arm 1 and 78 to arm 2. In 62 (10%) patients the protocol was not followed, 12 were lost to follow up after 4 months and in total 34 after 1 year. Of those in early remission 361 (96%) tapered prednisone after 4 months and 200 (53%) tapered MTX after 8 months. After 1 year, remission was achieved in 257 (69%) patients and 119 (32%, 20% of all patients) were in drug free remission.
Patients in arm 1 and 2 achieved remission in similar proportions after 8 months (30 (36%) versus 27 (35%), p=1.0), but after 1 year patients in arm 2 more often achieved remission than in arm 1 (32 (41%) vs 21 (25%), p=0.01). Patients in arm 2 who at 8 months tapered ADA+MTX combination to MTX monotherapy, more often remained in remission after one year than patients tapering poly-DMARDs+prednisone to MTX monotherapy in arm 1 (17/26 (65%) vs 11/30 (37%), p=0.02). After failing to achieve remission on poly-DMARDs+prednisone, 6/24 patients (18%) who switched to ADA achieved remission after one year, compared to 8/27 (30%) who failed on ADA+MTX and increased ADA (p=0.2). Of the total study population 53% were in remission after 1 year. Median (IQR) radiological damage progression after 1 year was 0(0–0) in patients who achieved early remission, and 0(0–0) and 0(0–0) in arms 1 and 2, respectively (p=0.2).
Conclusion: After one year of remission steered combination treatment, 53% of the patients with early arthritis achieved remission. Patients in early remission after initial treatment with MTX and prednisone most often achieved remission after one year (69%) and 32% were in drug free remission. Patients who failed to achieve early remission benefited more from a treatment strategy with adalimumab than with multiple DMARDs+prednisone. In this treat-to-remission cohort, radiological damage progression after 1 year was negligible in all patients.

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Genome-Wide Association Study to High-Throughput Cell-Based Phenotypic Screen Identifies Novel Chemical Inhibitors of CD40 Signaling.

Gang Li[1], Dorothee Diogo[1], Di Wu[1], Jim Spoonamore[2], Rheumatoid Arthritis Consortium International (RACI)[3], Eli Stahl[4], Nicola Tolliday[2] and Robert M. Plenge[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Broad Institute, Cambridge, MA, [3]Boston, [4]Brigham and Women's Hospital

Background/Purpose: Deriving therapeutic targets from human genetics linked with biological alterations of risk alleles may provide a more successful approach to drug development than traditional efforts that focus on biological insight alone. Here, we successfully translate a SNP association from a genome-wide association study (GWAS) in rheumatoid arthritis (RA) into a high-throughput screen (HTS) based on cellular phenotype in a human B cell line to identify inhibitors of CD40-mediated NF-κB signaling.

Methods: We fine-map the *CD40* risk locus in 7,222 seropositive RA patients and 15,870 controls genotyped on the Immunochip, together with deep sequencing of *CD40* coding exons in 500 RA cases and 650 controls. We use flow cytometry to measure CD40 protein levels on the surface of primary CD19+ from 90 healthy control individuals. We use gene expression arrays to measure CD40 RNA levels in peripheral blood mononuclear cells from 1,469 healthy control individuals. We use retroviral shRNA infection to perturb the amount of CD40 on the surface of a human B lymphocyte cell line (BL2). We develop a high-throughput NF-κB luciferase reporter assay in BL2 cells activated with trimerized CD40 ligand (tCD40L), and conduct an HTS of 1,982 chemical compounds and FDA-approved drugs. Counter-screens of the top "hit" compounds were performed in the BL2 line activated with both tCD40L and LPS, and in an additional B cell line, Ramos, activated with tCD40L and TNF. Two known and two novel compounds were tested for inhibition of tCD40-NFkB signaling in primary human CD19+ B cells by measuring CD86 expression with flow cytometry.

Results: A single common SNP at the CD40 locus explains the entire signal of association (rs4810485, $P=1.4\times10^{-9}$), without any evidence for independent rare variants contributing to RA risk. Subjects homozygous for the common RA risk allele have ~33% more CD40 on the surface of primary human CD19+ B lymphocytes than subjects homozygous for the non-risk allele ($P=10^{-9}$), a finding corroborated by expression quantitative trait loci (eQTL) analysis in PBMC's ($P<10^{-15}$). We observe a direct correlation between amount of CD40 protein and phosphorylation of RelA (p65), a subunit of the NF-κB transcription factor. Using our luciferase reporter assay, we identify 81 "hit" compounds (out of 1,982) that consistent inhibit luciferase activity following tCD40L activation. After a series of counter-screens and testing in primary human CD19+ B cells, we identify 2 "known" and 2 "novel" chemical inhibitors not previously implicated in inflammation or CD40-mediated NF-κB signaling. One known inhibitor is tranilast, a drug currently in a phase II clinical trial of RA; the other is a corticosteroid derivative. The two novel compounds represent promising tool compounds to develop new therapies to treat RA.

Conclusion: Our study demonstrates proof-of-concept that human genetics can be used to guide the development of phenotype-based, high-throughput small-molecule screens to identify potential novel therapies in complex traits such as RA.

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Strontium Ranelate in Knee Osteoarthritis Trial (SEKOIA): A Structural and Symptomatic Efficacy.

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Background/Purpose: Treatments for osteoarthritis focus on improving symptoms through non-pharmacological and pharmacological approaches. Strontium ranelate (SrRan), a treatment for osteoporosis, was shown to stimulate cartilage matrix formation in vitro, and to reduce radiographic spinal OA progression in osteoporotic women with spinal OA.

The objective of SEKOIA phase III study was to compare the efficacy of SrRan with placebo for reducing radiological progression of knee OA.

Methods: SEKOIA is a double-blind, placebo-controlled, randomized, 3-year study involving 1683 patients with symptomatic primary knee OA (Kellgren and Lawrence [KL] grade 2 or 3, joint space width [JSW] 2.5–5 mm) randomly allocated to SrRan 1 or 2g/day, or placebo. Primary endpoint was radiographic change in JSW of the medial tibiofemoral compartment from baseline to LOCF. Group comparisons were performed in the ITT using a general linear model with Dunnett's multiple comparison procedure with baseline JSW, center and sex as covariates. JSW was measured yearly using a validated computer-assisted centralised reading method. Secondary endpoints included radiological progression (JSN≥0.5mm)[1], radio-clinical progression (JSN≥0.5mm and WOMAC improvement≤20%)[2], WOMAC scores, knee pain, and adverse events.

Results: The ITT set included 1371 (82%) patients. Age was 63 ± 7 years, BMI was 30 ± 5 kg/m^2, JSW was 3.5 ± 0.8 mm. 61% were KL II. 69% were female. SrRan was associated with less progression of cartilage degradation, decrease in JSW was -0.23 ± 0.56 mm with 1g/day; -0.27 ± 0.63 mm with 2g/day and -0.37 ± 0.59 mm with placebo; estimated differences (SE) were 0.14(0.04),p<0.001 for 1g/day and 0.10(0.04),p=0.018 for 2g/day with no difference between doses. Results were confirmed in the Randomised Set and sensitivity analyses demonstrated minimal impact of missing post-baseline data.

There were less radiological and radioclinical progressors with SrRan 1 and 2 g/day:

Secondary criteria	Strontium ranelate 1 g/day (n=445)			Strontium ranelate 2 g/day (n=454)			Placebo value (n=472)
	n %	E (SE)* (95% CI)	p value	n %	E (SE)* (95% CI)	p value	
Radiological progression	99 (22%)	−10.80 (2.9) (−16.54;−5.06)	<0.001	116 (26%)	−7.50 (3.0) (−13.34;−1.66)	0.012	156 (33%)
Radioclinical progression	32 (8%)	−3.94 (1.98) (−7.83; −0.05)	0.049	28 (7%)	−5.12 (1.91) (−8.86;−1.37)	0.008	53 (12%)

*Estimated difference versus placebo

Greater reductions in total WOMAC score (p=0.045), pain (p=0.028) and physical function subscore (p=0.099), and knee pain (p=0.065) were observed with SrRan 2 g/day. SrRan was well tolerated: 86%, 88% and 87% reported an emergent adverse event (EAE) in the SrRan 1g, 2g and placebo group respectively, 17% of the patients in each group reported a serious EAE. 1 EAE in each SrRAn group, 3 in the placebo group led to death.

Conclusion: SrRan 1 and 2g/day delayed radiographic progression of knee OA, evidencing a structure-modifying effect. This structural effect is translated clinically into a lower number of patients having a radiological progression over thresholds known to be predictive of OA-related surgery suggesting that SrRan could reduce the number of patients needing knee surgery in the long-term. The structural effect was accompanied by symptom improvement at the dose of 2g/day.

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Efficacy and Safety of Tocilizumab in Patients with Polyarticular Juvenile Idiopathic Arthritis: Data From a Phase 3 Trial. Hermine Brunner[1], Nicolino Ruperto[2], Zbigniew Zuber[3], Caroline Keane[4], Olivier Harari[4], Andrew Kenwright[4], Rubén J. Cuttica[5], Vladimir Keltsev[3], Ricardo Xavier[3], Inmaculada Calvo Penades[3], Irina Nikishina[6], Nadina Rubio-Perez[7], Ekaterina Alekseeva[3], Vyacheslav Chasnyk[8], Jose Chavez[3], Gerd Horneff[9], Violetta Opoka-Winiarska[3], Pierre Quartier[10], Clovis A. Silva[3], Earl D. Silverman[11], Alberto Spindler[11], D. J. Lovell[12], Alberto Martini[11] and Fabrizio De Benedetti[13]. [1]Cincinnati Children's Hospital Medical Center and PRSCG, Cincinnati, OH, [2]Paediatric Rheumatology International Trials Organisation [PRINTO], Genova, Italy, [3]Paediatric Rheumatology International Trials Organisation–IRCCS [PRINTO], Genoa, Italy, [4]Roche, Welwyn Garden City, United Kingdom, [5]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [6]Scientific Research Institute of Rheumatology RAMS, Moskow, Moskow, Russia, [7]PRINTO, IRCCS G. Gaslini, Genoa, Italy, [8]International Investigator Consortium for MAS Diagnostic Criteria, Saint-Petersburg, Russia, [9]Centre of Pediatric Rheumatology, Sankt Augustin, Germany, [10]Necker-Enfants Malades Hospital, Paris, France, [11]Pediatric Rheumatology Collaborative Study Group [PRSCG], Cincinnati, OH, [12]Cincinnati Children's Hospital, Cincinnati, OH, [13]PRINTO and PRSCG, Genoa, Italy

Background/Purpose: Elevated IL-6 levels are associated with disease activity in patients (pts) with juvenile idiopathic arthritis (JIA).[1] Tocilizumab (TCZ), an IL-6 receptor inhibitor, was evaluated for the treatment of polyarticular-course JIA (pcJIA; RF+ and RF– poly- and extended oligoarticular JIA; systemic JIA was excluded) in the CHERISH study.

Methods: CHERISH is a 104-wk study in pts age 2–17 yrs with active pcJIA for ≥6 mo who failed MTX. In the first 16 wks, all pts received open-label (OL) TCZ every 4 wks (if body weight [BW] ≥30 kg, 8 mg/kg [n = 119]; if BW <30 kg, pts were randomly assigned to 8 mg/kg [n = 34] or 10 mg/kg [n = 35]). At wk 16, eligible pts (with ≥JIA ACR30 response) entered a 24-wk randomized (pts were assigned [1:1] to placebo [PBO] or to continue TCZ at the same dose), double-blind (DB) withdrawal period for evaluation of the primary endpoint (JIA ACR30 flare relative to wk 16). Pts who flared or completed the DB period entered an OL extension in which they received the same TCZ dose as in the lead-in period. Efficacy data (until wk 40) are presented for the ITT population; safety data are presented for the safety population to the cut date.

Results: 188 pts entered the initial lead-in period (77% girls; 79% and 46% were receiving concurrent MTX and oral corticosteroids [CS], respectively); 166 pts entered the DB period; 15 pts (8%) withdrew due to insufficient response, 3 (2%) due to adverse events (AEs), and 4 (2%) due to other reasons. The primary endpoint was met, and JIA ACR30/50/70 responses were significantly higher with TCZ compared to PBO at wk 40 (Table). Efficacy responses for the initial lead-in period at wk 16 are shown (Table). The degree of improvement was lower for these endpoints in the TCZ 8 mg/kg <30 kg BW group compared with the other 2 groups (TCZ 10 mg/kg <30 kg BW and TCZ 8 mg/kg ≥30 kg BW) (Table). At the time of the safety data cut, there were 184 pt-yrs (PY) of follow-up in the 188 pts enrolled. Rates/100PY of AEs and SAEs were 480 and 12.5; infections were the most common AEs (164/100PY) and SAEs (4.9/100PY). ALT and AST elevations ≥3× ULN were each reported in 3.7% and <1% of pts. Neutropenia (<1000 cells/mm^3) and thrombocytopenia (<50,000 cells/mm^3) occurred in 3.7% and 1.1% of pts. LDL-cholesterol ≥110 mg/dL occurred in 11.4% of pts. No grade 3/4 (>3 ULN) elevations of serum bilirubin were reported.

Table. Efficacy Endpoints

Randomized DB period (wks 16–40; ITT population: all pts who entered DB period)	All PBO n = 81	All TCZ n = 82	p^a
Primary endpoint: JIA ACR30 flare (relative to wk 16), n (%)^b	39 (48.1)	21 (25.6)	0.0024
Secondary endpoints (at wk 40 relative to day 0^c; ITT population: all pts who entered DB period), n (%)			
JIA ACR30	44 (54.3)	61 (74.4)	0.0084
JIA ACR50	42 (51.9)	60 (73.2)	0.0050
JIA ACR70	34 (42.0)	53 (64.6)	0.0032

Initial lead-in period (at wk 16: ITT population)	TCZ 10 mg/kg <30 kg BW n = 35	TCZ 8 mg/kg <30 kg BW n = 34	TCZ 8 mg/kg ≥30 kg BW n = 119	All TCZ N = 188
JIA ACR responses at wk 16,^{d} n (%)				
JIA ACR30	31 (88.6)	26 (76.5)	111 (93.3)	168 (89.4)
JIA ACR50	28 (80.0)	24 (70.6)	104 (87.4)	156 (83.0)
JIA ACR70	22 (62.9)	14 (41.2)	81 (68.1)	117 (62.2)
JIA ACR90	11 (31.4)	8 (23.5)	30 (25.2)	49 (26.1)

JIAACR core components at wk 16, mean change from baseline (% change from baseline)^e				
Active joints (0–71)	−16.8 (−63.4)	−12.5 (−55.6)	−13.0 (−73.0)	−13.6 (−68.2)
Joints with limitation in range of motion (0–67)	−13.2 (−61.8)	−8.3 (−49.9)	−9.6 (−66.0)	−10.1 (−62.4)
Parent-rated patient global assessment of well-being (VAS 0–100 mm)	−30.1 (−31.7)	−35.8 (−55.6)	−29.3 (−53.3)	−30.9 (−49.5)
Physician-rated global assessment of disease activity (VAS 0–100 mm)	−45.8 (−61.5)	−40.6 (−65.2)	−42.7 (−72.6)	−42.9 (−69.2)
Disability as measured by the CHAQ-DI (0–3)	−0.892 (−54.5)	−0.827 (−46.2)	−0.621 (−49.1)	−0.708 (−49.6)
ESR (mm/h)	−26.0 (−71.0)	−17.0 (−21.8)	−26.8 (−70.9)	−25.0 (−62.5)

^{a} Analysis adjusted for background MTX and/or CS therapy applied at wk 16.
^{b} Pts who withdrew or escaped (to OL TCZ) were classified as flared.
^{c} Pts who withdrew or escaped (to OL TCZ) or for whom endpoint could not be determined were classified as nonresponders.
^{d} Pts who withdrew or for whom the endpoint could not be determined were classified as nonresponders.
^{e} Pts who withdrew before wk 16 were excluded.

Conclusion: TCZ treatment in pcJIA was efficacious, with a sustained clinically meaningful improvement using a monthly regimen at doses of 8 mg/kg if BW ≥30 kg and 10 mg/kg if BW <30 kg. The safety profile is consistent with that in other TCZ-treated pts (eg, systemic JIA).[2]

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1598

Clinical and Serologic Predictors of Response in Rituximab-Treated Refractory Adult and Juvenile Dermatomyositis (DM) and Adult Polymyositis (PM) - the RIM Study. Rohit Aggarwal[1], Ann M. Reed[2], Dana P. Ascherman[3], Richard J. Barohn[4], Brian M. Feldman[5], Frederick W. Miller[6], Lisa G. Rider[6], Michael Harris-Love[7], Marc C. Levesque[1], Chester V. Oddis[1] and the RIM Study Group[8]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Mayo Clinic, Rochester, MN, [3]University of Miami, Miami, FL, [4]Department of Neurology, University of Kansas Medical Center, Kansas City, USA, Kansas City, MO, [5]The Hospital for Sick Children, Toronto, ON, [6]NIEHS, NIH, Bethesda, MD, [7]VA Medical Ctr, Washington, DC, [8]

Background/Purpose: The Rituximab in Myositis (RIM) Study evaluated 200 refractory myositis patients treated with rituximab, 83% of whom met the definition of improvement (DOI). The aim of this study was to identify the clinical and laboratory predictors of response in this cohort.

Methods: All patients failed corticosteroids and at least 1 other immunosuppressive (IS) agent and received rituximab at weeks 0/1 (Early) or 8/9 (Late). The 1° endpoint in this 44-week trial was time to achieve DOI [≥20% improvement in 3 of 6 core set measures (CSM) (includes manual muscle testing (MMT), muscle enzymes, HAQ, patient/parent global, physician global disease activity and extramuscular disease activity) with no >2 CSM worsening by ≥25% (excluding MMT)] at 2 consecutive visits. We analyzed the effect of the following baseline variables on the time to DOI: myositis subtype, demographics, laboratory [IgM, IgG, myositis-associated autoantibodies (MAA), CBC, creatinine], damage measures (global, muscle damage and atrophy and organ-related), disease activity and other clinical parameters (skeletal/GI/pulmonary/muscle disease activity, Raynaud, calcinosis, mechanic hands), CSM, medication (early vs. late rituximab, IS agents and corticosteroids) and MAA subset [anti-synthetase (anti-Syn), Mi-2, SRP, TIF1-γ, MJ, other autoantibodies and those without an MAA]. The Wilcoxon test was used to univariately evaluate the association of baseline variables with the time to DOI. A multivariate time-dependent proportional hazard model was built using forward selection ($\alpha=0.05$) based on univariate variables with $p<0.1$.

Results: 200 randomized patients (76 PM/76 DM/48 JDM) were analyzed (96 Early/104 Late). Table 1 lists the baseline variables which predicted time to DOI univariately. The multivariate model included autoantibodies (anti-Syn was the best DOI predictor followed by Mi-2 as compared to the 'no

MAA' subset), and global damage (lower damage had a better response). The effects of global damage diminished by week 20. Myositis subtype (JDM had a better response than adult myositis) was not statistically significant univariately, however, final model was stratified by the subtypes due to their clinical relevance and post hoc had statistical significance in multivariate models.

Table 1. Univariate predictive factors and final multivariate model

Univariate variable for predicting future DOI (0.1 level of significance)

Factor	Associated with more rapid achievement of DOI (Hazard Ratio)	p-value for Wilcoxon test for trend
Gender	males (1.28)	p=0.10
Autoantibody	Anti-Syn (2.83) Mi-2 (2.48), Other MAA (1.39) as compared with no MAA	p=0.001
White blood count	higher counts (1.44)	p=0.04
Muscle damage	lower damage (1.26)	p=0.02
Muscle atrophy	absence of atrophy (1.45)	p=0.02
Global damage	lower damage (1.30)	p=0.004
Most abnormal muscle enzyme	higher result (1.30)	p=0.09
Extramuscular disease activity	higher values (1.26)	p=0.07
Disability index	higher values (1.09)	p=0.09

Multivariate model based on the variables identified in univariate analysis

Autoantibody	Hazard ratio of DOI	P-value (comments)
no MAA	-	(Baseline)
Jo-1/other antiSyn	3.03	<0.01 (for adult PM or DM)
Mi-2	2.49	<0.01(for JDM or adult DM)
Other MAA (SRP, MJ, TIF1-γ, other)	1.38	0.140
Global Damage (dichotomized at median <23 vs. >23)	0.43	<0.01 for week 8, washes out by week 20

Conclusion: Anti-Syn and Mi-2 autoAbs strongly predicted improvement in rituximab-treated refractory myositis patients. JDM and lower disease damage predicted more rapid improvement early in course of treatment. It is unclear whether this effect is due to a delayed beneficial effect of rituximab in patients with higher damage and adult PM/DM. These results suggest that early, more aggressive therapy could be considered in some clinical and serologic myositis subsets to achieve a better therapeutic response and to avoid disease-related damage.

ACR Concurrent Abstract Session
Cell-cell Adhesion, Cell Trafficking and Angiogenesis
Monday, November 12, 2012, 2:30 AM–4:00 PM

1599

NF-Kb Inducing Kinase (NIK) Is a Key Regulator of Inflammation-Induced Angiogenesis. A.R. Noort[1], K.P.M. van Zoest[1], P. Koolwijk[2], D.V. Novack[3], M.J. Siemerink[1], P. P. Tak[4] and S.W. Tas[1]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Institute for Cardiovascular Research (ICaR-VU)/VU University Medical Center, Amsterdam, Netherlands, [3]Washington University School of Medicine, St. Louis, MO, [4]Academic Medical Center/ University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: In rheumatoid arthritis (RA) synovial tissue (ST) angiogenesis can be observed already in the earliest phase of disease, which may be critical in the switch from acute to chronic inflammation. The chemokine CXCL12, which is induced via the non-canonical nuclear factor-kB (NF-kB) pathway, plays an important role in angiogenesis, lymphocyte transendothelial migration, and the homing of endothelial progenitor cells. Therefore, the non-canonical pathway, with its key mediator NF-kB inducing kinase (NIK), may play an important role in pathological angiogenesis and the perpetuation of synovial inflammation in RA.

Objectives: To study the role of non-canonical NF-kB signaling in pathological angiogenesis in RA.

Methods: Expression of NIK and CXCL12 in RA ST was evaluated using immunofluorescence microscopy (IF). The angiogenic potential of endothelial cells (EC) was studied in vitro using the tube formation assay and siRNA-mediated gene silencing. Microvessel outgrowth was studied ex vivo by comparing WT and NIK$^{-/-}$ mice in the aortic ring assay. Physiological (developmental) angiogenesis was evaluated in these mice by isolectin B4 staining of the retina followed by confocal microscopy. Finally, the contribution of NIK to synovial angiogenesis was studied in vivo in antigen-induced arthritis (AIA).

Results: NIK was highly expressed in EC in RA ST and co-localized with the EC marker vWF in small (newly formed) blood vessels. NIK, p52 and CXCL12 were expressed both in EC in small blood vessels and in PNAd$^+$ high endothelial venules. In vitro, EC treated with stimuli that induce non-canonical NF-kB signaling (i.e. lymphotoxin, LIGHT, CD40L) significantly enhanced tube formation 2,5-fold (p<0.05), which could be completely blocked by siRNA targeting NIK or IKKα, but not completely by IKKβ (canonical NF-kB pathway). Aortic rings from WT and NIK$^{-/-}$ mice showed normal TNF- and VEGF-induced microvessel outgrowth. In contrast, whereas non-canonical NF-kB stimuli induced microvessel outgrowth in WT mice (unstim 29.94 ± 6.08 vs. LT 159.1 ± 50.24 vs. LIGHT 110.3 ± 17.68 (mm^2) p<0.05), no microvessel outgrowth was observed in aortic rings from NIK$^{-/-}$ mice (unstim 28.74 ± 15.89 vs. LT 45.9 ± 16.71 vs. LIGHT 43.41 ± 15.73 (mm^2)). In line with this, NIK$^{-/-}$ mice exhibited normal developmental angiogenesis in the retina, but a 50% reduction in pathological angiogenesis in synovial inflammation (blood vessels in synovial tissue WT 20 ± 5.07 vs. NIK$^{-/-}$10.2 ± 3.02).

Conclusion: NIK is preferentially expressed in EC in RA ST. Induction of non-canonical NF-kB signaling in EC resulted in enhanced angiogenesis in vitro, and siRNA-mediated selective blockade of this pathway abrogated these effects. Moreover, NIK$^{-/-}$ mice exhibited normal developmental and VEGF-induced angiogenesis, but reduced pathological angiogenesis in AIA. These findings point towards an important role of the non-canonical NF-kB pathway in pathological angiogenesis associated with chronic (synovial) inflammation. This could be exploited for the development of future new therapies for RA.

1600

Gene Targeting of an Integrin-Mediated Signaling Adaptor Molecule, Crk-Associated Substrate Lymphocyte Type Reduced the Severity of Collagen-Induced Arthritis. Its Possible Involvement in the Pathophysiology of Rheumatoid Arthritis. Satoshi Iwata, Tomoki Katayose, Yoshiko Kichikawa, Hiromi Ichihara, Hiroshi Kawasaki, Osamu Hosono, Hirotoshi Tanaka and Chikao Morimoto. The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Background/Purpose: It has been reported that the expression levels of β1 integrins and the ligands such as VCAM-1 are elevated in the affected joints of RA patients. Cas-L is a cytoplasmic docking protein downstream of β1 integrin-mediated signaling pathway and is essential for β1 integrin-mediated cell migration and costimulation in T cells. We found that the levels of Cas-L were markedly elevated in various tissues from HTLV-I tax transgenic mice, a murine model of RA. Interestingly, a large amount of Cas-L positive lymphocytes and leukocytes were shown to infiltrate into the inflamed joints, suggesting its roles for the pathophysiology of RA. To further evaluate the involvement of Cas-L in the development of RA, we analyzed collagen-induced arthritis using Cas-L knockout mice.

Methods: We immunized Cas-L knockout mice (KO) and wild-type mice (WT) on a C57BL6 background with the emulsion of chicken type II collagen (IIC) and complete Freund's adjuvant on day 0 and day 21. The animals were assessed for the severity and occurrence of arthritis. In addition, limb joints were assessed by HE staining, immunohistochemistry, and x-ray. Serum samples were collected on the day 21 and the levels

of multiple cytokines and chemokines were measured by Luminex. In vitro, IIC-specific proliferative response of lymphocytes from the draining lymph nodes (LN) was analyzed by ^{3}H-thymidine incorporation assay. CD4$^+$T cells were purified from splenocytes by MACS, and costimulatory response (CD3 plus fibronectin and CD3 plus CD28) were analyzed by the same assay. Furthermore, we made bone marrow chimera with WT (graft)/KO (host) and KO (graft)/WT (host), then challenged with collagen-induced arthritis.

Results: Although the overall incidence of arthritis was similar between KO and WT, the onset of the disease was retarded in KO, and the severity of arthritis was significantly reduced in KO compared to WT. By immunohistochemical analysis, the hindlimbs from WT showed more severe infiltration of inflammatory cells, bone destruction, inflammatory changes, and synovial thickening compared to KO. In WT, inflammatory cytokines such as TNF-α, IL- 17, IL-6 showed higher levels compared to KO. On the contrary, the level of anti-inflammatory cytokine IL-10 was lower than KO mice. Lymphocytes proliferative response against IIC was reduced in KO. Furthermore, costimulatory response of CD4+ T cells to CD3 plus fibronectin was reduced in KO, in contrast, the response to CD3 plus CD28 was higher in KO compared to WT. Finally, bone marrow chimera revealed that the severity of CIA was lower in KO (graft)/WT (host) than WT (graft)/KO (host).

Conclusion: Gene-targeting of Cas-L conferred the resistance against CIA with altered balance of the pro-inflammatory and anti-inflammatory cytokines. The costimulatory response of the T cells and IIc-specific response of lymphocytes were also altered. It seems that hematopoietic cells were more responsible for the gene-targeting effect of Cas-L based on the bone marrow chimera experiment. Taken together, Cas-L may play a pivotal role in the pathophysiology of collagen-induced arthritis. It is thus suggested that Cas-L may be a potential molecular target for the treatment of RA.

1601

Role of Focal Adhesion Kinase in Synovial Fibroblast Invasion and Arthritis. Miriam A. Shelef, David Bennin and Anna Huttenlocher. Univ of Wisconsin Schl of Med, Madison, WI

Background/Purpose: Rheumatoid arthritis is an inflammatory arthritis characterized by joint erosions and destruction. This damage is mediated in part by invasion of synovial fibroblasts into cartilage and bone. Cellular invasion has been extensively studied in cancer cells, but we are just beginning to understand the elements necessary for synovial fibroblast invasion. Focal adhesion kinase (FAK) is a protein scaffold and tyrosine kinase important for cancer cell migration and invasion. FAK may also play a role in synovial fibroblast invasion and arthritis. Phosphorylated FAK is increased in rheumatoid synovial tissue and localizes to focal adhesions in rheumatoid synovial fibroblasts. Also, FAK mediates IL-6 induction and is expressed in endothelial and immune cells. FAK inhibitors are in clinical trials for cancer, so if FAK were important for synovial fibroblast invasion and arthritis, FAK inhibitors might also be of benefit for treating rheumatoid arthritis.

Methods: Synovial fibroblasts derived from the synovial fluid of patients with rheumatoid arthritis were treated with vehicle control or two different FAK inhibitors, PF 562271 and PF 573228, and plated on Matrigel invasion chambers to assess the role of FAK in invasion. To dissect which steps of invasion require FAK activity, we assessed migration using fibronectin coated transwells and focal matrix degradation by plating synovial fibroblasts on coverslips coated with fluorescent gelatin. To determine the role of FAK in arthritis, we crossed established lines of mice to generate mice that overexpress TNFα, express tamoxifen inducible Cre recombinase, and carry FAK flanked by LoxP sites. These TNF$^+$Cre$^+$FAK$^{f/f}$mice spontaneously get arthritis due to overexpression of TNFα and can be induced to delete FAK by treatment with tamoxifen. Western blots were done to assess loss of FAK protein in splenocytes after tamoxifen treatment. Arthritis was assessed in FAK deficient and control arthritic mice by scoring paw swelling and deformity as well as testing grip strength from 2 to 5 months of age.

Results: Inhibition of FAK using either PF 562271 or PF 573228 resulted in decreased rheumatoid synovial fibroblast invasion through Matrigel and decreased migration through fibronectin coated transwells compared to vehicle control. Focal degradation of gelatin still occurs when FAK is inhibited. TNF$^+$Cre$^+$FAK$^{f/f}$mice treated with tamoxifen were found to have good deletion of FAK in splenocytes. Arthritic mice deficient in FAK did not

have significant alterations in arthritis by clinical scoring compared to arthritic mice without FAK deletion.

Conclusion: Consistent with findings in cancer cells, activated FAK is an important component of synovial fibroblast migration and the migratory component of invasion, but not focal matrix degradation. According to clinical arthritis scores, FAK does not appear to play a critical role in arthritis. Studies are ongoing to address if loss of FAK protein, as opposed to FAK inhibition, alters focal gelatin degradation and if joint erosions are altered in arthritis in the absence of FAK, which may be a more specific sign of synovial fibroblast dysfunction than clinical scores.

1602

Tie2 Signalling Induces a Pro-Inflammatory and Pro-Angiogenic Phenotype in Differentiated Macrophages, Independently of Macrophage Polarization Conditions, and Contributes to Production of Cytokines Elevated in Early Rheumatoid Arthritis. Samuel Garcia[1], Sarah Krausz[1], Carmen A. Ambarus[2], Bea Malvar Fernandez[1], Dominique L. Baeten[1], Paul P. Tak[3] and Kris A. Reedquist[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center, University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: Angiopoietin (Ang) -1 and -2 signalling to the Tie2 tyrosine kinase receptor has an essential role in blood vessel remodeling and angiogenesis. Ang-1, Ang-2 and Tie2 are all expressed in rheumatoid arthritis (RA) synovial tissue. Activated Tie2 is prominently observed in RA synovial macrophages, both Ang-1 and Ang-2 can cooperate with TNF to induce macrophage IL-6 production, and Ang-1 signaling to Tie2 promotes disease persistence and progression in early RA. Here, we examined how macrophage differentiation regulates expression of Tie2 and macrophage responses to Ang-1 and Ang-2, as well as the impact of Tie2 signalling on macrophage production of secreted products elevated in the synovial fluid (SF) of early RA patients.

Methods: Human healthy donor peripheral blood mononuclear cells were isolated from buffy coats and differentiated into macrophages in the presence of Ang-1 and Ang-2, the pro-inflammatory/classically activating cyokines GM-CSF and IFN-γ, or in the presence of the anti-inflammatory/alternatively activating cytokines M-CSF or IL-10. The expression of macrophage polarization markers and Tie2 was analyzed by flow cytometry and quantitative (q)-PCR. Macrophages were stimulated with TNF in the presence or absence of Ang-1 or Ang-2 and effects on gene expression assessed using low density q-PCR arrays, ELISA and luminex. Monocyte chemotactic responses were assessed using 96-well transwell systems.

Results: Macrophage Tie2 protein and mRNA expression was observed under all conditions, but failed to correspond to pro- or anti-inflammatory phenotypes, as it was highest in macrophages differentiated in IL-10 and IFN-g. Ang-1 and Ang-2 failed to induce macrophage polarization. Each polarization condition displayed a distinct expression profile of angiogenic factors. Ang-1 and Ang-2 alone failed to influence gene expression. Ang-1, and to a lesser extent Ang-2, synergized with TNF to stimulate expression of similar gene profiles regardless of macrophage polarization conditions. Significantly enhanced TNF-induced CXCL2, CXCL-3, CXCL-9, IL-6 mRNA expression was observed. Neither Ang-1 nor Ang-2 stimulated monocyte chemotaxis. However, conditioned medium from macrophages stimulated with TNF in combination with Ang-1 or Ang-2 demonstrated significantly enhanced chemotactic activity for monocytes, compared to conditioned medium from macrophages stimulated with TNF alone. Ang-1, but not Ang-2, significantly cooperated with TNF to induce macrophage production of cytokines elevated in the SF of early RA patients, including TGFalpha, FGF2, and IL-12B.

Conclusion: Our results demonstrate that Tie2 is functionally expressed in macrophages, regardless of macrophage polarization conditions. Stimulation of macrophage Tie2 with Ang-1, and to a lesser extent Ang-2, enhances TNF induced pro-inflammatory cytokine and chemokine expression. These results suggest that Tie2 signaling, in combination with TNF, induce a pro-inflammatory and pro-angiogenic profile in differentiated macrophages, and provide a molecular basis for the role of Tie2 in promoting disease progression in both early and established RA.

1603

Inhibitor of DNA Binding 1 As a Secreted Angiogenic Transcription Factor in Rheumatoid Arthritis. Takeo Isozaki[1], M. Asif Amin[1], Alisa E. Koch[2], Ali Arbab[3], Stephanie A. Shuman[1], Christine M. Ha[1], G. Kenneth Haines III[4] and Jeffrey H. Ruth[1]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI, [3]Henry Ford Hospital and Medical Centers, Detroit MI 48202, Detroit, MI, [4]Yale University, New Haven, CT

Background/Purpose: Rheumatoid arthritis (RA) is characterized by enhanced blood vessel development in joint synovium. This involves the recruitment of endothelial progenitor cells (EPCs), allowing for de novo vessel formation and pro-inflammatory cell infiltration. Inhibitor of DNA Binding 1 (Id1) is a transcription factor unique to EPCs that influences cell maturation. We hypothesized that Id1 could be secreted and expressed in RA, and influence blood vessel growth. We also wanted to define the contribution of this transcription factor in RA, and correlate it with CXCL16 expression, as EPCs also prominently express the only known CXCL16 receptor, CXCR6.

Methods: Enzyme Linked Immunosorbant Assay (ELISA) and Polymerase Chain Reaction (PCR) was used to examine Id1 levels in synovial fluids (SFs) and endothelial cells (ECs) respectively. Immunohistology and immunofluorescence (IF) histology was used to determine the expression of Id1 in RA compared to osteoarthritis (OA) and normal (NL) synovial tissues (STs). We used Matrigel angiogenesis and human dermal microvascular EC (HMVEC) migration assays to determine if recombinant human (rhuId1) and/or RA SF immunodepleted of Id1 alters angiogenic activity. Finally, CXCR6 deficient (CXCR6$^{-/-}$) and wild-type (wt) C57BL/6 mice were primed to develop K/BxN serum induced arthritis and evaluated for joint swelling. Joint tissues from these mice were examined for Id1 and correlated with CXCR6 expression and arthritis development.

Results: ST samples immunostained for Id1 showed heightened expression in RA compared to OA and NL ST. By IF staining, we found significantly more Id1 in RA compared to OA and NL vasculature, showing that Id1 expressing cells, therefore EPCs, are most active in vascular remodeling in the RA synovium. We also detected significantly more Id1 in RA compared to OA and other arthritis SFs by ELISA that highly correlated with CXCL16 levels (p<0.05, n=10, r=0.64 Pearson's Correlation). *In vitro* chemotaxis assays also showed that Id1 is highly chemotactic for HMVECs. Using *in vitro* Matrigel assays, we found that HMVECs form tubes in response to rhuId1 and sham depleted RA SF, and that Id1 immunodepleted from RA SF profoundly decreases tube formation. PCR showed that Id1 mRNA could be upregulated in both HMVECs and EPCs with tumor necrosis factor-α (TNF-α) or CXCL16, with highest amounts seen in EPCs in response to CXCL16. Finally, using the K/BxN serum induced arthritis model, we correlated EC CXCR6 with Id1 expression by immunohistochemistry. These findings were further validated by highly significant reductions in blood vessels and hemoglobin (Hb) content in joint tissues from K/BxN serum induced CXCR6$^{-/-}$ mice.

Conclusion: Our data indicates that Id1 correlates with CXCL16 in RA SF and that CXCR6$^{-/-}$ arthritic mice have notable reductions in Id1 expression and arthritis development, correlating with profound declines in vasculature and joint Hb content. We also found that Id1 is potently angiogenic, and can be upregulated in HMVECs and EPCs by TNF-α and especially CXCL16. These results indicate that CXCL16 and its receptor CXCR6 may be a central ligand-receptor pair that can be highly correlated with Id1 expression, EPC recruitment, and blood vessel formation in the RA joint.

Disclosure: T. Isozaki, None; **M. A. Amin**, None; **A. E. Koch**, None; **A. Arbab**, None; **S. A. Shuman**, None; **C. M. Ha**, None; **G. K. Haines III**, None; **J. H. Ruth**, None.

ACR Concurrent Abstract Session
Epidemiology and Health Services Research II:
Epidemiologic Risk Factors in the
Development of Rheumatic Disease
Monday, November 12, 2012, 2:30 PM–4:00 PM

1604

Parity and the Risk of Developing Rheumatoid Arthritis: Results From the Swedish Epidemiological Investigation of Rheumatoid Arthritis Study. Cecilia Orellana[1], Lars Klareskog[2], Lars Alfredsson[1] and Camilla Bengtsson[1]. [1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Rheumatoid arthritis (RA) is more common among women than among men and the gender difference in incidence seems to be most striking before menopause (1). The importance of hormonal/reproductive factors has been hypothesized to explain this difference, but the literature is scarce and contradictory. Parity has been suggested to decrease the risk of RA and postpone the disease onset but, on the contrary, a higher risk of RA in the post-partum period has been described (2). The aim of this work was to study the association between parity, post-partum period and age at first birth and the risk of developing RA in pre-menopausal women, by stratifying the cases according to presence/absence of antibodies to citrullinated peptides (ACPA).

Methods: Data from the Swedish population-based EIRA (Epidemiological Investigation of RA) case-control study comprising 603 incident cases aged 18–44 years old women and 906 controls (matched by age and residential area) was analyzed. Parity, post-partum period before the onset of symptoms and age at first birth were assessed by means of an identical questionnaire answered by the participants. In all analyses, nulliparous women were used as the reference group. Unconditional logistic regression analyses to obtain odds ratios (ORs) with 95% confidence intervals (CI) were performed.

Results: An increased risk of developing ACPA-negative RA in parous women compared with nulliparous women (OR 2.1 (95% CI 1.4–3.2)) was found. Women whose most recent delivery occurred the same year as the disease onset showed an increased risk of developing ACPA-negative RA (OR 2.6 (95% CI 1.4–4.7)). This risk decreased after 1 year (OR 1.8 (95% CI 0.9–3.6)) and reached the null value after 2 years (*p-value* for trend 0.0147). Women who delivered their first child at a younger age had an increased risk of developing ACPA-negative RA (*p-value* for trend 0.0158). No association between parity, post-partum period or age at first birth and the risk of ACPA-positive RA was observed.

Conclusion: Our results indicate that parity increases the risk of ACPA-negative RA in pre-menopausal women, but has no association with ACPA-positive RA. The increased risk seemed to be more pronounced in the post-partum period within 1 year after child delivery and among women who had their first child at young age. As previously described, a postponed onset of RA, comparable with the amelioration of the pre-established disease in pregnant women followed by a post-partum flare-up might explain these results in regards to the post-partum period. Further research is needed in order to explore the biological mechanisms behind our findings but the effect of hormonal/reproductive factors such as parity might partly explain the higher incidence of RA in pre-menopausal women.

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Disclosure: C. Orellana, None; **L. Klareskog**, None; **L. Alfredsson**, None; **C. Bengtsson**, None.

1605

Anti-Citrullinated Peptide Autoantibodies to Rheumatoid Synovium Epitopes in Women and Risk of Future Rheumatoid Arthritis. Elizabeth V. Arkema[1], Barbara L. Goldstein[2], William H. Robinson[3], Catriona Cramb[4], Jeremy Sokolove[5], Jing Cui[6], Susan Malspeis[6], Elizabeth W. Karlson[7] and Karen H. Costenbader[7]. [1]Harvard School of Public Health, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Stanford University, Palo Alto, CA, [4]VA Palo Alto Heatlh Care System and Stanford University, Palo Alto, CA, [5]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [6]Brigham and Womens Hospital, Boston, MA, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Recent studies have shown that anti-citrullinated protein antibodies (ACPA) are detectable years before rheumatoid arthritis (RA) diagnosis, representing a potential early marker of RA pathogenesis. The goal of this study was to investigate the presence of several ACPAs targeted to epitopes found in the rheumatoid synovium years prior to RA diagnosis, within a nested case-control study in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts.

Methods: We confirmed 196 incident RA cases (NHS: 139; 1976–2008, NHSII: 57; 1989–2009) with blood collected prior to RA symptoms by medical record review. Three controls were matched to each case on year of birth, race, menopausal status and post-menopausal hormone use, time of day, fasting status

at blood draw and timing in the menstrual cycle (pre-menopausal women in NHSII only). Sixteen ACPA antigens previously identified by protein mass spectrometry were coupled to spectrally distinct beads for analysis using the BioPlex platform using a Luminex 200 instrument. These peptides included epitopes derived from clusterin, enolase, fibrinogen, histone 2A and vimentin. Cutpoints for positivity were defined by ROC analyses. Conditional logistic regression models were used to estimate risk ratios and 95% confidence intervals (RR; [95% CI]) in each cohort separately and combined using meta-analysis random effects models for 13 of the ACPAs. Multivariable-adjusted models included alcohol intake and pack-years smoking, collected by questionnaire before blood draw. We adjusted for multiple comparisons using Bonferroni adjustment. Spearman correlation was used to determine whether the number of positive ACPA reactivities was associated with the time between blood draw and diagnosis (4 mo- 14 yr) among cases only.

Results: Mean time ($\pm$SD) from blood draw to diagnosis among cases was 8.4 ($\pm$4.8) years in NHS and 5.0 years ($\pm$2.7) in NHS2. Mean age ($\pm$SD) at RA diagnosis was 64.1($\pm$8.0) and 49.2 ($\pm$5.1) years in NHS and NHSII. In NHS, 57.9% and, in NHSII, 53.0% of cases were seropositive at diagnosis. In multivariable-adjusted conditional logistic regression analyses, antibody reactivity against clusterin, enolase, 3 of the fibrinogen, both of the histone 2A epitopes and citrullinated vimentin were strongly associated with RA risk (Table). Cases with blood drawn closer in time to diagnosis had a higher number of positive ACPAs (NHS: ρ corr =0.35, p<0.0001, NHSII: ρ corr=0.25, p=0.07).

Table. Anti-Citrullinated Peptide Autoantibodies (ACPA) and Risk of Rheumatoid Arthritis in NHS and NHSII

ACPA Target	NHS (139 cases/ 416 controls) +cases/ +controls	NHS II (57 cases/ 167 controls) +cases/ +controls	Combined··· AdjustedOR* (95%CI)	p-value	p-hetμ
Clusterin 221–240 Cit Cyclic	7/3	4/2	8.02 (2.69, 23.89)	<0.001	0.93
Clusterin 231–250 Cit sm1 cyclic	11/2	8/2	17.69 (5.68, 55.09)	<0.0001	0.84
Clusterin 231–250 Cit	15/4	8/1	17.62 (5.95, 52.17)	<0.0001	0.45
Enolase	6/2	4/3	9.53 (2.84, 31.99)	<0.001	1.0
Fibrinogen cit	2/0	0/2	-	-	-
Fibrinogen A 41–60 cit3 cyclic	7/2	2/2	6.52 (1.90, 22.43)	0.003	0.35
Fibrinogen A 211–230 Cit smCyclic	5/8	1/5	1.57 (0.58, 4.27)	0.38	0.45
Fibrinogen A 556–575 Cit	6/2	1/1	7.43 (1.81, 30.43)	0.005	0.76
Fibrinogen A 556–575 Cit smCyclic	14/3	7/2	14.99 (5.42, 41.41)	<0.0001	0.82
Fibrinogen A 616–635 cit3	7/1	4/2	13.85 (2.98, 64.32)	<0.001	0.64
Fibrinogen A 616–635 Cit3 smCyclic	13/0	4/2	-	-	-
Histone 2A/a-2 1–20 Cit	12/9	7/5	5.56 (2.56, 12.10)	<0.0001	0.65
Histone 2A/a 1–20 Cit sm2 Cyclic	15/10	9/3	6.72 (2.62, 17.25)	<0.0001	0.23
Vimentin	67/212	26/85	0.90 (0.64, 1.27)	0.55	0.51
Vimentin Cit	7/2	4/1	14.07 (3.77, 52.53)	<0.0001	0.83
Vimentin 58–77 Cit3 Cyclic sm1	6/0	7/2	-	-	-

*adjusted for cumulative alcohol intake and pack-years smoking
···Combined using random-effects meta-analysis models
p for heterogeneity between the two cohorts
16 separate ACPAs tested, cutoff with Bonferroni adjustment = 0.003

Conclusion: We have demonstrated that several of a panel of ACPAs targeted to the rheumatoid synovium are strongly associated with risk of future RA. The number of ACPAs recognized is associated with time to diagnosis, which suggests that epitope spreading occurs within 4 years of diagnosis and thus temporally proximal to the time of diagnosis.

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1606

Identifying a Link Between Uranium Exposure and Systemic Lupus Erythematosus in a Community Living near a Uranium Plant. Pai-Yue Lu[1], Leah C. Kottyan[1], Susan M. Pinney[2], Judith A. James[3], Changchun Xie[2], Jeanette M. Buckholz[2] and John B. Harley[4]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]University of Cincinnati, Cincinnati, OH, [3]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [4]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH

Background/Purpose: Effects of environmental exposures on the development of systemic lupus erythematosus (SLE) are potentially important and relatively unexplored in SLE pathogenesis. An excess of reported SLE cases in a community surrounding a former uranium ore processing plant provided an opportunity to evaluate the relationship between uranium exposure through downstream air or water and SLE. Our specific *a priori* objective was to explore the hypothesis that SLE patients will be found more frequently in community members exposed to high prior uranium exposure levels in the Fernald Community Cohort (FCC).

Methods: A nested case control study was performed with data from the FCC. The FCC is comprised of voluntarily enrolled individuals who lived during plant operation within 5 miles of a uranium ore processing facility in Fernald, OH and followed from 1990 to 2008, which was after the plant ceased operations. No uranium plant workers are included in this study. Potential SLE cases were identified with searches for ICD9 codes associated with lupus (710.0 and 695.4) and a medication code search for hydroxychloroquine. Sera from potential cases were screened for autoantibodies using the Bioplex 2200 multiplex assay and anti-cardiolipin antibodies using ELISA. Cases were confirmed using an operational definition that included American College of Rheumatology classification criteria and medical record documentation. Four age-, race-, and sex-matched controls were selected for every case. Cumulative uranium exposure was calculated for each individual with a dosimetry model developed by the Centers for Disease Control and Prevention. Covariates in the analysis included smoking history, alcohol intake history, and family history of SLE. Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI). For comparison, preliminary analysis with rheumatoid arthritis (RA, ICD9 code 714.0) was also performed.

Results: The FCC includes 4,187 individuals with low uranium exposure, 1,273 with moderate exposure, and 2,756 with high exposure. SLE was confirmed in 20 of 26 cases with an ICD9 code of 710.0, in 2 of 5 cases with an ICD9 code of 695.4, and in 2 of 43 other cases prescribed hydroxychloroquine. The female to male ratio among cases was 5 to 1. Of the SLE cases, 5 were in the low exposure group, 7 in the moderate exposure group, and 12 in the high exposure group. Following logistic regression modeling, SLE was found to be associated with high exposure (OR 4.81, 95% CI 1.38–16.75, p = 0.043). There was no association between low or moderate uranium exposure and SLE. In the FCC overall, RA occurs at the expected prevalence, while SLE is increased by 5-fold over the expected prevalence.

Conclusion: High uranium exposure is associated with SLE relative to matched controls in this sample of uranium exposed individuals, suggesting that our hypothesis is correct. Potential explanations for this relationship include the estrogen effects of uranium, somatic mutation from ionizing radiation, or effects of some other unidentified accompanying exposure. Whatever the cause for this association, understanding the basis of this relationship is likely to provide important fundamental insight into SLE pathogenesis.

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1607

The Association Between Thyroxin Substitution and Rheumatoid Arthritis; Results From the Swedish EIRA Study. Camilla Bengtsson[1], Henrik Källberg[1], Leonid Padyukov[2] and Saedis Saevarsdottir[3]. [1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden

Background/Purpose: Hypothyroidism is usually of autoimmune nature, in areas with sufficient iodine, and leads to chronic substitution treatment with thyroxin. The disease shares some risk factors with ACPA-positive rheumatoid arthritis (RA), i.e. smoking and the PTPN22 risk allele, while different alleles of the HLA-DRB1 locus are associated with these diseases (RA: *01, *04 and *10 (shared epitope, SE); hypothyroidism: *03)[1,2] We asked whether thyroxin substitution was associated with RA overall, the ACPA-positive or ACPA-negative subset, and whether an interaction with SE alleles was present.

Methods: Data from the Swedish population-based EIRA (Epidemiological Investigation of Rheumatoid Arthritis) case-control study was analysed. In total, 1947 incident cases and 2246 randomly selected controls (matched on age, sex, residency), aged 18–70 years, participated in the study. Those who started treatment with thyroxin before the year of onset were compared those without treatment. Participants who reported a history of thyroid cancer (1 case and 1 control) were excluded from the analyses. We calculated odds

ratios (OR) with 95% confidence intervals (CI) for RA overall and the ACPA-positive and ACPA-negative subsets, by means of unconditional logistic regression models. Adjustments for smoking and PTPN22 only marginally changed the results and were not retained in the final analyses. Interaction was evaluated by calculating the attributable proportion (AP) due to interaction and its 95% confidence interval (CI).

Results: The risk of RA among those with thyroxin substitution was doubled, compared with those without thyroxin substitution (OR=2.0, 95% CI 1.5–2.7). When divided by ACPA status, there were no major differences between these two subsets (ACPA-positive: OR=1.9, 95%CI 1.4–2.7); ACPA-negative: OR=2.2, 95%CI 1.5–3.1). The OR of ACPA-positive RA for the combination of thyroxin substitution and no SE was 1.4 (95% CI 0.7–3.0), compared with neither of these factors. The OR for the combination of no thyroxin substitution and SE was 5.7 (95% CI 4.6–6.9) and for the combination of thyroxin substitution and SE the OR was 12.0 (95% CI 7.1–20.4). Thus a strong interaction between SE and thyroxin substitution was observed (AP=0.5, 95% CI 0.2–0.8).

Conclusion: Thyroxin substitution, reflecting an underlying hypothyroidism, was associated with the risk of developing ACPA-positive and ACPA-negative RA later in life. Thyroxin substitution also interacted with the shared epitope in the development of ACPA-positive RA, indicating that in patients with hypothyroidism, the presence of the shared epitope alleles, provides an even higher risk of ACPA-positive RA. Our data suggest overlapping pathways in the development of two common autoimmune diseases.

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1608

Overweight and Obesity Increase Risk of Rheumatoid Arthritis in Women in a Large Prospective Study. Bing Lu[1], Chia-Yen Chen[2], Linda T. Hiraki[3], Karen H. Costenbader[1] and Elizabeth W. Karlson[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA

Background/Purpose: Several case-control studies have suggested that overweight and obesity may increase the risk of rheumatoid arthritis (RA), but the evidence is conflicting. We examined the relationship between pre-existing overweight or obesity in development of future RA in two large prospective cohorts, the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Methods: The NHS is a prospective cohort study established in 1976 that enrolled 121,700 US female registered nurses, ages 30–55 years. NHSII began in 1989, enrolling 116,608 female nurses aged 25–42 years. Lifestyle and environmental exposures and anthropometric measures have been collected through biennial questionnaires. The incident RA cases were identified using the previously validated connective tissue disease screening questionnaire followed by a medical record review, according to the 1987 ACR criteria. Body Mass Index (BMI) was calculated as weight /height ^{2} (kg/m^2). Overweight and obesity were defined as 25.0'BMI<30 kg/m^2 and BMI≥30.0 kg/m^2 respectively based on World Health Organization classification. We assessed the exposure variable using a time-varying status of overweight and obesity since baseline updated every two years up to 2006/2007. Cox proportional hazards models were used to estimate hazard ratios (HR) of RA, seropositive RA, and seronegative RA phenotypes after adjusting for potential confounders.

Results: During 2,769,593 person-years of follow-up from 1976 to 2008 in NHS and 2,139,702 person-years of follow-up from 1989 to 2009 in NHSII, 1292 incident cases of RA developed (903 in NHS, 389 in NHSII). The age-adjusted incidence rates of RA ranged from 30 to 36 /100,000 person-years in NHS, and 12 to 26 /100,000 person-years in NHSII across increasing levels of BMI. Overweight and obese women have increased risk of RA compared with women with BMI<25 (Table). The multivariate hazard ratios of RA in NHS were 1.19 (95% CI, 1.03–1.38) for overweight and 1.18 (95% CI, 0.98–1.42) for obesity respectively (p trend = 0.029). Consistent with the NHS, the HRs in NHSII were 1.78 (95% CI, 1.40–2.26) for overweight, and 1.73 (95% CI, 1.34–2.23) for obesity (p trend <0.001). Further stratified analyses in NHS demonstrated that the effect of overweight and obesity on RA risk was stronger in seronegative RA than in seropositive RA. The multivariate HRs of seronegative RA were 1.30 (95% CI,

1.03–1.63) for overweight and 1.34 (95% CI, 1.01–1.77) for obese, while the HRs of seropositive RA were 1.12 (95% CI, 0.92–1.36) for overweight and 1.08 (95% CI, 0.84–1.38).

Table. Hazard ratio for incident RA according to Body Mass Index (BMI) in NHS and NHSII

BMI, kg/m^2	NHS			NHSII		
	No. Cases	Person-years	Multivariable HR (95% CI)*	No. Cases	Person-years	Multivariable HR (95% CI)*
<25.0	448	1,515,002	1.00 (Referent)	151	1,243,050	1.00 (Referent)
25.0–29.9	294	802,751	1.19 (1.03,1.38)	129	502,787	1.78 (1.40,2.26)
≥30.0	161	451,840	1.18 (0.98,1.42)	109	412,141	1.73 (1.34,2.23)
p trend			0.029			<0.001

* Adjusted for age, smoking (pack-years), alcohol use, parity/breastfeeding, oral contraceptive use, menopausal status, post-menopausal hormone use.

Conclusion: In this long-term prospective cohort study of women, we found overweight and obesity were significantly associated with increased risk of developing future RA compared to women with BMI <25kg/m^2. Future studies are needed to confirm our findings in other populations.

1609

Circulating 25-Hydroxyvitamin D Level and Risk of Developing Rheumatoid Arthritis. Linda T. Hiraki[1], Jing Cui[2], Susan Malspeis[3], Karen H. Costenbader[4] and Elizabeth W. Karlson[4]. [1]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Womens Hospital, Boston, MA, [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Vitamin D has demonstrated immunomodulatory properties with potential etiologic implications for autoimmune diseases including rheumatoid arthritis (RA). However, a causal association between decreased vitamin D levels and increased RA risk has yet to be definitively demonstrated. Cross-sectional studies are not able to rule-out reverse causation. We examined the relationship between circulating 25-hydroxyvitamin D (25(OH)D) and incident RA in 2 nested case-control studies, in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts.

Methods: We conducted a nested case-control investigation of incident RA in prospective cohorts the NHS and NHSII. We included 170 cases with blood samples collected from at least 3 months to 14 years prior to RA diagnosis, each matched to 3 controls on age, menopausal status, postmenopausal hormone use, date, time and fasting status of blood draw. 25(OH)D levels measured by chemiluminescence immunoassay. We used conditional logistic regression to calculate the odds ratio (OR) and 95% confidence intervals for incident RA for continuous 25(OH)D, dichotomous levels categorized as insufficient(<=20ng/mL) vs. sufficient 25(OH)D and quartile cutoffs of 25(OH)D, using age-adjusted and multivariable adjusted models. We repeated the analyses stratified by categories of time between the blood draw and RA diagnosis (3 months to < 4 years, 4 years to < 8 years and >8 years). Random effects models were used to meta-analyze estimates of association from the two cohorts.

Results: Incident RA was confirmed in 123 NHS and 47 NHSII participants. Mean age at RA diagnosis was 64.3 ± 7.9 years for NHS and 49.4 ± 5.2 years for NHSII, 60% were rheumatoid factor positive. Mean time from blood draw to RA diagnosis was 8.3 ± 4.8 years for NHS and 5.0 ± 2.7 years for NHSII. Meta-analysis of crude and multivariable-adjusted conditional logistic models did not show significant associations between circulating 25(OH)D levels (continuously, dichotomously or in quartiles) and odds of RA. However, there was a 25% increased odds of developing RA with every 1ng/ml decrease in circulating 25(OH)D [OR 1.25 (95% CI 1.01, 1.54)] among those NHSII women who had blood analyzed between 3 months and <4 years prior to RA diagnosis (Table). There was no association between 25(OD)D levels and RA in longer time intervals to diagnosis.

Table. Odds ratios and 95% confidence intervals for rheumatoid arthritis associated with a 1ng/mL decrease in 25-hydroxyvitamin D

	NHS				NHSII				Pooled results		
	N cases	N controls	OR (95% CI)	p-value	N cases	N controls	OR (95% CI)	p-value	OR (95% CI)	p-value	p-heterogeneity
Total	123	368	0.99 (0.96,1.02)	0.51	47	138	1.02 (0.97,1.07)	0.42	1.00 (0.97,1.02)	0.9	0.3
Sero+ve	63	186	1.00 (0.95,1.04)	0.83	27	79	1.03 (0.95,1.12)	0.51	1.00 (0.97,1.04)	0.91	0.5
3mo-<4y	30	93	1.06 (0.97,1.03)	0.21	24	69	1.25 (1.01,1.54)	0.04	1.12 (0.96,1.03)	0.16	0.15

Conclusion: We did not find a significant overall association between circulating 25(OH)D levels and odds of developing RA among women in NHS and NHSII. However, we did detect an increased odds of RA associated with low 25(OH)D among women in the NHSII cohort only, with levels measured closest to RA diagnosis (>3months to <4 years). These results suggest that vitamin D levels fall in the time windows closest to RA diagnosis and may represent reverse causation.

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ACR Concurrent Abstract Session
Genetics and Genomics of Rheumatic Diseases
Monday, November 12, 2012, 2:30 PM–4:00 PM

1610

The DNA Methylation Signature in Fibroblast-Like Synoviocytes (FLS) Defines Critical Pathogenic Pathways in Rheumatoid Arthritis (RA).
David L. Boyle[1], Robert Shoemaker[2], David W. Anderson[2], Wei Wang[3] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]NexDx, Inc., San Diego, CA, [3]UCSD, La Jolla, CA

Background/Purpose: A DNA methylation signature has been characterized that distinguishes RA FLS from osteoarthritis (OA) and normal (NL) FLS. The presence of epigenetic changes in these cells suggest that rheumatoid FLS imprinting might contribute to pathogenic behaviour. Differentially methylated loci (DML) RA FLS are located in the promoters of numerous genes implicated in RA, including validated therapeutic targets like *TNF, CXCL10,* and *IL-1Ra*. To understand how methylated genes might participate in the pathogenesis of RA, we evaluated how DML in RA FLS cluster in the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

Methods: Genomic DNA was isolated from fifth passage RA (n=11), OA (n=11) and normal (NL) (n=6) FLS lines obtained at the time of joint replacement (OA, RA) or from the tissue bank (NL). Methylation was evaluated using the Illumina HumanMethylation450 chip. A Welch's t-test identified RA vs. OA and RA vs. NL DML using a false discovery rate, q-value, cut off of 0.05. Genes containing DML within their promoter regions ([-2.5 kb, 500 bp] of TSS) were labeled as differentially methylated genes (DMG). The significance of DMG in KEGG human pathways was determined and resulting p-values represented the fraction of randomly selected background gene sets that were at least as enriched in genes found in the tested pathway as the DMG set. A q-value threshold of 0.01 determined significance.

Results: 2109 DMGs in RA FLS were identified for KEGG analysis. 20 out of 252 KEGG pathways were significantly altered with q <0.01 for RA compared with OA or NL FLS. The greatest differences were in the Focal Adhesion pathway (q<10e-4), with 34 DMG, including key matrix genes (*COL1A2*), signaling genes (*MAPK10, PIK3CG* and *AKT2*), and integrins (*ITGA4, ITGA7, ITGA10*). The Cell Adhesion pathway (26 DMG; q<10e-4) was also differentially methylated, suggesting that RA FLS imprinted abnormalities could affect adhesion and migration. Additional critical pro-inflammatory pathways implicated in RA were also differentially methylated, including Toll-like Receptors and Complement Cascade. The former encompassed 17 DMG, including differential methylation *of TLR1, TLR4,* and *TLR5* as well as *RIPK1* and MAP kinases (q<10e-3). The latter included *C1QB, C3, C3AR1, C4A, C4A, C4B, C4B, C4BPA,* and *C8A*(18 DMG; q=10e-4). Perhaps most intriguing, the pre-defined KEGG "Rheumatoid Arthritis" pathway was significantly different in RA FLS compared to the controls (20 DMG; q<10e-4), while the "Systemic Lupus Erythematosus" pathway was not differentially methylated.

Conclusion: KEGG pathway analysis demonstrates non-random imprinting of RA FLS. The patterns include anomalies in key cell adhesion genes (integrins, focal adhesion) and inflammation genes (signalling and innate immunity). These persistent epigenetic alterations could contribute to the aggressive phenotype of RA synoviocytes and identify potential therapeutic targets that could modulate the pathogenic behaviour.

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1611

Targeted Deep Re-Sequencing Implicates Rare and Low Frequency Coding Variants in *IL23R, MEFV, TLR4,* and *NOD2* in Behçet's Disease Yohei Kirino[1], Qing Zhou[1], Yoshiaki Ishigatsubo[2], Nobuhisa Mizuki[2], Ilknur Tugal-Tutkun[3], Emire Seyahi[4], Yilmaz Ozyazgan[4], F. Sevgi Sacli[4], Burak Erer[5], Zeliha Emrence[6], Atilla Cakar[7], Duran Ustek[7], Akira Meguro[2], Atsuhisa Ueda[2], Mitsuhiro Takeno[2], Michael J. Ombrello[1], Colleen Satorius[1], Baishali Maskeri[8], Jim Mullikin[8], Hong-Wei Sun[9], Gustavo Gutierrez-Cruz[9], Yoonhee Kim[10], Ahmet Gül[11], Daniel L. Kastner[1] and Elaine F. Remmers[1]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [3]Istanbul, Turkey, [4]Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey, [5]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [6]Institute for Experimental Medicine, Istanbul University, Istanbul, Turkey, [7]Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey, [8]National Human Genome Research Institute, National Institutes of Health, Rockville, MD, [9]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [10]National Human Genome Research Institute, National Institutes of Health, Baltimore, MD, [11]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Background/Purpose: Genome-wide association studies (GWAS) have successfully identified common variants that contribute to Behçet's disease (BD) susceptibility. However, associations due to rare and low-frequency variants have not been evaluated. It has long been debated whether the innate immune system is involved in the pathogenesis of BD. Clinical manifestations such as episodic inflammation and neutrophil recruitment to the sites of inflammation strongly suggest that the innate immune response plays an important role, although genetic evidence to support this hypothesis is sparse. Recent advances in sequencing technology allow investigators to re-sequence targeted genes to discover novel variants in large collections of cases with complex genetic traits and genetically matched controls.

Methods: We performed deep re-sequencing of two GWAS-identified genes (IL23R and IL10) and eleven genes known to have roles in innate immunity (IL1B, IL1R1, IL1RN, NLRP3, MEFV, TNFRSF1A, PSTPIP1, CASP1, PYCARD, NOD2, and TLR4) in 382 cases and 384 controls in Japanese population and 384 cases and 384 controls in Turkish population. Non-synonymous variants identified by deep exonic re-sequencing were validated by individual genotyping of 4955 samples. For statistical analyses, we performed C-alpha test, adaptive sum test and step-up methods to identify the roles of rare and low-frequency variants associated with BD.

Results: We found a non-random distribution of rare and low-frequency variants in cases and controls implicating IL23R, MEFV, TLR4, and NOD2 in BD susceptibility. Adaptive sum test and step-up methods corroborated the results for IL23R in both populations and for TLR4 in the Turkish population. Carriage of MEFV-M694V, known to cause recessively inherited familial Mediterranean fever, conferred BD risk in Turkish samples (Cochran-Mantel-Haenszel meta analysis p=1.79×10^{-12}).

Conclusion: These findings implicate innate immune and bacterial sensing mechanisms in BD pathogenesis. We are currently extending our re-sequencing efforts to CCR1, KLRK1, KLRC1–4, STAT4, and ERAP1, common variants of which we recently identified by GWAS.

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1612

Ankylosing Spondylitis Is Associated with Single Nucleotide Polymorphisms in Loci Implicating Four Aminopeptidases. Philip Robinson[1], Adrian Cortes[1], Paul Leo[1], Australian-Anglo-American Spondylitis Consortium (TASC)[2], Wellcome Trust Case Control Consortium (WTCCC).[3], International Genetics of Ankylosing Spondylosis Consortium (IGAS)[4], David Evans[5] and Matthew A. Brown[1]. [1]University of Queensland Diamantina Insititute, Brisbane, Australia, [2]Brisbane, Australia, [3]Wellcome Trust Case Control Consortium, Wellcome Trust Case Control Consortium, United Kingdom, [4]IGAS, Igas, Australia, [5]Bristol University, Bristol, United Kingdom

Background/Purpose: The aim of the study was to examine regions implicated in autoimmune diseases for association with AS. A previous association with AS has been described in the aminopetidase *ERAP1*.

Methods: 9074 European and 1550 east Asian AS cases (defined by the modified New York Criteria), and 13607 European and 1567 Asian controls were studied. Samples were genotyped on the Illumina Infinium Immunochip (196,524 SNVs), clustering performed using Opticall, and analysis performed using linear mixed modelling (FaST-LMM) to control for population stratification.

Results: 9074 European and 1550 east Asian AS cases (defined by the modified New York Criteria), and 13607 European and 1567 Asian controls were studied. Samples were genotyped on the Illumina Infinium Immunochip (196,524 SNVs), clustering performed using Opticall, and analysis performed using linear mixed modelling (FaST-LMM) to control for population stratification.

Results: After QC and removal of non-polymorphic variants, 129,030 SNPs remained. The two previously described independent associations in *ERAP1* were replicated in the European cohort (rs30187, OR=0.77, p=1.3×10^{-41}; rs10050860, OR=0.77, p=3.2×10^{-32}), and suggestive association was noted with rs30187 in the Asian cohort (OR=0.81, p=2.1×10^{-5}). rs10050860 was found to have low MAF (0.037) in the Asian cohort and therefore for this SNP in this ethnic group, the study had low power. In the European cohort, controlling for the association with *ERAP1*, SNPs in *ERAP2* and *LNPEP* were also associated with AS (lead SNP: rs2910686, OR=1.17, p=1.3×10^{-16}). We have previously demonstrated that at ERAP1, disease-protective variants are associated with reduced aminopeptidase function. At ERAP2, the AS-protective G allele of rs2248374 causes a complete loss of ERAP2 mRNA and no expression of ERAP2 protein. In HLA-B27 negative AS cases association was observed with the *ERAP2* SNP also associated with Crohn's disease (rs2549794, OR=1.2, p=8×10^{-6}). Genomewide significant association was noted at chromosome 17q21 at a locus encoding the aminopeptidase NPEPPS (rs9901869, p=3.2 $\times10^{-14}$; OR = 0.88), a further aminopeptidase involved in peptide trimming prior to HLA Class I presentation.

Conclusion: This study identifies robust association with three loci housing four aminopeptidases, *ERAP1*, *ERAP2*, *LNPEP* and *NPEPPS*. At ERAP1 and ERAP2, protective genetic associations are associated with reduced aminopeptidase function. This implicates peptide handling as a major mechanism in the aetiology of both HLA-B27 positive and negative AS.

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The SLE-Associated *TLR7* Variant Confers Differential Gene Expression Modulated by Microrna-3148.

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Background/Purpose: We established an X-linked *TLR7* 3′UTR SNP (rs3853839) as a risk locus for SLE in 9,274 Eastern Asians ($P_{combined}$ = 6.5×10^{-10}). Risk-allele carriers have increased *TLR7* transcripts and more pronounced IFN signature than non risk-allele carriers. The current study sought replication of SLE-associated SNP(s) in non-Asian ancestries and explored the molecular mechanism underlying the identified genetic variant that affects TLR7 expression.

Methods: We conducted genotyping and imputation for 67–115 SNPs (varying among different ancestral backgrounds) covering ~80kb of *TLR7-TLR8* region in European Americans (EA), African Americans (AA) and Hispanics enriched for the Amerindian-European admixture (HS). Each SNP was assessed for the association with SLE. Haplotype-based conditional testing was conducted to distinguish independent signals from associated SNPs and Mantel-Haenszel testing was used in the trans-ancestral meta-analysis. Association of genotype and TLR7 expression was examined using the RT-PCR, flow cytometry and reporter assays. Pyrosequencing was used to measure allelic variations in *TLR7* transcript level.

Results: Our trans-ancestral fine-mapping confirmed the *TLR7* 3′UTR SNP rs3853839 as the only variant in *TLR7-TLR8* region exhibiting consistent and independent association with SLE (P_{meta} = 1.7×10^{-10}, OR [95%CI] =1.24 [1.18–1.34]) in 13,339 subjects of EA (3,936 cases vs. 3,491 controls), AA (1,679 vs. 1,934) and HS (1,492 vs. 807) ancestries. The risk G allele conferred elevated TLR7 expression in PBMCs from healthy individuals at both mRNA (P = 0.01 in men and 0.02 in women) and protein level (P = 0.009 in men and 0.038 in women). PBMCs from heterozygous women exhibited higher G/C allele ratios in *TLR7* transcripts 4 hours after incubation with actinomycin D (inhibitor of transcription initiation) than with vehicle control (P = 0.04), indicating a slower degradation of the G allele-containing transcripts. The non-risk allele, but not risk-allele, was predicted to match microRNA-3148 (miR-3148) at the second base in the binding site. Transcript levels of miR-3148 and TLR7 in PBMCs from 16 SLE patients and 21 normal controls were inversely correlated (R^2 = 0.255, P = 0.001), suggesting modulation of TLR7 expression by miR-3148. Overexpression of miR-3148 via transient transfection into HEK 293 cells led to more than 2-fold reduction in luciferase activity driven by the *TLR7* 3′UTR segment containing the non-risk allele compared to that containing the risk allele (P = 0.002).

Conclusion: We identified and confirmed a genome-wide significant association between the *TLR7* 3′UTR SNP and SLE susceptibility in 22,613 subjects of Eastern Asian, European American, African American and Hispanic ancestries (P_{meta} = 6.4×10^{-19}, OR [95%CI] =1.26 [1.20–1.32]). Reduced modulation by miRNA-3148 conferred a slower degradation of the risk allele containing *TLR7* transcripts, resulting in elevated levels of gene products and more robust type I IFN signature.

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Analysis of the Immunochip in a Large Cohort of Juvenile Idiopathic Arthritis Cases Identifies 17 Loci At Genome-Wide Significance.

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Background/Purpose: Genome-wide (GW) association studies have been hugely successful in the identification of susceptibility loci for autoimmune diseases, interestingly many of the loci are shared across these diseases. The regions identified now require more detailed fine-mapping to localize the association signal and identify putative functional variants. The Immunochip consortium was established to pool ~180 loci from 12 diseases to include on a custom

genotyping chip. Juvenile idiopathic arthritis (JIA) is the most common arthritic disease of childhood. Candidate gene studies have identified a number of common autoimmune genes that confer susceptibility to JIA. However, JIA has been less well studied using large-scale approaches. This study aimed to perform genotyping on the Immunochip to allow fine-mapping of previously associated regions and to identifying novel loci for JIA.

Methods: Genotyping was performed using the Immunochip in a large cohort from the UK, US and Germany comprising a total of 2816 JIA oligoarthritis and RF- polyarthritis cases and 13056 controls. Standard SNP and sample QC was performed, including removing samples with call rate <98%, outliers of mean heterozygosity and ancestral outliers. Each SNP was assessed for departure from an additive genetic model, and analyzed under the most appropriate model (either additive, dominant or recessive) using SNPGWA vers4.0 and adjusting for the top 5 principal components. Within regions reaching the GW significance threshold ($P<5\times10^{-8}$), conditional logistic regression was used to test for independent effects.

Results: This analysis has confirmed loci previously associated with JIA at $P<5\times10^{-8}$ (*HLA, PTPN22, PTPN2*), has strengthened the association of other previously investigated regions (*STAT4, IL2/IL21, IL2RA, SH2B3*) and has identified novel regions (*ANKRD55, TYK2, IRF1, UBE2L3, LNPEP, IL2RB, RUNX1, IL6R, ZFP36L1/RAD51B, FAS*) such that all 17 now reach GW significance. The *STAT4, PTPN2, IL2RA* regions show evidence for multiple independent effects, some of which are low-frequency variants. A further 9 novel loci have been identified at a suggestive level of significance ($P<1\times10^{-6}$). Some showed weak evidence previously (*COG6, CCR5*) and others have not been associated with JIA to date (*RUNX3, LTBR, PRM1*). The dense-mapping of some loci on the Immunochip along with bioinformatic analysis has refined the association to a single gene for 7 regions.

Conclusion: The Immunochip project enables cost-effective fine-mapping of autoimmune loci in diseases such as JIA. This analysis has confirmed and strengthened the association of previously associated genes as well as identified novel susceptibility loci for JIA. It highlights several crucial pathways, such as the IL2 pathway in JIA disease pathogenesis. Analysis of the Immunochip in this dataset, the largest cohort of JIA cases investigated to date, has greatly increased our knowledge of the genetic basis of susceptibility for JIA.

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Evidence for Distinct Roles of Environmental and Genetic Factors in the Emergence of Anti Citrullinated-Protein Antibodies Positive Rheumatoid Arthritis-an Epidemiological Investigation in Twins. Aase Haj Hensvold[1], Patrik KE Magnusson[2], Monika Hansson[1], Lena Israelsson[3], Cecilia Carlens[1], Johan Askling[4], Vivianne Malmström[1], Lars Klareskog[3] and Anca Irinel Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Swedish Twin Registry Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institute, Stockholm, Sweden, [4]Rheumatology Unit & Clinical Epidemiology Unit, Stockholm, Sweden

Background/Purpose: The aim of the current study was to investigate the influence of genetic and environmental factors in developing anti citrullianted-proteins antibodies (ACPA) and ACPA positive rheumatoid arthritis (RA), using a twin study approach.

Methods: We used a subset of the Swedish population based twin registry, which includes 12 590 monozygotic (MZ) and dizygotic (DZ) twins born 1958 or earlier, who had donated blood and provided information about smoking. RA was verified by data from national public care registers (1964–2009). All sera were analyzed for ACPA occurrence using a CCP2 ELISA with a cut off set to 25 U/ml. High titer of ACPA was defined as titers >75 U/ml. Twin concordance for ACPA occurrence was estimated by casewise concordance, tetrachoric correlation and odds ratios (OR). Odd ratios (OR) to develop ACPA and high titers of ACPA were calculated according to self-reported smoking status, cumulative dose of smoking and presence of any HLA_DRB1 shared epitope according to GWAS analysis. Twins were defined as smokers if they were or had been smoking regularly or occasionally. Cumulative dose of smoking was estimated by pack years.

Results: 350 out of 12590 tested individuals (2.8%) were positive for ACPA with 202 out of 12590 tested individuals (1.6%) having high titers of ACPA (>75 U/ml). 192 out of 12590 tested individuals were identified as having RA in the Swedish patient register during 1964–2009. The median age of the RA patients was 70 (range 53–94) and 73% were females. Monozygotic twins had an OR of 3.1 (95% CI 0.9–10) for developing ACPA, 7.9 (95% CI 1.7–37) for developing high titers of ACPA and 11.6 (95% CI 1.27–98.6) for developing ACPA+ RA if they had a co-twin with corresponding phenotype. Dizygotic twins had lower OR for developing ACPA (OR 1.8, 95% CI 0.5–5.8), high titers of ACPA (OR 3.6, 95% CI 0.8–16) and ACPA+ RA (OR 4.0, 95% CI 0.5–31.1) if they had a co-twin with corresponding phenotype. Smokers had an increased risk of developing ACPA (OR 1.33, 95% CI 1.08–1.63), high titer of ACPA (OR 1.63, 95% CI 1.22–2.18) and high titer ACPA+ without RA (OR 1.99, 95% CI 1.27–3.12) but not significantly increased OR for ACPA+ RA (OR 1.42, 95% CI 0.98–2.06). An increased cumulative dose of smoking was associated with ACPA, with the highest risk of developing ACPA among those smoking more than 10 pack years (OR 1.49, 95% 1.18–1.88). Presence of shared epitope conferred an increased risk of developing ACPA (OR 1.98, 95% 1.53–2.56), high titer ACPA (OR 3.12, 95% 2.15–4.54) and especially high titer ACPA+ RA (OR 7.09, 95% 3.69–13.65) with no significantly increased OR to develop high titer ACPA+ without RA (OR 1.17, 95% 0.81–1.69).

Conclusion: Results from this large population-based cohort of middle-aged twins and measurements of ACPA at one time point indicate that environment, life style and stochastic factors (such as smoking) may be more important than genetics in determining which individuals that develop ACPA, whereas genetic factors (and in particular shared epitope) may have a larger impact in determining which persisting ACPA-positive individuals that will ultimately develop arthritis.

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ACR Concurrent Abstract Session
Imaging of Rheumatic Diseases II: Magnetic Resonance Imaging
Monday, November 12, 2012, 2:30 PM–4:00 PM

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Comparison of Conventional and Wholebody Magnetic Resonance Imaging for Assessing Inflammation and Structural Damage in Psoriatic Arthritis and Axial Spondyloarthritis. René Panduro Poggenborg[1], Susanne Juhl Pedersen[2], Iris Eshed[3], Inge Juul Sørensen[2], Ole Rintek Madsen[4], J.M. Møller[5] and Mikkel Østergaard[6]. [1]Copenhagen University Hospital in Glostrup, Copenhagen, Denmark, [2]Glostrup Hospital, Copenhagen, Denmark, [3]Sheba Medical Center, Tel Hashomer, Israel, [4]Copenhagen University Hospital in Gentofte, Copenhagen, Denmark, [5]Copenhagen University Hospital in Herlev, Copenhagen, Denmark, [6]Copenhagen University Hospital Glostrup, Glostrup, Denmark

Background/Purpose: Wholebody magnetic resonance imaging (WBMRI) is a new imaging modality where patients are scanned from "head to toe" in one single scan, but with a lower resolution than conventional MRI (cMRI). The purpose was to investigate the ability of WBMRI for detection of inflammation and structural damage in psoriatic arthritis (PsA) and spondyloarthritis (SpA), and to compare findings with dedicated cMRI.

Methods: Patients with clinically active peripheral PsA (Moll and Wright, n=19) or axial SpA (ESSG, n=19) and healthy subjects (HS, n=12) were included. WBMRI was assessed for synovitis, bone marrow oedema (BME), and bone erosions at sites included in the 78-tender joint count (TJC). Furthermore, WBMRI fat infiltration, BME and bone erosions were evaluated in 23 discovertebral units (DVUs) and in sacroiliac joints (SIJ) (8 quadrants). Wholebody imaging were performed on a 3 tesla MRI unit with built-in bodycoil (sagittal and coronal T_1-weighted pre/post-contrast and STIR sequences), and 1½ tesla cMRI (SpA and HS: of spine and SIJ; PsA and HS: unilateral hand) were performed using T_1w pre/post-contrast and STIR sequences. The PsAMRIS-hand method (1) was used for scoring synovitis in finger joints in PsA and HS.

Results: Characteristics median (range): PsA/SpA/HS age 49 (23–79)/42 (26–61)/32 (20–61) yrs. PsA/SpA disease duration: 4(0–34)/17(5–48) yrs; 78-TJC: 11 (3–65)/3 (0–17), 76-swollen joint count: 5 (0–20)/1 (0–5), and BASDAI score 45(9–85)/55(2–93) mm.

By WBMRI more than 97% of spinal DVUs and SIJ quadrants could be evaluated, whereas evaluation of peripheral joints for synovitis and BME was possible in 66 % and 55 % of joints, respectively. It was possible to evaluate 56% of the finger joints with WBMRI. BME assessed in 78 joints by WBMRI was significantly more frequent in PsA/SpA than in HS ($p < 0.05$, see table). We found no statistically significant difference between groups in WBMRI synovitis assessed in all 78 joints, or only assessed in hand joints. In contrast, PsAMRIS-hand synovitis (scored 0–36) assessed by cMRI was higher in PsA than HS ($P < 0.0005$).

The table shows median (range) scores of WBMRI and cMRI findings in joints, DVUs, and SIJ quadrants.

	PsA		SpA		HS	
	WBMRI	cMRI	WBMRI	cMRI	WBMRI	cMRI
78-joint: Synovitis (0–78)	12 (1–45)	-	10 (0–28)	-	10 (2–40)	-
78-joint: BME (0–78)	4 (0–25)*	-	2 (0–15)*	-	2 (0–5)	-
Spine: BME (0–23)	2 (0–6)*	-	1 (0–11)	1 (0–8)	0.5 (0–2)	0 (0–3)
Spine: Fat infiltration (0–23)	0 (0–7)	-	1 (0–18)	2 (0–20)*	0 (0–6)	0 (0–3)
Spine: Bone erosion (0–23)	0 (0–1)	-	0 (0–0)	0 (0–2)*	0 (0–1)	0 (0–1)
SIJ: BME (0–8)	0 (0–2)	-	0 (0–8)*	0 (0–8)*	0 (0–2)	0 (0–2)
SIJ: Fat infiltration (0–8)	0 (0–8)	-	0 (0–8)*	2 (0–8)*	0 (0–4)	0 (0–4)
SIJ: Bone erosion (0–8)	0 (0–6)	-	0 (0–8)	2 (0–8)*	0 (0–8)	0 (0–4)

Mann-Whitney test was used for comparing PsA/SpA with HS. *P<0.05.

Significant correlation was found between WBMRI and cMRI in spinal/SIJ fat infiltration (Spearman's rho: 0.52/0.52, both P<0.005), SIJ BME (0.78, P<0.0001), and SIJ bone erosion (0.72, P<0.0001). In PsA, the sensitivity, specificity and accuracy of WBMRI synovitis in the hand were 35%, 80% and 66%, when cMRI was considered the gold standard reference.

Conclusion: WBMRI showed higher scores of peripheral and axial BME in PsA and SpA, compared to HS. Highly significant correlation was found between WBMRI and conventional MRI assessments of axial BME, fat infiltration and bone erosions. WBMRI has potential value for assessing axial and peripheral disease manifestations in PsA and SpA.

Ref
1) Østergaard, JRheum 2009

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Whole-Body Magnetic Resonance Imaging of Disease Manifestations in Axial and Peripheral Joints and Entheses in Rheumatoid Arthritis Patients.
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Background/Purpose: To investigate the ability of whole-body magnetic resonance imaging (WBMRI) to visualize synovitis, bone marrow edema and erosions in patients with rheumatoid arthritis (RA) and to examine the agreement between findings from WBMRI and clinical examination.

Methods: 3 Tesla WBMR images were acquired in a head-to-toe scan using an integrated quadrature body coil and 6 imaging stations in 20 patients with RA (14/6 women/men, aged median 54 [range 21–76] years, disease duration 6 [1–20] years) and at least 1 swollen or tender joint. Imaging time was 1 hour 25 min. STIR and pre- and post contrast T1-weighted images were evaluated for the presence/absence of disease manifestations in 76 joints, 30 entheses and in the spine by one experienced reader (IE). Each location was assessed as not imaged, imaged but not readable or readable. Clinical tender and swollen joint counts of 66 joints were performed.

Results: Signs of disease activity were more frequently found by MRI evaluation than by clinical evaluation, table 1.

Table 1. Proportions of joints with signs of synovitis, bone marrow edema, erosions and readable images, and clinical signs of joint involvement.

	Whole-body MRI Evaluation						Clinical Evaluation	
	Synovitis		Bone marrow edema		Erosions		Tender joints	Swollen joints
Joints evaluated	% with synovitis*	% Readable	% BME*	% Readable	% with erosions*	% Readable	% (N=18)	% (N=18)
Sternoclavicular	0	60	0	50	0	67.5	11	0
Acromioclavicular	50	85	35	85	0	87.5	ND	ND
Shoulder	61	90	33	90	10	97.5	33	6
Elbow	23	32.5	8	30	0	40	17	8
Wrist	67	82.5	45	82.5	19	80	36	19
1 CMC	92	60	65	50	16	92.5	19	0
1–5 MCP	28 (27–39)	84 (75–90)	12 (7–27)	79.5 (70–85)	3 (0–16)	89.5 (82.5–95)	25 (17–33)	25 (6–33)
1–5 PIP hands	15 (3–25)	77 (63–83)	7 (4–13)	71 (58–78)	3 (3–6)	83 (75–87.5)	31 (19–39)	11 (0–17)
2–5 DIP hands	0	63 (58–70)	0	56 (50–63)	0	72 (70–82.5)	13 (8–17)	0 (0–3)
Hip	25	100	10	100	0	100	17	NA
Knee	32	95	26	95	8	95	52	3
Ankles	50	100	7.5	100	5	100	52	22
MTP	35 (31–49)	95 (93–98)	31 (13–47)	92 (90–98)	18 (8–31)	99 (98–100)	36 (22–44)	11 (0–14)
PIP feet	10 (0–15)	79 (65–85)	9 (0–20)	60 (50–75)	0	94 (93–95)	2 (0–6) [0]	0 (0)
DIP feet	0 (0–3)	78 (68–78)	0	48 (48)	0	93 (93–95)	ND	ND

*Numbers given as % of the total number of readable joints, median (range). CMC: carpometacarpal joints; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints; DIP: distal interphalangeal joints; TMT: tarsometatarsal joints; NA: not applicable;ND: not done

Synovitis was most frequent in 1st carpometacarpal joints (CMC), wrist, the tarsometatarsal (TMT) and shoulder joints (92%, 67%, 63% and 61%, respectively). BME was most frequently present in CMC, wrist, shoulder and the acromio-clavicular joints (65%, 45%, 33% and 35%, respectively). Erosions were seen primarily in the wrist, MTP, CMC, shoulder and TMT joints (19%, 18%, 16%, 10% and 10%, respectively).

In the spine abnormal findings were less frequent. BME was seen in all cervical disco-vertebral units (DVUs) (7% of evaluated cervical DVUs), and in a few DVUs in the thoracic-lumbar spine (3% of evaluated thoracic- and lumbar DVUs). Fat infiltrations were found in the cervical and lumbar (but not thoracic) spine (3% of evaluated cervical and lumbar DVUs), and erosions were only seen in a single patient in the lumbar spine.

The most frequently involved entheses were those at greater trochanter, calcaneus, greater tuberosity of the humerus, medial condyle of the femur, and upper patella (60%, 26%, 26%, 16% and 13%, respectively, readability 75–100%). The entheses at costo-sternal joints 1 and 7, elbow, lower patella and tubers of the tibia were only readable in 40%, 10%, 25–35%, 5% and 0% of cases, respectively).

MRI findings (synovitis and BME) and clinical findings (tenderness and swelling) were not correlated, neither on the patient level (counts of involved joints) nor consistently on the level of individual joints.

Conclusion: Inflammation (synovitis and BME) in peripheral and axial joints and entheses could be identified by WBMRI, and was more frequent than detected clinically. 3T WB-MRI is a promising tool for evaluation of disease manifestations in RA patients. Optimization of positioning of the feet and hands and acquisition of images is needed.

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Prevalence of Inflammatory Sacroiliitis Assessed On MR Imaging of Inflammatory Bowel Disease: A Retrospective Study Performed On 186 Patients.
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Background/Purpose: Articular involvements are by far the most common extra-intestinal manifestations in inflammatory bowel disease (IBD). They include peripheral arthritis and inflammatory axial manifestation. Until now the prevalence of sacroiliitis in this same population was studied only on the structural plan. The main objective of this study was to estimate, for the first time, the prevalence of inflammatory sacroiliitis in IBD on digestive MRI defined according to ASAS (Assessment of SpondyloArthritis international Society) criteria. The secondary objective was to study the association between sacroiliitis and clinico-biological parameters in IBD.

Methods: This study was performed on 186 patients suffering from IBD followed in a gastroenterology department between 2004 and 2011: 131 with Crohn's disease (CD) (70.4%) and 55 with ulcerative colitis (UC) (29.6%). Clinico-biological and endoscopic data were collected and MR enterography or colonography was performed to assess IBD.

Two injected T1-weigthed sequences with fat saturation (FS) were used for the whole population: a coronal LAVA (liver acquisition with volume acceleration) sequence and an axial SPGR (spoiled gradient recalled) sequence. An additional injected axial LAVA sequence with FS was performed in 138 patients. On digestive MRI, sacroiliitis was scored blindly by two independent readers, a rheumatologist and a radiologist, according to ASAS criteria. The SIJ were graded bilateral, unilateral, normal and doubtful. In cases of discordance, the final diagnosis was obtained by consensus.

The association between sacroiliitis and the clinico-biological and radiological parameters of the digestive disease was analyzed by Fisher's exact test or the chi-square test (qualitative variables) and by Wilcoxon's test (quantitative variables) with a p value<0.05 as significant.

Results: The prevalence of inflammatory sacroiliitis was 16.7% (31 patients). SIJ were considered as normal in 144 cases (77.4%) and doubtful in 11 cases (5.9%). Female gender in CD (p=0.01) and advanced age in both diseases (p=0.03) were associated with sacroiliitis on MRI. Disease duration tended to be associated with sacroiliitis (p=0.06), while other parameters such as the type of IBD, localization and extension of IBD, surgical history, biological inflammation, digestive activity, and type of treatment were not associated with sacroiliitis on digestive MRI.

Conclusion: This study demonstrated for the first time the feasibility of using digestive MRI to establish the diagnosis of inflammatory sacroiliitis according to the ASAS criteria. Inflammatory sacroiliitis was evidenced by MRI in 1/6 patients suffering from IBD. This prevalence of sacroiliitis is probably underestimated due to technical and clinical factors (biologic treatment used). Added to clinico-biological data, MRI analysis should contribute to an earlier diagnosis of axial spondylarthritis in patients with IBD.

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Quantification of Bone Marrow Edema by Using Magnetic Resonance Imaging for the Assessment of Neck Pain Only Marginally Reflects Clinical Evaluation in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. Xenofon Baraliakos[1], Frank Heldmann[2], Ravi Suppiah[3], Fiona M. McQueen[4] and Jurgen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Ghana, [3]Department of Rheumatology, Nuffield Orthopaedic Centre, Oxford, United Kingdom, [4]University of Auckland, Auckland, New Zealand

Background/Purpose: Despite the differences in the pathogenesis of rheumatoid arthritis (RA) and ankylosing spondylitis (AS), neck pain is a frequent clinical symptom in both diseases that was recently shown to correlate with disease activity. In this study, we evaluated the correlation between subjective reports of neck pain and objective signs of inflammation by quantification of bone marrow edema (BME) as detected by MRI in patients with RA and AS.

Methods: MR images (STIR sequence) of the cervical spine together with clinical and laboratory data of 40 patients (34 RA, 6 AS) who had participated in the recently presented CASSANDRA trial were included. MRI were assessed by two readers who were blinded for clinical data using a recently published MRI scoring system, with quantification of the extension of BME in the atlantoaxial region, corpus, facet joints and processus spinosus of all cervical vertebrae, ranging from 0–57 points. In addition, presence or absence of degenerative changes was also recorded.

Results: Baseline characteristics, neck pain and MRI scores did not differ between RA and AS patients. The mean age was 57.5 ± 11.8 years, 33/40 patients (82.5%) were female, the mean symptom duration for neck pain was 10.6 ± 8.8 years, cervical rotation 51.0 ± 17.2 degrees, CRP 0.9 ± 1.3 mg/dl, ESR 19.8 ± 26.6 mm/1h, FFbH 58.1 ± 26.3 and the Northwick Park score was 46.0 ± 17.5. BME was detected in 24/40 patients (60%), 5 of which (20.8%) had atlantoaxial involvement, 18 had BME in the vertebral body (75%), 7 in the facet joints (29.2%) and 11 in the processus spinosus (45.8%). Degenerative changes were seen in 21/40 patients (52.5%). Of those 21 patients, all (100%) had also signs of BME in the corpus, while from the 19 patients without degenerative changes, only 3 patients (15.8%) had BME in the corpus. In the more detailed analysis of the total of 240 evaluated vertebral bodies, 27 (11.3%) vertebral bodies had degeneration and in parallel inflammation in the corpus, while 24 (10%) had only degeneration, 11 (4.6%) had only inflammation in the corpus, and 178 (74.2%) had neither lesion. There was no correlation between the amount or the extension of BME and clinical or laboratory parameters for neck pain or cervical spine mobility. However, a significant difference (p=0.038) was found for BME scores of patients with a pain intensity (0–10 NRS) of ≥ 5 (5.8 ± 6.5 scoring points) vs. < 5 (1.9 ± 25 scoring points). This was partly dependent on scores for the atlantoaxial region, although the mean number of scoring points did not differ. The correlation between readers was excellent (regression coefficient. 0.942).

Conclusion: This study shows that the majority of patients with RA and AS had objective signs of BME but also degenerative changes as assessed by MRI at different locations in the cervical spine. Assessment of the the presence of BME in the atlantoaxial region is important in clinical practice, in addition to degenerative changes, since its presence seems to influence the intensity of neck pain reported by these patients.

1620

Early Magnetic Resonance Imaging Measures Independently Predict 1- and 2-Year X-Ray Progression: Results From a Large Clinical Trial. Joshua Baker[1], Mikkel Østergaard[2], Paul Emery[3], Elizabeth C. Hsia[4], J. D. Lu[4], Daniel Baker[5] and Philip G. Conaghan[6]. [1]University of Pennsylvania, Philadelphia, PA, [2]Glostrup Hospital, Copenhagen, Denmark, [3]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [4]Janssen Research & Development, LLC/U of Penn, Spring House/Phila, PA, [5]Janssen Research and Development, LLC, Spring House, PA, [6]University of Leeds, Leeds, United Kingdom

Background/Purpose: Early predictors of progression in structural joint damage in RA are lacking. We evaluated if early MRI measures of inflammation and erosion at baseline, 12 and 24wks could predict subsequent progression in structural damage as measured by standard x-ray at 1 and 2 yrs of follow-up among 256 pts from GO-BEFORE, a large randomized trial of golimumab + MTX vs MTX alone in RA pts who were MTX-naïve.

Methods: Methods and results of the original trial have been published [1]. MRIs (contrast-enhanced; 1.5T) of the wrist and the 2nd-5th metacarpophalangeal joints of the dominant hand at baseline and wks 12, 24, 52, and 104 were obtained. MRIs were scored by 2 independent, blinded readers using the RA MRI Scoring (RAMRIS) system. X-rays (hands, wrists, forefeet at baseline, wk52, and104) were scored by 2 other, blinded readers using vdHS system. X-ray progression was defined as a change in vdHS score > 0.5 as it was in the original trial. MRI synovitis and bone edema scores were evaluated as continuous variables (per unit difference or change). Change in RAMRIS bone erosion scores was highly skewed, and was therefore dichotomized at >0.5. Multivariable logistic regression was used to determine if baseline and early measures of change in component RAMRIS scores predicted x-ray progression independent of clinical disease activity [DAS28(CRP)], change in DAS28(CRP), age, sex, baseline vdHS score, and treatment group.

Results: Higher baseline synovitis scores and *less improvement* in synovitis over the first 24 wks of follow up were both significantly and independently associated with a greater risk of x-ray progression at 1- and 2yrs (Table). Higher baseline bone edema and *less improvement* in bone edema were independently associated with a greater risk of x-ray progression at 1yr, and tended to be associated with progression at 2yrs. An increase in RAMRIS bone erosion score >0.5 at wk 24 significantly predicted x-ray progression at 1- and 2 yrs. Baseline and wk12 changes in MRI scores all significantly predicted x-ray progression at wk 52 (all p<0.05), and tended to be associated with x-ray progression at wk 104 (p=0.004–0.2).

Table. Multivariable-adjusted risk of x-ray progression at 1- and 2 years of follow-up based on early MRI measures at 24 wks (per 1 unit difference or change in respective RAMRIS score)

	vdHS Score Progression >0.5 Week 52 (N=216–234)		vdHS Score Progression >0.5 Week 104 (N=202–219)	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1*				
Baseline Synovitis	1.14 (1.04–1.24)	0.003	1.11 (1.01–1.21)	0.02
Δ Synovitis @ Wk 24	1.19 (1.06–1.33)	0.003	1.22 (1.07–1.38)	0.002
Model 2*				
Baseline Bone Edema	1.05 (1.01–1.09)	0.02	1.06 (1.02–1.11)	0.007
Δ Bone Edema @ Wk 24	1.12 (1.05–1.20)	0.001	1.06 (0.99–1.14)	0.07
Model 3*				
Baseline Bone Erosion	0.99 (0.97–1.01)	0.3	0.98 (0.95–1.01)	0.1
Δ Bone Erosion >0.5 @ Wk 24	2.85 (1.41–5.78)	0.004	4.42 (2.04–9.58)	<0.001

*adjusted for age, sex, DAS28(CRP) at baseline, change in DAS28(CRP) over the first 24wks, vdHS score at baseline, and treatment group.

1. Østergaard M, Emery P, Conaghan PG, et al. *Arthritis Rheum* 2011; 63(12): 3712–3722.

Conclusion: Early MRI measures at 12 and 24 wks independently predict x-ray changes at 1 and 2yrs of follow-up. These data support the use of MRI in clinical trials for early identification of pts with (OR who will develop) structural joint damage progression during follow up. This has implications for clinical trial design.

1621

In Vivo Synovial Oxygen Levels Are Inversely Related to Metabolic Turnover and Disease Activity in Rheumatoid and Psoriatic Arthritis Biologic Responders. Leonard C. Harty[1], John Ryan[2], Chin Teck Ng[3], Monika Biniecka[3], Aisling Kennedy[3], Eric J. Heffernan[4], Ursula Fearon[5] and Douglas J. Veale[1]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Ziltron, Unit 4, Castletroy Business Park, Plassey, Limerick, Ireland, [3]Translation Rheumatology Research Group, Dublin, Ireland, [4]St. Vincent's University Hospital, Dublin, Ireland, [5]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Hypoxia, leukocyte infiltration and dysfunctional vascularity play a key role in the pathogenesis of inflammatory arthritis (IA). We examine the relationship of metabolic turnover with synovial vascularity/invasion in IA patients.

Methods: RA and PsA patients with active knee joint synovitis were recruited and assessed clinically prior to contiguous MR and PET/CT imaging followed by arthroscopy, biopsy and pO_2 measurement pre- and post-TNFi therapy. Imaging protocols were standardised for MRI, and Fluorodeoxyglucose (18FDG) PET and image-data intensity resolution was optimised for synovial tissue. Cell-specific markers (CD3, CD4, CD8, CD68), blood vessel maturity and metabolic activity (GAPDH) were quantified by immunohistologic analysis and dual-immunofluorescence. Reduction of DAS28 ≥1.2 indicated a good clinical response. Mann Whitney U and Wilcoxon test were used to compare continuous variables and Spearman's Rho was used to assess correlations. $p < 0.05$ was considered statistically significant. SPSS version 18 was employed.

Results: 21 patients, RA(n=9) and PsA(n=12), mean (age 45±16, DAS 28, 4.6±1.2 and gender 6F:15M) were recruited. At baseline *in vivo* synovial pO_2 levels inversely correlated with PET (r=-0.6, p=0.03), DAS28 (r=-0.5, p=0.05) and was inversely associated with macroscopic synovitis. Furthermore, MRI correlated with macroscopic synovitis (r=0.5, p=0.04) and sub-linining CD68 expression (r=0.7, p=0.001). Lining layer and sub-lining GAPDH expression inversely correlated with synovial pO_2(r=0.8, p=0.03) pre/post TNFi. Biologic responders showed significant reduction in PET quantification (p=0.018) which was paralleled by corresponding decreases in MRI (p=0.012), macroscopic synovitis (p=0.005), vascularity (p=0.005) and CD68sl expression (p=0.01) and an increase in pO_2 levels from 22mmHG to 37 mmHG. In contrast PET quantification in non-responders was not associated with significant reductions in MRI or macroscopic/microscopic measures of disease. Furthermore pO_2 levels in non-responders were similar pre/post therapy (22mmHG vs 25mmHG). Figure 1 shows representative PET/MRI hybrid images in a responder patient pre/post TNFi demonstrating close association between metabolic turnover and site of inflammation.
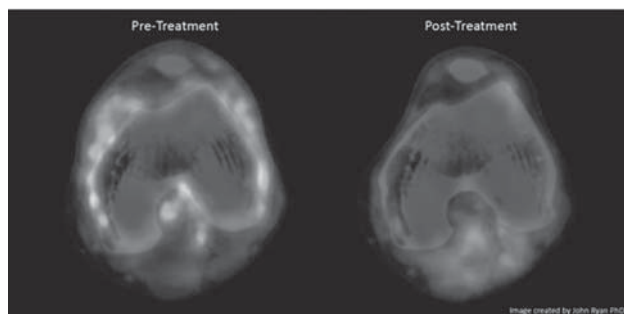
Figure 1. Hybrid PET/MRI images from the same patient before and after successful therapy demonstrating reduced inflammation and metabolism within the synovium of the knee joint.

Conclusion: This is the first study to show synovial metabolic activity and inflammation quantified by MR/PET are associated with *in vivo* hypoxia, cellular and molecular biomarkers in RA and PsA patients in response to biologic therapy. MR/PET may represent an important new imaging modality in assessing response to biologic therapy.

ACR Concurrent Abstract Session
Infection-related Rheumatic Disease
Monday, November 12, 2012, 2:30 PM–4:00 PM

1622

Characteristics of Patients with Infectious Cryoglobulinemia Vasculitis in the Absence of HCV Infection: Results From the French Nationwide Cryovas Survey. Benjamin Terrier Sr.[1], Isabelle Marie[2], Adeline Lacraz[3], Pauline Belenotti[4], Fabrice Bonnet[5], Laurent Chiche Sr.[4], Bruno Graffin Sr.[6], Arnaud Hot Sr.[7], Jean-Emmanuel Kahn[8], Thomas Quemeneur[9], Olivier Hermine Sr.[10], Jean-Marc Léger[11], Patricia Senet[12], Emmanuelle Plaisier[13], Xavier Mariette[14] and Patrice Cacoub Sr.[15]. [1]Cochin Hospital, Paris, France, [2]Service de médecine interne, CHU de Rouen, Rouen, France, Rouen, France, [3]Nephrology, CHU Bordeaux, Bordeaux, France, [4]Internal Medicine, CHU Marseille, Marseille, France, [5]Internal Medicine, CHU Bordeaux, Bordeaux, France, [6]Metz hospital, Metz, France, [7]Lyon hospital, Lyon, France, [8]Internal Medicine, Foch Hospital, Suresnes, France, [9]CHR de Valenciennes, Valenciennes, France, [10]Hôpital Necker, Paris, France, [11]Paris, France, [12]Tenon hospital, Paris, France, [13]Nephrology, Tenon Hospital, Paris, France, [14]Université Paris-Sud, Le Kremlin Bicetre, France, [15]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: Hepatitis C virus infection (HCV) is the main cause of mixed cryoglobulinemia vasculitis (CryoVas). Recent data are lacking regarding demographical, clinical and biological features of patients with infectious mixed CryoVas in the absence of HCV infection.

Objectives: To analyze the features of patients with infectious mixed CryoVas in the absence of HCV infection included in the French CryoVas survey. The objective of this survey is to describe the presentation and to evaluate efficacy and tolerance of treatments in patients with CryoVas.

Methods: Eighty-one French centers of Internal Medicine, Nephrology, Rheumatology, Hematology, Dermatology and Neurology from Universitary and general hospitals have included 260 patients with non-HCV mixed CryoVas diagnosed between January, 1995 and July, 2010. Among them, 18 patients presented with infectious mixed CryoVas. Demographical, clinical and biological data, as well as therapy and outcome, were assessed.

Results: 11 women and 7 men (sex ratio F/M 1.3), mean age 57.9 ±13.5 years, were analyzed. Infectious causes were: virus infection in 8 patients [hepatitis B virus (HBV) in 4, and cytomegalovirus, Epstein Barr virus, parvovirus B19 and human immunodeficiency virus in one case each], pyogenic bacterial infection in 6 patients, parasitic infection in 2 patients (ascaridiasis and leishmaniosis in one case each), and leprosy and candidiasis in one case each. Baseline manifestations were: purpura (78%), glomerulonephritis (28%), arthralgia/arthritis (28%), peripheral neuropathy (22%), necrosis (22%), cutaneous ulcers (17%), and myalgia (11%). No gastrointestinal, central nervous system or pulmonary involvement was observed. Cryoglobulinemia was type II in 12 patients (67%) and type III in 6 (33%). Histological confirmation of vasculitis was available in 72%.

As first-line therapy, 6 patients received corticosteroids, 1 cyclophosphamide and none rituximab, but 14 patients received anti-infectious specific therapy. Among the latters, 10 were in sustained remission of the disease, 2 died of the underlying infectious disease (bacterial septicemia and Candida pneumonia), and 2 had refractory or relapsing disease related to HBV infection treated with rituximab in addition to antiviral therapy, leading to complete remission. The 4 remaining patients who did not receive specific therapy had cytomegalovirus, Epstein Barr virus, parvovirus B19 and HBV infection, and remained in remission of the CryoVas.

Conclusion: In patients with infectious mixed cryoglobulinemia vasculitis in the absence of HCV infection, virus and pyogenic bacterial infections represent the main causes. Anti-infectious specific therapy is most frequently associated with sustained remission of the disease. Thus, immunosuppressive agents should be considered only in second-line in patients with refractory and/or life-threatening vasculitis.

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1623

Serum Biomarkers Signature Identifies Patients with Overt B-Cell Non-Hodgkin Lymphoma Associated with Mixed Cryoglobulinemia in Chronic HCV Infection. Benjamin Terrier Sr.[1], Wahiba Chaara[2], Guillaume Geri[3], David Saadoun[4], Michelle Rosenzwajg Sr.[5], Damien Sene Sr.[6], Adrien Six[2], David Klatzmann Sr.[5] and Patrice Cacoub Sr.[3]. [1]Cochin Hospital, Paris, France, [2]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [5]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Paris, France, [6]Groupe Hospitalier Pitié-Salpétrière, Université Pierre et Marie Curie, Paris, France

Background/Purpose: Hepatitis C virus (HCV) is associated with B-cell disorders, including mixed cryoglobulinemia (MC) and B-cell non-Hodgkin lymphoma (B-NHL). Early diagnosis of B-NHL in HCV-infected patients, in particular those with MC vasculitis, is critical to determine the optimal therapeutic management.

Aim: We hypothesized that combination of serum biomarkers could be used to identify B-NHL associated with MC in patients with chronic HCV infection.

Methods: 155 HCV infected patients have been included [median age 62 (31–85) years, M/F 70/85], with and without MC and/or B-NHL [57 patients without MC, 17 patients with asymptomatic MC, 62 patients with MC vasculitis, and 19 patients with MC vasculitis and B-NHL]. We measured serum levels of 8 markers previously described to be increased in patients with B-NHL i.e. soluble CD22, soluble CD27, soluble IL-2Ra, soluble CD137, free-light chains of immunoglobulins, heavy chains of immunoglobulins, gammaglobulins and C4 complement fraction. We used a multiparametric analysis in order to determine a signature that identifies patients with overt B-NHL associated with MC in chronic HCV infection.

Results: Serum levels were significantly different between patients without MC, patients with asymptomatic MC, patients with MC vasculitis and those with MC vasculitis and B-NHL: soluble CD22 (6.7 vs. 11.9 vs. 20.8 vs. 36.4 ng/ml, P<0.0001), soluble CD27 (71.9 vs. 75.7 vs. 122.9 vs. 263.9 U/ml, P<0.0001), soluble IL-2Ra (877 vs. 1035 vs. 2206 vs. 4044 pg/ml, P<0.0001), soluble CD137 (296 vs. 426 vs. 539 vs. 763 pg/ml, P<0.0001), free-light chains of immunoglobulins (ratio k/l 1.13 vs. 1.08 vs. 1.79 vs. 3.01, P<0.0001), heavy chains of immunoglobulins (ratio IgMk/IgMl 1.90 vs. 1.85 vs. 4.85 vs. 31.3, P<0.0001), gammaglobulins (14.1 vs. 17.0 vs. 12.1 vs. 6.0 g/l, P<0.0001) and C4 complement fraction (0.23 vs. 0.16 vs. 0.07 vs. 0.04 g/l, P<0.0001).

Using multiparametric analysis, we identified a signature involving soluble CD27, soluble IL-2Rα, gammaglobulins and C4 levels associated with the presence of overt B-NHL in HCV-infected patients. This signature had a sensitivity of 100%, a specificity of 63%, and positive and negative predictive values of 94 and 100% for discriminating patients with overt B-NHL and those without B-NHL.

Conclusion: Overall, our data indicate that serum biomarkers signature allows identifying patients presenting with overt B-NHL associated with mixed cryoglobulinemia vasculitis in chronic HCV infection, and requiring invasive explorations in order to demonstrate the presence of malignant lymphoma.

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1624

Deletion of HLA-B27 T Cells Underlies the Immunodominant Response to Influenza Infection On Class I MHC Transgenic Mice. Ali Akram[1] and Robert D. Inman[2]. [1]University of Toronto and University Health Network (UHN), Toronto, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: The role of HLA-B27 in modulating host response to infection is undefined, yet has important implications for the mechanism whereby B27 confers susceptibility to arthritis. Despite codominant expression of class I MHC (MHC-I) alleles, immune response to viral infections is characterized by a phenomenon called immunodominance (ImDc). The exact mechanisms of ImDc are not clear. Defining factors contributing to ImDc has proved difficult due to multiple MHC-I allele co-expression in humans and normal mice.

Methods: To overcome this limitation, we generated human MHC-I transgenic (Tg) mice which are deficient for endogenous mouse MHC-I molecules (i.e., H2-K$^{-/-}$/D$^{-/-}$, DKO) and express only one human MHC-I allele. To assess whether co-expression of additional MHC-I alleles influences the pattern of anti-flu CTL epitope recognition and ImDc, novel double MHC-I Tg mice were established on a DKO background.

Results: In flu-infected, double Tg HLA-A2/B7 or HLA-A2/B27 mice, IFN-γ ELISpot assays with the flu epitopes M1.58–66 (HLA-A2-specific) and NP418–426 (HLA-B7-specific) or NP383–391 (HLA-B27-specific) showed specific recognition of both peptides by both alleles respectively. In contrast, in flu-infected HLA-B7/B27 Tg mice a significantly reduced NP383-restricted CTL response was detected while there was no change in the response level of NP418-restricted CTL. Subsequent flu-specific studies revealed that co-expression of B7 and B27 is associated with i) a partial deletion of Vβ8.1$^+$ B27/NP383-restricted CD8$^+$ T cells and ii) a failure of Vβ12$^+$ CD8$^+$ T cell expansion following flu infection in B7/B27 Tg mice. Using chimeric mice, we confirmed that the lower number of naive B27-restricted CD8$^+$ T cells in B7/B27 Tg mice, compared to single Tg B27 mice, is due to negative selection of B27-restricted Vβ8.1$^+$ CD8$^+$ T cells.
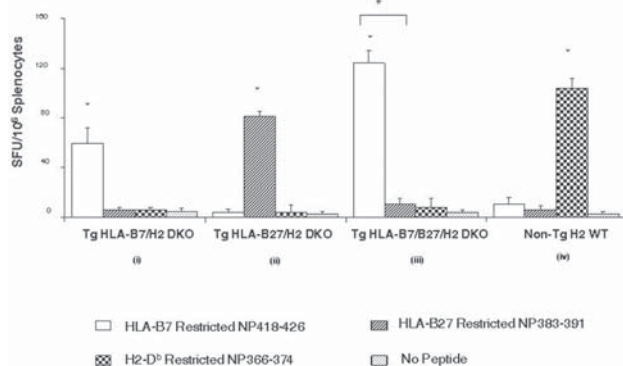
Conclusion: The pattern of allele co-expression critically influences the flu CTL response. The selective deletion of B27-restricted T cells has important implications for models defining the role that HLA-B27 plays in susceptibility to reactive arthritis and ankylosing spondylitis.

Disclosure: **A. Akram**, None; **R. D. Inman**, Abbott, Amgen, Merck, Pfizer, Sanofi-Aventis, 5.

1625

With Chlamydia Infection the Macrophage Serves As Gate-Keeper for Dissemination and Induction of Host Immunity. Eric Gracey[1] and R. D. Inman[2]. [1]Toronto Western Hospital, Toronto, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: The obligate intracellular pathogen, Chlamydia, is the most common cause of reactive arthritis (ReA). We have demonstrated that susceptibility to experimental Chlamydia-induced ReA is determined as early as day 4 post infection implicating the innate immune response. However the cellular and molecular mechanisms during this stage have yet to be determined. Here we demonstrate the importance of the macrophage in directing both innate and adaptive immune responses to Chlamydia, and limiting dissemination of the organism.

Methods: Clodronate liposomes (CL) were used to deplete peritoneal macrophages with PBS-liposomes (PL) acting as the control. Clodronate did not affect neutrophil or lymphocyte populations. Subsequent to macrophage depletion mice were infected IP with 107 IFU Chlamydia muridarum for either 7 or 14 days. Spleens, peritoneal lavage, peritoneal membranes and blood were harvested for analysis of immune response and Chlamydia load.

Results: There was no mortality, nor signs of systemic disease associated with Chlamydia challenge in macrophage-depleted mice. Inspection of peritoneal cavity cells at day 7 demonstrated depletion of Cd11b+F4/80+ macrophages (PL; 50% of cells, CL; 5% of cells) and a significant increase in CD11b+Ly6G+ neutrophils (PL; 10% of cells, CL; 60% of cells) was seen in the mice treated with clodronate liposomes. This was coupled with a 5-fold increase in Chlamydia 16sRNA load of these cells as assessed by qPCR. 16sRNA was only detected in blood samples only in the macrophage-depleted mice, reflecting dissemination of the organism beyond the site of local challenge. At day 14 post Chlamydia infection, depletion of macrophages was associated with a significant alteration of the adaptive immune response profile, with reduced numbers of Th1 cells and activated IFNy+, CD8+ cells. This was coupled with a 20-fold increase chlamydial load compared to control mice.

Conclusion: These data indicate that macrophages are crucial in defining effective host innate immune response to Chlamydia and thereby limiting dissemination of the organism. In addition, macrophages orchestrate the development of effective adaptive host response to the organism. These studies suggest that quantitative or qualitative alteration in macrophages may play a key role in the development of post-Chlamydia sequelae such as reactive arthritis.

Disclosure: E. Gracey, None; **R. D. Inman**, None.

1626

Frequent Conversion of Tuberculosis Screening Tests During Anti-Tumor Necrosis Factor Therapy in Patients with Rheumatic Diseases.
Chrisoula Hatzara, Emilia Hadziyannis, Anna Kandili, Stamatoula Tsikrika, Martha Minopetrou, Georgios Georgiopoulos and Dimitrios Vassilopoulos. Athens University School of Medicine, Athens, Greece

Background/Purpose: The most recent ACR Recommendations suggest annual screening for latent tuberculosis (TB) with standard tuberculin skin test (TST) or the newer interferon-gamma release assays (IGRAs), in patients with rheumatoid arthritis (RA) receiving biologics and risk factors for TB exposure. The rate and clinical significance of TB test conversion during biologic treatment, especially with anti-tumor necrosis factor (TNF) agents, has not been adequately studied so far. Our aim was to determine prospectively the rate of TB test conversion (TST, IGRAs) during anti-TNF therapy in patients with negative baseline screening.

Methods: Among a large cohort of rheumatic patients starting anti-TNF therapy, 50 consecutive patients with negative baseline TB screening (TST: < 5 mm, negative T.Spot®-TB and QuantiFERON®-TB Gold In Tube/QFT-GIT, negative CXR) were followed prospectively during anti-TNF therapy. One year later all patients underwent re-testing for TB with TST, both IGRAs and repeat CXR. Patients with a TB test conversion or changes in CXR underwent further evaluation for active TB.

Results: 50 patients (females/males=29/21, mean age=49.6±15 years) with various rheumatic diseases (RA: n=23, spondyloarthropathies/SpA: n=26, other: n=1) were enrolled in the study. Patients were treated with various anti-TNFs (adalimumab=20, etanercept=13, infliximab=13, golimumab=3, certolizumab=1) for one year. Retesting after one year, showed that 15 patients (30%) displayed conversion of at least one screening assay. Fourteen percent showed conversion of TST (n=7), 10% of T.Spot®-TB (n=5) and 6% of QFT-GIT (n=3). No patient had concomitant conversion of ≥ 2 screening tests while there was no history of remote or recent documented TB contact in the converted patients. Further work-up did not reveal any evidence of active TB in these patients. There were no significant differences in age, sex, disease diagnosis or duration, previous BCG vaccination, concomitant DMARD and/or steroid use or type of anti-TNF treatment between those who converted (n=15) vs those who did not (n=35).

Conclusion: Approximately one third of patients with negative TB screening at baseline develop conversion of at least one screening test during anti-TNF treatment. The clinical significance of these findings as well as the need for latent TB therapy in this patient group needs to be studied further.

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New Insights Into the Presentation and the Management of Hepatitis B Reactivation in Patients with Autoimmune Diseases and Inflammatory Arthritis. Nina Droz[1], Laurent Gilardin[2], Patrice Cacoub Sr.[3], Francis Berenbaum[4], Daniel Wendling[5], Bertrand Godeau[6], Anne-Marie Piette[7], Emmanuelle Dernis[8], Mikael Ebbo[9], Bruno Fautrel[10], Arsène Meikinian[11], Aude Rigolet[12], Sophie Rivière[13], Stanislas Pol[1], Loic Guillevin[14], Luc Mouthon Sr.[15] and Benjamin Terrier Sr.[1]. [1]Cochin Hospital, Paris, France, [2]Saint Antoine Hospital, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]AP-HP, St Antoine Hospital, Paris, France, [5]Minjoz University Hospital, Besancon, France, [6]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [7]Foch Hospital, Suresnes, France, [8]Centre Hospitalier, Le Mans, France, [9]Conception Hospital, Marseille, France, [10]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [11]Jean Verdier Hospital, Bondy, France, [12]Pitie-Salpetriere Hospital, APHP, UPMC Paris VI, Paris, France, [13]Lapeyronie, Montpellier, France, [14]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [15]Hopital Cochin, Paris, France

Background/Purpose: In patients with autoimmune diseases and inflammatory arthritis, immunosuppressive therapy may trigger Hepatitis B virus (HBV) reactivation, leading to significant morbidity and mortality.

Objective. To describe presentation, management and outcome of HBV reactivation occurring in patients treated for autoimmune diseases and inflammatory arthritis, and to evaluate predefined algorithm for its prevention.

Methods: French centers of Internal Medicine, Rheumatology and Hepatology have included 35 patients with HBV reactivation diagnosed between January, 2002 and March, 2012. HBV reactivation was defined as an increase >1 log IU/mL of HBV DNA levels or DNA reappearance in negative patients. Hepatitis was defined as an increase >3-fold the baseline value of alanine transaminase (ALT). We further performed an extensive literature review and provided a global analysis of 138 cases of HBV reactivations.

Results: Personal cases were treated for rheumatoid arthritis (RA, n=14), connective tissue disease (n=7), vasculitis (n=5), ankylosing spondylitis (n=4) or other diseases (n=5). At baseline, 23 (66%) patients were hepatitis B surface antigen (HBsAg) carriers, 11 had previous history of HBV infection (including 7 with HBs antibodies), and 1 patient had occult HBV infection. Reactivation occurred after a median time of 39 wk after initiation of corticosteroid (CS) and/or immunosuppressive (IS) therapy. At the time of reactivation, 30 (86%) patients were receiving CS, 11 (31%) methotrexate, 7 (20%) TNF-a blockers, 6 (17%) cyclophosphamide, 4 (11%) rituximab, 4 (11%) azathioprine, and tocilizumab and abatacept in 1 case each (3%). Median HBV DNA and ALT levels were 4.2 log IU/mL and 2-fold the baseline value, respectively, and were correlated (r=+0.49, P=0.004). Patients were clinically asymptomatic in 31 (89%) cases, while hepatitis occurred in 17 (49%), including severe hepatitis (>10-fold the baseline value) in 9 (26%). Management consisted in antiviral therapy in 32 (91%) patients, associated with discontinuation or decrease of CS/IS in 16 (46%). Neither fulminant hepatitis was noted, but one patient died of hepatocellular carcinoma.

After global analysis of HBV reactivations, reported patients were clinically asymptomatic in 102 (74%) cases, with severe hepatitis in 46 (33%) and death and/or fulminant hepatitis in 17 (12%). Reactivation kinetics differed according to the treatments used and baseline HBV status, with earlier reactivation occurring under rituximab or cyclophosphamide and in HBsAg+/HBV DNA+ patients. The use of predefined algorithm could have prevented 108 (78%) reactivations. Two reactivations occurred despite appropriate preemptive antiviral therapy. Finally, according to the algorithm, 28 patients would not have received preemptive therapy, including 2 HBcAb+/HBsAb+ Asian patients with RA receiving methotrexate or adalimumab who died of fulminant hepatitis.

Conclusion: This study provides new insights into HBV reactivations in patients with autoimmune diseases and inflammatory arthritis. Predefined algorithm seems to be effective to reduce the risk of HBV reactivation, but caution is warranted using monitoring of HBV markers.

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ACR Concurrent Abstract Session
Metabolic and Crystal Arthropathies: Basic Science
Monday, November 12, 2012, 2:30 PM–4:00 PM

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Epistatic Interaction Between Solute Carrier 2A9 Genotype and Sugar-Sweetened Beverage Consumption in the Determination of Gout Risk.
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Background/Purpose: Consumption of drinks sweetened with sugar or high fructose corn syrup increases both serum urate levels and the risk for gout. *SLC2A9* encodes a renal urate transporter that exchanges uric acid for glucose and fructose. Genetic variants in *SLC2A9* explain 3.5% of the variation in serum urate levels in European Caucasian (EC) populations and are strongly associated with gout in EC and New Zealand (NZ) Maori and Pacific Island (Polynesian) people. Because SLC2A9 transports both uric acid and simple hexose sugars we tested the hypothesis that *SLC2A9* genotype and sugar-sweetened beverage (SSB) consumption interact to determine the risk for gout.

Methods: NZ survey data from 1623 people with and without gout were used. Gout was determined by ARA preliminary classification criteria. SSB consumption was self-reported, including fruit juice, where one unit of drink was defined as a can or large glass. Data from the Atherosclerosis Risk in Communities (ARIC) study were also used (6003 EC controls and 153 primary gout cases determined by self-report). Two ancestral groups were studied; EC (NZ and ARIC) and NZ Polynesian. The NZ samples were genotyped for *SLC2A9* single nucleotide polymorphism (SNP) *rs11942223* using Taqman® technology. The ARIC samples had previously been genotyped for surrogate marker *rs6449173*. STATA v8.0 statistical software was used, with an interaction term included in the logistic regression analysis, derived from the ratio of the estimated odds ratio (OR) comparing exposed ($\geq$4 SSB/day) and unexposed (<4 SSB/day) *rs11942223* risk allele (T) homozygotes with the estimated OR comparing exposed and unexposed people positive for the *rs11942223* protective allele (C).

Results: The risk of gout associated with consuming $\geq$4 SSB/day without stratification by genotype was similar to the increased genetic risk observed in the T-allele homozygous groups (Table). However the normally protective C-allele conferred a considerable increase in risk for gout in individuals exposed to $\geq$4 SSB/day (for example OR increased from 0.51 to 4.93 in Polynesian. The genotype by interaction term (ORI) was significant in Polynesian (ORI=5.31, P=0.043) but not in EC (ORI =5.31, P=0.087) (all adjusted by sample set, age, sex, BMI). Combining the two groups revealed significant evidence for interaction (ORI=4.74, P=0.003).

Table. Risk of gout for $\geq$4 SSB/day stratified by genotype at SLC2A9

	European Caucasian			Polynesian (Maori/Pacific Island)		
	Obs	OR [95% CI][1]	P	Obs	OR [95% CI]	P
$\geq$4 SSB/day group unstratified	6735	1.88 [0.87–4.07]	0.11	1020	2.02 [1.37–2.98]	4.2×10^{-4}
T-allele homozygous, <4 SSB/day	6685	1.00	-	951	1.00	-
C-allele positive, <4 SSB/day		0.63 [0.47–0.84]	0.002		0.51 [0.28–0.93]	0.027
T-allele homozygous, $\geq$4 SSB/day		1.18 [0.48–2.91]	0.71		1.82 [1.19–2.77]	0.005
C-allele positive, $\geq$4 SSB/day		3.91 [0.74–20.70]	0.11		4.93 [1.14–21.33]	0.033

1. ORs were adjusted by BMI, age, sex, data set.

Conclusion: When exposed to high SSB consumption individuals with the normally gout-protective allele at *rs11942223* have a considerably elevated risk of gout. Our data suggest that SLC2A9-mediated uric acid transport is physiologically influenced by excess simple sugars derived from SSB, with excess SSB consumption negating the gout-risk discrimination normally mediated by *rs11942223*.

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Microarray Analysis of Acute and Intercritical Gout.
Alicia Rodriguez-Pla[1], Lynda Bennett[1], Kathryn H. Dao[2], Edwardo Delgado[2], Typhanie Maurouard[1], M. Virginia Pascual[1] and John J. Cush[3]. [1]Baylor Institute for Immunology Research, Dallas, TX, [2]Arthritis Care and Research Center, Dallas, TX, [3]Baylor Research Institute, Dallas, TX

Background/Purpose: We aimed to identify the immune mechanism underlying gouty inflammation using microarrays analysis and modular gene expression signatures.

Methods: Whole blood along with clinical and treatment data were collected from out-patients with gout. A total of 28 samples from 20 patients (18 males and 2 females; median age 53.5 years [range 39–82]; median disease duration 2.2 years [range 0–29.11]) and from 16 matched healthy controls were obtained. Thirteen patients had active disease at their first visit, and 7 had quiescent (intercritical) disease. Whole blood RNA was extracted using standard technologies and was hybridized to Illumina HT-12 chips. Genes differentially expressed (unpaired Student's t-test) in the first visit of all gout or active gout patients (fold change $\geq$2 and a p<0.05), were selected for further consideration. Ingenuity Pathways Analysis was performed and we also adopted a module based data mining strategy, which can facilitate biomarker and biological knowledge discovery.

Results: Two hundred and four genes were found differentially expressed in gout patients at their first visit regardless of clinical activity. When active patients were selected, 184 transcripts were found dysregulated. Innate immunity genes related to the interleukin-1 (IL1) signaling pathway were up-regulated (*ORM1/ORM2*, *BNIP3L*, *EPB49*, defensins, myeloperoxidase, elastase), whereas genes involved in adaptive immunity were down-regulated (*CD79A*, *CD79B*, *CBR* complex). Modular analysis permitted us to visualize alterations in 174/260 pre-defined modules. Of those, transcripts related to innate immunity cell types, including neutrophils, were increased. Those related to B cells, T cells, NK/cytotoxic and plasma cells were decreased. Interestingly, transcripts related to an early erythrocyte cell population previously described in other IL1-mediated diseases such as systemic onset Juvenile Idiopathic Arthritis (sJIA)/Still's disease and *S. aureus* infections were upregulated. In addition, modules related to inflammation and cell death were up-regulated, while those of proliferation, cell cycle, and mitochondrial stress were down-regulated. This modular pattern might represent a biomarker of innate immunity/IL1-related diseases.

Conclusion: Patients with gout display a blood transcriptional profile similar to that seen in IL-1 dominant or autoinflammatory diseases. This fits with the current knowledge about the involvement of the inflammasome in gout and patients response to IL-1 blockade. This profile is easily interpreted using our previously described modular analysis framework. Although larger, prospective studies including newly diagnosed patients on no treatment are needed to confirm these findings, our data suggest that it is possible to use blood gene expression analysis to identify molecular and cellular pathways linked to dysregulation of innate immunity.

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Genetic Variants of Serum Uric Acid and Gout: An Analysis of > 170,000 Individuals.
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Background/Purpose: Gout is a common and excruciatingly painful inflammatory arthritis caused by hyperuricemia. In addition to various lifestyle risk factors, a substantial genetic predisposition to gout has long been

recognized. The Global Urate Genetics Consortium (GUGC) has aimed to comprehensively investigate the genetics of serum uric acid and gout using data from $> 140,000$ individuals of European-ancestry, 8,340 individuals of Indian ancestry, 5,820 African-Americans, and 15,286 Japanese.

Methods: We performed discovery GWAS meta-analyses of serum urate levels (n=110,347 individuals) followed by replication analyses (n=32,813 different individuals). Our gout analysis involved 3,151 cases and 68,350 controls, including 1,036 incident gout cases that met the American College of Rheumatology Criteria. We also examined the association of gout with fractional excretion of uric acid (n=6,799). A weighted genetic urate score was constructed based on the number of risk alleles across urate-associated loci, and their association with the risk of gout was evaluated. Furthermore, we examined implicated transcript expression in cis (expression quantitative trait loci databases) for potential insights into the gene underlying the association signal. Finally, in order to further identify urate-associated genomic regions, we performed functional network analyses that incorporated prior knowledge on molecular interactions in which the gene products of implicated genes operate.

Results: We identified and replicated 28 genome-wide significant loci in association with serum urate ($P \leq 5 \times 10^{-8}$), including all previously-reported loci as well as 18 novel genetic loci. Unlike the majority of previously-identified loci, none of the novel loci appeared to be obvious candidates for urate transport. Rather, they were mapped to genes that encode for purine production, transcription, or growth factors with broad downstream responses. Besides SLC2A9 and ABCG2, no additional regions contained SNPs that differed significantly ($P < 5 \times 10^{-8}$) between sexes. Urate-increasing alleles were associated with an increased risk of gout for all loci. The urate genetic risk score (ranging from 10 to 45) was significantly associated with an increased odds of prevalent gout (OR per unit increase, 1.11; 95% CI, 1.09–1.14) and incident gout (OR, 1.10; 95% CI, 1.08–1.13). Associations for many of the loci were of similar magnitude in individuals of non-European ancestry. Detailed characterization of the loci revealed associations with transcript expression and the fractional excretion of urate. Network analyses implicated the inhibins-activins signaling pathways and glucose metabolism in systemic urate control.

Conclusion: The novel genetic candidates identified in this urate/gout consortium study, the largest to date, highlight the importance of metabolic control of urate production and urate excretion. The modulation by signaling processes that influence metabolic pathways such as glycolysis and the pentose phosphate pathway appear to be central mechanisms underpinned by the novel GWAS candidates. These findings may have implications for further research into urate-lowering drugs to treat and prevent gout.

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Osteoarthritis-Associated Basic Calcium Phosphate Crystals Induce IL-1β, IL-18 and S100A8 Production in a Tyrosine Kinase Dependent Manner. Geraldine M. McCarthy[1], Evanna Mills[2], Kingston Mills[2] and Aisling Dunne[2]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]Trinity College Dublin, Dublin 2, Ireland

Background/Purpose: Intraarticular basic calcium phosphate (BCP) crystals are present in the majority of osteoarthritic (OA) joints and are associated with severe degeneration. In vitro, BCP promote pro-inflammatory cytokine production and matrix metalloprotease (MMP) expression, suggesting a pathogenic role in OA. Recently it has been demonstrated that BCP crystals drive IL-1β and IL-18 production following activation of the NOD-like receptor, NLRP3. Here, we sought to determine whether uptake of BCP crystals leads to the activation of the membrane proximal kinases, Syk and PI3 kinase and to further characterise events downstream of Syk activation in order to identify novel molecular targets for the treatment of BCP related arthropathies.

Methods: Murine macrophages were stimulated with BCP crystals, with or without priming with a Toll-like receptor (TLR) agonist and IL-1β and IL-18 production was quantified by enzyme linked immunosorbent assay (ELISA). A role for Syk and PI3 kinase was determined with the use of the inhibitors, piceatannol and LY294002, respectively. Activation of the kinases was confirmed by western blotting using phospho-specific antibodies to Syk and PI3 kinase following treatment of cells with the crystals over a 30 minute time course. Finally, activation of the downstream kinase, ERK, and production of the damage associated molecule, S100A8, was assessed in the presence of piceatannol in order to determine if these events are associated with BCP dependent Syk activation.

Results: Physiological concentrations of BCP crystals (50mg/ml) induced robust IL-1β and IL-18 production in a Syk and PI3 kinase dependent manner. Treatment with the inhibitors piceatannol and Ly294002 led to a significant reduction in cytokine levels ($>80\%$) and activation of Syk and PI3 kinase was apparent after approximately 5 minutes treatment with the crystals. Phosphorylation of the downstream kinase, ERK, was prevented following treatment with the Syk inhibitor, piceatannol, thus identifying Syk kinase activation as a proximal event in BCP induced pro-inflammatory cytokine production. Finally, treatment of cells with BCP crystals led directly to the production of the danger-associated molecule, S100A8 and this was also dependent on activation of Syk.

Conclusion: Since S100A8 is considered a TLR 4 ligand, we propose a model whereby BCP crystals drive the production of S100A8 which in turn leads to the expression of pro-IL-1β and pro-IL-18 (Signal 1). In macrophages, BCP crystals can also induce the activation of the NLRP3 inflammasome (Signal 2) leading to the production of the mature forms of these cytokines. These events are dependent on tyrosine phosphorylation and we identify Syk kinase as a potential target for the treatment of BCP related pathologies.

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Arhalofenate Is a Novel Dual-Acting Agent with Uricosuric and Anti-Inflammatory Properties. Yun-Jung Choi, Vanina Larroca, Annette Lucman, Vic Vicena, Noe Abarca, Tim Rantz, Brian E. Lavan and Charles A. McWherter. Metabolex, Inc., Hayward, CA

Background/Purpose: In most patients with gout, elevated serum urate is linked to excess uric acid reabsoprtion in the proximal renal tubule by anion transporters/exchangers, including URAT1, OAT4 and OAT10. It is also known that initiation of serum urate lowering therapy (ULT) in gout patients significantly increases the risk of flares, a process that is believed to be mediated by mono sodium urate (MSU) crystal activation of the inflammasome with subsequent release of pro-inflammatory mediators, including IL-1β. Arhalofenate is an investigational drug which has completed phase 2 of development for the treatment of gout patients with hyperuricemia that are at risk for flares. The dual action of arhalofenate was studied for inhibition of uric acid uptake by renal urate transporters and for suppression of MSU crystal stimulated IL-1β production in isolated mouse macrophages and in a murine air pouch model.

Methods: The activities against the human urate transporters URAT1, OAT4 and OAT10 were determined using the uptake of ^{14}C-uric acid into human HEK293 cells transiently expressing the relevant transporter and compared to uptake into parental HEK293 cells. The anti-inflammatory response was evaluated following acute MSU crystal treatment of (1) mouse macrophages and (2) mouse in an air pouch model, in both cases measuring the elaboration of pro-inflammatory mediators including IL-1β.

Results: Arhalofenate inhibited uric acid uptake by all three transporters with IC$_{50s}$ of 92 μM for URAT1, 3 μM for OAT4 and 53 μM for OAT10. These results are pharmacologically relevant for inhibition of urate reabsoprtion because arhalofenate acid levels in human urine were found to be 116 $\pm$ 23 μM (Mean $\pm$ SEM) at a 600 mg dose. In thioglycolate-elicited intraperitoneal macrophages, arhalofenate acid (150 μM) suppressed IL-1β levels by 77% which was indistinguishable from dexamethasone (75%, p$<$0.05 by one-way ANOVA). In the murine air pouch model, arhalofenate treatment (250 mg/kg) for 3 days prior to MSU crystal induction resulted in 76 % reduction in the elaboration of IL-1β in response to MSU. This response was again similar to that observed for dexamethasone. The anti-inflammatory concentrations of arhalofenate acid are relevant to the human clinical exposures.

Conclusion: Arhalofenate is a novel anti-inflammatory uricosuric agent with the potential to target both serum uric acid reduction and the painful flares that accompany gout. The data from this study support that arhalofenate acts by mediating inhibition of renal transporters/exchangers of uric acid and by suppression of the production of IL-1β in response to MSU crystals in both *in vitro* and *in vivo* models of MSU crystal induced inflammation. These properties strongly support the continued clinical development of arhalofenate for treating elevated serum urate and lowering the risk of flares.

Disclosure: **Y. J. Choi**, Metabolex, Inc., 3; **V. Larroca**, Metabolex, Inc., 3; **A. Lucman**, Metabolex, Inc., 3; **V. Vicena**, Metabolex, Inc., 3; **N. Abarca**, Metabolex, Inc., 3; **T. Rantz**, Metaboelx, Inc., 3; **B. E. Lavan**, Metabolex, Inc., 3; **C. A. McWherter**, Metabolex, Inc., 3.

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Ulodesine (BCX4208) Add-On Therapy to Allopurinol 300mg Lowers Hypoxanthine and Xanthine Plasma Levels in a Dose-Dependent Fashion: Results From a 12-Week Randomized Controlled Trial in Patients with Gout. Shanta Bantia[1], Leigh Harman[1], Cynthia Parker[1], Damon Papac[2], Andreas Maetzel[1], Brian Taubenheim[1] and Alan S. Hollister[1]. [1]BioCryst Pharmaceuticals, Inc., Durham, NC, [2]Southern Research Institute, Birmingham, AL

Background/Purpose: Ulodesine (BCX4208) is an oral, once-daily, purine nucleoside phosphorylase (PNP) inhibitor in clinical development as add-on therapy for the chronic management of hyperuricemia in patients with gout. Based on the role of PNP in purine catabolism, inhibition of PNP should reduce hypoxanthine (HX), xanthine (X) and uric acid levels. Ulodesine has demonstrated dose-dependent decreases in serum uric acid (sUA) in multiple clinical trials both as a single agent and in combination with allopurinol[1]. Plasma X and HX concentrations are significantly higher in untreated gout patients compared to hyperuricemic and normal subjects[2]. Elevated plasma X and HX concentrations are also associated with kidney stones, as seen in xanthine oxidase (XO)-deficient patients and mice[3, 4]. Moreover, HX and X are implicated in the production of reactive oxygen species leading to oxidative stress, cell damage and cardiovascular effects[5]. The objective of the study is to measure plasma X and HX concentrations in gout patients receiving 300 mg/d allopurinol plus either placebo or ulodesine.

Methods: Two hundred-seventy eight subjects with gout and sUA ≥ 6.0 mg/dL on allopurinol 300 mg/d for at least 2 weeks were randomized to receive oral ulodesine 5, 10, 20, or 40 mg/d or placebo for 12 weeks while continuing allopurinol 300 mg/d. Blood samples were collected at baseline and day 85 into heparin tubes containing BCX34 (PNP inhibitor) to prevent purine metabolism during collection and processing. Plasma concentrations of X and HX were analyzed by LC/MS/MS. [$^{15}N_2$] xanthine and [D_2] hypoxanthine were used to generate surrogate standard curves for quantification of plasma X and HX concentrations. In normal healthy subjects, the mean (+ SD) concentrations of plasma X and HX were 56 ± 13 ng/mL and < 25 ng/mL, respectively.

Results: Ulodesine combined with allopurinol produced significant reductions in plasma X and HX concentrations from baseline, compared to placebo (Table). At baseline (subjects on allopurinol 300 mg/d), the mean (+ SD) concentrations of the plasma X and HX were 500 ± 408 ng/mL and 301 ± 293 ng/mL, respectively. The reduction in mean plasma X and HX concentrations with BCX4208 treatment in gout subjects was dose-dependent.

Table. Mean Change from baseline of Day 85 Plasma Xanthine and Hypoxanthine levels BCX4208–203 Study

Metabolite	Placebo (n=40)	5 mg/day (n=39)	10 mg/day (n=38)	20 mg/day (n=41)	40 mg/day (n=36)
			Change from baseline at day 85 LSM (SEM)		
Xanthine(ng/mL)	124.9 (76.33)	-66.6 (77.46)**	-114.6(74.25)***	-138.5 (69.03)***	-183.3 (75.19)***
Hypoxanthine(ng/mL)	-22.7 (70.36)	-48.9 (71.25)	-126.8 (68.21)	-165.6 (63.05)*	-201.3 (68.97)**

*p<0.05, **p<0.005, ***p<0.001 vs. placebo

Conclusion: Using a robust LC/MS/MS method and stabilization of plasma X and HX during blood collection and processing, oral ulodesine administration demonstrated dose-dependent mean reductions in plasma X and HX concentrations in gout patients while under treatment with allopurinol. These results confirm the mechanism of action of ulodesine.

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Disclosure: S. Bantia, BioCryst Pharmaceuticals, Inc, 3; **L. Harman**, BioCryst Pharmaceuticals, Inc, 3; **C. Parker**, BioCryst Pharmaceuticals, Inc, 3; **D. Papac**, BioCryst Pharmaceuticals, Inc, 5; **A. Maetzel**, BioCryst Pharmaceuticals Inc., 3; **B. Taubenheim**, BioCryst Pharmaceuticals, Inc, 3; **A. S. Hollister**, BioCryst Pharmaceuticals, Inc, 3.

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Delivering Mesenchymal Stem Cells to Arthritic Joints with Nano-Fiber Scaffold Resulted in Inhibition of Arthritis and Joint Damage in Arthritis Models. Xiangmei Zhang[1], Kunihiro Yamaoka[1], Koshiro Sonomoto[1], Masahiro Kondo[1], Shunsuke Fukuyo[1], Makoto Satake[2], Hiroaki Kaneko[2], Kazuhisa Nakano[1], Shingo Nakayamada[1], Yosuke Okada[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Integrative Technology Research Institute, Teijin Limited, Tokyo, Japan

Background/Purpose: Even though treatment of rheumatoid arthritis (RA) has emerged, aiming bone repair is still a challenge. Mesenchymal stem cells (MSCs) possess immunoregulatory function with pluripotency and efficacy on arthritis animal models has been reported by intra-venous or intra-peritoneal administration. Herein we have utilized nano-fiber poly-lactic-co-glycollic acid (PLGA) scaffold known for controlled biodegradability with less immunogenicity as an effective delivery system of MSCs to the arthritic joint.

Methods: MSCs were simply injected intra-articularly (IA) or intra-peritoneally (IP) or seeded on nano-fiber PLGA scaffold and implanted into bilateral ankles (IMP) of collagen-induced arthritis (CIA) rats at the time of immunization. Efficacy was evaluated clinically (arthritis score, body weight and hind paw thickness), radiologically (X-ray and micro-CT) and histologically (Hematoxilin-Eosin staining).

Results: Treatment of CIA with IMP significantly decreased the severity of arthritis while IA and IP showed less or no effect. Radiologic evaluation of bone destruction was also suppressed by IMP, but not by IA or IP. Histological analysis of the ankles indicated less inflammatory cell infiltration, synovial hyperplasia, pannus formation, resulting in less destruction of the cartilage and bone by IMP compared to IA and IP. Interestingly, size and weight of the spleen, draining lymph nodes in rats treated with IMP were significantly smaller than those treated with IA and IP. These phenomena were observed at both early phase (2 weeks after immunization) and late phase (6 weeks after immunization) of the disease course. Histological analysis of the draining lymph nodes revealed less or no chronic inflammation in the early phase and reduced germinal center formation at the late phase in rats treated with IMP compared to IA and IP treatment.

Conclusion: Local delivery of MSCs with nano-fiber PLGA scaffold significantly suppress arthritis and bone destruction with decreased immune response in the draining lymph node, while IA or IP had less or no effect. The amount of MSCs that we utilized in our study was far lower compared to the studies reported previously. Therefore, our results suggest the importance of MSCs to reside at the local inflammatory site for suppressing the inflammation and moreover regenerating the destructed bone sequentially.

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Polyarthritis Caused by TIARP (TNFAIP9) Deficiency Critically Dependent On Dysregulated STAT3, NF-κB Signaling and Cell Death in Macrophage. Asuka Inoue[1], Isao Matsumoto[1], Naoto Umeda[1], Yuki Tanaka[1], Satoru Takahashi[2] and Takayuki Sumida[1]. [1]University of Tsukuba, Tsukuba city, Ibaraki, Japan, [2]Department of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba, Tsukuba city, Ibaraki, Japan

Background/Purpose: TNFα-induced adipose-related protein (TIARP) is a six-transmembrane protein induced by TNFα and IL-6 in adipose tissue. Recently, we found that TIARP is dominantly expressed in splenic macrophages and joints of two arthritic mouse models (collagen induced arthritis;

CIA and glucose-6-phosphate isomerase (GPI) induced arthritis). In human, TIARP is also observed in human joints from patients with rheumatoid arthritis and clearly upregulated by TNFα stimulation, although the pathogenic mechanisms of arthritis remain unclear. In this study, to elucidate the role of TIARP in the development of arthritis, we have generated TIARP-deficient (TIARP$-/-$) mice.

Methods: (1) We generated TIARP$-/-$ mice in C57BL/6 (B6) background, and investigated several organs in aged (12-month-old) TIARP$-/-$ mice. The level of cytokines in the serum was measured by ELISA. (2) Peritoneal macrophages (PEM) were isolated and cultured with LPS or TNFα. Then, the production of IL-6 in culture supernatant was measured by ELISA. (3) We examined the role of TIARP in NF-κB pathway and apoptosis. PEM were cultured with TNFα, then fluctuation of NF-κB inhibitory molecule IκBα expression was detected by Western blotting. Apoptotic cells were detected by flowcytometry using anti-Annexin V antibodies. (4) We also examined the susceptibility of young (8–12-week-old) TIARP$-/-$ mice to CIA. CIA was induced by immunization with 200μg of chicken type II collagen (CII) emulsified in CFA to B6 mice, followed by boost immunization on day 21. The severity of arthritis was monitored by clinical score. (5) The level of anti-CII antibodies in the serum on day30 and 60 were measured by ELISA. (6) The level of IL-6 and TNFα in the serum on day 60 after CII immunization was measured. (7) We examined the effects of anti-IL-6 receptor mAb (MR16-1) on the development of arthritis in TIARP$-/-$ CIA mice. We injected 2mg of MR16-1 intraperitoneally on day 21 after CII immunization. (8) PEM were cultured with IL-6 for 1 h. The expression of STAT3, phosphorylated-STAT3 (p-STAT3) and SOCS3 were detected by Western blotting.

Results: (1) 80% of aged TIARP$-/-$ mice spontaneously developed arthritis. The levels of IL-6 in the serum from TIARP$-/-$ mice were significantly higher than WT mice. (2) PEM from TIARP$-/-$ produced high amount of IL-6 with LPS or TNFα stimulation. (3) PEM from TIARP$-/-$ mice showed sustained degradation of IkBα compared with WT by TNFα stimulation. TNFa-induced apoptotic cells were increased in WT but unchanged in TIARP$-/-$. (4) The severity of arthritis in TIARP$-/-$ was higher than that in WT. (5) The level of anti-CII antibodies was comparable between WT and TIARP$-/-$. (6) The serum IL-6 was significantly increased in TIARP$^{-/-}$ mice, whereas serum TNFα was not detected. (7) Administration of MR16-1 on day 21 significantly suppressed the progression of arthritis in TIARP$-/-$ CIA mice. (8) P-STAT3 expression was enhanced in TIARP$-/-$ compared with WT, whereas SOCS3 expression was comparable between WT and TIARP$-/-$.

Conclusion: These findings suggest that TIARP is a negative regulator in autoimmune arthritis through the suppression of IL-6 production, NF-κB, STAT3 signaling, and the induction of apoptosis.

Disclosure: **A. Inoue**, None; **I. Matsumoto**, None; **N. Umeda**, None; **Y. Tanaka**, None; **S. Takahashi**, None; **T. Sumida**, None.

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Commensal Gut-Derived Bacteria As Therapy for Systemic Autoimmune Disease. David Luckey[1], Eric Marietta[1], Harvinder S. Luthra[1], Robin Patel[1], Joseph A. Murray[1], Ashutosh Mangalam[2] and Veena Taneja[1]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease that leads to destruction of joints. Although etiology of RA is unknown, both genetic and environmental factors are involved in predisposition to develop RA. Genome wide association studies have shown that among the genetic factors, the strongest association of RA is with MHC region, the most significant being HLA-DRB1*0401 and DQ8. A recent study showed that patients with RA have an imbalance of gut microbiota suggesting its role in regulation of this disease. Analysis of fecal microbiota of patients with RA showed significantly less *Bifidobacteria* and bacteria of the *Bacteroides-Porphyromonas-Prevotella* group, and the *E. rectale–C. coccoides* group than the fecal microbiota of patients with non-inflammatory Fibromyalgia. Since these bacterial species are known to belong to the most common genera and groups in the human fecal microbiota, their absence in RA patients might suggest a protective role of these commensal bacteria in RA.

Methods: We have generated a mouse model of rheumatoid arthritis using HLA transgenic mice expressing RA-susceptible gene, HLA-DQ8 in the absence of their endogenous class II genes. Recently, we isolated *Prevotella histicola*, anaerobic commensal bacteria of Human gut, from bowel of a patient and have shown that it possesses anti-inflammatory activity.

Results: In this study we have tested our hypothesis if systemic disease like RA can be modulated via gut. HLA-DQ8 transgenic mice develop collagen-induced arthritis (CIA) following immunization with type II collagen (CII). We have used these transgenic mice to test if gut-derived commensal bacteria can regulate immune response and modulate arthritis. Treatment with *P. histicola* did not lead to any pathology in the gut. Transgenic mice immunized with CII and treated with *P. histicola* showed suppression of antigen-specific cellular immune response with a significant reduced production of inflammatory cytokines. Treatment with *P. histicola* led to generation of T regulatory cells in the gut and increased production of IL-10 in treated group compared to controls. Treatment of mice induced for arthritis in a therapeutic protocol led to a significant decrease in incidence (40% in treated versus 80% of control) and severity of arthritis.

Conclusion: *P. histicola* modulated immune responses in the gut thereby modulating systemic immune response and suppression of arthritis suggesting this treatment can induce tolerance in periphery leading to systemic immune suppression. Since bacteria being used for treatment is a gut-derived commensal, there are less likely to be significant side effects.

Disclosure: **D. Luckey**, None; **E. Marietta**, None; **H. S. Luthra**, None; **R. Patel**, None; **J. A. Murray**, None; **A. Mangalam**, None; **V. Taneja**, None.

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A Novel Peptide Inhibiting the Binding Between C1q and Immunoglobulin Ameliorates Joint Destruction in Rats with Collagen-Induced Arthritis. Yu Moriguchi and Tetsuya Tomita. Osaka University Graduate School of Medicine, Suita, Japan

Background/Purpose: C1q is the major subcomponent of the first component of complement protein. The activation of the complement is triggered by binding of C1q to the Fc fragment of immunoglobulin G (IgG). It has been reported that rheumatoid arthritis (RA) patients with high concentrations of C1q in their blood will suffer from joint destruction in the future. Since the activation of C1q is thought to be involved in this joint destruction, binding inhibitor between C1q and IgG will be one of the candidates of new anti-RA drug. The purpose of the present study is to identify the sequence essential for binding between C1q and IgG, to confirm the inhibitory capacity of the peptide with the same sequence, and to verify in a rat collagen-induced arthritis (CIA) model that the peptide has possibility to be a new therapeutic agent for RA.

Methods: To find the binding inhibitor, we constructed peptide array to identify amino acid sequences of C1q that is crucial for binding between C1q and IgG. Some sequences based on this peptide array analysis were subsequently confirmed to inhibit the binding between C1q and IgG, and the peptide with the most inhibitory sequence (R1 peptide) was determined. For in vivo application, rats with CIA were intraperitoneally injected with R1 peptide or methotrexate (MTX) starting after the onset of arthritis. Disease activity scores, radiographic scores, and histologic scores were evaluated on day 36. Cytokine expressions in the tissue were assessed by realtime RT-PCR. Spleen cell proliferation ex vivo in response to mitogens was examined. Osteoclast formation ex vivo induced by soluble receptor activator of nuclear factor KB ligand (sRANKL) and MCSF was examined. Immunohistochemistry was performed to verify the deposition of IgG and C1q in ankle joints.

Results: R1 peptide as well as MTX significantly decreased the disease activity scores of CIA. The mean radiographic and histologic scores were significantly lower in the R1-treated rats than in untreated rats. Steady state mRNA levels of TNF-a and IL-1b in ankle joints were decreased in R1-treated rats. There was a significant reduction in phytohemagglutinin-stimulated proliferation of spleen cells in R1-treated rats with the dose of 100 mg/kg day compared to the untreated. Furthermore the osteoclast-like cell differentiation induced by both sRANKL and MCSF was significantly inhibited in R1-treated rats compared to untreated and even MTX-treated rats. Lastly, immunohistochemistry revealed that the deposition of local C1q and was significantly suppressed in R1-treated rats.

Conclusion: The present study demonstrated that R1 peptide sequence could be essential for binding between C1q and IgG. Furthermore, R1 peptide suppresses the progression of joint destruction in a rat CIA model equivalently to MTX treatment, suggesting the peptide is a potential therapeutic agent for rheumatoid arthritis.

Disclosure: **Y. Moriguchi**, None; **T. Tomita**, None.

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Synovial Fibroblast Migration Is Modulated by the Focal Contact Protein Lasp-1. Adelheid Korb-Pap[1], Jan Hillen[1], Marianne Heitzmann[1], Catherine S. Chew[2], Stefan Butz[3], Dietmar Vestweber[3], Hermann Pavenstädt[1] and Thomas Pap[1]. [1]University Hospital Muenster, Muenster, Germany, [2]Medical College of Georgia, Augusta, GA, [3]Max Planck Institute of Molecular Biomedicine, Muenster, Germany

Background/Purpose: RA synovial fibroblasts (SF) have been suggested to contribute to the spreading of disease through their ability to leave cartilage destruction sites, migrate via the bloodstream and re-initiate the destructive process at distant articular cartilage surfaces. The underlying mechanisms are unclear, but the actin-crosslinking protein Lasp-1 is of interest in this context, because it localizes to the leading edges of migrating cells and is of importance for the metastatic dissemination of different tumors. Therefore, it is particularly important to investigate the role of Lasp-1 in synovial fibroblast migration and its effects on RA.

Methods: The expression of Lasp-1 in the hind paws of wt and hTNFtg mice, an established model for human RA, was investigated by immunohistochemistry. Western-blot analyses and immunofluorescence was performed to analyze Lasp-1 expression and sub-cellular distribution in SFs from wt and hTNFtg mice. The migratory capacity of SFs derived from wild-type, Lasp-1$^{-/-}$ and hTNFtg mice was studied in a modified scratch assay as well as in a transmigration assay using murine endothelioma cells (bEnd.5) as an endothelial barrier and TNF-alpha as a stimulus. Furthermore, we used Lasp-1 knockout mice for interbreeding studies with hTNFtg mice.

Results: Immunostainings and Western Blot analyses showed a prominent expression of Lasp-1 in synovial fibroblasts obtained from hTNFtg mice with a characteristic sub-cellular distribution localizing Lasp-1 to structures of cell adhesion and invasion. In the scratch assay, Lasp-1$^{-/-}$ SFs exhibited a significantly reduced migration rate after 2 days (-30% vs. wt, p<0.05). Although the migratory capacity of unstimulated wt SFs through the endothelial monolayer was generally low (-32% vs. hTNFtg, p<0.05), this was virtually abolished by the knock out of Lasp-1 (-78% vs. wt, p<0.05). TNF-alpha enhanced the migratory potential of wild-type SFs to a significantly higher extent than of Lasp-1 null SFs (+84%, p<0.05). Interestingly, interbred Lasp1$^{-/-}$/hTNFtg mice presented milder clinical symptoms and analyses of histopathology revealed less cartilage degradation than hTNFtg mice at an age of 14 weeks.

Conclusion: Our data provide first evidence that Lasp-1 regulates the migratory capacity of synovial fibroblasts and influences the severity of arthritis in hTNFtg mice. While the mechanisms of trans-endothelial migration of SFs are largely undiscovered, our data suggest that these cells - when activated - migrate through the formation of invasive and adhesive membrane structures such as invadopodia, where Lasp-1 is prominently localized. Thus, targeting Lasp-1 may be a promising strategy modulate the invasive and migratory behavior of synovial fibroblasts in RA.

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FLIP in Macrophages Promotes the Progression of Serum Transfer-Induced Arthritis. Qi Quan Huang[1], Robert Birkett[2], Renee E. Koessler[1], G. Kenneth Haines III[3], Harris R. Perlman[1] and Richard M. Pope[4]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Yale University, New Haven, CT, [4]Northwestern Univ Med School, Chicago, IL

Background/Purpose: Flip is well known as an anti-apoptotic protein induced by chronic inflammation that protects against death receptor-mediated apoptosis. Employing a FLIP myeloid lineage knock-out mouse line ($Flip^{d/f}$, $LysM^{cre/+}$), we identified that FLIP is essential for macrophage differentiation and survival and for granulocyte homeostasis. This study was performed to define the role of FLIP in myeloid cells in K/BxN anti-GPI serum transfer-induced arthritis.

Methods: Arthritis was induced by introducing 300ml anti-GPI serum collected from K/BxN mice into $Flip^{f/f}$, $LysM^{cre/+}$ mice and the age and gender matched littermate controls. Cell types and differential in peripheral blood were determined by complete blood count. Cell types present in various organs were determined employing multi-color fluorochrome-conjugated cell marker antibodies, analyzed by flow cytometry. The mouse ankles harvested at the indicated time points were fixed in 10% formalin for H&E histological staining, or frozen in −80°c for ELISA cytokines analysis.

Results: Similar to the $Flip^{f/d}$, $LysM^{cre/+}$ mice reported earlier, $Flip^{f/f}$, $LysM^{cre/+}$ mice exhibited a significant increase of circulating neutrophils and monocytes, multi-organ neutrophil infiltration, and significantly reduced mature macrophages in multi-effector organs, such as peritoneal cavity, although it was less severe. The $Flip^{f/f}$, $LysM^{cre/+}$ developed a significantly more severe of acute phase arthritis on days 2 and 4 post-induction compared to the controls. The development of arthritis stopped after day 4 and began to improve in $Flip^{f/f}$, $LysM^{cre/+}$ mice, while the controls continued to progressive, peaking at day 9. The arthritis was significantly reduced in the $Flip^{f/f}$, $LysM^{cre/+}$ mice between days 7 to day 14 compared with the controls. Histological analysis demonstrated more articular and extra-articular inflammation and neutrophils in the $Flip^{f/f}$, $LysM^{cre/+}$ ankles collected in day 2 and 4. In contrast, inflammation, cartilage destruction, erosion and pannus were significantly reduced on day 10 and/or 14 in the $Flip^{f/f}$, $LysM^{cre/+}$ mice. Further, IL-1b in the ankle joints was significantly higher in $Flip^{f/f}$, $LysM^{cre/+}$ ankles collected in day 0, 2 and 4, but not day 10 of arthritis compared with the controls. However, IL-1b in the ankle ankles positively correlated with arthritis in the control group, but no correlation was observed in the $Flip^{f/f}$, $LysM^{cre/+}$ mice. In preliminary experiments, the infusion of wild type macrophages into the $Flip^{f/f}$, $LysM^{cre/+}$ mice just after the injection of the anti-GPI serum resulted in less severe arthritis initially but more severe arthritis later in the course.

Conclusion: These studies demonstrate that FLIP in macrophages is essential for regulating neutrophil homeostasis and acute inflammation and that it promotes the progression of the effector phase of arthritis. The lack of association between inflammation and IL-1b in the $Flip^{f/f}$, $LysM^{cre/+}$ mice is consistent with diminished IL-1b signaling. These observations suggest that FLIP in macrophages is a potential target for the therapy in patients with rheumatoid arthritis.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety I
Monday, November 12, 2012, 2:30 PM–4:00 PM

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Long-Term Safety of Tocilizumab in Patients with Rheumatoid Arthritis and a Mean Treatment Duration of 3.7 Years. Mark C. Genovese[1], Anthony Sebba[2], Andrea Rubbert-Roth[3], Juan José Scali[4], Rieke Alten[5], Joel M. Kremer[6], Laura Pitts[7], Emma Vernon[7] and Ronald F. van Vollenhoven[8]. [1]Stanford University Medical Center, Palo Alto, CA, [2]University of South Florida, Tampa, FL, [3]University of Cologne, Cologne, Germany, [4]Durand University Hospital, Buenos Aires, Argentina, [5]Schlosspark Klinik, University Medicine Berlin, Berlin, Germany, [6]Albany Medical College, Albany, NY, [7]Roche, Welwyn Garden City, United Kingdom, [8]Karolinska Institute, Stockholm, Sweden

Background/Purpose: Tocilizumab (TCZ)—an IL-6 receptor inhibitor—has demonstrated efficacy in improving signs/symptoms, reducing joint damage, and improving physical function in rheumatoid arthritis (RA) patients (pts). This analysis assessed the long-term safety of TCZ (up to 5.8 y of exposure) in adult RA pts.

Methods: Analysis was performed in all pts who received ≥1 TCZ dose in 5 placebo-controlled trials (OPTION, TOWARD, RADIATE, AMBITION, LITHE), a clinical pharmacology study, or long-term extension studies. Data were pooled and analyzed from initial TCZ exposure to April 1, 2011 (cutoff).

Results: 4009 pts were included. Mean (median [range]) duration was 3.7 (4.6 [0.0–5.8]) y; total observation time was 14,994 pt-y (PY). Rates of serious adverse events (SAEs), serious infections, myocardial infarction (MI) SAEs, stroke SAEs, hepatic SAEs, and gastrointestinal (GI) perforations were stable over time (Table). The overall rate of AEs leading to withdrawal was 5.0/100PY (95% CI: 4.7, 5.4). Infections, laboratory abnormalities, and neoplasms were the most common AEs leading to withdrawal (0.97/100PY, 0.89/100PY, and 0.80/100PY). 8 pts withdrew because of anaphylaxis events; these were previously reported.[1] Rates/100PY (95% CI) were 14.6 (14.0, 15.3) for SAEs and 0.57 (0.45, 0.70) for deaths. The most common SAEs were infections, which occurred at a rate of 4.5/100 PY (95% CI: 4.1, 4.8); the most common serious infection was pneumonia (0.95/100 PY; 95% CI: 0.80, 1.12). Overall rates/100PY (95% CI) of MI SAEs, stroke SAEs, and hepatic

SAEs were 0.25 (0.18, 0.35), 0.31 (0.23, 0.42), and 0.04 (0.01, 0.09), respectively. The GI perforation rate was 0.20/100PY (95% CI: 0.13, 0.29). There were 194 confirmed malignancies, including 65 nonmelanoma skin cancer (NMSC) cases, corresponding to an overall rate/100PY (95% CI) of 1.29 (1.12, 1.49) and, excluding NMSC, of 0.86 (0.72, 1.02). SIR for malignancies (all sites) was 1.19 (0.99, 1.42), which was not statistically different from the US general population rate (SEER database).

Table. Event Rate/100 PY (95% CI) Over 12-Month Periods

	0–12 months	13–24 months	25–36 months	>36 months
AEs leading to withdrawal	9.3 (8.3 10.4)	4.5 (3.8 5.3)	4.1 (3.4 5.0)	3.2 (2.7 3.7)
SAEs	16.1 (14.7 17.4)	14.2 (12.9 15.7)	15.7 (14.2 17.2)	13.5 (12.5 14.5)
Serious infections	4.6 (4.0 5.4)	3.9 (3.3 4.7)	5.4 (4.6 6.3)	4.2 (3.7 4.7)
MI SAEs	0.29 (0.14 0.53)	0.17 (0.05 0.39)	0.29 (0.12 0.57)	0.26 (0.15 0.43)
Stroke SAEs	0.43 (0.24 0.71)	0.26 (0.11 0.52)	0.29 (0.12 0.57)	0.28 (0.16 0.45)
Hepatic SAEs	0	0.10 (0.02 0.29)	0.04 (0.00 0.20)	0.03 (0.00 0.13)
GI perforations	0.20 (0.08 0.42)	0.13 (0.04 0.34)	0.29 (0.12 0.57)	0.19 (0.10 0.34)

Conclusion: The safety profile of TCZ in the current analysis is consistent with that in prior TCZ analyses[1,2]; it remained stable over a mean treatment duration of 3.7 y, and no new safety signals have emerged. AE rates described herein are consistent with those reported in the RA population, and the overall rate of malignancies does not exceed reported background rates (SEER database).[3–10]

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1641

When Can Biological Therapy Be Resumed in Patients with Rheumatic Conditions Who Develop Tuberculosis Infection During Tumour Necrosis Factors Antagonists Therapy? Study Based On the Biobadaser Data Registry. Maria Victoria Hernández[1], Miguel A. Descalzo[2], Juan D. Cañete[1], Raimon Sanmarti[1] and BIOBADASER Study Group[3]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Spanish Society of Rheumatology, Madrid, Spain, [3]Madrid, Spain

Background/Purpose: Tuberculosis infection (TI) is one of the most serious adverse events related to tumour necrosis factor (TNF) antagonists. According to the current treatment guidelines (1), biological therapy may be resumed after completion of the treatment of active TI. However, during TI therapy, some patients undergo a relapse of the underlying inflammatory condition due to the prolonged duration of therapy. Our objective was to analyse whether patients suffering TI during biological therapy could reinitiate the biological therapy before completion of TI therapy with no relapse of TI.

Methods: Retrospective study based on data from the Spanish Biological Therapy registry (BIOBADASER), which has included 6479 patients from the beginning of the registry (February 2000) until November 2011. During this time, 52 cases of active TI requiring the withdrawals of biologicals were reported. We selected patients on TNF blockers who reinitiated biological treatment after development of TI. We analysed: demographic characteristics; diagnosis and disease duration; type of biological agent at TI diagnosis and mean time received; type of TI; mean time from TI diagnosis until biological therapy was resumed; type of biological agent reinitiated, and outcomes. To assess differences in the outcome of TI, we divided patients into 2 groups according to reinitiation of biological treatment before (group 1) or after (group 2) TI treatment completion.

Results: Twenty-seven patients (15 female, mean age 56.7 ± 15.1 years) reinitiated biological therapy after withdrawal due to TI. Diagnoses were: 14 rheumatoid arthritis; 6 ankylosing spondylitis; 3 psoriatic arthritis; 2 juvenile idiopathic arthritis; 1 undifferentiated spondyloarthropathy and 1 Behçet's disease. Mean disease duration was 18.8 ± 9.4 years. The type of TI was: pulmonary in 14 patients; disseminated tuberculosis in 12; cutaneous in 1. The TNF blocker received at TI diagnosis was: 6 patients infliximab, 2 etanercept and 1 adalimumab in group 1; and 14 infliximab, 3 adalimumab and 1 etanercept in group 2; with a median of treatment of 13 months. Biological therapy was reinitiated while patients were receiving TI treatment in 9 out of 28 patients (group 1), with a mean TI treatment of 2.25 ± 0.9 months. Fifty-six percent of group 1 patients reinitiated with the same biological agent, whereas in group 2 only 27.7% resumed the previous treatment. The underlying inflammatory condition improved in all patients. No patient of both groups had a relapse of TI after a follow-up of 49.2 ± 28.8 months (42 ± 30.7 in group 1 and 53.2 ± 27.8 in group 2).

Conclusion: Active TI in patients receiving TNF antagonists may not be a contraindication for the reinitiation of biological therapy before completion of TI treatment, especially in patients who experience a relapse of the underlying inflammatory disease, who have a favourable outcome of TI and who have received at least 2 months of tuberculostatic therapy.

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Biologics and Mortality Risk in Rheumatoid Arthritis - Results of a Population Based Study. Diane Lacaille[1], Michal Abrahamowicz[2], Eric C. Sayre[3] and John Esdaile[1]. [1]Arthritis Research Centre of Canada, University of British Columbia, Vancouver, BC, [2]McGill University, Montreal, QC, [3]Arthritis Research Centre of Canada, Vancouver, BC

Background/Purpose: Biologic agents, due to their effect on disease activity, may reduce the risk of premature mortality in rheumatoid arthritis (RA). We evaluated the association between exposure to biologics and risk of mortality in RA, using a population-based RA cohort with administrative health data.

Methods: Using administrative billing data from the Ministry of Health, we assembled a population-based cohort including all RA cases in the province who received care for RA between 01/1996 and 03/2006, using previously published RA criteria, with follow-up until 03/2010. Administrative data was obtained on all medications since 01/1996; MD visits, hospitalizations, and tests since 01/1990. For this study we identified all RA cases who used a biologic agent (anti-TNF, rituximab, anakinra or abatacept) during follow-up. Each biologic user was matched with one RA control who never used a biologic but used at least 3 DMARDs (to mimic coverage requirements) and with a recent (within 6 mos) change in DMARD. Controls were also matched on age, sex, calendar year of inclusion and closest propensity score, using a greedy matching technique. Matched controls were given the date of initiation of first biologic of the user they were matched to. A propensity score (PS) was calculated at time of initiation using markers of RA severity, as well as co-morbidities increasing risk of death. Despite selecting controls with the closest PS, matching was imperfect; therefore PS quintiles were added to the final multivariable model. Cox proportional hazard model (PHM) was used to estimate risk of death associated with biologic exposure, evaluated as a time dependent variable representing current or recent use of anti-TNF, where cases were considered exposed for up to 3 months after discontinuation. Time analyzed was from date of initiation to death or end of follow-up. PHM analysis was also adjusted for age, sex, RA duration, Charlson co-morbidity score, PS quintiles and the variables included in the PS model that were not balanced. Sensitivity analyses were carried out to test the robustness of results.

Results: Our sample includes 2156 biologic users and 2156 matched controls (mean (SD) age: 56.3(14.6), 74.7% females). We observed 573 deaths (326 in controls; 247 in biologic users). Exposure to biologics was associated with a reduced risk of death (aHR (95%CI): 0.25 (0.18; 0.36), p < 0.0001). A sensitivity analysis not requiring matched controls to have used 3 prior DMARDs or a recent change in DMARD yielded almost identical results (aHR (95%CI): 0.26 (0.18; 0.36), p < 0.0001). Another sensitivity analysis, without use of PS, but where the PS variables were allowed to enter the PHM and controls were only required prior use of one DMARD, yielded similar results (aHR (95%CI): 0.31 (0.22; 0.45), p < 0.0001). Limitations of

our study are those inherent to observational study, including possible effect of residual or unmeasured confounding, and selection bias from non-random allocation of treatment.

Conclusion: In a population-based cohort, exposure to biologics was associated with a significant reduction in mortality. Given the increased mortality risk of RA, this has important implications for health policy makers, health care providers and people with arthritis.

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Outcomes of Pregnancy in Subjects Exposed to Certolizumab Pegol.
Megan Clowse[1], Douglas C. Wolf[2], Christian Stach[3], Gordana Kosutic[4], Susan Williams[4], Ido Terpstra[5] and Uma Mahadevan[6]. [1]Duke University Medical Center, Durham, NC, [2]Atlanta Gastroenterology Associates, Atlanta, GA, [3]UCB Pharma, Monheim, Germany, [4]UCB Pharma, Raleigh, NC, [5]UCB Pharma, Brussels, Belgium, [6]University of California, San Francisco, San Francisco, CA

Background/Purpose: Certolizumab pegol (CZP) is an Fc-free, PEGylated, anti-TNF approved in the US for the treatment of Crohn's disease (CD) and rheumatoid arthritis (RA). Pre-clinical and clinical data suggest a lack of active neonatal Fc receptor-dependent placental transfer of CZP [1, 2]. There are few reports of pregnancy outcomes following exposure to CZP to date. This work provides additional information regarding the primary pregnancy outcomes in women exposed to CZP.

Methods: The global CZP safety database was searched for all medically confirmed cases of pregnancy through March 6, 2012. The proportion of live births, spontaneous miscarriages, and elective terminations for women directly exposed to CZP before or during confirmed pregnancy were compared to those expected for the general US population of pregnant women.

Results: Of 294 reported pregnancy events, 152 had known outcomes, 89 had unknown outcomes and 53 were ongoing. Of the 152 events with known outcomes, 139 were cases in which the mother had direct exposure to CZP, with 57 from the clinical trial program and 82 from post-marketing reports. The remaining 13 were cases with the father exposed to CZP resulting in 10 live births, 2 miscarriages and 1 elective termination. Of the 139 direct exposure cases with known outcomes, the underlying conditions were CD (N=107), RA (N=17) and healthy subjects (N=2) with 13 cases classified as other or having missing data. 91 of 139 cases were from the US. 103 of 139 pregnancies resulted in live births (see table) and the median gestational age was 38.3 weeks (data available for 40 births). 21 pregnancies ended in spontaneous miscarriage. 15 pregnancies resulted in elective termination. These results are similar to those reported in the general population in the US (see table). In 103 live births there were 2 reported cases of congenital disorder (Rate in the US general population is 3% [4]); 1 baby had mild, unilateral hydronephrosis on antenatal ultrasound and was described as healthy upon birth. The other baby had vesicoureteric reflux.

Population	Number of pregnancy events (N)	Live births	Miscarriages	Elective termination
Direct exposure to CZP from global safety database	139	103/139 (74.1%)	21/139 (15.1%)	15/139 (10.8%)
US General Population (National Vital Statistics Data - 1990 to 2004) [3]	6 390 000	64.3%	16.6%	19.1%

Conclusion: Currently available data from 139 pregnant women exposed to CZP, report outcomes consistent with the US National Vital Statistics data. Additional data from larger numbers of pregnant women exposed to CZP are required to validate acceptable safety and tolerability of CZP in pregnancy.

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Enhanced Pharmacovigilance Reporting of Malignancies in Children and Young Adults Taking Etanercept.
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Background/Purpose: Recent reports suggest an increased rate of malignancy in children with juvenile idiopathic arthritis (JIA) (Simard, A&R 2010;62:3776; Beukelman A&R 2012;64:1263). In 2011, the US FDA required TNF-blocker sponsors to initiate a 10-year postmarketing reporting commitment of all malignancies in children and young adults. We present the results to date for etanercept (ETN).

Methods: We reviewed all malignancies reported in patients ≤ 30 years (yrs) of age from clinical trials (CTs) and ARGUS (postmarketing cases, observational studies). Cases were included regardless of latency period, time on ETN, lack of tumor histology, reporting source (consumer, investigator, healthcare provider, regulatory agency, literature), or confounding factors. CT malignancy rates in ETN arms were compared with placebo/comparator arms. Exposure data used to generate ARGUS reporting rates were determined from the total mg of ETN dispensed from Nov 1998 through 31 Dec 2011 and from US market research-determined age distribution (birth-30 yrs, birth-11 yrs, 12–17 yrs, 18–30 yrs) extrapolated to the global market. Confidence intervals were not calculated for ARGUS rates as the ETN exposure data are estimates. Age-specific rates were generated from the Surveillance Epidemiology and End **Results** (SEER) database v7.0.9. ARGUS reporting rates and SEER rates for all malignancies and malignancy types with ≥ 5 cases are shown.

Results: In CTs, 1 malignancy each in ETN and placebo/comparator arms has been reported. ETN exposure was 231,404 patient-years (PY) (24,820 PY in birth-11 yrs; 38,099 PY in 12–17 yrs; 168,485 PY in 18–30 yrs). Rates observed per 100,000 PY in ARGUS and SEER, respectively for all malignancies were: age birth-30 yrs: 44.5 and 26.4; birth-11 yrs: 24.2 and 15.3; 12–17 yrs: 34.1 and 17.0; and 18–30 yrs: 46.9 and 42.1. Five or more cases of leukemia, lymphoma, melanoma, thyroid, and cervical cancers were reported. Rates for melanoma, thyroid, and cervical cancers seemed similar in ARGUS and SEER. Overall ARGUS leukemia rates seemed similar to SEER except for patients birth-11 yrs (12.1 and 5.4 per 100,000 PY, respectively) based on 3 cases. There were 23 cases of lymphoma. ARGUS rates of non-Hodgkin lymphoma seemed similar to SEER. Rates per 100,000 PY for Hodgkin disease (HD) in ARGUS and SEER were: birth-30 yrs: 3.9 and 2.2; birth-11 yrs: 12.1 and 0.4; 12–17 yrs 7.9 and 2.1; 18–30 yrs: 1.8 and 4.1.

Conclusion: In the ARGUS database, overall malignancy rates seemed higher than in the general pediatric population (SEER). Stratification by age suggests higher rates for those younger than 18 years old compared to SEER rate, consistent with a report of increased malignancy in all JIA patients (standardized rate = 79.3 per 100,000 PY), and untreated JIA patients (106.5 per 100,000 PY) (Beukelman 2012). No increased malignancy rate seemed to occur in the young adult age group. The overall lymphoma reporting rate was not increased; however, there was more HD in younger patients, most with long-standing disease and multiple immunosuppressive exposures.

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Combination of Isoniazid for Latent Tuberculosis with Traditional and/or Biologic Disease Modifying Anti-Rheumatic Drugs Is Well Tolerated in Patients with Rheumatic Diseases.
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Background/Purpose: Patients with rheumatic diseases (RD) are typically treated with conventional and /or biologic disease modifying anti-rheumatic drugs (DMARD's) including tumor necrosis factor inhibitors (TNFi). Prior to biologic initiation subjects are typically screened for latent tuberculous infection (LTBI) with tuberculin skin test (TST) or Quantiferon-Gold in Tube (QFN) assay (Cellestis) and chest x-ray (CXR). If positive, such patients are treated with Isoniazid (INH) for 9 months in addition to their standard therapy. Since both INH and DMARDs may be individually hepatotoxic, there is a concern for enhanced liver toxicity when those are

combined. We investigated the incidence of liver toxicity upon combination of traditional and/ or biologic DMARDs with INH in pts with RD.

Methods: One hundred and eighty patients with RD and a positive TST (≥5 mm induration) and/or QFN result, from a single institution were evaluated. Liver function tests (LFTs) including aspartate (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and total bilirubin (TB) were tested at baseline and every 8–12 weeks while on therapy. Subjects' serial LFTs over 6 months prior to INH initiation were used as controls for incident liver toxicity while on therapy. **Results** were expressed as –fold increases from upper limit of normal (x-fold ULN).

Results: Average duration of INH therapy was 8.8 ± 3.2 months. 180 patients underwent a mean of 4.2 tests while on INH; 177 baseline samples were collected, followed by 580 additional samples during INH treatment. The latter were compared to 259 samples serially collected from the respective subjects within 6 months prior to INH therapy (table). Patients received 1.85 ± 0.83 DMARDs, 88% of which was methotrexate at a dose of 19.2 ± 2.6 mg. One hundred forty seven (82%) subjects were on concomitant TNFi. 171/177 (96.6%) baseline AST, and 164/177 (92.6%) baseline ALT tests were normal (table); Any AST or ALT elevations above the ULN occurred in 13.5% and 10.8% of tests while on INH compared to 6.5% and 3.8% respectively prior to INH (p=0.004 and p=0.001 respectively). However, AST or ALT elevations ≥2-fold ULN occurred in 2.2% and 1.5% of tests on INH compared to 0.4% and 0.4% (respective p-values of 0.2 and 0.29). In 6 out of 180 pts (3.3%) INH was thought to be responsible for elevation of LFT's therefore necessitating withdrawal of the drug. None of the pts developed significant adverse events and LFT's normalized after INH was discontinued.

AST: 180 patients/177 baseline tests/ 578 tests on INH/ 258 tests prior to INH

Baseline-n, (%)		period on INH-n, (%)		prior to INH-n (%)		p-value
Normal	171/177 (96.6)	Normal	481/556 (87)	Normal	230/246 (93)	*0.004*
		Abnormal	75/556 (13.5)	Abnormal	16/246 (6.5)	*0.004*
		≥x1.5-fold	30/556 (5.4)	≥x1.5-fold	2/246 (0.8)	*0.001*
		≥x2-fold	12/556 (2.2)	≥x2-fold	1/246 (0.4)	0.2
Abnormal	6/177 (3.4)	Abnormal	9/22 (41)	Abnormal	7/12 (58)	0.47
		≥x1.5-fold	5/22 (23)	≥x1.5-fold	1/12 (8)	0.39
		≥x2-fold	3/22 (14)	≥x2-fold	1/12 (8)	1
		Normal	13/22 (59)	Normal	5/12 (42)	0.47

ALT: 180 patients/177 baseline tests/ 580 tests on INH/ 259 tests prior to INH

Baseline-n, (%)		period on INH-n, (%)		prior to INH-n (%)		p-value
Normal	164/177 (92.6)	Normal	477/535 (89.2)	Normal	225/234 (96.2)	*0.001*
		Abnormal	58/535 (10.8)	Abnormal	9/234 (3.8)	*0.001*
		≥x1.5-fold	18/535 (3.4)	≥x1.5-fold	2/234 (0.9)	*0.048*
		≥x2-fold	8/535 (1.5)	≥x2-fold	1/234 (0.4)	0.29
Abnormal	13/177 (7.3)	Abnormal	27/45 (60)	Abnormal	12/24 (50)	0.46
		≥x1.5-fold	11/45 (24.4)	≥x1.5-fold	10/24 (42)	0.17
		≥x2-fold	5/45 (11)	≥x2-fold	4/24 (16.7)	0.7
		Normal	18/45 (40)	Normal	12/24 (50)	0.29

Conclusion: Despite the heightened concern for significant hepatotoxicity, the combination of traditional and/ or biologic DMARDs with INH is clinically well tolerated; the incidence of significant LFT elevations is uncommon in compliant and regularly monitored patients.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment II: Clinical Aspects/Pregnancy
Monday, November 12, 2012, 2:30 PM–4:00 PM

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The Mechanism of Umbilical Cord Mesenchymal Stem Cells in the Upregulation of Regulatory T Cells by TGF-β1 in Systemic Lupus Erythematosus. Lingyun Sun, Dandan Wang, Lin Lu and Xia Li. Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Umbilical cord (UC) derived mesenchymal stem cells (MSCs) have shown immunoregulation on various immune cells. The aim of this study is to investigate the mechanism of UC-MSCs in the upregulation of peripheral regulatory T cells in patients with systemic lupus erythematosus (SLE).

Methods: Peripheral blood mononuclear cells (PBMC) from 20 SLE patients and normal controls were co-cultured with UC-MSCs at the ratios of 1:1, 10:1 and 50:1 respectively for 72 hours, and the proportions of $CD4^+CD25^+Foxp3^+$ regulatory T cells were analyzed by flowcytometry. PBMC and serum from active SLE patients and normal controls were used to stimulate UC-MSCs, TGF-β1 mRNA expressions on UC-MSCs were detected by real-time PCR. Supernatant TGF-β1 levels were determined by ELISA. The TGF-β1 small interfering RNA (siRNA) was used to interfere TGF-β1 expression on UC-MSCs, then to determine its effect on the regulation of SLE Treg cells. TGF-β1 inhibitor was added in the culture system of UC-MSCs and PBMC from active SLE patients to observe its role on the upregulation of Treg cells by UC-MSCs.

Results: UC-MSCs could dose-dependently upregulate peripheral $CD4^+CD25^+Foxp3^+$ Treg proportion in SLE patients, which was not depended on cell-cell contact. UC-MSCs had no regulatory effect on Treg cells in normal controls. Compared with the non-stimulated group and normal PBMC stimulated group, PBMC from SLE patients significantly promoted TGF-β1 mRNA expression on UC-MSCs (relative gene expression was 1.00 ± 0.09, 1.95 ± 0.62, 4.20 ± 2.34, respectively, both $P<0.05$). Supernatant TGF-β1 levels were significantly elevated in the presence of SLE PBMC. Serum of SLE patients (5%) enhanced TGF-β1 mRNA expression on UC-MSCs (12.19 ± 4.49), remarkably higher than fetal bovine serum cultured group (1.33 ± 0.06, $P<0.01$) and normal control serum cultured group (2.53 ± 0.72, $P<0.01$). Additionally, TGF-β1 siRNA interfered UC-MSCs failed to upregulate Treg cells in SLE patients (SLE PBMC + TGF-β1siRNA UC-MSCs group $2.33\% \pm 0.99\%$ *vs.* SLE PBMC group $1.80\% \pm 0.65\%$, $P>0.05$). Furthermore, in the presence of TCR stimulation, TGF-β1 specific inhibitor SB431542 significantly inhibited the regulatory role of UC-MSCs on Treg cells in SLE patients (SLE PBMC+UC-MSCs+SB431542 group $4.58\% \pm 2.10\%$ *vs.* SLE PBMC+UC-MSCs group $7.85\% \pm 3.54\%$, $P<0.05$).

Conclusion: Immune microenvironment in SLE patients can significantly stimulate TGF-β1 expression on UC-MSCs, which plays an important role in the upregulation of Treg cells in patients. This study provides a new mechanism for the regulation of Treg cells by UC-MSCs in SLE.

Disclosure: L. Sun, None; **D. Wang**, None; **L. Lu**, None; **X. Li**, None.

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Critical Management Decisions in Cardiac Neonatal Lupus: The Role of Fluorinated Steroids. Peter M. Izmirly[1], Sara Sahl[1], Amit Saxena[1], Nathalie Costedoat-Chalumeau[2], Jean-Charles Piette[3], Munther A. Khamashta[4], Cecilia Pisoni[5], Deborah Friedman[6] and Jill P. Buyon[1]. [1]New York University School of Medicine, New York, NY, [2]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [5]Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina, [6]New York Medical College, Valhalla, NY

Background/Purpose: Life-threatening cardiac manifestations of neonatal lupus (cardiac-NL) include complete block, endocardial fibroelastosis (EFE) and dilated cardiomyopathy (DCM), all supportive of intense fibrosis at the AV node and beyond. The overall case fatality rate is 17.5% but ranges from 7.8% for isolated block to 46% when the block is accompanied by more extensive disease. Both prevention and treatment with fluorinated steroids (FS) have been considered but results are inconclusive and even conflicting, a disconcerting situation given the potential for maternal toxicity. Accordingly, we reviewed the records from the U.S. Research Registry for Neonatal Lupus (RRNL), and the French and U.K. Registries to ascertain whether the use of FS conferred a survival benefit for fetuses with cardiac-NL or prevented the recurrence of cardiac-NL.

Methods: Data from the RRNL were analyzed to determine whether the use of FS affected survival at six months. Isolated third degree block and risk factors associated with a poor prognosis for cardiac-NL (HR<50, DCM and EFE) were evaluated individually or in combination given the likelihood of more than one poor prognostic factor being present. The effect of FS on survival once hydrops was detected was also addressed. The efficacy of prophylactic FS was assessed in an international historical cohort.

Results: In 276 cases of cardiac-NL, sufficient data were available regarding medications used during pregnancy; 150 were treated with FS. Not unexpectedly, FS were most often used when disease extended beyond the AV node. Neither maternal race/ethnicity nor health status influenced the use

of FS. In isolated 3rddegree block, 2.6% (2/78) died by 6 months postpartum despite the use of FS compared to 0/74, in those never given FS, p=.50. In those with HR < 50 bpm, 0 of 25 exposed to FS died compared to 0 of 18 unexposed to FS. Of the 12 cases with EFE (present or absent block) 11 received FS and only 1 died (9.9%) which was an elective termination. In cases where DCM was present (with or without block) 25% (1/4) died by 6 months postpartum despite the use of FS compared to 20.0% (1/5) never given FS. In cases with ≥ 2 risk factors, 16.7% (1/6) exposed to FS died by 6 months postpartum compared to 33.3% (2/6) unexposed. In fetuses with hydrops, 55.6% (15/27) receiving FS died compared to 81.8% (9/11) who did not receive FS, p=.16. When terbutaline was added to FS for hydrops, 50.0% (5/10) died compared to 58.8% (10/17) not receiving terbutaline. With regard to prophylaxis, recurrent cardiac-NL occurred in 14.3% (2/14) of pregnancies of mothers given FS compared to 19.3% (47/257) in those not treated with FS, p=.58.

Conclusion: These data suggest that fetuses with isolated 3rd degree block, even those who develop severe bradycardia in absence of other risk factors, do well and the addition of FS does not improve the 6 month survival rate. FS may be beneficial in cardiac-NL cases which develop hydrops or have multiple poor prognostic factors. Available evidence does not support the use of FS to reduce the recurrence rate of cardiac-NL.

Disclosure: P. M. Izmirly, None; **S. Sahl**, None; **A. Saxena**, None; **N. Costedoat-Chalumeau**, None; **J. C. Piette**, None; **M. A. Khamashta**, None; **C. Pisoni**, None; **D. Friedman**, None; **J. P. Buyon**, None.

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Lupus Anticoagulant At First Pregnancy Visit Is Predictive of Pregnancy Loss. Michelle Petri[1], Anil Mankee[1], Ehtisham Akhter[1], Hong Fang[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Multiple factors, including proteinuria, antiphospholipid syndrome, thrombocytopenia and hypertension, are predictive of pregnancy loss in SLE. In the PROMISSE study of mediators of pregnancy loss, only a battery of lupus anticoagulant tests (Dil PT, dRVVT, PTT LA, and KCT) were predictive of adverse pregnancy outcomes (including pregnancy loss, preterm birth, pre-eclampsia, and small for gestational age). We examined the predictive value of one baseline lupus anticoagulant test (dRVVT) with pregnancy loss alone in women with SLE.

Methods: This analysis is based on pregnancies that were observed from 1987 to 2011. After excluding twin pregnancies, there were 402 pregnancies from 326 different women. We determined the percentage of women who had a pregnancy loss in groups defined by potential risk factors. Generalized Estimating Equations were used to calculate p-values, accounting for repeated pregnancies of the same woman.

Results: The age at pregnancy was <20 years (3%), 20–29 (50%), 30–39 (43%), and over 40 (3%). 59% were Caucasian and 34% African-American. Predictors of pregnancy loss are shown in the table. Lupus anticoagulant at the 1stvisit was highly predictive of pregnancy loss (and ever being positive was also associated, although less so).

Table 1. Proportion with Pregnancy Loss, by characteristics of the patients.

Patient Characteristic		Proportion (%) with miscarriage	P-value[2]
	All	46/402 (11%)	
Age	<20	1/13 (8%)	0.38
	20–29	20/202 (10%)	
	30–39	19/172 (11%)	
	40+	6/12 (50%)	
Ethnicity	Caucasian	28/235 (12%)	0.77
	African American	14/135 (10%)	
	Other	4/31 (13%)	
Year of conception	1986–1994	14/115 (12%)	0.32
	1995–1999	13/83 (16%)	
	2000–2004	10/80 (13%)	
	2005+	9/122 (7%)	
RVVT measured in first trimester[1]	Normal	16/187 (9%)	0.0022
	High (>45)	6/15 (40%)	
	No first-trimester measure	24/200 (12%)	
Ever positive for high RVVT	No	26/278 (9%)	0.030
	Yes	20/117 (17%)	
	Unknown	0/7 (0%)	

		Proportion (%) with miscarriage	P-value[2]
Anticardiolipin-IGG measured in first trimester[1]	Normal	11/127 (9%)	0.96
	High	1/11 (9%)	
	No first-trimester measure	34/264 (13%)	
Anticardiolipin ever present	No	16/158 (10%)	0.41
	Yes	30/241 (12%)	
	Unknown	0/3 (0%)	
Moderately active lupus	No	27/281 (10%)	0.012
	Yes	7/27 (26%)	
	Unknown	12/94 (13%)	
Low Complement in first trimester	No	23/227 (10%)	0.37
	Yes	11/78 (14%)	
	Unknown	12/97 (12%)	
Anti-dsDNA in first trimester	No	18/198 (9%)	0.18
	Yes	15/104 (14%)	
	Unknown	13/100 (13%)	
Mean Prednisone dose in first trimester	<10 mg	23/220 (10%)	0.60
	10+	11/88 (13%)	
	Unknown	12/94 (13%)	

[1]Based on the average of the measures during the first trimester or prior to miscarriage if miscarriage occurred in first trimester.
[2]Excludes the unknowns in the calculations.

Conclusion: The strongest predictor of pregnancy loss in SLE is the lupus anticoagulant in the first trimester by dRVVT testing. In contrast to the PROMISSE study, 3 lupus anticoagulant assays were not necessary. In addition, moderate disease activity by the physician global assessment was also predictive of pregnancy loss, but not low complement, anti-dsDNA, or anticardiolipin. These data suggest that treatment of the lupus anticoagulant should be considered, even in the absence of prior history of miscarriage.

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French Cohort Study of 141 Cases of Autoimmune Congenital Heart Block. Kateri Levesque[1], Alice Maltret[2], Mohamed Hamidou[3], Moez Jallouli[4], Jean Loup Pennaforte[5], Pauline Orquevaux[5], Jean-Charles Piette[6], Zahir Amoura[4], Francois Barriere[7], Jérome Le Bidois[2], Laurent Fermont[2], Laurence Cohen[8], Olivier Meyer[9], Olivier Fain[10], Arnaud Theulin[11], Hugues Lucron[12], Francois Sassolas[13], Holly Bezanahary[14], Gaëlle Guettrot-Imbert[15], Pascal Seve[13], Elizabeth Diot[16], Nathalie Morel[1], Christophe Deligny[17], Elisabeth Villain[2] and Nathalie Costedoat-Chalumeau[18]. [1]Groupe Hospitalier Pitié-Salpétrière, Paris, France, [2]Groupe Hospitalier Necker - Enfants Malades, Paris, France, [3]Hôtel Dieu, Hôpital Universitaire de Nantes, Nantes, France, [4]CHU Pitié-Salpêtrière, Paris, France, [5]CHU Reims, Reims, France, [6]Paris, [7]CHU Nantes, Nantes, France, [8]Institut Jacques Cartier, [9]Hopital Bichat, Paris, France, [10]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, Bondy, France, [11]Strasbourg University Hospital, Strasbourg, France, [12]CHU Fort-de-France, Fort de France, Martinique, [13]CHU Lyon, Lyon, France, [14]University Hospital of Limoges, Limoges, France, [15]Hopital Gabriel Montpied, Clermont-Ferrand, France, [16]Department of Internal Medicine, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire de Tours, Tours, France, Tours, France, [17]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [18]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France

Background/Purpose: Cardiac neonatal lupus manifestations mainly include congenital heart block (CHB), endocardial fibroelastosis and dilated cardiomyopathy. We report the preliminary results of the French registry of neonatal lupus.

Methods: This French registry was established in 2000 and includes foetuses or children with neonatal lupus, born to mothers with anti-SSA or/and anti-SSB antibodies. This database has Institutional Review Board approval. Here, we report data on CHB.

Results: 141 cases of CHB born to 124 mothers were included. When the first CHB was diagnosed, 45 mothers (36 %) had an autoimmune disease: 16 had systemic lupus erythematosus (1 with an antiphospholipid syndrome), 15 had Sjögren syndrome, and 14 had another connective tissue disease (CTD). After a median follow-up period of 5.6 years, [0.03–36.5], 85 women (60%) had a diagnosis of autoimmune disease (Sjögren syndrome in 33, systemic lupus erythematosus in 32, and other CTD in 20).

At the time of the CHB diagnosis, 24 (17%) of the pregnant women were treated with corticosteroids, 13 (9.2%) with hydroxychloroquine, and 21

(14.9%) with acetylsalicylic acid. The median term at diagnosis of CHB was 22 WG [16–37 WG]. Twenty-two foetuses (15.6%) were also diagnosed with endocardial fibroelastosis. Among the 141 fetuses with CHB, there were 9 intrauterine deaths, 10 elective terminations of pregnancy, and 122 (86.5%) children born alive at a median term of 37 WG [28–40]. After a median follow-up period of 5.6 years, [0.03–36.5], 11 children (9%) had died. Three died in the neonatal period (2 from complication of CHB and one from prematurity) and 8 later on at a median age of 10 months [2–60]. Of those 8 children, 7 deaths were attributed to a cardiomyopathy associated with CHB, and one to a nosocomial infection.

Ninety five children (77.8 %) had a pacemaker, implanted at a median age of 3.7 months [0.01–14.4]. Fifteen children (12.3%) developed a cardiomyopathy requiring a medical treatment and 9 of those 15 children died from complications of this cardiomyopathy. There was no cardiac transplantation.

After a first pregnancy complicated with a CHB, 57 women had a total of 84 subsequent pregnancies. The following pregnancies were complicated by a CHB in 20.2% of cases (n=17). There were 14 cases of CHB in the 52 pregnancies non-exposed to hydroxychloroquine (26.9%) versus 3 cases in the 32 pregnancies exposed to hydroxychloroquine (9.4%; p=0.052).

Conclusion: 87% of foetuses diagnosed with CHB were alive at birth, and 9% died during a median follow up of 5.6 years. A pacemaker was inserted in 77.8% of the cases. Our data confirm that the use of hydroxychloroquine may protect against recurrence of CHB in a subsequent pregnancy (Izmirly et al, Circulation. 2012 May 24. [Epub ahead of print]*). An international prospective study is ongoing to confirm this point (PATCH study; ClinicalTrials.gov Identifier: NCT01379573).

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Abnormal Serologies in the Absence of Clinical Activity Do Not Predict New or Recurrent Lupus Nephritis During Pregnancy. Jill Buyon[1], Aanam Aslam[2], Marta M. Guerra[2], Michael D. Lockshin[2], Carl A. Laskin[3], Ware Branch[4], Lisa R. Sammaritano[2], Michelle Petri[5], Joan T. Merrill[6], Allen D. Sawitzke[7] and Jane E. Salmon[2]. [1]New York University School of Medicine, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, [4]Univ of Utah, Salt Lake City, UT, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]University of Utah Medical Ctr, Salt Lake City, UT

Background/Purpose: Renal disease is a critical concern of physicians counseling lupus patients regarding pregnancy. In patients without a history of kidney disease, does pregnancy increase the risk of first time involvement? In patients with previous renal disease, does pregnancy raise the likelihood of a renal flare? In both cases, prediction of outcome is challenging in a clinically stable patient with serologic activity (abnormal anti-dsDNA antibodies coupled with low complements). Accordingly, our objective was to assess serologic activity as a predictor of renal flares during pregnancy in patients with less than 1 gram of protein at enrollment in a large, prospective, multicenter, mutiethnic study.

Methods: The PROMISSE Study (**P**redictors of p**R**egnancy **O**utcome: Bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic **L**upus **E**rythematosus) prospectively evaluated 391 pregnant SLE patients. Exclusion criteria were multi-fetal pregnancy, prednisone >20mg/d, proteinuria >1gm/24hr, and creatinine >1.2mg.dL. A renal flare was defined by proteinuria increase of >500mg with or without hematuria and/or red blood cell casts. Of the 391 patients, 121 (31%) had preexisting renal disease as defined by ACR SLE criteria and/or a renal biopsy in 53 of whom 4% were Class I or II, 62% were Class III or IV, 13% were Class III/IV & V, and 21% were Class V. Overall at enrollment, 17% had only positive anti-dsDNA, 12% had only hypocomplementemia, 20% had both, and 51% were normal for both parameters.

Results: 16 renal flares occurred in 121 patients with previous renal disease. All had proteinuria, 5 (31%) had hematuria, and 1 (6%) had red blood cell casts. There were no differences between biopsy classes for patients with and without renal flares. Of the 29 patients with a history of renal disease and

both anti-dsDNA and hypocomplementemia, 5 (17%) had a renal flare. In 44 patients with either serology alone, 7(16%) had renal flares. In 48 patients with neither serology, 4 (8%) had renal flares. 5 patients were treated with increased prednisone. 3 treated patients and 2 untreated patients developed pre-eclampsia. Other adverse pregnancy outcomes included 3 (19%) fetal/neonatal deaths and 2 (13%) with SGA <5th %ile in the 16 patients with renal flares. In 270 patients with no history of kidney disease, only 3 renal flares occurred. Of the 50 patients with no history of renal disease and both anti-dsDNA and hypocomplementemia, 2 (4%) had new onset proteinuria; one was treated and developed pre-eclampsia. In 150 patients with neither serology, 1 had new onset proteinuria which was treated and had SGA <5th %ile. None of 70 with either serology alone had renal flares.

Conclusion: These data provide evidence that clinical quiescence or stability at the time of conception favors good renal outcomes during pregnancy regardless of serologic activity. Increased proteinuria (not uniformly requiring prednisone) occurred in 13% of patients with previous renal disease and 1% of those without a history of kidney disease. Thus, in counseling women with lupus who are contemplating pregnancy, abnormal serology alone should not lead to advising against pregnancy even in patients with previous renal disease.

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Higher Corticosteroid Doses Early in Disease Have A Long-Term Influence On Metabolic Syndrome in Systemic Lupus Erythematosus: Data from an International Inception Cohort. Ben Parker[1], Murray B. Urowitz[2], Dafna D. Gladman Gladman[2], Mark Lunt[3], Ian N. Bruce[4] and Systemic Lupus International Collaborating Clinic (SLICC)[5]. [1]University of Manchester, Manchester, United Kingdom, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [4]Arthritis Research UK Epidemiology Unit and NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [5]Toronto

Background/Purpose: The Metabolic Syndrome (MetS) is a clustering of metabolic abnormalities associated with an increased risk of developing diabetes and atherosclerosis, and may add to the increased cardiovascular (CV) risk seen in SLE. We examined the potential impact of markers of inflammation and corticosteroid exposure over time on the prevalence of MetS during the first 2 years of follow-up in an international inception SLE cohort.

Methods: Recently diagnosed (<15 months) SLE patients from 30 centres across 11 countries were enrolled into The Systemic Lupus International Collaborating Clinics Registry for Atherosclerosis (SLICC-RAS) inception cohort from 2000 onwards. Baseline and annual assessments recorded clinical and laboratory data, and therapeutic exposures. MetS was defined according to the 2009 International Diabetes Federation Consensus Statement. A longitudinal analysis of the first 2 years of follow-up was performed using random effects logistic regression which was time-adjusted and took into account multiple visits. The analysis examined the association between MetS and disease activity, disease phenotype and corticosteroid exposure over the first 2 years of follow-up. Variables representing exposure at baseline and follow-up, as well as over-time, were assessed. Significant factors in regression analyses, adjusted for age, sex, ethnicity, and time, were included in the final model.

Results: We recruited 1494 patients with a mean (SD) age at enrolment and disease duration of 35.2 (13.4) years and 24.1 (18.0) weeks respectively. The prevalence of MetS was 239/1494 (16%) at enrolment, 193/1065 (12.6%) at year 1 and 207/894 (13.5%) at year 2. The highest prevalence at enrolment was in patients of Korean (30.1%) and Hispanic (31.3%) ethnicity. In multiple regression analyses current corticosteroid use (odds ratio (95% confidence interval) 1.97 (1.35, 2.87)); daily average prednisolone dose (mg) (1.03 (1.02, 1.05)); peak oral prednisolone dose (mg) (1.03(1.02, 1.04)); immunosuppressant use (1.69 (1.25, 2.28)); SLICC/ACR-DI ≥1 (3.14 (2.01, 4.89)); preceding MetS status (7.94 (5.52, 11.42)); active renal disease (2.76 (1.89, 4.03)) and higher SLEDAI-2K (1.06 (1.03, 1.09)) were associated with MetS. Anti-malarial use was protective (0.45 (0.32, 0.63)). In the final model preceding MetS status, higher peak corticosteroid dose (mg) at enrolment, elevated anti-dsDNA at enrolment, increasing age, and Hispanic ethnicity were all independently associated with MetS over time (Table 1).

Table 1. Random effects model of MetS predictors over time in SLICC-RAS

Variable	Adjusted OR (95% CI)
Preceding MetS (y/n)	4.83 (2.93,7.87)
Peak prednisolone dose at enrolment (mg)	1.02 (1.01,1.03)
Elevated anti-dsDNA at enrolment (y/n)	1.86 (1.19,2.81)
Age (years)	1.03 (1.01,1.05)
Hispanic ethnicity	3.47 (1.76,6.86)

Conclusion: The risk of developing MetS can be determined early in the SLE disease course, with subsets of patients more prone to MetS. Higher doses of steroids in very early disease influence the development of MetS over the subsequent 2 years. Therefore even from disease onset, steroid doses should be individually tailored in order to minimise longer-term CV risk.

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ACR Concurrent Abstract Session
Vasculitis: Clinical Trials
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Rituximab Versus Azathioprine for Maintenance in Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis. Loic Guillevin[1], Christian Pagnoux[2], Alexandre Karras[3], Chahera Khoutra[4], Olivier Aumaitre[5], Pascal Cohen[6], Francois Maurier[7], Olivier Decaux[8], Hélène Desmurs-Clavel[4], Pierre Gobert[9], Thomas Quemeneur[10], Claire Blanchard-Delaunay[11], Pascal Godmer[12], Xavier Puechal[13], Pierre-Louis Carron[14], Pierre yves Hatron[15], Nicolas Limal[16], Mohamed Hamidou[17], Maize Ducret[18], Florence Vende[19], Elisa Pasqualoni[19], Bernard Bonnotte[20], Philippe Ravaud[21], Luc Mouthon Sr.[22] and French Vasculitis Study Group (FVSG)[23]. [1]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [2]Mount Sinai Hospital, Toronto, ON, [3]Hôpital Européen Georges Pompidou, APHP, Paris, France, [4]Hospices Civils de Lyon, Hôpital Louis Pradel, Lyon, France, [5]Centre Hospitalier de Clermont-Ferrand, Clermont-Ferrand, France, [6]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France, [7]Division of internal Medicine, CHR Metz, Metz, Metz, France, [8]Hôpital Sud, Rennes, France, [9]Centre Hospitalier d'Avignon, Avignon, France, [10]CHR de Valenciennes, Valenciennes, France, [11]Centre Hospitalier, Niort, France, [12]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [13]Hôpital Cochin, Paris, France, [14]Centre Hospitalier de Grenoble, Grenoble, France, [15]Hôpital Claude Huriez, Université Lille II, Lille, France, Paris, France, [16]Hôpital Henri Mondor, APHP, Creteil, France, [17]Hôtel Dieu, Hôpital Universitaire de Nantes, Nantes, France, [18]Centre Hospitalier d'Annecy, Annecy, France, [19]Hôpital Bicbat, APHP, Paris, France, [20]Centre Hospitalier de Dijon, Dijon, France, [21]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [22]Hopital Cochin, Paris, France, [23]Paris, France

Background/Purpose: Once ANCA-associated vasculitis (AAV) remission has been achieved with CS and cyclophosphamide (CYC), maintenance therapy usually relies on azathioprine (AZA) or methotrexate. However, 18- and 28-month relapse rates remain high, 15% and 28%, respectively. Although rituximab (RTX) has been demonstrated to be as effective as CYC for induction of complete remission by 6 months, some retrospective studies showed that more than half of the patients without maintenance relapsed within 2 years. The results of a prospective, randomized, controlled trial of RTX vs AZA to maintain AAV remission are reported (MAINRITSAN, NCT 00748644). (Sponsor: Assistance publique Hôpitaux de Paris, Grants: Programme Hospitalier de Recherche Clinique, Rituximab was provided in part by Roche).

Methods: Once remission was obtained with a conventional regimen, patients with newly diagnosed (2/3 of the enrollments) or relapsing (1/3) AAV were randomly assigned to receive a 500-mg RTX infusion on D1, D15, 5.5 months later, then every 6 months for a total of 5 infusions over 18 months, or AZA for 22 months at the initial dose of 2 mg/kg/d. The primary endpoint was the major relapse rate (EULAR/ACR criteria) at 28 months. Other outcome measures were the severe adverse event (SAE) rate (WHO definition) associated with each maintenance regimen. We hypothesized that the RTX arm would have a 50% lower relapse rate than that of AZA, and a similar safety profile.

Results: Among the 114 patients (50 men/64 women; mean age, 55±13 years; 91 newly diagnosed and 23 relapsers) participating in the study (59 in the AZA arm, 55 in the RTX arm): 86 had granulomatosis with polyangiitis, 23 microscopic polyangiitis and 5 kidney-limited diseases. The main clinical manifestations at diagnosis or last relapse included ENT involvement in 88 (77.2%), lung in 69 (60.5%) and kidney in 82 (71.9%). Eighty-four (73.7%) patients have already completed their 28 months of follow-up; the last patient visit and trial closure are scheduled in 10/2012. So far, major relapses have occurred in 18 (15.7%) patients: 2 (3.6%) in the RTX arm and 16 (27.1%) in the AZA arm, with 3 AZA-arm deaths (1 sepsis, 1 pancreatic cancer, 1 mesenteric ischemia). Thirty-three experienced SAE: 18 related to AZA, 15 to RTX. In the AZA arm, 12 infections (1 fatal) and 1 skin cancer were observed vs 11 infections (none fatal) in the RTX arm.

Conclusion: The results of this study demonstrated that 500 mg of RTX every 6 months was superior to AZA to maintain AAV remission. The infection frequencies were comparable in the 2 arms, and other SAE were infrequent and resolved in most patients.

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Outcomes in Patients with Granulomatosis with Polyangiitis (Wegener's) Treated with Short Vs. Long-Term Maintenance Therapy. Jason Springer, Benjamin Nutter, Carol A. Langford, Gary S. Hoffman and Alexandra Villa-Forte. Cleveland Clinic Foundation, Cleveland, OH

Background/Purpose: Disease remission can be successfully achieved in the majority of patients (pts) with Granulomatosis with polyangiitis (Wegener's) (GPA). After remission (rem) is achieved continued treatment with immunosuppressive agents is used to maintain rem. There is limited data on long term outcomes for pts continuing maintenance therapy beyond 18 months (mo). The aim of this study was to determine rem maintenance outcomes in pts treated long term (>18 mo) vs. short term (≤18 mo). The primary outcome was relapse rate.

Methods: A retrospective chart review was performed of pts with GPA from a single Vasculitis Center from 1992 to 2010. Inclusion criteria: 1) 1990 ACR criteria for GPA, 2) induction therapy provided with daily cyclophosphamide (CYC) or weekly methotrexate (MTX); 3) rem achieved; 4) maintenance therapy initiated immediately following discontinuation of induction therapy; 5) maintenance therapy with either MTX or azathioprine (AZA); 6) duration of remission ≥18 mon; 7) chronologic documentation of rem and relapse. Rem was defined as a BVAS/WG score of 0 and relapse was defined as a score that changed from 0 to ≥ 1 following a period of rem.

Results: 157 pts were included out of 797 screened. Median age at diagnosis was 46. Follow-up ranged from 18 mo to 16.8 years(yr) (mean 3.1 yr). Induction therapy with CYC was used for severe disease (78% cases) and MTX (22% cases) for mild to moderate disease. Mean starting doses of maintenance medications were prednisone (pred) 19 mg/d, MTX 16.5mg/wk and AZA 112mg/d. There was no difference between groups in regards to initial organ manifestations, pred dose at rem, maintenance drug used or pulse dose methylprednisolone (MP) at diagnosis. When duration of treatment was compared using a univariate model the long term group showed a 29% reduction in hazard ratio for relapse (HR0.71 [95%CI 0.43, 1.18], p=0.18). Treatment for > 36 mo showed 66% reduction in hazard ratio for relapse (HR0.34 [95%CI 0.15, 0.76], p=0.008). When length of treatment was considered as a continuous factor, longer courses had an inverse relationship with the risk of relapse (HR0.77 [95%CI 0.65, 0.92]; p= 0.003). After adjusting for pred dose, length of maintenance therapy continued to show a significant inverse relationship with risk of relapse (HR0.58 [95%CI 0.4, 0.83]; p=0.003). Univariate analysis revealed no association with risk of relapse and BVAS at diagnosis, ANCA status or pulse MP. When relapse characteristics were compared between groups there was no difference in severity of relapse as measured by BVAS/WG, but a higher rate of relapse with peripheral neuropathy (15% vs 1.43%, p=0.033) occurred in the short term group. Relapses in the long-term group occurred in 88.9% after stopping therapy. Of pts on therapy at relapse 52% were on < 15mg/wk MTX and 75% on ≤ 50mg/d AZA. No differences between the two groups in overall adverse events or GPA related morbidity.

Conclusion: Our data demonstrate that pts receiving long term maintenance therapy have fewer relapses and have a similar adverse events profile as pts treated for < 18 mos. Discontinuation and low doses of maintenance therapy are associated with a high relapse rate.

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Primary Endpoint Failure in the Rituximab in ANCA-Associated Vasculitis Trial. Eli Miloslavsky[1], Ulrich Specks[2], John H. Stone[3] and RAVE/ITN Research Group[4]. [1]Massachusetts General Hopsital, Boston, MA, [2]Mayo Clinic, Rochester, MN, [3]Massachusetts General Hospital, Boston, MA, [4]Bethesda

Background/Purpose: The RAVE trial demonstrated that rituximab (RTX) is non-inferior to cyclophosphamide (CYC) for remission induction in severe ANCA-associated vasculitis. The primary endpoint was a disease activity score (Birmingham Vasculitis Activity Score/Wegener's granulomatosis; BVAS/WG) of 0 and a prednisone dose of 0 mg/d at month 6. We explored the reasons for primary endpoint failure (PEF) in RAVE.

Methods: PEFs were classified according to one of the following hierarchical reasons: early treatment failure (ETF) (advance of disease in one or more organs or failure to respond to treatment by BVAS/WG reduction in the first month); severe flare; limited flare; adverse event (AE); BVAS/WG > 0 at 6 months; prednisone > 0 mg/d at 6 months despite BVAS/WG of 0; or other.

Results: Eighty-two of 197 pts (42%) were PEFs: 36 (36%) in the RTX group, 46 (47%) in CYC (P=0.09). Nine were ETFs (7 RTX, 2 CYC; P=0.17). Baseline characteristics of pts classified as ETFs did not differ from those of other pts in age, sex, ANCA type, disease, new diagnosis vs relapse, baseline BVAS/WG, or creatinine. Most ETFs were due to progressive glomerulonephritis (5/9: 4 RTX, 1 CYC) or recurrent pulmonary hemorrhage (3/9). All ETFs were treated with CYC. One ETF (RTX) died from sepsis/respiratory failure. All other ETFs improved, with resolution of pulmonary disease and improvement of renal function.

Fifteen RTX pts were PEFs because of disease flares (4 severe, 11 limited), compared with 23 CYC pts (9 severe, 14 limited). Neither B cell detectability nor ANCA titer predicted disease flare well in the first 6 months, and the correlation was particularly poor among RTX-treated pts. B cells remained undetectable in 65% of flares (50% CYC, 92% RTX). Among disease flares, only 24% had rises in ANCA titers at the time of flare (36% CYC, 0% RTX).

Of the 13 severe flares, 11 were treated by blinded crossover. Nine of 11 blinded crossovers achieved remission (BVAS of 0 and prednisone dose of 0mg) within 6 months after crossover. Limited flares were typically controlled by an increase in prednisone dose. Among pts with limited flares, the mean BVAS/WG at 6 months was 0.9 and the mean prednisone dose 9.3 mg/d. Six pts were PEFs because of BVAS/WG > 0 at 6 months (2 RTX, 4 CYC; mean 2.0), and 11 were PEFs because of failure to taper prednisone to 0 mg/d (7 RTX, 4 CYC; mean 9.3 mg/d). Twelve pts (9 CYC, 3 RTX) discontinued because of AEs.

Table 1 Reasons for primary endpoint failure in RAVE

	RTX	CYC/AZA	P
ETF	7	2	0.17
Severe flare	4	9	0.16
Limited flare	11	14	0.53
Adverse event	3	9	0.08
BVAS/WG > 0	2	4	0.45
Prednisone dose > 0mg	7	4	0.54
Other	2	4	0.45
Total	36	46	

Conclusion: There were multiple reasons for PEF but the distribution of causes was similar between groups. ETFs and pts who flared typically improved following a treatment intervention according to best medical judgment, blinded crossover, or increase in prednisone dose. B cell detectability and ANCA titers correlated poorly with flares in the first 6 months, particularly those in the RTX group.

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An Open-Label Trial of Abatacept in Mild Relapsing Granulomatosis with Polyangiitis (Wegener's). Carol A. Langford[1], David Cuthbertson[2], Gary S. Hoffman[1], Jeffrey Krischer[2], Carol McAlear[3], Paul A. Monach[4], Philip Seo[5], Ulrich Specks[6], Steven R. Ytterberg[6], Peter A. Merkel[3] and for the Vasculitis Clinical Research Consortium[3]. [1]Cleveland Clinic, Cleveland, OH, [2]University of South Florida, Tampa, FL, [3]University of Pennsylvania, Philadelphia, PA, [4]Boston University, Boston, MA, [5]Johns Hopkins Vasculitis Center, Baltimore, MD, [6]Mayo Clinic, Rochester, MN

Background/Purpose: Granulomatosis with polyangiitis (Wegener's, GPA) is a primary systemic vasculitis that carries a high predilection for relapse. An area of unmet need has been treatment options for patients with mild relapsing GPA, many of whom require long-term glucocorticoids. T-cell activation has been implicated in the pathophysiology of GPA. We conducted an open-label trial to examine the safety and efficacy of abatacept (CTLA4-Ig) in patients with mild relapsing GPA.

Methods: Standardized definitions were used to identify patients with mild relapsing GPA. 20 patients were treated with abatacept 10mg/kg IV days 1, 15, 29 and monthly thereafter. Patients on methotrexate (MTX), azathioprine (AZA), or mycophenolate mofetil (MMF) at enrollment continued these agents without dosage increase. Prednisone ≤ 30 mg daily was permitted at entry, but the dose had to be tapered down to the pre-relapse dose by month 2. Safety and efficacy data were collected at each infusion, disease activity was assessed by the BVAS/WG, damage was assessed by the Vasculitis Damage Index (VDI). Patients received abatacept until meeting criteria for early termination or until the common closeout date of 6 months after enrollment of the last patient.

Results: Disease characteristics of the 20 enrolled patients are outlined in the Table.

Variable	Value at Study Entry
Age (range)	45 years (17–73)
Female/Male	9/11
PR3-cANCA	80%
MPO-pANCA	10%
GPA duration mean (range)	100 months (5–326)
BVAS/WG mean (range)	3.1 (1–6)
VDI mean (range)	2.5 (0–7)

Organ Involvement	Before Study Entry (Ever)	Active Disease at Study Entry
Constitutional	85%	30%
ENT	100%	90%
Musculoskeletal	75%	50%
Cutaneous	60%	40%
Mucous membranes	25%	5%
Lung	70%	30%
Kidney	40%	-
Eye	30%	-
Nerve	20%	-

Of the 20 patients, 14 (70%) were on either MTX (N=7), AZA (N=3), or MMF (N=4). 14 patients had taken prednisone during the 12 months prior to enrollment, 13 were on at the time of enrollment, and 15 (75%) received prednisone during the first 2 months of study treatment. The maximum prednisone doses were 30 mg (N=3), 20 mg (N=3), 12–15 mg (N=2), 10 mg (N=4), 7.5 mg (N=1), 5 mg (N=2) with only 5 having a dose increase at trial entry. During the study, 11 of the 15 patients on prednisone reached a dose of 0 mg. 10 of the 14 patients who had been on long-term prednisone were able to discontinue prednisone and 7 of these remained off the drug until common closing. Of the 20 patients, 18 (90%) had disease improvement, 16 (80%) achieved remission (BVAS/WG=0) at a median of 3.75 months (range 1–19), and 14 (70%) reached common closing. 6 (30%) met criteria for early termination due to increased disease activity but none had severe disease; 3 of 6 achieved remission and relapsed at a median of 8.33 months (range 6–10). The median duration of remission before common closing was 12 months (range 4–21). 9 serious adverse events occurred in 7 patients, including 7 infections that were successfully treated.

Conclusion: In this population of patients with mild relapsing GPA, abatacept was well tolerated and was associated with disease remission and discontinuation of prednisone in a high percentage of patients. These findings suggest that abatacept warrants further study as a possible treatment option for patients who have non-severe, relapsing GPA.

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Treatment of Systemic Necrotizing Vasculitides in Patients ≥65 Years Old: Results of the Multicenter Randomized Cortage Trial. Christian Pagnoux[1], Thomas Quemeneur[2], Jacques Ninet[3], Elodie Perrodeau[4], Elizabeth Diot[5], Xavier Kyndt[6], Benoit de Wazières[7], jean-Luc Reny[8], Xavier Puéchal[9], Pierre-Yves Leberruyer[10], Olivier Lidove[11], Philippe Vanhille[6], Pascal Godmer[12], Aimé Albrah-Sadiki[13], Boris Bienvenu[14], Pascal Cohen[15], Luc Mouthon Sr.[16], Philippe Ravaud[4], Loic Guillevin[17] and French Vasculitis Study Group (FVSG)[11]. [1]Department of Internal Medicine, National Referral Center for Necrotizing Vasculities and Systemic Sclerosis, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Université Paris – Descartes, Paris, France, Paris, France, [2]CHR de Valenciennes, Valenciennes, France, [3]Department of Nephrology and Internal Medicine, Hôpital Edouard Herriot, Lyon, France, Lyon, France, [4]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [5]Department of Internal Medicine, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire de Tours, Tours, France, Tours, France, [6]Valenciennes, France, [7]Department of Internal Medicine and Gerontology, Hôpital Universitaire Carémeau, Nîmes, France, Nimes, France, [8]Geneve, Switzerland, [9]Hôpital Cochin, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [10]Reims, France, [11]Paris, France, [12]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [13]Hôpital Cochin, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, 27 rue du faubourg Saint Jacques, Paris, 75014, France, Paris, France, [14]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, Caen, France, [15]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France, [16]Hopital Cochin, Paris, France, [17]Cochin University Hospital, Paris, France

Background/Purpose: To optimize the therapeutic strategy for the elderly with systemic necrotizing vasculitides (SNV; polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or eosinophilic GPA (EGPA)).

Methods: We conducted a multicenter randomized controlled trial on patients ≥65 years old with newly diagnosed SNV to compare conventional therapy (based on Five-Factor Score-assessed disease severity: for all, ≥28 mo of corticosteroids (CS) alone or combined with 500-mg/m^{2}cyclophosphamide (CYC) IV pulses every 2–3 wk until remission for EGPA or PAN with FFS≥1 and GPA or MPA, then switched to maintenance azathioprine (AZA) or methotrexate (MTX)) and an experimental regimen, specifically designed for faster CS dose-tapering and systematic but reduced CYC exposure (for all, ≥9 mo of CS and 500-mg fixed-dose IV CYC pulse, given every 2–3 wk, and switched after a maximum of 6 pulses to maintenance AZA or MTX). Trial follow-up closure was scheduled 3 yr after enrollment of the last patient. The primary judgment criterion was time to first severe adverse event (SAE: morbidity and mortality) hypothesizing a 30% reduction of experimental arm SAE rate. Secondary endpoints included first remission, death, relapse rates and quality-adjusted time without symptoms or toxicity (Q-TWiST).

Results: Between July 2005 and February 2008, 108 patients were randomized; 4 were excluded (early consent withdrawn, wrong diagnosis, protocol violations). Mean age at diagnosis of the analyzed patients (52 in each arm; 55 males, 49 females; 8 PAN, 13 EGPA, 37 GPA, 46 MPA; 91 ANCA-positive) was 75.2±6.3 yr, with a maximum of 92 yr for 1 MPA patient. FFS=0 for 7 PAN (4 in the conventional arm, 3 in the experimental arm) and 10 EGPA patients (5 in each arm). Baseline clinical features were evenly distributed between arms (fever, 53%; arthralgias, 38%; lung, 64%; ENT, 40%; kidney, 69%; heart, 20%; skin, 35%; peripheral nervous system, 25%; central nervous system, 3%); mean serum creatinine level at diagnosis was 234±199 μmol/l and C-reactive protein 102±87 mg/l. Mean follow-up was 28±11 mo. Hazard ratio for first SAE (primary endpoint) for experimental vs conventional treatment was 0.61 [95% CI, 0.38–0.97], i.e., 39% lower SAE rate (3-yr event-free survival: 37.6% [95% CI, 26.4–53.7] in experimental vs 19.2% [95% CI, 10.9–34.1] in conventional treatment arms; p=0.04). Ninety-one (88%) patients achieved remission with their assigned treatment (47 in experimental treatment arm vs 44 in conventional; p=0.37); 21 (20%) patients died (8 vs 13, respectively; p=0.22) of uncontrolled vasculitis for 7 of them (2 vs 5) and/or infection for 6 (2 vs 4); 16 vs 11 patients suffered ≥1 relapse(s), with comparable 3-yr relapse-free–survival rates (53.2% [CI 95%, 40.7–69.6] vs 54.2% [95% CI, 41.9–70]). Respective Q-TWiST rates were 30.97 and 28.72 (mean difference, 2.25 [95% CI, –1.72 to 6.76]; p=0.29).

Conclusion: Treating SNV in the elderly with a specific regimen limiting exposure to CS and fixed low-dose IV CYC pulses coud become the standard of care because of its lower SAE risk, and similar 3-yr remission and relapse rates, compared to conventional therapy.

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Peg-IFNa/Ribavirin/Protease Inhibitor Combination Is Highly Effective in HCV-Mixed Cryoglobulinemia Vasculitis. David Saadoun[1], Stanislas Pol[2], Pascal Lebray Sr.[3], François Blanc[4], Gilles Pialoux[5], Alexandre Karras[6], Dorothée Bazin[7], Emmanuelle Plaisier[8] and Patrice Cacoub Sr.[9]. [1]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpêtrière, Paris, France, [2]Hepatology, Cochin Hospital, Paris, France, [3]Hôpital Pitié Salpétrière, Paris, France, [4]hôpital Montpellier, Montpellier, France, [5]hôpital Tenon, Paris, France, [6]Hôpital Européen Georges Pompidou, APHP, Paris, France, [7]Nouvel Hôpital Civil, Strasbourg, France, [8]Nephrology, Tenon Hospital, Paris, France, [9]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: The standard of care treatment of patients presenting a HCV-mixed cryoglobulinemia (MC) vasculitis includes Peg-IFNa plus Ribavirin, w/wo Rituximab. Thirty to 40% of patients are non-responders or relapsers to such combination.

To analyze the safety and efficacy of a Peg-IFNa/Ribavirin/Protease inhibitor combination on HCV-MC vasculitis.

Methods: Open label prospective single-center cohort study, 27 patients with HCV-MC vasculitis entered the study, of whom 13 with sufficient follow-up were analysed. Peg-IFNa/Ribavirin was associated to Telaprevir (375 mg three times daily, 8 patients) or Boceprevir (800 mg three times daily, 5 patients).

Results: Mean age 61 years, 54% women, all 13 HCV genotype 1 patients received previous antiviral therapy with Peg-IFNa/Ribavirin, including 5 (38%) relapsers and 8 (62%) non-responders; 10 (77%) had been also treated by Rituximab. Mean HCV RNA level was 5.85Log copies/mL; Metavir fibrosis score was of stage 4 in 6 cases, stage 3 in 4 cases and stage 2 in 3 cases. Twelve patients (92%) had a type II IgMk MC and 1 had a type III. Main HCV-MC manifestations included purpura (n=10), polyneuropathy (n=10), arthralgia (n=6), and kidney involvement (n=3). The mean serum MC, C4 and rheumatoid factor levels were of 1.3 g/l, 0.09 g/l and 157 IU/ml, respectively. After 1 month of Peg-IFNa/Ribavirin/protease inhibitor, 11 (85%) patients showed an early virological response (HCV RNA level <1.1 Log copies/mL). Nine (69%) patients showed a complete clinical response of MC vasculitis and 4 (31%) were partial responders. After 3 months of Peg-IFNa/Ribavirin/protease inhibitor, MC serum level dropped from 1.3 to 0,3g/l while C4 level increased from 0.09 to 0.13g/l. All 13 patients experienced at least one treatment side effect including asthenia in 92%, anaemia in 84%, neutropenia and bacterial infection in 53%, nausea and low grade (<3) skin eruption under Telaprevir in 30% and thrombocytopenia in 15%.

Conclusion: Peg-IFNa/Ribavirin/protease inhibitor combination seems highly effective in HCV-MC vasculitis. Such therapeutic regimen should be administered cautiously considering the high rates of side effects.

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ACR Concurrent Abstract Session
Cytokines, Mediators, and Gene Regulation II
Monday, November 12, 2012, 4:30 PM–6:00 PM

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Signal Transducer and Activator of Transcription 3 Induced Synovial Invasion and Migration Is Mediated in Part Through the Notch/Hypoxia-Inducible Factor 1α Pathways. Wei Gao[1], Douglas J. Veale[2] and Ursula Fearon[3]. [1]Translational Rheumatology Research Group, Dublin, Ireland, [2]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [3]Translation Rheumatology Research Group, Dublin, Ireland

Background/Purpose: To examine the role of Signal Transducer and Activator of Transcription 3 (STAT3) in mediating synovial cell-cell interactions, migration/invasion and key downstream signaling pathways in the inflamed synovial tissue.

Methods: Phospho-STAT3 (p-STAT3) expression in synovial tissue was quantified by immunohistology/immunoflourecence and Western blot. Notch-1 IC, HIF1α, p-STAT3 and total-STAT3 protein levels were assessed in synovial fibroblasts under normoxic and hypoxic (3%) conditions by Western Blot. In parallel gene expression of the Notch-1 receptor, its ligand DLL-4 and downstream target genes (*hrt-1, hrt-2*) were quantified by Real-time PCR. Synovial fibroblast migration, invasion, matrigel network formation and MMP2/9 in-gel zymography were quantified under normoxic and hypoxic (3%) conditions in the presence of STAT3 inhibitor (WP1066). Using RA synovial explants *ex-vivo*, the effect of the STAT3 inhibitor (WP1066) on IL-6, IL-8 and IL-10 expression were assessed by ELISA.

Results: Nuclear expression of p-STAT3 was demonstrated in RA synovial tissue, localised to the sub-lining and lining layer regions. p-STAT3 expression was significantly higher in inflamed synovial tissue compared to normal synovial tissue. Hypoxia (3%) induced p-STAT3, Notch-1 IC, HIF1α protein expression in synovial fibroblasts, an effect that was inhibited by the presence of WP1066. Similarly hypoxia-induced Notch-1 receptor, DLL-4 and *hrt-1, hrt-2* gene expression were inhibited in the presence of WP1066. Functionally hypoxia-induced synovial fibroblast invasion, matrigel network formation, migration, and pro-MMP-2/-9 activities, were inhibited in the presence of STAT3 inhibitor. Finally we demonstrated in RA synovial explants *ex-vivo* that WP1066 significantly decreased IL-6, IL-8 expression and significantly increased anti-inflammatory cytokine IL-10 expression.

Conclusion: p-STAT3 is increased in RA synovial tissue and mediates synovial fibroblast migrational and invasive processes. Furthermore these effects may in part be mediated through Notch-1/HIF1α interactions.

Disclosure: W. Gao, None; D. J. Veale, Abbott Laboratories, 2, MSD, 2, Opsona, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2; U. Fearon, None.

1659

Ptpome Profile of Rheumatoid Arthritis Fibroblast-Like Synovio-cytes: A Novel Role for the Tyrosine Phosphatase SHP-2 As a Modulator of Invasion and Survival. Stephanie Stanford[1], Michael Maestre[1], Beatrix Bartok[2], David L. Boyle[2], Heather Arnett[3], Tomas Mustelin[4], Gary S. Firestein[2] and Nunzio Bottini[1]. [1]La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA, [3]Amgen, Inc., Seattle, [4]Sanford-Burnham Institute for Medical Research, La Jolla, CA

Background/Purpose: Fibroblast-like synoviocytes (FLS) in the synovial intimal lining are key mediators of inflammation and joint destruction in rheumatoid arthritis (RA). These cells assume a tumor-like phenotype in RA, aggressively invading the extracellular matrix and producing cartilage-degrading proteases and inflammatory cytokines. The behavior of synovial fibroblasts is controlled by multiple interconnected signal transduction pathways involving reversible protein phosphorylation. However, little is known about the role of the protein tyrosine phosphatases (PTPs) in FLS function. The objective of this study was to define all of the PTP genes (PTPome) expressed in FLS and determine if any play a role in the rheumatoid synoviocyte phenotype

Methods: Comparative screening was conducted of the PTPome expression in FLS from patients with RA or osteoarthritis (OA) by qPCR. Cell permeable anti-sense oligonucleotides were used to suppress PTPs, such as SHP-2, and achieved 90% knockdown. Transwell FLS invasion assays were performed using Matrigel-coated inserts. FCS or PDGF were used as chemoattractants, and invasion was quantified by propidium iodide (PI) staining of insert membranes. Transwell FLS migration assays were carried out using FCS as a chemoattractant, and migration was quantified by staining cells with Celltracker green. FLS apoptosis was quantified by flow cytometry staining with PI and Annexin V. MMP and cytokine gene induction after TNF stimulation were quantified by qPCR. Western blotting of cell lysates using phosphospecific antibodies was used to assess activation of signaling pathways.

Results: FLS display abundant expression of genes belonging to all of the known subfamilies of PTPs. Of these, only *PTPRK*, *PTPN11*, *PTPN14* and *DUSP3* expression were increased in RA (n=11) compared to OA (n=10) FLS (p<0.05). Subsequent studies focused on *PTPN11*, which encodes SHP-2, because that it is a well-documented proto-oncogene. SHP-2 knockdown in RA FLS with antisense led to increased basal apoptosis (162% increase, p<0.05) and impaired invasion (71% decrease, p<0.05) and migration (44% decrease, p<0.05) in response to FCS or PDGF. SHP-2-deficient RA FLS displayed decreased activation of focal adhesion kinase and mitogen-activated

protein kinases, such as JNK, in response to PDGF. Knockdown of SHP-2 also significantly suppressed TNF-mediated induction of MMPs and adhesion molecules, including MMP-1 (79% decrease, p<0.05), MMP-2 (64% decrease, p<0.05), VCAM-1 (93% decrease, p<0.05), and Cadherin-11 (77% decrease, p<0.05). Decreased gene expression correlated with a dramatically reduced induction of JNK phosphorylation in cell lysates.

Conclusion: These findings demonstrate a novel role for the proto-oncogene SHP-2 as a key mediator of FLS function. SHP-2 promotes the invasiveness and survival of RA FLS and, due to its higher expression in RA compared with OA FLS, could contribute to the unique aggressive phenotype of the rheumatoid cells. Therefore, SHP-2 could be a novel therapeutic target for RA.

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1660

Development of a Bruton's Tyrosine Kinase (Btk) Inhibitor, ONO-4059: Efficacy in a Collagen Induced Arthritis (CIA) Model Indicates Potential Treatment for Rheumatoid Arthritis (RA). Toshio Yoshizawa, Yuko Ariza, Yoshiko Ueda, Shingo Hotta, Masami Narita and Kazuhito Kawabata. Ono Pharmaceutical Co., Ltd., Osaka, Japan

Background/Purpose: Rheumatoid arthritis (RA) is characterized by leukocyte infiltration, synoviocyte hyperplasia and osteoclastogenesis, and tyrosine kinases have key roles in the signaling pathways that regulate these processes. Bruton's tyrosine kinase (Btk) is a key regulator of B-cell receptor (BCR) function. B-cell receptors play a central role in signal transduction pathways regulating survival, activation, proliferation, and differentiation of B-lineage lymphoid cells. Furthermore, Btk mutations in humans cause X-linked agammaglobulinaemia, an inherited disorder characterized by severe B-cell specific defects, including the complete absence of B-cells in the periphery. The effectiveness of B-cell targeted therapy in the treatment of RA (e.g., Rituximab), further supports the role of B-cells in RA. ONO-4059 is a highly potent and selective Btk inhibitor with an IC$_{50}$ in the sub-nmol/L range. The activity of ONO-4059 was evaluated in a mouse collagen induced arthritis (CIA) model.

Methods: Male DBA/1J mice were immunized on days 0 and 21 with Freund's Complete Adjuvant containing bovine type II collagen. Mice were randomized to three treatment groups starting from day 22 to 36 and received oral ONO-4059, once daily at doses of 1 mg/kg, 3 mg/kg and 10 mg/kg respectively. The mice were weighed weekly and scored daily for signs of arthritis. Each paw was scored and the sum of all four scores was recorded using the Arthritic Index (AI). The maximum possible AI score was 16. Joint histology on day 36 was evaluated for cartilage damage, bone damage, extra-articular inflammation and pannus. To further characterize the effect of ONO-4059 in the CIA model, human monocytes were stimulated with immobilized hIgG or TLR-9 ligand (CpG-B) for 18 hr. TNFα and IL-6 production was determined by Luminex.

Results: Treatment with ONO-4059 resulted in a dose-dependent inhibition of arthritis severity and bone damage in the CIA model. The mean disease score of the ONO-4059-treated animals was 10.9, 5.3 and 2.3 for the 1, 3 and 10 mg/kg dose groups respectively. In comparison, the mean score in the vehicle-treated animals was 13. In a cell-based assay, ONO-4059 prevented FcγR-induced TNFα and IL-6 production in monocytes with IC$_{50}$ values of 5.66 nM and 22.4 nM, respectively. ONO-4059 also suppressed TLR9-induced TNFα and IL-6 production in monocytes with IC$_{50}$ values of 4.45 nM and 12.4 nM, respectively. Furthermore, ONO-4059 prevented B-cell activation in the 10 nM range but it had no effects on T-cell activation.

Conclusion: ONO-4059 is a highly potent and selective oral Btk inhibitor. We have demonstrated that ONO-4059 potently and dose-dependently reversed clinical arthritis and prevented bone damage in the CIA model. The cellular and molecular mechanisms by which Btk mediates inflammation are not fully understood. This data supports that ONO-4059 inhibits immune-receptor signaling in multiple cells through Btk inhibition and these preliminary results suggest that ONO-4059 may be a promising therapeutic approach for patients with rheumatoid arthritis and warrants further investigation.

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1661

CCR1 Potentiates Gouty Inflammation Following Initial CXCR2-Dependent Neutrophil Recruitment to Sites of Monosodium Urate Crystal Deposition in Mice. Robert P. Friday[1], Terry K. Means[2], Melissa Tai[2], Christian D. Sadik[2] and Andrew D. Luster[2]. [1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital, Charlestown, MA

Background/Purpose: During attacks of acute gouty arthritis, monosodium urate (MSU) crystals elicit a potent neutrophilic inflammatory response in the affected joint, causing exquisite pain and often signs of systemic inflammation such as fever. IL-1β plays a critical role in the development of gouty arthritis, as demonstrated by studies of IL-1β and NLRP3 knockout mice and the effectiveness of IL-1 blockade in treating or preventing gouty arthritis in humans. However, mechanisms of neutrophil trafficking to sites of MSU crystal deposition during gouty inflammation have not been fully characterized, and our understanding of these pathways depends upon knowledge of the chemokine responses elicited by MSU crystals and their interface with chemotactic receptors on neutrophils. Deletion of the chemokine receptor CXCR2 in mice has been shown to impair initiation of MSU crystal-induced inflammation in the air pouch model of gouty arthritis, but the other major murine neutrophil chemotactic receptors – CCR1, BLT1 and C5a – have not been systematically studied.

Methods: Using the murine air pouch model of gouty arthritis, we have: (1) characterized the chemokine and cytokine profile of MSU crystal-induced inflammation using a multiplex bead immunoassay and (2) probed the time course of chemokine and cytokine production and neutrophil recruitment in CCR1-null, CXCR2-null, and CCR1-CXCR2 double knockout mice.

Results: While our findings confirm that CXCR2 is critical for the initiation of neutrophilic inflammation in MSU crystal-challenged air pouches, mice lacking CCR1 also fail to achieve the expected maximal neutrophilic response to MSU crystal challenge (at 8 hours post crystal challenge). Although CXCR2-null mice generate a very high level of KC and LIX (ligands for CXCR2) in the air pouch within 2 hours of MSU crystal challenge, MIP-1α and MIP-1β (ligands for CCR1), which typically appear 3–4 hours after crystal challenge, are not produced in these mice.

Conclusion: We propose that CXCR2 and CCR1 act sequentially to initiate and potentiate neutrophil infiltration during gouty inflammation, with CCR1 chemokine ligand generation being dependent upon neutrophils entering the inflammatory site in response to CXCR2 chemokine signals. These data broaden our understanding of coordinate chemokine-mediated neutrophil recruitment in a model of MSU crystal-induced arthritis and suggest that there may be a role for chemokine receptor modulation in the management of acute gouty arthritis in humans.

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Anti-IL-6 Therapy Impairs Intestinal Repair Through Inhibition of Epithelial Proliferation After Injury. Kristine Kuhn, Hiroyuki Miyoshi, Nicholas A. Manieri, Nicole P. Malvin, Vinieth Bijanki, Paul Allen and Thaddeus S. Stappenbeck. Washington University School of Medicine, St. Louis, MO

Background/Purpose: Inhibition of IL-6 is used for treatment of rheumatoid arthritis and now being investigated as biologic therapy for a wide variety of autoimmune conditions, including systemic lupus erythematosus, spondyloarthritis, vasculitides, and inflammatory bowel disease. Many of these conditions are complicated by intestinal inflammation. Yet little is known about the role of IL-6 in the bowel. Animal models have suggested that IL-6 signaling protects intestinal epithelial cells from apoptosis during toxin mediated injury with oral dextran sodium sulfate and C. rodentium infection.

Methods: We have begun to investigate the role of IL-6 in the intestine using two in vivo models of intestinal disease. First, we utilized the dnKO murine model of spontaneous colitis. These mice are transgenic for a dominant negative *Tgfbr2* on T cells and are deficient in the *IL10rb* gene; both of these signaling pathways contain genes with risk alleles for autoimmunity. Antibiotics can inhibit spontaneous colitis that develops in these mice, and cohousing with unmanipulated littermates leads to colitis within days. We then utilized a biopsy wound model in which a colonoscope is used to introduce forceps which biopsy the colonic mucosa and make a wound which can then be evaluated as the tissue repairs itself.

Results: We found that treatment of dnKO mice with an inhibitory antibody for IL-6 at the time of cohousing led to more severe colitis as observed by increased inflammatory infiltrates and crypt drop-out when compared to control antibody treated mice. Evaluation of the intestinal epithelium with BrdU staining demonstrated significantly increased epithelial proliferation in dnKO mice treated with control antibody but nearly absent staining in the anti-IL-6 treated mice. After biopsy wound injury of wild type mice, IL-6 levels peak early, within 24 hours, and decline to undetectable levels by day 6. Mice deficient for IL-6 demonstrate impaired intestinal wound healing due to a severe epithelial proliferative defect. By in situ hybridization, we identify intestinal epithelial cells and endothelial cells as significant producers of IL-6 in both models. In order to further define the mechanism by which IL-6 could be controlling intestinal epithelial proliferation and repair, we evaluated its role in primary 3D cultures of intestinal crypt organoids. In these cultures, cellular proliferation was significantly inhibited when the inflammatory cytokines TNF-α and IFN-γ were added. However, the addition of IL-6 to the cultures resulted in the restoration of cellular proliferation, even in the presence of TNF-α and IFN-γ.

Conclusion: These data demonstrate the importance of IL-6 for intestinal epithelial proliferation after injury. The absence of IL-6 early after injury in the intestine, such as the case when anti-IL-6 therapy is used, may lead to severe defects in healing, increasing the risk for adverse events.

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G Protein Signaling Modulator 3 Is a Key Regulator of Monocyte-Driven Inflammatory Arthritis. Matthew J. Billard, Patrick M. Giguére, Brian Buckley, Marcus W. McGinnis, Roman Timoshchenko, Peng Liu, David P. Siderovski and Teresa K. Tarrant. University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: Monocytes are critical to rheumatoid arthritis (RA) disease pathogenesis and are recruited to the inflamed synovium by inflammation-driven chemokines. G protein signaling modulator 3 (GPSM3) is a newly discovered member of the novel family of GoLoco motif proteins known to regulate G protein heterotrimer assembly and function, a mechanism by which chemokine receptors signal. GPSM3 is selectively expressed in monocytes and may regulate monocyte function through chemokine G protein coupled receptor (GPCR) interactions, which in turn may affect inflammatory arthritis disease expression.

Methods:
• GPSM3-deficient monocytic cells were generated from the parental THP-1 cell line and a GPSM3-deficient mouse was created.
• A monoclonal antibody to GPSM3 (mAb 35.5.1) was developed and GPSM3 expression was analyzed by immunoblotting lysates from hematopoietic lineage-derived human cell lines.
• Migration studies of Ly6C+ splenocytes were conducted using Transwell inserts (5 μm pore size) and analyzed for chemotaxis by flow cytometry.
• Monocytic subsets in the spleen were enumerated using multicolor flow cytometry.
• Collagen Antibody Induced Arthritis (CAIA) was induced using the 5 clone Chondrex antibody cocktail and LPS booster on GMSM3$-/-$ and wild type mice per manufacturer's instructions.
• The levels of various intra-articular proinflammatory chemokine receptors and cytokines known to be important to RA and CIA disease pathogenesis were evaluated by quantitative PCR.

Results: GPSM3 expression is predominantly restricted to the monocytic lineage and modulated during monocyte differentiation. Data with GPSM3-deficient mice show that CAIA is blunted clinically and histopathologically with specifically reduced intra-articular *IL-6,IL-1β*, *CCR2,* and *CX3CR1* expression. *Ex vivo* results show a GPSM3-dependent decrease in ligand-specific migration of Ly6C+ CD11b+ spenocytes to the proinflammatory monocyte chemokines CCL2, CX3CL1, and chemerin.

Conclusion: Proinflammatory functions of monocytes critical to RA development are reliant on GPSM3 function. Having a single protein target for RA therapeutic intervention that appears to selectively affect proinflammatory monocyte infiltration into the joint represents a paradigm shift from previous therapeutic attempts at single cytokine or chemokine neutralization.

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Autoantibodies Are Associated with Subclinical Atherosclerosis and Cardiovascular Endpoints in Caucasian and African American Women in a Prospective Study: the Multi-Ethnic Study of Atherosclerosis (MESA). Darcy S. Majka[1], Rowland W. Chang[1], Richard M. Pope[2], Marius C. Teodorescu[3], Elizabeth W. Karlson[4], Thanh Huyen T. Vu[5], Joseph Kang[6] and Kiang Liu[1]. [1]Northwestern University, Chicago, IL, [2]Northwestern Univ Med School, Chicago, IL, [3]TheraTest Laboratories Inc, Lombard, IL, [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Northwestern University, Feinberg School of Medicine, Chicago, IL, [6]Northwestern University, Feinberg School of Medicine, Chicago, IL

Background/Purpose: Although the association between rheumatoid arthritis (RA) and cardiovascular disease (CVD) is established, the exact mechanism is not known. Subjects who later develop RA were shown to have increased risk of myocardial infarction (MI) in the preclinical period prior to RA symptoms indicating that autoimmunity might be a risk factor for CVD. Therefore, we tested the hypothesis that RA-related autoantibodies are independent risk factors for subclinical atherosclerosis and subsequent clinical CVD events.

Methods: MESA is a multicenter population based study cohort prospectively collecting CVD outcome and risk factor data in 6814 middle-aged to elderly multi-ethnic participants since 2000. At MESA baseline, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP-2) by ELISA and coronary artery calcium (CAC) by CT were measured in 6557 AA, Caucasian, Hispanic and Chinese participants who were then followed for 7.1 years for coronary heart disease (CHD) Hard endpoints (MI, resuscitated cardiac arrest, CHD death) and CVD Hard endpoints (MI, cardiac arrest, CHD death, stroke, stroke death). We assessed the associations between baseline RF/anti-CCP and CAC stratified by race/gender using logistic regression adjusting for traditional CVD risk factors. We used Cox regression to determine race/gender-specific associations between RF/anti-CCP and clinical CVD endpoints.

Results: 12.2% had CAC >=300; After 7.1 years, 3.0% had Hard CHD endpoints; 4.8% had Hard CVD endpoints. RF IgM, RF IgA and anti-CCP were positive in 15.9%, 8.7%, and 2.0%, respectively. 4.0% were positive for both and 20.6% were positive for either RF isotype. RA-related autoantibody positivity varied with race and was highest in AA's (RF: p<0.001, anti-CCP: p<0.003). RF and anti-CCP were associated with CAC in Caucasian and AA women after adjustment for traditional risk factors (Table 1). Table 2 demonstrates strong associations between RA-related autoantibodies and clinical CVD events in AA women. There were no clear associations in Hispanic and Chinese participants.

Table 1. Adjusted* Odds Ratios (95% CI) of Having Degrees of CAC by Autoantibody Positivity in Caucasian Women and AA Women

RA-related Autoantibodies	CAC Levels		
	0<CAC<99 vs. CAC=0	99<CAC<300 vs. CAC=0	CAC>300 vs. CAC=0
Caucasian Women (N=1,323)			
RF IgM	**2.2 (1.5–3.3)**	1.4 (0.8–2.7)	1.5 (0.8–2.8)
RF IgA	1.7 (0.9–3.1)	0.9 (0.3–2.5)	**2.3 (1.0–5.5)**
Either RF isotypes	**2.0 (1.4–3.0)**	1.2 (0.7–2.2)	**1.7 (1.0-3.1)**
Both RF isotypes	2.2 (0.9–5.0)	1.5 (0.5–4.9)	2.1 (0.7–6.7)
CCP	0.9 (0.3–2.7)	1.5 (0.5–5.3)	0.9 (0.2–4.4)
AA Women (N=1000)			
RF IgM	1.2 (0.8–1.8)	1.4 (0.8–2.5)	1.5 (0.8–2.8)
RF IgA	1.0 (0.6–1.8)	**2.2 (1.1–4.2)**	2.4 (1.2–5.0)
Either RF isotypes	1.2 (0.8–1.7)	1.6 (0.9–2.7)	1.4 (0.8–2.6)
Both RF isotypes	1.1 (0.5–2.3)	**2.7 (1.1–6.3)**	4.0 (1.6–9.6)
CCP	2.0 (0.9–4.8)	1.1 (0.2–5.1)	**4.0 (1.3–12.5)**

*Adjusted for age, smoking status, BP, BMI, HDL-c, LDL-c, DM, aspirin use, and cholesterol and BP medication use.

Table 2. Adjusted* Hazard Ratios (95% CI) for the Incidence of Clinical Cardiovascular Events over 7.1 Years Follow Up by Autoantibody Positivity

	Caucasian Women	
RA-related Autoantibodies	CHD Hard Endpoints (N=31)	CVD Hard Endpoints (N=56)
RF IgM	1.2 (0.4–3.0)	1.8 (0.9–3.4)
RF IgA	1.1 (0.3–4.5)	0.5 (0.1–2.2)
Either RF isotypes	1.2 (0.5–3.0)	1.6 (0.8–3.0)
Both RF isotypes	0.8 (0.1–6.1)	0.4 (0.1–3.1)
CCP	NA	NA
AA Women		
	CHD Hard Endpoints (N=19)	CVD Hard Endpoints (N=37)
RF IgM	1.7 (0.7–4.5)	**2.1 (1.1–4.0)**
RF IgA	**5.0 (1.9–12.7)**	3.4 (1.7–6.9)
Either RF isotypes	**2.5 (1.0–6.4)**	2.7 (1.4–5.1)
Both RF isotypes	**4.5 (1.6–13.0)**	3.3 (1.5–7.3)
CCP	1.1 (0.1–8.3)	2.3 (0.7–7.7)

*Adjusted for age, smoking status, BP, BMI, HDL-c, LDL-c, DM, aspirin use, and cholesterol and BP medication use. CHD Hard event outcomes include MI, resuscitated cardiac arrest, and CHD death. CVD Hard events include MI, cardiac arrest, CHD death, stroke, and stroke death.

Conclusion: This study demonstrates that RA-related autoantibodies are associated with subclinical and clinical atherosclerosis in a population based cohort. These findings indicate autoimmune factors may play a role in the pathogenesis of atherosclerosis, even in individuals without RA.

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Associations of Race and Ethnicity with Overall Mortality and Cardiovascular Events Among Patients with End-Stage Renal Disease Due to Lupus Nephritis. Jose A. Gomez-Puerta[1], Sushrut Waikar[2], Graciela S. Alarcon[3], Jun Liu[4], Daniel H. Solomon[1], Wolfgang C. Winkelmayer[5] and Karen H. Costenbader[1]. [1]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [2]Division of Nephrology, Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [5]Stanford University School of Medicine, Stanford, CA

Background/Purpose: Patients with SLE and lupus nephritis (LN) are at elevated risks of cardiovascular disease. Past studies have suggested that African American patients with SLE may be at higher cardiovascular risk than White patients. A large recent study of individuals with end-stage renal disease (ESRD) of any cause showed effect modification of the race-mortality association by age and demonstrated increased mortality among young African American compared to White patients. However, there is little information about mortality and cardiovascular risks among patients with ESRD due to LN, differentiated by race and ethnicity. We tested for differences in mortality and cardiovascular event rates in patients with ESRD due to LN, by race and ethnic group.

Methods: Individuals age ≥18 years with incident LN ESRD (ICD-9 code 710.0) between 1995 and 2008 were identified in the US Renal Data System (URDS). Covariates at baseline were ascertained from the Medical Evidence Report (a standardized form including sociodemographics, clinic data and laboratory measures collected at dialysis initiation). LN was consider as primary cause of renal failure according to the attending nephrologist. Multiple imputation was used for missing baseline data [albumin, body mass index and estimated glomerular filtration rate (eGFR)]. The hazard ratios (HR) for mortality and cardiovascular events (myocardial infarction, heart failure, hemorrhagic and ischemic stroke) during follow-up through December 31, 2008 were estimated using multivariable-adjusted Cox regression

Results: We identified 12,533 patients with ESRD due to LN. Mean age at ESRD onset was 40.7 ± 14.9 years; 81.6% were women and 49% were African American. The total number of deaths, cardiovascular events and their incident rates are shown in Table. Compared to Whites, African Americans had higher risk of death (1.30 [95%CI 1.21–1.39]) and heart failure (1.35 [95%CI 1.24–1.47]). Conversely, Asian patients had lower risk of mortality 0.68 [95%CI 0.65–0.92] and heart failure (0.67[0.50–0.90]).

Hispanic patients had lower rates of mortality (0.74 [95%CI 0.66–0.82]), heart failure (0.82;95%CI 0.71–0.97), myocardial infarction (0.69;95%CI 0.49–0.98), and ischemic stroke (0.68; 95%CI 0.48–0.85) than non-Hispanics.

Table. Hazard Ratios for Mortality and Cardiovascular Events in 12.533 patients with ESRD due to Lupus Nephritis, US patients 1995–2008

	Mortality Total events=4789 Fully-Adjusted HR	Heart Failure Total events=2276 Fully-Adjusted HR	Myocardial Infarction Total events=464 Fully-Adjusted HR	Ischemic Stroke Total events=456 Fully-Adjusted HR	Hemorrhagic Stroke Total events =162 Fully-Adjusted HR
Race					
White	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Asian	0.68 (0.65–0.92)	0.67 (0.50–0.90)	0.88 (0.50–1.56)	0.62 (0.33–1.16)	1.95 (0.93–4.11)
African American	1.30 (1.21–1.39)	1.23 (1.07–1.41)	0.97 (0.77–1.23)	0.85 (0.67–1.07)	1.09 (0.71–1.65)
Native	1.17 (0.86–1.58)	1.20(0.81–1.78)	0.57 (0.18–1.8)	0.51 (0.16–1.60)	2.05 (0.72–5.83)
Ethnicity					
Non-Hispanic	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Hispanic	0.74 (0.66–0.82)	0.83 (0.71–0.97)	0.69 (0.49–0.98)	0.68 (0.48–0.85)	0.81 (0.46–1.45)

IR: Incidence rate
*Multivariable model adjusted for sex, age at ESRD onset, sex, calendar year of ESRD onset, race, Hispanic ethnicity, smoking, comorbidities (hypertension, diabetes, coronary artery disease, chronic heart failure, cerebrovascular disease, peripheral vascular disease, cancer, chronic obstructive pulmonary disease), body mass index, albumin, eGFR, employment status, Medicare A+B, and region of residence (Northeast, South, Midwest or West US).)

Conclusion: Race and ethnicity are associated with mortality and cardiovascular outcomes among LN ESRD patients. While African American patients had significantly higher rates of death and heart failure than Whites, Asian and Hispanic patients had lower rates of these outcomes. The causes of these disparities are not understood, but are likely multifactorial, including genetic, socioeconomic, and environmental factors. Moreover, lower than expected mortality among Hispanic patients has been observed in other studies as well and may be due to people returning to their native countries for end of life care (Borrell LN, Am J Public Health, 2012).

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Short Term Use of Glucocorticoids Is Not Associated with Acute Risk of Myocardial Infarction. Steven C. Vlad[1], David T. Felson[1], Donald R. Miller[2] and Yuqing Zhang[1]. [1]Boston University, Boston, MA, [2]Edith Nourse Rogers Memorial VA Hospital, Bedford, MA

Background/Purpose: Observational studies of both chronic and short term glucocorticoid (GC) use have suggested an elevated risk of acute myocardial infarction (MI). However this could be a result of confounding by indication; i.e. some condition for which a GC is prescribed is also a risk factor for MI. This study's aim was to examine whether 'burst' GC use serves as a trigger for acute MI or whether any effect is likely to be the result of confounding by indication.

Methods: We used national Veterans Administration (VA) data from fiscal year 1998 through 2008 to compare the risk for MI during and around periods of GC use compared to periods of non-use using the self-controlled case series study design, a case only design which compares risks within persons, thus limiting confounding. Based on prescription records we first developed a cohort of subjects who had only used 'burst' GCs, defined as dispensed oral prescriptions of [2] 30 days with at least 42 days between consecutive prescriptions; we excluded persons who received GCs during their first 60 days of follow-up or who could have received GCs during a prior hospitalization. From these, we selected those persons who had a first MI requiring hospitalization (cases) using validated ICD-9 codes; we excluded cases who had an MI within the first year of follow-up (to limit the number with possible recurrence). We focused on the period in which each subject was using GCs, as well as 42 days before and after to account for confounding by indication and any residual GC effects. The risk of MI in each of these periods was compared to that in the remaining follow up time period. We controlled for age in 5 year bands (18–24, 25–29, 30–34, > 80).

Results: There were 1632 cases of MI among burst GC users. 97.5% were men. Mean age at MI was 66.8 (sd 11.4) years; 66.9 (11.4) in men, 59.5 (12.9) in women. 75.4% of subjects were white, 10.1% African American, 5.0% Hispanic, 10.0% other. All cases had only 1 GC prescription for a median duration of 6 (Q1, Q3: 6, 10) days and median

average daily prednisone equivalent dose of 17.5 (17.5, 22.0) mg. The incidence rate ratio (IRR) of MI rose over the 42 days prior to the GC prescription from baseline to 7.5, and then dropped while the GC was being used. The risk essentially returned to baseline after GC was discontinued. See table.

	No. cases of MI in risk period	Incidence rate ratio	95% CI
Total number of cases	1632		
Reference risk period	1469	1.0	-
Time before GC prescription			
42–29 days prior to prescription	13	1.4	0.8, 2.4
28–15 days prior to prescription	22	2.3	1.5, 3.6
14–8 days prior to prescription	33	7.5	5.3,10.7
7–1 days prior to prescription	30	6.8	4.7, 9.8
Time while GC is being used			
days 0–6 on GC	16	4.4	2.7, 7.3
days 7–30 on GC	5	2.9	1.2, 7.1
Time after GC prescription			
1–7 days after discontinuation	5	1.1	0.5, 2.7
8–14 days after discontinuation	6	1.4	0.6, 3.0
15–28 days after discontinuation	21	2.2	1.4, 3.4
29–42 days after discontinuation	12	1.2	0.7, 2.2

Conclusion: Our results suggest that any elevated risk of MI from GC use could be due to confounding by indication: in this study the risk rose before the GC prescription was issued, suggesting that the MI was associated with some other factor for which the GC might also have been prescribed at a later time.

Disclosure: S. C. Vlad, None; **D. T. Felson**, None; **D. R. Miller**, None; **Y. Zhang**, URL, 2.

1667

Impact of Rheumatoid Arthritis On Recognition of Hypertension in a Medically Homed Population. Christie M. Bartels[1], Heather Johnson[2], Katya Voelker[2], Patrick Mc Bride[2] and Maureen Smith[1]. [1]Univ of Wisconsin School of Medicine and Public Health, Madison, WI, [2]Univ of Wisconsin School of Medicine and Public Health, Madison

Background/Purpose: Numerous studies report increased cardiovascular disease (CVD) events and others describe increased arterial stiffness in patients with rheumatoid arthritis (RA). Still, hypertension diagnosis rates in RA reports are often lower than expected by age. We tested the hypothesis that RA is a risk factor for missed hypertension diagnosis, given the importance of hypertension for CVD risk.

Methods: Using a cohort design we studied all medically homed adult patients from a large multispecialty practice who met Joint National Committee-7 (JNC-7) hypertension diagnostic criteria but lacked baseline diagnosis or treatment to compare new recognition of hypertension in patients with and without RA. "Medically homed" definitions required ≥2 primary care visits over ≥12 months (2009–11), and RA/inflammatory arthritis algorithms required two ICD-9 claims of 714 in 24 months. Cox proportional hazard modeling was used to examine the impact of RA on hypertension recognition.

Results: Among 33,947 medically homed patients with baseline undiagnosed and untreated hypertension, 575 patients had RA codes. After an average of 14 months follow up, 49% of RA patients compared to 42% without RA remained undiagnosed. RA patients had equal annual primary care visits (mean 1.5 v. 1.6), more total provider visits (mean 7.5 v. 4.6) and longer mean observation time, yet were less often diagnosed. In multivariate modeling controlling for socio-demographic factors, comorbidity, and utilization factors, the presence of rheumatoid arthritis decreased the likelihood of hypertension diagnosis or treatment by 21% [Hazard Ratio 0.79, Confidence Interval 0.71–0.89].

Hypertension recognition was lower in RA than other comorbidities (Table 1), and contrasted with increased hypertension recognition in patients with diabetes or kidney disease. RA patients were older (mean 62 v. 57 years), more female, weighed less, and were more likely to see an internist for primary care, and in the final adjusted model, younger age, white race, Medicaid, and non-internal medicine primary care provider predicted lower hypertension recognition.

Table 1. Cox Proportional Hazards Model for Hypertension Recognition

	Unadjusted % Diagnosed	Adjusted HR	95% CI
Rheumatoid Arthritis	51	0.79	0.71–0.89
Depression	51	0.88	0.83–0.93
Hyperlipidemia	68.7	1.33	1.29–1.37
Diabetes	71.4	1.22	1.18–1.27
Chronic Kidney Disease	64.1	1.13	1.06–1.20
Ischemic Heart Disease	66.8	1.00	0.95–1.06
Peripheral Vascular Disease	67.1	1.09	1.03–1.16
Congestive Heart Failure	65.1	0.9	0.84–0.96
TIA/Stroke	55.3	0.9	0.84–0.96

Model also includes age, gender, weight, language, Medicaid, and utilization

Conclusion: In this sample of medically homed patients meeting JNC-7 criteria for hypertension those with RA were 21% less likely to be diagnosed or treated despite more total visits, compared to those without RA. Given that both hypertension and RA increase cardiovascular risk, rheumatologists may need to actively help to improve hypertension recognition to modify CVD risk.

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1668

Improving the Accuracy of Cardiovascular Risk Prediction in Rheumatoid Arthritis with a New Predictive Model Using the 10-Year Prospective Carre-Study. Alper M. van Sijl[1], Inge A.M. van den Oever[1], Mike J.L. Peters[2], Vokko P. van Halm[3], Alexandre E. Voskuyl[2], Yvo M. Smulders[2] and Mike T. Nurmohamed[1]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Academic Medical Centre, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which is associated with an increased cardiovascular (CV) risk. Traditional CV risk factors do not fully explain the increased CV risk and prediction of future CV disease in RA by CV risk estimates (Framingham and Reynolds) has shown to be inadequate. The present study investigated whether future CV disease in RA can be accurately predicted by demographic factors, CV risk factors, RA-related factors, CV risk estimates and surrogate markers of CV disease, or a combination of all.

Methods: 10-year incidence rate of CV disease was determined in a prospective cohort of 353 RA-patients. CV risk factors, RA-related factors and surrogate markers of CV disease were assessed at baseline. Predictive models of separate variables or in combinations were created using stepwise backward logistic regression analyses and areas under the curve (AUC) were calculated using receiver operating curves (ROC) analyses.

Results: After 10 years, there were 58 events over 2361 patient years of follow-up. CV disease incidence was 16.4%, while 10-year CV risk estimates with SCORE and Framingham underestimated this risk with 5.9% and 13.0%, respectively. From ROC analyses, a model was created which seemed to predict CV disease incidence better than the already available 10-year CV risk estimates (AUC 0.801 vs. 0.712, respectively). For RA patients without prior CV disease, the model consisted of age, gender, use of statins and prednisone, body-mass index, diastolic blood pressure, LDL cholesterol, total cholesterol to HDL-cholesterol ratio, C-reactive protein, HAQ and ESR.

Table 1. Comparison of incident cardiovascular (CV) disease with 10-year CV risk estimates

	All RA-patients (n=349)	Prior CV disease excluded (n=295)
Follow-up characteristics		
Total follow-up, years	2361	2042
Cases of CV disease, number	58	41
Incidence rates/1.000 patient years		
Total CV disease	24.6	20.1
CV mortality	3.4	3.4
Coronary artery disease	14.4	12.2
Cerebrovascular disease	6.3	4.9
Peripheral arterial disease	4.7	2.9
Observed and predicted 10-year CV disease incidence		
Observed 10-year CV disease incidence, %	16.4	13.9
Predicted 10-year CV disease risk at baseline according to SCORE-formula, %	5.9	4.9
Predicted 10-year CV disease risk at baseline according to Framingham-formula, %	13.0	11.0
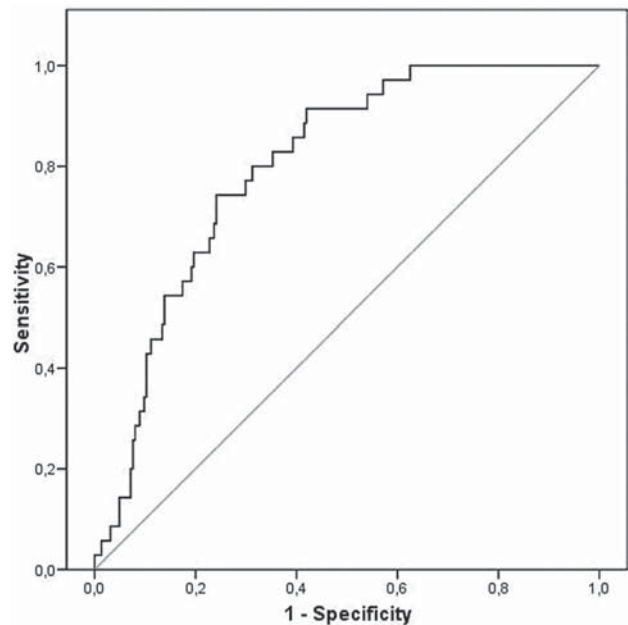
Figure 1. ROC curve for the prediction of incident CV disease using a model consisting of demographical factors, CV risk factors and RA related factors

Conclusion: 10-year CV risk estimates did not accurately predict the actual CV risk in a population of RA patients. A combined model of demographic factors, CV risk factors and RA related factors more accurately predicted the actual CV risk. Future studies should corroborate these findings and consider whether modification of pre-existing risk models will improve the CV risk assessment in RA patients.

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Infection Risk After Orthopaedic Surgery in Patients with Inflammatory Rheumatic Diseases, with Focus On Discontinuation of TNF-Alpha-Inhibitors. Catrina B. Scherrer[1], Anne AF Mannion[1], Diego Kyburz[2], Markus Vogt[3] and Ines A. Kramers-de Quervain[1]. [1]Schulthess Clinic, Zürich, Switzerland, [2]Center of Exp. Rheumatology, Zurich, Switzerland, [3]Cantonal Hospital Zug, Baar, Switzerland

Background/Purpose: Infections after orthopaedic surgeries are feared complications, leading to costly treatments and successive interventions. A higher postoperative infection risk is discussed in patients with inflammatory rheumatic diseases (IRDs). This is especially relevant since patients with aggressive diseases frequently need orthopaedic surgery. In a retrospective study of a large cohort of orthopaedic surgeries the risk of postoperative infections was examined in relation to diagnosis, type of surgery and preoperative management of conventional disease modifying medication (cDMARDs) and tumor necrosis factor alpha (TNF-α)-inhibitors.

Methods: 37'137 patients (50'359 surgeries) were followed in the hospital's surgery registry over 8 years. Diagnoses were categorized as inflammatory or degenerative/posttraumatic and operation-related infections were registered. In a subgroup with known medication prior to surgery the preoperative management and influence on the infection rate was analyzed. Chi-squared test was used to assess associations between two discrete variables. Univariate and multiple logistic regression analyses were used to identify risk factors for infection. Odds ratios (OR) together with the corresponding 95% confidence intervals (95%CI) were provided.

Results: Among the 50'359 surgeries 422 (0.8%) surgery-related infections were identified, 373/47'887 (0.8%) cases in the degenerative group and 49/2'472 (2.0%) in the IRD group, indicating a significantly higher infection rate in the IRD group (OR=2.576, 95%CI 1.907, 3.479; p<0.001). Complete information on medication use and its discontinuation or otherwise prior to surgery was available for 1'329/2472 (54%) cases in the IRD group. The use of TNF-α-inhibitors was documented in 171/1'329 (13%) cases. In 49/171 (29%) cases, TNF-α-inhibitors were discontinued more than three adminis-

tration intervals before surgery. These were considered "ex-users". This occurred more often with drugs having a short administration interval. In the remaining 122/171 (71%) cases, the time lag was 3 administration intervals or less, and these were considered "at risk". The use of more than one cDMARD (OR=2.425, 95%CI 1.034, 5.688; p=0.042) and TNF-α-antagonists before surgery (OR=2.627, 95%CI 1.119, 6.168; p=0.027) were each associated with an increased infection rate. The risk of infection was almost 10-fold when surgery was performed within one administration interval (OR=10.047, 95%CI 1.170, 86.286; p=0.035). Approximately 81% of the patients treated with infliximab were in this group ($\leq$1 administration interval), whereas only 33% of the users of adalimumab and 24% of the etanercept users had their last intake of the drug one administration interval or less before surgery.

Conclusion: The risk of postoperative infection is elevated in patients with IRDs compared to degenerative/posttraumatic cases. Special attention should be paid when more than one cDMARD or TNF-α-inhibitors with long administration intervals are used. The last intake of TNF-α-inhibitors should be at least more than one administration interval before surgery, as the risk of postoperative infection is significantly increased if surgery occurs within this period.

ACR Concurrent Abstract Session
Muscle Biology, Myositis and Myopathies:
Pathogenesis in Idiopathic Inflammatory Myopathies
Monday, November 12, 2012, 4:30 PM–6:00 PM

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Microarray Analysis for miRNA Expression in Juvenile Dermatomyositis (JDM). Dong Xu[1], Akadia Kachaochana[2], Gabrielle A. Morgan[2], Elio F. Vanin[3], Marcelo Bento Soares[3] and Lauren M. Pachman[1]. [1]Division of Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Children's Hospital of Chicago Research Center, Cure JM Myositis Center, Chicago, IL, [3]Cancer Biology & Epigenomics Program, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: JDM, the most common of the idiopathic inflammatory myopathies, is a systemic vasculopathy, associated with premature development of cardiovascular disease. Studies by others had implicated miRNA −10a in atherosclerosis. MicroRNAs (miRNAs) are short, non-coding RNAs and inhibit mRNAs by binding to complementary sequences on target mRNAs, resulting in translational repression or target degradation and gene silencing. **Hypothesis:** miRNA-10a may play a role in the vasculopathy of untreated JDM.

Methods: After informed consent (IRB# 2008–13457) and under MRI guidance a diagnostic muscle biopsy was obtained from the involved area in untreated children with definite/probable JDM. The patient population consisted of 10 girls and 7 boys, the mean age was 6.0 ± 2.9 years old, and their race was: White 77.8%, Hispanic 16.7%, White/Indian 5.6%; for the controls, the 3 girls, 3 boys were white and their mean age was 12.1 ± 3.8 years old. Total RNA was extracted from muscle biopsy samples and used for Exiqon miRNA DNA microarray analysis. Validation of differentially expressed miRNAs and their putative target mRNAs was conducted by TaqMan qPCR.

Results: Of 1435 mature human miRNAs on the Exiqon miRNA DNA microarray, 335 miRNAs were expressed in JDM and control samples. The expression analysis identified 20 miRNAs that were significantly differentially expressed (p<0.05). Several of these miRNAs, e.g. miR-10a [Fold Change (FC)= −1.96], miR-10b (FC= −1.62) and miR-142-5p (FC= 2.17), regulate inflammatory pathways. To validate those differentially expressed miRNAs, we performed qPCR for miR-10a, miR-10b and miR-142-5p. Our results showed that miR-10a and miR-10b levels were decreased by 3.58 and 2.41 fold respectively; and miR-142p level was increased by 2.90 fold. Those altered microRNA expression levels were consistent with the results from miRNA DNA microarray data. Homeobox A1 (*HOXA1*) gene is a well-known target of miR-10a and it is negatively regulated by miR-10a. To confirm whether *HOXA1 gene* was up-regulated because miR-10a expression was decreased significantly in JDM, we conducted qPCR for the *HOXA1* gene. The results documented that the *HOXA1 gene* was significantly increased by 2.12 ± 1.14 fold (p<0.01) in JDM compared to controls.

miR-10a plays an important role in regulation of NFkB pathway: decreased miR-10a lowers NFkB degradation and promotes inflammatory biomarker gene expression. Further investigation showed that inflammatory biomarker genes, *IL-6* and *VCAM-1*, were significantly elevated in JDM compared with controls: *IL-6* and *VCAM-1* gene expression levels were increased by 2.81 ± 2.16 and 2.93 ± 1.45 fold respectively (p<0.01).

Conclusion: Profiling identified 20 differentially expressed miRNAs in JDM compared to controls. Decreased miR-10a expression and increased *HOXA1*, *IL-6* and *VCAM-1* gene expression demonstrated that specific miRNAs, miR-10a and 10b may play a role in the regulation of the inflammatory pathway in JDM. We speculate that miRNA-10a may be associated with the vasculopathy characteristic of JDM and that their mimics may be of value in therapy.

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Characterization of Jo-1 Autoantibodies in Patients with Inflammatory Myopathy and Interstitial Lung Disease. Kyle P. Chiang[1], Varun Gauba[1], Darin Lee[1], Minh-Ha T. Do[1], Jie J. Zhou[2], Feng Wang[2], Ying Buechler[1], Leslie Nangle[1], Zhiwen Xu[2], John Mendlein[1], Melissa Ashlock[1] and Jeffrey M. Greve[1]. [1]aTyr Pharma, San Diego, CA, [2]Hong Kong University of Science and Technology, Kowloon, Hong Kong

Background/Purpose: Anti-Jo-1 autoantibodies (Jo-1 Abs), directed against histidine tRNA synthetase (HisRS1), are detected in a high proportion of patients with both autoimmune inflammatory myopathy (IM) and interstitial lung disease (ILD), progressive and debilitating conditions for which no drugs are specifically approved. These patients receive immunosuppressive therapy which can be needed on a chronic basis to control their symptoms. In some individuals continued respiratory deterioration may occur despite immunosuppressive treatment, and may lead to fatal outcomes. Several lines of evidence indicate that Jo-1 Ab may have pathogenic roles in IM and ILD. We and others have demonstrated that HisRS1 and HisRS1-derived proteins possess immune-regulatory activities in addition to their roles in protein synthesis. As a key element of our effort to develop novel therapies for IM and ILD, we performed a detailed characterization of the Jo-1 Abs present in diverse populations of patients.

Methods: A large panel of sera from healthy volunteers, IM patients with and without Jo-1 Abs, and patients with Jo-1 Abs for which the formal clinical diagnoses were unknown was obtained from a commercial vendor. Plate-based immunoassays were developed to determine: i) the Jo-1 Ab titers by ELISA; (ii) Jo-1 Ab isotypes; (iii) the absolute concentration of IgM and IgG Jo-1 Ab; iv) epitopes recognized by Jo-1 Abs using a panel of recombinant human HisRS1 protein fragments and alternatively-spliced forms (including those expressed in muscle and lung); v) Jo-1 Ab affinity (by surface plasmon resonance); and vi) circulating levels of HisRS1.

Results: A wide range of Jo-1 Ab titers were found and these values correlated with the absolute amount of Jo-1 Abs. The Jo-1 Ab titers and concentrations exhibited a broad range, with higher concentrations found in patients diagnosed with IM compared to those without a formal clinical diagnosis. Jo-1 Ab IgM was detected in some patients. The specific epitopes recognized by Jo-1 Abs were distributed across the entire HisRS protein and were interpreted in reference to the recently determined 3-D structure of human HisRS. The epitopes recognized varied considerably among subjects. Jo-1 Ab affinities measured were in the range of 10 – 0.01 nM. Circulating levels of HisRS1 protein were detected in some individuals.

Conclusion: This molecular characterization of Jo-1 Abs provides deeper insight into the human autoimmune response to HisRS1 that occurs in a population of human subjects with autoimmune diseases. Ongoing serial analysis of individual patients will provide greater insight into the progression of Jo-1 Abs with respect to isotypes, affinities, recognized epitopes, and their relationship to disease status. These data provide a framework for developing strategies to address the impact of Jo-1 Abs in IM and ILD.

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Myosin Skews Effector Immune Cells of Scurfy Mice to Target Muscles in an Adoptive Transfer Model of Myositis. Nicholas Young[1], Rahul Sharma[2], Alexandra Friedman[1], Benjamin Kaffenberger[1] and Wael N. Jarjour[3]. [1]The Ohio State University Medical Center, Columbus, OH, [2]University of Virginia Health System, Charlottesville, VA, [3]Ohio State University, Columbus, OH

Background/Purpose: Myositis is associated with an inflammatory process that results in pronounced muscle weakness and is observed in some regulatory T cell (Treg) deficient mouse models. Autoimmune pathogenesis has been strongly implicated in myositis and is the focus of both standardized and emerging therapeutics. It has been shown that patients with dermatomyositis have decreased numbers of Tregs in peripheral blood and at skin lesions when compared to healthy controls. Scurfy (Forkhead box P3, FOXP3-/y) mice lack Tregs and display autoimmune inflammation of multiple organs, but exhibit very little evidence of myositis. In contrast, Syt7 (Synaptotagmin 7) mice which have no Treg deficits develop an inflammatory response involving the muscles. We hypothesized that Treg deficient myositis could be induced by myosin protein and that muscle-specific inflammatory effector cells could be suppressed through Treg supplementation.

Methods: We crossed scurfy mice with Syt7 mice, which results in a double knockout that is deficient in Treg cells and membrane resealing. Lymph node preparations of these double knockout mice or scurfy mice were adoptively transferred into Rag1[null] males with or without Tregs isolated using Dynabeads from wild-type mice or with purified myosin protein. Histology of muscle tissue was examined four weeks post-injection. Immunohistochemistry was performed on flash frozen and/or paraffin embedded tissue.

Results: Scurfy lymph node preparations injected into Rag1[null] males intraperitoneally in conjunction with purified myosin protein induced robust skeletal muscle inflammation. The infiltrates consisted predominantly of $CD4^+$ and $CD8^+$ T cells, limited macrophages, but no B cells. Even more robust myositis was seen in similar experiments using lymph node preparations from Syt7/FOXP3 double knockout mice. However, myositis was not seen in adoptive transfers using single knockout mice. This myositis was completely suppressed with the co-transfer of purified Treg cells from wild type mice.

Conclusion: Taken together, these data demonstrate the critical role of the muscle antigen, myosin, in the pathogenesis of myositis. Hence, myosin could be one possible target antigen of the immune response. We also demonstrate the roles of Treg deficiency and aberrant muscle antigen release in the induction of myositis and the role of Treg as a therapeutic tool to treat myositis.

This novel model has the potential of examining the interplay between chemical injury and inflammatory pathogenesis in myositis. Ongoing work will use this model to examine the myopathy associated with statins and will examine the role of other endogenous muscle tissue antigens in this disease.

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1673

Clinical Phenotypes of Caucasian Adult and Juvenile Dermatomyositis Patients with Anti-MDA5 Autoantibodies. Zoe Betteridge[1], Sarah Tansley[1], Harsha Gunawardena[2], Lucy R. Wedderburn[3], Hector Chinoy[4], Robert G. Cooper[5], Jiri Vencovsky[6], Lenka Plestilova[7], Ingrid E. Lundberg[8], Katalin Danko[9], Melinda Vincze[9], Neil McHugh[1], UK JDRG[10] and EuMyoNet[11]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]North Bristol NHS Trust, Bristol, United Kingdom, [3]University College London (UCL), London, United Kingdom, [4]The University of Manchester, Manchester, United Kingdom, [5]Hope Hospital, Salford, United Kingdom, [6]Institute of Rheumatology, Prague, Czech Republic, [7]Institute of Rheumatology, Prague 2, Czech Republic, [8]Karolinska Institutet, Stockholm, Sweden, [9]University of Debrecen, Debrecen, Hungary, Debrecan, Hungary, [10]London, United Kingdom, [11]Stockholm, Sweden

Background/Purpose: Autoantibodies to MDA5 have been previously reported in Japanese patients with dermatomyositis (DM) and are associated with clinically-amyopathic DM and rapidly progressing interstitial lung disease (ILD). These autoantibodies also occur in juvenile Japanese DM patients in association with ILD. Anti-MDA5 has also been reported in a cohort of mixed ethnicity, where it was found to be associated with ILD and severe vasculopathy. Here we report on the frequency and clinical manifes-

tations of anti-MDA5 autoantibodies in a large international multicenter cohort of Caucasian adult and juvenile myositis patients.

Methods: Serum was available from 1331 adult myositis patients (480 DM) recruited to the EuMyoNet repository and 172 JDM patients recruited to the UK JDRG. Sera were screened for autoantibodies by immunoprecipitation (IPP) using radio-labelled K562 cell extract. Sera with immunoprecipitates at approximately 140 kDa were tested for anti-MDA5 autoantibodies by ELISA using recombinant MDA5 (Cambridge BioSciences). Clinical data were collected on standardised proformas. Sera from 169 systemic sclerosis, 40 SLE and 50 healthy controls were also analyzed by IPP. Statistical analysis was performed using SPSS and Fishers Exact Test.

Results: Anti-MDA5 autoantibodies were found in the sera of 12 JDM patients and 25 adults. The frequency in the JDM cohort was 7.0%, in comparison to 1.9% in the overall adult myositis population and 3.8% in the adult DM group. Anti-MDA5 autoantibodies were not found in any patients with PM or any control sera. As with previous reports, there was an association between ILD and anti-MDA5 (p=0.044) in the adult DM patients. However, contrary to previous reports, this was not seen to be rapidly progressing, with no known ILD related fatalities in the anti-MDA5 positive group. In comparison, ILD was not found to be a significant association in the JDM anti-MDA5 positive group, with no patients having ILD reported as a clinical manifestation. Similarly to previous report, anti-MDA5 positive patients had significantly more ulceration (skin: p=0.047 and mouth: p=0.039), in the JDM cohort, compared with the anti-MDA5 negative group. Whilst ulceration data was unavailable in the adult population, the presence of anti-MDA5 was significantly associated with Gottron's papules (p<0.001).

Conclusion: We report the presence of anti-MDA5 autoantibodies in a large cohort of Caucasian JDM and adult myositis patients. The frequency of anti-MDA5 autoantibodies varies between adults and children, along with differences in the clinical profile. As with previous reports, the presence of anti-MDA5 is associated with the presence of severe cutaneous features in both JDM and adults. However, in this study ILD was only an association in the adult population, suggesting differences in pathogenesis or aetiology. This study also highlights differences in clinical manifestations between different ethnic groups, with the ILD in our adult patients being much less severe in comparison to previous reports on Japanese patients.

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Myeloid Related Proteins Induce Muscle Derived Inflammatory Mediators in Juvenile Dermatomyositis. Kiran Nistala[1], Hemlata Varsani[1], Helmut Wittkowski[2], Thomas Vogl[3], Petra Krol[4], Vanita Shah[1], Kamel Mamchaoui[5], Paul Brogan[1], Johannes Roth[3] and Lucy R. Wedderburn[1]. [1]University College London (UCL), London, United Kingdom, [2]Muenster, Germany, [3]University of Muenster, Muenster, Germany, [4]Prague, Czech Republic, [5]Paris, France

Background/Purpose: The etiopathogenesis of Juvenile Dermatomyositis (JDM) remains poorly understood. In particular the contribution of monocytes or macrophages, which are frequently observed to be an infiltrate within muscle tissue very early in the disease process, is unknown. We hypothesised that these cells secrete the pro-inflammatory S100 proteins myeloid related peptide (MRP)-8/14 which may then contribute to muscle pathology in JDM.

Methods: In this study of 75 JDM patients, serum MRP8/14 levels were compared with clinical measures of disease activity. Muscle biopsies taken early in disease were assessed by immunohistochemistry to determine the frequency and identity of MRP-expressing cells. The effects of MRP stimulation and ER stress on muscle were tested *in vitro*. Serum or supernatant levels of cytokines were analysed by multiplex immunoassay.

Results: Serum MRP8/14 correlated with physician's global assessment of disease activity in JDM (r^2=0.26, p=0.006), functional assessment (CHAQ, r^2=0.31, p=0.0498), and strength/stamina (CMAS, r^2=0.28, p=0.028). MRP8/14 was widely expressed by CD68+ macrophages in JDM muscle tissue. When cultured with human myoblasts, MRP8 led to the secretion of MCP-1 and IL-6, which was enhanced by ER stress. Both inflammatory mediators were detected in significantly higher levels in the serum of JDM patients compared to healthy controls.

Conclusion: This study is the first to identify serum MRP8/14 as a biomarker for disease activity in JDM. We propose that tissue infiltrating macrophages secreting MRP8/14 may contribute to myositis, by driving the local production of cytokines directly from muscle.

Disclosure: **K. Nistala**, None; **H. Varsani**, None; **H. Wittkowski**, None; **T. Vogl**, None; **P. Krol**, None; **V. Shah**, None; **K. Mamchaoui**, None; **P. Brogan**, None; **J. Roth**, None; **L. R. Wedderburn**, None.

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Myositis Autoimmunity and Muscle Weakness Are Linked to TNF-Alpha Suppression of Micrornas-1, 133, and 206 in Myoblasts and Myocytes.
Robert Georgantas III[1], Katie Streicher[1], Steven A. Greenberg[2], Lydia Greenlees V[3], Wei Zhu[4], Philip Brohawn[4], Brandon W. Higgs[4], Megan Czapiga[5], Chris Morehouse[4], Laura Richman[3], Bahija Jallal[4], Koustubh Ranade[5] and Yihong Yao[3]. [1]Medimmune, Inc, Gaithersburg, MD, [2]Brigham Women's Hospital, Harvard Medical School, Boston, MA, [3]MedImmune, Gaithersburg, MD, [4]MedImmune, LLC, Gaithersburg, MD, [5]MedImmune, Inc, Gaithersburg, MD

Background/Purpose: The molecular basis of myopathies such as dermatomyositis, polymyositis and inclusion-body myositis, which are characterized by chronic muscle inflammation followed by long term skeletal muscle wasting, are poorly understood.
Methods: We compared expression levels of inflammatory cytokines and microRNAs to identify those differentially expressed between muscle biopsies from myositis patients (N = 24) and healthy donors (N = 17). We then used human and mouse *in vitro* myoblast-to-myocyte differentiation models to determine those differentially expressed cytokines and microRNAs that affect myoblast differentiation.
Results: We observed increased expression of inflammatory cytokines including TNF-alpha (fold change = 3.8 to 8.8-fold, P-values < 0.045), and decreased expression of microRNAs miR-1 (fold changes = -2.8 to -8.7, P-values $< 2.0\times10^{-4}$), miR-133a (fold changes = -3.9 to -5.0, P-values $< = 4.0\times10^{-4}$), miR-133b (fold changes = -2.7 to -7.8, P-values $<4.2\times10^{-4}$), and miR-206 (DM = -2.8-fold, P = 0.012) which are known to be critical to adult skeletal muscle differentiation. TNF-alpha inhibited expression of miR-1, 133a/b, and 206 and suppressed differentiation of C2C12 myoblasts to myocytes/myotubes in an NF-kb dependent manner. This block in differentiation by TNF-alpha was relieved by overexpression of *miR-1*, miR-*206* or *miR-133*.
Conclusion: Taken together these results provide a new mechanistic link between a pro-inflammatory cytokine and the degenerative pathology of myositis, and suggest new therapeutic approaches for this disease.

Disclosure: **R. Georgantas III**, Medimmune, Inc, 3, AstraZeneca, 1; **K. Streicher**, AstraZeneca, 1, Medimmune, Inc, 3; **S. A. Greenberg**, Medimmune, Inc, 2; **L. Greenlees V**, AstraZeneca, 1, Medimmune, Inc, 3; **W. Zhu**, AstraZeneca, 1, MedImmune, 3; **P. Brohawn**, AstraZeneca, 1, MedImmune, 3; **B. W. Higgs**, AstraZeneca, 1, MedImmune, 3; **M. Czapiga**, AstraZeneca, 1, Medimmune, Inc, 1; **C. Morehouse**, AstraZeneca, 1, MedImmune, 3; **L. Richman**, AstraZeneca, 1, Medimmune, Inc, 3; **B. Jallal**, AstraZeneca, 1, MedImmune, 3; **K. Ranade**, AstraZeneca, 1, Medimmune, Inc, 3; **Y. Yao**, AstraZeneca, 1, MedImmune, 3.

ACR Concurrent Abstract Session
Pediatric Rheumatology: Clinical and Therapeutic Disease II: Juvenile Idiopathic Arthritis II
Monday, November 12, 2012, 4:30 PM–6:00 PM

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Abatacept As First Line Biological Treatment for Severe Juvenile Idiopathic Arthritis-Related Uveitis. A Multicenter Study.
Carolina Birolo[1], Maria Elisabetta Zannin[1], Svetlana Arsenyeva[2], Rolando Cimaz[3], Elisabetta Miserocchi[4], Margarita Dubko[5], Chantal Deslandre[6], Fernanda Falcini[7], Maria Alessio[8], Francesco La Torre[9], Ekaterina Denisova[10], Irina Nikishina[11] and Francesco Zulian[12]. [1]University of Padua, Padua, Italy, [2]Scientific Research Institute of Rheumatology RAMS, Moskow, Russia, [3]A. Meyer Children's Hospital, Florence, Italy, [4]Scientific Institute San Raffaele, University Vita-Salute, Milan, Italy, [5]Saint-Petersburg Pediatric Medical Academy, Saint-Petersburg, Russia, [6]Cochin Hospital, Paris, France, [7]Department of Internal Medicine, Rheumatology Section, University of Florence, Florence, Italy, [8]University of Naples Federico II, Naples, Italy, [9]DIMIMP-University, Rheumatologic Section, Bari, Italy, [10]Helmgoltz Moscow Recearch Institute of Eye Diseases, Moskow, Russia, [11]Scientific Research Institute of Rheumatology RAMS, Moskow, Moskow, Russia, [12]University of Padua, Padova, Italy

Background/Purpose: Anterior uveitis is a serious complication of Juvenile Idiopathic Arthritis (JIA). Recently, Abatacept (ABA) has been used in children with JIA-uveitis who had failed previous anti-TNF agents but little is known about its efficacy as first-line biological agent in severe JIA-related uveitis. Aim of the present study was to compare safety and efficacy of ABA used as first biological agent (ABA1st) with ABA used after one or more anti-TNF agents (ABA2nd), in patients with severe JIA-related uveitis.
Methods: A retrospective multicenter collection of data of patients with severe, MTX-resistant JIA-related uveitis treated with ABA at a monthly dosage of 10 mg/kg, administered intravenously as first line or second line biological agent, was performed. Absolute frequency of uveitis flares before and after ABA treatment, changes in ocular complications and ABA-related side effects have been recorded. The number of active joints was also assessed at each visit.
Results: Thirty-five JIA patients (33 females, 2 males) with a mean 12.5 years of age, and 7.7 years of uveitis duration have been treated with ABA for 19.6 months (range 5–42). Twenty-seven patients with MTX-refractory uveitis and at least 12 months follow-up entered study. 11 were included in the ABA1st group and 16 in the ABA2nd group. Age at uveitis onset, number of uveitis flares during 12 months before ABA and number of complicated uveitis were comparable in the two groups. The mean uveitis duration was significantly shorter in ABA1st (5.1 versus 9.5 years, $p=0.009$). The mean frequency of uveitis flares during the 12 months before and after ABA decreased from 4.1 to 1.0 in ABA1st ($p=0.001$) and from 3.5 to 1.1 in ABA2nd ($p=0.001$). The efficacy was comparable in both groups and in all ABA showed a better performance after the first six months of treatment as 21/30 (70%) uveitis flares occurred during the first semester. Pre-existing ocular complications improved or remained stable in all but 2 patients. 15/22 patients (68.2%) with active arthritis at baseline were in remission at 12 months follow-up; in the others, the mean number of active joints decreased from 10.1 to 7.0. In this regard, no significant difference was observed between the two ABA treatment modalities. Two patients (7.4%) experienced adverse events (1 post-infusion headache, 1 weight gain) but no serious events were observed. Two patients (7.4%) withdrew from the study (after 5 and 9 months) because of ABA inefficacy on both ocular and articular symptoms.
Conclusion: Abatacept, used as first-line biological treatment or after one or more anti-TNF agents, induced a comparable sustained improvement of refractory JIA-related uveitis. Efficacy was more evident during the second semester in both groups. Abatacept represents a treatment of choice in patients failing standard immunosuppressive treatment and/or anti-TNF agents for severe JIA-related uveitis.

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Safety and Efficacy of Intra-Articular Infliximab Therapy for Treatment Resistant Temporomandibular Joint Arthritis in Children.
Matthew L. Stoll, Anthony B. Morlandt, Suwat Teerawattanapong, Daniel Young, Peter D. Waite and Randy Q. Cron. University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Temporomandibular joint (TMJ) arthritis occurs in as much as 80% of children with juvenile idiopathic arthritis (JIA) and can result in substantial facial deformity. TMJ arthritis often responds poorly to systemic immunosuppressive therapy. Intra-articular corticosteroid injections (IACI) are of benefit in approximately 50% of JIA patients with TMJ arthritis, but repeated injections are often ineffective. Multiple studies have shown benefit of IA infliximab injections (IAII) in treating chronic arthritis, including to the TMJ in one case report, so we used IAII of the TMJs in JIA patients with TMJ arthritis refractory to both repeated IACI and to systemic arthritis therapy.
Methods: Chart review was performed for all children with JIA treated at a single center who received one or more IAII (5–10 mg/injection) to the TMJs. Outcomes assessed were maximal incisal opening (MIO) measurements and pre- and post-contrast magnetic resonance imaging (MRI) findings. Specifically, we compared pre- versus post-IACI and pre- versus post-IAII MRI studies for changes in the acute (synovial fluid, synovial enhancement, marrow edema) and chronic (synovial hypertrophy, condylar head flattening and erosions, disc displacement) findings associated with TMJ arthritis. Assessments of improved, unchanged, or worsened were made by two independent reviewers based upon the official reports, and adjudicated by a radiologist based upon the actual films in instances of disagreement. Institu-

tional Review Board, and Hospital Pharmacy and Therapeutics Committee, approvals were obtained prior to reporting and treating, respectively.

Results: 24 children with JIA and treatment-refractory TMJ arthritis underwent bilateral IAII of the TMJs, of whom 23 had MRIs at all three timepoints (pre-IACI, post-IACI, post-IAII). 23/24 (96%) were on a biologic, with or without concurrent conventional disease-modifying agents; 1 child received methotrexate as monotherapy. Their MIOs (mean ± SEM; in mm) were unchanged before and after both IACI (44.0 ± 1.3 versus 44.6 ± 0.7, p = 0.813) and IAII (44.6 ± 0.7 vs 44.5 ± 0.9, p = 0.840.) However, MRIs revealed improved or halted progression of acute changes in 31 out of 46 TMJs (67%) and of chronic changes in 29 out of 46 TMJs (63%), compared to 15/46 (33%) and 19/46 (41%), respectively, with repeated use of IACI (p = 0.002 and 0.052, respectively). No side effects (infections, nerve damage, cosmetic alterations, prolonged discomfort) were noted after 7.4 person-years of follow-up among 22 patients.

Conclusion: IAII halted or reversed the progression of TMJ arthritis in the majority of JIA patients who were refractory to systemic arthritis therapy and repeated IACI TMJ injections. The IAII TMJ injections were safe in the short term. It remains unknown whether repeated injections of IAII will be of benefit to treatment refractory TMJ arthritis in children with JIA. Future studies will evaluate the efficacy of infliximab versus long-acting corticosteroid injections as initial therapy for TMJ arthritis in children with JIA.

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1678

Safety and Efficacy of Adalimumab in Children with Active Polyarticular Juvenile Idiopathic Arthritis Aged 2 to <4 Years or ≥4 Years Weighing <15 Kg. Daniel J. Kingsbury[1], Pierre Quartier[2], Gina Patel[3], Vipin Arora[3], Hartmut Kupper[4] and Neelufar Mozaffarian[3]. [1]Legacy Emanuel Children's Hospital, Portland, OR, [2]Unite d'Immuno-Hematologie et Rhumatologie Pediatriques, Paris, France, [3]Abbott, Abbott Park, IL, [4]Abbott GmbH and Co. KG, Ludwigshafen, Germany

Background/Purpose: Adalimumab (ADA) is approved for use in moderate to severe JIA in patients (pts) ≥4 yrs old in the US, EU, and Japan. ADA has not been studied in pts <4 yrs old, and limited data are available in pts ≥4 yrs old weighing <15 kg. The primary objective of this study was to assess the safety of ADA in pts 2 to <4 yrs old or ≥4 yrs old weighing <15 kg with moderately to severely active polyarticular onset/polyarticular course JIA. The secondary objectives were to evaluate the pharmacokinetics (PK) and clinical effectiveness of ADA in these pts.

Methods: This is an interim analysis of the multicenter, open-label, phase 3b ADA study in pts 2 to <4 yrs old or ≥4 yrs weighing <15 kg with moderately to severely active JIA in the US and EU. ADA was given subcutaneously every other wk, 24 mg/m^2 BSA up to 20 mg/dose, for a minimum of 24 wks and continued until pts reached 4 yrs old and weighed 15 kg. Concomitant methotrexate use was allowed. Adverse events (AE) were collected throughout the treatment period and include safety data up to 96 wks. Serum trough concentrations of ADA were determined for each subject using validated methods. Key effectiveness endpoints were the proportion of pts achieving PedACR30/50/70/90 at wk 24. Other outcomes included tender joint count (TJC), swollen joint count (SJC), Pain on Passive Motion (POM75), Limitation on Passive Motion (LOM69), Active Joint Count (AJC73), Child Health Assessment Questionnaire (DICHAQ), and Physician's and Parent's Global Assessment of Disease (PhGA and PaGA).

Results: 88% of the pts were female. At baseline, mean age=3 yrs, mean weight=13 kg, mean duration of JIA=12 months, and 39% had elevated CRP (≥0.9 mg/dL). AE incidence rates through 96 wks included: any AEs (84%, 27/32), serious AEs (16%, 5/32), infectious AEs (69%, 22/32), and serious infections (9%, 3/32). No deaths, malignancies, opportunistic infections/TB, congestive heart failure, demyelinating disease, allergic reactions, lupus-like syndrome, or blood dyscrasias were reported. The mean serum ADA trough concentrations achieved a steady-state of 7–8 μg/mL at weeks 12 and 24 (n=15). Of 32 pts enrolled, 31 completed 24 wks of ADA treatment; 90% achieved PedACR30 and 70% achieved PedACR70 (**Table 1**).

Table 1. PedACR Response at Week 24

	Response Rate[a] N=30	Response Rate[b] N=32
PedACR30, n (%)	27 (90.0)	27 (84.4)
PedACR50, n (%)	25 (83.3)	25 (78.1)
PedACR70, n (%)	22 (73.3)	22 (68.8)
PedACR90, n (%)	11 (36.7)	11 (34.4)

[a]Observed. [b]Nonresponder imputation.

Improvements in other JIA outcomes were also seen at wk 24 of ADA treatment (**Table 2**).

Table 2. JIA Outcomes at Week 24[a]

	Mean Change (SD) from Baseline
Tender Joint count (TJC75)[b]	-3.0 (5.5)
Swollen Joint Count (SJC66)[b]	-6.3 (5.8)
Pain on Passive Motion (POM75)[b]	-3.9 (7.3)
Limitation on Passive Motion (LOM69)[b]	-5.6 (5.6)
Active Joint Count (AJC73)[b]	-7.0 (5.7)
Child Health Assessment Questionnaire (DICHAQ)[b]	-0.5 (0.7)
PhGA of Disease Activity[b] (VAS 0–100 mm)	-45.3 (21.3)
PaGA of Disease Activity[b] (VAS 0–100 mm)	-32.2 (29.7)
PaGA of Pain[b] (VAS 0–100 mm)	-29.5 (28.3)
CRP[c] (mg/dL)	-0.2 (3.2)

[a]Observed data. [b]n=30; [c]n=28.

Conclusion: The safety profile, PK, and effectiveness of ADA were similar to that seen in older pediatric patients with JIA, demonstrating that ADA is also safe and effective in younger patients 2 to <4 yrs old or ≥4 yrs old weighing <15 kg with active polyarticular JIA.

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1679

Cumulative Long-Term Safety and Efficacy of Abatacept in Children with Juvenile Idiopathic Arthritis: Results up to 7 Years of Follow-up. D. J. Lovell[1], N. Ruperto[2], R. Mouy[2], E. Paz[2], N. Rubio-Perez[2], C. A. Silva[2], C. Abud-Mendoza[2], R. Burgos-Vargas[2], V. Gerloni[2], J. A. Melo-Gomes[2], C. Saad-Magalhaes[2], J. Chavez[2], C. Huemer[2], A. Kivitz[2], F. Blanco[2], I. Foeldvari[2], Michael Hofer[3], H. Huppertz[2], C. Job Deslandre[2], K. Minden[2], A. Flores Nunez[4], A. J. Block[5] and A. Martini[2]. [1]Cincinnati Children's Hospital, Cincinnati, OH, [2]PRINTO, IRCCS G. Gaslini, Genoa, Italy, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genoa, Italy, [4]PRINTO, IRCCS Hospital para el Niño Poblano, Puebla, Mexico, [5]Bristol-Myers Squibb, Princeton, NJ

Background/Purpose: We previously reported the efficacy and safety of abatacept (ABA) in patients with juvenile idiopathic arthritis (JIA) in the AWAKEN trial[1], during the 4-month open-label ABA lead-in phase and 6-month double-blind (DB) (ABA vs placebo [PBO]) period. Long-term efficacy and safety were also described for 153 patients who received open-label ABA in the long-term extension (LTE) for ≥21 months.[2] We now report efficacy and safety data from the cumulative LTE for an additional ~30 months of exposure up to 7 years of total follow-up.

Methods: Patients entered the LTE and received open-label intravenous ABA if they were a non-responder (NR) in the 4-month open-label lead-in phase, or if they either experienced a flare or completed the 6-month DB withdrawal phase while receiving ABA or PBO. Efficacy is reported up to Day 1681 of the LTE (~Year 5.5 of the study), and safety is reported up to 7 years of treatment at study completion.

Results: 190 patients entered the AWAKEN trial, with 153 entering the LTE (58/60 patients from the DB ABA group, 59/62 from the DB PBO group, and 36/47 NR patients from the open-label phase). Cumulative exposure was 606.2 years. At the start of the LTE, 46/58 (79%, ABA) and 31/59 (53%, PBO) had achieved an ACR Pediatric 50 response. Mean response of those who received PBO during the DB phase recovered completely within 6 months after re-instating ABA therapy in the LTE and these results were combined with those of patients in the ABA group starting from LTE Month 6 (Figure). ACR Pediatric 50, 70 and inactive disease rates are shown. Of the open-label responders, 32/110 (29%, Day 169) to 36/79

(46%, Day 1177) had inactive disease status. Of the NR, 4/13 (31%) achieved inactive disease at the end of the trial. There was one death (accidental; unrelated). The major reason for discontinuation in the LTE was lack of efficacy in 24 patients (15.7%, 11 were NR); 6 discontinuations due to AEs (3/6 due to serious AEs); 13, loss to follow-up; 10, withdrawal of consent; and 18 "other" (not efficacy or safety). Thirty patients (19.6%) had serious AEs; most were unrelated and were primarily musculoskeletal or infectious events. Incidence rate (per 100 patient-years [pt-yrs]) of SAEs in the LTE (5.6/100 pt-yrs) did not increase versus the 6-month DB rate (6.8/100 pt-yrs). No malignancy was reported. Of the 153 patients entering the LTE, 69 patients completed the trial (29, 27 and 13 in the original ABA, PBO and NR groups, respectively).

ACR Pediatric 50, 70 and Inactive disease response rates during LTE for all Period A responders who entered LTE (as observed data)
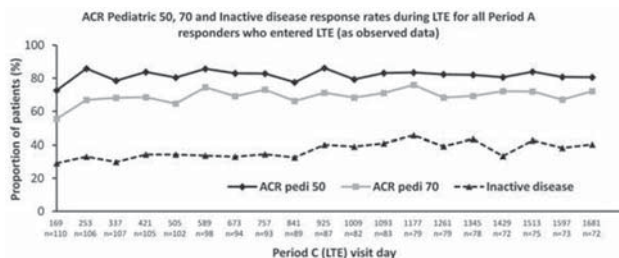
Conclusion: These data demonstrate the sustained efficacy of abatacept in JIA patients. Additional exposure of ~30 months did not change the safety profile of abatacept in these patients when compared to prior LTE experience.[2]

1. Ruperto N, et al. *Lancet* 2008;**372**:383–91.
2. Ruperto N, et al. *Arthritis Rheum* 2010;**62**:1792–802

1680

Diagnostic Value of the Assessment of Spondyloarthropathy International Society (ASAS) Criteria for Children with Enthesitis Related Arthritis (ERA): A Single Center Study of 124 Patients.

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Background/Purpose: Enthesitis Related Arthritis (ERA) is a common subtype (36%) of Juvenile Idiopathic Arthritis (JIA) seen in India [1]. These criteria do not distinguish between axial and peripheral arthritis. The new ASAS criteria [2,3] do, and have to date been applied only to the adult population. This distinction is important from both the diagnostic and therapeutic viewpoint. Therefore, we applied the ASAS criteria to our ERA patients. This is the first study of its kind.

Methods: Data on JIA patients at our centre is collected on detailed proformas at onset and thereafter quarterly. All ERA patients seen over a three year period from May 2009–12 were included. ASAS axial and peripheral spondyloarthritis (SpA) criteria were retrospectively applied to this cohort, taking all features within 6 months of disease onset.

Results: *ERA:* 124 children were identified, 102 were boys. Median age of onset was 10.9 years; median delay to diagnosis 5months. ERA features: 64 had arthritis *and* enthesitis; 60 had Enthesitis *or* Arthritis with ≥ 2 of the following: SI tenderness and/or inflammatory spinal pain 28%, HLA-B27 97.6%, Family history of medically confirmed HLA-B27-associated disease 9.7%, Anterior uveitis 16.1%, Onset of arthritis in a boy after 6 yr of age 83.8%.

ASAS criteria: All 124 ERA patients could be classified per the ASAS criteria. The prevalence of each item is in Table1. No patient in this cohort had

isolated inflammatory back pain (IBP) without any other feature of SpA. Thirty five children had axial and 89 peripheral SpA. Only 1 patient had imaging evidence of sacroiliitis with no back pain. All children in this study with axial complaints had IBP.

Table 1.

SpA features	Axial SpA	Axial SpA	Peripheral SpA	Peripheral SpA
	Low back pain >3months + Sacroiliac imaging + ≥1 SpA feature n=29	Low Back Pain + HLAB27 + ≥2 SpA features n=6	Arthritis or Enthesitis or Dactylitis + ≥1 SpA feature n=88	Arthritis or Enthesitis or Dactylitis + ≥2 SpA feature n=1
IBP	29 (100%)	6 (100%)	NA	NA
Arthritis	25 (86.2%)	5 (83.3%)	88 (100%)	1 (100%)
Enthesitis (heel)	9 (31%)	0 (0%)	NA	NA
Uveitis	3 (10.3%)	1 (16.67%)	16 (18.18%)	NA
Dactylitis	0 (0%)	0 (0%)	3 (3.4%)	0 (0%)
Psoriasis	0 (0%)	0 (0%)	0 (0%)	NA
Crohn's/Ulcerative Colitis	1 (3.4%)	1 (16.67%)	1 (1.13%)	NA
Good response to NSAIDs	23 (79.3%)	5 (83.33%)	NA	NA
Family h/o SpA	7 (24%)	0 (0%)	NA	0 (0%)
HLAB27	29 (100%)	6 (100%)	87 (98.86%)	NA
Elevated ESR*	20 (69%)	4 (100%)	NA	NA
Preceding infection	NA	NA	6 (6.81%)	NA
SI imaging	NA	NA	5 (5.68%)	NA
Enthesitis (any)	NA	NA	46 (52.27%)	0 (0%)
IBP ever	NA	NA	NA	0 (0%)

*CRP replaced by ESR

Additional data: 97.6% patients were HLAB27 positive, 19.4% had hip disease and 28.2% of SI joint MRIs were positive. A further 12 patients developed new onset inflammatory back pain over the observation period of 3 years.

Conclusion: The ASAS axial and peripheral SpA criteria can be applied to all children with ERA and have a sensitivity of 100%, peripheral SpA is 2.5 times as common as the axial SpA. Thus in the pediatric population the entry criteria should be peripheral and not axial disease. This has important implications for deciding therapeutic pathways in children with axial or peripheral disease and gives an oppurtunity to childen with SpA to be recruited into clinical trials with same diagnostic criteria as for adults. We plan to expand the application of these criteria to the undifferentiated and psoriatic arthritis categories of JIA as well.

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2. Rudwaleit M, et al. The ASAS classification criteria for peripheral SpA. Ann Rheum Dis; 2011; 70(1):25–31.
3. van der Heijde Dse et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in axial SpA. Ann Rheum Dis.2011;70(6):905–8.

1681

Increased Arterial Stiffness in Juvenile Idiopathic Arthritis (JIA) Patients Compared with Matched Controls - a Pilot Study.

Hanne Aulie[1], Mette-Elise Estensen[2], Anne Marit Selvaag[1], Patrick Segers[3], Oyvind Molberg[1], Vibke Lilleby[1], Svend Aakhus[2] and Berit Flatø[1]. [1]Department of Rheumatology, Oslo University hospital, Rikshospitalet, Oslo, Norway, [2]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [3]IBiTech-bioMMeda, Ghent University, Ghent, Belgium

Background/Purpose: Systemic arterial properties in adult patients with JIA are not well described. The aim of this study was to evaluate arterial properties in young adults with JIA compared with age- and sex-matched controls.

Methods: Nineteen patients (37.7±3.4 years) were randomly selected from a cohort of 88 JIA-patients who were followed from their first referral to Oslo University Hospital in 1980 −85 and had active disease more than 14 years after disease onset. Of the 19 patients, 2 had systemic JIA, 3 polyarticular RF negative, 1 polyarticular RF positive, 3 oligoarticular persistent, 5 oligoarticular extended, 3 enthesitis related, 1 psoriasis arthritis and 1 had undifferentiated arthritis. The patients were investigated after a mean disease duration of 29.2 ±1.3 years and compared with 19 age- and sex-matched controls.

Aortic root pressure and flow data were obtained non invasively by brachial arterial blood pressure, calibrated carotid arterial pulse trace and aortic annular Doppler flow recordings. The systemic arterial properties were described by the total arterial compliance (C), characteristic aortic impedance

(Z_0), and peripheral arterial resistance (R) obtained from estimation of 3-element windkessel model (WK) parameters (C, Z_0, R), by Fourier analyses of central aortic pressure and flow data (Z_0).

Results: (table)

Table.

Variables	JIA-patients Mean ± SD	Controls Mean ± SD	P-value (unpaired t-test)
BMI	25.7 ± 4.9	25.3 ± 4.0	0.785
Systolic blood pressure (mmHg)	117 ± 15	114 ± 11	0.443
Diastolic blood pressure (mmHg)	69 ± 9	68 ± 9	0.535
Heart rate (beats/s)	67 ± 11	60 ± 8	0.043
Cardiac output(l min −1)	5.3 ± 1.1	5.3 ± 0.9	0.982
R (mmHg/(ml/s))	1.04 ± 0.21	1.00 ± 0.23	0.564
Z_0 Windkessel Model (WK) (10^-3 mmHg/ml/s)	77 ± 25	58 ± 20	0.016
C Pulse pressure method (PPM) (ml/mmHg)	1.21 ± 0.24	1.44 ± 0.34	0.022

The proximal aortic stiffness, evaluated by Z_0,was significantly higher in the JIA-patients compared to the healthy controls (p=0.016). The patients also had lower total arterial compliance (C) (p=0.022), but the arterial resistance (R) was not different (p= 0.564). The heart rate was higher in the patients than in the controls (p=0.043), but the blood pressure did not differ between the groups (p=0.443, p=0.535).

Conclusion: In spite of similar blood pressure, JIA patients have stiffer proximal aorta and lower total arterial compliance than matched controls. This indicates that JIA-patients with long term active disease experience significant alteration of arterial function.

Disclosure: H. Aulie, None; **M. E. Estensen**, None; **A. M. Selvaag**, None; **P. Segers**, None; **O. Molberg**, None; **V. Lilleby**, None; **S. Aakhus**, None; **B. Flatø**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects III:
Rheumatoid Arthritis and Cardiovascular Disease
Monday, November 12, 2012, 4:30 PM–6:00 PM

1682

Sustained Clinical Remission (Disease Activity Score 28 Elke.E.A. Arts[1], Jaap Fransen[1], Alfons A. den Broeder[2], Calin Popa[1] and Piet L.C.M. van Riel[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands

Background/Purpose: Chronic inflammation appears to be an independent risk factor for CVD in rheumatoid arthritis (RA), but there is no clear difference in CVD risk between RA patients with low or high disease activity [(1;2)]. Possibly, only if disease activity is very low ('remission') it may protect against CVD. The objective of this study was to investigate the association between clinical remission (DAS28<2.6) and the risk of CVD in patients with RA.

Methods: RA patients from the Nijmegen inception cohort were selected if they had at least one year follow-up. Patients were seen at 3-month intervals and the DAS28 was assessed at each visit. Cardiovascular events included myocardial infarction (MI) and stroke, transient ischemic attack, angina pectoris and peripheral arterial disease. Remission was defined as DAS28<2.6. A continuity rewarded score (ConRew) was calculated: a score of 1 was rewarded if DAS28<2.6 and a score of 2 was rewarded if DAS28<2.6 at the previous visit too. The ConRew score was divided by the maximal possible score (100% if always in remission) and this was used in the analysis. The crude data were analysed using Kaplan-Meier survival analysis, divided in two groups according to the median of the ConRew ratio. The risk of CVD in RA patients was analysed using a Cox-proportional hazard model, with ConRew ratio as the independent variable, and time to CVD event as the dependent variable. Considered confounders were age, gender, prior CVD, rheumatoid factor (RF), anti-CCP and DAS28, HAQ, medication for CVD prevention, glucocorticosteroid use, cholesterol levels and systolic blood pressure at baseline. Missing values were imputed using multiple imputation, results of the analysis are based on the pooled data.

Results: A total of 770 RA patients were selected for analysis. Patients had a mean±SD age of 56±13 at baseline, 61% female, 76% RF positive with a mean±SD DAS28 at baseline of 5.1±1.4. In total, 153 CV events were registered. Age, gender, prior CV event, and TC:HDL ratio, medication

for CV prevention, HAQ and DAS28 at baseline were included as confounders. Results from the Kaplan-Meier survival analysis in the crude data (figure 1) showed that patients who were less in remission, maximum ConRew score <10%, were more likely to develop CVD than patients who scored ≥ 10%, (p<0.001). In the Cox proportional hazards model, it was shown that a higher ConRew score had a protective effect for developing CVD (OR 0.48 [95% CI 0.66–0.83]), corrected for confounders.
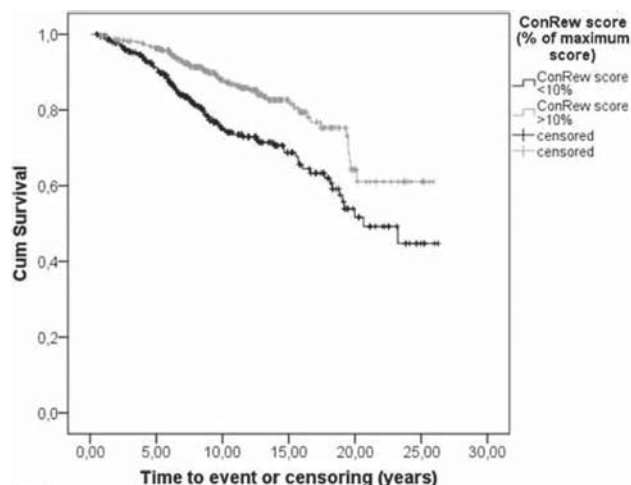
Figure 1. Cumulative survival curves for RA patients with a ConRew score (% of maximum score) <10% and ≥10%.

Conclusion: Sustained remission in patients with RA is significantly associated with a reduced excess risk of CVD. Maintaining tight control of disease activity in RA patients to achieve remission is therefore important for the prevention of CVD events.

References
[1]Radovits et al. Ann Rheum Dis. 2009;68:1271–76.
[2]Arts et al. [abstract]Arthritis Rheum. 2011;63(supplement 10):2585

Disclosure: E. E. A. Arts, None; **J. Fransen**, None; **A. A. den Broeder**, None; **C. Popa**, None; **P. L. C. M. van Riel**, None.

1683

Associations Between Lipid and Rheumatoid Arthritis Genetic Factors, and Low Density Lipoprotein Levels in RA Patients. Katherine P. Liao[1], Dorothee Diogo[1], Tianxi Cai[2], Jing Cui[3], Raul N. Guzman P.[4], Vivian Gainer[4], Shawn N. Murphy[4], Susanne Churchill[4], Isaac Kohane[1], Elizabeth W. Karlson[5] and Robert M. Plenge[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Brigham and Womens Hospital, Boston, MA, [4]Partners Healthcare Systems, Boston, MA, [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: In epidemiologic studies, low density lipoprotein (LDL), a major risk factor for cardiovascular disease (CVD), is lower in RA patients than the general population; despite this RA patients have a higher risk of CVD. Recently, the genetic determinants of LDL in the general population have been elucidated. We hypothesized that these LDL genetic factors are associated with higher LDL levels in RA and further, that RA genetic factors also influence LDL levels.

Methods: We studied an RA cohort of 1837 subjects based in a large academic center. We genotyped subjects' blood samples for published alleles associated with higher LDL levels (26 alleles) and RA risk (48 alleles including HLA shared epitope). To study associations between genetic factors and LDL levels, we created LDL and RA composite genetic risks scores (GRS): an aggregate count of the number of LDL and RA alleles for each individual. We selected the 1st LDL measurement in the electronic medical record as the outcome and excluded subjects with ≥1 statin prescription prior to the 1st LDL. We tested the associations between the LDL GRS and LDL, and the RA GRS and LDL levels by fitting separate linear regression models adjusted by age, gender and LDL measurement year. To determine whether RA genetic factors in aggregate were independently associated with LDL, we fitted a linear regression model with both the LDL and RA GRS, adjusted by age, gender and LDL measurement year. We further stratified each model by gender.

Results: 1072 RA subjects had LDL measured prior to a statin prescription. Characteristics: 81% female, 68% ACPA positive, mean LDL 119 mg/dL. We observed a significant association between the LDL GRS and higher LDL (p=8.0×10^{-4}); carriage of 1 additional LDL allele was associated with a 2.3 mg/dL increase in LDL. The RA GRS was not associated with LDL in all RA cases, however the association was significant among female RA cases: carriage of 1 additional RA risk allele was associated with a 0.75 mg/dL decrease in LDL (p=0.03) (FIGURE). Among female RA cases, the RA GRS remained significantly inversely associated with LDL (p=0.02) when added to a model with LDL GRS.
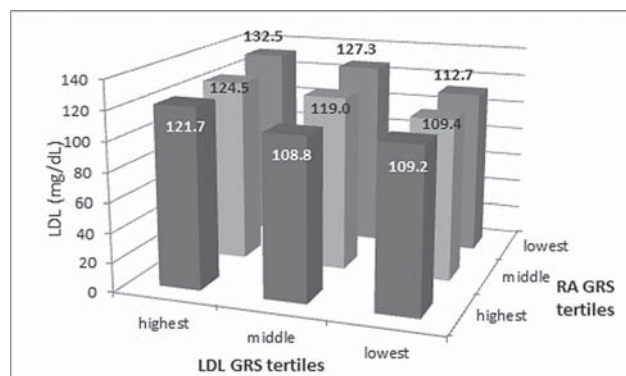
Figure. Mean LDL levels among female RA cases grouped by tertiles of LDL and RA genetic risk scores (GRS).
[Note: Subjects in the highest LDL GRS tertile carry the highest number of LDL alleles; similarly subjects in the highest RA GRS tertile carry the highest number of RA risk alleles in the cohort. No significant interaction was observed between RA GRS tertiles and LDL GRS tertiles.]

Conclusion: LDL genetic factors were significantly associated with higher LDL levels in RA cases. Our finding that RA genetic factors were significantly associated with lower LDL levels in female RA cases provides a genetic link to epidemiologic observations of lower LDL levels in RA compared to the general population.

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1684

Increased Risk of Major Cardiovascular Events in a Nationwide Cohort of Rheumatoid Arthritis Patients Treated with Biological Agents. Signe Abitz Winther, Peter Riis Hansen, Søren Lund Kristensen, Lene Dreyer, Ole Ahlehoff, Louise Linde, Christian Torp-Pedersen and Jesper Lindhardsen. Copenhagen University Hospital Gentofte, Hellerup, Denmark

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular disease, but in contrast to the well-established risk of myocardial infarction (MI), the results from studies on RA-related risk of stroke have been inconsistent. Also, we recently found an association between RA and atrial fibrillation (AF), which is an important risk factor for stroke. Most of these data, however, stem from more dated cohorts where the RA-specific treatment was less aggressive than today. Consequently, this study examined the incidence of MI, stroke and AF in a large, unselected, nationwide cohort of biologically treated RA patients.

Methods: In Denmark, biological RA treatment is provided at no cost, but patients are required to be registered and followed in the DANBIO registry. All RA patients treated with biological agents during the period 2001–2009 were matched with 10 individuals from the general population by age and sex at the start of biological therapy. Through individual-level linkage to the National Patient Register, the National Register of Medicinal Products (national prescription database) and the National Civil Register, participants were characterized with respect to comorbidity, pharmacotherapy and socio-economic status and subsequently monitored for the outcomes of interest (MI, stroke, or AF) until emigration, death, or December 31, 2010. Incidence rates were calculated and multivariable proportional hazard models were fitted to estimate risk of outcomes in terms of hazard ratios.

Results: A total of 3872 RA patients and 38720 controls were included. Cohort participants were predominantly women (74%) and had a mean age of 56 years. Cardiovascular and RA-specific characteristics are listed in Table 1.

The cohort was followed for a mean of 4.5 years during which 639 MIs, 867 strokes and 804 cases of AF occurred. The risk of all outcomes was significantly increased in biologically treated RA patients with a 95% excess risk of MI, 31% excess risk of stroke, and 35% excess risk of AF in the fully adjusted analysis (Table 2).

Table 1. Baseline characteristics

	Biologically treated RA patients n=3872	Controls n=38720
Age	56 (±13) years	56 (±13) years
Females	2861 (74%)	28610 (74%)
Follow-up	4.5 years	4.5 years
Pharmacological treatment		
Aspirin	403 (10.4%)	3604 (9.3%)
Beta blockers	462 (11.9%)	3574 (9.2%)
RAS inhibitors	554 (14.3%)	5057 (13.1%)
Lipid-lowering drugs	333 (8.6%)	3917 (10.1%)
NSAIDs	2710 (70.0%)	8691 (22.4%)
DMARDs	2944 (76.0%)	0 (0.0%)
Charlson co-morbidity index	0.06 (±0.36)	0.06 (±0.39)
Previous CV disease		
Myocardial infarction	107 (2.8%)	704 (1.8%)
Stroke	68 (1.8%)	795 (2.1%)
Atrial fibrillation	103 (2.7%)	777 (2.0%)
Socioeconomic status (1=low to 4=high)	2.51 (1.04)	2.50 (1.13)
RA-specific characteristics		
RA duration	8 (3–16) years	-
HAQ score	1.25 (0.73–1.75)	-
DAS28crp score	5.1 (4.1–5.9)	-
CRP	14 (7–32) mg/l	-

HAQ, Health Assessment Questionnaire; DAS, Disease activity score; RAS, Renin-angiotensin system; NSAID, Non-steroidal anti-inflammatory drug; DMARD, Disease-modifying anti-rheumatic drug; CV, cardiovascular; CRP, C-reactive protein. Numbers are means (±SD), n (%) and medians (interquartile range) as appropriate.

Table 2. Risk of adverse cardiovascular events in biologically treated RA patients versus controls (reference)

	Myocardial infarction		Stroke		Atrial Fibrillation	
	RA	Controls	RA	Controls	RA	Controls
Events (n)	106	533	98	769	103	701
Incidence rate (events per 1000 py)	5.7	2.8	5.2	4.1	5.7	3.9
Risk models	**Hazard ratios (95% CI)**					
Unadjusted	1.98 (1.60–2.44)		1.31 (1.06–1.62)		1.41 (1.14–1.73)	
As above + co-morbidity and socioeconomic status	2.02 (1.63–2.49)		1.33 (1.08–1.65)		1.42 (1.15–1.75)	
As above + CV medication and previous CV disease*	1.95 (1.57–2.43)		1.31 (1.05–1.63)		1.35 (1.09–1.68)	

py, person-years; CI, confidence interval; CV, cardiovascular.
* Covariates included individually (as outlined in Table 1).

Conclusion: In a large, nationwide and well-characterized cohort of RA patients treated with biological agents, the risk of MI was approximately two times higher than in the general population, while the excess risk of stroke and AF was less pronounced. The results indicate that despite aggressive treatment of RA the risk of major cardiovascular events is increased in these patients.

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1685

Differential Impact of Cardiac Risk Factors On Coronary Plaque Presence and Features in Asymptomatic Patients with Rheumatoid Arthritis Compared to Controls. George A. Karpouzas[1], Jennifer Malpeso[2], Tae-Young Choi[2], Silvia Munoz[1] and Matthew Budoff[2]. [1]Harbor-UCLA, Torrance, CA, [2]Harbor-UCLA Medical Center, Torrance, CA

Background/Purpose: Traditional cardiac risk factors (CRFs) associate with myocardial infarction (MI) risk in both Rheumatoid arthritis (RA) and

the general population. Subclinical atherogenesis has been linked to higher risk of future clinical events. However, the independent role of individual CRFs on coronary plaque presence and characteristics in asymptomatic, coronary artery disease (CAD)-naïve subjects with RA is unknown. We evaluated potential differences in the contribution of traditional CRFs on coronary plaque presence, quantitative and qualitative features in asymptomatic subjects with RA compared to controls.

Methods: One hundred and fifty RA subjects and 150 age and sex-matched controls underwent 64-slice coronary computed tomography angiography (CTA), a modality that reliably evaluates plaque presence, severity, burden, and composition as non-calcified (NCP), mixed or partially calcified (MP), or fully calcified (CP). A 15-segment American Heart Association model was used for evaluation. Quantitative plaque characteristics included segment involvement score (SIS- number of affected segments out of 15 evaluated/ patient), segment stenosis score (SSS-degree of luminal stenosis per segment, graded 1–4 and averaged over 15 evaluated segments/ patient), and plaque burden score (PBS-plaque extent per segment, graded 1–3 and averaged over 15 segments/ patient). Logistic and multivariable regression analysis models adjusted for age, gender, and all CRFs were used to assess differences in plaque prevalence and quantitative measures, between groups.

Results: Quantitative plaque measurements were significantly higher in RA; SIS=2.02±2.28 vs. 0.9±1.25, SSS=3.03±4.43 vs. 0.98±1.7, and PBS= 2.75±3.82 vs. 0.98±1.44, all with p<0.0001. Hypertension was significantly and differentially associated with higher risk of plaque prevalence in RA [adjusted OR=4.3 (1.83–10.1)- figure 1a]. Additionally, in the context of RA, the presence of male gender, hypertension and diabetes were associated with higher mean differences in the proportion of involved segments, plaque severity, and burden vs. their absence, compared to those imparted in controls (all with p<0.05- figure 1b, c, d respectively). Importantly, these differences segregated exclusively in MP and CP but not NCP.
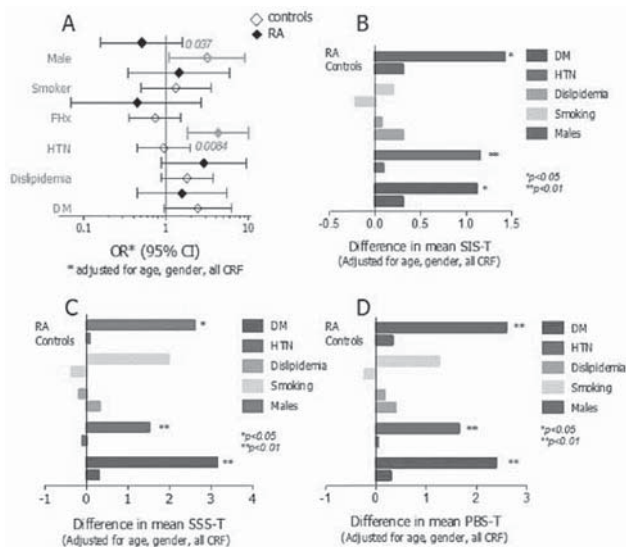
Conclusion: Hypertension strongly and differentially associates with coronary plaque presence in CAD-naïve, asymptomatic subjects with RA compared to controls. In RA, male gender, hypertension and diabetes are associated with significant differences in plaque severity, burden and number of involved segments compared to presence of those factors in controls, specifically for MP and CP.

Disclosure: **G. A. Karpouzas**, None; **J. Malpeso**, None; **T. Y. Choi**, None; **S. Munoz**, None; **M. Budoff**, None.

1686

Vertebral Fracture Assessment-Detected Abdominal Aortic Calcification Enhances Cardiovascular Disease Risk Stratification of Rheumatoid Arthritis Patients. Ausaf Mohammad[1], Derek Lohan[1], Diane Bergin[1], Sarah Mooney[1], John Newell[2], Martin O'Donnell[1], Robert J. Coughlan[1] and John J. Carey[1]. [1]Galway University Hospitals, Galway, Ireland, [2]National University of Ireland, Galway, Ireland

Background/Purpose: Osteoporosis and cardiovascular disease (CVD) are major comorbidities and CVD is the leading cause of death among patients with rheumatoid arthritis(RA). Traditional CVD risk prediction tools i.e., Framingham risk score(FRS) under-estimate the risk of CVD in RA. Novel biomarkers and better risk prediction tools are needed. Many RA patients undergo DXA today as part of an osteoporosis assessment, which may include a vertebral fracture assessment(VFA). VFA technology has been shown to reliably detect and quantify abdominal aortic calcification-(AAC). VFA-detected AAC is an independent robust marker of CVD in other populations. It is unknown whether VFA-detected AAC is a useful marker of CVD in RA. We aimed to determine whether VFA-detected AAC is independently associated with CVD in RA patients and compared its utility to the FRS for CVD risk assessment in RA patients.

Methods: A cross-sectional study of our RA cohort at a University Hospital. We included RA patients aged ≥40 years who met 1987 ACR criteria for RA, had a DXA and VFA scan available for analysis and access to their medical records to ascertain their CVD risk factors and details. The study was approved by our local I.R.B. Two blinded consultant musculoskeletal radiologists independently reviewed all VFA scans to determine AAC using an established 24-point scale. We determined if AAC was independently associated with prevalent CVD using multivariable logistic regression. The ability of the FRS and AAC for determining the presence of CVD was assessed using ROC curve analyses.

Results: 1330 patients were screened. 603 met the inclusion criteria: mean age 56 years, 74% female, 76% sero-positive and 43% smokers. 230 had ≥1documented CVD event. Overall AAC was present in 211 of subjects: 11% was mild (<9 points), 57% moderate (9–16) and 32% severe(>16 points). The proportion of patients with AAC was substantially greater in subjects with CVD than those without(76% Vs 10%, p <0.05). VFA-detected AAC was significantly better than traditional risk factors for determining the presence of CVD. In multivariable analyses both the presence and severity of AAC was significantly and independently associated with prevalent CVD (OR 2.70; 95% CI 1.8 to 3.2). Both the FRS (AUC 0.58) and AAC (AUC 0.85) were significant predictors of CVD events (Fig. 1). The addition of VFA-detected AAC to the FRS significantly enhanced the performance of the FRS for determining CVD (AUCs increased from 0.58 to 0.79, p<0.001).
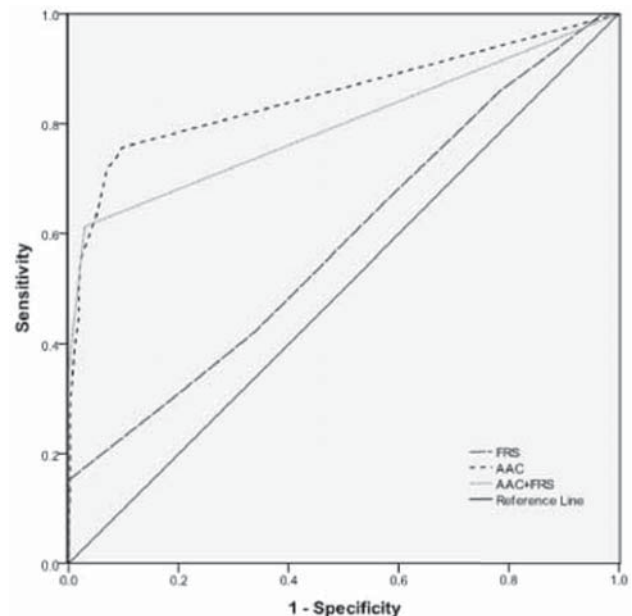
Fig. 1. Additive Effect of AAC on FRS for Predicting CVD in RA Patients*

Conclusion: VFA-detected AAC is an important marker of CVD risk in RA patients, and out-performs traditional risk prediction tools. Further studies are needed to examine the utility of DXA-detected AAC in CVD assessment in RA patients.

Disclosure: **A. Mohammad**, None; **D. Lohan**, None; **D. Bergin**, None; **S. Mooney**, None; **J. Newell**, None; **M. O'Donnell**, None; **R. J. Coughlan**, None; **J. J. Carey**, None.

1687

The Risk of Atrial Fibrillation in Patients with Rheumatoid Arthritis Compared to the General Population: A Large Cohort Study. Seoyoung C. Kim[1], Jun Liu[2] and Daniel H. Solomon[3]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [3]Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Background/Purpose: It is well-known that rheumatoid arthritis (RA) is associated with cardiovascular disease such as myocardial infarction. However, little evidence exists on the risk of atrial fibrillation (AF) in patients with RA. The objective of this study was to estimate the incidence rates (IR) and rate ratios (RR) of AF among patients with RA compared to those without RA.

Methods: We conducted a large population-based cohort study using the US commercial insurance claims data. The RA cohort included adults with at least two diagnoses of RA and at least one prescription for a disease-modifying anti-rheumatic drug (DMARD). Subjects who never had a diagnosis of RA matched on age, sex, and index date with a 5:1 ratio were selected as a comparison cohort. Follow-up began with the first prescription for a DMARD for RA patients and the 2nd physician visit date for non-RA patients after a 12-month baseline period. Patients with history of any cardiac arrhythmia, cardiovascular surgery and anticoagulant users during the baseline period were excluded. Primary outcome was an inpatient diagnosis of AF and secondary outcome was an outpatient or inpatient diagnosis combined with a dispensing of anticoagulant within 10 days after the first diagnosis of AF. We calculated IRs and RRs of AF with 95% confidence intervals (CI). Multivariable Cox proportional hazards models compared the risk of AF between RA and non-RA patients.

Results: The study population included 20,891 RA and 104,455 non-RA patients. Mean (SD) age was 52 (12) years and 74% were women. During a mean follow-up of 2 years, 0.8% of RA patients and 0.6% non-RA patients developed AF as inpatient. **Table** shows the IRs for primary outcome and secondary outcome. The RR was 1.4 (95% CI, 1.2–1.7) for primary and 1.3 (95% CI, 1.0–1.6) for secondary outcome in RA patients, compared to age- and sex- matched subjects without RA. After adjusting for comorbidities such as cardiovascular disease and thyroid disease, various medications and health care utilization characteristics, the risk of AF was not increased in RA (hazard ratio 1.0, 95% CI: 0.8–1.3) compared to non-RA patients.

Table. Incidence rates per 1,000 person-years (95% confidence interval) and rate ratios (95% confidence interval) of atrial fibrillation (AF) in patients with and without rheumatoid arthritis (RA).

	RA	Non-RA	Age- and sex-matched RR	Fully adjusted RR
Inpatient AF	4.1 (3.5–4.8)	2.9 (2.7–3.2)	1.4 (1.2–1.7)	1.0 (0.8–1.3)
Inpatient and outpatient AF with an anticoagulant dispensing	2.6 (2.2–3.2)	2.1 (1.9–2.3)	1.3 (1.0–1.6)	1.0 (0.7–1.3)

Conclusion: Our results showed that the incidence of AF was similar in both RA and non-RA patients. The risk of AF was not increased in patients with RA compared to non-RA patients after adjusting for various comorbid conditions and medications.

Disclosure: S. C. Kim, Pfizer Inc, 2, Takeda Pharmaceuticals, 2; **J. Liu**, None; **D. H. Solomon**, Amgen & Lilly, 2, Corrona, 5, Pfizer Inc, 2.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Human Etiology and Pathogenesis I:
Early Pathogenesis of Rheumatoid Arthritis
Monday, November 12, 2012, 4:30 PM–6:00 PM

1688

Evolution of Preclinical Autoimmunity in Individuals At Risk for Development of Rheumatoid Arthritis. Hani S. El-Gabalawy[1], David B. Robinson[1], Irene Smolik[1], Donna M. Hart[1], Elizabeth D. Ferucci[2], Marianna M. Newkirk[3], Marvin J. Fritzler[4], Catriona Cramb[5], Jeremy Sokolove[5] and William H. Robinson[5]. [1]University of Manitoba, Winnipeg, MB, [2]Alaska Native Tribal Health Consortium, Anchorage, AK, [3]McGill University Health Centr, Montreal, QC, [4]University of Calgary, Calgary, AB, [5]Stanford University, Palo Alto, CA

Background/Purpose: Rheumatoid arthritis (RA) is prevalent, severe, and predominantly seropositive in many North American Native (NAN) populations. We have shown a strong tendency towards familial clustering of RA, and high prevalence of RA autoantibodies and other risk factors in the first-degree relatives (FDR) of NAN RA patients. We have prospectively followed a large cohort of NAN FDR to better understand the preclinical events that lead to RA onset.

Methods: In total we recruited 310 FDR of NAN RA patients who were followed annually with questionnaires and joint examination. Plasma samples were gathered at each visit for biomarker analysis. Individuals who developed new joint symptoms between the annual visits were assessed, and the visit at which at least one swollen joint was detected was deemed to be the onset of inflammatory arthritis (IA).

We used a custom multiplex bead-based autoantigen array on the BioPlex platform to analyze the profile of autoantibodies against citrullinated antigens exhibited by FDR at various time points prior to, and during, the period of disease onset. The autoantigen targets were chosen based on proteomic analysis of synovial tissue and on previous analyses of a large number of RA patients and healthy controls. Levels of total circulating IgG and IgM immune complexes (IC) were measured using a C1q capture assay.

Results: At the baseline visit, 22% FDR had anti-citrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF). This longitudinally followed cohort had a mean age at study enrollment of 35 ± 13 yrs. and 65% were female. Three FDR had definite RA at study entry and were followed as probands. Six FDR met the criteria for new onset IA after a median follow-up of 62 mo. (range 12–73). Of these 6 individuals, 2 were ACPA+ at baseline, one of whom was also RF+. In the period leading up to the development of IA, epitope spreading was evident in the ACPA response, with new targeting of citrullinulated epitopes from fibrinogen, vimentin, clustrin, biglycan. Notably, development of detectable IgM RF in most cases occurred subsequent to ACPA epitope spreading, and was within months of development of IA. An increase in IC levels was also detected in these FDR. A further 4 FDR demonstrated ACPA epitope spreading and had persistent arthralgia but no detectable synovitis at the time of reporting. To date, none of the 16% FDR who were initially RF+ but ACPA- have developed ACPA or IA. The 3 FDR who had RA at study entry were strongly positive for multiple ACPA autoantigens and did not demonstrate epitope spreading during the follow-up period.

Conclusion: The observations made in this prospectively followed cohort of high-risk NAN FDR who ultimately developed ACPA positive IA are consistent with the hypothesis that the autoimmune responses preceding the development of synovitis exhibit three stages: 1) initial breaking of immunological tolerance to citrullinated antigens; 2) epitope spreading of the ACPA response; and 3) development of RF. The latter event, which is likely associated with the formation of pathogenic immune complexes, may be the most proximal event preceding the development of clinically detectable synovitis. This hypothesis provides the framework for actionable stages of preclinical RA autoimmunity.

Disclosure: H. S. El-Gabalawy, None; **D. B. Robinson**, None; **I. Smolik**, None; **D. M. Hart**, None; **E. D. Ferucci**, None; **M. M. Newkirk**, None; **M. J. Fritzler**, Inova Diagnostics, Inc., 5; **C. Cramb**, None; **J. Sokolove**, None; **W. H. Robinson**, None.

1689

Anti-Peptidylarginine Deiminase 3/4 Cross-Reactive Antibodies: A Novel Biomarker with Clinical and Mechanistic Implications in Rheumatoid Arthritis. Erika Darrah[1], Jon T. Giles[2], Herbert Bull[3], Felipe Andrade[1] and Antony Rosen[1]. [1]The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Columbia University Medical Center, New York, NY, [3]Consultant, Westfield, NJ

Background/Purpose: Peptidylarginine deiminases (PADs) have emerged as key participants in the pathogenesis of rheumatoid arthritis (RA) due to their expression in inflamed RA synovium and ability to citrullinate autoantigens. In addition, PAD4 autoantibodies are present in 35% of RA patients. The unexpected expression of PAD3 in neutrophils prompted us to investigate PAD3 as a potential autoantigen in RA.

Methods: Anti-PAD3 antibodies were detected by immunoprecipitation of [^{35}S]Methionine-labeled PAD3. Sera were obtained from 36 healthy controls, 44 RA patients from a convenience sample, and 194 patients from a longitudinal cohort study of subclinical cardiovascular disease in RA (ESCAPE RA). In ESCAPE RA, disease activity and severity were assessed at baseline and two additional time points, with the final visit occurring an average of 39±4 months post-baseline. Radiographs of the hands and feet were obtained at the first and third visits and scored according to the

Sharp-van der Heijde (SvdH) method. Recombinant human PAD3 and PAD4 were used for anti-PAD competition assays. The effect of autoantibodies on PAD4 enzymatic activity was accessed by measuring citrullination of benzoyl-arginine ethyl ester (BAEE) and histone H3 following pre-incubation with patient or control IgG.

Results: Anti-PAD3 autoantibodies were present in 18% of RA sera in the convenience sample, 12% of ESCAPE RA sera, and 0% of healthy controls. Anti-PAD3 antibodies were only detected in anti-PAD4 positive sera and were found through competition experiments to be PAD3/PAD4 cross-reactive autoantibodies. Analysis of clinical features revealed that patients with PAD3/PAD4 antibodies had a higher baseline SvdH score compared to anti-PAD4 only patients (2.5 fold; p=0.039) and anti-PAD negative patients (4.5 fold; p<0.001), even after adjusting for cohort-specific indicators of radiographic damage. Furthermore, patients with anti-PAD3/PAD4 antibodies had a 50% higher rate of radiographic progression (i.e. any longitudinal increase in SvdH) compared to PAD antibody negative individuals (p=0.004), despite equivalent therapeutic intervention. Strikingly, PAD3/PAD4 autoantibodies increased the catalytic efficiency of PAD4 (160-fold at 0.2mM Ca^{2+}) by dramatically decreasing the enzyme's requirement for calcium from a $K_{0.5}$ of 3.0 mM to a $K_{0.5}$ of 0.5mM, rendering the enzyme responsive to calcium concentrations now within the physiological range (0.2–1mM). This effect was observed with the macromolecular substrate histone H3 but not with the small molecule BAEE, indicating that anti-PAD3/PAD4 antibodies do not affect the fundamental catalytic properties of PAD4. These autoantibodies influence the binding and catalysis of histone H3, and achieve activities of PAD4 which normally require supraphysiologic calcium concentrations. It remains to be determined how broadly this property extends to other macromolecular substrates.

Conclusion: These studies describe a novel biomarker associated with erosive joint damage in RA. PAD3/PAD4 cross-reactive antibodies may contribute to disease pathogenesis by activating PAD4 enzymatic function and identify a patient subgroup in whom PAD inhibition may be particularly beneficial therapeutically.

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1690

Citrullination within the Atherosclerotic Plaque: A New Potential Target for Anti-Citrullinated Protein Antibodies. Jeremy Sokolove[1], Orr Share[1], Matthew Brennan[1], Lauren J. Lahey[1], Amy H. Kao[2], Eswar Krishnan[3], Mary Chester Wasko[4] and William H. Robinson[5]. [1]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [2]Allegheny Singer Research Institute, Pittsburgh, PA, [3]Stanford University, Stanford, CA, [4]Temple University School of Medicine, Pittsburgh, PA, [5]Stanford University, Palo Alto, CA

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular disease due to accelerated atherosclerosis. This risk has mainly been limited to seropositive population as measured by the presence of rheumatoid factor (RF). We hypothesized that citrullination of proteins within the atherosclerotic plaque, including citrullinated fibrinogen (cFb), could be targeted by circulating anti-citrullinated protein antibodies (ACPA) thus forming stimulatory immune complexes which further propagate the progression of atherosclerosis.

Methods: We performed proteomic and immunohistochemical studies of atherosclerotic lesions to identify citrullinated proteins. Lysates were prepared from atherosclerotic segments of human aortic arch obtained at autopsy, subjected to 1 and 2-D PAGE, and probed by western blot for the presence of citrulline modified proteins and fibrinogen. Plaque lystates were immunoprecipitated with anti-fibrinogen antibody and subjected to immunoblot with anti-modified citrulline antibodies. Paraffin sections of several human coronary artery plaques were examined by immunohistochemistry for the presence of citrullinated proteins, PAD4 enzyme, and fibrinogen. Levels of anti-CCP2, anti-citrullinated vimentin (cVim), and anti-cFb were measured in a cohort of 135 women with RF+ RA (93% anti-CCP2+) of at least 2 years duration who were well characterized for the presence of atherosclerosis by electron beam CT scan for levels of coronary artery calcification, and multiple linear regression performed to assess the association of these antibodies with calcified plaque burden.

Results: 1 and 2-D western analysis demonstrated several citrulline modified proteins within plaque lysate and the presence of cFb was confirmed by re-probing of the western blot membrane for fibrinogen. Immunoprecipitation of plaque lysate with anti-fibrinogen showed strong citrullination demonstrated by anti-citrulline antibody staining and mass spectroscopy.

Additionally, immunoprecipitation of plaque lysate with RA patient-derived IgG again identified citrullinated fibrinogen by mass spectroscopy. Immunohistochemistry demonstrated co-localization of (i) citrullinated proteins, (ii) PAD4, and (iii) fibrinogen within the coronary artery atherosclerotic plaque. Finally, levels of anti-cFb, anti-cVim, and anti-CCP2 were associated with the increased atherosclerosis as measured by coronary calcium score. In age adjusted models, ACPA titers accounted for approximately 35% of variance in total calcium score and for each standard deviation increase in level of each ACPA, there was an increase in coronary artery calcium score of 400–500 units (anti-cFb P=0.02, anti-cVim P<0.01, anti-CCP2 P=0.01).

Conclusion: Citrulline modified proteins including citrullinated fibrinogen are prevalent within the atherosclerotic plaque and levels of ACPA are associated with degree of atherosclerotic burden. This observation suggests that humeral targeting of citrullinated epitopes, specifically cFb, within the atherosclerotic plaque could provide a mechanism for accelerated atherosclerosis observed in patients with ACPA+ RA.

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Early Signs of Subclinical Inflammation and Local Antibody Production in Early Rheumatoid Lungs. Gudrun Reynisdottir[1], Reza Karimi[2], Jimmy Ytterberg[3], Vijay Joshua[1], Helga Olsen[2], Aase Haj Hensvold[1], Anders Harju[3], Johan Grunewald[2], Sven Nyren[4], Anders Eklund[2], Lars Klareskog[5], Roman Zubarev[6], Magnus Skold[2] and Anca Irinel Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Division of Respiratory Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [5]Karolinska Institute, Stockholm, Sweden, [6]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: The aims of the current study was to investigate if inflammatory lung changes are present in RA patients early in the disease process and to address the contribution of these changes to disease initiation.

Methods: 105 RA patients with symptom duration less than 1 year at the time of diagnosis and naive to DMARD treatment and 43 non-RA individuals, matched for age, smoking and gender were subject to high-resolution computer tomography (HRCT) of the lungs. In a subgroup of patients (n=21) bronchoscopy was performed and BAL samples as well as mucosal large bronchial biopsies were retrieved. Histological analysis for identification of inducible bronchia associated lymphoid tissues (iBALT), PAD enzymes, CD3, and HLA-DR expression were performed. Presence of ACPA was tested by ELISA in the serum and BAL. Mass spectrometry was used for identification of citrullinated epitopes in 6 of the lung biopsies and additional 8 synovial RA biopsies. Contingency tables and chi-square test as well as a generalized linear model were used for analysis of the clinical data. Man-Whitney test was used to analyze differences in immunohistochemistry double blind semi-quantitative scores between independent groups.

Results: A large majority of ACPA+ RA patients (59%, 41/70) presented with HRCT lung abnormalities, as compared to only 34% (12/35) of ACPA- patients and 28% (12/43) of the controls (p<0.05). ACPA positive smokers had increased levels of expression of PAD enzymes in BAL. iBALT formation and higher expression of HLA-DR was observed in bronchial biopsies of ACPA positive RA. A majority of serum ACPA positive RA patients subjected to lung bronchoscopy had detectable levels of ACPA in the BAL fluids both IgA and IgG. IgG from BAL fluids of ACPA-positive patients showed a higher ACPA reactivity as compared to serum IgG from the same patients. Mass spectrometry identified 5 proteins in the synovium (in total 8 sites) and 4 in the lungs (in total 6 sites) containing citrullinated residues. Two vimentin derived citrullinated peptides were present in a majority of both synovial and lung biopsies with slightly higher citrullinated/unmodified peptides ratios in the smokers as compared to non-smokers.

Conclusion: Lung HRCT abnormalities and subclinical inflammation are present already at the earliest visit to a rheumatology specialist early after disease onset in ACPA+ RA patients. These findings suggest that the lungs might be the primary local initiation sites of the anti-citrulline response in RA.

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Lung Microbiome Differs in Subjects with Rheumatoid Arthritis-Related Autoimmunity without Inflammatory Arthritis Compared to Healthy Seronegative Controls. M. Kristen Demoruelle[1], Jill M. Norris[2], V. Michael Holers[1], Kevin D. Deane[1] and J. Kirk Harris[3]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Colorado School of Public Health, Aurora, CO, [3]Aurora, CO

Background/Purpose: Emerging data suggest that microorganisms and mucosal inflammation may play a role in the etiology of rheumatoid arthritis (RA). Furthermore, our published findings of inflammatory airways disease in a high proportion of RA-related autoantibody positive subjects without inflammatory arthritis (IA), some of whom later developed classifiable RA, suggest that the lung may play a role in early RA pathogenesis. Therefore, investigations of the lung microbiome in subjects at risk for future RA may provide insight into RA pathogenesis.

Methods: 13 CCP positive cases without IA and 9 healthy seronegative controls were identified through community screening. Induced sputa was collected from all subjects. DNA extractions for microbiome analysis were performed using Qiagen EZ1 Advanced platform. Established protocols with barcoded PCR primers were used to construct multiplexed amplicon pools and assign sequences to the appropriate subject sample. Microbial prevalence and median relative abundance in sputa were compared using Explicet.

Results: Cases were older and more frequently male than controls (Table), and more cases had been smokers, although they had quit smoking a median of 9 years prior to sputa collection. Bacteria were identified by rRNA pyrosequencing ($>1,000$ sequences per sample). Good's coverage was $>98.9\%$ for all samples. 80 genera were identified across all samples with an average of 30 per sample. Relative abundance of *Haemophilus* and *Neisseria* was elevated in cases compared to controls (p=0.04) (Table), and there was a trend toward increased relative abundance of *Streptococcus* in cases. There was no significant difference in *Porphyromonas*, *Prevotella* and *Mycoplasma* between groups.

Lung Microbiome Differences in Subjects with and without Serum Positivity for Rheumatoid Arthritis-Related Autoantibodies

	Autoantibody positive cases N=13	Autoantibody negative controls N=9	p-value
Age, median (range)	57 (30-85)	33 (26-56)	<0.01
Female, N (%)	5 (39%)	8 (89%)	0.02
Current smoker, N (%)	0 (0%)	1 (11%)	0.23
Ever smoker, N (%)[1]	7 (54%)[2]	1 (11%)	0.05
Anti-CCP3.1 positive, N (%)[1] Median (range)	13 (100%) 49 (32 to >400)	0 (0%) 3 (1-8)	<0.01
Genus classification			
Haemophilus			
% Prevalence[3]	85	100	0.04[5]
Relative abundance (%)[4]	2.0	0.6	
Neisseria			
% Prevalence[3]	100	77	0.04[5]
Relative abundance (%)[4]	4.9	1.0	
Streptococcus			
% Prevalence[3]	100	100	0.20[5]
Relative abundance (%)[4]	30.4	18.0	
Prevotella			
% Prevalence[3]	100	100	0.20[5]
Relative abundance (%)[4]	12.4	25	
Porphyromonas			
% Prevalence[3]	85	100	0.87[5]
Relative abundance (%)[4]	1.1	1.5	
Mycoplasma			
% Prevalence[3]	100	67	0.90[5]
Relative abundance (%)[4]	1.4	0.1	

1. CCP3.1 (IgA/IgG) ELISA, Inova Diagnostics, Inc. Positive level ≥20 units
2. Median duration of smoking cessation prior to sputa testing = 9 years (range 3-20)
3. % Prevalence = number of subjects with organism present
4. Median relative abundance of each organism compared to all organisms in the sample
5. P-value comparing prevalence and relative abundance in Ab(+) cases and Ab(-) controls

Conclusion: These results show differences in sputa microbiota between RA-related autoantibody positive cases without IA and controls. This is particularly intriguing because our prior work has shown that 9 of these autoantibody positive cases had inflammatory airways disease on lung imaging, raising the possibility of a mechanistic link between the microbiome, mucosal inflammation and generation of RA-related autoimmunity in the lung. A caveat in this small pilot study is the unknown influence on the lung microbiome of differences in age and sex between groups. Also, differences in smoking history between groups may affect results as smoking is known to alter the lung microbiome. However, smoking is also associated with CCP positivity in established RA, albeit through unknown mechanisms. As such, it is possible that a mechanism that drives CCP generation is smoking (or other inhaled factor)-related changes in the lung microbiota. Additional study, including speciation of organisms and prospective

follow-up of larger numbers of subjects and controls, is needed to determine the biologic relevance of the lung microbiome to the pathogenesis of early RA.

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Oncogenic Activation of MAPK in Rheumatoid Arthritis Synovial Fibroblasts. Niloofar L. Farmani[1], Keith K. Colburn[2], Grace Chan[3], Erica Li[3], Emil Heinze[1], Antonia Rubell[3], Robert Nishimura[4] and Richard H. Weisbart[3]. [1]Olive View-UCLA Medical Center, Sylmar, CA, [2]Loma Linda Univ Medical Center, Loma Linda, CA, [3]VAGLAHS, Sepulveda, CA, [4]The David Geffen School of Medicine at UCLA, Los Angeles, CA

Background/Purpose: Transformed synovial fibroblasts (SF) mediate joint-specific damage in rheumatoid arthritis (RA) by expressing integrins and metalloproteinase that promote adhesion to and invasion of cartilage. The mechanism of SF transformation is unknown, but is critical for the rational design of specific therapies to prevent joint erosion in RA. We recently identified aberrant BRAF splice variants in synovial fibroblasts from some RA patients and demonstrated their role in RA fibroblast proliferation, results that suggest a primary role for oncogenic transformation of RA SF. The current studies were designed to further evaluate the role of oncogenesis in RA SF transformation.

Methods: Aberrant BRAF splice variants and mutations in KRAS were identified in RA SF by RT-PCR. The function of aberrant BRAF splice variants was evaluated in NIH-3T3 fibroblasts transfected with an expression vector containing cDNA of BRAF splice variants. Mitogen-activated protein kinase (MAPK) activation in transfected NIH-3T3 cells was determined by phosphorylation of MEK and ERK. The role of BRAF and CRAF in SF transformation was determined by RNAi, and Membrane-Type 1 Matrix Metalloproteinase (MT1-MMP) was identified in cells with MT1-MMP-specific antibodies. Collagen invasion by transfected NIH-3T3 cells was evaluated in an *in vitro* collagen invasion assay.

Results: SF from 6/9 RA patients had kinase "Dead" aberrant BRAF splice variants. NIH-3T3 cells transfected with aberrant BRAF splice variants constitutively activate MAPK, produce MT1-MMP, and invade collagen. Since "Dead" BRAF forms dimers with CRAF to activate MAPK we evaluated the role of CRAF in MAPK activation by RNAi. MAPK activation was inhibited by siRNA specific for BRAF and CRAF. Since MAPK activation by "Dead" BRAF also requires activated KRAS we looked for KRAS mutations in RA SF and identified mutations in 7/9 RA patients.

Conclusion: Our results suggest that joint-specific oncogenesis is responsible for synovial fibroblast transformation in some patients with RA.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety II
Monday, November 12, 2012, 4:30 PM–6:00 PM

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Infection Risk in Patients with Low Immunoglobulins Following Rituximab Treatment in Rheumatoid Arthritis. Ronald F. van Vollenhoven[1], Gregg J. Silverman[2], Clifton O. Bingham III[3], Patrick Durez[4], Patrica B. Lehane[5], Nicola Tyson[5] and Elena Fisheleva[5]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]NYU School of Medicine, New York, NY, [3]Johns Hopkins University, Baltimore, MD, [4]University Hospital St Luc, UCL, Brussels, Belgium, [5]Roche Products Limited, Welwyn Garden City, United Kingdom

Background/Purpose: This study analyzed infection rates in patients (pts) with low immunoglobulin (Ig) serum concentrations following rituximab (RTX) treatment in RA clinical trials.

Methods: Pooled analysis of clinical trial data from the All-Exposure population (all pts exposed to at least one/part of a RTX infusion) who developed low IgM or IgG (defined as below lower limit of normal [LLN] for ≥ 4 mth [or 2 consecutive study visits]) after ≥ 1 RTX course. Low IgG/IgM at baseline screening (IgG <5.65 and IgM <0.55 mg/mL) were exclusion

criteria for trial entry. Igs were generally measured every 8–16 wks. Pts with low Ig were permitted to receive RTX retreatment. Infection rates were assessed before and during/after low IgM/IgG and compared with pts who never developed low Ig and the All-Exposure population. Pts received IV methylprednisolone prior to RTX infusions and concomitant MTX. In addition, stable background doses of oral corticosteroids (≤10 mg/day prednisone or equivalent) and NSAIDs were permitted throughout.

Results: Of 3194 pts who received ≤17 RTX courses over 9.5 yrs, 22.4% (n=717) developed low IgM and 3.5% (n=112) low IgG for ≥4 mth. All had measurable Ig levels. No increases in overall infection rates were observed in pts during/after low IgM/IgG vs before documentation of low Ig (Table). For IgG, serious infection (SIE) rates were similar before and during/after low IgG, but both were significantly higher than in pts who never developed low IgG. At baseline these pts were on average older, had longer disease duration, lower mean CD19+ count, lower mean IgG levels (8.4 vs 13.2 mg/mL), higher mean anti-CCP levels, and had received more non-biologic DMARDs vs those who did not develop low IgG. Baseline oral steroid use was similar across subgroups and all pts received 100 mg IV corticosteroid prior to RTX infusion. For IgM, SIE rates were not significantly higher during/after low IgM vs before low IgM, and were similar to rates in pts who never developed low IgM. In pts with low IgG or IgM, the SIE profile was consistent with RTX clinical experience as most infections affected the lower respiratory tract. Analysis of SIE onset in relation to timing of low Ig was limited due to discrete protocol-defined time points for Ig assessments. Other limitations included low pt numbers in some subgroups and lack of placebo comparator.

Infection rate in pts with low Ig

	Pts with IgG <LLN*			Pts with IgM <LLN*		
	Before <LLN (n=112)	During/after <LLN (n=112)	Pts who never had IgG <LLN (n=3082)	Before <LLN (n=717)	During/after <LLN (n=717)	Pts who never had IgM <LLN (n=2477)
Total PY	223	307	11432	1171	2084	8707
Infections, n	325	262	9179	1264	1699	6803
Rate/100PY (95% CI)	146 (131–162)	85 (76–96)	80 (79–82)	108 (102–114)	82 (78–86)	78 (76–80)
SIE, n	18	28	425	34	98	339
Rate/100PY (95% CI)	8.0 (5.08–12.80)	9.13 (6.30–13.22)	3.72 (3.38–4.09)	2.9 (2.07–4.06)	4.70 (3.86–5.73)	3.89 (3.50–4.33)

*below LLN for ≥4 mth

Conclusion: Following RTX treatment, low Ig concentrations (particularly IgM, less often IgG) were observed. Pts with low IgM had no increased risk of infection or SIE. For the small subgroup of pts with low IgG (112/3194 [3.5%]), a higher SIE rate was seen both before and during/after the development of low IgG, suggesting that these pts had a higher *a priori* risk of developing SIEs, possibly associated with demographic and/or clinical characteristics rather than with low IgG itself. Thus, for both Ig classes, SIE rates were similar before and during/after development of low Ig.

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Prolonged Exposure to Subcutaneous and Intravenous Abatacept in Patients with Rheumatoid Arthritis Does Not Affect Rates of Infection, Malignancy and Autoimmune Events: Results From Pooled Clinical Trial Data. M. C. Genovese[1], M C. Hochberg[2], R. B. Cohen[3], M. E. Weinblatt[4], J. Kaine[5], E. Keystone[6], P. Nash[7], I. Delaet[8] and R. Alten[9]. [1]Stanford University, Palo Alto, CA, [2]Department of Medicine, University of Maryland, Baltimore, MD, [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [4]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [5]Sarasota Arthritis Research Center, Sarasota, FL, [6]Mount Sinai Hospital, Toronto, ON, [7]University of Queensland, Brisbane, Australia, [8]Bristol-Myers Squibb, Princeton, NJ and Bristol-Myers Squibb, Hopewell, VA, [9]Schlosspark-Klinik, University Medicine, Berlin, Germany

Background/Purpose: Disease-modifying therapies for RA have proven efficacy, but these drugs may have selective toxicities, such as malignancy, that may increase with duration of treatment. Periodic re-evaluation of incidence rates (IRs) allows assessment of any cumulative or new events over time. Using the largest pool of integrated abatacept clinical trial data to date, we investigated the long-term (LT) safety of subcutaneous (SC) and intravenous (IV) abatacept.[1,2]

Methods: Data were pooled from the cumulative (double-blind and open-label short-term [ST] and open-label LT extension) periods of 13 clinical studies, including one Phase II and four Phase III trials with SC abatacept,[1] and two Phase II and six Phase III trials with IV abatacept.[2] IRs for adverse events (AEs), serious AEs (SAEs), infection, malignancy and autoimmune AEs were calculated as events per 100 patient-years (pt-yrs) of exposure (Poisson 95% CI). IRs for the cumulative period were compared with IRs originally estimated from the pooled ST periods of the eight IV abatacept clinical studies.[2]

Results: A total of 6028 patients received IV or SC abatacept during the cumulative period, with abatacept exposure of 16,670.56 pt-yrs; 1167 patients received abatacept for >5 yrs. IRs of AEs, SAEs, infections or serious infections did not increase in the cumulative relative to ST periods (Table). The most frequently reported serious infections in the cumulative period were pneumonia (IR: 0.43 [0.34, 0.54]), upper respiratory tract infection (0.18 [0.12, 0.26]) and cellulitis (0.15 [0.10, 0.23]). There was no increase in IRs between the ST and cumulative periods for hospitalized, opportunistic or tuberculosis infections. The IRs of overall malignancy, combined lymphomas and lung cancers did not increase in the cumulative versus the ST periods; the most common malignancies in the cumulative period were basal cell carcinoma (IR: 0.46 [0.36, 0.58]), squamous cell carcinoma (IR: 0.15 [0.09, 0.22]), breast cancer (IR: 0.12 [0.07, 0.19]) and squamous cell carcinoma of the skin (0.08 [0.04, 0.14]). The IR of autoimmune AEs during the cumulative period was comparable to the ST period, the most common event being psoriasis (IR: 0.51 [0.40, 0.63]).

	ST period (N=3173)	Cumulative (ST + LT) period (N=6028)
Exposure, pt-yrs	2330.82	16,670.56
AE	386.70 (372.31, 401.51)	213.95 (208.33, 219.68)
SAE	18.10 (16.37, 19.97)	13.24 (12.63, 13.88)
Death	0.51 (0.27, 0.90)	0.60 (0.49, 0.73)
Infection	98.00 (93.20, 102.99)	66.33 (64.33, 68.37)
Hospitalized	3.33 (2.63, 4.16)	2.37 (2.14, 2.63)
Serious infection	3.68 (2.94, 4.55)	2.57 (2.32, 2.83)
Malignancy	1.55 (1.09, 2.15)	1.35 (1.18, 1.55)
Autoimmune event	2.07 (1.53, 2.75)	1.83 (1.62, 2.05)

Presented are incidence rates, calculated as events/100 pt-yrs (Poisson 95% CI), unless otherwise stated; includes events occurring up to 56 and 60 days post-last dose for Phase III and II studies, respectively; ST=Short-term; LT=Long-term

Conclusion: Based on the cumulative short-term and long-term exposure of 6028 patients to IV or SC abatacept (16,670.56 pt-yrs), the incidence rates and events reported with long-term abatacept treatment were similar to those reported in the short-term, with no increase in rate for any event with increasing exposure. These findings demonstrate that IV and SC abatacept are both well tolerated over the long-term.

[1]Alten R et al. *Arthritis Rheum* 2011;**63**(10 Suppl):S150.
[2]Hochberg M et al. *Arthritis Rheum* 2010;**62**(10 Suppl):S164.

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Quantitative Evaluation of Dermal Atrophy by High-Resolution Ultrasonography, Comparing Between Patients Under Long-Term Treatment with Prednisolone or Methylprednisolone. Tim Pottel[1], Christoph Schäfer[2] and Gernot Keyβer[2]. [1]06114 Halle (Saale), Germany, [2]06120 Halle (Saale), Germany

Background/Purpose: The katabolic effects of a systemic treatment with glucocorticoids can lead to a progressive atrophy of the skin. Clinical observation suggests a more pronounced effect of methylprednisolone compared with prednisolone. Therefore, a study was undertaken to correlate the cumulative doses of the respective steroids with the skin thickness measured by high-resolution sonography, comparing patients with rheumatic disorders

receiving long-term prednisolone and patients with renal transplants taking methylprednisolone.

Methods: The study included 92 patients, 47 of them after renal transplantation and immunosuppressive therapy with methylprednisolone, 45 with rheumatic diseases and prednisolone treatment, including 29 cases with rheumatoid arthritis. The cumulative steroid doses were recorded by chart review. Patients were included, if they had at least two years of glucocorticoid treatment, had a complete documentation of their steroid intake at least every three months and were free of relevant dermal diseases. The measurement of dermal thickness was performed by high-resolution ultrasound, using an 18 MHz probe, at three standardized locations at volar and dorsal forearm.

Results: There were no differences in the cumulative steroid doses between both groups, after adjusting for equivalent doses. However, patients receiving methylprednisolone revealed a significantly more pronounced dermal atrophy, compared with patients taking prednisolone. (mean dermal thickness 0,77 mm, standard error 0,023 in group with prednisolone treatment; 0,65 mm, standard error 0,018 in methylprednisolone group) (t-test; $p=5*10^{-4}$). By Pearsonxs correlation we identified a statistical interaction between the mean dermal thickness and type of glucocorticoid used (Pearsonxs r $= -0,41$; $p=2*10^{-5}$). Multiple regression analysis revealed, that methylprednisolone had a more pronounced negative influence on skin atrophy than prednisolone (regression coefficient $\beta= -0,15$; p$= 2,3*10^{-7}$). The association between cumulative dose of the last two years and degree of atrophy was significantly represented by $\beta= -0,011$; p$=0,035$, however only significant for cumulative steroids of last or last half year in methylprednisolone.

Dermal Thickness of Standardised Location at Dorsal Forearm
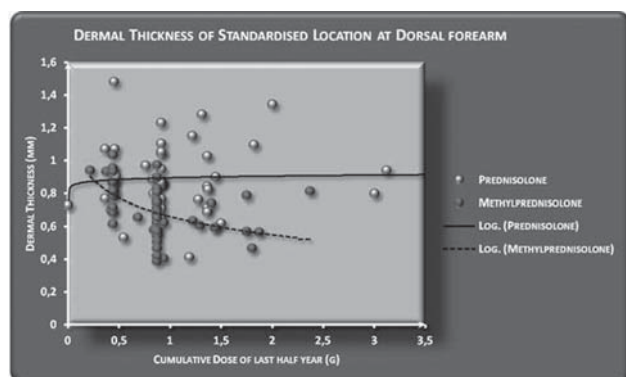
Conclusion: In our study, the long-term use of methylprednisolone was associated with a more pronounced dermal atrophy compared with prednisolone, particularly prominent in the last half year before data collection by measurement. The katabolic effects of methylprednisolone may be more pronounced that those of prednisolone, even after the adjustment for equivalent doses.

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Meta-Analysis of Malignancies, Serious Infections, and Serious Adverse Events with Tofacitinib or Biologic Treatment in Rheumatoid Arthritis Clinical Trials. Sima Ahadieh[1], Tina Checchio[1], Thomas Tensfeldt[1], Jonathan French[2], Sriram Krishnaswami[1], Richard Riese[1], Sujatha Menon[1], Mary G. Boy[1] and Jamie L. Geier[3]. [1]Pfizer Inc., Groton, CT, [2]Metrum Research Institute, Tariffville, CT, [3]Pfizer Inc., New York, NY

Background/Purpose: Patients with rheumatoid arthritis (RA) experience adverse events (AEs) attributed to both the disease and its treatment. Tofacitinib is a novel oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. To contextualize events within the tofacitinib clinical trial program, a meta-analysis was completed in patients with RA receiving biologic drug therapy within a randomized clinical trial (RCT) setting to identify and quantify safety endpoints of: malignancies excluding non-melanoma skin cancer (NMSC), serious infections (SIs), and serious AEs (SAEs).

Methods: Medline, Embase, PubMed, and summary basis of approvals from regulatory submissions were searched to identify RCTs for abatacept, rituximab, etanercept, infliximab, certolizumab, golimumab, adalimumab, and tocilizumab in RA. The search identified >300 papers from which data from 80 RCTs, representing more than 31,000 subjects, were extracted for analysis for the three endpoints. Non-RCTs, long-term extensions, and observational studies were excluded from the literature results. Tofacitinib results from five RCTs (Phase 3 [P3]) are presented. The dependent variable for the analysis was the incidence rate (IR) of an event/100 patient-years (pt-yrs). Data were analyzed using a random effects meta-analysis model. The IR data were log transformed to avoid negative confidence intervals (CIs). An imputation methodology was applied to account for IRs of zero and a sensitivity analysis was performed to assess the effects of adjustment on the individual and overall mean, as well as the impact on the estimated variance surrounding each study arm.

Results: Estimated IRs for endpoints of malignancies, SIs, and SAEs revealed similar rates among biologic therapies used to treat RA. Across all biologic therapies, point estimates ranged from 0.8 to 1.4 events/100 pt-yrs for malignancies; 2.5 to 6.5 for SIs; and 10.7 to 22.0 for SAEs. Event rates for tofacitinib were 0.62 (95% CI 0.36, 1.07) events/100 pt-yrs for malignancies (Figure 1); 2.91 (2.27, 3.74) events/100 pt-yrs for SIs; and 10.3 (9.00, 11.78) events/100 pt-yrs for SAEs, all in P3. The 95% CIs for tofacitinib were contained within the range of published estimates.

Drug	Number of trials	Malignancy Events / 100 pt-yrs (95% CI)	No. of patients	Patient years
Abatacept	3		1989	1187
Rituximab	2		1020	738
Tocilizumab	6		2801	1289
Infliximab	8		1859	2025
Etanercept	5		1409	1314
Certolizumab	2		603	271
Golimumab	5		2227	1284
Adalimumab	9		1803	1489
TNF inhibitor*	28		8211	6502
Tofacitinib Phase 3	5		3030	2098
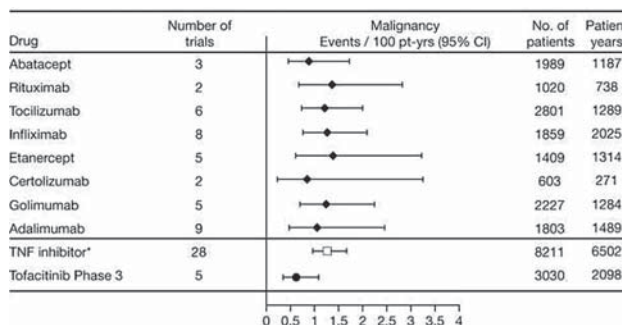
* Estimate from 28 TNF inhibitor studies

Conclusion: This RCT meta-analysis provides a quantitative assessment of the incidence of important safety events reported with therapies for the treatment of RA. Overall, tofacitinib event rates for malignancies, SIs, and SAEs were comparable to published rates for approved biologic therapies. Future analyses are warranted to estimate relative effects (treatment comparisons), model studies with no events (IR=0), and account for study population differences.

1698

Predictors of Discontinuation of Biologics in 2,281 US Patients with Rheumatoid Arthritis. Sofia Ramiro[1], Frederick Wolfe[2], David J. Harrison[3], George Joseph[3], David H. Collier[3], Désirée van der Heijde[4], Robert Landewé[5] and Kaleb Michaud[6]. [1]Academic Medical Center, University of Amsterdam, The Netherlands and Hospital Garcia de Orta, Almada, Portugal, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Amgen Inc., Thousand Oaks, CA, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Academic Medical Center, University of Amsterdam and Atrium Medical Center, Heerlen, Netherlands, [6]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Identifying predictors of discontinuation of biologic treatment for Rheumatoid Arthritis (RA) has clinical and research importance given the chronicity of RA and high costs and potential side effects of these agents. Our aim was to identify predictors of biologic discontinuation in patients with RA.

Methods: We studied patients with RA starting their first biologic while participating in an ongoing US longitudinal cohort study (1998 –2011). Patients provided all medication use, demographics, and clinical status via semiannual questionnaires. Discontinuation was analyzed through Cox multivariable regression models with baseline predictors adjusted by the biologic drug class patients were on (anti-TNF vs other) and a variable reflecting the onset after Jan 1, 2005, when more biologic treatment options became available. Three pre-specified prediction models were developed, a "research" model, with all significant variables, a "clinical" model, reflecting variables

more commonly used in clinical practice and one restricted to patients that started a biologic after Jan 1, 2005. Forward selection was performed until the best-fit model was obtained, taking confounding effects into account.

Results: A total of 2,281 RA patients initiated their first biologic; 1,100 (48%) discontinued. Age, smoking status and comorbidity index were positive baseline predictors of discontinuation (Table). Methotrexate use and higher SF-36 PCS and MCS scores were associated with less risk of discontinuation. In the "clinical" model, patient global assessment was positively associated with discontinuation. The discontinuation among patients starting biologics after 2005 was associated with a higher patient global assessment and inversely predicted by BMI.

Table. Hazard ratios (95% CI) of baseline predictors of biologic discontinuation in RA

	Research model	Clinical model	≥2005 model
Age (years)	1.01 (1.00;1.01)	1.01 (1.00;1.01)	**
BMI (kg/m2)	§	§	0.97 (0.94;0.99)
Patient global (0–10)	**	1.05 (1.03;1.08)	1.13 (1.06;1.20)
Comorbidity index (0–9)	1.08 (1.04;1.13)	1.11 (1.06;1.15)	**
Smoking	1.21 (1.01;1.45)	1.23 (1.03;1.47)	§
MTX	0.83 (0.73;0.94)	0.84 (0.74;0.95)	§
SF-36 MCS (0–100)	0.99 (0.98;0.99)	¥	**
SF-36 PCS (0–100)	0.99 (0.98;0.99)	¥	§

Adjusted for biologic drug class (anti-TNF vs other) and onset≥2005
§ Not included in the multivariable model (not significant in the univariable model) **Not selected during multivariable regression analysis (p≥0.05)
¥ Not included in this short "clinical" model (to present a model with variables more used in clinical practice)

Conclusion: Worse overall health strongly predicted biologic discontinuation in RA. Co-medication with methotrexate independently contributed to a lower biologic discontinuation. A higher number of comorbidities and a smoking status were also predictive of biologic discontinuation. The predictors of discontinuation might guide the clinician when starting a biologic therapy. While these are important factors leading to discontinuation, their impact is lessened when there are more biologic therapies to choose from.

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1699

Neutropenia After Rituximab in Rheumatoid Arthritis and Other Autoimmune Diseases Is a Rare Events: Date From the Autoimmunity and Rituximab Registry. Jean Hugues Salmon[1], Patrice P. Cacoub Sr.[2], Bernard G. Combe[3], Jean Sibilia[4], Beatrice Pallot Prades[5], Olivier Fain[6], Alain G. Cantagrel[7], Maxime Dougados[8], Olivier Meyer[9], Philippe Carli[10], Edouard Pertuiset[11], Isabelle Pane[12], Philippe Ravaud[13], Xavier Mariette[14] and Jacques-Eric Gottenberg[15]. [1]Rheumatology, Reims, France, [2]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [3]Hopital Lapeyronie, Montpellier, France, [4]CHU Hautepierre, Strasbourg, France, [5]Saint Etienne university hospital, Saint Etienne, France, [6]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [7]Place du Docteur Baylac, Toulouse, France, [8]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [9]Hopital Bichat, Paris, France, [10]Toulon, France, [11]Ch Rene Dubos, Pontoise, France, [12]Hotel Dieu University Hospital Paris, France, [13]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [14]Université Paris-Sud, Le Kremlin Bicetre, France, [15]Strasbourg University Hospital, Strasbourg, France

Background/Purpose: Limited data are available regarding the proportion and severity of late onset neutropenia after RTX in large and unselected populations of patients with various autoimmune diseases. The largest series included 209 patients followed up to 1 year (162 patients with rheumatoid arthritis (RA) and 47 patients with other autoimmune diseases) and identified 11 RTX-induced neutropenia (5.2%) (Tesfa D, A&R 2011).
Methods: The AutoImmunity and Rituximab registry (AIR) has included 2653 patients (2000 patients with RA including 1975 patients with at least 1 follow-up visit, and 653 patients with AIDs, including 649 patients with at least 1 follow-up visit). Patients are prospectively followed up every 6 months

for 5 years. For each neutropenia episode registered, the clinician in charge of the patient was asked to fill a specific questionnaire.
Results: A neutropenia was confirmed by clinicians in 85 patients (48 RA and 37 AIDs (17 systemic lupus erythematosus, 12 vasculitis, 1 primary Sjögren's syndrome, 1 myositis, and 6 other AIDs). In 35 patients, neutropenia resulted from other reasons than RTX (chronic autoimmune-disease related neutropenia, other drug-induced neutropenia, blood malignancies). RTX-induced neutropenia according to the clinician was observed in 50 patients (32 RA [1.6% of all patients with RA], 18 AIDs [2.8% of patients with AIDs]: 8 SLE, 7 vasculitis, 1 myositis, 2 other AIDs). 6 patients (12%) (1 RA, 5 AIDs) had neutrophils < 500/mm^3, 9 (18%) (8 RA, 1 AIDs) had neutrophils between 500 and 1000/mm3 and 35 (70%) (23 RA and 12 AIDs)patients had neutrophils between 1000 and 1500/mm3.

RTX-induced neutropenia occurred after a median of 6.7 months in RA and 6.3 months in AIDs after the last infusion of the 1st cycle (25 patients, 50%), 2d cycle (16 patients, 32%), 3d cycle (2 patients, 4%), 4th or subsequent cycle (7 patients, 14%). 5 patients 1 RA, 2 SLE, 1 vasculitis and 1 other AID, 4 with neutrophils < 500/mm3, 1 between 500 and 1000/mm3) (5.9%) developed a non opportunistic serious infection (2 urinary and 1 bronchopulmonary infections, 12 isolated fevers) and required G-CSF injections, with a favorable outcome. 25 patients (50%) were retreated with RTX after resolution of their neutropenia and a new episode of neutropenia occurred in 8 of them.
Conclusion: Late-onset neutropenia can occur after RTX and infrequently results in serious infections. One third of the patients with RTX-induced neutropenia recurred in case of realization of a new cycle of RTX. Thus, monitoring of white blood count should be performed after RTX. However, in this large registry of patients with autoimmune diseases, the frequency of RTX-induced neutropenia is much lower than that previously reported in patients treated with RTX for lymphoma.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Spondyloarthritis II
Monday, November 12, 2012, 4:30 PM–6:00 PM

1700

Prevalence of Spondyloarthritis in Anterior Uveitis Patients: The Sentinel Study. Miguel Cordero Coma[1] and Xavier Juanola[2]. [1]Unidad de Uveítis. Hospital Universitario de León, León, Spain, [2]Hospital Universitari de Bellvitge, Barcelona, Spain

Background/Purpose: Anterior uveitis (AU) is the most common form of uveitis in western countries with an annual incidence rate of about eight new cases for every 100,000 inhabitants. AU may occur in the absence of associated systemic disease. However, it has been reported that about 25% of AU patients have an associated systemic condition; the most commonly associated one being seronegative spondyloarthritis (SpA). Since many of the conditions initially diagnosed as idiopathic anterior uveitis are later found to be a SpA-associated disorder, we hypothesised that a higher than expected rate of associated-SpA might be found by using a systematic clinical evaluation protocol in AU patients.
Methods: Prospective multicentre non-comparative cohort study. Patients with no previous diagnosis of any associated immune-mediated condition and clinically significant AU were included in this study. Clinically significant AU was defined as either recurrent AU (at least two episodes) or non-recurrent HLAB27 + associated AU. All patients included in the study underwent a complete physical and ophthalmologic examination and a thorough check-up of their systems including x-ray and MRI study of the sacroiliac joints, for those in which SpA was clinically suspected.
Results: A total of 199 patients from 29 tertiary referral centres were included in the study. From all included patients suffering from AU, 148 patients (74.3%) were HLAB27+. After an initial systematic clinical evaluation protocol, 122 patients (61.3%) were newly diagnosed with a type of spondyloarthritis, of which 94 patients (47.2%) fullfilled the ASAS criteria for axial spondyloarthritis and 28 patients (14%) fullfilled the ASAS criteria for peripheral spondyloarthritis. A positive HLAB27 haplotype was found in 89 (94%) of patients newly diagnosed with axial spondyloarthritis and in 20 (71.4%) of those patients newly diagnosed with peripheral spondyloarthritis.

Other associated diagnoses included ankylosing spondylitis, diagnosed based on New York criteria, in 78 patients (39.2%), psoriasis in 10 patients (5%), inflammatory bowel disease in 3 patients (1.5%), and reactive arthritis in 1 patient (0.5%).

Conclusion: These preliminary results show that in a large prospective cohort almost 75% of patients with clinically significant idiopathic AU have an associated underlying SpA which more than double that of previously reported prevalence. The diagnosis of idiopathic uveitis seems to depend greatly on the extent of the evaluation for an underlying condition. These results should be considered in the management and therapeutic decision-making for patients with recurrent AU.

1701

Validation of the New ASAS Criteria for Classification of Early Spondyloarthritis in the Esperanza Cohort.

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Background/Purpose: To validate the new axial and peripheral ASAS criteria in patients with early spondyloarthritis (SpA) and the full spectrum of clinical manifestations under clinical practice conditions.

Objectives: 1) To analyze the validity of the ASAS classification criteria for SpA in an early multisite cohort; 2) to describe the characteristics of the new-onset SpA cohort from the ESPERANZA program and 3) to analyze the positive and negative predictive value of the ASAS, Amor, and ESSG criteria in this cohort.

Methods: Cross-sectional study of all patients with new-onset SpA referred to units within the ESPERANZA program. Selection criteria for the program are: Patients under 45 years of age with, at least, one of the follow: a) a two-year history of inflammatory back pain; b) back or joint pain in the presence of psoriasis, anterior uveitis, radiographic sacroiliitis, family history of SpA or positive HLA-B27; or c) asymmetric arthritis. A validation analysis of criteria sets was performed with the rheumatologist opinion as gold standard. We excluded patients who did not meet the referral criteria and those in which the radiograph on HLA-B27 were not available. The predictive ability of individual criteria was analyzed versus the physician's opinion, thus only patients with a diagnosis could be included.

Results: 1179 patients were included for Esperanza program, but only 775 met inclusion criteria. Low-back pain was the primary reason for referral (73.7%). The mean age of the sample was 33.1 ± 7.1 years and 55.4% were men. The mean time from symptoms was less than a year (11.9 ± 6.6 months). A percentage of 69.5% (538) of patients were diagnosed with SpA, and 30.5% (237) were diagnosed with No SpA. The most frequent joint manifestations in patients with SpA were inflammatory back pain (67.5%) and the presence of peripheral arthritis (18%); the prevalence of HLA-B27 in this population was 55.6%, and the most frequent extra-articular manifestation was psoriasis (13.9%). A total of 67.9% patients with chronic back pain met the ASAS axial criteria, peripheral ASAS in 56.3% (without chronic back pain) and full ASAS in 65.1%. Sensitivity and specificity of the full ASAS criteria set was 65% and 93%, a little higher or axial ASAS, 68% sensitivity and 95% specificity; and for peripheral ASAS, 56% and 85%, respectively. Sensitivity and specificity for ESSG criteria, and Amor criteria are presented in Table 1.

Table 1. Results of the validation analysis and predictive ability (N = 775)

Criteria	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive predictive value (CI 95%)	Negative predictive value (CI 95%)
ASAS axial	68 (63,73)	95 (91,98)	97 (94,98)	58 (53,64)
ASAS axial-imaging	43 (38,48)	98 (95,99)	98 (94,99)	45 (40,50)
ASAS axial-HLA B27	50 (45,55)	96 (93,99)	97 (93,99)	48 (43,53)
ASAS peripheral	56 (48,65)	85 (71,94)	92 (83,97)	40 (30,50)
ASAS total	65 (61,69)	93 (89,96)	95 (93,97)	54 (49,59)
ESSG	58 (54,62)	90 (86,94)	93 (90,96)	49 (44,53)
Amor	59 (55,63)	86 (81,90)	90 (87,93)	48 (43,53)

Conclusion: The sensitivity and specificity of the ASAS criteria are higher than the ESSG and Amor criteria, so in early SpA forms the ASAS criteria may replace both criteria. However, the sensitivity for the ASAS criteria in this new-onset SpA is lower than in previous studies, what may limit their ability to detect early forms, particularly in populations in which MRI is not available under standard clinical practice or in population with a low prevalence of HLA-B27.

1702

Tumor Necrosis Factor Blocking Agents Inhibit the Progression of Preclinical Atherosclerosis in Patients with Ankylosing Spondylitis.

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Background/Purpose: Ankylosing spondylitis (AS) is associated with an increased cardiovascular (CV) risk that might be due to the chronic underlying inflammatory process. It is still unknown whether strong anti-inflammatory treatment with tumor-necrosis factor (TNF) inhibitors reduce the increased CV risk in AS. We investigated whether preclinical atherosclerosis and elasticity of the carotid arteries in patients with AS changed after use of TNF-inhibitors.

Methods: 67 out of 82 AS patients who underwent ultrasonography at baseline were measured again after 5 years. Assessments of medication use, AS related factors, CV risk factors and arterial parameters (including intima-media thickness (IMT) and Young's elastic modulus (YEM)) were repeated at follow-up. Spearman's rank correlation were used to investigate the correlation between changes in AS related factors or CV risk factors with changes in arterial wall parameters.

Results: After a mean follow-up of 5 years, 11 AS patients (16%) discontinued their use of TNF inhibitors. IMT did not change significantly ($+0.012$, p-value= 0.561) in those who continued the use of TNF inhibitors as compared to AS patients who discontinued use of TNF inhibitors ($+0.060$, p-value=0.025). Also, vascular elasticity (as measured with YEM) improved significantly in patients who continued TNF inhibitors ($+0.031$, p-value=0.002) but not in patients who discontinued TNF inhibitors. Correlations were found between 1. Unfavourable changes in BASDAI, BASG, BASMI and increase in IMT, and 2. Unfavourable changes in total cholesterol, LDL-cholesterol, total-HDL-cholesterol ratio and decrease in vascular elasticity (as measured with YEM).

Table 1. Correlations between changes in AS- and CV related factors and changes in arterial wall characteristics

	Intima-media Thickness		Young's Elastic Modulus	
	Correlation coefficient	p-value	Correlation coefficient	p-value
AS related factors				
BASDAI	0.308*	0.013	-0.201	0.117
BASFI	0.113	0.368	0.081	0.533
BASG	0.311*	0.012	-0.167	0.195
BASMI	0.327*	0.007	-0.062	0.632
ESR	0.030	0.822	-0.085	0.533
CRP	0.042	0.752	-0.114	0.401
CV risk factors				
Systolic blood pressure	-0.075	0.559	-0.102	0.440
Diastolic blood pressure	-0.109	0.395	-0.016	0.902
Pulse pressure	0.002	0.986	-0.100	0.446
Body-mass index	-0.084	0.516	0.005	0.968
Total cholesterol	0.309*	0.042	-0.276	0.076
HDL-cholesterol	0.081	0.612	0.137	0.401
LDL-cholesterol	0.251	0.123	-0.277	0.097
Total- to HDL-cholesterol ratio	0.117	0.462	-0.319*	0.045

* $p < 0.05$
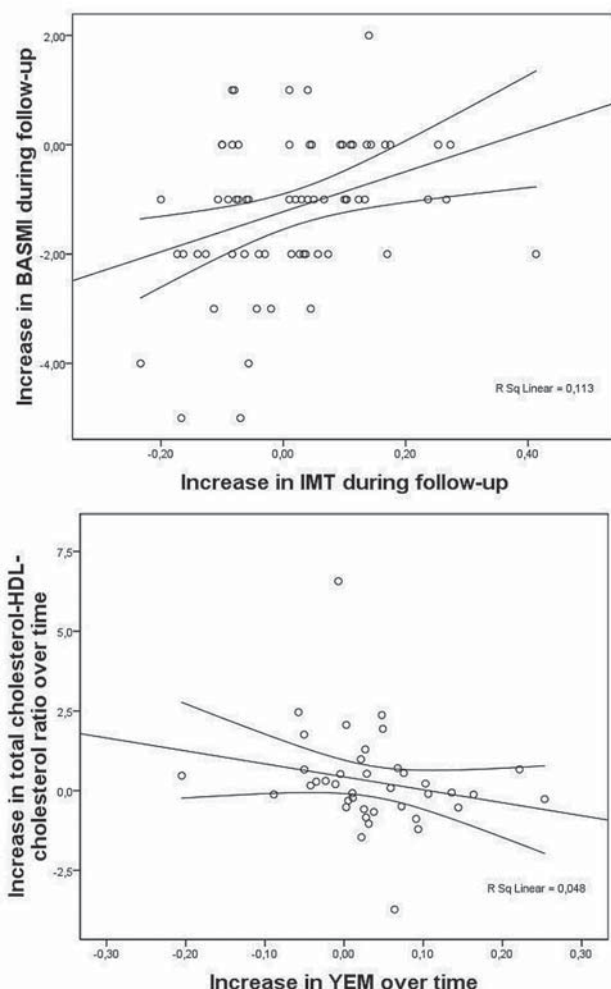
Figure 1. Changes in IMT and BASMI, YEM and Total cholesterol to HDL-cholesterol ratio.

Conclusion: Continuous use of TNF-inhibitors might stabilize or slow down IMT progression in AS patients, reflecting a decreased CV risk in these patients. Unfavourable changes in IMT were associated with equally unfavourable changes in AS related factors and unfavourable changes in vascular elasticity (as measured with YEM) were associated with unfavourable changes in lipid levels. The exact mechanism by which TNF inhibition modulates CV risk might be explained by different mechanisms (AS related factors and IMT vs. lipid levels and YEM).

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1703

Relationship Between Tobacco Smoking and Radiographic Spinal Progression in Axial Spondyloarthritis: The Role of Inflammatory Activity.
Denis Poddubnyy[1], Hildrun Haibel[1], Joachim Listing[2], Elisabeth Märker-Hermann[3], Henning Zeidler[4], Jürgen Braun[5], Martin Rudwaleit[6] and Joachim Sieper[7]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]Dr. Horst Schmidt Kliniken, Wiesbaden, Germany, [4]Medizinische Hochschule, Hannover, Germany, [5]Rheumazentrum Ruhrgebiet, Herne, Germany, [6]Endokrinologikum Berlin, Berlin, Germany, [7]Charité Universitätesmedizin Berlin, Berlin, Germany

Background/Purpose: Cigarette smoking is associated with functional impairment [1, 2] and radiographic severity of ankylosing spondylitis (AS) [3, 4]. Moreover, smoking status at baseline was found recently to be an independent predictor of radiographic spinal progression in the whole group of axial spondyloarthritis (SpA) [5]. However, the nature of relationship between smoking and radiographic spinal progression in SpA remains unclear.

The objective of the current analysis was to investigate a relationship between smoking intensity, radiographic spinal progression and activity of systemic inflammation in patients with axial SpA.

Methods: In total, 210 patients with axial SpA (115 with AS according to the modified New York criteria and 95 with nrSpA) from the German Spondyloarthritis Inception Cohort (GESPIC) were selected for this analysis of spinal radiographs at baseline and after 2 years of follow-up. Spinal radiographs were centrally collected, digitized, and subsequently scored according to the mSASSS independently by two trained readers, who were blinded for time point and all clinical data. Smoking status and smoking intensity (non-smoker, 10 cigarettes a day and less, 11 to 20 cigarettes, and more than 20 cigarettes a day) were assessed retrospectively every 6 months during 2 years of follow-up.

Results: 139 patients (66.2%) were considered to be non-smokers throughout the entire follow-up period of 2 years, 43 patients (20.5%) smoked 10 cigarettes a day and less (as a mean over two years), 22 patients (10.5%) smoked 11–20 cigarettes and only 6 patients (2.9%) smoked more than 20 cigarettes a day and, therefore, were pooled with the group of 11–20 cigarettes a day. The mean mSASSS change over 2 years was 0.52 ± 1.72 in non-smokers vs 0.47 ± 1.48 in a ≤10 cigarettes/day group (p=0.30) vs 2.2 ± 4.6 in >10 cigarettes/day group (p=0.077 vs. non-smokers, p=0.35 vs. ≤10 cigarettes/day group). Significant radiographic progression (defined as an mSASSS worsening by 2 units and more over 2 years) was observed in 10.1% of non-smokers vs 18.6% in smokers of ≤10 cigarettes a day (p=0.14 vs non-smokers) vs 28.6% in smokers of >10 cigarettes a day (p=0.012 versus non-smokers). Importantly, the same trend was observed for the serum level of C-reactive protein as a marker of inflammatory activity: 6.3 ± 6.6 mg/l in non-smokers vs 8.6 ± 10.3 mg/l in smokers of ≤10 cigarettes a day vs 12.4 ± 12.9 in smokers of >10 cigarettes a day (p=0.021 vs non-smokers).

Conclusion: Tobacco smoking has a clear dose-dependent effect on radiographic spinal progression in axial SpA, which is likely to be related to a non-specific augmentation of inflammation by the components of the tobacco smoke.

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1704

New Threshold Values for Spinal Mobility Measures Based On a Large Nationally Representative Sample of U.S. Adults Ages 20–69 Years.
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Background/Purpose: Spinal mobility measures are widely utilized for diagnosis and assessment of disease severity in patients with Ankylosing Spondylitis. The previously proposed threshold values for spinal metrology were determined based on distributions of these measures in convenience samples of healthy volunteers. Herein, we report population based percentile reference range values for selected spinal mobility measures in a <u>nationally representative sample</u> of 5103 U.S. adults ages 20–69 years examined in the 2009–10 U.S. National Health and Nutrition Examination Survey (NHANES).

Methods: Occiput-to-Wall Distance (OWD), Thoracic Expansion (TE), Anterior Lumbar Flexion (modified Schober) were measured by trained examiners in a standardized fashion. Specifically, the difference in chest circumference expansion between complete exhalation and maximal inhalation was measured at the xiphisternum level. For the modified Schober test, the initial measurement point was a line marked at the level of the superior margin of the lateral iliac crests, then a second mark was placed 10 cm above it. NHANES sample weights and survey design variables were used.

Results: In this nationally representative sample, 4% of subjects had an OWD of more than zero. Based on the commonly used thresholds of 2.5 or 5 cm for chest expansion, 13.6% and 62.4% of the sample had "out of range" values, respectively. Assuming that lumbar flexibility has a similar range if the measurements start at the level of lateral iliac crest rather than at the L5-S1

level, the commonly used threshold of 3.5 cm for the modified Schober was applied, resulting in 44.2% of the general population having "out of range" values.

In the present study, the upper 95th percentile of OWD measurement was zero while the 5th percentile measurements for TE and modified Schober were both 2.0. The mean (±standard error) OWD, Thoracic Expansion, and modified Schober test were 0.21 (±0.03), 4.8 (±0.06), and 3.8 (±0.03) cm, respectively. The spinal metrology parameters were significantly associated with body mass index, gender, and age. Therefore, we next excluded participants with morbid obesity (body mass index>35). This did not change the threshold values for OWD and modified Schober test but the 5th percentile for TE increased to 2.3. Furthermore, we calculated the percentiles for the spinal mobility measures stratified according to age and gender (Table 1).

Table 1. Percentile Cut Points[1] in cm. for Arthritis Body Measures: NHANES 2009–10

Age (years)	Occiput-Wall Distance		Thoracic Expansion		Modified Schobers	
	Men	Women	Men	Women	Men	Women
20–35	0	0	2.7	2.5	2.3	2.2
36–49	0	0	2.4	2.3	2.2	1.8
50–69	6.3	0	1.9	1.8	1.9	1.6

[1] Occiput-to-Wall Distance-upper 95th percentile; Thoracic Expansion/Modified Schober-lower 5th percentile.

Conclusion: In this nationally representative sample, we verified the threshold of zero for OWD. However, the currently utilized clinical cut points for TE and Schober Test appear to assign "abnormal" values to a large portion of the general population. Using population based percentile reference range values, we recommend new threshold values for TE and the modified Schober Test in the overall population or stratified by age and gender.

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1705

Effect of Certolizumab Pegol On Inflammation of Spine and Sacroiliac Joints in Patients with Axial Spondyloarthritis: 12 Week Magnetic Resonance Imaging results of a Phase 3 Double Blind Randomized Placebo-Controlled Study. Désirée van der Heijde[1], Walter P. Maksymowych[2], Robert B. M. Landewé[3], Christian Stach[4], Bengt Hoepken[4], Andreas Fichtner[4], Danuta Kielar[5] and Jurgen Braun[6]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Alberta, Edmonton, AB, [3]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [4]UCB Pharma, Monheim am Rheim, Germany, [5]UCB Pharma, Brussels, Belgium, [6]Rheumazentrum Ruhrgebiet, Herne, Germany

Background/Purpose: Axial spondyloarthritis (axSpA) includes both ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA) and is defined by the ASAS criteria.[1] It is characterized by bone marrow edema of sacroiliac joints (SIJ) and spine leading to chronic back pain. RAPID-axSpA (NCT01087762) is the first report of the effect of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, on inflammation of spine and SIJ in axSpA pts, including both AS and nr-axSpA pt populations, using MRI.

Methods: The ongoing 158-Wk RAPID-axSpA trial is double-blind and placebo controlled to Wk24, dose-blind to Wk48 and then open label to Wk158. Recruited pts had adult-onset active axSpA defined by the ASAS criteria,[1] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, spinal pain ≥4 on a 10 point NRS, and CRP > upper limit of normal or sacroiliitis on MRI. Pts must have failed ≥1 NSAID. Pts could have been secondary failures to 1 previous TNF inhibitor. The pt population reflected the broad axSpA population, including AS pts also meeting the modified New York criteria and nr-axSpA pts who met the ASAS MRI or clinical criteria. Pts were randomized 1:1:1 to placebo (PBO), or 400mg CZP at week (Wk) 0, 2 and 4 (loading dose, LD) followed by either 200mg CZP every 2 weeks (Q2W) or 400mg CZP every 4 weeks (Q4W). MRI scans of the SIJ and spine[2], using short-tau-inversion recovery sequences, were performed at baseline (BL) (±3 days) and Wk12 and evaluated using an analysis of covariance model. MRI endpoints were change from BL in the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ score for inflammation

and in the Berlin modification of AS spine MRI score for disease activity in the spine (ASspiMRI-a). MRIs were performed in a subset of the pts. Data are reported for all pts who had MRI scans at both BL and Wk12 (the MRI set).

Results: 325 pts were randomized, of which 153 were included in the MRI set. In the MRI set, BL characteristics were similar between treatment groups (PBO/CZP 200mg/CZP 400mg), apart from C-reactive protein (23.9/14.7/15.3 mg/L) and prior anti-TNF exposure (30.0/12.2/9.3%). AS pts had longer symptom duration at BL compared to nr-axSpA pts (mean 12.4 vs. 8.5 yrs). Within the MRI imaging set, BL SPARCC MRI SIJ scores were comparable between AS and nr-axSpA populations while Berlin ASspiMRI-a scores were higher in AS patients. Improvements in SPARCC MRI SIJ scores and ASspiMRI-a Berlin modification were observed in both CZP dose arms compared to PBO in the overall and in both AS and nr-axSpA populations (Figure). Greater reductions in SIJ inflammation were observed for pt subgroups with <5 yr symptom duration, age <45 yrs and in males.
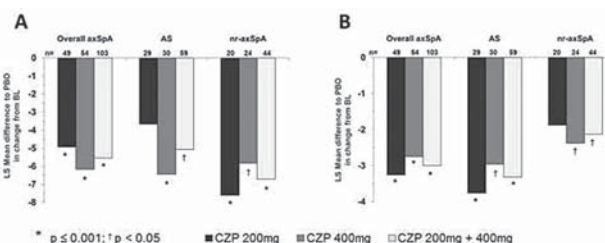
Figure. LS mean difference to placebo for change from BL in SPARRC scores in SIJ (**A**) and in the ASspiMRI-a Berlin Modification in the spine (**B**) at Week 12

Conclusion: CZP reduced inflammation in the SI joints and spine, as assessed by MRI in pts with axSpA, and in both AS and nr-axSpa populations.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects
and Treatment III: Cardiovascular
Monday, November 12, 2012, 4:30 PM–6:00 PM

1706

Predictive Atherosclerotic Risk Factors At Inception in a Multicentre, Multinational Cohort. Murray B. Urowitz[1], Dominique Ibanez[1], D. D. Gladman[1] and SLICC[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto, ON

Background/Purpose: Patients with systemic lupus erythematosus (SLE) develop premature atherosclerosis (AS). This study examines predictive factors at inception for atherosclerotic vascular events (AVE) over a maximum 10 years of followup in a multicenter, international inception cohort.

Methods: An inception cohort of SLE patients from 31 centres from 12 countries has been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. At yearly visits demographic and cardiovascular risk factors are collected and vascular events (VE) are described and attributed on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), stroke, and transient ischemic attack (TIA). Diagnosis of an event was confirmed using standard clinical criteria and diagnostic tests where appropriate. Attribution to AS was made by physicians on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Analysis was done using descriptive statistics and Cox proportional Hazard model.

Results: Of the inception cohort of 1844 SLE patients 93 had VE due to non-AS causes (e.g. active SLE or thrombosis) and 350 patients had only enrolment data leaving 1401 patients. 31 patients had 41subsequent AVE after enrollment. The mean time to AVE or last clinic followup was 5 years. distribution Patients' race/ethnicity distribution was as follows: 51% Caucasian, 16% Black, 17% Asian 12% Hispanic 4% other. At enrollment risk factors for AS are shown in the table 1.

	Patients without AVE no=1370	Patients with AVE n=31	P value
Age	34.6 ± 13.1	56.0 ± 13.8	<0.0001
Sex, %	90.6	58.1	<0.0001
Diabetes, %	3.2	10.7	0.06
Framingham risk Score Mod/High, %	1.5	25.0	0.001
Smoker ever, %	35.7	61.3	0.004
Obese, %	29.3	53.6	0.01
Hypertension, %	32.6	60.0	0.003
Hypercholesterolemia, %	34.7	50.0	0.12
Increased LDL*, %	33.3	33.3	1.00
Increased Creatinine, %	23.5	47.8	0.01

*LDL=low density lipoprotein

Table 2. Time to Event Analysis 1 risk factor at a time

	Hazard Ratio	95% CI	p value
One risk factor at a time			
Age	1.09	1.07,1.12	<0.0001
Caucasian	3.39	1.46,7.87	0.005
Male	6.30	3.09,12.87	<0.0001
FRS Mod/High	13.15	3.99,43.22	0.0001
Smoker ever	2.95	1.43,6.09	0.003
Obesity	2.92	1.39,6.14	0.005
Hypertension	3.10	1.49,6,43	0.002
Hypercholesterolemia	1.85	0.90,3.77	0.09
Stepwise regression with all above variables			
Age	1.09	1.06,1.11	<0.0001
Male	4.07	1.84,9,04	0.0006

*FRS=Framingham Risk Score

Conclusion: Only age and male sex remain significant risk factors for AVE in a multivariate analysis of a multicentre inception cohort followed for a mean of 5 years.

Disclosure: M. B. Urowitz, None; D. Ibanez, None; D. D. Gladman, None;

1707

The Association of Serum Biomarkers and Metabolic Syndrome with Subclinical Atherosclerosis in Systemic Lupus Erythematosus: A Controlled Analysis in Patients with No Clinical Disease Activity. Semra Ertan-Demir[1], Ahmet Yasar Cizgici[1], Gaye Erten[2], Bahar Artim-Esen[1], Yasemin Sahinkaya[1], Özlem Pehlivan[1], Nilüfer Alpay-Kanitez[1], Kadri Atay[1], Huseyin Oflaz[1], Gunnur Deniz[2] and Murat Inanc[1]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Istanbul University, Institute of Experimental Medicine (DETAE), Istanbul, Turkey

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased risk of developing atherosclerotic cardiovascular disease (CVD). In addition to traditional CVD risk factors or metabolic syndrome (MetS), SLE related factors may contribute to increased risk. The aim of this study was to assess subclinical atherosclerosis and the potential role of inflammatory mediators, vascular endothelial cell activation markers and adipocytokines in SLE in presence or absence of MetS.

Methods: We studied 82 female SLE patients (35 with Mets, 47 without Mets) and 28 female healthy controls (HC) with no history of CVD. Mets were defined according to NCEP ATP III. Disease activity according to SLEDAI and SLICC damage score were determined. Subclinical atherosclerosis was screened by measuring carotid intima media thickness (CIMT) by B-mode ultrasonography. Serum levels of high sensitivity C-reactive protein(hs-CRP), tumor necrosis factor α(TNFα), interleukin 6(IL-6), soluble interceluler adhesion molecule 1 (sICAM-1), sE-selectin, leptin and visfatin

were measured. Additional analysis were done for premenopausal patients. The comparison of groups was done by variance analysis and chi-square test when appropriate.

Results: The mean age of MetS+ SLE was 45± 11, MetS- was 33±9, HC was 28±6 mean disease duration of the patients were 84 ± 62 months. Most of the SLE patients (%79) were premenopousal. SLE patients were in clinical remission (mean SLEDAI= 1.06). Mean SLICC damage score was 0,29. CIMT values were higher in SLE patients than HC (mean CIMT left: 1.35±2,52mm vs 0.54±0,08mm right 1,28±2,40mm vs. 0,55±0,07mm, p=0,001). Only hsCRP, sICAM-1 and leptin levels were higher in SLE patients than HC (p=0,001) and were correlated with carotid IMT values (left r= 0,3, p=0,02; r=0,47, r=0,35, p=0,001). The biomarkers studied were not related to serological or hematological activity. SLE mets+ group has higher CIMT values than SLE mets- (mean CIMT left: 1,74±3,17mm vs 1,06±1,91mm right: 2,11±3,54mm vs. 0,66±0,07mm p=0,001). hsCRP and leptin levels were significantly higher in SLE Mets + than SLE Mets- (p= 0,003, p=0,001). When SLE patients in premenopause were analysed, CIMT values were higher in SLE patients than HC (CIMT left: 1,1±1,9mm vs 0,54±0,08mm, p=0,02, right: 1±1,6mm vs 0,55±0,07mm, p=0,03). hsCRP, sICAM-1 and leptin levels were higher in SLE patients (p=0,03, p=0,001, p=0,014). Only leptin levels were correlated with CIMT values (right r= 0,315, p=0,002). In premenopausal SLE patients, mets+ group has higher IMT values than mets- (mean CIMT left: 1,21±2,07mm vs 1,07±1,92mm p=0,013, right: 1,72±2,83mm vs. 0,66±0,12mm p=0,001). Only leptin levels were higher in Mets+ than Mets- patients (p=0,005).

Conclusion: In mainly premenopausal women with SLE without a history of CVD, CIMT values were found increased and related to Mets. This implies the importance of investigating Mets in identifying patients with subclinical atherosclerosis. Some biomarkers in SLE, especially leptin was increased in patients with Mets and correlated with carotid IMT values, suggesting a relationship with subclinical atherosclerosis. The longitudinal follow-up of Mets and biomarkers may facilitate the prevention of overt CVD in SLE.

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1708

Systemic Lupus Erythematosus Cardiovascular Risk Equation. Michelle Petri[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Accelerated atherosclerosis remains the major late cause of death in SLE. Yet, the "traditional" cardiovascular risk equations (Framingham, Reynolds, SCORE) consistently underestimate the risk. This may lead to under-recognition and under-treatment. We sought to construct a data-driven risk equation of cardiovascular risk in SLE, based on data collected in a longitudinal cohort.

Methods: To derive the score, risk factors were calculated based on variables measured in the first two years of cohort participation (mean systolic blood pressure, mean SLEDAI, etc). Cox Proportional Hazards models were constructed to determine the variables that affected the risk of a subsequent CVE. Using the results, a formula to calculate the risk of a CVE within the next 10 years was derived. There were 1342 patients, 93% female, 56% Caucasian, 38% African-American, and 6% other ethnicities. There were 109 cardiovascular events: 52 strokes, 26 MI, 18 angina/CABG, and 13 claudications.

Results: Table 1 shows the estimates for the association between predictors and risk of a CVE.

Table 1.

	Beta	Hazard Ratio (95% CI)	P-value	Integer Score
Age (for each 5 years over 40)	0.252	1.29 (1.15,1.44)	<0.0001	1
Male (vs. female)	0.552	1.74 (0.98,3.09)	0.060	2
Systolic Blood Pressure 140 or more	0.791	2.21 (1.37,3.56)	0.0012	3
Cholesterol over 160	0.743	2.10 (1.16,3.83)	0.015	3
Smoking	0.677	1.97 (1.31,2.96)	0.0012	3
Diabetes	0.407	1.50 (0.91,2.48)	0.11	2
Mean SLEDAI of 2 or more	0.730	2.08 (1.22,3.53)	0.0069	3
History of Lupus Anti-coagulant	0.744	2.10 (1.40,3.16)	0.0003	3
Low Mean C3	0.583	1.79 (1.14,2.82)	0.012	2

Using this model, the risk of a CVE within 10 years is $1-0.9875^{(Hazard\ Ratio)}$. For example, if someone is 50 years of age, male, with high systolic blood pressure, then the hazard ratio is $(1.0510)x(1.74)x(2.21) = 6.26$. The risk of a CVE in 10 years is then $1-0.9875^{(6.26)} = 7.6\%$. In the absence of SLE risk factors, the estimated 10-year risk from our formula is higher than would be projected based on the Framingham formula. This is especially true if there are SLE-related risk factors. Table 2 shows a few scenarios.

Table 2. Examples

	Estimated 10-year risk based on our formula	Estimated 10-year risk based on Framingham formula
Woman, age 50, SBP=150, Chol=150	4.5%	4.7%
Woman, age 50, SBP=150, Chol=220	9.2%	7.8%
Woman, age 50, SBP=150, Chol=220, Lupus Anticoagulant	18.3%	7.8%
Woman, age 50, SBP=150, Chol=220, High disease activity	18.1%	7.8%
Woman, age 50, SBP=150, Chol=220, Low complement	15.8%	7.8%

Using the approach employed by the Framingham study, the regression coefficients were rounded to integers (Table 1) to create a simpler score. The score is the sum of the number of points earned for each risk factor. For example, a 50 year old man with high SBP would get a score of $2+2+3=7$. Then, to calculate the 10 year risk, use Table 3.

Table 3. Percent risk of a CVD within 10 years

Score	0	1	2	3	4	5	6	7	8	9	10
% Risk	1.3	1.6	2.1	2.6	3.4	4.3	5.5	7.0	8.9	11.3	14.2

Conclusion: A data-driven SLE Cardiovascular Risk Score can better estimate 10-year cardiovascular risk than the Framingham equation. Its use can lead to appropriate use of imaging and intervention.

Disclosure: M. Petri, None; **L. S. Magder**, None.

1709

Biomarkers of Atherosclerosis Are Associated with Progression of Non-Cardiovascular Damage in Patients with SLE. Sarah J. Kim, Jennifer M. Grossman, Brian Skaggs, Elaine Lourenco, Lori Sahakian, John D. FitzGerald, Nagesh Ragavendra, Christina Charles-Schoeman, Alan H. Gorn, Bevra H. Hahn and Maureen A. McMahon. UCLA David Geffen School of Medicine, Los Angeles, CA

Background/Purpose: Studies have shown that even after taking traditional cardiac risk factors into account, SLE patients have up to 50-fold higher risk of developing atherosclerotic (ATH) cardiovascular disease. We previously identified several biomarkers associated with the progression of atherosclerosis in SLE, including pro-inflammatory high-density lipoprotein (piHDL), leptin, sTWEAK, and homocysteine. These 4 biomarkers plus increased age combined into a "high oxidative stress" variable was also highly associated with progression of ATH in SLE. The goal of this study was to investigate the association between biomarkers of ATH and overall progression of non-ATH, lupus-related damage.

Methods: Systemic Lupus International Collaborating Clinics/ACR damage index (SDI) was used to score damage progression in 159 SLE patients enrolled in the longitudinal "Biomarkers of Atherosclerosis in SLE" cohort study between January 2004 and September 2008. Lupus-related damage scores were determined using the SDI at baseline and at the time of the 2–3 year follow-up carotid ultrasound excluding scores in cardiovascular domains. The associations between accumulation of any lupus-related non-ATH damage and biomarkers of atherosclerosis were examined using the chi-square test for dichotomous variables and Student's t-test for continuous variables (SPSS Inc, Chicago, IL).

Results: After excluding cardiovascular and cerebrovascular events from the SDI score, new carotid plaque at 2 year follow-up was present in 34% of patients with non-ATH SDI score increase as opposed to 18% in patients without SDI change (p=0.01). In patients with SDI increase, mean homocysteine (p=0.037), sTWEAK (p=0.043) and leptin (p=0.02) levels were significantly higher than in those without SDI change. The combination

high-oxidative stress variable was found in a higher proportion of patients with SDI increase (50% vs 28.9%, p=0.02), and was associated with a higher mean SDI increase (0.52±0.94 vs 0.19±0.47, p=0.02). In multivariate analysis controlling for lupus medications, baseline SDI, and other potential confounders, high-oxidative stress was associated with a 2.9-fold increased odds for progression of non-atherosclerotic damage (p=0.02), and lifetime cumulative prednisone use >20g was associated with 2.6-fold increased odds (p=0.046).

Conclusion: Non-atherosclerotic lupus-related damage as measured by SDI scoring is associated with presence of carotid plaque, high-oxidative stress and elevated levels of homocysteine, sTWEAK, and leptin. Patients with baseline biomarkers for atherosclerosis progression have higher incidence of overall progression of non-ATH disease damage which may serve as important predictors for lupus disease course.

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1710

Increase in Vitamin D Improves Disease Activity and Systolic Blood Pressure in Systemic Lupus Erythematosus. Kayode J. Bello[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Vitamin D deficiency has also been associated with different chronic conditions including cardiovascular diseases such as coronary artery disease, cardiac failure and hypertension. In SLE, it may be associated with the interferon gene signature. We investigated whether an increase in vitamin D levels was associated improvement in disease activity and blood pressure in SLE patients.

Methods: 1006 SLE patients were followed in a prospective observational study for 138 weeks (July 2009–March 2012). Serum 25-hydroxyvitamin D levels were measured at routine clinic visits. Patients with low 25-hydroxyvitamin D levels (<40 ng/mL) were supplemented with 50,000 units Vitamin D_2 weekly, and $Ca/D_3$200 units twice daily. Data analysis was done using longitudinal regression models with one-slope and two-slope models, controlling for race, age, age squared, sex, prednisone, hydroxychloroquine, and date (SAS Institute Inc. Cary, North Carolina, SAS 9.2).

Results: There were a total of 5935 visits with serum 25-hydroxyvitamin D measurements from 1006 different SLE patients. They were 91% female, mean age was 49.6 (SD = 13.2), 54% Caucasian, 37% African-American and 8% other ethnicity. The number of visits per patient ranged from 1 to 16. 110 (11% had 1 visit, 313 (31%) had 2–5 visits, 517 (51%) had 6–9 visits, and 65 (6%) had 10–16 visits.

Table. Difference in mean disease measure per 20 ng/mL increase in vitamin D based on longitudinal regression models with one or two slopes

Disease Measure	One-slope Model		Model allowing slope to differ before and after 40 ng/mL			
	Slope[1] (95% CI)	P-value	Slope[1] over range of 0–40 ng/mL (95% CI)	P-value	Slope[1] over range of 40+ ng/mL (95% CI)	P-value
Physician Global Assessment	-0.01 (-0.03,0.01)	0.21	-0.04 (-0.08,-0.01)	0.026	0.01 (-0.02,0.04)	0.68
SLEDAI-SLEDAI	-0.02 (-0.11,0.07)	0.65	-0.22 (-0.41,-0.02)	0.032	0.12 (-0.01,0.24)	0.065
Systolic BP	-2.13 (-2.79,-1.48)	<0.0001	-3.91 (-5.21,-2.63)	<0.0001	-0.86 (-1.73,0.02)	0.055
Log Urine Protein/Creatinine	-0.02 (-0.03,-0.01)	<0.0001	-0.04 (-0.05,-0.02)	0.0004	-0.01 (-0.01,0.00)	0.24
Log HSCRP	-0.02 (-0.09,0.06)	0.64	-0.06 (-0.20,0.09)	0.45	0.02 (-0.12,0.15)	0.82

[1]Slopes are interpretable as difference in mean level of disease per 20ng/mL increase in vitamin D.

There was significant improvement in both the PGA and SELENA-SLEDAI in those with low vitamin D (<40ng/mL), when vitamin D was increased by 20 ng/mL. There was also improvement in systolic blood pressure and urine protein/creatinine.

Conclusion: After a long follow-up in this SLE Cohort, there was statistically significant improvement in disease activity in those with low

vitamin D levels, who increased their vitamin D levels. We also found significant improvement in both systolic blood pressure and urine protein/creatinine with increase in vitamin D. This analysis suggests vitamin D supplementation in SLE patients with low vitamin D levels may have beneficial effects on disease activity and on blood pressure, one of the major predictors of accelerated atherosclerosis in SLE.

Disclosure: **K. J. Bello**, None; **H. Fang**, None; **L. S. Magder**, None; **M. Petri**, None.

1711

Association of Vascular Calcification and Perivascular Adipose Tissue of the Descending Aorta with Cardiovascular Events in SLE. Kelly J. Shields[1], Emma Barinas-Mitchell[2], Amy H. Kao[3], Susan Manzi[4] and Kim Sutton-Tyrrell[2]. [1]Lupus Center of Excellence/ASRI/West Penn Allegheny Health System, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Allegheny Singer Research Institute, Pittsburgh, PA, [4]West Penn Allegheny Health System, Pittsburgh, PA

Background/Purpose: Women with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD). We have shown that clinically CVD-free women with SLE have an increased volume of descending aortic perivascular adipose tissue (aPVAT). This small adipose depot was also associated with aortic calcification (AC) independent of overall adiposity. Thus, we hypothesized that clinically CVD-free women with SLE increased aPVAT volume and premature vascular calcification measured by AC and coronary artery calcification (CAC) will predict cardiovascular events. (CVE).

Methods: Women participating in the "Heart Effects on Atherosclerosis and Risk of Thrombosis in SLE" (HEARTS) study were clinically CVD-free and diagnosed with SLE for at least 2 years. CAC/AC were measured using electron beam computed tomography (EBCT) and quantified by Agaston scoring. The aPVAT was quantified using commercially available software and standard attenuations values for adipose tissue (−190 to −30 HU). Participants were followed for incident CVE confirmed by a physician. (SLE without CVE, n=128; SLE with CVE n=28). CVE included myocardial infarction, congestive heart failure, stroke, transient ischemic attack, angina, blood clot, percutaneous coronary intervention, and catherization.

Results: Twenty eight participants (17%) experienced a first CVE within 4.6 +/− 12 months (Mean +/− SD) with three participants having multiple CVE. There were no differences in surrogate adiposity measures such as waist-to-hip ratio (p=0.58) or BMI (p=0.23) by CVE status suggesting similar adipose distribution. Traditional CVD risk factors such as age (p=0.008), systolic blood pressure (p=0.0053), pulse pressure (p=0.0047), hypertensive status (p=0.0039), CRP (p=0.0081) and homocysteine levels (p=0.017) were all significantly greater in SLE women with CVE. The SLE women with CVE were more likely to have AC (p=0.0052). There were no differences in CAC (p=0.21) or aPVAT (p=0.17) between SLE groups with and without CVE. Aortic PVAT was associated with adiposity measures such as BMI (r_s=0.515,p<0.0001), waist-to-hip ratio (r_s=0.332,p=0.0001), and circulating inflammatory markers such as CRP (r_s=0.393,p<0.0001). In univariate models using Cox proportional-hazards regression, CAC (Hazard ratio/HR [95%CI]: 2.43 [1.1–5.5], p=0.03) was a predictor of first CVE, but AC (p=0.74) and aPVAT (p=0.20) were not predictors. In the multivariable Cox regression models, age per 5 years (HR 1.61 [1.3–2.1], p=0.0001) and CRP (HR 1.10 [1.0–1.2], p=0.0055) remained predictors of first CVE.

Conclusion: Traditional CVD risk factors were independent predictors of first CVE in women with SLE in this study. The clinically CVD free SLE women experiencing a CVE were more likely to have hypertension along with AC indicating premature vascular dysfunction. CAC was an independent predictor of first CVE emphasizing the significant influence of calcification in this vascular bed. Aortic PVAT was found to be significantly associated with traditional CVD risk factors, but not found to be predictive of first CVE. Considering our previous findings, aPVAT and AC may be considered precursors to measurable subclinical CAC.

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ACR Concurrent Abstract Session
**Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's –
Clinical Aspects and Therapeutics II**
Monday, November 12, 2012, 4:30 PM–6:00 PM

Monday, November 12

1712

The Submaximal Heart and Pulmonary Evaluation: A Novel Noninvasive Test to Identify Pulmonary Hypertension in Patients with Systemic Sclerosis. Elana J. Bernstein[1], Jessica K. Gordon[1], Robert F. Spiera[1], Lisa A. Mandl[1] and Evelyn M. Horn[2]. [1]Hospital for Special Surgery, New York, NY, [2]New York Presbyterian Hospital/Weill Cornell Medical College, New York, NY

Background/Purpose: Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg on right heart catheterization (RHC), is a leading cause of death in patients with systemic sclerosis (SSc). Although RHC is the gold standard for diagnosing PH, it is an expensive, invasive test with significant associated risks. Transthoracic echocardiogram (TTE) and pulmonary function testing (PFT) are standard noninvasive screening methods used to assess SSc patients for PH. However, both are limited in their ability to distinguish between SSc patients with and without PH. The existence of an accurate, noninvasive technique to screen for PH in the SSc population is an important unmet need.

The submaximal heart and pulmonary evaluation (SHAPE) is a noninvasive, submaximal stress test that consists of a 5.5 inch high step that patients step up and down on for 3 minutes. During the test, end tidal carbon dioxide, which is equivalent to the ratio of cardiac output to pulmonary blood flow and reflects the severity of PH, is monitored. Our aim was to assess the correlation between change in end tidal carbon dioxide (ΔP_{ETCO2}) from rest to end-exercise on the SHAPE test and mPAP on RHC. We hypothesized that ΔP_{ETCO2} would be strongly negatively correlated with mPAP.

Methods: This is a retrospective cohort study of patients with limited cutaneous (lc) or diffuse cutaneous (dc) SSc who underwent a SHAPE test and RHC between November 2008 and May 2012. Charts of 679 patients in an academic cardiology practice were reviewed; 70 patients had a diagnosis of SSc, 19 of whom had undergone both a SHAPE test and RHC and were included in this study. The primary outcome was correlation between ΔP_{ETCO2} and mPAP. Statistical analysis was performed using Spearman's correlation and multivariable linear regression.

Results: The mean age of subjects was 61 years (± 12.5); 84% were female, 84% had lcSSc, and 79% had PH. ΔP_{ETCO2} was significantly negatively correlated with mPAP (r = −0.82, p < 0.0001) (see Table). In a multivariable linear regression model evaluating the relationship between ΔP_{ETCO2} and mPAP, and controlling for age, sex, time between SHAPE and RHC, and change in medications between SHAPE and RHC, ΔP_{ETCO2} remained significantly associated with mPAP (β = −1.91, p < 0.001). The SHAPE had better sensitivity, specificity, positive predictive value, and negative predictive value for PH than did TTE or PFTs.

Performance Characteristics and Correlation of SHAPE, TTE, and PFTs with RHC (N=19)

Test*	Sensitivity**	Specificity**	Positive Predictive Value (PPV)**	Negative Predictive Value (NPV)**	Spearman's Correlation†	P-value for Spearman's Correlation
SHAPE (ΔP_{ETCO2} < 4 mmHg)	100%	75%	93.8%	100%	-0.82	0.0001
TTE (systolic pulmonary artery pressure [sPAP] > 35 mmHg)	80%	25%	80%	25%	0.74	0.0004
PFTs (forced vital capacity/ diffusion capacity [FVC/ DLCO] > 1.6)††	91.7%	75%	91.7%	75%	0.53	0.034

* Cut-points were derived from the literature
** Using RHC as the gold standard for diagnosis of PH (mPAP ≥ 25 mmHg)
† Correlation is with mPAP on RHC
†† 16 of the 19 patients had PFTs with DLCO

Conclusion: ΔP_{ETCO2} as measured by the SHAPE has a very strong, statistically significant negative correlation with mPAP on RHC, and is better correlated with mPAP than are sPAP on TTE or FVC/DLCO. The SHAPE has excellent sensitivity, specificity, PPV, and NPV in this small group of SSc patients with a high prevalence of PH. The SHAPE may be a better screening test for PH in patients with SSc than TTE or PFTs. Larger prospective studies investigating the ability of the SHAPE to distinguish between SSc patients with and without PH are needed.

Disclosure: **E. J. Bernstein**, None; **J. K. Gordon**, None; **R. F. Spiera**, None; **L. A. Mandl**, None; **E. M. Horn**, None.

1713

Developing an Index for Disease Activity and Therapeutic Response in Connective Tissue Disease Related Interstitial Lung Disease: Results From A Delphi Exercise: Delivering A Consensus On Domains.

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Background/Purpose: Lack of reliable and valid measures of disease activity and clinical response in patients with connective tissue disease (CTD)-related interstitial lung disease (ILD) makes clinical trial design difficult. From a multi-tiered investigation to develop consensus on criteria in both CTD-ILD and idiopathic pulmonary fibrosis (IPF), we report results of expert voting from a 3-tiered Delphi exercise to identify domains 'important' to measure in a 1 year randomized controlled trial (RCT) in IPF and CTD-ILD.

Methods: Using OMERACT methodology, 270 experts nominated 23 "domains" and 616 "instruments" that were assembled into an initial voting survey for a 3-tiered Delphi exercise with survey items anchored by degree of importance on a 9-point Likert scale with <insufficiently familiar> as a voting option. All stages of data collection used a custom-designed secure web-site that included related articles and opportunities for participants to upload commentary supporting or refuting importance of each item.

Tier 1 Analysis: A cut-off median <4 was applied to the results. Final review demanded 100% consensus agreement for dismissal of an item based on lack of: 1. Face validity, 2. Content validity (more suited to diagnostic, demographic, or inclusion criteria) and 3. Feasibility in a multicenter trial.

Tiers 2 and 3 Analysis: To protect against bias introduced by using an arbitrary cut-off, cluster analysis was implemented to identify patterns of consensus within the data.

Results: 90% of invited experts: 137 pulmonary, 102 rheumatology and 4 cardiology specialists from 32 countries/6 continents participated. 74% and 69% of participants considered ILD and rheumatologic lung disease respectively as their primary field of research or clinical interest. Recidivism after Tier 1 was <1% with each subsequent Tier. Five common domains with their candidate instruments were identified for CTD-ILD and IPF (Table 1). Three domains identified for CTD-ILD: biomarkers, cough and medications await nominal group decisions.

Table 1. Results of Tier 3

DOMAINS (median/mean ratings)		Candidate Instruments
Dyspnea		Borg Dyspnea Index
CTD-ILD	IPF	Dyspnea 12
(8.0/7.8)	(8.0/8.1)	Medical Research Council (MRC) Breathlessness (Chronic Dyspnea) Scale
		Modified MRC Dyspnea Scale
		Borg Dyspnea Index - Pre and Post Exercise
Health Related Quality of Life (HRQoL)		Medical Outcomes Trust Short Form-36 Health Survey
CTD-ILD	IPF	St. George's Dyspnea Respiratory Questionnaire
(8.0/7.7)	(8.0/7.8)	Visual Analogue Scale of Patient Assessment Disease Activity
		Ability to Carry Out Activities of Daily Living (ADLs)
		Health Assessment Questionnaire Disability Index (HAQ-DI)
Lung Imaging		Extent of Honeycombing on HRCT
CTD-ILD	IPF	Extent of Reticulation on HRCT
(9.0/8.3)	(9.0/8.3)	Extent of Ground Glass Opacities on HRCT
		Overall Extent of Interstitial Lung Disease on HRCT
Lung Physiology/Function		Supplemental Oxygen Requirement
CTD-ILD	IPF	Forced Vital Capacity on Spirometry
(9.0/8.7)	(9.0/8.7)	Diffusion Capacity of Lung for Carbon Dioxide
		6 MWT with Maximal Desaturation on Pulse Oximetry
		6 MWT for Distance
Survival		Time to Decline in Forced Vital Capacity
CTD-ILD	IPF	Progression Free Survival
(8.0/8.2)	(9.0/8.4)	Time to Death

Conclusion: Development of valid, discriminatory and feasible outcome measures to assess disease progression and therapeutic responses is essential for performing RCTs in CTD-ILD. This is the first comprehensive, multi-disciplinary, international effort to assess domains for study of ILD. Experts identified a core set of domains including radiographic, physiologic and patient-reported outcomes culled from a large number of candidate items. A research agenda focusing on candidate biomarkers and domains requiring instrument development has emerged. Broad participation from a multidisciplinary ILD research community reflects the high perceived need in this area.

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Gender Differences in Systemic Sclerosis: Relationship to Disease Specific Clinical Manifestations and Estradiol Levels.

Christine Peoples, Mary Lucas, Zengbiao Qi, Thomas A. Medsger Jr. and Carol A. Feghali-Bostwick. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by inflammation, autoantibody production, and increased production of extracellular matrix (ECM), resulting in fibrosis. We demonstrated that estradiol (E2) promotes the development of a fibrotic phenotype, and serum levels of E2 were significantly elevated in female patients with diffuse cutaneous SSc (dcSSc) (postmenopausal, no hormone replacement therapy [HRT]) when compared to controls. Prompted by these findings, we compared gender differences in disease type, disease specific clinical manifestations, disease severity, and analysis of serum E2 levels in patients with SSc.

Methods: Using the University of Pittsburgh Scleroderma Databank and Serumbank, we identified a total of 2,503 patients (1985–2011) with a clinical diagnosis of SSc. Differences between male and female patients were examined, including disease type, disease specific clinical manifestations including organ system involvement and autoantibody profile, and disease severity using the modified Medsger Disease Severity Scale. Serum levels of E2 in male dcSSc patients (N = 89) were measured using ELISA. We utilized t-test, Chi-square test of proportions, and Fisher's exact where appropriate.

Results: There were 1,994 female and 509 male patients with SSc. Most patients were Caucasian (89% in males, 91% in females, p = 0.37). Men with SSc were significantly more likely to have dcSSc than women (p < 0.0001). Males had significantly higher incidence of pulmonary fibrosis (PF) (p < 0.0001), cardiac involvement (p < 0.0001), mean maximum modified Rodnan skin score (p < 0.001), and presence of tendon friction rubs (p = 0.0002). Males also had a significantly higher prevalence of anti-Scl-70 autoantibody as compared to females (p < 0.0001), whereas females had a significantly higher prevalence of anti-centromere antibody (p < 0.0001) with a trend of higher prevalence of anti-U1RNP (p = 0.068) and anti-PM-Scl (p = 0.055). Males also had more severe vascular (p = 0.012), joint (p = 0.013), skin (p = 0.046), pulmonary (p < 0.0001), and cardiac involvement (p = 0.011) in addition to PF (p = 0.0001). For patients with dcSSc, there were 317 males and 939 females. Males had significantly higher incidence of PF (p = 0.0001) and GI involvement (p = 0.0488). There were no significant differences in regards to peripheral vascular, muscle, pulmonary arterial hypertension, or renal involvement. The mean Health Assessment Questionnaire score was significantly higher in females vs. males (p < 0.001). Serum E2 levels were elevated in patients with dcSSc compared with controls. E2 levels were also significantly higher in male dcSSc patients as compared to female dcSSc patients (p = 0.035).

Conclusion: SSc is more severe in male than female patients, especially regarding skin, pulmonary, cardiac, and GI involvement. This can be explained, in part, by increased circulating levels of E2, a pro-fibrotic hormone. Blocking the actions of E2 represents a viable therapeutic approach, especially with the wide availability of estrogen receptor antagonists and aromatase inhibitors.

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1715

Imatinib Mesylate (Gleevec™) in the Treatment of Diffuse Cutaneous Systemic Sclerosis: Results of a 24 Month Open Label, Extension Phase. Jessica K. Gordon[1], Morgana L. Davids[1], Kamini Doobay[1], Jamie N. Mersten[1], Cynthia Magro[2], Horatio F. Wildman[2], Stephen L. Lyman[1], Mary K. Crow[1] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill-Cornell Medical Center, New York

Background/Purpose: Imatinib mesylate (IM) has been shown to decrease fibrosis in preclinical models and is a treatment of interest for Systemic Sclerosis (SSc). We have previously reported the results of our open label trial. In that study, 24/30 of patients tolerated 1 year of therapy and demonstrated a 22% improvement in the Modified Rodnan Skin Score (MRSS) as well as improvement or stability in measures of pulmonary function. Patients from the initial phase of that trial were eligible to continue treatment with IM in a 24 month extension phase of this open label trial.

Methods: This was a phase IIa, open-label, single-arm clinical trial in extension-phase. Patients with dcSSc were treated with imatinib at 200 to 400 mg daily and were assessed every 3 months for safety, MRSS, and measurement of additional outcome measures for an additional 24 mos. Pulmonary function testing, high resolution CT of the chest, and echocardiography were performed as part of standard clinical care.

Results: 24 patients completed the 12 month initial phase of the imatinib trial. 17/24 patients enrolled in the extension phase and 13 continued treatment with imatinib for 24 months. The median age was 48 (18,61). 76% were female. 65% were Caucasian. The mean disease duration from the first non-Raynaud's symptom of SSc was 2.7 ± 2.1 years in this group at the time of enrollment in the initial phase. 29% were anti-scl70-positive. The baseline MRSS was 23.8 ± 9.2 at the start of the extension phase. Patients who entered the extension phase had experienced a mean improvement in MRSS of 7.1±4.8 points during the initial one year trial.

92 AEs were recorded, 43% of which were felt to be at least possibly related to IM and these were all Grade 1 or 2. 7 SAEs occurred, none of which were felt to be related to the IM. The most frequently noted side effects were muscle pain, fatigue, nausea, and edema.

The MRSS decreased from a median of 24 (IQR 18, 31) at the beginning of the extension phase to 18 (13, 29) after an additional 12 months of IM extension (n=15, p=0.08) and to 16 (13, 24) with an additional 24 mo of IM extension (n=13, p=0.002.) In 12 patients, the FVC at baseline of extension was 92 (71.0, 105.0) and was 85 (67.0,

105.0) % predicted after 24 months, p=0.09. The hemoglobin adjusted DLCO at baseline was 77% predicted (63.0, 108.0) and was 74.5% (53.5, 92.0) at 24 mo, p=0.019. When the subgroup of patients with ILD is examined (n=6), the FVC is 61% (59.0, 90.0) at baseline and 62.5% (54.5, 70.0) at 24 mo, p=0.25, and the DLCO is 63% (55.0, 63.0) to 50% (46.0, 53.5), p=0.13. Two patients developed incident mild interstitial lung disease as seen on CT during the 24 month period of follow-up. Significant changes were not observed in ESR, SHAQ, or SF-36 mental and physical components.

Conclusion: A total of 36 months of imatinib treatment was tolerable to a subset of patients with dcSSc. Although improvement in MRSS is observed in this subset, conclusions cannot be drawn regarding efficacy given the open label nature of this study. The utility of imatinib and/or other TKIs should be evaluated in a controlled fashion to better evaluate efficacy in the treatment of SSc patients.

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1716

Outcomes Linked to Intensive Treatment Trials in Systemic Sclerosis. Svetlana I. Nihtyanova[1], Voon H. Ong[2] and Christopher P. Denton[3]. [1]Royal Free Hospital, Medical School, London, England, [2]UCL Medical School, London, England, [3]UCL, London, United Kingdom

Background/Purpose: A number of clinical trials using intensive immunosuppression followed by autologous haematopoietic stem cell transplantation (HSCT) in systemic sclerosis (SSc) are underway or have been recently completed. Inclusion criteria for these trials aim to recruit cases with poor outcome, so that potential treatment-related complications, including significant early mortality are justified. Exclusion criteria are selected to minimise treatment related mortality, especially from the conditioning regimen, by defining severe organ-based disease that might preclude HSCT.

We explored morbidity and mortality in a cohort of SSc patients that fulfil the eligibility criteria for one of those trials (ASTIS) but who have been treated with standard immunosuppression.

Methods: Patients were identified from a cohort of 398 incident SSc cases with disease onset between 1995 and 1999, using ASTIS trial inclusion criteria (age 16–65 years; diffuse cutaneous (dc)SSc with disease duration ≤ 4 year *plus* modified Rodnan skin score (mRss) ≥ 15 *plus* either respiratory, renal or cardiac involvement *or* dcSSc with disease duration ≤ 2 years *plus* mRss ≥ 20 *plus* ESR > 25mm/1st h and/or Hb < 11g/dL) and exclusion criteria, relating to severe organ disease (respiratory, renal or cardiac) and malignancy.

Results: Of the 146 dcSSc cases, 87 fulfilled the inclusion and 66 satisfied both inclusion and exclusion criteria for the ASTIS trial. The final group was 82% female and 82% Caucasian. At the time patients fulfilled the trial eligibility criteria, mean age was 47 (range 17–65) years and disease duration was 20 months (range 1–44). Mean mRss was 30 (range 15–54), 23 (35%) of the patients carried anti-topoisomerase I antibody, 11 (17%) anti-RNA polymerase antibody and 4 (6%) anti-U3RNP antibody. Smoking status was known for 57 of the patients - 21% were current, 21% past and 58% were non-smokers.

Pulmonary fibrosis (PF), confirmed by high resolution CT was present in 55 (83%) of the patients, scleroderma renal crisis (SRC) in 2 patients (3%) and cardiac SSc in 5 patients (7.5%). Cumulative incidence of severe organ disease at 5 and 10 years of follow-up were 44% and 53% for clinically significant PF, 5% and 15% for PH, 5% and 7% for SRC and 13% for cardiac SSc.

Survival among the 66 patients was 95% at 2, 89% at 5 and 72% at 10 years. Survival among patients with present or past smoke exposure was marginally worse (87% at 5 and 74% at 10 years) compared to non-smokers (97% at 5 and 81% at 10 years), but difference was not significant. We also analysed all 87 patients who fulfilled the inclusion criteria only, not excluding those with severe organ disease or malignancy and survival among those was marginally worse (86% at 5 years and 68% at 10 years) confirming that the more severe cases that would be excluded from HSCT protocols do indeed have a worse outcome.

Conclusion: Our findings demonstrate that survival of cases that would have been eligible for ASTIS trial is substantially better than might have been predicted historically, especially when excluding patients with severe organ disease that are not suitable for HSCT. This must be taken into account when long-term outcomes for trials such as ASTIS are considered.

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1717

Autologous Lipostructure in the Treatment of Fibrotic Perioral Changes in Systemic Sclerosis: A Pilot Study. Nicoletta Del Papa[1], Fabio Caviggioli[2], Domenico Sambataro[1], Eleonora Zaccara[1], Gabriele Di Luca[1], Valeriano Vinci[2] and Marco Klinger[3]. [1]G. Pini Hospital, Milano, Italy, [2]UOC Chirurgia Plastica, Multimedica Holding SpA, Università degli Studi di Milano, Milano, Italy, [3]Istituto Clinico Humanitas, Università degli Studi di Milano;, Milano, Italy

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by varying degree of fibrosis in skin and other tissues. Therapeutic options for fibrotic changes are very limited. Particularly aesthetic and facial dysfunctions are followed by important oral and facial manifestations with loss of skin folds around mouth, thinned and rigid lips and tongue rigidity. Limitation of mouth opening leads to deterioration in dental health and decreases the quality of life in SSc patients.

We performed a prospective pilot study to evaluate whether the autologous fat administration in SSc patients can improve the functional limitations related to the impairment of the perioral sclerotic tissue.

Methods: 20 patients with the diffuse form of SSc (mean age + SD $34.5+15$ yrs and disease duration of $11+10$ yrs) were treated by topical perioral administration of autologous fat graft. All the patients had perioral skin fibrotic changes with limited opening of the mouth ($< 50mm$) and limited accessibility to the oral cavity. Lipofilling was performed according to the Coleman tecnique, with scar release and implantation into parallel tunnels on multiple layers under the scars. A volume of 5 to 7 cc was injected using an 18-gauge needle. Follow-up was performed at 1, 3 and 6 months postoperatively by evaluating measure of inter-incisal distance and dermal thickness by high frequency ultrasound (US). A pre-treatment and 24 week post-treatment evaluation of microcirculatory abnormalities was made using labial video capillaroscopy and skin biopsy.

Results: All patients made good postoperative recovery without major complications. Sixteen of 20 patients had an immediate subjective improvement of their skin stiffness obviously attributable to release of severe scar contractures. One month after lipofilling, the median measure of inter-incisal distance was significantly increased in comparison with the score before treatment (p=0.038). Three and 6 months after treatment, the median measures were increased further (p<0.02). US evaluations showed that skin thickness resulted significantly lower after treatment (p<0.001). Four patients underwent two lipofilling sessions because of improvement with the first lipofilling but had remaining sclerotic perioral areas. Interestingly 2 patients reporting trigeminal neuropathy, showed the complete resolution of painful syndrome. Finally, labial capillaroscopy of treated patients showed significant improvement in microvascular patterns after lipofilling in term of a more homogeneous capillary density, increased length and reduced diameter shapes. Skin capillary density measured by Hematoxylin Eosin and Safran staining showed upregulation of vessel number by 1.80-fold after lipostructure.

Conclusion: Our study suggest that fat grafting treatment of fibrotic perioral changes in SSc can provide immediate and long-lasting benefits in terms of both aesthetic and functional improvement, and should be considered as a component of comprehensive care. In addition, we provides evidences that adipose tissue graft has the potential to favour neovascularization in SSc. The cellular and/or tissue mechanisms underlying these changes need further investigation.

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1718

Cost Effectiveness of Nurse-Led Care for People with Rheumatoid Arthritis: A Multicentre RCT. Mwidimi Ndosi[1], Martyn Lewis[2], Claire Hale[1], Howard Bird[1], Sarah Ryan[2], Helen Quinn[1], Elizabeth McIvor[3], Julia Taylor[4], Gail Burbage[5], Deborah Bond[6], Jo White[7], Debbie Chagadama[8], Sandra Green[9], Lesley Kay[10], Adrian V. Pace[11], Victoria Bejarano[12], Paul Emery[13] and Jackie Hill[1]. [1]University of Leeds, Leeds, United Kingdom, [2]Keele University, Staffordshire, United Kingdom, [3]Stobhill Hospital, Glasgow, UK, Glasgow, United Kingdom, [4]Poole Hospital NHS Trust, Poole, United Kingdom, [5]King's Mill Hospital, Mansfield, United Kingdom, [6]Queen Elizabeth Hospital King's Lynn, King's Lynn, United Kingdom, [7]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8]Royal London Hospital, London, United Kingdom, [9]Weston General Hospital, Weston-Super-Mare, United Kingdom, [10]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [11]Russells Hall Hospital, Dudley, United Kingdom, [12]Barnsley Hospital, Barnsley, United Kingdom, [13]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom

Background/Purpose: Despite the establishment of the innovative rheumatology nurse-led clinics (NLC) in the UK, the evidence of their cost-effectiveness is unknown. This study aimed at determining the cost effectiveness of NLC in patients with rheumatoid arthritis (RA).

Methods: This was a 10-centre, RCT where patients were randomized to either NLC or rheumatologist-led clinic (RLC). Adults with both stable and active RA were recruited. The interventions were delivered by 9 clinical nurse specialists (Mdn experience = 10 years) and 10 rheumatologists (Mdn experience = 9 years).

The primary outcome was the average change (from baseline) in disease activity score (DAS28) assessed at weeks 13, 26, 39 & 52. The EQ-5D was used to derive Quality-of-Life-Adjusted-Year (QALY) utility values.

Mean differences (MD) between the groups were estimated using linear models controlling for baseline covariates following per-protocol (PP) and intention-to-treat (ITT) strategies. The economic evaluation jointly estimated cost relative to quality adjusted life years (QALYs) and DAS28. Only ITT results are reported here: missing data being accounted through multiple imputation. Joint parameterization was achieved via bootstrap evaluation of the imputed datasets, and estimates plotted using cost-effectiveness planes and cost effectiveness acceptability curves.

Results: Demographics and baseline characteristics of patients under NLC (n = 91) were comparable to those under RLC (n = 90). They had a mean age (SD) of 58.5 (11.6), disease duration of 9.9 (10.7) years and 74% were female.

Average DAS28 change scores were higher in the NLC group (MD = −0.15, 95%CI = −0.45, 0.14) while average QALYs were higher in the RLC group (MD = 0.018, 95%CI = −0.037, 0.073).

Overall mean healthcare and National Health Service costs (UK-pounds) were higher in the RLC group compared to the NLC group (MD = 230, 95%CI = −406, 865 and MD = 223, 95%CI = −405, 850 respectively (approx. 360 US-dollars per person).

Figure 1 shows cost utility planes for healthcare costs. NLC was 'dominant' in respect of costs relative to change in DAS28 but not in respect of cost relative to QALY. Cost-effectiveness of NLC in relation to QALY is dependent on willingness-to-pay (WTP); this being the most likely cost-effective strategy for a WTP not in excess of ≤12,777 (i.e. 20,073 US-Dollars) for the healthcare perspective, and slightly less for the NHS perspective.

RLC = Rheumatologist-led clinic; NLC = Nurse-led clinic
Incremental health care cost / QALY / DAS28 change values denote bootstrap mean difference for the RLC group minus NLC group (adjusted for age, gender, centre, baseline DAS28 and baseline EQ-5D)
Percentages in the four quadrants (Graphs A&B) denote the percent of the total (5000) bootstrap cost-effect estimates that fell within each quadrant.

Figure 1. Economic evaluation (healthcare costs − ITT results).

Conclusion: This was the first economic evaluation of rheumatology NLC in the UK. While the findings indicate that NLC is likely to be a cost-efficient service under a cost-minimisation approach, we are not able to draw firm conclusions on cost-effectiveness given the variation in results between DAS28 and QALY.

1719

What Do Patients Put up with for the Benefit They Get From Methotrexate? Sandra M. Robinson[1], Peta S. Heslop[1] and David Walker[2]. [1]North Tyneside General Hospital, North Shields, United Kingdom, [2]Freeman Hospital, Newcastle Upon Tyne, United Kingdom

Background/Purpose: As with all effective drugs, Methotrexate (MTX) comes with a range of side effects. Some such as pneumonitis are severe enough to require the drug to be stopped. Others such as nausea are more about what a patient will tolerate. We were aware that many patients were tolerating side effects in order to take MTX. If the benefits outweigh the problem, then the medical advice would be to continue. This also applies to patients taking methotrexate in combination with TNFis where there is considerable advantage from taking the combination. For this reason there was little interest in exploring methotrexate "tolerability". However, there is now good evidence that Tocilizumab works as well alone as in combination with Methotrexate. This offers the possibility that some patients struggling with methotrexate may be better off on Tocilizumab monotherapy rather than a TNFi and their MTX. We were interested to quantify the tolerability problems of patients continuing on Methotrexate therapy.

Methods: 100 consecutive patients seen in outpatient clinics, who were taking a stable dose of MTX and planning to continue, were surveyed. A study sheet was completed seeking information on the effectiveness of the MTX, their concordance with treatment and any side effects they were getting. They were specifically asked about: nausea; fatigue; mouth ulcers and hair loss and asked to rate them on a VAS.

68 were female and 32 were male with an average age of 59 (24 – 84 yrs). 89 were on oral and 11 on subcutaneous injections. 75 patients were suffering from RA, 18 patients from psoriatic arthritis with 7 patients having other indications.

Results: Efficacy averaged 6.5 being similar in men and women (6.7 & 6.4). 56% complained of at least one side effect. The side effects and the judged severity are shown in the table. VAS scores for severity averaged in the range 3.5 to 5. Sex differences were apparent. Men were less likely to complain of problems, in particular hair loss and nausea. Whether this relates to tolerance or intolerance is not clear. Only 10% "forgot" to take their MTX for an average of 2 weeks in a year. 5 chose not to take an average of 2.6 doses in a year. These patients had higher intensity of side effects (6–9.5).

	Nausea*	Mouth Ulcers	Hair Loss**	Fatigue	Other S/Es	Any Side Effect
WOMEN n=68	4.3 (±2.5) n=22 (32%)	4.3 (±2.9) n=18 (26%)	3.5 (±2.2) n=13 (19%)	5.0 (±1.9) n=17 (25%)	5.5 (±3.4) n=6	4.6 n=43 (63%)
MEN n=32	3.4 (±2.1) n=4 (13%)	2.7 (±2.0) n=9 (28%)	0.0 n=0 (0%)	4.3 (±0.8) n=3 (9%)	2.8 (±0.6) n=3	2.8 n=13 (41%)
TOTALS	n=26	n=27	n=13	n=20	n=9	n=56

Chi Test x^2
*p<0.05 **p<0.01

Conclusion: Patients are putting up with a lot of side effects, which are outweighed by the benefits of MTX for them. When a biologic is necessary to control their disease, some patients may be attracted by one that does not require combination with MTX.

1720

Cardiovascular Risk Management in Rheumatoid Arthritis Is Nurse Led Intervention Effective? Fiona Niddrie[1] and Gabor AC Major[2]. [1]Bone and Joint Institute; Royal Newcastle Centre, Newcastle, Australia, [2]Bone&Joint Institute; Royal Newcastle Centre, Newcastle, Australia

Background/Purpose: There is a recognised increase in the incidence of heart disease in patients with rheumatoid arthritis (RA)

Surveys of usual practice however frequently show a significant gap in the management of cardiovascular (CV) risk factors[1].

This study was undertaken with the aim of reviewing our experience and if a management gap was found, to see if this could be effectively and efficiently addressed by a nurse led initiative

Aim:

To identify the extent of awareness and management of CV risk factors in patients with RA attending a general rheumatology clinic

To explore the feasibility of a nurse led assessment programme and evaluate its effectiveness in managing CV risk

Methods: The medical records of all patients with RA were audited at the time of their scheduled review visit for the extent of CV risk assessment that had been completed and recorded by the treating rheumatologist in the previous 12 months.

Patients were then asked about their knowledge of CV risk and about assessments that had been undertaken through their family physician

A standard letter highlighting the increase in CV risk in RA together with the patient's CV risk factor assessment was then sent to the family physician, with recommendation to address any apparent deficiencies

Patients were seen again 6 months later and the completeness and effectiveness of CV risk management reviewed

Results: *Patient awareness* of the increased CV risk in RA was only 19%

Initial review showed that in the prior 12 months 86% of patients had had a blood pressure (BP) check; 31% had adequate serum lipid and 39% had glucose/HbA1c measurement; 42% had their weight and height recorded and 75% of smokers had received counselling

At the 6 month review of the first 150 patients all patients had had their BP checked. 79 (53%)were on active treatment. 17 had their treatment changed and 1 was newly started

Comprehensive assessment of lipids rose from 31% of patients to 60%; and for glucose/Hba1c from 39% to 62%. Two patients had treatment changes and one was newly started

Counselling of the 30 patients who smoked and the 103 with abnormal body mass index (BMI) resulted in 2 patients quitting smoking. 59 (39%) showed an improved BMI with 2 returning to ideal body weight

Average time per patient encounter was 26 mins at an estimated cost, excluding laboratory costs, of $21.03 AUS per patient encounter

Conclusion:

1 A significant gap in the routine management of CV risk factors was identified
2 Patient awareness of the increased risk of CV disease in RA is low
3 A nurse led intervention programme is feasible and effective in addressing the problems of CV risk factor management in patients with RA, but needs to be adequately resourced

Reference
1 Webster R J et al. MJA 2009; 191: 324–329

1721

Development of User-Focused Standards of Care for Rheumatoid Arthritis the www.Eumusc.Net Project - Work Package 5. Michaela Stoffer[1], Josef S. Smolen[2], Anthony D. Woolf[3], Tanja A. Stamm[4] and EUMUSC.net working group WP 5[5]. [1]Medical University of Vienna, A-1090 Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [3]Royal Cornwall Hospital, Truro Cornwall, United Kingdom, [4]Medical University of Vienna, Vienna, Austria, [5]Truro Cornwall, United Kingdom

Background/Purpose: The EUMUSC.net project facilitates cooperation between EU Member States and promotes a comprehensive European strategy to optimise musculoskeletal health.

The purpose of Work package 5, as a part of the EUMUSC.net project, was to develop evidence based and user-focused standards of care (SOC), for Rheumatoid Arthritis (RA).

Methods: A systematic review of international documents covering SOC for RA was conducted. National scientific societies, social leagues and health professional associations were contacted via the EULAR secretariat and asked to provide relevant documents. Documents concerning pharmacological and non-pharmacological interventions published after 2002 were included.

The obtained documents were evaluated based on the AGREE II criteria (www.agreetrust.org). All recommended methods to treat RA were extracted, as well as information on them and all recommendations given. Each of these methods was discussed in a consensus group meeting of 21 EUMUSC.net researchers and patient representatives from different countries regarding

priority and relevance in their home countries as well as possible interrelation with other methods. A scheme was developed with groups of interventions and formulated in a way that could be understood by users. To this end, conventional DMARDs, biological agents, NSAIDs, were grouped under pharmacological treatment. Giving up smoking, weight control and physical activity were grouped under Lifestyle Interventions.

Results: 49 types of therapies or other interventions, such as DMARDs, biological agents, exercise based-, activity based interventions, were extracted from the documents and could be grouped into seven types of interventions, namely Pharmacological Treatment, Monitoring, Lifestyle Interventions, Surgery, Education/Information/Self Management, Non-Pharmacological Treatment and Access to care.

From these data 16 user-focused standards of care were formulated.

SOC Table

Examples for the 16 Standards of Care

SOC 1	People with symploms of RA should have timely access (6 weeks) to a clinician/health professional competent in making a (differential) diagnosis.
SOC 3	People with RA should receive a treatment plan individually developed between them and their clinician.
SOC 5	People with RA should be fully assessed for symptoms, disease activity, damage, comorbidity and function at diagnosis; these assessments should also be done annually; if disease is not within target, clinical assessment should be done at least 3 monthly (all clinical variables) and possibly more frequently upon significant worsening.
SOC 6	People with RA should have rapid access to care when they experience significant worsening of the disease.
SOC 7	People with RA should be treated with a disease modifying anti-rheumatic drug as soon as the diagnosis is made.

Conclusion: The lay version of the user-focused SOC will be available in all 23 official languages of the European Union for the information of people with RA across all member states. This work should contribute to the harmonization of RA treatment in Europe.

1722

Exploring How Patients with Rheumatoid Arthritis Use a Methotrexate Decision Aid for Making Treatment Choices. Linda C. Li[1], Anne F. Townsend[2], Paul M. Adam[3], Catherine L. Backman[1], Sydney Brooks[4], Gwen A. Ellert[5], Allyson Jones[6], Otto Kamensek[2], Cheryl Koehn[7], Diane Lacaille[2], Jenny Leese[8], Colleen Maloney[2], Elaine Yacyshyn[6], Charlene Yousefi[2] and Dawn Stacey[9]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Vancouver, BC, [3]Mary Pack Arthritis Centre, Vancouver, BC, [4]The Arthritis Society, Ontario Division, Toronto, [5]Trelle Enterprises Inc, Vancouver, BC, [6]University of Alberta, Edmonton, AB, [7]Vancouver, BC, [8]Arthritis Research Centre, Vancouver, BC, [9]University of Ottawa, Ottawa, ON

Background/Purpose: For patients with rheumatoid arthritis (RA), making treatment decisions can be overwhelming. The literature describes a sense of ambivalence among patients with chronic diseases toward medication use. For people considering methotrexate (MTX) for RA, we have developed a web-based decision aid called ANSWER. It consists of six animated patient stories and narrated information on the evidence of MTX for RA, and questionnaires to clarify individuals' treatment preferences. ANSWER asks patients to consider two options: 1) take MTX as prescribed, or 2) discuss options other than MTX with their doctors. At the end of the program, it produces a one-page summary with the patient's preferred treatment choices and questions, which can be presented to the doctor at the next medical visit. The current study aimed to understand patients' experiences with this new MTX decision aid.

Methods: This qualitative study was conducted within a proof-of-concept study on the ANSWER. Individuals were recruited from rheumatologists' clinics, patient groups and social networking sites. Eligible participants were those who had been diagnosed with RA, had been prescribed MTX but were unsure about starting it, and with access to the internet. Of the 30 participants enrolled, 11 were randomly selected to participate in an in-depth telephone interview on 3 broad topics: 1) their experience with the ANSWER, 2) their use of the Internet for health information, and 3) their views on disseminating

the ANSWER to others with RA. We conducted thematic content analysis to understand their experiences.

Results: Eight women and 3 men, aged 31 to 65 years, were interviewed. All participants were MTX naïve at the time of enrolment, with disease duration from less than 1 week to 16 years. Of the 11 participants, 7 were able to make a decision after using ANSWER, and 4 remained unsure. Our analysis identified 3 main themes: 1) *Seeking confirmation*: regardless of their prior level of knowledge on RA and MTX, participants constantly compared what they learnt from ANSWER and sought confirmation with their own knowledge, even some of which was inaccurate. 2) *Amplifying reluctance*: while using ANSWER, participants' doubts about using MTX increased when they encountered information that did not align with their own experience with the disease. 3) *Clarifying thoughts*: By completing the ANSWER's preference clarification questionnaire, some participants were able to reach the 'best option' for them. Several participants commented that ANSWER legitimized the practice of asking questions during medical visits and advocating for themselves.

Conclusion: Our preliminary findings highlight the power of patients' prior knowledge and experiences with RA on how they approach the information presented in a decision aid. This suggests that decision aids should address myths about RA, in addition to presenting the evidence of treatment options. Moreover, as the ANSWER serves only to initiate the discussion between patients and their doctors about MTX, further strategies are needed to support ongoing patient-doctor communication during medical visits.

1723

The Development of the Rheumatoid Arthritis Patient Priorities in Pharmacological Intervention Outcome Measures. Tessa Sanderson[1], John R. Kirwan[2], Marianne Morris[1], Jon Pollock[1], Robert Noddings[2], Anne Watts[2] and Sarah Hewlett[1]. [1]University of the West of England, Bristol, United Kingdom, [2]Bristol Royal Infirmary, Bristol, United Kingdom

Background/Purpose: Previous research developed a set of 8 priority treatment outcomes generated by patients to complement the professionally developed ACR core set for RA. These outcomes were pain, activities of daily living (ADL), visible joint damage, mobility, life enjoyment, independence, fatigue, and valued activities.[1] This abstract reports face validity in existing instruments (Phase 1), and the construction of new Numerical Rating Scales (NRS) where validated measures did not exist (Phase 2).

Methods: Phase 1: Two consultation meetings with patient research partners (N=18) were held. Patient research partners discussed and voted on their preferences for scales identified in the literature for each of the 8 priorities, except VJD (no scales could be found).

Phase 2: Two focus groups with RA patients (N=8) were facilitated. Draft scales constructed from the Phase 1 discussions were used. Feedback on the stem question, time frame, anchors and layout was recorded and transcribed verbatim.

Results: Existing NRS for pain[2], ADL[2] and fatigue[3] were voted as acceptable. However, patient research partners strongly recommended that severity of, importance of and ability to cope with each priority outcome be assessed, resulting in 24 questions (21 new). Visual joint damage created the most discussion, with concerns that the word 'damage' would be upsetting to newly diagnosed patients. PRP understood 'mobility' diversely, but a consensus was reached that it should focus on 'getting around outside the home'. In relation to valued activities, patients stressed that the stem question should focus on current activities, not those valued pre-diagnosis: "It needs to say 'currently'. You know, if you're asking about how a drug changes your life over four months, or six months or whatever it is, you know, it's kind of what your current expectation, how that's changed" (PE, p.30). Feedback on layout included making the questions in each domain visually separate using shaded boxes, underlining key words and putting the instructions in bullet points.

Conclusion: Existing instruments did not capture the patient perspective in 5 of the 8 priority outcomes. User involvement has been essential in developing the new patient-reported outcomes. An ongoing study will test the sensitivity of the 24 RAPP-PI NRS compared to the Disease Activity Score.

[1]Sanderson et al. AC&R 2010;62(5):647–656. [2]Gossec et al. ARD 2011;70:935–942. [3]Nicklin et al. AC&R 2010;62(11):1559–1568.

1724

Pandemic Influenza Immunization in Primary Antiphospholipid Syndrome (PAPS): A Trigger to Autoantibody Production? Danielle M. Medeiros[1], Cleonice Bueno[1], Ana Cristina M. Ribeiro[1], Ana L. G. Calich[1], Karina Rossi Bonfiglioli[1], Vilma S. Viana[1], Jozelio F. Carvalho[1], Clovis Artur Silva[2] and Eloisa Bonfá[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: There are scarce data suggesting that pandemic influenza vaccination may induce antiphospholipid (APL) autoantibodies in inflammatory rheumatic diseases, particularly in systemic lupus erythematosus patients. However, there is no study evaluating the APL autoantibodies induction in primary antiphospholipid syndrome (PAPS) patients. The objective was to perform short and long-term evaluations of a large panel of APL autoantibodies following pandemic influenza A/H1N1 non-adjuvant vaccine in PAPS patients and healthy controls. Lupus specific antibodies were also investigated in these patients.

Methods: Forty-five PAPS patients (Sapporo criteria) and 33 healthy controls were vaccinated with monovalent, inactivated H1N1 vaccine (Butantan Institute/Sanofi Pasteur, São Paulo, Brazil). They were prospectively assessed at pre-vaccination, 3 weeks and 6 months after vaccination. APL autoantibodies were determined by an enzyme-linked immunosorbent assay (ELISA) and included: anti-cardiolipin (aCL) IgG/IgM and anti-β2GPI IgG/IgM antibodies (Inova Diagnostics, USA); anti-annexin V IgG/IgM, anti-phosphatidyl serine IgG/IgM and anti-prothrombin IgG/IgM (Orgentec Diagnostica, Germany). Anti-Sm was determined by ELISA (Inova Diagnostics, USA) and anti-dsDNA by indirect immunfluorescence. Arterial and venous thromboses were also clinically assessed. The statistical analyses were carried out with qui square test, McNemar′s test and one-way repeated measures analysis of variance (ANOVA).

Results: Pre-vaccination frequency of at least one APL antibody was significantly higher in PAPS patients compared to controls (58% vs. 21%, p=0.003). The overall frequencies of APL antibody at pre-vaccination, 3 weeks and 6 months after immunization remained unchanged in patients (p=0.89) and controls (p=0.83). Further analysis of each evaluated antibody in PAPS revealed that their percentages at pre-vaccination and after 3 weeks and 6 months were also comparable (p>0.05): aCL IgG (42%, 38% and 42%), aCL IgM (22%, 20% and 24%), anti-β2GPI IgG (22%, 22% and 20%), anti-β2GPI IgM (15%, 15% and 18%), anti-annexin V IgG (4.5%, 4.5% and 2.5%), anti-annexin V IgM (uniformly negative), anti-phosphatidyl serine IgG (38%, 35% and 38%), anti-phosphatidyl serine IgM (15%, 13% and 13%), anti-prothrombin IgG (20%, 15% and 18%) and anti-prothrombin IgM (2.5%, 2.5% and 2.5%). The same pattern was observed for the control group (p>0.05). At 3 weeks, 2 PAPS patients developed a new but transient APL antibody (moderate titer aCL IgG and IgM) whereas at 6 months, new APL antibodies were observed in 6 PAPS patients: 3 moderate titer aCL IgM, 1 moderate anti-β2GPI IgM, 1 low anti-phosphatidyl serine IgG and 1 low anti-prothrombin IgG. Fluctuations of antibody levels were not detected for any evaluated antibody (p>0.05). Of note, anti-Sm and anti-dsDNA autoantibodies were consistently negative during all evaluations. No new arterial or venous thrombosis events occurred during the study period.

Conclusion: This was the first study to demonstrate that pandemic non-adjuvant influenza A/H1N1 in PAPS patients does not trigger a change in APL antibody profile or induce lupus specific autoantibodies.

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1725

ANTI-Factor Xa Antibodies ARE Significantly Increased in Patients with Systemic LUPUS Erythematosus and Antiphospholipid Syndrome. Bahar Artim-Esen, Charis Pericleous, Ian Mackie, Yiannis Ioannou, Anisur Rahman, David A. Isenberg and Ian Giles. University College London, London, United Kingdom

Background/Purpose: Increased levels of antibodies against different serine proteases (SP) have been identified in patients with the Antiphospholipid Syndrome (APS) compared with healthy controls. These anti-SP antibodies have been shown to alter the function of these coagulation factors, hence may be important in the pathogenesis of thrombotic manifestations of the APS. Few studies however, have examined the prevalence of anti-SP antibodies in patients with other autoimmune rheumatic disease (ARD). Previously, we found raised levels of IgG against the SP - thrombin (Thr) in patients with APS as well as patients with systemic lupus erythematosus (SLE) who lacked APS compared with healthy controls. Therefore, in this study, we examined the prevalence and specificity of anti-SP antibodies in patients with APS compared with other ARD and healthy controls.

Methods: Serum was obtained from 265 patients (at University College London Hospital) with: APS, n=59; SLE and no APS (SLE/APS-), n=106; rheumatoid arthritis (RA), n=30; Sjögren's syndrome (SS), n=25, myositis (Myo), n=23; systemic sclerosis (SSc), n=22; and 40 healthy controls (HC). Of the patients with APS: 34 had primary APS and 25 had SLE/APS; whilst 46 had thrombotic and 13 non-thrombotic APS. In patients with SLE/APS-57 were aPL positve (SLE/aPL+) and 49 aPL negative (SLE/aPL-). All other ARD and HC were aPL negative. Serum was tested for the presence of IgG directed against: - Thr; Factor Xa (FXa); Factor VIIa (FVIIa); and phosphatidylserine (PS)/FXa complexes by ELISA. Results were expressed as percentage of binding compared with a positive serum control and a positive value was defined as being $\geq$ 3SD above the mean of healthy controls.

Results: IgG anti-FXa antibodies were only found in patients with SLE (n=52, 49.1%) and APS (n=20, 34.5%) whilst healthy and all other disease control groups completely (n=0) lacked these IgG (p<0.05). IgG anti-Thr antibodies were also found in patients with APS (n=21,36.2%) and SLE/APS- (n=59, 55.7%) more frequently than in HC (n=2, 5%, p<0.05). In contrast, to anti-FXa IgG the detection of anti-Thr IgG lacked specificity as they were also found in patients with RA (n=9, 30%), SS (n=10, 40%), Myo (n=11, 47.8%) and SSc (n=6, 27.3%) at frequencies which were not significantly different compared with APS but significantly increased in SLE/APS- compared with RA (p<0.05) and SSc (p<0.01). IgG against anti-PS/FXa complexes were found more frequently (p<0.05) only in patients with SLE/APS- (n=35, 33%) compared with APS (n=8, 13.8%), SS (n=1, 4%), Myo (n=1, 4.3%), SSc (n=0) and HC (n=0) groups. There were no significant correlations between frequency of any of the anti-SP antibodies tested or with aPL positivity. Furthermore, the prevalence of anti-SP IgG in the APS group was not specific to patients with SLE/APS.

Conclusion: Anti-Thr, anti-FVIIa, anti-FXa and anti-PS/FXa IgG are not specific to patients with APS. Our finding that anti-FXa IgG were unique to patients with APS and SLE/APS- may indicate that these IgG interfere with the inflammatory rather than coagulant effects of FXa. Further experiments are now underway to clarify the precise pathological and diagnostic significance of anti-FXa IgG in these patients.

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1726

Lack of Correlation Between Mannose-Binding Lectin Gene Polymorphisms and the Thickness of the Carotid Artery Intima-Media (IMT) in Primary Antiphspholipid Syndrome. Antonio Barrera-Cruz[1], Luis J. Jara-Quezada[2], Gabriela Medina[3] and Miguel A. Saavedra Salinas[4]. [1]Instituto Mexicano del Seguro Social, México, Mexico, [2]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico, [3]Hospital de Especialidades Centro Medico Nacional La Raza, Mexico City, Mexico, [4]Hospital de Especialidades, Mexico City, Mexico

Background/Purpose: Serum mannose-binding lectin (MBL) is a recognition molecule of the lectin pathway of complement with antimicrobial and anti-inflammatory actions. Several polymorphisms have been reported for the MBL2 gene. These variants are associated with low MBL serum concentration and are risk factors of infectious diseases, atherosclerosis and autoimmune diseases (1).Systemic lupus erythematosus patients with associated antiphospholipid syndrome have a higher prevalence of MBL-deficient

genotypes. (2). Patients with primary antiphospholipid syndrome (PAPS) have carotid intima-media thickness, a marker of accelerated atherosclerosis. However, the role of MBL-deficient genotypes in PAPS is unclear.

Objectives: To investigate the prevalence of MBL-deficient genotypes in PAPS and its association with carotid intimamedia thickness (IMT).

Methods: Blood samples were obtained from 48 patients with PAPS and matched with 111 healthy controls by age and gender, in a relation 1:2. Demographic, clinical data, cardiovascular risk factors and antibody profile were recorded. Total DNA was extracted from total blood with DNA isolation kit for mammalian blood (ROCHE). PCR-RFLP (Restriction Fragment Length Polymorphisms) reactions were performed on 50 ng of genomic DNA. MBL exon 1 PCR products were incubated with Mbo II, Ban I at 37°C, and Mwo I at 60°C for 1 h. MBL promoter gene region PCR products were incubated with Drd I and Btg I overnight at 37°C. The products were analyzed by electrophoresis using silver staining of polyacrylamide gel electrophoresis. Colour Doppler with high resolution B mode carotid ultrasonography was performed in patients to measure intima-media thickness (IMT).

Results:

Table 1. Descriptive statistics of population

Variables	PAPS (n=48)	Controls (n=111)	p
Female gender,%	85.4%	82%	0.65
Age, y (mean± SD)	44.4 ± 11.50	42.64 ± 9.87	0.31
Exón region			
AA, C54,%	72.9%	73.9%	0.52
AD, C52,%	27.1%	26.1%	0.52
Promotor region			
LX/LY	22.9%	9%	*0.02
LY/LY	77.1%	91%	*0.02
LYA/A	54.2%	66.7%	0.15
LXA/A	18.8%	7.2%	*0.04
LXA/D	4.2%	.9%	0.21
LYA/C	0	0	–
LYA/D	22.9%	25.9%	0.84

*Statistically significant p < 0.05

Table 2. Correlation between MBL-deficient genotypes and carotid IMT in PAPS

Promotor region	ACC right p Sig. (2-tailed)	Correlation Coefficient	ACC left p Sig. (2-tailed)	Correlation Coefficient
LYA/A	.056	.277	.977	.004
LXA/A	.326	−.145	.957	−.008
LXA/D	.671	−.063	.357	.134
LYA/D	.264	−.164	.674	−.061

Conclusion: This study shows a high prevalence of MBL-deficient genotypes in the promotor region of the MBL2 gene (LX/LY, LXA/A) in patients with PAPS. However, MBL variant alleles were not significantly associated with carotid IMT. The accelerated atherosclerosis in PAPS could be consequence of genetic, immunological, and environmental risk factors. A prospective study is necessary in order to confirm these results.

Disclosure: A. Barrera-Cruz, None; **L. J. Jara-Quezada**, None; **G. Medina**, None; **M. A. Saavedra Salinas**, None.

1727

Affinity Purified Antibodies Directed to Domain I of β2GPI Are Pathogenic in a Mouse Model of Thrombosis. Charis Pericleous[1], Patricia Ruiz-Limon[2], Zurina Romay-Penabad[2], Ana Laura Carrera Marin[2], Acely Garza-Garcia[3], Lucy Murfitt[3], Paul C. Driscoll[4], Ian Giles[1], Yiannis Ioannou[1], Anisur Rahman[1] and Silvia S. Pierangeli[2]. [1]University College London, London, United Kingdom, [2]University of Texas Medical Branch, Galveston, TX, [3]MRC National Institute of Medical Research, London, London, United Kingdom, [4]MRC National Institute of Medical Research, London, United Kingdom

Background/Purpose: Circulating IgG antiphospholipid antibodies (aPL) against β2-glycoprotein I (aβ2GPI) are a serological hallmark for diagnosis of the antiphospholipid syndrome (APS). We and other groups have shown that aPL targeting domain I (DI) of β2GPI (aDI) are APS-specific, predominantly correlating with (venous) thrombosis. We have also demonstrated that recombinant DI inhibits aPL-induced thrombosis in a mouse microcirculation model. To date however, no study has confirmed a direct pathogenic link between aDI and features of the APS. We have now employed the same mouse model to determine the thrombogenic potential of affinity purified polyclonal aDI IgG derived from APS sera.

Methods: Serum from one female APS patient was incubated with his-tagged DI coupled to nickel beads to adsorb aDI antibodies. The bead-serum mix was then spun, serum re-collected and antibodies bound to DI-coupled beads were eluted. IgG from re-collected serum (aDI-poor) and eluted fractions (aDI-rich) was then obtained by protein G purification. Serum and IgG fractions (100mg/mL) were tested for aCL (GPLU), aβ2GPI (GBU, in-house calibrator) and aDI (GDIU, in-house calibrator) activity.

For in vivo experiments, CD1 mice weighing between 32–39g were injected twice with $100\mu g/mL$ aDI-poor or aDI-rich IgG, or IgG from healthy volunteers (NHS-IgG) as a control (4–5 animals per group). 72h after the first injection, the size (μm^2) of induced thrombi in the femoral vein was determined (Circulation 1996;94:1746–1751). Tissue factor (TF) activity (pM/mg.mL^{-1}protein) was determined in homogenates of pooled carotid arteries and peritoneal macrophages using a chromogenic assay. Mouse serum was obtained on the day of surgery and tested for the presence of circulating whole human IgG.

Results: Purified aDI-rich IgG displayed high aCL (90GPLU), aβ2GPI (95GBU) and aDI (50GDIU) activity whilst aDI-poor IgG displayed high aCL (90GPLU) but reduced aβ2GPI (47GBU) and aDI (17GDIU) activity. NHS-IgG was negative in all assays. aDI-rich IgG induced significantly larger thrombi compared to aDI-poor and NHS-IgG (p<0.001). In addition, aDI-rich IgG induced the greatest increase in TF activity in carotids (1.4 fold) and peritoneal macrophages (3.3 fold) compared to NHS-IgG. In contrast, aDI-poor IgG induced smaller thrombi and less macrophage TF activity compared to aDI-rich IgG and did not increase carotid TF activity above that of NHS-IgG (Table 1).

Table 1. Effects of polyclonal IgG in an in vivo model of thrombosis

Mice/ treatment	Thrombus size (μm^2)	TF activity (†) carotids (pM/mg.mL^{-1}protein)	TF activity (†) peritoneal macrophages (pM/mg.mL^{-1}protein)
NHS-IgG	525 ± 136	149.8 ± 21.1	30.6 ± 4.1
aDI-poor	953 ± 258 *	134.9 ± 29.1	55.3 ± 10.1
aDI-rich	2076 ± 511**	212.9 ± 49.7	101.2 ± 14.1

(*) *Statistically significant <0.001 to NHS-IgG*
(**) *Statistically significant <0.001 to NHS-IgG and aDI-poor*
(†) *mean of two measurements*

Conclusion: This is the first study to directly demonstrate the thrombogenic potential of affinity purified aDI IgG in vivo. Despite aDI-poor IgG retaining aCL and, to a lesser extent, aβ2GPI activity, significantly larger thrombi and elevated TF activity were induced with aDI-rich IgG. Our findings support the concept that although circulating aPL recognizing different domains of b2GPI can be pathogenic, the major population that drive thrombosis are directed against DI.

Disclosure: C. Pericleous, None; **P. Ruiz-Limon**, None; **Z. Romay-Penabad**, None; **A. L. Carrera Marin**, None; **A. Garza-Garcia**, None; **L. Murfitt**, None; **P. C. Driscoll**, None; **I. Giles**, None; **Y. Ioannou**, None; **A. Rahman**, None; **S. S. Pierangeli**, None.

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Purified IgG From Antiphospholipid Syndrome Patients with Pregnancy Morbidity Alone Inhibit Trophoblast Migration and Activate a TLR4 MyD88 Independent Pathway. Katie Poulton, Vera Ripoll, Charis Pericleous, Yiannis Ioannou, Anisur Rahman and Ian Giles. University College London, London, United Kingdom

Background/Purpose: Patients with the Antiphospholipid Syndrome (APS) have circulating antiphospholipid antibodies which cause vascular thrombosis (VT) and/or pregnancy morbidity (PM). Previously we have shown that IgG isolated from patients with APS-VT alone caused activation of p38MAPK and NFκB signalling pathways and up-regulation of tissue factor activity in monocytes. These effects were not seen with IgG from patients with APS-PM alone or healthy controls. TF up-regulation caused by the APS-VT samples was reduced by p38MAPK, NFκB, and TLR4 inhibitors, thus implicating a TLR4-MyD88 dependent signalling mechanism (J Immunol, 2010;184:6622). Therefore, in this study we examine whether IgG isolated from patients with different manifestations of the APS have differential effects upon similar pathways leading to activation and migration of trophoblast cells which are more relevant to PM.

Methods: IgG was isolated by protein G purification from serum of 5 patients with APS and VT alone (IgG-VT), 5 patients with APS and PM alone (IgG-PM) and 5 healthy controls. To investigate the intracellular signalling

pathways induced by these IgG, a single sample for each of the 3 groups was produced by pooling IgG from the 5 subjects in that group. A human first trimester trophoblast (HTR-8) cell line was incubated with 100 μg/mL IgG from each group. Time course experiments were then performed and mRNA expression of TLR4 and related adaptor protein TRIF was measured using quantitative PCR. The activation of p38MAPK, ERK and NFκB signalling pathways was also examined in cell extracts by immunoblot. Trophoblast migration was determined using a collagen-based cell invasion assay.

Results: Only IgG-PM increased TLR4 mRNA expression (at 6 and 24 hours) and TLR4 (non-MyD88 dependent) adaptor protein TRIF mRNA levels (at 6 hours) compared with IgG-VT and healthy control IgG in HTR-8 cells. None of the APS (VT or PM)-IgG however, increased phosphorylation of TLR4-MyD88 dependent p38MAPK, ERK or NFκB signalling pathways at any (15 minutes, 2 and 6 hour) time points measured in these cells compared with control IgG. IgG-PM caused the greatest inhibition of trophoblast (HTR-8) migration (with 27% inhibition) compared to untreated controls at 48 hours. In contrast, IgG-VT caused minimal (8%) inhibition of trophoblast migration comparable to levels seen with healthy control IgG.

Conclusion: IgG isolated from patients with APS-related PM preferentially inhibit trophoblast cell migration compared with IgG from patients with VT alone. IgG isolated from patients with APS-related PM also activate trophoblast cells via a TLR4 MyD88 independent pathway. This is the reverse of our previous finding in monocytes that were only activated by APS-IgG from patients with VT and not from those with PM. Further experiments are now required to characterise the mechanistic and prognostic implications of these findings.

Disclosure: K. Poulton, None; **V. Ripoll**, None; **C. Pericleous**, None; **Y. Ioannou**, None; **A. Rahman**, None; **I. Giles**, None.

1729

Ribophorin II Is Involved in the Tissue Factor Expression Mediated by Phosphatidylserine-Dependent Antiprothrombin Antibody On Monocytes.
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Background/Purpose: Antiphospholipid syndrome (APS) is characterized by thrombosis and the presence of antiphospholipid antibodies (aPL). Tissue factor (TF), the major initiator of the extrinsic coagulation system, is induced on monocytes by aPL in vitro. Phosphatidylserine-dependent antiprothrombin antibody (aPS/PT) recognized the phophatidylserin/prothrombin (PS/PT) complex, and is highly associated with APS. We have previously reported that 231D, a mouse monoclonal aPS/PT, induced TF expression on monocytes. However, the cell surface receptor for the binding of PS/PT complex leading to the activation of cell signaling pathways and TF expression is unknown.To investigate the membrane protein involved in the binding of Prothrombin (PT) and aPS/PT to cell surface and the induction of TF expression on monocytes.

Methods: 1) Unknown PT binding membrane protein on monocyte was screened by a proteomics technique using immunoaffinity chromatography and mass spectrometric analysis. FLAG-tagged human PT (FLAG-PT) was constructed and the expression vector encoding FLAG-PT was transfected into HEK293T cells. The expression of full length FLAG-PT in the culture supernatant was evaluated by immunoblotting. RAW 264.7 cells with FLAG-PT were incubated and applied for affinity chromatography with anti-FLAG antibody-conjugated Sepharose beads. The purified fraction was subjected to SDS-PAGE and detected with Coomassie Brilliant Blue staining. Immunopurified proteins were analyzed by an online-nano LC-MS/MS. Obtained MS/MS data were searched against nrNCBI database MASCOT algorithm. 2) The binding between PT and Ribophorin II (RPN2) was analyzed by enzyme-linked immunosorbent assay (ELISA) with purified His-tagged human RPN2 (His-RPN2). 3) RPN2 expression on cell surface of CD14 positive cells and RAW 264.7 cells was analyzed by flowcytometeric analysis. 4) To elucidate the role of RPN2 in TF mRNA expression, RAW 264.7 cells treated with RPN2 small interfering RNA (siRNA) expression and TF mRNA was determined by real-time PCR.

Results: 1) Amoung many proteins confirmed in the spectrometry, RPN2 a part of an N-oligosaccharyl transferase complex was identified as the candidate molecule to be the membrane protein involved in the PT binding to

cell surface. 2) The binding between PT and His-RPN2 was confirmed by ELISA. 3) Flowcytometoric analysis showed the expression of RPN2 on monocyte cell surface. 4) Treated cells with RPN2 siRNA showed significantly reduction of the TF expression mediated by PT and 231D (Fig).
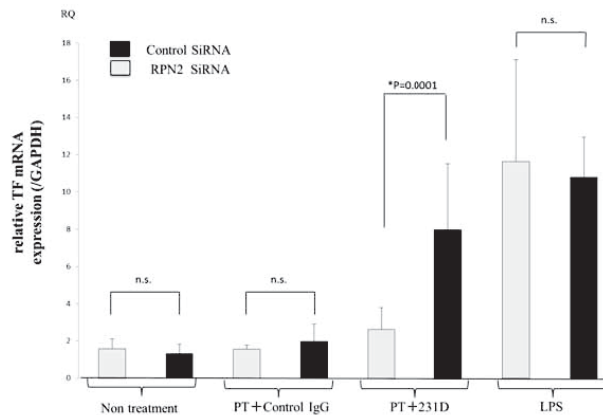
Fig. RAW264.7 cells transfected with RPN2-siRNA were incubated with monoclonal aPS/PT (231D). TF mRNA was quantitated by Real Time PCR.

Conclusion: RPN2 was detected as a major PT binding molecule by proteomics analysis. RPN2 may be involved in the pathophysiology of thrombosis in patients with APS.

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1730

Antiphosphatidylethanolamine Is Not Associated with Thrombosis or Pregnancy Loss in Systemic Lupus Erythematosus.
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Background/Purpose: Phosphatidylethanolamine, a zwitterionic phospholipid, is a major component of the cell plasma membrane. Phosphatidylethanolamine exerts both anticoagulant and procoagulant activities in different conditions. The prevalence of anti-phosphatidylethanolamine antibodies has been reported to be higher in patients with recurrent pregnancy losses or a history of thrombosis. We studied the association of anti-phosphatidylehtanolamine (anti-PE) with thrombosis and pregnancy loss in SLE, compared with the lupus anticoagulant.

Methods: Stored plasma samples from 268 SLE patients were tested for IgG and IgM antiphosphatidylethanolamine by ELISA. The lupus anticoagulant (LAC) was detected using dRVVT with confirmatory testing.

Results: Anti-PE was found in 9 (6.6%) patients with a history of any thrombosis, 6 (6.8%) with a history of venous thrombosis and in 2 (4.6%) with stroke. Table 1 shows the association of any thrombosis, venous thrombosis, stroke and pregnancy loss with anti-PE and with the lupus anticoagulant. No significant association was found between anti-PE and thrombosis, venous thrombosis, stroke or pregnancy loss. Anti-PE was significantly associated with the lupus anticoagulant (Table 2).

Table 1. Associations of aPE and Lupus Anticoagulant with Thrombosis and Pregnancy loss

	Assay	Group with the event N (% positive)	Group without the event N (% positive)	Odds Ratio	95% CI	P-value when age, gender, and ethnicity were controlled
Any Thrombosis	Anti-PE	9 (6.6)	8 (6.1)	1.1	0.4,3.1	0.85
	LAC	47 (39.2)	14 (12.2)	4.4	2.1,8.90	<0.0001
Venous Thrombosis	Anti-PE	6 (6.8)	11 (6.1)	1.2	0.4,3.3	0.76
	LAC	32 (41.6)	29 (18.4)	3.1	1.6,5.90	0.0005
Stroke	Anti-PE	2 (4.6)	15 (6.7)	0.7	0.1,5.4	0.71
	LAC	16 (41.0)	45 (23.0)	2.5	1.20,5.40	0.018
Pregnancy Loss	Anti-PE	0 (0.0)	4 (9.3)	0.62	0.03,15.9	0.78
	LAC	1 (16.7)	7 (18.4)	0.98	0.93,1.0	0.34

Table 2. Association of Anti-PE with Lupus Anticoagulant

Assay	Lupus anticoagulant Positive (n = 61) N (% positive)	Lupus anticoagulant Negative (n = 174) N (% positive)	Odds Ratio	(95% CI)	P-value
Anti-PE(IgG or IgM)	8 (13.1)	8 (4.6)	3.1	(1.1,8.7)	0.036

Conclusion: Anti-PE (IgG or IgM) is associated with the lupus anticoagulant by dRVVT. We found that the lupus anticoagulant by dRVVT was a stronger predictor of any thrombosis, venous thrombosis and stroke than anti-PE. In contrast to other studies, there was no association of anti-PE with thrombosis or pregnancy loss. In SLE, neither the lupus anticoagulant nor anti-PE was associated with a history of pregnancy loss.

Disclosure: E. Akhter, None; **H. Fang**, None; **N. Bardin**, None; **M. San Marco**, None; **M. Petri**, None.

1731

IgA Anti-$\beta_2$glycoprotein I Antibodies Are Pathogenic in a Mouse Model of APS. Patricia Ruiz Limon[1], Zurina Romay-Penabad[2], Ana Laura Carrera Marin[1], Elizabeth Papalardo[2] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Univ of TX Medical Branch, Galveston, TX

Background/Purpose: Recently exclusive IgA anti-b$_2$Glycoprotein I (ab$_2$GPI) seropositivity - in the absence of any other antiphospholipid (aPL) antibodies- has been reported particularly in SLE patients. A significant proportion of those (70–80%) were found to have Antiphospholipid Syndrome (APS)-clinical manifestations (e.g. thrombosis and/or pregnancy losses). APL antibodies of the IgG and IgM isotypes have been shown to be pathogenic *in vivo*, but whether IgA ab$_2$GPI antibodies are thrombogenic in mice is unknown. Here we examined the effects of affinity purified IgA ab$_2$GPI antibodies isolated from patients with exclusive IgA ab$_2$GPI positivity on thrombus formation and tissue factor (TF) upregulation in mice.

Methods: IgA was isolated from pooled sera of four patients (IgA-APS) with isolated IgA ab$_2$GPI titers ($\geq$80 SAU) - two had strokes, one had a confirmed deep vein thrombosis and one had two pregnancy losses - and from normal human serum (IgA-NHS) using a Immobilized Jacalin column (Pierce Biotechnology). IgA ab$_2$GPI in the IgA-APS and in the IgA-NHS preparations was determined by ELISA (INOVA Diagnostics), the protein concentration by the Bradford method and the lupus anticoagulant by using a modified silica clotting time (SCT). CD1 mice weighing between 26–30 g were injected twice with 100 μg/ml of IgA-APS or IgA-NHS. Seventy hours after the first injection, the size of induced thrombi in the femoral vein was determined as described (Circulation 1996; 94: 1746–1751). Tissue factor activity was determined in homogenates of pooled carotid arteries and in peritoneal macrophages using a chromogenic assay. Student's t test was used to determine differences in mean thrombus sizes between IgA-APS and IgA-NHS treated mice.

Results: IgA-APS and IgA-NHS were rendered endotoxin free by the Limulus amebocyte lysate assay, and did not have detectable levels of IgG or IgM. The IgA-APS preparation but not the IgA-NHS was positive for IgA ab$_2$GPI (103.7 SAU) and LA (SCT ratio IgA-APS/IgA-NHS) =2; normal <1.2. Results of thrombus sizes and TF activities in mice treated with IgA-APS and IgA-NHS are shown in the table.

Mice Treatment (n= # of animals)	Thrombus size (μm^2) Mean $\pm$ SD	TF activity in carotid homogenates (pM/mg/ml) protein. Mean $\pm$ SD	TF activity in peritoneal macrophages (pM/mg/ml) protein. Mean $\pm$ SD
IgA-NHS (n=5)	389 $\pm$ 70	214.8 $\pm$ 8.6	154.3 $\pm$ 63.7
IgA-APS (n=5)	675 $\pm$ 210*	628.0 $\pm$ 70.7 [2.6 fold increase over IgA-NHS]	532.5 $\pm$ 13.6 [3.5 fold increase over IgA-NHS]

*statistically significant, p=0.02.

Conclusion: This data show for the first time that IgA ab$_2$GPI antibodies are thrombogenic and upregulate TF in mice. Detection of IgA ab$_2$GPI antibodies - currently not included in the classification criteria for APS - may further identify a group of patients with APS-associated clinical manifestations that otherwise would have been missed with tests used routinely in the clinical laboratory to confirm APS.

Disclosure: P. Ruiz Limon, None; **Z. Romay-Penabad**, None; **A. L. Carrera Marin**, None; **E. Papalardo**, None; **S. S. Pierangeli**, None.

1732

Annexin A5 Resistance Identifies a Subset of Thrombosis Patients in Systemic Lupus Erythematosus. Ehtisham Akhter[1], Hong Fang[1], Xiao Xuan Wu[2], Jacob Rand[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Montefiore Medical Center, Bronx, NY

Background/Purpose: Annexins are a family of structurally related proteins that bind to phospholipids in a calcium dependant manner. Annexin A5 (AnxA5), present on the surfaces of human endothelial cells, platelets and trophoblasts has potent anticoagulant activity that is a consequence of its forming 2-dimensional crystals over phospholipid bilayers, shielding the phospholipids from availability for coagulation. Antiphospholipid antibodies (aPL) disrupt the crystallization of AnxA5 over phospholipid membrane and expose the underlying phospholipid membrane for coagulation reactions. aPL-mediated disruption of AnxA5 has been correlated with thrombosis in the antiphospholipid syndrome. We investigated the association of resistance to AnxA5 anticoagulant activity (A5R assay) with thrombosis in SLE, compared with the lupus anticoagulant (LAC).

Methods: Stored plasma samples from 296 SLE patients, 150 of whom had prior thrombosis, were assayed for annexin 5 resistance. The A5R assay was performed as previously described (Blood. 2007; 109: 1490–94). We considered assay results that were < 3 SD below the mean (<140%) of 30 normal healthy control plasmas to be abnormal, and between 2–3 SD (147–153) to be borderline. The lupus anticoagulant (LAC) was detected using dRVVT with confirmatory testing.

Results: Resistance to AnxA5 anticoagulant activity was found in 45 SLE patients (15%). Table 1 shows the association of any thrombosis, venous thrombosis and stroke with A5R and with LAC. A5R was consistently associated with increased risk for thrombosis. A5R was also highly associated with a positive LAC (p<0.0001). In the small number of SLE patients with negative LAC, no association between A5R and thrombosis was found.

Table 1. Association of AnxA5 Resistance and Lupus Anticoagulant with Thrombosis

	Assay	Thrombosis Number (%) positive	No thrombosis Number (%) positive	Odds Ratio	95% CI	P-value when age, sex, and race were controlled
Any Thrombosis	A5R	27 (18%)	18 (13%)	2.1	(0.90,5.20)	0.097
	LAC	50 (39%)	14 (11%)	0.96	(0.94,0.98)	<0.0001
Venous Thrombosis	A5R	22 (23%)	23 (12%)	2.3	(0.90,5.90)	0.070
	LAC	34 (41%)	30 (17%)	0.97	(0.95,0.98)	<0.0001
Stroke	A5R	10 (20%)	35 (14%)	2.7	(0.80,8.40)	0.095
	LAC	18 (43%)	46 (22%)	0.98	(0.96,0.99)	0.0021

Conclusion: We found that, in SLE patients, the lupus anticoagulant by dRVVT was a stronger predictor of any thrombosis, venous thrombosis and stroke than A5R. Annexin A5 resistance was strongly associated with the lupus anticoagulant. In patients negative for lupus anticoagulant, there was no association of A5R and thrombosis. In summary, A5R identifies a subset of about half of of SLE patients with thrombosis in whom this specific mechanism for thrombosis is operative. We speculate that this finding may allow the development of treatments that target this specific mechanism.

Disclosure: E. Akhter, None; **H. Fang**, None; **X. X. Wu**, None; **J. Rand**, AnxA5 Resistance assay, 9; **M. Petri**, None.

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Effect of Hydroxychloroquine (HCQ) On the Annexin A5 Resistance Assay (AnxA5-RA) in Antiphospholipid Antibody (aPL)-Positive Patients: Preliminary Results of an Ongoing Prospective Study. Alana B. Levine[1], Jacob H. Rand[2], Xiao Xuan Wu[2], JoAnn Vega[1], Glendalee Ramon[1], Stephen L. Lyman[1], Doruk Erkan[1] and Michael D. Lockshin[1]. [1]Hospital for Special Surgery, New York, NY, [2]Montefiore Medical Center, Bronx, NY

Background/Purpose: One proposed mechanism of aPL-mediated thrombosis is disruption of the AnxA5 shield, allowing initiation of coagulation reactions on phospholipid surfaces. The AnxA5-RA measures the resistance to AnxA5 anticoagulant activity in the plasmas of aPL-positive patients. Based on *in vitro* studies, HCQ interferes with aPL binding to cell surfaces and helps repair disrupted AnxA5 shields; however, no *in vivo* human studies exist. The purpose of this ongoing prospective study is to determine the effect of HCQ on the AnxA5-RA in aPL-positive patients; here we present the preliminary baseline results.

Methods: As part of the ongoing study, aPL-positive patients (positive lupus anticoagulant [LA], anticardiolipin antibody [aCL] $\geq$ 40GPL/MPL, and/or anti-β_2-glycoprotein-I [aβ_2GPI] antibody $\geq$ 40 SGU/SMU at two time points at least 12 weeks apart) starting HCQ are recruited to give blood at baseline, 6 weeks, and 12 weeks (primary outcome measure: AnxA5-RA; secondary outcome measures: LA, aCL, aβ_2GPI, D-dimer and anti-domain-I β_2GPI antibody [aDI-β_2GPI]). As a control group, aPL (LA, aCL, and aβ_2GPI)-negative systemic lupus erythematosus (SLE) patients starting HCQ are also recruited. For the purpose of this preliminary analysis, we compared the baseline characteristics of aPL-positive patients to aPL-negative SLE patients (Mann-Whitney test).

Results: Baseline data from 15 aPL-positive patients (mean age 43.3 ± 12.0 years [range 27–61], 10 [67%] female, 13 [87%] Caucasian; 10 had antiphospholipid syndrome, 5 asymptomatic aPL) were compared to 7 aPL-negative SLE patients (mean age 40.0 ± 16.3 years [range 22–64], 7 [100%] female, 4 [57%] Caucasian). Thirteen (87%) of the 15 aPL-positive patients had positive AnxA5-RA; 9/13 (69%) were triple aPL-positive, 2/13 (15%) were double aPL-positive (both aCL- and aβ_2GPI-positive) and 2/13 (15%) were single aPL-positive (one aCL- and one aβ_2GPI-positive only). Seven (47%) of 15 aPL-positive patients had aDI-β_2GPI; 5/7 (71%) were triple aPL-positive and 2/7 (29%) were single aPL-positive (aβ_2GPI). No patients in the control group had positive AnxA5-RA or aDI-β_2GPI. Baseline AnxA5-RA and aDI-β_2GPI results, but not D-dimer levels, differed in aPL-positive patients versus aPL-negative SLE controls (Table).

	aPL (+), n:15	aPL (−) SLE, n:7	p	Reference Range
AnxA5-RA (%)				Negative ≥ 153
- Mean ± SD	130.1 ± 15.6	175.7 ± 24.5		Borderline 140–152.9
- Median (IQR)	127.9 (117.7–132.2)	173.9 (156.8–193.7)	0.0004	Positive <140
aDI-β2GPI (mg/L)				Negative <1.66
- Mean ± SD	4.11 ± 3.94	0.70 ± 0.56		Borderline 1.66–2.29
- Median (IQR)	2.14 (1.52–7.16)	0.70 (0.20–1.09)	0.002	Positive >2.29
D-dimer (µg/mL)				Normal
- Mean ± SD	1.87 ± 0.67	1.93 ± 1.64		0.8–2.3
- Median (IQR)	1.73 (1.60–2.34)	1.28 (1.14–2.00)	0.37	

AnxA5-RA: Annexin-A5 resistance assay; aDI-β_2GPI: anti-domain-I β_2-glycoprotein-I antibody; SD: standard deviation; IQR: interquartile range

Conclusion: Based on the preliminary baseline results of our ongoing prospective study, aPL-positive patients detected based on criteria tests also have positive AnxA5-RA and aDI-β_2GPI; our findings support the use of these non-criteria tests to detect aPL in the clinical setting. The effect of HCQ on outcome measures will be determined by the analysis of our longitudinal data.

Disclosure: A. B. Levine, None; **J. H. Rand**, Inventor, 9; **X. X. Wu**, None; **J. Vega**, None; **G. Ramon**, None; **S. L. Lyman**, None; **D. Erkan**, None; **M. D. Lockshin**, None.

1734

Clinical Accuracy for Diagnosis of Antiphospholipid Syndrome in Systemic Lupus Erythematosus: Evaluation of 23 Possible Combinations of Antiphospholipid Antibody Specificities.

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Background/Purpose: The clinical accuracy of testing for antiphospholipid antibody (aPL) both, as individual tests and/or in combination, is still being investigated. We aimed to identify a panel of tests that may provide the best accuracy for diagnosing the antiphospholipid syndrome (APS) in a wide cohort of patients with Systemic Lupus Erythematosus.

Methods: This study included 230 patients (218 women, mean age 42.7±11.9 years, mean disease duration 12.2±8.7years), all fulfilling the 1982 criteria for Systemic Lupus Erythematosus. Lupus anticoagulant (LA), anti-cardiolipin (aCL), anti-$\beta_2$glycoprotein I (anti-b2GPI), solid phase anti-prothrombin (aPT), anti-phosphatidylserine/prothrombin (aPS/PT), and anti-phosphatidylethanolamine (aPE) antibodies were tested in all. Sensitivity, specificity and predictive values were calculated. The diagnostic accuracy for each combination of tests was assessed by ROC and their area under the curve analysis (AUC) as well as by the Youden's index (YI).

Results: Testing for 6 aPL derived in 23 possible combinations of results. Among them, LA+ anti-β_2GPI+aPS/PT had the best diagnostic accuracy for APS as a whole, and individually for both thrombosis and pregnancy loss (AUC 0.712, OR3.73 [95% CI 1.82–5.38], p=0.0001, YI= 0.32; AUC 0.709, OR3.75 [95% CI 2.13–6.62], p=0.0001, YI=0.37 and AUC 0.677, OR4.82 [95%CI 2.17–10.72], p=0.0007, YI=0.38; respectively) and the best specificity when compared to all the other obtainable combination of tests. Triple positivity for LA+anti-β_2GPI+aPS/PT was more strongly associated with clinical events (thrombosis and/or Pregnacy Loss) than double or single positivity (OR23.2 [95%CI 2.57–46.2] vs. OR7.3 [95%CI 2.21–25.97], OR5.7 [95%CI 2.12–17.01] or OR3.11 [95%CI 1.56–7.8] for single positivity for LA, aPS/PT and anti-β_2GPI, respectively).

Conclusion: Combining LA, anti-β_2GPI and aPS/PT improves the diagnostic power and helps in stratifying the risk for each patient, according to their aPL profile.

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Independent Validation of the Antiphospholipid Score (aPL-S) for the Diagnosis of Antiphospholipid Syndrome (APS).

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Background/Purpose: The so called "antiphospholipid score (aPL-S)" was recently developed and validated (1). This score was shown to be a useful quantitative index for diagnosing APS and to be valuable as a predictive marker for thrombosis in autoimmune diseases. We aimed to independently validate the aPL-S by applying the proposed score system to our cohort of SLE patients. (1. Otomo et al. Arthritis Rheum 2012; 64: 504).

Methods: We applied the aPL-S to a cohort of 211 consecutive SLE patients, all attending our Lupus Clinic. aPL-S was calculated for each patient by adding together the points corresponding to the risk factors as described. To validate the aPL-S, we adapted the proposed score using our in house cut-off values for aPL testing as previously reported or according to the current guidelines, as appropriate.

Results: Overall, 81 patients fulfilled criteria for APS and 73 patients had a history of thrombosis (48 arterial, 41 venous). Out of 144 women who had ever been pregnant, 61 had a history of pregnancy loss. Higher values of aPL-S were seen in patients who experienced thrombosis and/or pregnancy loss when compared to those without clinical events (median 17 [0–86] vs. 4 [0–31], p<0.001). When analysing clinical subgroups, patients who experienced thrombosis or pregnancy loss showed higher aPL-S compared to those without clinical events (median 18 [0–86] vs. 4 [0–27], p<0.001 for thrombosis; 7 [0–69] vs. 3 [0–29], p=0.029 for pregnancy loss). When the cut-off level for the aPL-S was defined as 30, as per the original study (1) the sensitivity and specificity of the aPL-S were 39% and 95%. The PPV of an aPL-S ≥30 was 36%, whereas the NPV was 91%.

Conclusion: We demonstrated that the aPL profile can be successfully quantified by the aPL-S in an independent cohort of SLE patients. The aPL-S correlated with a history of thrombosis and pregnancy loss in our cohort, suggesting that the aPL-S is a suitable quantitative marker for APS.

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The Estimated Prevalence of Antiphospholipid Antibodies in the General Population with Pregnancy Morbidity.

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Background/Purpose: AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) is an international research network created to conduct well-designed clinical trials in persistently antiphospholipid antibody (aPL)-positive patients. One of the first needs of APS ACTION was to know the true prevalence of aPL in the general population with pregnancy morbidity (PM).

Methods: The search for "aPL" and multiple keywords regarding the pregnancy outcomes of interest (early/late pregnancy loss [PrL], intrauterine growth restriction [IUGR], preeclampsia [PEC] and HELLP syndrome) was completed in PubMed. A total of 47 full-text papers were collected and analyzed for the type of outcome, the aPL tests used (criteria tests *vs.* non criteria), the definition of "positive aPL" (low, medium, high, other), the confirmation of aPL (at least 6–12 weeks apart), and the prevalence of positive aPL in the study population. The median prevalence and interquartile range (IQR) of different aPL tests were calculated based on the combine analysis of all the papers.

Results: Out of 47 papers, the outcome of interest was PrL in 32 (68%), IUGR in 6 (13%), PEC in 20 (42%), and/or HELLP syndrome in 6 (13%). Despite the limitations of the literature, the table demonstrates the estimated aPL prevalence in patients with different type of PM. These limitations were: *a) the definition of "pregnancy outcome"* was highly heterogeneous (66% of the studies did not define the PrL based on the Updated Sapporo Criteria; 31% did not specify the number and/or the gestational week of the PrL; 47% of the early PrL studies included patients with less than 3 events; and 85% included patients with events before and after 10 weeks in the same analysis); b) *nomenclature of late PrL* was controversial due to the overlap between terms such as abortion, intrauterine fetal death, and stillbirth; fetal malformations were rarely excluded (36%); c) *IUGR* was defined as <5th percentile in 33% of the studies and <10th percentile in 50%; 17% of the papers included no cut-off values; d) *PEC severity* was identified only in 50% of the studies; e) *the numbers of patients* included in all studies were relatively small (median 70; IQR 29–162); f) *aPL type* (6%) *or isotype* (32%) has not been specified in 38% of the studies; g) *aCL and/or aβ2GP-I ELISA cut-off* was not available in 11% of the studies and "low titer" (<20U) was used in 21% of the papers; and h) *the confirmation of aPL* was performed only in 9 studies (19%).

Median, % (IQR)	LA	aCL[**]	ab2GPI[***]	aPL[****]	Average (%)
PrL	9.5 (7.3–12.5)	6 (2–16)	5 (2–8)	14.5 (13.8–15.3)	9
– Early PrL	0	2 (2–5)	4.5 (2.8–7.8)	–	5
– Late PrL	22 (12.5–25.5)	9 (1–10.5)	4 (3–5.3)	21.5 (15.3–27.8)	11
IUGR	2 *	17 (8.5–24)	–	–	13
PEC	2 (1.5–5.5)	3 (1–12)	5 (4.5–6)	7 (4–11)	7
Severe PEC	16 (12.5–17.25)	9 (0.1–25)	5 (3.5–6.5)	16 (14.5–18)	15
HELLP	53 *	2 (2–10)	4 (2–4)	43.5 (23.8–63.3)	16

* Only one study; ** aPL tests were reported as aCL, aCL IgG, and/or aCL IgM; *** aPL tests were reported as ab₂GPI, ab2GPI IgG, and/or ab2GPI IgM; **** aPL tests were not specified

Conclusion: The current best estimates of aPL prevalence in patients with PM are impaired by several limitations of the literature including the definition of obstetric outcomes and "positive aPL". One of the goals of APS ACTION is to improve upon existing literature in order to address the precise magnitude of the problem.

Diffuse Alveolar Hemorrhage Caused by Primary Antiphospholipid Syndrome.

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Background/Purpose: Diffuse alveolar hemorrhage (DAH) is an uncommon but severe complication of primary antiphospholipid syndrome (APS). The available literature is limited to very few case reports. We aim to describe the clinical characteristics, treatment and outcomes of patients with DAH due to primary APS managed at our institution.

Methods: A retrospective review of the medical records of all consecutive adults evaluated at Mayo Clinic with DAH secondary to primary APS between January 1, 1997 and December 31, 2011 was conducted. APS was diagnosed using the revised Sapporo classification criteria. DAH was defined as the presence of bilateral alveolar pulmonary infiltrates with a confirmatory bronchoalveolar lavage (BAL) documenting bloody return and/or >20% hemosiderin laden macrophages (HLM). Patients with documented connective tissue diseases, ANCA associated vasculitis or anti-GBM disease were excluded.

Results: A total of 17 patients (men=12) were identified, all of them white. The median age (interquartile range, IQR) was 43 years (36–47). The median time from diagnosis of APS to development of DAH was 1661 days (495–3605). Three patients underwent lung biopsy showing capillaritis. The median percentage of HLM was 87% (81–98), BAL differential cell count was predominantly neutrophilic, median 30% (18–60). All patients were treated with high doses of glucocorticoids; six of whom did not respond, requiring more aggressive immunosuppression. Mycophenolate mofetil was used in seven patients; none achieved remission. Azathioprine was used in six patients; no remission was noted in five and one patient did not tolerate it. Cyclophosphamide was used in seven patients; remission was achieved only in three patients. Plasma exchange was performed in two patients with no response. Intravenous gamma-globulin was used in four patients with remission seen only in one patient. Rituximab was used in 6 patients; two patients achieved remission and one was lost to follow up. Only the two patients treated successfully with rituximab are off glucocorticoids. Five patients died, four from complications of uncontrolled DAH and one from complications of autologous stem cell transplant conditioning regimen for treatment of refractory DAH/ APS. Median time to death from diagnosis of DAH was 70 days (44–721).

Conclusion: To the best of our knowledge, we present the largest series of DAH secondary to primary APS. There is a long gap between the diagnosis of APS and the first episode of DAH. Alveolar fluid shows predominantly neutrophilic inflammation. This disease carries a very poor prognosis with very limited successful therapeutic options. B-cell targeted immunosuppression with either cyclophosphamide or rituximab may have the highest likelihood to induce remission and should be considered early.

Myocardial Dysfunction and Valvulopathy Worsens with Time in Patients with Antiphospholipid Syndrome: A 10-Year Follow-up Study.

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Background/Purpose: Valvular disease represents the most common cardiac manifestation among patients with antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) positive for antiphospholipid antibodies (aPL). Diastolic dysfunction of the left and right ventricle has also been observed in these groups of patients. The purpose of the present study is to describe the evolution of valve involvement and myocardial dysfunction over time in patients with SLE and/or APS and investigate possible associations with clinical and laboratory characteristics.

Methods: One hundrend and fifty patients had been assessed by transthoracic echocardiography 10 years ago. Structural and functional (regurgitation or stenosis) valvular abnormalities and diastolic function parameters ('E' and 'A' waves, E to A ratio, deceleration time (DT), isovolumic relaxation time (IVRT)) for the left and right ventricle had initially been

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recorded. The longitudinal arm of the study finally included 17 patients with primary APS (PAPS), 23 with SLE-asscociated APS (SLE/APS), 19 with SLE positive for aPL without APS and 23 with SLE negative for aPL, for the present echocardiographic re-evaluation.

Results: The proportion of patients with valvulopathy increased from 39.3% in the initial cohort to 64.7% among PAPS and 61.5% among SLE patients. Worsening of valvular lesions during the 10 year follow-up period was detected in approximately one third of the examined population including PAPS and SLE patients, either positive or negative for aPL. Disease duration and presence of SLE/APS were the only significant risk factors for progression of isolated mitral and combined valvular disease; there was an 1.5 times higher risk for progression for every 5 years of increase in disease duration (OR:1.54, 95% C.I:1.05–2.25, $p=0.027$ and OR:1.63, 95% C.I: 1.13–2.36, $p=0.009$, respectively) and 3.5 times higher risk for SLE/APS patients (OR:3.57, 95% C.I:1.19–10.70, $p=0.023$ and OR:3.51, 95% C.I:1.27–9.67, $p=0.015$, respectively). Presence of aPL, aPL titres, presence of comorbidities and other clinical characteristics did not have any significant effect on progression of valvular lesions. No treatment regimen seemed to have a prophylactic role in preventing occurrence of de novo valvular lesions or in halting progression of preexisting valvulopathy. Left ventricular diastolic dysfunction similarly progressed over time with DT and IVRT being equally prolonged in each of the 4 groups ($p<0.05$). Right ventricular DT was significantly prolonged in each of the 3 SLE groups ($p<0.001$), but IVRT increased only in SLE/APS patients ($p=0.040$).

Conclusion: Progression of valvulopathy, as detected by transthoracic echocardiography, was observed in the majority of patients with either SLE or APS, despite treatment of underlying disease. Secondary APS in SLE and disease duration were independent risk factors for progression of valvular disease. Ventricular diastolic dysfunction, primarily of the left ventricle, similarly progressed over the 10 year period.

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Primary and Secondary Antiphospholipid Syndrome in Childhood.
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Background/Purpose: Antiphospholipid syndrome (APS) is an auto-immune disease characterizered by positive antiphospholipid antibodies and potentially life-threatening thrombotic events. APS can be classified as primary or secondary to other disease. In childhood, secondary APS is frequently associated with Systemic Lupus Erythematosus (SLE). Few longitudinal childhood APS cohorts have been described, and the proportion of patients who present with APS prior to an eventual diagnosis of SLE in childhood is unknown. The aims of the study are: (1) To determine the proportion of patients with primary versus secondary APS in childhood; (2) To determine the proportion of patients initially diagnosed with primary APS who eventually develop SLE.

Methods: A retrospective single centre cohort study of all patients diagnosed with APS at The Hospital for Sick Children between 1999 and 2011 was conducted. Data from the neurology (stroke/sinus venous thrombosis), haematology (thrombosis) and rheumatology databases were collected. All patients who fulfilled the Revised Sapporo Criteria for the diagnosis of APS prior to their 18th birthday were included. Chart reviews were conducted to extract relevant data, including demographic, clinical and laboratory data.

Results: Fifty three children were identified; 13 (25%) with primary APS (pAPS); 40 (75%) with secondary APS, of which 13 (33%) were diagnosed with APS secondary to SLE (APS-SLE), and 27 (67%) with APS secondary to other disease (sAPS) (Figure 1). Demographics and clinical characteristics are in Table 1. Three (23%) APS-SLE patients were initially diagnosed with pAPS who were later diagnosed with SLE after a mean of 2.8 years; the remainder of SLE patients developed APS after a mean of 1.3 years. 15% (2/13) of pAPS patients had persistent features of incipient SLE (<4/11 of the ACR classification criteria for SLE) after mean follow-up of 4.2 years. Majority of patients with APS were males, except patients with APS-SLE. Only 26% of sAPS patients met LAC laboratory criteria. In the sAPS group, arterial strokes were the most common thrombotic event.

Table 1. Basic demographic and clinical characteristics of patients diagnosed with APS.

	Primary APS	Secondary APS to SLE	Secondary APS to other disease	Overall cohort
Gender (M:F)	9:4	5:8	21:6	35:18
Age at diagnosis in years mean, (range)	12 (0–17)	13.7 (4–17)	4.1 (0–16)	8.4 (0–17)
Duration of follow-up from APS diagnosis mean, (range)	3.5 (1–6.1)	3.0 (1–7.6)	7.4 (1–13.2)	5.3 (1–13.2)
LAC criteria for APS met	77% (10/13)	92% (12/13)	26% (7/27)	55% (29/53)
ACL IgG criteria for APS met	69% (9/13)	77% (10/13)	78% (21/27)	75% (40/53)
Thrombosis site (number of events)				
Deep vein thrombosis	5	6	8	19
Pulmonary embolus	5	4	1	10
Arterial Stroke	5	2	14	21
Sinus venous thrombosis	3	3	4	10
Hepatic/portal vein	3		1	4
Inferior vena cava	1	1	2	4
Renal vein		1	1	2
External iliac artery			2	2
Jugular vein	1			1
Splenic vein		1		1
Retinal vein		1		1
Aorta			1	1
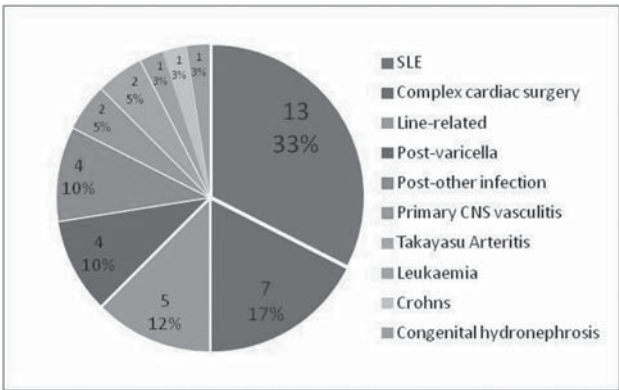
Figure 1. APS secondary to other diseases, divided into aetiology.

Conclusion: The majority of childhood APS are secondary to underlying disease, with SLE being the most frequent cause. Five patients with primary APS had incipient SLE, 3 later developed SLE. For children diagnosed with APS, we recommend a thorough evaluation for SLE at diagnosis and during follow-up.

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Impairment of Quality of Life in Patients with Antiphospholipid Syndrome.
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Background/Purpose: Quality of life (QoL) is an important outcome in clinical care especially in patients with chronic disease such as systemic lupus

erythematosus (SLE). In antiphospholipid syndrome (APS) which can be associated to SLE, QoL has not been clearly evaluated. Therefore our objective was to assess QoL in patients with antiphospholipid antibodies (aPL) and/or SLE in particular according to their APS status (thromboembolic history or obstetrical morbidity).

Methods: QoL was assessed in a multicentre cohort study using The Medical Outcomes Study Short-Form 36 (MOS-SF-36) in patients with aPL and/or SLE without anticoagulant treatment at inclusion. A score from 0 to 100 was calculated for each dimension and each component was normal at 50. QoL scores were compared between groups of patients and to the general population.

Results: One hundred and fifteen patients were included (mean age 42 ± 14 years-old, 85 women). Seventeen patients had SLE and aPL, 16 only SLE and 82 only aPL. Fifty-eight patients were asymptomatic (i.e. without thrombotic or obstetrical history), while 57 patients had a history of one or several thrombotic manifestations and in 54 patients APS was diagnosed. The presence of APS was associated to a significant impairment of QoL on both mental component summary (MCS) (40.4 ± 11.9 vs 45.7 ± 10.4, p=0.01) and physical component summary (PCS) (46.6 ± 9.6 vs 49.3 ± 8.4, p=0.03) scores compared to those without APS (Fig. 1). Furthermore, in patients with history of arterial thrombosis compared to those without, Qol was dramatically impaired on all dimensions and both MCS (35.9 ± 12.8 vs 44.6 ± 10.6, p=0.008) and PCS (40.3 ± 10.2 vs 49.5 ± 8.1, p<0.001) scores (Fig. 2). Comparisons of QoL scores between patients with SLE and/or aPL and general population according to age and sex, showed a significant impairment of the majority of dimensions of QoL especially in men between 35 to 54 years-old, and in women between 25 to 54 years-old.
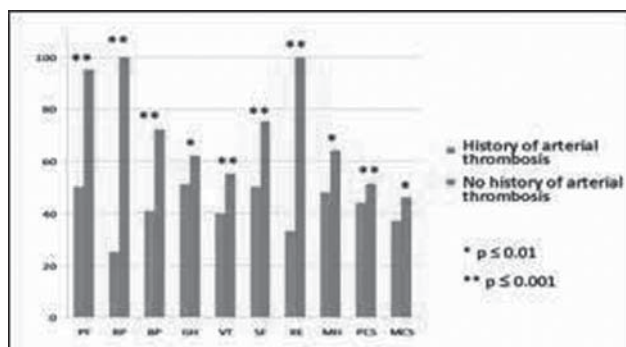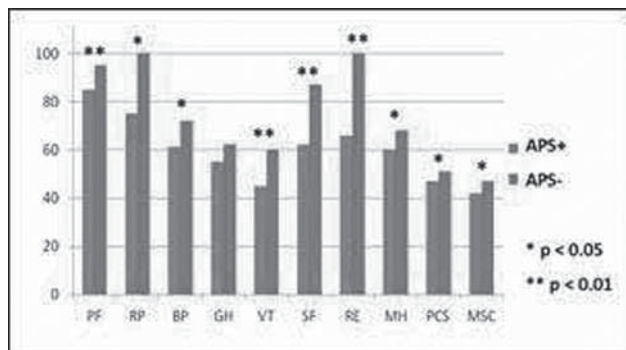
Conclusion: In patients with aPL and/or SLE, the presence of APS is associated with a significant impairment of QoL assessed by MOS-SF-36. History of arterial thrombosis was associated to the greatest impairment of QoL. Compared to the general population, we showed that these young patients experienced a decreased QoL which should be taken into account on everyday APS patient management.

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Suppression of Glomerulonephritis in NZB/W F1 Mice by a Selective Inhibitor of Bruton's Tyrosine Kinase (RN486). Paola Mina-Osorio, Jacob LaStant, Natalie Keirstead, Toni Whittard, Stella Stefanova, Alka Patel, Jennifer Postelnek, John Woods, Soo Min, Yong Kim, Julie Demartino, Satwant Narula and Daigen Xu. Hoffmann-La Roche, Nutley, NJ

Background/Purpose: Bruton tyrosine kinase (Btk) is a Tec family kinase that participates in B cell receptor (BCR), Toll-like Receptor (TLR) and chemokine receptor signaling. It is expressed in all cell lineages of the hematopoietic system, except for T cells, and it plays a critical role in B cell development and function. We have recently reported a potent and highly selective competitive inhibitor of Btk RN486, which blocks the Btk kinase activity with an IC50 of 4.0 nM. This compound inhibits BCR and FcR-mediated signaling and is efficacious in murine models of arthritis. Here we tested RN486 in the NZB/NZBW model of lupus.

Methods: Animals were randomized into two groups based on the serum anti-dsDNA antibody levels and proteinuria measured at 30 weeks of age. Beginning at 32 weeks of age one group of mice was fed chow formulated with 30mg/kg of RN486 equivalent to 0.225 mg/g of chow, while the other group received regular chow *ad libitum* for 8 weeks.

Results: Treatment of NZB/W F1 mice with RN486 completely prevented the progression of proteinuria in 32 week-old mice. In contrast, a normal progression of the proteinuria scores until the termination of the study at 40 weeks of age was observed in animals fed with regular chow. This effect was associated with decreased IgG antibody deposition and decreased glomerular nephritis at the histological level. At the cellular level, there was a dramatic inhibition of B cell activation upon BCR crosslinking in vitro in peripheral blood B cells, as determined by the induction of CD69 by flow cytometry which is used as a pharmacodynamic marker. The IgG anti-dsDNA antibody secretion was almost completely abolished in the treated group as determined by ELISA and total splenocyte ELISpot. In contrast, the anti-dsDNA antibody secretion from bone-marrow derived plasma cells was not significantly inhibited, suggesting that similarly to other B-cell depleting therapies, the main target population corresponds to short-lived plasma cells in the spleen. This hypothesis was confirmed by flow cytometry data demonstrating complete depletion of a CD138hi population of cells in the spleen that was not detectable in the bone marrow. Interestingly, the compound inhibited IgG but not IgM anti-dsDNA secretion suggesting that pharmacological blockade of Btk resembles the previously reported transgenic expression of low endogenous Btk levels in B cells. Finally, we studied the effect of our compound in acute TLR9-mediated responses in vivo and found a dose-dependent inhibition of CpG-induced IL-12 secretion. In line with this result, the animals treated with RN486 for eight weeks had lower levels of IL-12 in the serum.

Conclusion: Our results demonstrate that Btk selective inhibition is efficacious in an animal model of lupus via plasma cell depletion and inhibition of BCR and TLR9-dependent stimulation.

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A Novel Murine Model of B Cell-Mediated Proteinuria Suggests Cytokines Mediate Podocyte Injury. Alfred H. Kim[1] and Andrey S. Shaw[2]. [1]Washington Univ School of Med, St. Louis, MO, [2]Washington University School of Medicine, Saint Louis, MO

Background/Purpose: B cell depletion therapies have been efficacious in several glomerulopathies. The contributions of B cells to proteinuria and foot process effacement remain unknown. The development of a murine model of B-cell induced proteinuria would enhance our understanding of immune-based glomerular diseases.

Methods: The B cell model antigen model hen egg lysozme (HEL) was biotinylated and complexed to avidin. Following intravenous (IV) injection in mice, purified naïve HEL-specific B cells were adoptively transferred and proteinuria assessed using PAGE. Kidneys were processed for immunofluo-

rescence (IF), H&E and PAS staining, and scanning electron microscopy (SEM). Cultured podocyte membrane ruffling was assessed with DIC videomicroscopy.

Results: HEL embedded within the glomerular basement membrane (GBM) following IV injection. Proteinuria occurred after the transfer of HEL-specific B cells and was associated with foot process effacement. No antibody or complement deposition was observed in the GBM. 2-photon microscopy of live mice demonstrated that HEL-specific B cells arrested trafficking within glomeruli in the presence of HEL.

The rapid kinetics of proteinuria induction suggested cytokines secreted by activated intraglomerular B cells may be responsible. We hypothesize that activation of the small Rho GTPase Rac is important in podocyte injury by virtue of its ability to regulate the actin cytoskeleton. Using murine cultured podocytes, we measured membrane ruffling in the presence of cytokines as a surrogate for Rac activation. IL-4 significantly increased cultured podocyte membrane ruffling and induced foot process retractions on ex vivo fragments of renal cortex. Hydrodynamic DNA immunization of wild-type 129 mice with plasmid encoding IL-4 lead to proteinuria.

Conclusion: We have developed a novel model of B cell-induced proteinuria with foot process effacement. Furthermore, these data demonstrate that cytokines can induce alterations in foot process morphology, leading to proteinuria. This has important implications in therapies preserving podocyte function in glomerular disease.

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IL-5-Induced FasL[+] Regulatory B Cells Are Inhibited by IL-4 and Cyclosporine. Matthew W. Klinker[1], Brian R. Alzua[1], Tamra J. Reed[1], David A. Fox[2] and Steven K. Lundy[1]. [1]University of Michigan, Ann Arbor, MI, [2]Univ of Michigan Med Ctr, Ann Arbor, MI

Background/Purpose: We previously identified a subset of regulatory B cells that express the apoptosis-inducing molecule Fas ligand (FasL), and reported that these B cells were expanded by IL-5. This study tested the effects of IL-4, another type 2 cytokine, on the growth and function of FasL^{+} B cells, and sought to identify pathways downstream of the IL-5 receptor important for FasL^{+}B cell function.

Methods: B cells were purified from mouse splenocytes by CD19^{+} MACS beads and cultured with a monolayer of CD40L-expressing fibroblasts in the presence or absence of cytokines. After culture, surface expression of phenotypic markers was assessed by flow cytometry. Cytokine release from stimulated B cells was measured by ELISA. The ability of stimulated B cells to induce apoptosis was measured by culturing B cells with activated T cells from TCR-transgenic mice and assessing apoptosis in CD4^{+}cells by Annexin V/propidium iodide staining. Cyclosporine was used to determine the effects of inhibiting the calcineurin signaling pathway on regulatory B cell function.

Results: B cells stimulated with IL-5 displayed regulatory B cell functions, including increased expression of FasL, antigen-specific killing of CD4^{+}T cells, and secretion of IL-10. Unexpectedly, the addition of IL-4 to B cell cultures completely abrogated the ability of B cells to induce apoptosis in target T cells and secrete IL-10, and instead induced the secretion of IL-6. Both IL-4 and IL-5 stimulated similar levels of B cell proliferation, and the combination of both cytokines had an additive effect on proliferation. IL-5-stimulated B cells resembled marginal zone B cells, with increased surface expression of CD80, CD86, CD9 and CD5, and reduced CD23 expression. This change in surface phenotype was also inhibited by IL-4. Finally, the calcineurin inhibitor cyclosporine prevented the induction of FasL expression and IL-10 secretion mediated by IL-5.

Conclusion: IL-4 inhibits the regulatory B cell functions induced by IL-5, such as FasL-mediated induction of apoptosis in CD4^{+} T cells and secretion of IL-10. The IL-5 receptor utilizes a calcineurin-dependent pathway for induction of FasL^{+} regulatory B cells. These findings suggest that while IL-4 has regulatory effects on T cells in inflammatory diseases such as rheumatoid arthritis, it may have an opposing role on B cells by antagonizing the IL-5-mediated induction of FasL[+] regulatory B cells.

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Regulatory B Cells Supress the Progression of Fatal Autoimmunity in Lupus-Prone Mice. Yuriy Baglaenko[1], Nan-Hua Chang[1], Evelyn Pau[2] and Joan E. Wither[1]. [1]Toronto Western Research Institute, University Health Network, Toronto, ON, [2]Toronto Western Hospital, University Health Network, Toronto, ON

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disorder characterized by the production of anti-nuclear antibodies (ANA) which form immune complexes and promote end-organ damage. Studies in our lab have focused on identifying genetic defects that contribute to a loss of immune regulation in autoimmune prone New Zealand Black (NZB) mice. Previous work has shown that the introgression of a NZB chromosome 1 (c1) interval extending from 135 to 179 Mb onto the non-autoimmune C57BL/6 (B6) background results in increased B and T cell activation, elevated ANA levels, and fatal kidney disease. Despite the presence of mapped susceptibility loci on NZB c4, introgression of an interval extending from 30 to 150Mb onto the B6 background resulted in the expansion of splenic NKT and CD5^{+} B cells in the absence of autoimmunity. To further investigate the role of NZB c4 in autoimmunity, bicongenic (c1c4) mice were produced with both NZB c4 and c1 intervals. Although bicongenic mice had c1 autoimmune augmenting genes, c1c4 mice had reduced renal disease, increased survival, and a shift towards less pathogenic IgG1 autoantibodies. Interestingly, bicongenic mice retained the expansion of splenic CD5^{+} B cells. Recent studies on experimental autoimmune encephalitis and arthritis models have identified a non-redundant role for a population of IL-10 producing CD5^{+}CD1d^{hi} regulatory B cells in preventing disease progression. Given the consistent expansion of splenic CD5^{+} B cells in bicongenic mice, we sought to investigate their role in the suppression of fatal autoimmunity.

Methods: Cellular phenotypes were examined by flow cytometry of de novo splenocytes. Intracellular production of IL-10 or IFNγ and IL-17 was measured following 4 to 5 hour stimulation with LPS, PMA and Ionomycin or PMA and Ionomycin, respectively. Serum levels of anti-nuclear antibodies were measured by ELISA. Adoptive transfer experiments were performed by injecting 5–10 million B cells intravenously into c1.Thy1[a]IgH[a] recipients.

Results: There was a significant increase in IL-10 producing B cells in bicongenic and c4 mice when compared to B6 and c1 controls. Interestingly, the expansion of IL-10 producing cells in c1c4 and c4 mice is distinct from previously documented B regulatory populations and localizes to the CD5^{+}CD1d^{int} B cell compartment. There was an inverse correlation between the levels of anti-ssDNA IgG and the frequency of IL-10 producing B cells in c1c4 but not B6 mice suggesting that they may play a role in disease suppression. There was no correlation between the proportion of conventional Treg or iNKT cells and anti-ssDNA IgG antibodies. In support of a direct suppressive capacity for the expanded CD5^{+} B cells, adoptive transfer of total B cells from c4, but not B6, mice into autoimmune prone c1.Thy1[a]IgH[a] recipients reduced the proportion of activated B cells, germinal centre B cells, memory/effector T cells, and IFN-g or IL-17-secreting T cells.

Conclusion: Taken together, these data indicate the presence of a phenotypically novel IL-10 producing B cell population in c4 mice which can suppress the progression of fatal autoimmunity.

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Amelioration of Experimental Autoimmune Arthritis by Adoptive Transfer of Foxp3-Expressing Regulatory B Cells Is Associated with the Regulatory T Cell/T helper 17 cell Balance. Young Ok Jung[1], Yu Jung Heo[2], Mi Kyung Park[3], Mi-La Cho[4], Seung Ki Kwok[5], Ji Hyeon Ju[2], Kyung Su PARK[2], Sung Hwan PARK[2], Ho Youn Kim[2] and Jun-Ki Min[6]. [1]Seoul, South Korea, [2]Catholic University, Seoul, South Korea, [3]The Catholic University of Korea, Seoul, South Korea, [4]Catholic University of Korea, Seoul, South Korea, [5]The Catholic University, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea

Background/Purpose: Foxp3 is a key regulator of the development and function of regulatory T cells (Tregs), and its expression is thought to be T cell-restricted. We hypothesized that B cells can express Foxp3 and B cells expressing Foxp3 may play a role in preventing the development of collagen-induced arthritis (CIA).

Methods: Protein and mRNA expression of Foxp3 in CD19^{+} B cells from mice was determined by flow cytometry, western blotting, and RT-PCR. Confocal microscopy was used to visualize the location and expression of Foxp3 in B and T cells. Foxp3 expression was modulated in CD19^{+} B cells by transfection with shRNA or using an over-expression construct. *In vitro* suppressive activity of Foxp3-expressing B cells on T cell proliferation was assessed by a ^{3}H-thymidine incorporation assay. In addition, Foxp3-transfected B cells were adoptively transferred to CIA mice. Therapeutic effects were evaluated by clinical symptoms and joint histopathology.

Results: We found that lipopolysaccharide (LPS) or anti-IgM stimulation induced Foxp3 expression in B cells. Foxp3-expressing B cells were found in the spleens of mice. To generate Foxp3-expressing B cells *in vitro*, we transfected CD19^{+} B cells with a Foxp3 over-expression construct. Over-expression of Foxp3 conferred a contact-dependent suppressive ability on proliferation of responder T cells. Down-regulation of Foxp3 by shRNA caused a profound reduction in proliferation of responder T cells. Adoptive transfer of Foxp3^{+}CD19^{+} B cells attenuated the clinical symptoms of CIA significantly with concomitant suppression of IL-17 production and enhancement of Foxp3 expression in *CD4^{+} T cells* from splenocytes.

Conclusion: Our data indicate that Foxp3 expression is not restricted to T cells. The expression of Foxp3 in B cells is critical for the immunoregulation of T cells and limits autoimmunity in a mouse model.

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Semaphorin 3A Increases the Regulatory Characteristics of B-Regulatory Cells. Zahava Vadasz[1], Aharon Kessel[2] and Elias Toubi[2]. [1]Bnai-Zion Medical Center, Haifa, Israel, [2]Bnai-Zion Medical Center, Israel

Background/Purpose: Semaphorin3A (sem3A) and neuropilin-1 (NP-1), are important regulatory molecules, previously reported by us to play role in lupus glomerulonephritis. In a recent study we demonstrated that sema3A expression on B-regulatory cells (B-regs) of systemic lupus erythematosus (SLE) patients is significantly decreased when compared to that on B-regs of normal individuals. Aiming to achieve a better characterization of B-regs (previously identified by us as CD19+CD25^{high}CD1d^{high}IL-10^{high} TGF-β^{high}), we asked whether other regulatory/stimulatory molecules are differently expressed on B-regs of SLE patients. We also asked whether the addition of sem3A into a culture of B cells could possibly immuno-modulate the expression of these molecules on B-regs.

Materials and Methods: The expression of CD72 and TGF-β (inhibitory molecules), and of CD100 (a stimulatory molecule) was assessed on B-regs of both normal individuals and SLE patients. We then added sema3A to cultured B cells and assessed their regulatory properties after 24 hours. Cell cycle analysis was also done in order to evaluate

Results: 1. The expression of both CD72 and TGF-β was significantly decreased (37.88%, 8.6%) and of CD100 (12.78%) on B-regs of SLE patients vs that on normal B-regs. (49.26%, 14.74%, 21.55% respectively; P=0.001)

2. Twenty four hours following the addition of sema3A to cultured B cells, a significant increase of TGF- β, CD72 and NP-1 molecules and decrease of CD100 on B-regs was noticed. However, this effect of sema3A on B cells was altered in SLE patients when compared to that of normal B cells.

Conclusion: 1. This is the first study were the above studied regulatory molecules are shown to be altered on B regs of SLE patients. 2. Sema3A enhances the regulatory properties of B regs, but this effect is also shown to be altered in SLE.

Disclosure: **Z. Vadasz**, None; **A. Kessel**, None; **E. Toubi**, None.

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Gemin5 Is a New Target of Autoantibodies That Are Produced in Tight Connection with Antibodies to Snrnps and Survival of Motor Neuron (SMN) Complex. Jason YF Chan, Yi Li, Angela Ceribelli, Eric S. Sobel, Westley H. Reeves, Edward K.L. Chan and Minoru Satoh. University of Florida, Gainesville, FL

Background/Purpose: Most targets of autoantibodies in systemic rheumatic diseases are multiprotein-nucleic acids complex. Small nuclear ribonucleoproteins (snRNPs, Sm and U1RNP), key functional components of the mRNA splicing, are one of the most common targets of autoantibodies in systemic lupus erythematosus (SLE) and other systemic autoimmune dis-

eases. Survival of motor neuron (SMN) complex that plays a key role in snRNPs assembly and interacts with snRNPs has recently been identified as a novel target of autoantibodies in polymyositis/dermatomyositis (PM/DM). Autoantibodies to gemin5 that interacts with SMN complex were examined in unselected cohort of rheumatology clinic.

Methods: Sera from patients seen at the Center for Autoimmune Disease (n = 1966, including 453 SLE, 132 scleroderma, 125 PM/DM, 130 Rheumatoid Arthritis, 61 Sjögren's syndrome) were screened for autoantibody specificities by immunoprecipitation (IP) using ^{35}S-labeled K562 cells extract. Anti-gemin5 antibodies were initially screened by IP of ~170kD protein and confirmed by IP-western blot (IP-WB) and antigen-capture ELISA using anti-gemin5 monoclonal antibodies. Sera of interest were also tested by WB using purified gemin5 and immunofluorescent antinuclear (ANA)/cytoplasmic antibodies

Results: Nineteen sera with anti-gemin5 antibodies were identified. All except one (18/19) also had anti-snRNPs (13 anti-U1RNP, 5 anti-U1RNP+ Sm) and one had anti-SMN complex antibodies without anti-snRNPs. Among 18 with anti-snRNPs, 13 clearly had anti-SMN complex antibodies, 3 were inconclusive while 2 were negative. Anti-gemin5 sera were also positive for anti-snRNPs, thus showed nuclear speckled pattern and Cajal body ANA staining. In WB using affinity-purified gemin5, 10 sera were clearly positive, confirming their direct reactivity with gemin5. Anti-gemin5 was found in 6% of anti-snRNPs positive Caucasian or African American and 15% in Latin American. Diagnoses include 10 SLE, one each of SSc and PM and 7 undifferentiated connective tissue disease (UCTD). Clinical features of SLE in anti-gemin5+snRNPs (+) patients were similar to those of anti-snRNPs (+) patients except for absence of discoid lesions, seizures, and anti-phospholipid antibodies (0% vs 48%, P < 0.0001) in the former group. Among anti-gemin5 (+), 4 cases had symmetrical muscle weakness and elevated muscle enzymes and 32% (7/19) had at least one of these, suggesting muscle involvement may be common in this subset. Raynaud's phenomenon was seen in 73%, interstitial lung disease (ILD) in 25%, and sclerodactyly in 14% of anti-gemin5 patients. A case of PM with anti-TIF1beta and U1RNP antibodies developed anti-gemin5 and SMN antibodies a few months later, consistent with the idea of epitope spreading within macromolecular complex.

Conclusion: Anti-gemin5 antibodies are produced in tight association with anti-snRNPs and anti-SMN complex antibodies in SLE and other systemic rheumatic diseases. Clinical features of anti-gemin5+snRNPs antibody positive patients are similar to those with anti-snRNPs although muscle involvement may be more common.

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Antibody Secreting Cells Arising After Vaccination of Lupus Patients May Produce High Affinity Autoantibodies. Kenneth Smith[1], Jennifer Muther[1], Angie Duke[1], Emily McKee[1], Alina Lorant[1], Patrick C. Wilson[2] and Judith A. James[3]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Chicago, Chicago, IL, [3]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: Vaccinating SLE patients with influenza and pneumococcal vaccines is generally considered safe and effective. However, conflicting reports regarding the impact of vaccination on autoantibody production exist. Whether vaccination might facilitate affinity maturation of autoantibody specificities or cause novel specificities to arise is difficult to determine from serum antibody measurements alone. In order to study this question on a *per antibody* basis, we have isolated and expressed human monoclonal antibodies from SLE patients following vaccination with both the influenza vaccine and Pneumovax23. Our technique utilizes antibody secreting cells arising from a memory response to produce antibodies specific to the vaccine. Furthermore, in autoimmune donors we can further characterize the antibodies with respect to common autoimmune specificities.

Methods: We developed a technology that allows us to make fully human monoclonal antibodies from any antigen currently approved as a vaccination in humans. This allows us to make human monoclonal antibodies which are highly specific to the vaccine antigen(s). This technology is based on the discovery of a population of B cells (ASCs), which arise 7 days after vaccination and produce antibody that is specific for the vaccine antigen. These cells can be sorted and their antibody genes cloned to express the antigen-specific antibody from each ASC. We are also capable of reverting the antibodies to their germline configurations to examine the role of somatic hypermutation in their auto-specificities.

Results: Two interesting antibodies were characterized from two SLE donors, one following vaccination with the influenza vaccine (2_156p1E05) and the other following vaccination with Pneumovax23 (pn134p1D02). Although antibody 2_156p1E05 does not bind to influenza virus, it is the first example of a fully human high affinity antibody to Sm (8×10^{-10}M). By line immunoblot, we show that it binds to SmD. When reverted to its naïve/germline configuration, this antibody loses all binding to Sm indicating that such binding arose during somatic hypermutation. Unlike 2_156p1E05, pn134p1D02 does bind to *S. pneumoniae* serotype 5 polysaccharide with high affinity (2×10^{-10}M). However, by line immunoblot, we show that it also binds to nRNP A.

The serum of the donor of 2_156p1E05 was also carefully analyzed over a three year period and this patient's antibody response to Sm clearly affinity matured, increasing in overall affinity in each year. Since this antibody does not bind influenza, it is unclear whether the vaccine played a role in this maturation, however, pn134p1D02 clearly binds polysaccharide and arose or matured after vaccination with Pneumovax23.

Conclusion: The ability to analyze the autoimmune response of a patient with SLE after vaccination on a *per antibody* basis allows us to determine whether new auto-specificities may occur after vaccination. Although this does not appear to be a common event, the fact that it can occur does indeed indicate that vaccination has the potential to increase autoantibody production and potentially clinical flares in select SLE patients.

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Targeting of CD22 by Epratuzumab Potentially Raises the Threshold of B Cell Receptor Activation. N. Sieger[1], S.J. Fleischer[1], K. Reiter[1], H.E. Mei[1], A. Shock[2], G. Burmester[1], C. Daridon[1] and T. Dorner[1]. [1]Charité University Medicine Berlin, Berlin, Germany, [2]UCB Pharma, Slough, United Kingdom

Background/Purpose: CD22, a member of the sialic acid-binding immunoglobulin-like lectins (Siglec) family, is exclusively expressed on B cells at mature stage and is lost upon plasma cells differentiation. CD22 mediates migration by modulating cell-cell interaction and negatively regulates B-cell receptor (BCR) signaling. By recruiting a tyrosine phosphatase to its intracellular tail, CD22 acts as an inhibitory co-receptor of the BCR via de-phosphorylation of signaling molecules such as spleen tyrosine kinase (Syk) and subsequent phospholipase C (PLC)-γ2-triggered Ca^{2+} fluxes. The ligand of CD22 is α-2,6-sialic acid residues present on many proteins, including CD22. Sialo-interactions appear to be crucial for optimal CD22 function and can occur in *cis* (to ligands on the same cell surface) or *trans* (to ligands on neighboring cells). The humanized anti-CD22 monoclonal antibody epratuzumab, currently in phase III clinical trials in SLE, modulates adhesion molecule expression and B cell migration *in vitro*; however, the potential of CD22-ligation with sialic acid to regulate BCR signaling has not been delineated.

Methods: To investigate the impact of epratuzumab on the B cells response, the recruitment of CD22 to the BCR after epratuzumab incubation on peripheral blood B cells from healthy volunteers was studied by confocal microscopy. The *In vitro* effects of epratuzumab on BCR-induced signaling was evaluated by analyzing the phosphorylation status of the BCR-signaling molecules Syk and PLC-g2 by flow cytometry. To assess the importance of sialo-interactions on epratuzumab-induced effects, peripheral blood mononuclear cells were treated with neuraminidase (to remove sialic acid) and BCR-induced phosphorylation (Syk and PLC-γ2) was monitored with or without epratuzumab incubation. Finally, to monitor B cell activation after epratuzumab incubation, the concentration of intracellular Ca^{2+} was monitored by flow cytometry after BCR stimulation.

Results: We have shown by confocal microscopy that incubation with epratuzumab or a F(ab$'$)$_2$ fragment of epratuzumab specifically induced the recruitment of CD22 to the CD79a molecule associated to the BCR on B cells. When B cells are pre-treated with epratuzumab, we observed a reduction of the phosphorylated Syk and PLC-γ2 induced by BCR stimulation. This reduction was observed in the same manner when the cells were pre-incubated with F(ab$'$)$_2$ fragment of epratuzumab which excludes an inhibitory effect dependent on FcR signaling. The reduction of BCR-induced kinase phosphorylation was demonstrated in both CD27$^-$ naïve and CD27$^+$ memory B cells. Interestingly, preventing sialo-interactions of CD22 partially reduced the inhibitory effect of epratuzumab on Syk and PLC-γ2 phosphorylation. In addition, a F(ab$'$)$_2$fragment of epratuzumab reduced the BCR-induced calcium flux.

Conclusion: Taking these data together, these data show that targeting CD22 with epratuzumab potentially raises the threshold for BCR activation and therefore would provide additional control of B cell function. Furthermore, the analysis of CD22 ligation by epratuzumab would provide further understanding of CD22 biology in human autoimmune diseases.

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Phosphoprotein Changes Induced with Epratuzumab, an Antibody Targeting CD22 On B Cells. S. Lumb[1], N. Torbett[2], I. Vandrell[2], H. Turner[2], M. Page[1], P. Hales[1], A. Maloney[1], B. Vanhaesebroeck[2], P. Cutillas[2] and A. Shock[1]. [1]UCB Pharma, Slough, United Kingdom, [2]Activiomics Ltd., London, United Kingdom

Background/Purpose: Epratuzumab is a monoclonal antibody targeting CD22 that is currently in phase III clinical trials in systemic lupus erythematosus (SLE) patients. CD22 is found almost exclusively on B cells and *in vitro* culture with epratuzumab down-regulates B cell receptor (BCR)-dependent cell signaling and B cell activation events. The objective of this study was to investigate epratuzumab-dependent changes in phosphoprotein signals in activated B cells using a recently developed LC-MS/MS methodology (TIQUAS™ or Targeted Quantification of Cell Signalling).

Methods: B cells were purified from human tonsils (n=8 donors) by mechanical homogenisation followed by Ficoll-Hypaque gradient centrifugations. T cells were depleted by E-rosetting using 2 aminoethylisothiouronium bromide (AET) treated sheep red blood cells. The resulting B cells were counted and analysed by flow cytometry for purity, typically B cells preparations were >90%pure. 4×10^7 cells B cells were then stimulated through the BCR using anti-IgM for 2 minutes with or without prior pre-incubation with epratuzumab or IgG1 isotype control for 1 hour. Immediately following stimulation the cells were harvested in ice cold PBS buffer containing phosphatase inhibitors, pelleted by centrifugation and lysed in a urea based lysis buffer containing phosphatase inhibitors. The cell lysates were sonicated on ice and quantitated by BCA protein assay. 500μg of cell extracts were subject to protease digestion and TiO2 phosphopeptide enrichment. LC-MS-MS phosphoproteomic analysis was performed using a label-free quantification strategy. A mixed linear effect statistical model was applied to the quantitation output which comprised data for 3825 distinct phosphorylation sites. The phosphopeptide data set was imported into Ingenuity Pathway Analysis (IPA) and mapped to canonical pathways for further analysis.

Results: This analysis was able to identify statistically significantly regulated phosphorylation sites in response to pre-incubation with epratuzumab using adjusted p- and q- threshold values of <0.05, although the most significant changes generally showed no more than a 2-fold difference from signals induced by BCR stimulation alone. Among the changes observed were BCR-specific downstream signals on a broad range of protein family types: adaptor proteins (SHC1), kinases (ERK1/2, p38delta), phosphatases (SHIP1), histones (H1) and transcription factors (NFAT). Additionally, there was down-modulation of the phosphorylation of Ser717 on CD22 itself.

Conclusion: Pre-incubation of human tonsil-derived B cells with epratuzumab induced discrete but statistically significant changes in phosphoprotein signals after BCR activation. Such observations may enable a better understanding of how epratuzumab modulates B cell functions *in vitro* and possibly in patients with SLE.

Disclosure: **S. Lumb**, UCB Pharma, 3; **N. Torbett**, Activiomics Ltd., 3; **I. Vandrell**, Activiomics Ltd., 3; **H. Turner**, Activiomics Ltd., 3; **M. Page**, UCB Pharma, 3; **P. Hales**, UCB Pharma, 3; **A. Maloney**, UCB Pharma, 3; **B. Vanhaesebroeck**, Activiomics Ltd., 3; **P. Cutillas**, Activiomics Ltd., 3; **A. Shock**, UCB Pharma, 3.

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Effect of Repeated Infusions of Rituximab in Patients with Primary Sjögren's Syndrome. Maria Perez-Ferro, Sheila Recuero, Fredeswinda I. Romero, Cristina Serrano, Maria J. Rodriguez-Nieto, Julio Gomez-Seco, Teresa Presa, Javier R. Godo, Gabriel Herrero-Beaumont and Olga Sanchez-Pernaute. Jimenez Díaz Foundation University Hospital, Madrid, Spain

Background/Purpose: To assess the safety and efficacy of repeated infusions of rituximab (RTX) in patients with primary Sjögren syndrome (PSS).

Methods: Patients with PSS were selected for RTX treatment in case of severe glandular disease or any potentially threatening extra-glandular manifestations. Patients received 2 doses of 1000 mg RTX with a 2-week interval. RTX courses were thereafter programmed every 6 months, for 2 years. The patients were evaluated every 3 months. Criteria for discontinuation were disease progression, appearance of adverse events or inactive disease. At baseline, activity measures and B cell subsets in peripheral blood were studied. Global disease activity was scored with ESSDAI. Descriptive data are expressed in average (limits). Statistical differences between baseline and final measures and the association of disease characteristics at baseline with a favorable outcome were analyzed with non-parametric tests.

Results: 12 patients (11 women) fulfilling inclusion criteria, with a mean age of 60 (42–82) year-old and disease duration of 5.9 (1 – 16) years have been enrolled. Eleven patients had extra-glandular active disease at baseline, consisting of arthritis (6 p), ILD (6 p), Raynaud's phenomenon (5 p), peripheral neuropathy (3 p), and exanthema (3 p). Anti-Ro antibodies were positive in 10 cases, anti-La were found in 4 and rheumatoid factor in 6 cases. At baseline, global B cell counts were within normal range, with a prominent shift towards naïve cells (68% of all CD19+ cells). Interestingly, this appeared to be a favorable marker, since percentage of naïve cells was negative correlated with RF titers (rho −0.84, p < 0.02) and was significantly associated to prednisone dose reduction at end points (rho 0.983, p < 0.005).

The patients have received a total dose of 42500 mg RTX, 3750 mg (500–6000) per patient, over an observation period of 13 (3 – 23) months. During this period, 2 treatments were withdrawn, 1 due to an acute Epstein Barr virus infection at the first RTX course and the second one due to sustained remission. Two additional infections were observed during follow-up, neither of them leading to discontinuation. At endpoints, daily prednisone was tapered in 10 mg/d (Z −2.2, p 0.028). The average ESSDAI dropped from 4.1 (1–9) to 2.2 (0–4), Z −2.33, p 0.02, and showed an adjusted change of −4.22 points per year of follow-up. The change in ESSDAI was correlated to the cumulative dose of RTX (rho 0.665, p < 0.02). Reduction of prednisone was positively correlated to the number of RTX courses and the cumulative dose of RTX. Finally, no reconstitution of the B cell subpopulations has been found over the observation period.

Conclusion: In this cohort of patients with Sjögren's syndrome, RTX showed a favorable safety profile as well as a possible benefit in the short-term control of the process. Although these results should be taken with caution, they suggest that B cell depletion can fill a gap in the management of difficult to treat Sjögren's syndrome.

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Depletion of CD4-Effector Memory T Cells and Clonally Expanded IgG4 Memory B Cells May Explain the Therapeutic Efficacy of Rituximab in IgG4-Related Disease: Studies Using Flow Cytometry and Single-Cell Sequencing. Hamid Mattoo[1], Arezou Khosroshahi[2], Vinay Mahajan[1], Mollie Carruthers[2], John Stone[1] and Shiv Pillai[2]. [1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Massachusetts General Hospital, Boston, MA

Background/Purpose: The clinical effectiveness of rituximab-mediated B cell depletion in chronic inflammatory disorders such as multiple sclerosis and Type I diabetes, which are not believed to be autoantibody-driven conditions, has not been explained satisfactorily. A mechanistic explanation is also lacking for the efficacy of rituximab in IgG4-related disease (IgG4-RD), a chronic inflammatory disorder characterized by fibrosis that might be T cell mediated. Although CD4+ T cells contribute to the activation of B cells during T-B collaboration, activated B cells are required in turn both for the generation of T follicular helper cells and for the induction and maintenance of CD4+ memory T cells. We hypothesize that in IgG4-RD, some as yet unidentified antigens induce T follicular helper cell-mediated B cell activation and the subsequent generation of a Th2 type of CD4+ effector and memory T cell response. The fibrosis that characterizes this disorder may reflect the generation of a B cell-dependent pathogenic Th2 cell response to these uncharacterized antigens.

Methods: We performed detailed flow cytometry studies on B and T cell populations before and after treatment with rituximab in four patients, accompanied by single cell cloning studies of IgG4 memory B cells.

Results: We have detected an expansion of circulating IgG4 memory B cells and of CD4+ effector memory T cells in subjects with active IgG4-RD (a, b). Rituximab therapy not only mediates the depletion of all circulating B cells in IgG4-RD, including the expanded IgG4 memory B cells, but also of the CD4+ effector memory T cell population. Single cell cloning of IgG4 memory B cells from subjects with active disease followed by sequencing of matched Ig heavy and light chains reveals the possible expansion of a few IgG4 B cells with common V_H and V_L usage.
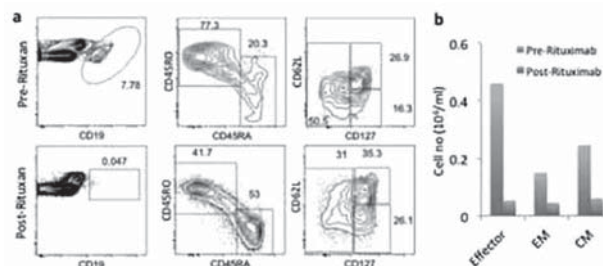
Conclusion: These results support the notion that B cell depletion with rituximab mediates loss of the disease-promoting effector memory CD4+ T cells in IgG4-RD. These studies offer the possibility that the inciting antigen(s) in IgG4-RD may be identified in due course as a result of the identification of clonally-expanded B cells.

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A Rheumatoid Factor Paradox: Inhibition of Rituximab-Induced Complement Dependent Cytotoxicity of B Cells. Jonathan D. Jones[1], Irene Shyu[1], Marianna M. Newkirk[2] and William F. C. Rigby[1]. [1]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [2]McGill University Health Centr, Montreal, QC

Background/Purpose: Rheumatoid factor (RF) is an autoantibody directed against the Fc portion of IgG antibodies. It is found in ~80% of patients with rheumatoid arthritis (RA). It has been postulated that RF potentiates immune complex disease in RA by enhanced fixation of complement. Rituximab (RTX), an antibody targeting CD20 on B cells, exhibits increased efficacy in seropositive patients with refractory RA. We hypothesized that this improved efficacy was due to the ability of RF to enhance the ability of RTX to mediate complement dependent cytotoxicity, leading to enhanced synovial depletion of B cells.

Methods: We developed a model assay system of RTX to mediate complement dependent cytotoxicity (CDC) using the Daudi human B cell line modified to grow in serum-free media. CDC was determined by propidium iodide staining 30 minutes after combining Daudi cells with RTX 10 μg/ml and human sera (1%; as a source of complement) from healthy donors and patients. The effect of RF on RTX-CDC was determined by the following methods: i) Comparison of CDC by RF+ sera vs RF- sera; ii) Addition of monoclonal IgA or IgM RF to seronegative sera; iii) Mixing studies of RF+ and RF- sera.

Results: In the presence of 1% human sera, RTX resulted in rapid (minutes) and profound (>50%) Daudi cell death. This effect was complement dependent as proven by a lack of Daudi cell death by RTX in serum free media, heat-inactivated serum, and C5 deficient serum. A surprising variation in the ability of human sera to mediate RTX-CDC was observed. The mean percent of RTX-CDC ranged from healthy donors 54% (n=15), RF+ RA patients 47% (n=40), RF- RA patients 88% (n=15), non-RA patients 83% (n=15). Remarkably, sera with an IgM RF >250 IU/ml resulted in a mean CDC of 13% compared to sera with IgM RF 9–100 IU/ml having a mean CDC of 74%. A similar effect of increasing IgA RF concentration was seen but was not as profound an effect as IgM RF. Mixing of RF+ sera with RF-sera demonstrated the reduced RTX-CDC, indicating the presence of an inhibitor. The identity of RF as the inhibitory factor was demonstrated by the ability of either purified monoclonal IgM RF or monoclonal IgA RF added to RF- sera to mediate near complete inhibition of CDC at concentrations of 50 μg/ml and 10 μg/ml, respectively. The inhibitory effect of RF could be blocked by excess IgG. In addition, we observed that RF did not alter RTX binding to CD20 on B cells. Therefore, we conclude that RF blocks the ability of early complement components to be recruited to the IgG Fc portion of RTX.

Conclusion: Contrary to our original hypothesis, RF inhibits RTX induced CDC *in vitro*. Thus, the enhanced efficacy of RTX in seropositive RA patients cannot be easily attributed to modulation of B cell depletion through CDC. This result is surprising given the roles of RF in immune complex clearance and complement activation. Not only does this generate a new set of insights into the biologic role of RF, it indicates that high RF levels may potentially modulate the efficacy of any therapeutic monoclonal antibody.

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Disruption of Dominant B-Cell and Plasma Cell Clones in Rheumatoid Arthritis Synovium by Rituximab Correlates with Treatment Response.

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Background/Purpose: Autoreactive B lymphocytes are thought to play an important role in rheumatoid arthritis (RA). B-cell depletion therapy by rituximab (RTX) has shown that targeting B-cells can result in clinical improvement. Unfortunately, the depletion is transient and might result in disease relapse. Hence, analysis of the B-cell/plasma cell compartment in synovium (ST) in patients undergoing RTX therapy might help to identify autoreactive cells responsible for disease persistence and relapse.

Objective: To compare the B-cell/plasma cell repertoire in ST at baseline, 4 weeks and 16 weeks after RTX treatment using a newly developed high-throughput sequencing protocol.

Methods: Eleven RA patients were included and treated with two intravenous infusions of 1000mg RTX without additional methylprednisolone. At baseline, all patients fulfilled ACR criteria for RA, were ACPA+ and had a DAS28score >3.2. At week 24, nine patients demonstrated moderate to good EULAR responses, two patients were marked as non-responders. Immunohistochemistry stainings were performed on formalin-fixed paraffin embedded sections using antibodies against CD22 and CD138. mRNA was isolated from consecutive samples and full-repertoire analysis of the B-cell receptor (BCR) heavy-chain was performed with primers for all V(ariable)-genes. All amplified products encode the CDR3, a unique sequence that defines a unique clone. The number of sequences reflects the amount of BCRs produced by that clone and can be used as a measure for 'dominance' of that particular clone. >40,000 bead-bound sequences were analyzed using a Genome Sequencer FLX (Roche/454). Clones with a frequency of >0,5% were arbitrarily considered as dominant clones.

Results: Clones were detected in equal numbers at baseline and 4 weeks after RTX in all patients. However, after 16 weeks the number of dominant clones significantly increased compared to baseline (mean +55,3%, p=0.04). In line, there was a significant decrease in the number of non-dominant clones compared to baseline (mean −47.7%, p=0.03). This mirrored the regression of clinical symptoms measured by the DAS28 score as well as subsequent declines in the number of CD138+ plasma cells in the synovium 16 weeks after the infusion. In 5 patients, 17.9% of the dominant clones at baseline was still detectable after 16 weeks (mean, SD 8.0%), half of these were dominant at both time points (mean 8.8%, SD 4.6%). In the remaining 6 patients dominant clones at baseline were not at all retrieved 16 weeks after RTX. Interestingly, the latter group showed better treatment responses determined by the ΔDAS28score (−0.76 (SD 0.37) and −2.2 (SD 0.79) DAS28 points resp., p=0.005, r^2=0.58).

Conclusion: Our observations suggest a disruption of dominant clones and a repopulation of distinctly different clones 16 weeks after rituximab. The persistence of dominant clones was associated with decreased treatment response. Further analysis of clones persistence, amongst others during disease relapse, might help to characterize disease-associated B-cells and/or plasma cells, and identify novel biomarkers for treatment response.

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The Alternative ΔCD20 Transcript Variant Is Not Expressed in B Cells and Synovial Tissue From Patients with Rheumatoid Arthritis.

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Background/Purpose: Determining predictive factors for response to biologics may help to select appropriate treatment in patients with RA. Rituximab (RTX) is a chimeric monoclonal antibody directed against the membrane CD20 protein present on B cells. Predictive factors for good response to RTX therapy in RA have been identified and included the presence of rheumatoid factors and anti-CCP antibodies. A spliced mRNA transcript of CD20 (ΔCD20) has been observed in B cell lines from patients with lymphoma and leukaemia (1). This transcript is coding for a non anchored membrane protein and its expression is associated with resistance to RTX in patients with haematological malignancies.

Objectives: To determine whether ΔCD20 is expressed by circulating B cells and synovial tissue from patients with RA and whether it could be a factor for non response to RTX therapy in RA.

Methods: 23 RA patients (17 F, age (mean ± SEM): 60.1 ± 2.7 years; disease duration: 13.3 ± 1.7 years, positive rheumatoid factors: 19/23; positive anti- CCP antibodies: 19/23) and 20 healthy controls (HC) (15 F, age: 59.6 ± 2.5 years) were evaluated. Patients were under DMARDs, low corticosteroids (< 10 mg/l) or anti TNFa agents, but none received or had received RTX. Five patients with RA requiring treatment with RTX were also evaluated prior to the first RTX infusion and during a one year follow- up study. CD20 mRNA expression study was performed using RT-PCR assay allowing first to discriminate full length CD20 (membrane CD20) from ΔCD20 transcripts. A more sensitive RT-PCR assay, using a specific primer spanning the splice fusion area was then used to detect specifically only the ΔCD20 transcript. This analysis was performed on peripheral blood B cells from patients with RA and HC and synovial tissue from RA patients obtained during surgery.

Results: RA patients had mild active disease (DAS28 score: 3.3 ± 0.3; CRP levels: 6.8 ± 1.9 mg/l). Number of circulating B cells per μl was not different between RA patients and controls (mean ± SEM, range: 184 ± 22, 18–437 *vs* 211± 27, 63–408, respectively). Among all the 23 RA samples, although full length CD20 expression was always detected, we were unable to detect ΔCD20, even with the more sensitive RT-PCR assay permitting to identify the spliced transcript form. Among the 5 patients who received RTX, 4 well responded to the treatment. Both responders and non responder patients did not express ΔCD20 before RTX administration and during the follow-up study. ΔCD20 was also not detected in synovial tissue samples from 5 patients with RA.

Conclusion: The present study showed that, on the contrary of leukemic or lymphoma B cells, RA B-cells and synovial tissue from RA patients do not express ΔCD20, suggesting that this transcript may be a molecular marker of malignancies rather than a factor predictive to RTX response in auto-immune diseases like RA. We are currently examining whether B cell stimulation may help to evidence ΔCD20 expression in RA B-cells.

1- Henry C *et al.*, Blood, 2010;115:2420–9

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Peripheral Blood B Cell Subsets and BAFF/APRIL Receptor Expression, Together with Circulating BAFF and APRIL Levels, Are Disturbed in Rheumatoid Arthritis but Not in Ankylosing Spondylitis.

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Background/Purpose: B cells play a critical role in systemic autoimmune disease and especially rheumatoid arthritis (RA). BAFF and APRIL are involved in B cell activation and survival. B cell depletion therapies may target specific B cell subsets and/or B cell activating factors or receptors. Few studies have evaluated the distribution of the different peripheral blood B cell subsets in RA as well as the expression of BAFF/APRIL receptors. Ankylosing spondylitis (AS) is an inflammatory rheumatic disease without current evident contribution of B cells to the inflammatory response.

Objectives: To evaluate the distribution of circulating B cell subsets and their expression of BAFF/APRIL receptors (TACI, BCMA and BAFF-R) as well as the circulating levels of BAFF and APRIL in patients with RA or AS compared to healthy controls (HC).

Methods: 59 patients with RA (ACR criteria, 12 M, age [mean ±SEM; years]: 58 ± 1.5, disease duration: 10.1 ± 1.5; all under traditional DMARDs, no biologics, corticosteroids < 10 mg/day N= 33), 61 patients with AS (modified NY criteria; 46 M; age: 46 ± 1.8, disease duration:11.6 ± 1.2; all under NSAIDs or traditional DMARDs) and 61 HC (13 M; age: 43.6 ± 1.8) were evaluated. For each subject, peripheral blood B cell subsets were assessed using multi-color flow cytometry. B cell subsets were analysed according CD27, CD38 and IgD staining (naive B cells: CD27- IgD+ CD38lo, transitional: CD27- IgDlo CD38hi, pre-GC: CD27+IgD+CD38hi, post-GC: CD27+IgD-CD38lo). The expression of BAFF-BR3, TACI and BCMA was analysed on each subset. RFI was calculated by dividing the MFI of the marker divided by MFI of the isotype-matched mAb. Cells were analysed using a FACSCantoII and FACSDiva Software (BD Biosciences). BAFF and APRIL serum levels were determined by ELISA using commercially available kits (Bender MedSystems and R&DSystems) respectively.

Results: Circulating BAFF and APRIL levels were increased in RA compared to HC (1100.5 ± 62.5 vs 904.9 ± 29.4 pg/ml, p= 0.01 and 19116.3 ± 4918.6 vs 5699.2 ± 1034.5 pg/ml, p < 0.001, respectively), while no difference was observed in the levels of these activating B-cell factors in AS and HC. The ratio BAFF levels/peripheral B cell count was also significantly increased in RA (p = 0.04). The following B cell subsets were decreased in RA compared to HC: total B cells (p= 0.004), naïve B cells (p = 0.02), transitional B cells (p < 0.001), while post GC and CD27^{+} B cells were not different. B-cell subsets were comparable in AS and HC. Expression of BAFF and APRIL receptors were increased in the RA group, especially TACI on CD19^{+} B cells, transitional B cells and pre GC B-cells (all p < 0.05) and BCMA on CD19^{+}, naive B cells, transitional B cells, memory B cells, pre-GC and post-GC B-cells (p < 0.05) while BAFF-R RFI was comparable in RA and HC. The expression of BAFF/APRIL receptors did not differ between AS and HC.

Conclusion: Overall, our data confirm that B cell responses are altered in RA with biased repartition of B cell subsets, elevated levels of B cell activating cytokines and increased expression of their receptors. These results may be helpful for guiding and /or monitoring B cell targeted therapies in RA. In contrast, no alteration was observed in AS patients excluding an involvement of disturbed B cell responses in AS.

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B Cell Activating Factor Receptor Expression After Rituximab: Comparison of Patients with Rheumatoid Arthritis and Thrombotic Thrombocytopenic Purpura.

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Background/Purpose: B cell depletion therapy based on rituximab (RTX) is an effective therapy for Rheumatoid Arthritis (RA) and for Thrombotic Thrombocytopenic Purpura (TTP). Serum B cell activating factor (BAFF) levels are within normal limits in patients with RA prior to RTX therapy, but may be raised in TTP. BAFF levels rise after RTX in both diseases. Nearly all mature B cells express BAFF-receptor (BAFF-R) in normal individuals. We have previously described lower % of naïve and memory B cells expressing BAFF-R in RA at relapse following RTX. Here, we present B cell phenotypes and %BAFF-R+ve cells in TTP patients at repopulation and in both diseases in repopulated patients in remission after RTX. **Results** were also analyzed in relation to serum BAFF levels.

Methods: Phenotypes and %BAFF-R+ve naive (CD27-) (NB) and memory (CD27+) (MB) B cells were performed using FACS analysis. Healthy controls (HC), patients with TTP, either repopulating or in remission were compared with RA repopulated patients remaining in remission after RTX (Mann Whitney U test).

Results: Median time to repopulation in TTP patients was 6 months, range 4–7. Time of sampling after RTX in repopulated patients ranged from 8–38 months in RA remission patients and 10–68 months in TTP remission patients. In remission, NB cells remained high with slow regeneration of MB in both RA and TTP. As previously shown in RA, % BAFFR +ve cells in TTP were low at repopulation in both NB and MB cells. However, % BAFFR +ve cells reached normal levels in TTP patients remaining in remission months after repopulation, but stayed low in patients with RA, independent of time after last RTX cycle or number of cycles. BAFF levels remained elevated in RA patients in remission as opposed to TTP. There was a significant inverse correlation between BAFF levels and % BAFF-R +ve NB and MB cells in TTP patients in remission (p<0.001; r^2>0.70 in both) but not in patients with RA.

Median + range	HC (n:5)	TTP Repopulation (n:4)	TTP Remission (n:14)	RA Remission (n:9)
Naïve B cells %	71 (59–84)	86 (35–98)	93 (86–98)	96 (66–98)
Memory B cells %	29 (16–40)	13 (1.3–64)	6 (1.1–13)	3 (1–34)
%BAFFR+ve in NB	100 (99–100)**	66 (17–80)**	95 (29–99)*	52 (18–88)*
%BAFFR+ve in MB	99 (98–99)**	44 (18–86)**	88 (41–98)*	42 (22–62)*
BAFF levels (ng/ml)	1 (0.98–1.09)	2.3 (1.70–2.70)	1.42 (0.90–3.30)*	6 (1.70–11.70)*

*p <0.01
**p<0.05

Conclusion: Repopulation of B cells after RTX follows similar patterns in patients with TTP and RA, with naïve B cells predominant. The finding that %BAFF-R+ve B cells was lower in remission in RA but not in TTP after RTX suggests a disease specific dysregulation, consistent with an auto-immune phenotype already present in repopulating B cells.

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Serum BAFF Levels and Relationship with BAFF Binding Receptors in Patients with Rheumatoid Arthritis Relapsing After B Cell Depletion Therapy.

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Background/Purpose: B-cell-activating-factor (BAFF) coordinates differentiation of B cells into immunoglobulin secreting cells (ISC) by binding to 3 different receptors (BBRs), namely BAFF-R, transmembrane activator and Calcium signal modulating cyclophilic ligand interactor (TACI) and B cell maturation antigen (BCMA). BAFF levels rise after B cell depletion therapy based on rituximab (BCDT) and remain raised in some patients at relapse. BAFF-R expression is reduced in relapsing patients after BCDT. We examined the level of BBR expression at relapse in relation to serum BAFF levels.

Methods: BBRs % expression was examined on B cell sub-populations defined using combinations of CD19, CD38 and IgD. Serum BAFF levels were determined using a Human Quantikine[O] BAFF/BLyS Immunoassay ELISA kit. We studied 10 Healthy Controls (HC), 10 RA patients before BCDT (Pre-BCDT) and 20 patients with RA at relapse, including 10 patients who had relapsed within 3 months after repopulation (Concordant Relapse:

C-R) and 10 patients who had relapsed >3 months after repopulation (Discordant Relapse: D-R).

Results: Following BCDT, BAFF levels rose and were significantly raised at relapse in both patient groups (C-R: median 2.19 ng/ml; 0.96–4.55, D-R: median 1.90 ng/ml; 1.14–6.47) when compared to HC (median 1.11 ng/ml; 0.89–1.24; p=0.02; p=0.002, respectively) and D-R only compared with patients pre-BCDT (1.39 ng/ml; 0.84–2.39; p=0.05). In the C-R group, 5/10 patients and in the D-R group 4/10 patients had BAFF levels > 2.4 ng/ml. In patients with raised BAFF levels, in all B cell subsets except plasmablasts, %BAFF-R+ cells were significantly reduced compared with HC. % TACI+ cells were significantly reduced only in post-Germinal Center (GC) B cells in both relapsing patient cohorts. When serum BAFF levels were within normal limits, %BAFF-R+ transitional B cells in C-R patients were significantly lower than in D-R patients and HC, with other B cell populations following similar patterns as in total cohorts. %TACI positive cells remained significantly reduced in post-GC populations in D-R patients only, compared with HC.

Conclusion: Patients with a C-R pattern of relapse maintained lower % BAFF-R+ B cells in transitional population compared with HC and D-R patients, independent of BAFF levels. This suggests that a proportion of this newly repopulating naïve B cell population is already committed to differentiation to ISC in patients with a concordant pattern of relapse. Reduced %TACI+ B cells in post-GC populations from D-R patients with normal BAFF levels may reflect a lack of up-regulation of TACI or downregulation due to internalisation or shedding of bound BAFF. Our results highlight probable differences in B cell biology in patients with different patterns of relapse following BCDT.

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Expression of Surface APRIL and Its Receptor, TACI, Is Upregulated On B Cells From Systemic Lupus Erythematosus and Rheumatoid Arthritis Patients. Abby Jones Weldon[1], Sheri Hsu[2], Seyed K. Nazeri[3], Saru Sachdeva[2], Jennifer Gonzalez[1], Andrea D. Parra[1], Abigail Benitez[1], Keith K. Colburn[4], Ioana Moldovan[4] and Kimberly J. Payne[1]. [1]Loma Linda University, Loma Linda, CA, [2]Loma Linda University Medical Center, Loma Linda, CA, [3]Loma Lida University Medical Center, Loma Lida, CA, [4]Loma Linda Univ Medical Center, Loma Linda, CA

Background/Purpose: Autoimmune disease affects more than 23 million Americans. Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) are chronic, systemic B-cell mediated autoimmune diseases. During normal B cell development, autoreactive B cells are eliminated by negative selection processes that include receptor editing, anergy, or apoptosis. The increased numbers of autoreactive B cells in SLE and RA suggests that these patients have defects in negative selection that occurs during the immature stages of B cell development. The tumor necrosis factor (TNF) family members APRIL and BAFF have been shown to promote the survival of immature and naive B cells in mouse models of autoimmune disease. Elevated levels of BAFF and APRIL may contribute to the breakdown of negative selection mechanisms. Serum levels of APRIL and BAFF are elevated in patients with SLE and RA and surface forms of these proteins have been detected on normal and/or malignant B lineage cells. Using flow cytometry we found surface forms of APRIL and BAFF on peripheral blood B cells from SLE and RA patients. The aim of this study is to compare surface expression of APRIL and BAFF and their receptors on B cells from SLE and RA patients to normal B cells and to elucidate their roles in B cell-mediated autoimmunity.

Methods: Venous peripheral blood (PB) samples were collected from normal, RA, and SLE patients through an IRB-approved protocol. SLE and RA diagnosis was confirmed using American College of Rheumatology (ACR) criteria. Peripheral blood mononuclear cells (PBMCs) were separated from whole blood by red blood cell lysis. Human adult peripheral blood samples were stained for seven-color flow cytometry to assess co-expression of CD24, CD21, IgD, IgM, CD38, CD27, CD256 (APRIL), CD257 (BAFF), CD267 (TACI), and BR3 (BAFF-R). Stained cells were analyzed using a MACSQuant Analyzer (Miltenyi) and FlowJo analysis software (Tree Star). Mean fluorescence intensities (MFI) for surface APRIL and other markers on B cells from RA and SLE patient samples were compared to normal controls by one-tailed, unpaired t-test, p<0.05.

Results: Peripheral blood B cells obtained from normal (n=11), SLE (n=13), and RA (n=12) were characterized by flow cytometry. The MFI of APRIL, BAFF, BAFFR and TACI on CD19+IgM+ B cells of RA and SLE patients were compared to normal PB. Surface APRIL expression was significantly higher on B cells from RA (p=0.0083) and SLE (p=0.0146) patients as compared to normal donors. The receptor, TACI, which binds both APRIL and BAFF was also increased on B cells from RA (p=0.0114) and SLE (p=0.0146) patients.

Conclusion: Expression of surface APRIL and the TACI receptor are significantly higher on B cells from RA and SLE patients as compared to normal B cells. These results show that in SLE and in RA the patient's B cells themselves serve as a reservoir of surface APRIL that provides a potential source of stimulation for the TACI receptors that are also upregulated on these cells. These data implicate surface APRIL and TACI in B-cell mediated autoimmune disease. Ongoing studies are focused on establishing the relationship between the level of surface APRIL expression and disease activity.

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A Gene Expression Signature to Monitor Depletion of Plasma Cells Following MEDI-551 (anti-CD19) Administration. Katie Streicher, Chris Morehouse, Christopher Groves, Bhargavi Rajan, Fernanda Pilataxi, Kim Lehmann, Philip Brohawn, Kathleen McKeever, Volker Knappertz, Ronald Herbst, Yihong Yao and Koustubh Ranade. MedImmune, LLC, Gaithersburg, MD

Background/Purpose: Production of pathogenic autoantibodies by inappropriately self-reactive plasma cells (PC) is a hallmark of autoimmune diseases. MEDI-551 is an anti-CD19 antibody which is expected to significantly deplete PC, distinct from anti-CD20 targeted therapy which does not deplete PC. Low PC numbers in whole blood (usually 0.5% of total cells) and their instability, make it challenging to implement routine flow cytometry assays to measure PC levels in clinical trials. To address this limitation, we developed a robust gene-expression based assay which can be easily implemented in clinical trials to measure the PC population.

Methods: Based on literature and whole genome microarray analysis of sorted cellular fractions and purified PC, we identified genes (IGHA, IGJ, IGKC, IGKV, and BCMA) whose expression is highly significantly enriched in PC. We developed a signature score combining expression levels of these genes to estimate PC counts in whole blood. Flow-sorted cells obtained from healthy volunteers were used to assess the sensitivity, specificity, and reliability of detecting alterations in PC numbers using this gene expression signature.

Results: We demonstrated clinical utility of this PC signature using samples from patients enrolled in CP-200, a Phase I single dose-ranging trial (N = 27) of MEDI-551 in scleroderma. MEDI-551 caused a robust depletion of the PC gene signature in whole blood and skin, with maximum depletion reaching approximately 98% and 90%, respectively. Up to 90% B cell depletion was observed in blood and skin. At 85 days following MEDI-551 administration, the last timepoint evaluated, PC and B cell levels recovered up to 65% of baseline.

Conclusion: This newly developed gene-expression based PC signature provides a robust and straightforward way to accurately measure PC levels in the clinic. By applying this PC signature, we demonstrated significant depletion of PC cells by MEDI-551, an anti-CD19 monoclonal antibody. In combination with flow cytometry data, this PC signature will help inform dosing decisions for future trials of MEDI-551, as well as provide the ability to correlate clinical activity with baseline PC levels or with the extent/duration of PC depletion.

Disclosure: K. Streicher, AstraZeneca, 1, MedImmune, LLC, 3; **C. Morehouse**, AstraZeneca, 1, MedImmune, 3; **C. Groves**, AstraZeneca, 1, MedImmune, LLC, 3; **B. Rajan**, AstraZeneca, 1, MedImmune, LLC, 3; **F. Pilataxi**, AstraZeneca, 1, MedImmune, LLC, 3; **K. Lehmann**, AstraZeneca, 1, MedImmune, LLC, 3; **P. Brohawn**, AstraZeneca, 1, MedImmune, LLC, 3; **K. McKeever**, AstraZeneca, 1, MedImmune, LLC, 3; **V. Knappertz**, AstraZeneca, 1, MedImmune, LLC, 3; **R. Herbst**, AstraZeneca, 1, MedImmune, LLC, 3; **Y. Yao**, AstraZeneca, 1, MedImmune, LLC, 3; **K. Ranade**, AstraZeneca, 1, MedImmune, LLC, 3.

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Suppression of Rheumatoid Arthritis B Cells by XmAb5871, an Anti-CD19 Monoclonal Antibody That Co-Engages the B Cell Antigen Receptor and the FcγRIIb Inhibitory Receptor. Seung Y. Chu[1], Karen Yeter[2], Roshan Kotha[2], Erik Pong[1], Yvonne Miranda[1], Hsing Chen[1], Sung-Hyung Lee[1], Irene Leung[1], John R. Desjarlais[1], William Stohl[2] and David E. Szymkowski[1]. [1]Xencor, Inc., Monrovia, CA, [2]University of Southern California Keck School of Medicine, Los Angeles, CA

Background/Purpose: XmAb®5871 is a humanized and Fc-engineered antibody that coengages CD19, part of the B cell receptor (BCR) complex, with the inhibitory receptor FcγRIIb (CD32b). This antibody is in clinical development as a potential therapy for RA and SLE, and we have previously characterized its immunosuppressive effects on B cells from normal and SLE donors. In this study, we assessed whether XmAb5871 similarly inhibits activation of RA B cells. Because XmAb5871 activity requires its Fc domain to bind with high affinity to FcγRIIb, we also assessed whether rheumatoid factor (RF), an anti-IgG Fc autoantibody, could interfere with its therapeutic mechanism.

Methods: Blood from RA (N = 50) and normal (N = 72) donors was obtained with IRB approval. PBMC were analyzed by flow cytometry for expression of CD19, CD27, CD32b and CD86. Phosphorylation of FcγRIIb following incubation of PBMC with XmAb5871 was determined by phosphowestern blotting. XmAb5871-mediated suppression of intracellular calcium flux triggered by anti-CD79b in PBMC loaded with Fluo-4 NW dye was quantified by flow cytometry. Inhibition by XmAb5871 of CD86 expression on anti-CD79b-stimulated B cells was determined in whole blood. Plasma RF and ACPA levels were measured by ELISA. Demographic and clinical characteristics of RA patients were correlated with results from in vitro assays.

Results: RA and normal B cells expressed CD19 and CD32b, the targets of XmAb5871. There was a smaller memory (CD27+) B cell compartment in RA (P = 0.003). CD32b expression was higher on naive (CD27-) (P = 0.0018) but not on memory B cells (P = 0.85) from RA vs. normal donors. BCR-mediated calcium flux was suppressed by XmAb5871 in RA and in normal B cells (67% vs. 50%, respectively; P = 0.0038). This inhibition was associated with FcγRIIb activation in RA and normal B cells (average 10-fold induction in both). Baseline CD86 expression was increased in naive and particularly in memory B cells of RA donors (P = 0.04 and < 0.0001, respectively). XmAb5871 efficiently inhibited CD86 induction in RA and normal B cells (76% vs. 62%, respectively; P = 0.0055). Notably, there was no effect of RF or ACPA levels on drug efficacy (R^2= 0.002 and 0.021, respectively). Among RA patients, functional effects of XmAb5871 did not correlate with age, sex, years from diagnosis, extra-articular manifestations, tender or swollen joint counts, DAS28, erosive disease, or use of methotrexate, hydroxychloroquine, corticosteroids, or TNF antagonists. A history of rituximab treatment was associated with fewer memory B cells and reduced CD32b expression (P = 0.003 and 0.040, respectively). Nonetheless, the functional effects of XmAb5871 on B cells from these patients were not different from those in the RA cohort at-large.

Conclusion: The FcγRIIb inhibitory pathway in B cells from RA patients can be amplified by an antibody engineered to co-engage FcγRIIb and CD19 with high affinity. The potency observed across multiple measures of B cell function in RA and normal donors and the lack of interference by physiological levels of RF and ACPA in RA patient sera suggests that XmAb5871 may represent a new therapeutic strategy to suppress autoreactive B cell populations in RA and related autoimmune diseases.

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IL-6 Receptor Inhibition by Tocilizumab Modulates Double Negative (CD19+IgD-CD27-) B Cells in RA. Zafar Mahmood[1], Khalid Muhammad[1], Petra Roll[1], Stefan Kleinert[1], Thomas Dörner[2] and Hans Peter Tony[1]. [1]University of Würzburg, Würzburg, Germany, [2]Charite Universitätsmedizin Berlin and DRFZ, Berlin, Germany

Background/Purpose: Double negative (CD19+IgD-CD27-) B cells have been reported to be part of human memory B cell compartment. Detailed studies of DN B cells in autoimmune diseases like rheumatoid arthritis (RA) and during different B cell targeted therapies are sparse. Therefore we analyzed in detail these cells in RA patients under IL-6 R inhibitor tocilizumab.

Methods: DN B cells were phenotypically analyzed from RA patients (mean age ~61 years) at baseline and 12, 24 and 48 weeks after tocilizumab treatment. Additionally, single B cell sorting technology followed by nested PCR approach was used to study mutational pattern of Ig- receptors VH genes.

Results: The phenotypic analysis of DN B cells in RA patients (n=33) and healthy individuals (n=22) showed a significantly expanded population (p=0.034) of these cells in RA. DN B cells showed a heterogeneous mixture of IgA, IgG and IgM expressing cells with clear dominance of IgG+ cells. Pre-therapy analysis of rearranged IgR sequences from patients (n=7) revealed comparable but diversified mutational pattern of DN B cells comprising mutated and non-mutated sequences. During tocilizumab, DN B cells showed significantly reduced mutational frequency in their Ig-receptors with a marked reduction of the mutated Ig-receptors at week 12 (p<0.0001), 24 (p=0.0147) and 48 (p=0.0017) during treatment.

Conclusion: Our data suggest expanded DN B cells population in RA which are susceptible to IL-6R inhibition in vivo by tocilizumab. Particularly, acquisition of mutations was substantially altered in DN B cells. These results indicate that DN B cells have dependence on the IL6/IL6R system for differentiation in vivo which can be modulated by anti-IL6R therapy.

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The Role of SYK in Human B CELL Activation and Its Relevance to Autoimmune Diseases. Shigeru Iwata[1], Kunihiro Yamaoka[1], Hiroaki Niiro[2], Kazuhisa Nakano[1], Sheau-Pey Wang[1], Koichi Akashi[2] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Kitakyushu, Japan, Kitakyushu, Japan, [2]Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, Fukuoka, Japan

Background/Purpose: B cells play a pivotal role in pathological processes of autoimmune diseases. Spleen tyrosine kinase (Syk) functions as a key molecule in B-cell receptor (BCR)-mediated signaling. However, the underlying mechanisms of Syk in autoimmune diseases such as RA and SLE remain unclear.

Methods: Purified naïve (CD27−) and memory (CD27−) B cells from healthy donor were stimulated with BCR cross-linking, soluble CD40L, and CpG-ODN2006. The role of Syk was evaluated with a specific Syk inhibitor: BAY61–3606. B cell line (Raji) and PBMCs from RA and SLE patients were utilized to assess the detailed molecular mechanism of activated B cells and involvement in the pathology of RA and SLE.

Results: BCR-crosslinking, in conjunction with CD40 and TLR-9 stimulations, efficiently activate B cells and induced various functions such as proliferation and differentiation especially in memory B cells, while specific Syk inhibitors completely abrogated them to background levels. It is noteworthy that BCR-crosslinking markedly induced expression of TNF receptor-associated factor (TRAF)-6 but not TRAF-2,-3 and -5. Additional CD40 and TLR9 stimulations further induced expression of TRAF-6 and phosphorylation of NF-κB, while a Syk inhibitor again significantly inhibited them. Strong phosphorylation of Syk were observed in B cells from RA (n=62) and SLE patients(n=58) compared with healthy donors (n=27). Levels of Syk phosphorylation were higher in SLE patients positive for anti-dsDNA antibodies than those negative for them and also well correlated with the disease activity score such as SLEDAI. On the other hand, Syk phosphorylation were higher in RA patients most positive for anti-CCP antibodies than those negative for them, however, not correlated with the disease activity score such as DAS28, CDAI and SDAI.

Conclusion: Syk-mediated BCR-signaling is prerequisite for optimal induction of TRAF-6, thereby allowing efficient propagation of TLR9-signaling critical for proliferation and differentiation of human memory B cells. Moreover, we suggest that Syk-mediated signaling on B cells is involved in pathological process in autoimmune diseases via producing autoantibody, however, more dominantly in pathology of SLE compared with RA.

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B Cells in Early Rheumatoid Arthritis: ZAP-70 More Than SYK Characterize Seropositive Disease. Anna Laura Fedele, Barbara Tolusso, Elisa Gremese, Silvia Laura Bosello, Angela Carbonella, Silvia Canestri and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: B cells are involved as central players in the pathogenesis of rheumatoid arthritis (RA). Our aim was to define whether a specific B cell subset characterizes the early phases of the disease and is associated with a peculiar RA phenotype.

Methods: 105 ERA patients (81.0% females; mean age 54.7 ± 15.2 years; 73.3% autoantibodies-AAB positive) and 30 healthy controls (HC) were studied. Baseline clinical and immunological characteristics and inflammatory status were assessed. Peripheral blood samples were analyzed by flow cytometry for the distribution of circulating B cell subsets by staining with surface markers CD19, CD45, CD38, CD27 and IgD and intracellular marker ZAP70. Plasma levels of IL-6 and BAFF were also determined with ELISAs. The expression of ZAP-70 and SYK was analized in B cells of 22 ERA patients, using the RealTime ready Assay method.

Results: ERA patients showed a higher percentage of naïve-activate B cells and a lower percentage of memory B cells compared to HC, as confirmed by a higher ratio between Bm2+Bm2'/eBm5+Bm5 (3.4±3.5 in ERA and 1.7±0.9 in controls, *p=0.003*). AAB positive patients showed a higher percentage of CD19+/CD38+CD27+ (4.0±5.0%) compared to AAB negative ones (2.2±2.8%, *p=0.05*). The expression of ZAP-70 in B cells was similar in ERA patients and controls. Dividing patients for the AAB seropositivity, AAB+ ERA patients showed higher percentage of CD19+/ZAP70+ cells compared to AAB- (5.1±6.3 vs 2.5±2.4, *p=0.01*) and also to HC (2.2±1.4, *p=0.05*). In ERA patients, the percentage of ZAP70+ B cells correlated directly with the percentage of CD19+/IgD-CD27- cells (r=0.338, p=0.001), plasma BAFF levels (r=0.26, p=0.01) and with Anti-MCV (r=0.27, p=0.01), ACPA (r=0.23, p=0.02) and RF-IgA (r=0.28, p=0.01) AAB titers. ZAP-70 transcription in B cells of subjects seropositive for autoantibodies was significantly higher than in seronegative ones (3.4 ± 2.8 vs 1.2 ± 1.0 respectively; p=0.04), data confirmed by an higher ratio ZAP70/SYK in AB+ compared to AB- (2.9 ± 1.6 vs 1.2 ± 1.0 respectively; p=0.01). Moreover, the expression of ZAP-70 correlated positively with the expression of SYK (r=0.66, p=0.003) and showed a trend for an association with the espression of ZAP70 protein, evaluated by flow-cytometry (r=0.41, p=0.09).

Conclusion: ZAP-70 positive B cells characterize AAB positive RA and the expression of ZAP-70 might be a possible complementary biomarker of seropositive disease.

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Rheumatoid Arthritis Is Associated with Signaling Alterations in Naturally Occurring Autoreactive B-Lymphocytes. Taras Lyubchenko, Ganna Liubchenko, Holly C. Appleberry, Christopher C. Striebich, Karen E. Franklin, Lezlie A. Derber and V. Michael Holers. University of Colorado Denver, Aurora, CO

Background/Purpose: Alterations in B cell immune tolerance are important in the development of autoimmune rheumatoid arthritis (RA). Recent studies in healthy human subjects have identified a subset of potentially autoreactive CD19+CD27-IgD+IgMlow/- late transitional cells that constitute ~2.5% of peripheral blood B cells and have anergic signaling properties. These cells are hyporesponsive to antigen receptor stimulation *in vitro* and have the capacity to produce autoreactive antibodies (Abs). The function and signaling properties of these cells have not been characterized in RA (or any other human autoimmune disorder to date). Early alterations in signaling profile of these cells are of significant value for the prediction of the onset of autoimmunity as pathogenic Abs and other clinical manifestations of RA are detectable only after a prolonged period of autoantibody expansion.

Methods: Phosphorylation of intracellular signaling proteins and intracellular Ca2+ levels in CD19+CD27-IgD+IgMlow/- B cells at baseline and in response to *in vitro* BCR stimulation with polyclonal anti-human Ig were measured by multicolor flow cytometry in the peripheral blood cells from 32 normal healthy control donors and 20 patients with RA. Signaling properties of anergic B cells were compared to other peripheral blood B cell populations both in normal controls and RA patients.

Results: B cell signaling profiles at baseline and in response to anti-BCR stimulation were examined in 32 healthy donors (mean age 35.7; male/female ratio 0.68) and 20 RA patients (mean age 55.9; male/female ratio 0.54) from UC Denver Hospital Rheumatology Clinic. RA patients were recently diagnosed; most were serum RF and/or anti-CCP positive and have not undergone B cell targeted treatments. No significant phenotypic or quantitative differences were found between IgM+ and CD19+CD27-IgD+ IgMlow/- B cell subsets obtained from RA patients and normal controls. CD19+CD27-IgD+IgMlow/- B cells from RA patients demonstrated increased baseline total phospho tyrosine (pTyr) protein phosphorylation as compared to normal controls. In contrast to the control group, in RA patients, CD19+CD27-IgD+IgMlow/- B cells total pTyr and Ca2+ responses to anti-BCR stimulation resembled those of normal non-anergic IgM+ B cells. Comparison of baseline phosphorylation levels of individual signaling molecules between unstimulated RA and control CD19+CD27-IgD+IgMlow/- B cells revealed pronounced increases in Blnk, SHP2 and Jnk in the RA group. Comparison of signaling properties CD19+CD27-IgD+IgMlow/- B cells in RA patients and healthy controls revealed a reversal of pTyr and Ca2+ anergic signaling features in patients, accompanied by phosphorylation decreases of Blnk, Syk, SHP2, CD19.

Conclusion: CD19+CD27-IgD+IgMlow/- B cells under normal conditions showed characteristic signaling inhibition, which was reversed in this cell population in RA patients. A distinct phosphoryation pattern for major signal transduction proteins in CD19+CD27-IgD+IgMlow/- B cells in RA patients as compared to healthy controls at baseline and in response to BCR stimulation was demonstrated.

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Synovial Gene Expression and Response to Rituximab: Preliminary Data. Yasser El-Sherbiny[1], Sarah Churchman[1], Frederique Ponchel[1], Paul Emery[2] and Edward M. Vital[1]. [1]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]University of Leeds, Leeds, United Kingdom

Background/Purpose: Quality and duration of response to rituximab in rheumatoid arthritis have not been completely explained. In the synovium, three studies have indicated a relationship between higher plasma cell numbers at baseline and worse, or shorter lasting responses[1,2,3]. In this study we measured synovial expression of genes involved in B-cell biology, cell survival and trafficking and inflammation.

Methods: Synovial arthroscopic biopsies were collected and snap frozen from patients at baseline and 26 weeks after rituximab. Immunohistochemistry was performed for CD3, CD19, CD20cy, CD138 and CD68 using the Menarini universal staining kit and scored for positive cells/mm^{2} using digital image analysis. The remainder of the tissue was used for RNA extraction. A 48 gene custom Taqman array was designed, including cell lineage markers (CD19, CD20, CD3, CD138, CD68), genes of the BAFF-APRIL system, immunoglobulins, cytokines, chemokines and adhesion molecules implicated in RA synovitis or cell trafficking, and a reference gene (HPRT). Informative data are available from 32 biopsies before and 23 post treatment.

Results: As previously reported, IHC showed complete B-cell depletion in synovium in 22/25 patients using both CD19 and CD20cy antibodies.

Plasma cells (CD138) were not significantly reduced and post-treatment. CD138 IHC-score was lower in patients with sustained clinical response (>12 months), and these patients also had significantly lower post-treatment rheumatoid factor titre. CD138 IHC score correlated with baseline CXCL13 (R=0.738, p<0.001), and negatively with baseline EGF (R=−0.617, p=0.006). Post-treatment plasma cell IHC-score also correlated significantly with immunoglobulin kappa and heavy constant chain gene expression, but none of the immunoglobulin genes was significantly associated with sustained response.

Comparing EULAR responders and non-responders, there were trends to higher baseline CD20 gene expression in non-responders (p=0.079) and greater reduction in CXCL13 (p=0.066) and MMP (p=0.024) in responders.

Lower expression of ICAM (p=0.021), FGF (p=0.044), CD20 (p=0.055) and p53 (p=0.025) and higher expression of APRIL (p=0.029) at baseline was associated with normalisation of CRP after therapy. Furthermore, these patients also showed a significantly greater reduction in expression of CD4, CD55, CD68, CXCL12, EGF, FGF, ICAM, PECAM, STAT5, TGF-beta, APRIL and BAFF (all p<0.05).

Conclusion: Preliminary results indicate important differences in synovial gene expression in patients with clinical response to rituximab, notably in relation with genes involved in cell trafficking and survival.These results may help elucidating reasons for, and consequences of plasma cell survival.

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Circulating Plasmablasts As a Source of Anti-Citrullinated Protein Antibodies in Patients with Rheumatoid Arthritis. Priscilla Kerkman, Ellen I.H. van der Voort, Leendert A. Trouw, Tom W.J. Huizinga, René E.M. Toes and Hans Ulrich Scherer. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Anti citrullinated protein antibodies (ACPA) are highly specific for rheumatoid arthritis (RA) and predict disease onset and severity. Accumulating evidence indicates that ACPA could play an important role in RA pathogenesis by contributing to inflammation and joint destruction. So far, however, little is known on the characteristics of ACPA producing B cells. In this study, we set out to define ACPA producing B cells in more detail in order to allow for specific targeting of these cells.

Methods: Peripheral blood CD19 positive B cells from patients with ACPA positive RA (n=30) were isolated using magnetic beads. In addition, B cell subsets were purified by FACS-sorting based on the expression of surface markers CD19, CD20 and CD27. Isolated B cell populations were either cultured in vitro in the presence of anti-IgM, IL-21 and BAFF on a layer of irradiated CD40L transfected fibroblasts, or left in medium without additional stimulation. Following culture for 6 and/or 13 days, supernatants were assessed for the presence of ACPA-IgG and non-specific total IgG by ELISA.

Results: Following stimulation, ACPA could be detected in up to 100% of culture wells. Both the average ACPA titer in the wells as well as the percentage of positive wells correlated with measures of disease activity. No reactivity was observed against the arginine containing control antigen. No ACPA production was detectable by B cells isolated from ACPA negative RA patients or healthy controls. Of interest, ACPA were also produced spontaneously ex-vivo without stimulation. Active ACPA production was detectable for extended periods of time (up to 4 weeks). FACS-sorting experiments comparing isolated B cell subsets indicated that spontaneous ACPA production resides, for a large part, in the circulating plasmablast population. Spontaneous ACPA production was still observed after depletion of the CD20 positive B cell population.

Conclusion: We show that ACPA producing plasmablasts circulate in the peripheral blood of ACPA positive RA patients in a disease activity dependent manner. Ex vivo, these plasmablasts were not short-lived and were not targeted by an anti-CD20 antibody. These observations enhance our understanding of ACPA producing B cells and could be relevant for future targeted therapies.

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The Absolute Concentration of Anti Citrullinated Protein Antibodies in Serum and Synovial Fluid in Relation to Total Immunoglobulin-Concentrations. Annemiek Willemze, Jing Shi, Marlies Mulder, Gerrie Stoeken-Rijsbergen, Tom W. J. Huizinga, René E. M. Toes and Leendert A. Trouw. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The presence of anti-citrullinated protein antibodies (ACPA) is one of the most predictive factors for the development of rheumatoid arthritis (RA). Nonetheless, relatively little information is present on the absolute concentration ACPA in serum and synovial fluid in relation to total Ig-concentrations. Here, we estimated the relatively abundance of ACPA immunoglobulins in serum and synovial fluid using a quantitative approach.

Methods: ACPA from synovial fluid and serum samples were purified using high affinity strep columns coupled with biotinylated Cyclic Citrullinated Peptide (CCP). A control column (CCP-arginine) was used to guarantee the specificity of the antibody. Total IgG, IgA, IgM and anti-CCP isotype reactivity were measured by Enzyme-linked immunosorbent assay (ELISA).

Results: ACPA were successfully isolated as substantial amounts of antibodies were eluted from sera of ACPA positive patients and neglectable amounts of antibodies were eluted from sera of ACPA negative patients. In serum samples and synovial fluid of ACPA-positive RA patients with high ACPA-levels at least one percent of total IgG was IgG ACPA. Furthermore IgM-ACPA was most abundant in synovial fluid samples as compared to serum samples (with the highest enrichment in the range of 1 IgM ACPA for every 33 total IgM antibodies). IgA, IgG and IgM ACPA were more abundantly present in synovial fluid as compared to paired serum and plasma samples.

Conclusion: IgG-ACPA is present in high concentrations in synovial fluid and serum, as at least 1 in every 100 antibodies present are ACPA in patients with high ACPA-levels. Strikingly, IgM-ACPA is abundantly present in synovial fluid. Given the short half life of IgM, these data indicate the presence of a continuous ongoing autoimmune response in the synovial compartment that is hallmarked by the activation of IgM-ACPA producing B cells.

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Affinity Purification and Characterisation of Anti-CCP Antibodies From Plasma and Synovial Fluids of Patients with Rheumatoid Arthritis. Elena Ossipova[1], Catia Cerqueira[1], Evan Reed[1], Nastya Kharlamova[1], Lena Israelsson[1], Rikard Holmdahl[2], Anca Irinel Catrina[1], Vivianne Malmström[3], Yngve Sommarin[4], Lars Klareskog[1], Per Johan Jakobsson[1] and Karin Lundberg[1]. [1]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Euro-Diagnostica AB, Malmö, Sweden

Background/Purpose: Autoimmunity in rheumatoid arthritis (RA) is characterized by autoantibodies to citrullinated proteins/peptides (ACPA). These antibodies (present in 60–70% of patients) antedate clinical onset and associate with an erosive disease course, suggesting a direct pathogenic involvement in disease initiation and progression. With this study, we aimed to utilise plasma and synovial fluids (SF) from patients with RA, for the purification of ACPAs reactive with the peptides used in the CCP2 ELISA assay. Furthermore, to characterise their frequency in plasma and SF as well as reactivity with different autoantigen-derived peptides.

Methods: Plasma (n=16) and SF (n=26) samples were collected, with informed consent and ethical approval, from RA patients with anti-CCP2 IgG levels above 300AU/ml. Total IgG was isolated on Protein G columns, and subsequently applied to CCP2 affinity columns, kindly donated by EuroDiagnostica. Flow through and eluate fractions were assayed for antibody responses using the CCP2 ELISA, as well as in-house ELISAs, for analysis of reactivity to citrullinated peptides from a-enolase, vimentin, fibrinogen and collagen type II.

Results: Pure and intact anti-CCP IgG antibodies were efficiently isolated from plasma and SF samples. No citrulline-reactivity was detected in the CCP2 column flow through fractions. Purified anti-CCP IgG from different patients showed differences in binding to CCP2 ELISA plates (assayed at the same antibody concentration), still a majority showed reactivity with the four citrullinated autoantigen-derived peptides. Purified anti-CCP IgG also bound citrullinated, but not uncitrullinated, human fibrinogen, by Western blot, while the corresponding CCP2 column flow through IgG bound neither citrullinated nor uncitrullinated fibrinogen. A median of 1.5% of the IgG pool in plasma and 2.2% in SF, with four SF samples reaching 6%, were CCP2-reactive.

Conclusion: Here we demonstrate an efficient and robust method to isolate anti-CCP IgG from plasma and SF. Furthermore, that ACPAs reactive with epitopes on different citrullinated autoantigens (i.e. a-enolase, vimentin, fibrinogen and collagen type II), which are largely non-cross-reactive, are captured by the CCP2 column. These purified anti-CCP IgG molecules will provide us with new opportunities to investigate functional and structural aspects of human anti-citrullinated protein/peptide antibodies, including pathogenicity.

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Recognition of Citrullinated and Carbamylated Proteins by Human Antibodies: Specificity, Cross-Reactivity and the "AMC-Senshu" Method. Jing Shi[1], George Janssen[1], Peter van Veelen[1], Janwouter Drijfhout[1], Antony Cerami[1], Tom Huizinga[2], Leendert A. Trouw[3] and René E.M. Toes[3]. [1]LUMC, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Leiden University Medical Centre, Leiden, Netherlands

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) play an important role in the diagnosis and prognosis of Rheumatoid Arthritis (RA). The Anti-Modified Citrulline (AMC) ('Senshu') method is the most frequently used method to detect citrullinated proteins. Recently, we identified antibodies against carbamylated proteins (anti-CarP) and wished to know whether the 'AMC-Senshu' method could discriminate citrullinated and carbamylated proteins. More importantly, we also wished to know to what degree human autoantibodies can discriminate between these two modifications.

Methods: We analyzed the reactivity of the 'AMC-Senshu' method and selected sera of RA patients on western blots targeting citrullinated, carbamylated or non-modified Fetal Calf Serum (FCS) and Fibrinogen (Fib). The levels of ACPA and anti-CarP antibodies in sera before and after ACPA depletion were compared and potential cross-reactivity analysed.

Results: The 'AMC-Senshu' method strongly stained both citrullinated and carbamylated FCS and as well as citrullinated and carbamylated Fib but not the non-modified counterparts. This indicates that this method can not discriminate between these two modifications. Using patient sera we demonstrate that autoantibodies present in human serum can be specific for either carbamylated Fib or citrullinated Fib. In addition many RA patients can be double positive for both reactivities. To analyze if these patients are double positive because of cross-reactivity or because they contain two antibody families we used ACPA depletion columns to deplete all ACPA followed by analysis of ACPA levels and anti-CarP levels. After ACPA depletion, more than 98% of ACPA in the sera were depleted while more than half of anti-CarP antibodies remained in the flow through in 5 out of 7 samples tested. These data indicate that part, but not all anti-CarP antibodies are cross-reactive to citrullinated epitopes.

Conclusion: In conclusion, the 'AMC-Senshu' method identifies both citrullinated and carbamylated proteins. In contrast human autoantibodies can discriminate between these two modifications indicating the presence of two separate families of autoantibodies, one directed against citrullinated protein and one directed against carbamylated proteins with a limited degree of cross-reactivity.

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Anti Carbamylated Protein Antibodies (Anti-CarP) Are Present in Arthralgia Patients and Predict the Development of Rheumatoid Arthritis. Jing Shi[1], Lotte van de Stadt[2], Nivine Levarht[1], T.W.J. Huizinga[3], R. E. M. Toes[3], Leendert A. Trouw[4] and Dirkjan van Schaardenburg[2]. [1]LUMC, Leiden, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Leiden University Medical Centre, Leiden, Netherlands

Background/Purpose: Recently, we discovered a new autoantibody system in rheumatoid arthritis (RA): anti carbamylated protein antibodies (anti-CarP). These antibodies have additional prognostic value in predicting joint destruction when compared to anti-citrullinated protein antibodies (ACPA). However, it is not yet known whether anti-CarP antibodies are present before the diagnosis of RA and whether they have predictive value for the development of RA. Therefore we studied whether anti-CarP antibodies are present in arthralgia patients and whether their presence associates with the development of RA.

Methods: Sera of 340 arthralgia patients without clinical signs of arthritis and 32 healthy controls were measured for the presence of anti-CarP IgG antibodies. One hundred eleven arthralgia patients (33%) were IgM-rheumatoid factor (IgM-RF) positive/anti-cyclic citrullinated peptide 2 (aCCP2) negative and 229 (67%) were aCCP2 positive. Patients were followed for the development of RA (2010 criteria). The median follow up time was 36 months. Cox regression analysis was performed to compare the risk of developing RA between Anti-CarP positive and negative arthralgia patients in follow up time.

Results: The arthralgia cohort consisted of 340 IgM-RF and/or aCCP positive patients. Anti-CarP antibodies were present in sera of 113 (39%) of the tested patients. A total of 120 patients developed RA after a median (IQR) of 12 (6–24) months. The presence of anti-CarP antibodies was associated with the development of RA in the whole arthralgia cohort even after correction for RF and aCCP2 status (HR: 1.56; 95%CI: 1.06–2.29; p = 0.023), as well as in the aCCP2 positive subgroup (OR: 2.231; 95%CI: 1.31–3.79; p = 0.003).

Conclusion: Anti-CarP antibodies were present in arthralgia patients and their presence predicted the development of RA independent of aCCP2 antibodies.

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Expansion of Autoreactive Unresponsive CD21$^{-/\text{Low}}$ B Cells in Sjögren's Syndrome Associated Lymphoproliferation. David Saadoun[1], Benjamin Terrier Sr.[2], J. Bannock Sr.[3], T. Vazquez Sr.[4], C. Massad Sr.[3], Florence Joly Sr.[5], Michelle Rosenzwajg Sr.[6], Damien Sene Sr.[7], Philippe Benech Sr.[5], David Klatzmann Sr.[6], Eric Meffre Sr.[3] and Patrice Cacoub Sr.[8]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Cochin Hospital, Paris, France, [3]Yale University School of Medicine, New Haven, CT, [4]CNRS UMR 7211 and INSERM U959, Paris, France, [5]Prediguard, Marseille, France, [6]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Paris, France, [7]Groupe Hospitalier Pitié-Salpétrière, Université Pierre et Marie Curie, Paris, France, [8]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: Primary Sjögren's syndrome (pSS) is the autoimmune disease associated with the higher risk of developing non-Hodgkin lymphoma.

Objective: To determine the nature of B cells driving lymphoproliferation in pSS.

Methods: B cell subsets and function were analyzed in peripheral blood from 66 adult patients with pSS [including 15 patients with B-cell lymphoproliferative disorder (LPD)] and 30 healthy donors, using flow cytometry, calcium mobilization, and gene array analysis. We tested by ELISA the reactivity of recombinant antibodies isolated from single B cells from pSS-LPD.

Results: We report here the expansion of an unusual CD21$^{-/\text{low}}$ B-cell population which correlates with lymphoproliferation in pSS patients. A majority of CD21$^{-/\text{low}}$ B cells from pSS patients expressed autoreactive antibodies, which recognized nuclear and cytoplasmic structures. These B cells belonged to the memory compartment because their immunoglobulin genes were mutated. They were unable to induce calcium flux, become activated, or proliferate in response to B-cell receptor and/or CD40 triggering, suggesting that these autoreactive B cells may be anergic. However, CD21$^{-/\text{low}}$ B cells from pSS remained responsive to TLR9 stimulation. Gene array analyses of CD21$^{-/\text{low}}$ B cells revealed molecules specifically expressed in these B cells and that are likely to induce their unresponsive stage.

Conclusion: pSS patients who display high frequencies of autoreactive and unresponsive CD21$^{-/\text{low}}$ B cells are susceptible for developing lymphoproliferation. These cells remain in peripheral blood controlled by functional anergy instead of being eliminated, and chronic antigenic stimulation through TLR stimulation may create a favorable environment for breaking tolerance and activating these cells.

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Hyperammaglobulinemia in Primary Sjögren's Syndrome Is Induced by Triggering of TLR7 and 9. Susanna Brauner[1], Marika Kvarnstrom[1], Gunnel Nordmark[2] and Marie Wahren-Herlenius[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology, Uppsala, Sweden

Background/Purpose: Multiple B cell aberrances have been linked to primary Sjögren's syndrome (pSS), including autoantibody production and a skewed B cell differentiation. Further, approximately 50% of all patients with pSS display hypergammaglobulinemia.

Chloroquine-derived antimalarial drugs, commonly used in treatment of pSS, are thought to mediate their therapeutic effect by inhibiting the endosome, and thereby affecting TLR7 and 9 signaling. However, so far little is known about why chloroquines have a beneficial effect.

Methods: Freshly prepared PBMCs from untreated and chloroquine-treated pSS patients and healthy controls were sorted by flow cytometry. Naïve IgD+ B cells were cultured eight days with class-switch inducing agents; anti-CD40, BAFF, Imiquimod (TLR7) and CpG (TLR9), all supplemented with IL-10. Culture supernatants were analyzed for IgM and IgG concentrations and cells were phenotyped by flow cytometry. Microarray-based mRNA expression analysis was performed on PBMC from untreated pSS patients and controls.

Results: Upon induction of class-switch, B cells will secrete IgM and subsequently IgG and some will develop further into plasma cells expressing CD138.

When stimulating with TLR7 and 9 agonists significantly higher titers of IgM and IgG were observed in supernatants of cells from pSS patients compared to controls. Further, a significantly increased proportion of CD138+ plasmablasts were observed in the cultures established from pSS patients compared to controls. No significant differences were observed when stimulating with other class-switch inducing agents (CD40, BAFF). To further support our findings an mRNA expression analysis of unmanipulated PBMCs from pSS patients (n=14) and controls (n=18) was performed. Key genes in the endosomal TLR pathways, including TLR7 and 9, TNFAIP3 and IRF5, were significantly up regulated in pSS patients. However, the signaling pathways of CD40 and BAFF were unaffected.

Class-switch was also induced in B cells from patients treated with antimalarial drugs. Interestingly, lower levels of IgG and IgM were seen in chloroquine treated patients, compared to untreated pSS patients. In concordance, fewer plasmablasts were detected in the choloroquine-treated patients.

Conclusion: More than 50% of patients with primary Sjögren's syndrome display hypergammaglobulinemia. We show here that B cell class switch and IgG production is increased in pSS patients after endosomal TLR triggering, and that this can be inhibited *in vivo* by treatment with antimalarials. Our data confirm the importance of TLR7 and 9 pathways in driving the disease and clinical phenotype of pSS.

1774

Identification of Target Antigens of Anti-Endothelial Cell Antibodies in Patients with ANCA-Associated Systemic Vasculitis: A Proteomic Approach. Alexis Régent[1], Hanadi Dib[2], Guillaume Bussone[1], Mathieu C. Tamby[1], Nicolas Tamas[2], Christian Federici[3], Cédric Broussard[3], Loic Guillevin[4] and Luc Mouthon Sr.[1]. [1]Hopital Cochin, Paris, France, [2]Université Paris Descartes, Paris, France, [3]Inserm U1016, Institut Cochin, CNRS UMR 8104, Paris, France, [4]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France

Background/Purpose: Anti-endothelial cell antibodies (AECA) are frequently detected in anti-neutrophil cytoplasm antibodies (ANCA)-associated systemic vasculitis (AAV) and are considered to play pathological roles but their antigenic specificities are still unknown. We used a proteomic approach combining two-dimensional electrophoresis and immunoblotting to identify the target antigens of AECA in patients with ANCA-associated vasculitis.

Methods: Sera from 30 ANCA-associated vasculitis patients (12 with Granulomatosis with polyangeitis (GPA), 9 with microscopic polyangeitis (MPA), 9 with Churg Strauss syndrome (CSS)), tested in pools of 3 sera, were compared to a sera pool from 12 healthy controls (HC). Serum IgG reactivity was analyzed by use of a 2-D electrophoresis and immunoblotting technique with normal human umbilical vein endothelial cell (HUVEC) antigens.

Results: Serum IgG in the HC sera pool recognized 85 protein spots and serum IgG from patients with AAV recognized 134±65 different protein spots. We focused on protein recognized by at least 3/4 pools of patients with GPA and 2/3 pools of patients with MPA and CSS and not by HC and identified 20, 7 and 8 proteins, respectively. In addition, among the 330 spots recognized by at least one pool of patients with AAV, ten different spots were recognized by at least 6/10 pools. Among identified proteins, IgG reactivity was detected against alpha-enolase, lamin A/C and protein disulfide-isomerase A3. Interestingly, Ingenuity Pathway Analysis revealed that most of these antigens interact with TGF-β, immunoglobins and inflammatory complexes such as Jun and MAPK.

Conclusion: AECA detected in patients with AAV recognize cellular targets playing key roles in cell biology. Target antigens interact with protein and complexes known to play a crucial role in AAV pathophysiology.

ACR/ARHP Poster Session C
Cell-cell Adhesion, Cell Trafficking and Angiogenesis
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

1775

The Phosphoinositide 3-Kinase Pathway Regulates Fibroblast-Like Synoviocyte Invasion. Beatrix Bartok[1], Deepa Hammaker[2] and Gary S. Firestein[3]. [1]UCSD, La Jolla, CA, [2]Univ of California San Diego, La Jolla, CA, [3]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Cartilage destruction mediated by invasive fibroblast-like synoviocytes (FLS) plays a central role in pathogenesis of RA. Increased cell migration and degradation of extracellular matrix are fundamental to these processes. The Class I phosphoinositide 3-kinases (PI3K) control cell survival, proliferation and migration, which might be involved with cartilage damage in RA. PI3Kdelta isoform expression was recently identified as a key regulator of FLS growth and survival, suggesting that it could contribute to synoviocyte aggressive behavior. Therefore, we assessed the role of PI3Kdelta in synoviocyte invasion and matrix degradation using isoform selective PI3K inhibitors.

Methods: FLS were cultured in Matrigel coated transwells. PI3K inhibitors or vehicle were added to the upper chamber and PDGF was used as a chemoattractant in the lower chamber. The invading cells were quantified by staining the filters with 1% crystal violet. F-actin was visualized with Rhodamin phalloidin and analyzed with fluorescent microscopy. Rac1 activation was measured using PAK1/PBD GST pull down and quantified by Western blot analysis. PI3K inhibitors included: pan (GDC-0941), PI3Kalpha (A66), PI3Kbeta (TGX-221), PI3Kgamma (AS-252424), PI3Kdelta (INK007 and CAL-101) and PI3K-delta/gamma (INK055 and IPI-145).

Results: PDGF-directed invasion was completely inhibited by the pan PI3K inhibitor (1 uM). To define the role of the individual isoforms, we tested the effect of the isoform selective PI3K inhibitors. PI3Kdelta inhibition (INK007) significantly decreased the number of invading cells, with 60±5% inhibition at 1 uM (p< 0.04). Similar results were observed with two other inhibitors with distinct chemical structures (CAL-101 and INK055). The PI3Kalpha inhibitor decreased invasion by 40±5% while PI3Kbeta and PI3Kgamma inhibitors had no effect. Phalloidin staining was then used to visualize FLS actin rearrangement in response to PDGF with or without PI3K inhibitors. PI3Kdelta inhibition by INK007, CAL-101 and IPI-145 decreased lamellipodia formation by 50±6% (p<0.05). Similar inhibition was seen with the pan PI3K inhibitor, while the selective inhibitors of PI3Kalpha, PI3Kbeta or PI3Kgamma had no effect. We then hypothesized that PI3Kdelta might modulate activation of Rho GTPases in synoviocytes, which regulate actin organization. PI3Kdelta inhibition with INK007 had no effect on baseline Rac1 activation but blocked activation in response to PDGF by 95±6% (p<0.03). Similar findings were observed with the pan PI3K inhibitor, while PI3Kalpha inhibition had no significant effect.

Conclusion: PI3Kdelta is a major regulator of FLS migration and invasion and functions by inhibiting Rac1 activation and modulating F actin cytoskeleton rearrangement. These observations, together with previous findings that PI3Kdelta regulates FLS growth and survival, suggest that PI3Kdelta inhibition could be chondroprotective in RA by modulating synoviocyte growth, migration and invasion.

1776

Anti-SSA/Ro Mediated Injury to the Endothelium Via Urokinase Plasminogen Activator Receptor/Tgfbeta Activation: Implications in the Pathogenesis of Congenital Heart Block. Paraskevi Briasouli[1], Mark Halushka[2], Jill P. Buyon[3] and Robert M. Clancy[4]. [1]New York University Medical Center, New York, NY, [2]John Hopkins PAthology, Baltimore, MD, [3]NYU School of Medicine, New York, NY, [4]New York University School of Medicine, New York, NY

Background/Purpose: One mechanism by which anti-Ro antibodies are linked to the pathogenesis of (cardiac-NL) neonatal lupus is the increased urokinase plasminogen activator (uPA)/urokinase-type plasminogen activator receptor (uPAR)-dependent plasminogen activation and subsequent triggering of TGFbeta signaling. Immunologic staining of affected hearts reveals cell specific expression of uPA on endothelial cells and infiltrating macrophages in areas of inflammation and fibrosis. Since plasminogen/plasmin-dependent TGFbeta signaling has a documented role in endothelial cell survival, this study evaluated the association of anti-Ro and an injury pathway in the fate of the cardiac vasculature.

Methods: Adhesion, tube formation, TGFbeta activation assays were used to assess the effect of antibodies on endothelial cell function. Immunohistology of cardiac-NL autopsies were conducted to evaluate diseased vasculature.

Results: Human IgGs were used from a healthy control (nl-IgG) and a mother whose serum contained reactivity to all the components of the SSA/Ro-SSB/La complex and whose child had cardiac-NL (CHB-IgG). Adherence was enumerated (colorimetric dye) after vascular endothelial cells (CD3 cell line) were incubated with CHB-IgG (0.03 mg/ml, 2 hr) or nl-IgG, with or without plasmin inhibitor aprotinin (10 μg/ml) or TGFbeta inhibitor SB5543 (10μM). CHB-IgG coincubation significantly reduced EC adhesion on ECM (collagen-coated surfaces) compared with nl-IgG (0.38 ± 0.1 vs 0.89 ± 0.09 respectively (adhesion units, scale 0–3), p=0.02, n=3). The CHB-IgG decreased adhesion was reversed in the presence of either aprotinin or SB5543. Further evidence to implicate a plasmin/TGFbeta axis was provided by the observation that ECs treated with CHB-IgG, but not nl-IgG, increased luciferase activation of a TGFbeta reporter cell line (TMLC) (432 ± 20 vs 138 ± 12 RLU respectively, p = 0.003; n = 3), an effect abrogated by cotreatment with aprotinin or SB5543. Vessel formation was evaluated by visual inspection of networks after ECs were plated on matrigel (8 hr). Exposure of ECs to CHB-IgG but not nl-IgG markedly attenuated blood vessel formation *in vitro* which again was reversed by cotreatments with aprotinin and SB5543 as observed in the adhesion studies (n=4). As further proof of concept, during migration of ECs on collagen-coated surfaces, confocal microscopy revealed colocalization of uPAR with anti-Ro60 (but not anti-Ro52 or anti-RNP) at the tips of migrating cells. Evaluation *in vivo*, showed that in a fetal CHB heart, protein expression of CD31 (a surface marker of endothelium lining blood vessels) was at a substantially lower level in septal regions with involved inflammation when compared with a healthy zone of atrial tissue.

Conclusion: These results suggest that anti-SSA/Ro interference during the remodeling events occurring in angiogenesis results in increased uPAR-dependent uPA activity with generation of active TGFbeta. This then leads to the attenuation of adhesion and new vessel development and ultimately a loss of vasculature in the septal region of affected hearts.

1777

The Bioenergetic Role of HIF-1 and HIF-2 During Angiogenesis of Human Microvascular Endothelial Cells. Martin Hahne, Cindy Strehl, Manuela Jakstadt, Paula Hoff, Timo Gaber, Gerd R. Burmester and Frank Buttgereit. Charité University Medicine, Berlin, Germany

Background/Purpose: Hypoxia and angiogenesis are features of inflamed and injured tissues. The transcription factors Hypoxia inducible factor (HIF)-1 and (HIF)-2 control cellular metabolic response to decreased oxygen tension thereby promoting angiogenesis with implications on the pathogenesis of rheumatoid arthritis (RA). Our studies aims to knockdown HIF-1α and HIF-2α in human microvascular endothelial cells (HMEC), respectively, in order to investigate resulting effects on angiogenesis and bioenergetics under hypoxic versus normoxic conditions.

Methods: Specific knockdown of HIF-1α or HIF-2α was achieved using lentiviral-based shRNA technology. Angiogenesis of transduced HMECs was studied by investigating both tubuli and node formation under hypoxia (<1% O_2) versus normoxia (~18% O_2). Expression of hypoxia driven genes involved in metabolic response to hypoxia *(GAPDH, PGK, GLUT1)* was quantified by realtime RT-PCR. Bioenergetic state of the cells was investigated via ADP/ATP measurements.

Results: Knockdown of HIF-1α led to a loss in the hypoxia induced node (p=0.007) and tubuli formation (p=0.09). HIF-2α knockdown also resulted in a significant loss of hypoxia induced formation of tubuli (p=0.04). Focussing on bioenergetics, we found hypoxia to significantly induce *PGK* (p=0.0004) and *GAPDH* (p=0.049) in control cells. Interestingly, HIF-1α knockdown – but not HIF-2α knockdown – resulted in a loss of hypoxic induction of *PGK*expression.

In both HIF-1α (p=0.01) and HIF-2α (p=0.13) knockdown cells, hypoxia was still capable of inducing *GAPDH*, but the effect was much less pronounced in HIF-1α knockdown cells.

Hypoxia did not up-regulate *GLUT1*, neither in control nor in HIF-1α and HIF-2α knockdown cells, respectively.

We also found the ADP/ATP ratio to be similar in control and HIF-1α or HIF-2α knockdown cells under normoxia. Under hypoxic conditions, however, HIF-1α knockdown cells showed a significantly enhanced ADP/ATP ratio (p<0.05) – indicating that less ATP is available – compared to control cells. This was not the case in HIF-2α knockdown cells.

Conclusion: HIF-1α and HIF-2α are both key regulators of angiogenesis. However, they do differ in their ability to regulate cellular energy metabolism. This leads us to conclude that HIF-2α does directly influence angiogenesis via regulating the synthesis of proangiogenic factors (1), whereas HIF-1α affects angiogenesis via effects on cellular energy metabolism.

These findings provide new insights into regulation of angiogenesis in inflamed (hypoxic) tissues and are, therefore, considered to be of clinical relevance in RA.

(1) Hahne et al. Angiogenic potential of HMECs – analysis of two HIFa isoforms and their overlapping functions. 75. Annual Scientific Meeting of the American College of Rheumatology, Chicago, USA, 4–9 November 2011. Abstract in Arthritis & Rheumatism 2011;63(10)Supplement:S10

1778

Adenosine A2A Receptor (A_{2A}R) Activation Stimulates Increased Expression of Collagen-1 and Collagen-3 by Different Signaling Pathways in Normal Human Dermal Fibroblasts. Miguel Perez Aso[1] and Bruce N. Cronstein[2]. [1]NYU Univ Medical Center, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Pathological fibrosis in the skin and other organs is the hallmark of scleroderma and other fibrosing diseases. Adenosine, acting at A_{2A}R, plays a critical role in wound healing and fibrosis of the skin and previous studies have demonstrated that blockade or deletion of A_{2A} receptors prevents dermal fibrosis in response to bleomycin, a murine model of scleroderma. Moreover, A_{2A}R blockade enhances the strength of scars by, in part, diminishing the collagen 3 (Col3) content of the scar relative to Col1 content. Here we determined whether expression of Collagen-1 (Col1) and Col3 proceed by different signaling pathways.

Methods: Col1 and Col3 expression were determined by Western-Blot analysis of normal human dermal fibroblasts (NHDF).

Results: Surprisingly the concentrations of the A_{2A}R agonist CGS21680 required to increase Col1 expression were significantly lower than those required to increase Col3 (0.1μM: $147\pm6\%$ for Col1 [p<0.01, n=23] vs 1μM: $155\pm16\%$ for Col3, [p<0.01, n=18] although increases in both were completely blocked by the A_{2A}R-antagonist SCH58261 (0.1μM). The selective Protein kinase A (PKA) activator 8-Cl-cAMP markedly increased Col1 expression (0.1μM: $280\pm74\%$ [p<0.01, n=3), but inhibited Col3 expression by as much as $68\pm11\%$ (p<0.01, n=4). PKA inhibition by PKAi prevented the CGS21680-stimulated increase in Col1 but elicited an increase of Col3 at lower concentrations than in the absence of PKAi (0.1μM, $110\pm10\%$ versus $182\pm30\%$ [p<0.05, n=4). In contrast, stimulation with the specific Epac activator 8-CPT-2'-O-Me-cAMP did not affect Col1, but increased Col3 production by $362\pm85\%$ (p<0.05, n=3). Inhibition of AKT, erk, p38 and JNK with LY294002 (10μM), U0126 (1μM), SB203580 (1μM) and SP600125 (20μM), respectively, demonstrated that increased expression of Col1 and Col3 depend on AKT and p38. However, CGS21680 0.1μM increased Col3 only upon ERK or JNK blockade, an effect similar to PKA inhibition.

Conclusion: Our work strongly suggests that at nanomolar concentrations of CGS21680 PKA activity prevails over Epac, thereby activating Col1 expression and inhibiting Col3 but in the mmolar range, the PKA/ERK/JNK inhibition of Col3 is overcome by activation of Epac/p38 and Pi3K/AKT. These observations may explain the dramatic decrease of the Col1/Col3 ratio in hypertrophic and immature scars, where adenosine is present in μmolar ranges, when compared to normal skin, where adenosine concentration varies from 30 to 300nM.

1779

The Loss of Syndecan-4 Aggravates Inflammatory Colitis in Mice.

Athanasios Stratis[1], Dominik Bettenworth[1], Mareike Fröhling[1], Peter Paruzel[1], Adelheid Korb-Pap[1], Corinna Wehmeyer[1], Berno Dankbar[1], Frank Echtermeyer[2], Andreas Lügering[1] and Thomas Pap[1]. [1]University Hospital Muenster, Muenster, Germany, [2]University Hospital Hannover, Hanover, Germany

Background/Purpose: Syndecan-4 (sdc4) is a transmembrane heparan sulfate proteoglycan. Several studies have implicated sdc4 in cell-matrix adhesion, cell migration, differentiation, proliferation and play an important role during the inflammation in rheumatoid arthritis. Modulation of inflammatory signals by sdc4 may occur either through mere binding of cytokines, in which case sdc4 acts as decoy receptor or through initiation of sdc-dependent signalling following sdc4 complex formation. While arthritic cartilage damage is decreased in sdc4-deficient mice most likely due to reduced sdc4 signaling, osteopontin- mediated liver damage has been shown to be increased in these mice due to the lack of scd4 decoy receptor function. Based on this dual effects of sdc4, we investigate if the loss of sdc4 changes the natural course of murine experimental colitis.

Methods: Colitis was induced in sdc4$^{-/-}$ mice and in C57BL/6 WT mice by DSS. The course of colitis was monitored by weight loss as well as assessment of colon length and blinded histological scoring of colonic changes at the end of the experiment. In addition, sdc4$^{-/-}$ and C57BL/6 WT mice were orally gavaged with 5×10^8 colony-forming units (CFU) of *Citrobacter rodentium (C. rodentium)*. Fecal excretion of *C. rodentium* and changes of body weight were monitored. At day 21 post infection, inflammatory changes of the colon were evaluated histologically.

Results: Beginning from day 5 after start of DSS-administration, sdc4$^{-/-}$ mice lost dramatically more body weight compared to WT animals (day 8: 24.8%±1.9 vs. 9.2%±3.1; p=0.008). In accordance with the increased loss of body weight, the colon length of sdc4$^{-/-}$ mice was significantly shortened (63.3 mm±2.4 vs. 74.8±2.3; p=0.01) and the histological damage according to the Dieleman-Score was markedly aggravated (16AU±3.7 vs. 3.4AU±0.2; p=0.016). At day 19 post infection, the fecal excretion of *C. rodentium* in sdc4$^{-/-}$ was prolonged compared to WT animals (2.5×10^5±6.8×10^3 vs. 9.6×10^3 ±6.5×102; p=0.01). Histological damage of colonic mucosa, reflected by lengthening of crypts, was increased in Sdc4$^{-/-}$ mice (14.3AU±1.3 vs. 10.2AU±0.9; p=0.03).

Conclusion: Our results show that like in inflammatory liver damage, sdc4 seems to have protective effects in intestinal inflammation. Future studies are needed to analyze the underlying mechanisms and to determine if these effects are due to a decoy receptor function of sdc4 or whether sdc4 complex formation and signalling is involved.

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Association Between Chondrocyte Hypertrophy and Angiogenesis of Cartilage in Osteoarthritis

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Background/Purpose: Chondrocyte hypertrophy is commonly observed in OA cartilage, associated with matrix mineralization and vascularization. In our previous work, we demonstrated that hypertrophic differentiation of chondrocytes is initiated by serum-enriched medium in long-term culture in alginate beads suggesting a role played by blood supply in the hypertrophic differentiation of chondrocytes in OA.

As hypertrophic differentiation of chondrocytes is an important feature of osteoarthritis (OA), we developed a model of culture in order to study the functional consequences of hypertrophic OA chondrocytes. The aim of this study was to investigate the link between hypertrophic differentiation of chondrocytes and angiogenesis in OA in order to demonstrate that OA hypertrophic chondrocytes expressed an angiogenic phenotype and that some specific factors could be implicated in both processes.

Methods: Articular OA chondrocytes were cultured for 28 days in alginate beads in medium containing 2% Ultroser G (UG) or 10% Fetal Bovine Serum (FBS). DNA was quantified by fluorimetry. The expression of hypertrophy markers genes type X collagen (col10a1), runt-related factor 2 (runx2) and matrix metalloprotease 13 (MMP13) and a screening of angiogenic factors was evaluated by RT-PCR. Alkaline phosphatase (AP) activity and 5'phosphodiesterase activity of NTPPPH were quantified by specific enzymatic methods. Non-hypertrophic and hypertrophic human OA chondrocyte conditioned media were used to perform functional tests with huvecs: migration, invasion and wound healing assays. Data were analyzed by one-way ANOVA.

Results: In alginate beads, chondrocytes cultivated in serum-supplemented medium underwent a hypertrophic differentiation process characterized by significant increased expression of hypertrophic markers and mineralization enzymes (col10a1: p<0.05; runx2: p<0.01; MMP13: p<0.001; PA: p<0.001; NTPPPH: p<0.001). Functional angiogenesis assays showed that chondrocyte hypertrophy positively influenced migration (p<0.0001), invasion (p<0.0001) and wound healing (p=0.0005) of endothelial cells. Among the screened angiogenic factors, bone sialoprotein (BSP) was highly upregulated in hypertrophic chondrocytes (p<0.05).

Conclusion: Our culture model allowed to mimic hypertrophic differentiation of chondrocytes and to investigate the relationship between this process and functional invasion and migration of endothelial cells, two functional steps in the process of angiogenesis. The results obtained in this study highlighted BSP as a specific factor that could be implicated in hypertrophic differentiation of chondrocytes and cartilage angiogenesis.

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Functional Analysis of the Primary Cilium in Rheumatoid Arthritis Synovial Fibroblasts.

Kerstin Klein[1], Beat A. Michel[1], Alexander Vogetseder[2], Renate Gay[1], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Department of Pathology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: The primary cilium is a microtubule-based, polarized, antenna structure that emanates from the cell surface of most mammalian cell types. It serves as a sensor that mediates reactions to mechanical and chemical signals from the environment and is therefore, a crucial factor in the communication with neighbouring cells and the environment.

We aimed to investigate the functional role of the primary cilium expressed on synovial fibroblasts (SF) in the pathogenesis of rheumatoid arthritis (RA).

Methods: The expression of the primary cilium was verified in serum-starved RASF by immunofluorescence microscopy using acetylated tubulin as a marker and by transmission electron microscopy. Ciliogenesis of RASF was disrupted by transfection of siRNA targeting the ciliary components kinesin family member 3a (KIF3a) and intraflagellar transport 88 homolog (IFT88). RASF were stimulated with TNF-α (10ng/ml) and IL-1β (1ng/ml). Differentially expression of transcripts in RASF transfected with KIF3a siRNA with and without cytokine stimulation was screened using Microarrays (Affymetrix). Migration and adhesion properties of transfected RASF were analysed by scratch assay (n=3) and a fibronectin-based adhesion assay (n=7), respectively.

Results: The primary cilium was detected on the surface of RASF. Migration of RASF with blocked formation of the primary cilium due to transfection with siRNA targeting KIF3a or IFT88 was reduced compared to RASF transfected with scrambled siRNA. RASF adhesion to fibronectin was induced by TNF-α (2.1 fold ± 0.9, n.s.) and IL-1β (2.3 fold ± 1.3, p<0.05), and was reduced in KIF3a siRNA transfected RASF (TNF-α: 1.2 fold ± 0.7, p<0.05; IL-1β: 1.3 fold ± 0.7, p=0.1142). In the whole genome expression analysis, 1321 transcripts were more than 2-fold up or down regulated in

RASF transfected with *KIF3A* siRNA and 1243 transcripts were more than 2-fold up or down regulated in the *KIF3A*siRNA transfected group stimulated with cytokines compared to control groups. 213 transcripts appeared to be differentially expressed under stimulated as well as under unstimulated conditions.

Conclusion: Our data show a functional role of the primary cilium in the migratory and adhesive properties of RASF. Since disruption of ciliogenesis in RASF altered their response to stimulation with TNF-α and IL-1β, we hypothesise that the primary cilium also plays a key role in the transmission of pro-inflammatory signals in RASF.

Disclosure: **K. Klein**, none, 2; **B. A. Michel**, None; **A. Vogetseder**, None; **R. Gay**, none, 2; **S. Gay**, none, 2; **C. Ospelt**, None.

ACR/ARHP Poster Session C
Cytokines, Mediators, and Gene Regulation
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Dual Effects of Soluble FasL and Membrane Bound FasL On Fibroblast-Like Synoviocytes Cells (FLS) From Rheumatoid Arthritis (RA) Patients. Rachel Audo[1], Flavia Calmon-Hamaty[1], Bernard Combe[2], Michael Hahne[1] and Jacques Morel[2]. [1]IGMM, CNRS UMR5535, Montpellier, Montpellier, France, [2]Hopital Lapeyronie, Montpellier, France

Background/Purpose: Membrane bound FasL (mFasL) is able to induce fibroblast-like synoviocytes (FLS) cell death. In experimental arthritis mouse models, injection of agonistic antibody (Ab) anti-Fas decreased the symptoms. However, soluble FasL (sFasL) is increased in RA patients serum and correlated with disease activity. These results indicated that mFasL could be protective whereas sFasL could be deleterious suggesting that they could have different functions. We therefore analyzed the effect of different FasL preparation mimicking sFasL or mFasL on RAFLS proliferation, apoptosis and cytokines production.

Methods: RAFLS were treated with different FasL preparations (FasL-Flag± Ab anti-Flag, FasL-Fc or sFasL) or with agonistic Ab anti-Fas. Apoptosis was then analyzed by FACS on basis of the annexin V-FITC binding and TOPRO-3 up-take. Proliferation was measured using tritiated thymidine. Signaling pathways was analyzed by western blot and their influence was assessed using chemical inhibitors. VEGF, IL-6 and IL-8 were measured using commercial ELISA.

Results: FasL-Flag alone (mimicking sFasL) was not able to induced FLS apoptosis (8%±8 n=5) while proliferation was significantly activated (3.3±1 fold; n=5; p<0.05). Similarly, sFasL was only able to strongly induce RAFLS proliferation (8.1±3.3 fold; n=3). In an other hand, membrane bound FasL (FasL-Flag+Ab anti-Flag) significantly induced RAFLS apoptosis (52%±18; n=5) but also a slighter but significant proliferation (2.2±0.3 fold; n=4). Duality of mFasL was confirmed using agonistic Ab anti-Fas. (mimicking mFasL) with pro-apoptotic (38%±18; n=2) and proliferative effect (2.5±0.15 fold). Finally, growing concentration of FasL-Fc leads to aggregation of the protein, mimicking mFas or sFasL at high and low concentration respectively. Dose responses confirmed mFasL and sFAsL effects. FasL activated Akt and ERK (n=5) but also activated caspase-8. A pan-caspases inhibitor (z-VAD-FMK) prevented mFasL-induced apoptosis, but also blocked mFasL and sFasL-induced proliferation (n=4). Moreover, sFasL but not FasL-Fc, induced significant production of VEGF, IL-6 and IL-8 in RA FLS. In addition, we observed that FasL-Fc was also able to induce OAFLS apoptosis but in contrast to RAFLS, neither FasL-Fc nor sFAsL was able to significantly induced apoptosis of OAFLS (n=3).

Conclusion: mFasL induces preferentially RAFLS apoptosis, whereas sFasL only induces RAFLS proliferation and cytokines production. Proliferative effect of sFasL was only seen on RAFLS but not on OAFLS. According to what we have already described for TRAIL, caspases are involved in FasL-induced apoptosis and proliferation. This is the first demonstration of sFasL and mFasL have different effects on RAFLS proliferation and cytokines production. sFasL by enhancing RAFLS proliferation and cytokines could have a deleterious role in RA. Therefore, its blockage could be a therapeutic tool to prevent RA.

Disclosure: **R. Audo**, None; **F. Calmon-Hamaty**, None; **B. Combe**, None; **M. Hahne**, None; **J. Morel**, None.

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TNFα Influences *RasGRP1* and *RasGRP3* Expression Levels in PBMC, B and T Cells. Marie-Laure Potier[1], Martine Hiron[1], Clément Guillou[1], Céline Derambure[1], Olivier Boyer[2], Xavier Le Loët[3], Olivier Vittecoq[3] and Thierry Lequerré[3]. [1]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [2]Inserm 905, Institute for Biomedical research, University of Rouen, Rouen, France, [3]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen Cedex, France

Background/Purpose: Rheumatoid arthritis (RA) is the most common inflammatory arthritis. B and T lymphocytes play a central role in the pathophysiology of RA. RasGRP is a member of the CDC25 family of Ras guanyl nucleotide exchange factors. RasGRP1 is expressed in T and B cells whereas RasGRP3 is only expressed in B cells. In previous studies, we have shown that *RasGRP3*expression level significantly decreased in Peripheral blood mononuclear cells (PBMC) from RA patients responders to adalimumab after 3 months, leading to the question of TNFα involvement in pathways including RasGRP1 and RasGRP3. Objectives: To study TNFα effect on RasGRP1 and RasGRP3 expression levels *in vitro*.

Methods: We measured by qRT-PCR, *RasGRP1* and *RasGRP3* expression levels, i) in PBMC from 3 healthy controls (HC), ii) in negative selected B and T cells from PBMC isolated from 3 buffy coat. In each condition, cells were cultured with or without BCR or TCR stimulation for 4 days and TNFα was added for 24 or 48 hours. Immunofluorescence staining was performed to check the cell purity and B and T cells stimulation by flow cytometry. Moreover, IL-2 production was measured by ELISA in T-cells before and after TNFα stimulation. In addition, TNFα effects on cell proliferation were evaluated by [3H] thymidine incorporation by the B and T cells.

Results: In B cells, TNFα induced an increase of *RasGRP1* (p<0.001) and *RasGRP3* (p<0.001) expression levels in absence of BCR stimulation. In the same way, in T cells, TNFα induced an increase of *RasGRP1* (p<0.001) and *RasGRP3* (p<0.001) expression levels in absence of TCR stimulation. Furthermore, TNFα induced a significantly increased of IL-2 production (p<0.05) in unstimulated T-cells. However, TNFα have no effects on B and T cells proliferation

Conclusion: This study suggests the *RasGRP1* and *RasGRP3* regulation by TNFα, independently of B and T cells stimulation. The increasing of *RasGRP3* and *RasGRP1* in B and T cells specifically *via* TNFα binding on its receptors could promote the activation and proliferation of B and T cells using another signaling pathway than BCR and TCR. This second pathway could explain the maintenance of B and T cells activation by an independent antigen pathway.

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1784

Dual Function of Interleukin-33 in Fibroblast-Like Synoviocytes in Patients with Rheumatoid Arthritis. Min W. So[1], Bon S. Koo[1], You J. Kim[1], You-G Kim[1], Wook J. Seo[2], Chang-K Lee[1] and Bin Yoo[1]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Seoul Veterans Hospital, Seoul, South Korea

Background/Purpose: IL-33 is a new member of the IL-1 cytokine family. Recent studies in an animal model of murine collagen-induced arthritis and human rheumatoid arthritis (RA) have suggested that IL-33 may be important as an endogenous danger signal (alarmin) in the pathogenesis of RA. IL-33 mRNA and protein expression are induced in RA fibroblast-like synoviocytes (FLS) following TNF-α/IL-1β stimulation, and IL-33 protein is mainly detected in the nucleus of these cells. The nuclear localization of IL-33 in IL-1β/TNF-α stimulated cells suggests that it may have a regulatory function inside the cell, as has been shown previously for IL-1α and IL-1F7b. The purpose of our study was to analyze the role of extracellular and intracellular IL-33 as an alarmin or regulator of nuclear transcription in RA FLS.

Methods: Synovial tissues from RA patients fulfilling the ACR criteria were obtained during open joint replacement. RA synovial samples were digested, subsequently cultured for 7 days and 3-passaged cells were used for all experiments. For analysis, quantitative RT-PCR, confocal analysis, western blot analysis, and ELISA were performed.

Results: IL-33 and ST2 (receptor of IL-33) mRNA expression increased in RA FLS stimulated with poly I:C (10 ug/ml) as a TLR3 ligand, IL-1β (10 ng/ml), and TNF-α (10 ng/ml). However, IL-33 release was not detected in

the culture supernatant. Similar to previous observations, IL-33 was released from damaged FLS. After identification of the ST2 on FLS by confocal analysis, FLS was stimulated with IL-33. Exogenous IL-33 stimulation (10–100 ng/ml) of RA FLS increased IP-10 and RANKL mRNA expression and treatment with anti-ST2 blocked this expression. The role of intracellular IL-33 as a nuclear protein was evaluated using IL-33 siRNA. Silencing of IL-33 increased MMP-1, 3, 13, IL-6, 8, and MCP-1 mRNA expression compared to the scrambled control in RA FLS stimulated with poly I:C, IL-1β, and TNF-α. In addition, we observed that the silencing of IL-33 induced significant degradation of IκBα and increased of NF-κB activity. These findings reveal a novel role for IL-33 as a negative modulator of NF-κB activity.

Conclusion: IL-33 has dual, opposing functions. As a pro-inflammatory cytokine, IL-33 induced the expression of IP-10 and RANKL mRNA. These effects may induce bone erosion by enhancing osteoclastogenesis in RA. In contrast to extracellular IL-33, intracellular IL-33 acted as negative modulator of NF-κB activity and suppressed the expression of many pro-inflammatory cytokines and pro-destructive molecules in RA FLS.

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1785

MiR-30* Family Negatively Regulates B-Cell Activating Factor (BAFF) Synthesis in Rheumatoid Synoviocytes. Ghada Alsaleh[1], Antoine Francois[1], Lucas Philippe[1], Jean Sibilia[1], Jacques-Eric Gottenberg[1], Philippe Georgel[2] and Dominique Wachsmann[1]. [1]EA4438 Laboratoire Physiopathologie des Arthrites, Illkirch-Strasbourg, France, [2]Laboratoire d'ImmunoGénétique Moléculaire Humaine, Strasbourg, France

Background/Purpose: In rheumatoid arthritis (RA) resident cells of the joint, fibroblast-like synoviocytes (RA FLS) acquire an aggressive phenotype in response to extrinsic factors such as PAMPs or DAMPs and intrinsic factors such as microRNAs. They produce large amounts of cytokines and among them the B cell-activating factor (BAFF) which allows them to collaborate with auto-immune B cells. We found that the miR-30* family of microRNAs (miR-30a*, d* and e*), which differ only 1 to 3 nucleotides, was predicted to potentially target the 3'-UTR region of BAFF. As BAFF is also up-regulated in the skin and the serum of systemic sclerosis patients, the aim of this study was to evaluate the role of miR-30* in the regulation of BAFF synthesis in fibroblasts isolated from either RA or SSc patients.

Methods: FLS and HDF were isolated from RA synovial tissues (n=6) or from skin from normal individual (n=3) or SSc patients (n=3) and were stimulated with TLR3 ligand (poly I:C) and IFN-γ for 3 days. RT-qPCR was performed to evaluate miRNA and mRNA expression. Transient transfection of RA-FLS and SSc-HDF with mimic miR-30* was performed using the Human Dermal Fibroblast NucleofectorTM kit from Amaxa. All assays were performed 24h post transfection.

Results: We first showed by qRT-PCR that like RA-FLS, SSc-HDF synthesized and released BAFF in response to poly I:C and IFN-γ. Conversely, HDF from normal subjects (NHDF) released BAFF only in response to IFN-γ. Using qRT-PCR, we demonstrated that miR-30a* and miR-30e* expression was strongly down regulated in RA-FLS, SScHDF and NHDF stimulated with either poly I:C or IFN-γ. Interestingly, NHDF which did not release BAFF in response to poly I:C expressed higher levels of miR-30a* and miR-30e* in response to poly I:C. MiR-30d* was not expressed constitutively or after activation by poly I:C and IFN-γ by each cell type. To evaluate whether miR-30* regulates BAFF expression in poly I:C and IFN-γ-activated RA-FLS and HDF, we transfected cells with miR-30* mimics. Transfection of the mimics induced a strong down-regulation of BAFF synthesis and release in response to poly I:C and IFN-γ. Moreover, we transiently transfected into HEK-293 cells a reporter construct that contain the firefly luciferase gene fused to the BAFF 3'-UTR containing the putative miR-30* interactor site along with miR-30*. We observed a downregulation of the luciferase activity, indicating that the 3'-UTR of BAFF mRNA is directly targeted by miR-30*.

Conclusion: Our data strongly suggest a critical role of miR-30* in the regulation of the expression of BAFF which could play an important role in the regulation of the auto-immune response in RA and SSc.

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1786

Targeting CD1c-Expressing mDCs to Inhibit Increased Thymus and Activation Regulated Chemokine Levels in RA. M.R. Hillen, F.M. Moret, F.P.J.G. Lafeber, C.E. Hack, T.R.D.J. Radstake and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: Thymus and activation regulated chemokine (TARC) is a chemotactic factor that attracts cells expressing CCR4, including CD4 T cells with Th2, Th17 and Treg phenotypes. TARC is known as a critical mediator in atopic diseases but is also present at sites of inflammation in autoimmune diseases. In synovial fluid (SF) of rheumatoid arthritis (RA) patients CCR4 is expressed on Th17 cells and mast cells that together are indicated to make up most IL-17 producing cells, suggesting that TARC plays an important role in attraction of IL-17 producing cells to the synovium. In addition, TARC can attract myeloid dendritic cells (mDCs) and fibroblasts. Immune cells such as CD1c-expressing mDCs and CD4 T-cells are potent TARC-producing cells. The aim of this study was to investigate if TARC is associated with RA pathogenesis and whether depletion of CD1c mDCs prevents production of high TARC concentrations.

Methods: TARC ELISA was performed on SF of 100 RA and 50 OA patients. Percentages of CD1c mDCs in SF of 10 RA patients were determined using flowcytometry. Mononuclear cells (MC) were isolated from the blood of healthy controls (HC) and blood or SF of RA patients and juvenile idiopathic arthritis (JIA) patients. CD1c mDCs were isolated with MACS and stimulated with TSLP for 24 hours and TARC levels were measured in supernatants. Alternatively, CD1c-expressing cells were depleted from MC using MACS and TARC levels were measured upon stimulation with TSLP or IL-7 (n=6).

Results: SF from RA patients contained significantly higher concentrations of TARC as compared to SF from OA patients (78.9 vs 9.2 pg/mL, p<0.0001). TARC levels in SF of RA patients correlated with percentages of CD1c mDCs present in SF (Rs= 0.68, p=0.035). Isolated CD1c mDCs from the synovial fluid of RA patients produced TARC directly *ex vivo* and produced significantly higher TARC levels compared to paired mDCs from the blood (26.4 vs 1.2 pg/mL, p<0.01). CD1c mDCs and SFMCs from RA and JIA patients produced more TARC compared to paired PB counterparts when stimulated with TSLP (926 vs 128 pg/mL, p<0.01) (or IL-7, p<0.01). Moreover, depletion of CD1c cells from MC significantly reduced TARC production induced by stimulation with TSLP (mean inhibition 76%, p=0.031).

Conclusion: Increased TARC levels in correlate with the percentages of CD1c-expressing mDCs present in RA SF; these mDCs produce enhanced TARC levels directly *ex vivo* and production is increased upon stimulation with TSLP. TARC production is markedly decreased when CD1c cells are depleted. As TARC is an important attractor of a range of inflammatory cells, preventing TARC production by targeting CD1c mDCs could be a novel therapeutic approach in RA.

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Evolution of the Cytokine and Chemokine Profile in Patients Receiving Oral Daily Vitamin D: Results From a Randomized Controlled Trial. Benjamin Terrier Sr.[1], Marlène Garrido[2] and Patrice Cacoub Sr.[3]. [1]Cochin Hospital, Paris, France, [2]Pitié-Salpétrière, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: Immunomodulatory effects of vitamin D were recently described *in vitro*, notably the expansion of regulatory T cells able to suppress inflammatory responses and the decrease of Th17 cells. However, studies of its effect *in vivo* in humans are lacking.

Objective: To explore the impact on inflammatory markers of a 6-month daily oral administration of vitamin D3 1000 IU versus no vitamin D, in aged patients with vitamin D insufficiency all receiving strontium ranelate.

Methods: A prospective, international phase III study with a 6-month double-blind period was performed to assess the efficacy and safety of a daily oral administration of strontium ranelate 2 g/vitamin D3 1000 IU fixed combination versus strontium ranelate 2 g alone. 150 patients (75 per group) included in this study were selected, after matching between the 2 groups for age, gender and baseline vitamin D level. Serum samples were collected at baseline and after 6 months of treatment. Quantitative analyses of 25 cytokines were performed using Luminex to study the impact of vitamin D daily oral administration on cytokine and chemokine profile. Statistical

analysis was done using Wilcoxon matched pairs test (P value < 0.05 was considered significant).

Results: Sixty-nine women and 6 men were included in each treatment group, with a mean age 67.1 ± 7.0 years in the vitamin D group and 66.8 ± 8.3 years in the non-vitamin D group. Baseline vitamin D serum level was 44.9 ± 15.5 nmol/L in the vitamin D group and 44.6 ± 13.8 nmol/L in the non-vitamin D group.

Some cytokines/chemokines levels decreased over the 6-month follow-up only in the vitamin D group whereas they remained stable in the non-vitamin D group, i.e. IFN-α (40 at baseline vs. 34 pg/mL after 6 months of treatment, P=0.03), IL-1β (16 vs. 11 pg/mL, P=0.07), IL-15 (52 vs. 40 pg/mL, P=0.001), MIP-1α/CCL3 (44 vs. 39 pg/mL, P=0.008) and TNF-α (7.0 vs. 2.9 pg/mL, P<0.0001).

The only cytokine that varied significantly only in the non-vitamin D group and remained stable in the vitamin D group was IL-12 that increased over the 6-month follow-up (127 at baseline vs. 146 pg/mL after 6 months of treatment, P=0.002).

IL-1RA, IL-2R and MCP-1/CCL2 did not differ significantly between the 2 arms of treatment, and remain stable over the 6-month follow-up. GM-CSF, IL-4, IL-8/CXCL8, IP-10/CXCL10 and MIP-1β/CCL4 decreased while eotaxin increased in both groups.

Many other cytokines and chemokines levels remain below the sensitivity threshold of the test used, that preclude any conclusion regarding their evolution i.e. IFN-γ, IL-2, IL-5, IL-6, IL-7, IL-10, IL-13, IL-17, MIG/CXCL9 and RANTES.

Conclusion: In this study designed to assess the efficacy and safety of a daily oral administration of strontium ranelate/vitamin D3 combination versus strontium ranelate alone, a statistically significant decrease of pro-inflammatory cytokines and chemokines serum levels in patients receiving vitamin D was observed. Further studies are necessary to assess the clinical relevance of such vitamin D-induced pro-inflammatory cytokines/chemokines variations.

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TSLP Induces TNFα Production by CD1c Myeloid Dendritic Cells and Myeloid DC-Activated T Cells From Rheumatoid Arthritis Patients. F.M. Moret, T.R.D.J. Radstake, J.W.J. Bijlsma, F.P.J.G. Lafeber and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: Thymic stromal lymphopoietin (TSLP) is well known for its potent activation of myeloid dendritic cells (mDCs) to induce Th2-mediated immune responses. Fibroblasts from rheumatoid arthritis (RA) patients produce TSLP upon TLR and TNFα stimulation. Recently, we have shown that increased intra-articular TSLP concentrations in RA patients potently activate TSLPR-expressing mDCs from peripheral blood (PB) and synovial fluid (SF) of RA patients to secrete T cell attractant chemokines and to potently increase T cell activation. In addition, TSLP and its receptor play a crucial role in promoting Th17-driven collagen-induced arthritis. Since TNFα is a crucial pro-inflammatory and tissue-destructive mediator in RA, we assessed the capacity of TSLP to regulate TNFα production by CD1c mDCs and CD4 T cells in RA patients as compared to healthy controls (HC).

Methods: CD1c mDCs, isolated from PB as well as SF of RA patients (n=6), were stimulated with TSLP for 20 hours and TNFα production was measured by multiplex immunoassay. Washed TSLP-activated CD1c mDCs from PB (n=13) and SF (n=5) of RA patients and from PB of HC (n=5) were added to autologous CD4 T cells in the absence of additional stimuli, cultured for 6 days and subsequently proliferation was measured. Additionally, T-cell TNFα production was measured by ELISA upon restimulation with ionomycin/PMA.

Results: TSLP significantly stimulated the production of TNFα by mDCs from PB and SF (PB from 99 to 378 pg/ml, p<0.03 and SF from 170 to 355 pg/ml, p<0.03). Upon incubation with TSLP, TSLPR-expressing mDCs from PB potently stimulated proliferation of autologous CD4 T cells as compared to unstimulated mDCs (ratio T cell:DC 5:1, from 1503 to 16036 cpm, p<0.01). TSLP-mDCs from SF had a strongly increased capacity to activate CD4 T cells (ratio T cell:DC 5:1, from 26395 to 57387 cpm, p<0.05). Enhanced proliferation was associated with increased production of TNFα (ratio T cell:DC 5:1, PB from 3498 to 9225 pg/ml, p=0.001 and SF from 8951 to 18415 pg/ml, p<0.05). TNFα production by TSLP-mDC activated T cells from PB of RA patients was higher as compared to HC (RA from 3498 to 9225 pg/ml and HC from 3522 to 5686 pg/ml), although this was not statistically significant.

Conclusion: TSLP potently induces TNFα production by CD1c mDCs and mDC-activated CD4 T cells from RA patients. Considering the fact that TNFα can induce TSLP secretion by synovial fibroblasts this suggests a novel positive feedback loop of TNFα and TSLP that contributes to immunopathology of RA.

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Evidence for an Additive Effect of Tumor Necrosis Factor Alpha and Hypoxia to Promote Bone Destruction in Arthritis. Shankar Revu[1], Akilan Krishnamurthy[1], Vivekananda Sunkari[2], Ileana R. Botusan[2], Xiaowei Zheng[2], Sergiu-Bogdan Catrina[2] and Anca Irinel Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden

Background/Purpose: Hypoxia is a major feature of the inflamed rheumatoid arthritis synovial membrane and promotes osteoclasts formation *in vitro*. We aimed to investigate the molecular mechanisms by which hypoxia contribute to bone destruction in the presence of local inflammation.

Methods: Osteoblast-like cells were cultured in normoxic (21% O_2) or hypoxic (1% O_2) conditions with or without tumor necrosis factor (TNF)-α. Receptor activator of the NF-kB ligand (RANKL) and osteoprotegerin (OPG) were detected by rtPCR, Western blot and ELISA. siRNA deletion of HIF-1a, HIF-2a and VHL was performed in osteoblasts. Interaction between hyocia inducible factor (HIF) and RANKL was investigated by promoter chromatin immunoprecipitation (ChIP). Chemical hypoxia using dimethyloxalylglycine (DMOG) and TNFα were tested on osteoclast formation from peripheral blood mononuclear cells of RA patients and on osteologic bone discs. Statistical analysis was performed using one-way ANOVA.

Results: Exposure of osteoblasts to hypoxia resulted in a significant increase in RANKL mRNA and cellular protein expression and a concomitant decrease of soluble OPG. Small interfering RNA against HIF-2α but not HIF-1α was able to abolish hypoxia effect on RANKL expression. Chromatin immunoprecipiation assay confirmed the direct interaction between HIF-2α with at least one hypoxia responsive element (HRE) in the RANKL promoter. Presence of TNFα had an additive effect with hypoxia to increase RANKL expression. Hypoxia mimicking by DMOG demonstrated an additional direct effect on osteoclastogenesis with an additive effect of hypoxia and TNFα to promote osteoclastogenesis and bone resorption *in vitro*.

Conclusion: Hypoxia promotes HIF-2a dependent RANKL up-regulation and osteoclastogenesis and has an additive effect with pro inflammatory cytokines to promote bone destruction.

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Notch Promotes Matrix Metalloproteinase 13 Expression by Inducing Interleukin-6 in Primary Murine Chondrocytes. Stefano Zanotti and Ernesto Canalis. Saint Francis Hospital and Medical Center, Hartford, CT

Background/Purpose: Notch1 to Notch4 are transmembrane receptors that determine cell differentiation and function. Interactions of Notch with its ligands result in the cleavage of the Notch intracellular domain (NICD), which translocates to the nucleus to induce gene expression. Notch suppresses collagen type II a1 (*Col2a1*) and induces collagen type X a1 (*Col10a1*) expression in murine chondrocytes. Activation of Notch signaling was observed in human osteoarthritic chondrocytes, although it was not reported whether Notch plays a role in the progression of osteoarthritis. Matrix metalloproteinase (Mmp)13 is a collagen-degrading enzyme expressed by osteoarthritic chondrocytes, and overexpression of Mmp13 in murine articular chondrocytes causes joint degeneration, demonstrating that Mmp13 contributes to cartilage matrix degradation. Interleukin (Il6) is a secreted inflammatory molecule that suppresses *Col2a1* and induces *Mmp13* expression in chondrocytes. Il6 is expressed by osteoarthritic chondrocytes, and Notch induces Il6 in synoviocytes, but it was not reported whether Notch regulates Il6 expression in chondrocytes. To understand whether Notch regulates the expression of gene markers of osteoarthritis, we investigated the effects of Notch on *Mmp13* and *Il6* expression in primary murine chondrocytes, and tested whether Il6 mediates the effects of Notch.

Methods: Notch was induced in chondrocytes from *Rosa*[Notch] mice, where the *Rosa26* promoter is followed by a STOP cassette flanked by *LoxP* sites, and the NICD coding sequence. Primary chondrocytes from 3 to 4 day old *Rosa*[Notch] mice were infected with an adenoviral vector expressing Cre recombinase, which excises the STOP cassette and induces expression of NICD directed by the *Rosa26* promoter. As controls, parallel cultures of *Rosa*[Notch] chondrocytes were infected with an adenoviral vector expressing green fluorescent protein (GFP).

To document Notch activation, *Rosa*[Notch] chondrocytes were transfected with Notch reporter constructs. To assess the effects of Notch on gene expression, changes in mRNA levels were analyzed by quantitative reverse transcription PCR. To investigate whether Il6 mediates the effects of Notch in *Rosa*[Notch] chondrocytes, cells were cultured in the absence of serum and exposed to an inhibitory monoclonal murine antibody against Il6, or to a murine immunoglobulin G, either under basal conditions or in the context of Notch activation.

Results: NICD overexpression in *Rosa*[Notch] chondrocytes transactivated Notch reporter constructs and induced Notch target genes, demonstrating activation of Notch signaling. The effects of Notch on the expression of *Col2a1* and *Col10a1* were confirmed. NICD induced *Mmp13* and *Il6* mRNA levels, and exposure of *Rosa*[Notch] chondrocytes to an inhibitory Il6 antibody opposed the induction of *Mmp13* by Notch, whereas it did not modify the effects of Notch on *Col2a1* and *Col10a1* expression.

Conclusion: Activation of Notch signaling in primary chondrocytes induces expression of gene markers of osteoarthritis. Induction of *Mmp13* by Notch is mediated by Il6, whereas the effects of Notch on the expression of chondrocyte gene markers are determined by alternate mechanisms.

Disclosure: **S. Zanotti**, None; **E. Canalis**, None.

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Different Mechanisms Responsible for IVIG Inhibition of Immune Complex Versus TLR Stimulated Interferon-Alpha. Alice Wiedeman[1], Fabian Käsermann[2], Sylvia Miescher[2] and Keith B. Elkon[1]. [1]University of Washington, Seattle, WA, [2]CSL Behring, Bern, Switzerland

Background/Purpose: SLE immune complexes (IC) induce IFN-α production by stimulation of TLR7 and 9 in plasmacytoid dendritic cells (pDC). Serum from normal human donors inhibits IC-induced IFN-α *in vitro* and both C1q and IgG have been identified as inhibitory serum components. Since pooled IgG (IVIG) is used for therapy of autoimmune diseases and the sialylated subfraction implicated in its mode of action, we addressed how IVIG regulates IFN-α production by pDC.

Methods: Normal human peripheral blood mononuclear cells (PBMC) or negatively selected pDC were stimulated with SLE IC or the TLR 7 and 9 agonists, Loxoribine (Lox) or CpG-A respectively. IFN-α was quantified in the supernatants by ELISA. Unsorted IVIG or IVIG that had been enriched (SNA+) or depleted (SNA-) of the sialylated subset by a lectin affinity column or digested into Fc or F(ab')2 fragments were added to stimulated cultures. SLE IC containing Alexa Fluor 647 labeled SmRNP antigen was allowed to bind to PBMC with or without pretreatment with FcγRII blocking antibody or IVIG Fc, and the binding to pDC quantified by flow cytometry.

Results: IVIG dose-dependently inhibited SLE IC-induced IFN-α ($\sim$20%, 50%, and 95% inhibition by treatment with 50, 500, and 5000 μg/mL IVIG, respectively). Inhibition was Fc-dependent (500 μg/mL IVIG inhibited 50% of IFN-α compared to molar equivalents of F(ab'2), <10%, and Fc, 60%, p<0.01), but was sialylation-independent. IgG Fc inhibited SmRNP IC binding to pDC (50% of pDC bind IC, which was reduced to 20% with 167 μg/mL Fc, p<0.001). In contrast, TLR agonist-induced IFN-α was only modestly (10–20%) inhibited by high doses (5000 μg/mL) of IVIG and inhibition was significantly higher by the SNA+ versus SNA- fraction of IVIG (Lox: 90% and 40%, p<0.001; CpG 75% and 0%, p<0.001, for SNA+ versus SNA- respectively). Furthermore, the inhibitory activity was contained in the F(ab')2 fragment. The inhibitory activity of sialylated IVIG was not direct on pDC, but required the presence of monocytes (depletion of CD14+ monocytes reduced inhibition by 500 μg/mL SNA+ IVIG after Lox stimulation of IFN-α from 70% to 0%, p<0.05 while depletion of CD19+ B cells or CD56+ NK/NKT cells had no effect). Monocytes produced prostaglandin E2 (PGE2) specifically in response to the sialylated IVIG subset (10–20 ng/mL with SNA+ IVIG compared to undetectable quantities with SNA- IVIG, p<0.05). Furthermore, blockade of PGE2 from the monocyte supernatants reduced inhibitory activity to <10%, and addition of PGE2 blocked IFN-α production.

Conclusion: IVIG Fc directly inhibits production of IFN-α in response to SLE IC by blocking IC binding to FcγRIIa on pDC. In contrast, the SNA+ subset of IVIG inhibits TLR agonist stimulation of IFN-α by inducing the production of PGE2 by monocytes. Understanding these disparate mechanisms of IVIG inhibition of IFN-α will provide novel methods for immunomodulation and may allow use of smaller amounts of subcomponents of IVIG for therapy.

Disclosure: **A. Wiedeman**, CSL Behring, 2; **F. Käsermann**, CSL Behring, 3; **S. Miescher**, CSL Behring, 3; **K. B. Elkon**, Hoffman La Roche, 5, Resolve Therapeutics, 4.

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Identification of the Antimicrobial Peptide LL-37 As a Potential Mediator of Synovial Inflammation in Rheumatoid Arthritis. Petra Neregård[1], Marianne Engström[1], Erik Af Klint[1], Birgitta Agerberth[2] and Anca Irinel Catrina[1]. [1]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden

Background/Purpose: LL-37, a member of the cathelicidin family of host defense peptides, has a broad range of antimicrobial and immunomodulatory effects that potentially can have an impact on the regulation of the adaptive immune system. In this study we aimed to investigate a potential role for LL-37 in mediating chronic synovial inflammation.

Methods: 49 patients meeting the 1987 American College of Rheumatology (ACR) criteria for RA were recruited for this study. We evaluated LL-37 by immunohistochemistry in synovial biopsy samples obtained before and after a mean of 8 weeks of treatment from 15 patients treated with adalimumab, 12 patients treated with etanercept and 11 patients treated with methotrexate, as well as from 11 patients prior to and 2 weeks after injection with intraarticular glucocorticoids. LL-37 was also evaluated in synovial biopsies obtained from 10 healthy volunteers. Microscopic results were analyzed by double-blind semi-quantitative analysis. Synovial localization of LL-37 was performed by double fluorescent stainings for LL-37 and cell surface markers. LL-37 was detected in synovial fluid by Western blots. Statistical analysis was performed using Wilcoxon test for paired comparisons and Man-Whitney test for comparisons of independent samples.

Results: LL-37 was expressed in most of the RA synovial biopsies both in the lining and sublining layers and readily identified in the synovial fluid. Serial and double-fluorescent immunostaining for cell surface markers identifies granulocytes (CD66 positive cells) and macrophages (CD68 positive cells) as main cells expressing LL-37. Inflamed synovial tissue obtained from active arthritis prior to treatment expressed higher levels of LL-37 as compared to healthy individuals. Treatment with adalimumab, etanercept and intraarticular glucocorticoids but not methotrexate resulted in a significant down-modulation of LL-37 expression.

Conclusion: Our results demonstrate presence of LL-37 in the context of chronic synovial inflammation and show specific regulation of this molecule by distinct anti-rheumatic agents. Further investigation to reveal the functional consequences of our findings on synovial antimicrobial and inflammatory activity is needed.

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The Cyclooxygenase/Prostaglandin-E$_2$ Pathway Is Critical for Autocrine IL-17A Production by Th17 Cells Upon Synovial Fibroblast Interaction. Sandra M.J. Paulissen[1], Jan Piet van Hamburg[2], Nadine Davelaar[1], Patrick S. Asmawidjaja[3], Johanna M.W. Hazes[4] and Erik Lubberts[3]. [1]Erasmus MC, University Medical Center, Rotterdam, Rotterdam, Netherlands, [2]Erasmus MC, Rotterdam, Netherlands, [3]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [4]Erasmus Medical Center, Rotterdam, Netherlands

Background/Purpose: Recently, we have shown that Th17, but not Th1 cells, from patients with early rheumatoid arthritis (RA) are potent activators of RA synovial fibroblasts (RASF) resulting in autocrine IL-17A production. This IL-17A production results in a pro-inflammatory loop, which is characterized by an up-regulation in pro-inflammatory cytokines and cartilage degrading enzymes. The autocrine IL-17A production by Th17 cells is critical for the perseverance of the pro-inflammatory loop, but the mechanism underlying the autocrine IL-17A induction is unclear. The objective of this study is to investigate the mechanism responsible for the autocrine IL-17A induction upon Th17-RASF interaction.

Methods: CD4+CD45RO+CCR6+ (Th17) and CD4+CD45RO+ CCR6− (Th1) cells were isolated by fluorescence-activated cell sorting

(FACS) sorting from healthy controls and early RA patients. These cells were co-cultured with RASF, in the presence of neutralizing antibodies directed against soluble IL-6R (anti-sIL-6R) and/or IL-1β, and celecoxib. Gene expression profiles were generated and supernatant was collected for cytokine analyses by enzyme-linked immunosorbent assay (ELISA).

Results: Gene expression analyses revealed that the genes encoding for IL-6 and IL-1β were up-regulated in Th17-RASF cultures. These data were confirmed by ELISA and quantitative polymerase chain reaction (Q-PCR), respectively. Since IL-1β and IL-6 may be involved in IL-17/Th17 polarization we examined the contribution of these cytokines on the autocrine IL-17A loop. Blockade of IL-1β and IL-6 significantly suppressed IL-17 production. However the effects of IL-1β and IL-6 blockade were limited, indicating the requirement of an additional mechanism.

Interestingly, the genes encoding for cyclo-oxygenase-2 (COX-2) and prostaglandin-E-synthase (PTGES), which are involved in prostaglandin-E$_2$ (PGE$_2$) synthesis, were also up-regulated in Th17-RASF cultures. This was associated with a dramatic increase of PGE$_2$ production in Th17-RASF cultures compared to Th1-RASF cultures. Treatment of Th17-RASF cultures with celecoxib, a COX-2 inhibitor, resulted in significant and specific inhibition of the fraction of IL-17A producing cells and the IL-17A levels. No inhibitory effects were found on IFN-γ and TNF-α production. Moreover, celecoxib treatment functionally inhibited the pro-inflammatory loop as production of the pro-inflammatory mediators IL-6 and IL-8 and tissue destructive enzymes MMP-1 and MMP-3 were significantly suppressed.

Conclusion: These findings show the critical role of the COX/PGE$_2$ pathway in the autocrine IL-17A production upon Th17 and synovial fibroblast interaction. Inhibition of this pathway down-regulates the pro-inflammatory feedback loop induced by Th17-RASF interaction leading to less production of pro-inflammatory cytokines and destructive mediators.

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1794

Matrix Metalloproteinase 3 and Acute Phase Proteins As Markers of Disease Activity and Radiographic Damage in Early Rheumatoid Arthritis. Mahmood MTM Ally[1], Bridget Hodkinson[2], Pieter W.A Meyer[1], Eustasius Musenge[3], Mohammed Tikly[4] and Ronald Anderson[1]. [1]University of Pretoria, Pretoria, South Africa, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]University of Witwatersrand, Johannesburg, South Africa, [4]Division of Rheumatology, University of the Witwatersrand, Johannesburg, South Africa

Background/Purpose: Although matrix metalloproteinase-3 (MMP-3) is believed to be intimately involved in the immunopathogenesis of rheumatoid arthritis (RA), relatively little is known about its relationships to: i) proven genetic markers of disease susceptibility and biomarkers of immune-mediated tissue damage; and ii) disease activity in early RA in comparison with that of the acute phase reactants, C-reactive protein (CRP) and serum amyloid A (SAA).

Methods: Circulating concentrations of MMP-3 were measured by an ELISA procedure in serum specimens from 128 disease-modifying, anti-inflammatory drug-naïve patients with RA of $\leq$ 2 years duration. These were correlated with shared epitope (SE) genotype, a spectrum (16) of circulating chemokines/cytokines representative of various types of inflammatory and structural cells, acute phase reactants, autoantibodies, and a cartilage breakdown product (COMP), as well as with clinical indices of disease.

Results:. While no associations with SE genotype were evident, serum MMP-3, which was elevated in 56,25% of patients (p<0,0001), was broadly, albeit variably, correlated with most of the chemokines/cytokines (r values = 0.18–0.33, P <0.03–<0.0001), COMP (r = 0.22, P <0.014), and, most notably, CRP and SAA (respective r values of 0.40 and 0.41, (P <0.0000). In the case of clinical indices, MMP-3 correlated with the simplified disease activity index (SDAI, r = 0.29, P < 0.0001), but not with radiographic changes, erosions or nodulosis. However, the correlations of CRP and SAA with SDAI were stronger (respective values of 0.63 and 0.54, P <0.001 for both).

Conclusion: In early RA, MMP-3 is significantly associated with disease activity, inflammatory mediators and cartilage breakdown, and is a potential biomarker of disease severity, but is less useful than CRP and SAA in early RA.

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1795

Correction for Basophil and Monocyte Frequencies Identifies Specific Gene Expression Differences Associated with SLE Disease Flare: Interim Report From the Bold (Biomarkers of Lupus Disease) Study. Mikhail G. Dozmorov[1], Nicolas Dominguez[1], Stan Kamp[2], Cory Giles[1], Jonathan D. Wren[1], Sudhakar T. Sridharan[3], Joan T. Merrill[1], Judith A. James[4] and Joel M. Guthridge[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [3]Pfizer Inc, Collegeville, PA, [4]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: Heterogeneity of clinical manifestations and pathogenic mechanisms has complicated treatment of SLE patients. The BOLD study allows evaluation of gene expression changes associated with disease flare without the impact of background immunosuppressants which have confounded previous studies.
Objectives: 1. Define immune functions or pathways impacted by disease activity. 2. Evaluate gene expression differences due to variations of cell subsets. 3. Uncover cell specific biological pathways that are associated with lupus disease activity.

Methods: The BOLD study enrolled patients with active disease at the baseline visit (BV) who were withdrawn from background immunosuppressive therapy and given intramuscular steroids to induce improvement (IV), and followed until flare (FV). An interim profiling of gene expression on 15 SLE patients was performed. Cell specific significance analysis of microarrays (csSAM) compares gene expression between two groups, each separately deconvolved to yield cell specific expression. The false discovery rate (FDR) for cell specific differentially expressed genes (DEG) between groups is assessed via permutations. csSAM analysis was performed comparing the BV to IV, IV to FV and BV to FV. Bioinformatics analysis of pathways and gene functions was performed using the sets of DEG.

Results: Correction for basophil frequencies yielded a FDR of 25% and identified 502 DEG comparing BV and IV. Genes overrepresented in signaling pathways associated with SLE included LCK, CD44, CD40LG, SOS1, TNFRSF13C (BLyS receptor), SLAMF1, IRF8, TNFAIP3, TNFRSF4, MIF, FCGR1A and FCGR1B. Comparing IV to FV, (representing a transition from low to high disease state without immune suppression on board), deconvolution on monocyte frequencies identified 68 DEG with an FDR of 25% at the FV. Genes in the p38 MAP Kinase, ERK/MAPK, IFN signaling, and IL-12 pathways were enriched. Comparing BV to FV, (same patients with active disease on and off immune suppressants), deconvolution on basophil frequencies using an FDR of 39% yielded 1421 DEG. Pathways overrepresented included antigen presentation and apoptosis. When assessing function enrichment, "antibody response" was overrepresented by 27 genes (p=2.27E-06) including BTK, CD86, TLR2, TNFRSF13B (TACI), and TNFSF13B (BLYS).

Conclusion: Basophil and monocyte adjusted DEG analysis suggests that pathways associated with SLE signaling, apoptosis, antigen presentation, and antibody response functions are associated with changes in gene expression at transitions between high and low disease activity. These biomarkers could identify therapeutic targets or identify patients who are or are not good candidates for different targeted therapies.

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Anti-IL-20 Targets Local Tissue Inflammation As Opposed to Systemic Inflammation. Amanda L. Blasius[1], Joshua N. Beilke[1], Hal Blumberg[1], John Bui[1], Jennifer H. Cox[1], Tom Cox[1], Heidi J. Jessup[1], Phillip L. Kong[1], Steven D. Levin[1], Valerie H. Odegard[1], Jason A. Stucky[1], Evan P. Thomas[1], Joseph A. Wahle[1] and John Rømer[2]. [1]Novo Nordisk Inflammation Research Center, Seattle, WA, [2]Novo Nordisk, Måløv, Denmark

Background/Purpose: In a recent Phase 2a clinical trial in patients with rheumatoid arthritis, the novel human anti-IL-20 monoclonal antibody NNC0109-0012 was shown to reduce disease activity (DAS28-CRP) and had a favourable safety/tolerability profile. In RF-positive and anti-CCP-positive patients it also improved the ACR20/50/70 responses. Response to anti-IL-20 therapy was rapid, with patients showing significant improvements in DAS scores as early as 1 week after treatment. Expression of IL-20 and its receptor chains IL-20R1, IL-20R2, and IL-22R has previously been demonstrated in synovium from patients with RA. The safety and efficacy data support the

hypothesis that anti-IL-20 works locally in the joint without modulating systemic inflammation. To test this hypothesis, human peripheral immune cells from blood and lymphoid tissue were evaluated as IL-20 target cells.

Methods: An extensive collection of immune cell subsets derived from human blood and tonsil were analyzed, both directly after isolation and following *ex vivo* activation. Expression of IL-20R1, IL-20R2, and IL-22R was detected by flow cytometry and/or qPCR. In parallel, cell responsiveness to IL-20 was evaluated by measuring the phosphorylation of STAT3 following treatment of cells with IL-20. Further functional readouts of IL-20 responsiveness included measurement of proliferation and cytokine production in response to IL-20 treatment.

Results: The cell types evaluated included B cells, CD8^{+} T cells, CD4^{+} T cell subsets, NK cells, dendritic cells, monocytes, macrophages, mast cells, basophils, eosinophils, and CD34+ hematopoietic stem cells. The IL-20R2 subunit was detected on several cell types, including monocytes, macrophages, and tonsillar B cells. However, co-expression of the IL-20 receptor beta chain and one of the two alpha chains, requirements for a functional IL-20 receptor, was not detected on human peripheral immune cells under resting or activated conditions. Consistent with this, there was a lack of responsiveness to IL-20 as monitored by phosphorylation of STAT3. Finally, whole blood cultured with IL-20 failed to induce a response as measured by cytokine and chemokine production. This overall lack of response contrasted to non-immune cell types involved in local inflammation, such as keratinocytes.

Conclusion: The paucity of IL-20 receptor expression and IL-20 responsiveness by peripheral immune cells correlates with the absence of systemic immune suppression in the Phase 2a clinical trial of NNC0109-0012. In combination with earlier data showing expression of IL-20 in synovial tissues, these data suggest that IL-20 is restricted to acting locally on inflamed synovium in patients with RA.

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Wnt Signaling Pathway Status, Determined by Serum Dkk-1 and R-Spondin 1 Levels, in Rheumatoid Arthritis and Ankylosing Spondylitis. Byoong Yong Choi[1], Hyon Joung Cho[1], Eun Ha Kang[1], Yeong Wook Song[2] and Yun Jong Lee[1]. [1]Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Seoul National University Hospital, Seoul, South Korea

Background/Purpose: Dickkopf-1 (Dkk-1), known as inhibitor of Wnt signaling pathway, is involved in joint damage in inflammatory arthritis. While R-spondin 1 (Rspo1) reported to protect against bone destruction through antagonizing Dkk-1 in murine arthritis model, the Rspo1 levels in inflammatory arthropathy such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS) has not been investigated. We determined the circulating levels of Rspo1 and Dkk-1 in patients with RA or AS and investigated their clinical implication.

Methods: Serum sample were collected from 60 RA patients (mean age±SEM 53.3± 1.55, 54 females), 55 AS patients (36.7± 1.61, 8 females), and age-and gender-matched 65 healthy subjects (44.7±1.80, 35 females). Sera from 13 RA patients treated with anti-TNF-α agents were also collected at baseline and 12 weeks. Clinical and laboratory data included age, gender, body mass index, disease duration, medication history, ESR and CRP. Disease activities in RA and AS were measured by DAS28 or BASDAI respectively. Radiographic joint damages in RA were assessed by the modified Sharp/Van der Heijde score (Sharp score). Serum Rspo1 and Dkk-1 levels were determined by sandwich ELISA.

Results: Serum Rspo1 levels were significantly decreased in RA patients when compared to those in healthy subjects (p<0.0001). However, their levels were comparable between AS patients and healthy subjects. While serum Dkk-1 levels in AS patients were significantly lower than those in healthy subjects (p=0.001), those in RA were significantly higher (p<0.0001). Thus, the ratios of Dkk-1/Rspo1 were significantly elevated in RA patients but significantly suppressed in AS patients (both p<0.0001). Dkk-1/Rspo1 ratios in RA patients with high disease activities (DAS28 > 5.1) were much higher than those in RA patients with low disease activities (DAS28 < 2.6, p=0.012). However, Dkk-1/Rspo1 ratios were not correlated with Sharp scores in RA patients and not different between AS patients with

and without syndesmophyte. Serum DKK-1 levels wre not changed but Dkk-1/Rspo 1 ratios were decreased by anti-TNF-α treatment (p=0.0134). Glucocorticoid treatment (p=0.003) or presence of osteoporosis (p=0.044) was associated with increased Dkk-1/Rspo-1 ratios.

Conclusion: This study demonstrated inappropriate suppression of Wnt signaling pathway, presented by high Dkk-1/Rspo1 ratios, in RA and activation of Wnt signaling pathway in AS. However, the ratios of Dkk-1/Rspo1 levels were not directly associated with the cumulative radiographic change in RA patients although their levels were affected by RA disease activity.

1798

Macrophage Migration Inhibitory Factor Regulates Dual-Specificity Phosphatases Via Glucocorticoid Induced Leucine Zipper. Huapeng Fan, Devi Ngo, Ran Gu and Eric Morand. Monash University, Melbourne, Australia

Background/Purpose: Macrophage migration inhibitory factor (MIF) plays a pivotal role in promotion of inflammatory diseases such as rheumatoid arthritis (RA). MIF has previously been shown to oppose the action of glucocorticoids, by regulating the expression of dual-specificity phosphatase (DUSP)-1 (syn. MAPK phosphatase-1 (MKP-1)) and thereby to amplify MAP kinase signalling and up-regulate multiple cytokines and chemokines. Glucocorticoids also act by regulation of glucocorticoid induced leucine zipper (GILZ). Whether MIF opposition of glucocorticoid actions involves modulation of other DUSPs or GILZ is unknown. Therefore, the aim of this study was to examine the effects of MIF on the expression of DUSPs and GILZ.

Methods: Bone marrow derived macrophages and dermal fibroblasts were isolated from WT, MIF^{−/−} and GILZ^{−/−} mice. The expression of a panel of DUSPs and GILZ, and TNF and IL-6, were investigated by real time RT-PCR, Western blotting and ELISA.

Results: In MIF^{−/−} macrophages, multiple DUSPs, including DUSP1/MKP-1, but also DUSP 2, 5, 6, 8, 9, 10, 16, and 19, were significantly increased. GILZ mRNA and protein were significantly increased in MIF^{−/−} macrophages and fibroblasts, and GILZ expression induced by Dex was also significantly greater in MIF^{−/−} cells. Correspondingly, recombinant MIF inhibited GILZ expression, MIF inhibited the expression and nuclear translocation of the transcription factor FoxO3a, and FoxO3a silencing reversed the effect of MIF deletion on GILZ. The basal and Dex-induced expression of the panel of MIF-regulated DUSPs was significantly reduced in GILZ^{−/−} cells, and accordingly, LPS-induced TNF and IL-6 were significantly increased in GILZ^{−/−} cells.

Conclusion: These studies indicate a previously unsuspected broad regulatory effect of MIF on multiple DUSPs. Moreover, we identify FoxO3a-dependent regulation of GILZ by MIF, and a corresponding regulatory effect of GILZ on DUSPs and cytokine expression. The results suggest that GILZ-mediated regulation of DUSP expression mediates the antagonistic effect of MIF on glucocorticoid actions.

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ONO-4059 - A Novel Small Molecule Bruton's Tyrosine Kinase (Btk) Inhibitor, Suppresses Osteoclast Differentiation and Activation. Yuko Ariza, Toshio Yoshizawa, Yoshiko Ueda, Shingo Hotta, Masami Narita and Kazuhito Kawabata. Ono Pharmaceutical Co., Ltd., Osaka, Japan

Background/Purpose: Bruton's tyrosine kinase (Btk) is primarily expressed in B cells, mast cells, platelets, myeloid cells and osteoclasts. Osteoclast differentiation is regulated by signaling pathways activated by receptor activator of nuclear factor-κB ligand (RANKL), macrophage colony-stimulating factor (M-CSF) and immunoreceptor tyrosine-based activation motif (ITAM). Phosphorylation of ITAM results in the activation of phospholipase C-γ through activation of non-receptor tyrosine kinases Btk and Syk. However, the functional hierarchy of these two kinases has not been fully elucidated. To explore the distinct functions of Btk and Syk, we examined their relative contributions to osteoclast differentiation and activation using inhibitors to both Btk and Syk.

Methods: Human osteoclast precursors were differentiated with 33 ng/mL of M-CSF and 66 ng/mL of RANKL for 7 days. Increasing concentrations

(1 nM to 1000 nM) of ONO-4059 and Syk inhibitors were incubated with the cells for 7 days. Osteoclast differentiation was evaluated by TRAP staining followed by light microscopy and quantitation of TRAP+ cells containing at least three nuclei. To evaluate osteoclast function, cytokine production and Btk and Syk signaling were determined by ELISA and Western Blot analysis, respectively.

Results: Both ONO-4059 and the Syk inhibitor specifically inhibited the activity of Btk and Syk, respectively. ONO-4059 dose-dependently inhibited the M-CSF and RANKL-driven osteoclast differentiation by 70% (IC_{50}: 0.853 nmol/L). Surprisingly, the effect of the Syk inhibitor on osteoclast differentiation was much lower (n=3, 30% inhibition). ONO-4059 also reduced the secretion of MIP-1α and RANTES in bone marrow cell culture, with a weaker effect observed in bone marrow with the Syk inhibitor.

Conclusion: Btk, but not Syk, appears to play a pivotal role in osteoclast differentiation and activation. Rheumatoid arthritis (RA) is often complicated by generalized osteopenia due to increased bone resorption by osteoclasts. These preliminary results suggest that the selective, oral Btk inhibitor, ONO-4059 may be a novel therapeutic target for rheumatoid arthritis (RA) to suppress bone erosion and inflammation.

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Macrophages in Hypoxic Rheumatoid Joints Preferentially Express Hypoxia Inducible Transcription Factor-2. Sarah Aynsley[1], Ursula Fearon[2], Anthony G. Wilson[3] and Munitta Muthana[4]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [3]Section of Musculoskeletal Sciences, University of Sheffield, Sheffield, United Kingdom, [4]University of sheffield, Sheffield, United Kingdom

Background/Purpose: In rheumatoid arthritis (RA), the influx of inflammatory cells as well as the aggressive proliferation of fibroblast-like synovial cells (FLS) outstrips the oxygen supply from blood vessels leading to joint hypoxia. Macrophages accumulate in hypoxic disease sites including RA joints where they possess broad pro-inflammatory, destructive and remodeling potential leading to inflammation and joint destruction. Macrophages respond to hypoxia by up regulating the hypoxia inducible transcription factors– HIF-1 and -2 normally degraded in the presence of oxygen. This study will attempt to understand the relative contribution of HIF-1 and HIF-2 expressing macrophages in RA and the genes/mechanisms involved in their activation.

Methods: We obtained arthroscopy sections from RA patients for which tissue oxygen levels had been measured. This consisted of a random sample of mild (~40mmHg), moderate (~15mmHg) & severe (~3mmHg) joint hypoxia. We also used samples from a second cohort of patients scored with mild or severe disease (based upon extent of synovitis and vascularity), a sub group of which were also receiving anti-TNF therapy. Sections were immunostained with anti-HIF 1 and 2 and co-localised with the pan-macrophage marker CD68 as well as other macrophage markers (Flt-1, CD147, CD206 and Tie2).

Results: In patients with mildly hypoxic joints, macrophages (CD68+) predominately expressed HIF-1 (20%) and CD147 and were found in small clusters localised to the lining layer, whilst macrophages in patients with severely hypoxic joints were in greater numbers (73%), throughout the biopsy. These macrophages predominately expressed HIF-2+ (>75%), Flt-1, Tie2 and CD206. A similar pattern was observed in patients with severe disease where sections expressed more HIF-2+Flt-1+ macrophages compared to those with mild scores (15 cells per field of view compared to 5 for mild $p<0.01$). There was no significant difference in HIF-1 expression. Interestingly, this HIF-2+ macrophage subpopulation was absent in patients who had been successfully treated with anti-TNF.

Conclusion: In patients with severely hypoxic joints macrophage numbers were significantly greater than in patients with mild hypoxia and predominantly expressed HIF-2+, which activates genes associated with both inflammation and angiogenesis. These cells expressed M2-like macrophage markers including Flt-1, Tie2 & CD206, important in tissue remodeling and angiogenesis. We are currently investigating the gene expression profile of these subpopulations using laser capture micro-dissection and gene arrays and will further study their relevance in animal models of RA using transgenic mice with targeted deletions of HIF-1 or HIF-2 in myeloid cells.

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1801

Biological Roles of C5orf30 in Rheumatoid Arthritis. Munitta Muthana[1], Sachin Khetan[2], Gbadebo Adeleke Adeleke[2], Simon Tazzyman[2], Sarah Aynsley[1], Fiona Morrow[1], Sarah Hawtree[1], Barbara Ciani[1] and Anthony G. Wilson[3]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Dr, Sheffield, United Kingdom, [3]Section of Musculoskeletal Sciences, University of Sheffield, Sheffield, United Kingdom

Background/Purpose: A recent genome wide association study identified the variant rs26232 in the first exon of an uncharacterized gene *C5orf30*. In addition, this variant is also associated with severity of radiological joint damage suggesting a role in tissue breakdown. To date there is no function assigned for *C5orf30* and neither the gene or protein coded show homology to any known functional sequences. However, C5orf30 is highly conserved in chimpanzee, dog, cow, mouse, chicken, and zebrafish (orthologs). The aim of this study is to determine the biological roles of *C5orf30* in health and RA.

Methods: Real time PCR and western blotting was used to determine *C5orf30* transcript and protein levels in fibroblast-like synovial cells (FLS-stimulated with TNF & hypoxia) and peripheral blood leukocytes isolated from RA patients and healthy individuals. Immunohistochemistry using synovial samples was used to determine cellular expression using anti-*C5orf30* and antibodies to macrophages (CD68), fibroblasts (5B5), T (CD3) & B (CD19) cells. To investigate gene function siRNA was used to knockdown *C5orf30* in synovial FLS *in vitro* and we have used morpholino antisense oligonucleotide (MO)-mediated knocked down of *C5orf30* in zebrafish embryos (fms:mcherry) *in vivo*.

Results: Expression of *C5orf30* was detected at lower levels in peripheral blood leukocytes of RA patients compared to healthy controls (117 patients vs. 102 controls, $p=0.00052$). *C5orf30* was expressed in joint FLS and was found to be up regulated following treatment with hypoxia (8-fold) and down-regulated by TNF-a (0.5-fold). Confocal microscopy revealed *C5orf30* was strongly expressed in both the nuclear and cytoplasmic compartment of synovial lining cells including macrophages and fibroblasts but not B & T cells. *C5orf30* was undetectable in arthroscopy sections obtained from osteoarthritis or control (knee replacement) patients. So far, 80% *C5orf30* knockdown has been achieved in FLS without affecting cell viability. Interestingly, MO-mediated knockdown of *C5orf30* impeded zebrafish development and increased total macrophage numbers by 40% compared to knockdown of a scrambled control MO.

Conclusion: *C5orf30* is expressed at both the transcript & protein level in synovial cells but not in circulating PBMC obtained from RA patients, suggesting that *C5orf30* is expressed in a tissue-specific manner. We are currently assessing the morphological phenotype and function arising from *C5orf30* siRNA knockdown in FLS using confocal microscopy and matrigel invasion assays. NMR and mass spectrometry experiments are on the way to determine the three-dimensional structure of *C5orf30* and its potential protein-binding partners.

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1802

Interleukin-29 Modulates Proinflammatory Cytokine Production in Synovial Inflammation of Rheumatoid Arthritis. Miaojia Zhang, Fang Wang, Lingxiao Xu and Wenfeng Tan. the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA., Nanjing, China

Background/Purpose: The immunoregulatory function of interleukin (IL)-29 has recently been recognized. However, little is known about the involvement of IL-29 in the pathogenesis of rheumatoid arthritis (RA). We here investigated the potential role of IL-29 in the synovial inflammation of RA.

Methods: The transcript levels of IL-29 and its specific receptor IL-28Rα in peripheral blood mononuclear cells (PBMC) and synovium were determined by real-time reverse transcription-polymerase chain reaction (real-time PCR). The concentrations of IL-29 in serum and synovial fluid (SF) were quantified by enzyme-linked immunoassay (ELISA), and the correlation of serum IL-29 levels with disease activity in RA patients was investigated. Furthermore, the expression of IL-29 in RA synovium was examined by immunohistochemistry and double immunofluorescence analysis. Finally, the expression of IL-6, IL-8, IL-10, IL-17 and matrix-metalloproteinase-3 (MMP-3) in synovial fibroblasts upon IL-29 stimulation was determined by real-time PCR.

Results: IL-29 and IL-28Rα mRNA expression in PBMC were significantly increased in patients with RA compared with healthy controls (HC). The serum levels of circulating IL-29 were higher in RA than those in HC. RA SF also conferred the increased IL-29 levels compared to osteoarthritis (OA) SF. However, serum IL-29 levels showed no significant correlation with the RA disease activity. IL-29 was markedly elevated in RA synovium compared to tissues from HC, and was mostly expressed in the lining region of synovium. Moreover, IL-29 was expressed predominately in synovial macrophages and fibroblasts. RA synovial fibroblasts exposed to IL-29 specifically upregulated IL-6, -8 and MMP-3, downregualted IL-10, but showed no effect on IL-17.

Conclusion: The findings in the present study indicate, for the first time, that IL-29 is dysregulated in patients with RA, which may contribute to the RA pathogenesis via inducing the production of proinflammatory cytokines, chemokines or matrix-metalloproteinases in synovial fibroblasts.

1803

Chemokine-Like Receptor 1 (CMKLR1), a G Protein Coupled Receptor Expressed On Proinflammatory Monocytes in Arthritis, Is Negatively Regulated by GRK3. D. Stephen Serafin[1], Roman Timoshchenko[2], Marcus W. McGinnis[3] and Teresa K. Tarrant[4]. [1]Thurston Arthritis Research Center, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina Sch of Med, Chapel Hill, NC, [4]UNC School of Medicine, Chapel Hill, NC

Background/Purpose: Chemokine-like receptor 1 (CMKLR1) is a G protein coupled receptor (GPCR) expressed by inflammatory monocytes that are pathogenic in human diseases such as psoriasis and lupus. Its cognate ligand, chemerin, is a chemoattractant for invading inflammatory cells and is present in the synovial lining of rheumatoid arthritis (RA), osteoarthritis (OA), and psoriatic arthritis (PsA) patients. In OA, chemerin is thought to contribute to both the extracellular matrix breakdown of cartilage as well as joint inflammation.

CMKLR1 is a newly discovered GPCR, which as a class of receptors are phosphorylated by G-protein receptor kinases (GRKs) to turn off GPCR signaling. Due to the significant role of chemerin/CMKLR1 interaction in human inflammatory arthritis, we chose to examine the unknown regulatory mechanism of CMKLR1 by GRKs.

Methods: Isoforms GRK3 and GRK2 were separately knocked down in human monocytic THP-1 cells using shRNA and confirmed via quantitative real time PCR. Migration to chemerin (100 ng/mL) was measured by fluorescence emission through the BD Falcon 96-Multiwell Insert System or flow cytometry through 5 μM Transwells over 3 hrs.

A modified Tango assay was used to measure β-arrestin recruitment to CMKLR1. HTLA cells were over expressed with CMKLR1 and GRK2 or GRK3 via calcium phosphate precipitation. Cells were stimulated with 1 μM of chemerin and after 24 hours, luminescence was measured on a Trilux plate reader.

Results: CMKLR1 recruits β-arrestin in a ligand-dependent dose response. β-arrestin recruitment to CMKLR1 is mediated preferentially by GRK3 as compared to GRK2. THP-1 cells deficient in GRK3 showed enhanced chemotaxis to chemerin when compared to control cells.

Conclusion: We conclude that the chemerin/ CMKLR1 axis plays an important role in targeting monocytes to sites of inflammation and is negatively regulated by GRK3.

1804

TNF-Like Protein 1A/Death Receptor 3 Pathway Regulates Osteoclastogenesis and Is Associated with Erosive Disease in Rheumatoid Arthritis. Fraser L. Collins[1], Michael D. Stone[2], Rhian Goodfellow[3], Ernest Choy[4], Edward C. Wang[1] and Anwen S. Williams[1]. [1]Cardiff University, Institute of Infection and Immunity, Cardiff, United Kingdom, [2]University Hospital Llandough, Cardiff & Vale University Health Board, Cardiff, United Kingdom, [3]Cardiff University, Cardiff, ENGLAND, United Kingdom, [4]Cardiff University School of Medicine, Cardiff, United Kingdom

Background/Purpose: Bone erosion is a characteristic feature of inflammatory arthritides, such as rheumatoid arthritis (RA). Death Receptor 3 (DR3) and its only known ligand TNF-like protein 1A (TL1A) have been identified as key regulators of osteoclastogenesis in murine models of arthritis (Bull MJ, Williams AS et.al. J.Exp.Med. 2008). We investigated the potential mechanisms by which the DR3/TL1A pathway orchestrates osteoclast (OC) formation in humans and assessed the impact of DR3 signalling upon bone pathology in RA.

Methods: CD14$^+$ monocytes were obtained from healthy females (n=8). Cells were cultured on ivory discs (with macrophage-colony-stimulating factor (M) and receptor activator of nuclear factor-κB ligand (R)) for 7, 10 and 14 days $\pm$ TL1A (10 and 100ng/ml). Osteoclastogenesis and area of disc resorbed were quantified. Levels of TNFα and MMP-9 were measured by ELISA. Serum samples were obtained from consenting normal human volunteers (n=12) and RA patients (n=36) attending outpatient clinic who fulfilled the ACR classification criteria.TL1A and TNFα were measured by ELISA. Ethical approval for this study was granted by the Bro-Taf Health Authority. All data is expressed as mean$\pm$SEM value.

Results: A significant dose-dependent increase in osteoclastogenesis was observed after addition of exogenous TL1A ($P<0.01$; 2-way ANOVA) in our *in vitro* human system. Cell counts per mm^2, at end-point, were comparable for each condition tested (M+R=480$\pm$49; M+R+TL1A-10=517$\pm$62 and M+R+TL1A-100=475$\pm$59). However, TL1A (100ng/ml) doubled the number of OC observed on each ivory disk (12$\pm$3; OC per mm^2) when compared against controls (6.8$\pm$2; $P<0.05$). These OC were functionally active, evidenced by their capacity to resorb a bone substrate. TL1A (100ng/ml) induced a potent 5-fold increase in bone resorption (5.19$\pm$3%) over control cultures (1.33$\pm$0.43%, $P<0.01$); the effect was dose-dependent. This was accompanied by a significant ($P<0.01$; 2-way ANOVA) dose and time dependent elevation in bone-matrix degrading MMP-9 secretion. MMP-9(μg/ml) increased from 4.8$\pm$1.1 to 7.5$\pm$1 for controls versus TL1A (100ng/ml) activated cultures on day 14. These data reveal a new mechanism for DR3's resorptive function in bone. This action was independent of TNFα; the cytokine was not detected in any of our culture conditions studied. In serum collected from RA patients, TL1A levels were significantly elevated ($P<0.05$) over normal healthy individuals (3.0$\pm$0.6 versus 0.2$\pm$0.2 ng/ml). Serum levels of TL1A were also significantly higher in RA (rheumatoid factor positive) patients with erosive disease over those who had no detectable radiographic changes at time of sampling (3.9$\pm$0.8 and 0.5$\pm$0.2 ng/ml). TNFα was not detected in any of the samples assayed.

Conclusion: Our findings reveal TL1A to be a key regulator in osteoclastogenesis and imply that the TL1A/DR3 pathway contributes to osteoclast-driven bone pathology associated with RA.

1805

The Pro-Fibrotic Cytokines IL-33 and IL-13 Modulates Dermal Fibrosis Via the A2A Adenosine Receptor. Ross C. Radusky[1], Jessica L. Feig[2], Bruce N. Cronstein[3], Andrew G. Franks[4] and Edwin SL Chan[1]. [1]New York University School of Medicine, New York, NY, [2]New York Univ School of Medicine, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY, [4]New York University, New York, NY

Background/Purpose: We have previously demonstrated that the nucleoside adenosine mediates collagen production and induce dermal fibrosis in *in vitro* and *in vivo* models. IL–13 expression is upregulated in tissues characterized by high levels of adenosine (adenosine deaminase-deficient mice). However, the receptor(s) and mechanism involved in this upregulation are unknown. Here, we further characterize the contributions of endogenous adenosine and adenosine A$_{2A}$and A$_{2B}$receptors in skin fibrosis via IL-33 and IL-13 signaling.

Methods: Human dermal fibroblasts were treated with A$_{2A}$ receptor agonist (CGS-21680), A$_{2A}$ antagonist (ZM241385); A$_{2B}$ (BAY606583), and A$_{2B}$antagonist (MRS1706). Fold changes in the expression of IL-13 and associated receptors were analysed after 2 hours. Message for IL-33, IL-13 and three IL-13 receptor proteins – IL-13Rα1, IL-13Rα2 and IL-4R, were assessed using quantitative real-time PCR and compared to untreated controls.

Results: Stimulation of the A$_{2A}$ receptor with CGS-21680 induces expression of IL-13 and three IL-13 receptors: IL-13Rα1, IL-13Rα2, and IL-4R. A 2.8x increase in expression was found for IL-13Rα1 (p<0.05), 3.4x increase for IL-13Rα2 (p<0.05), and 3.9x increase for IL-4 (p<0.05) was seen. IL-33 expression was increased by 8.6x (p<0.05). These elevations were all blocked by the A$_{2A}$ receptor antagonist. Stimulation of the A$_{2B}$receptor alone does not cause significant changes in the expression of the receptors studied.

Conclusion: Despite efforts at investigating the mechanisms underlying fibrogenesis in the skin of patients with scleroderma, no effective antifibrotic therapy exists. The nucleoside adenosine induces expression of pro-fibrotic cytokine IL-13 and particularly its cognate receptors IL-13Rα1, IL-13R α2, and IL-4. Furthermore, Upregulation of IL-33 may in part contribute to the induction of IL-13 expression by A2A receptors. These findings suggest that blockade of the A_{2A} receptor may be useful as a novel therapeutic modality to prevent dermal fibrosis in scleroderma.

Disclosure: R. C. Radusky, None; **J. L. Feig**, None; **B. N. Cronstein**, Canfite BioPharma, 1, NIH, URL Pharma, OSI, 2, Bristol-Myers Squibb, Novartis, URL, Regeneron, Gismo Therapeutics, 5, Arthritis Foundation, SLE Foundation, 6, Patents on use of adenosine receptor antagonists to treat or prevent fibrosis. Multiple other patents; **A. G. Franks**, None; **E. S. Chan**, None.

1806

A Novel Angiopoetin2/TEK Tyrosine Kinase Receptor Mediated Effect On Leukocyte Cell Influx and Oxidative Damage in Inflammatory Arthritis. Emese Balogh[1], Chin T. Ng[1], Douglas J. Veale[2], Ursula Fearon[1] and Monika Biniecka[1]. [1]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: The Angiopoietin2 (Ang2)/TEK Tyrosine Kinase Receptor (Tie2) signalling pathway acts synergistically with VEGF/flk as critical regulators of new vessel growth, morphology and stability possibly through TNFα sensitization. The aim of this study was to assess the synovial tissue levels of VEGF, Ang2 and Tie2 in inflammatory arthritis patients and examine the effect of TNF inhibitors (TNFi) on VEGF expression and angiopoietin/Tie2 signaling. Moreover we correlated these data with changes in clinical outcomes, hypoxia and oxidative damage.

Methods: Forty four patients with inflammatory arthritis (RA n=30 and PsA n=14) underwent needle arthroscopy. All subjects had actively inflamed knee joints and were assessed pre-TNFi treatment, with a subgroup (n=20) pre/post TNFi therapy. All patients underwent full assessment including DAS28-CRP, macroscopic vascularity/synovitis, synovial biopsy and *in vivo* tissue pO$_2$ (tpO$_2$) was measured using a novel LICOX probe. Immunohistology and dual-immunofluorescence were used to quantify vascular factors (VEGF, Ang2 and Tie2), cell specific markers (CD3, CD68) and markers of oxidative damage (8-oxo-dG and 4HNE).

Results: At baseline the mean synovial tissue pO$_2$ (tpO$_2$) level was profoundly hypoxic at 25.9 mmHg, equivalent to an ambient oxygen tension 3.4%. VEGF, Ang2 and Tie2 were expressed throughout the synovium localised in the lining layer, sub-lining and vascular regions. VEGF expression correlated with macroscopic synovitis (r=0.41, p=0.031) and vascularity (r=0.40, p=0.034). High Ang2 expression was associated with greater synovitis (r=0.56, p=0.013) and number of CD68+ cells (r=0.53, p=0.013). Tie2 expression was significantly associated with CD3+ cells (r=0.39, p=0.023) and CD68+ cells (r=0.46, p=0.010) and with high ESR and CRP (both r=0.37, p=0.047). Treatment with TNFi showed a significant reduction in expression of Tie2 (p=0.034) and Ang2 (p=0.021) and this was paralleled by an increase in tpO2 levels from mean 22.8 mmHg to 30.3 mmHg. Finally, a significant association between increased ΔVEGF, ΔAng2 and ΔTie2 with high DNA damage (Δ8-oxo-dG) and lipid peroxidation (Δ4-HNE) was demonstrated (both r>0.53, p<0.05), strongly suggesting an interplay between oxidative stress and angiogenesis in a progression of chronic inflammatory arthritis.

Conclusion: This data suggests that the Ang2/Tie2 signalling pathways may mediate in part the downstream effects of TNF blockade. Furthermore, this is the first evidence to suggest that Ang2/Tie2 maybe directly involved in leukocyte cell influx regulation and oxidative damage within the inflamed joint.

Disclosure: E. Balogh, None; **C. T. Ng**, None; **D. J. Veale**,,,,,; **U. Fearon**, None; **M. Biniecka**, None.

1807

Regulation of Inflammatory Responses in Tumor Necrosis Factor-Activated and Rheumatoid Arthritis Synovial Macrophages by Janus Kinase Inhibitors. Anna Yarilina[1], Kai Xu[1], Chunhin Chan[1] and Lionel B. Ivashkiv[2]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, Weill Medical College of Cornell University, New York, NY

Background/Purpose: Small molecule inhibitors of the Janus kinases (JAKs) have been developed as anti-inflammatory and immunosuppressive agents and are currently undergoing testing in clinical trials. Tofacitinib/CP-690,550 (more potent in inhibiting JAK3 and JAK1) and Ruxolitinib/INCB-018424 (selective inhibitor of JAK1/2) have demonstrated clinical efficacy in rheumatoid arthritis (RA). However, the mechanisms that mediate the beneficial actions of these compounds are not well understood. In this study, we examined effects of JAK inhibition on inflammatory responses in human blood-derived and RA synovial macrophages, with a focus on the key pathogenic cytokine TNF that activates JAK-STAT signaling indirectly and with delayed kinetics.

Methods: In vitro studies were performed with peripheral blood macrophages from healthy donors treated with TNF and synovial fluid macrophages from patients with RA. Levels of activated signal transducer and activator of transcription (STAT) proteins and other transcription factors were detected by Western blot, and genes expression was measured by real-time PCR. In vivo effects of JAK inhibitors were evaluated in the K/BxN serum-transfer model of arthritis.

Results: JAK inhibitors suppressed activation and expression of STAT1 and downstream target genes encoding inflammatory chemokines (CXCL9, 10, 11) in TNF-stimulated and RA synovial macrophages. Unexpectedly, both compounds attenuated a late wave of *IL1B* induction by TNF. Furthermore, CP-690,550 significantly decreased *IL6* expression in RA synovial macrophages. In addition, both inhibitors decreased nuclear localization of NF-kB subunits in TNF-stimulated and RA synovial macrophages. Both JAK inhibitors augmented nuclear levels of NFATc1 and cJun, followed by increased formation of osteoclast-like cells. However, only CP-690,550 dramatically increased resorptive activity of these cells. CP-690,550 significantly inhibited inflammation and joint swelling in K/BxN arthritis that is dependent on macrophages but not on lymphocytes.

Conclusion: Taken together, our data demonstrate that JAK inhibitors suppress inflammatory functions of macrophages, in part by altering cell responses to the key pathogenic cytokine TNF. These findings suggest that suppression of macrophages and innate immunity may contribute to the therapeutic efficacy of JAK inhibitors in RA.

Disclosure: A. Yarilina, None; **K. Xu**, None; **C. Chan**, None; **L. B. Ivashkiv**, None.

1808

Immune Activating Effects of Co-Stimulation of TLR Agonists and Cytokines On Primary and Immortalized Keratinocytes From a Patient with a *CARD14* Mediated Pustular Psoriasis (CAMPS) and Healthy Controls. Yongqing Chen[1], Yin Liu[2], Yan Huang[1], Carole Yee[3], Alison MacBride[4], Anne Bowcock[5], Michelle Lowes[6] and Raphaela T. Goldbach-Mansky[7]. [1]Translational Autoinflammatory Disease Section, Office of the Clinical Director NIAMS, Bethesda, MD, [2]NIAMS, Bethesda, MD, [3]NCI, NIH, Bethesda, MD, [4]NIAID, NIH, Bethesda, MD, [5]Washington University, St. Louis, MO, [6]Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY, [7]Translational Autoinflammatory Diseases Section NIAMS NIH, Bethesda, MD

Background/Purpose: Through producing inflammatory cytokines and chemokines, keratinocytes play an important role along with hematopoietic cells in mediating an inflammatory response in psoriasis and other inflammatory skin conditions. Keratinocyte-produced cytokines include IL-1a, IL-6, IL-8, IL-23, TNF, IL-36α, β, and γ, etc. Recently, autosomal dominant mutations in *CARD14* have been shown to cause a disease severity spectrum of plaque psoriasis, pustular psoriasis and pityriasis rubra piliaris. CARD14 is mainly expressed in the keratinocytes in skin. As blockade of IL-12/23 has been very successful in inhibiting skin inflammation in psoriasis and in our pediatric patient with CAMPS, and more recently blockade of IL-17A/F in psoriasis, we hypothesize that keratinocyte activation may be the primary trigger of hematopoietic cell recruitment into the skin and that therapy with IL-12/23 inhibitors and more recently with IL-17 inhibitors may either block keratinocytes directly or through the prevention of IL-17 production, and that inhibition of keratinocyte activation might significantly contribute to the treatment success with these agents in controlling skin inflammation.

Methods: We generated primary and immortalized keratinocyte cell lines from a patient with CAMPS, a patient with *CARD14* negative plaque psoriasis and 3 foreskin samples. We examined the immune function of keratinocytes in co-stimulation assays with a panel of TLR agonists and pro inflammatory cytokines, measuring IL-8 in cell culture supernatant as initial readout for keratinocyte activation. We assayed cytokine receptor expression on keratinocytes. In some experiments gene expression of other cytokines (CCL20, IL-6 and S100A7 (psoriasin)) were assayed by qRT-PCR. Statistical analysis was performed using paired/unpaired t-tests.

Results: Keratinocytes can be activated by the agonists through TLR3, Poly IC; TLR5, Flagellin; and TLR9, Type B CpG oligonucleotides to produce IL-8. Keratinocytes have a number of cytokine receptors, such as IL-1R, IL-6R, IL-17R, IL-23R, IL-36R, TNF-R, etc, and get stimulated through IL-17A, IL-1a/b, and less through TNF, IL-36γ. However, they do not get stimulated through IL-12 or IL-23. IL17A synergizes with Poly IC, Flagellin, and also with TNF but not with IL-36γ, IL-12 or IL-23. Based on all TLRs and cytokine stimulation at 24hr, the keratinocytes from a patient with the *CARD14* mutation have higher IL-8 production than control cells and keratinocytes from a patient with severe plaque psoriasis. Expression studies show that under co-stimulation of TNF and IL-17A, mRNA expression of CCL20 and IL-6 occurs early at 4hr, but S100A7 is maximally expressed later at 24hr.

Conclusion: TLRs stimulating through TLRs 3, 5 and 9 and some hematopoietic-produced cytokines particularly IL-17 have direct synergic effects on keratinocyte activation. *CARD14* mutant keratinocytes are more sensitive to these positive stimulants than keratinocytes from a patient with regular psoriasis and health controls. Our data suggest that *CARD14* mutations sensitize keratinocytes to heightened responses to TLR agonists and co stimulation with other inflammatory cytokines and is likely the crucial cytokine in promoting skin inflammation.

Disclosure: **Y. Chen**, None; **Y. Liu**, None; **Y. Huang**, None; **C. Yee**, None; **A. MacBride**, None; **A. Bowcock**, None; **M. Lowes**, None; **R. T. Goldbach-Mansky**, None.

1809

Serum IFNα Activity in Systemic Lupus Erythematosus Drops in Response to Immunosuppressive Therapy Only When There Is Concurrent Clinical Response. Elzbieta E. Jacek[1], Elena Gkrouzman[1], Mikhail Olferiev[2], Nancy Pan[1], Roland Duculan[3], Kyriakos A. Kirou[3] and Mary K. Crow[3]. [1]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, New York, NY, [2]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery, New York, NY

Background/Purpose: The type I interferon (IFN-I) signature, describing expression in PBMC of a large set of gene transcripts induced by IFN-I, and increased serum IFNα functional activity are characteristic of many patients with systemic lupus erythematosus (SLE) and are candidate biomarkers of disease activity. However, previous studies have not consistently demonstrated whether IFNα activity is useful for monitoring disease activity and assessing the effect of therapy in lupus patients.

Methods: From a cohort of 60 lupus patients with available serum data of IFNa activity, 15 were identified who experienced a) at least 1 severe flare as determined by the SELENA-SLEDAI instrument, and b) had a follow-up visit no longer than 3 months after the occurrence of a severe flare. In the 15 patients identified, there were 21 occurrences of a severe flare, with a follow-up visit no longer than 3 months later. IFNα activity at the time of those visits was measured using an in vitro reporter assay in which WISH epithelial cell line cells (highly responsive to stimulation with IFN-I) were cultured with patient sera and relative expression of IFIT1 and IFI44, IFN-I-responsive genes, was quantified using RT-PCR. The IFN-I score was calculated by converting relative expression values to IFN units/ml, using a standard curve acquired from dose response stimulations of WISH cells with 1–100 units/ml of recombinant IFNα. Clinical improvement was defined according to the SLE Responder Index (SRI) as: 1) improvement in SLEDAI by at least 4 points; 2) no 2 B or 1 A as recorded in the BILAG; 3) no increase in Physician Global Assessment by more than 0.3 points.

Results: Out of 21 severe flares identified, 12 fulfilled the clinical improvement criteria (responses) during the next visit (<3 months). In those cases, IFNα score decreased significantly (from a median of 12.67 to 2.3, p=0.005), and there was also a significant decrease in the SLEDAI score (from a median of 13 to 5, p=0.0025). The remaining 9 cases which did not fulfill the clinical improvement criteria (no responses) showed statistically unchanged IFNα and SLEDAI scores. Immunosuppressive therapies were similar in both groups, including mycophenolate mofetil in 10/12 responses and in 5/9 non-responses. Pulse steroids were used in 6/12 responses and 4/9 non-responses. Only 1 pulse steroid therapy in each group was given less than 7 days before serum was obtained for IFNa levels.

Conclusion: Our data indicate that a decrease in IFN-I serum activity following a severe clinical flare may be a sensitive and reliable tool for monitoring the disease state of lupus patients and confirming the effectiveness of therapies used to treat severe flares.

Disclosure: **E. E. Jacek**, None; **E. Gkrouzman**, None; **M. Olferiev**, None; **N. Pan**, None; **R. Duculan**, None; **K. A. Kirou**, None; **M. K. Crow**, None.

1810

Identification and Characterization of Synthetic Small Molecule Macrocycle Antagonists of Human IL17A. David Livingston, Sethu Alexander, Julian Bond, Timothy Briggs, Andrew Fraley, Stephen Hale, Tanya Landsman, Richard Martinelli, Kelley Shortsleeves, Nick Terrett and Nathan Walsh. Ensemble Therapeutics, Cambridge, MA

Background/Purpose: IL17A has been demonstrated to be a key pro-inflammatory cytokine in human rheumatoid arthritis and in several rodent models of arthritis. Synthetic macrocycles are more amenable to optimization for metabolic stability and oral absorption than biotherapeutics. The aim of this investigation was to identify high-affinity macromolecule binders of human IL17A, to quantify their inhibitory potency against IL17A-dependent cytokine production in human cells, and to determine if active compounds could inhibit a delayed-type hypersensitivity response in mice.

Methods: DNA programmed chemistry (DPC) libraries were generated to synthesize in vitro libraries of non-peptidic synthetic macrocycles of molecular weight 600–1000 kDa. Compounds binding to immobilized IL17A were identified by PCR and DNA sequencing. Two compounds were resynthesized and characterized by 1) competitive ELISA to determine affinity for human IL17A, 2) inhibition of IL17A-driven IL-6 production in human rheumatoid arthritis synovial fibroblasts (RASF) and human HT-29 adenocarcinoma cells, 3) inhibition of other pro-inflammatory human cytokine activities, such as IL-1β, IL-6, IL-22, and TNFα, and 4) efficacy in a delayed-type hypersensitivity (DTH) mouse model. The DTH model used a 1-fluoro-2,4-dinitrobenzene (DNFB) sensitizer, which was applied to the animals at day 0. On day 7, compounds dissolved in DMSO were dosed by intraperitoneal (i.p.) injection at a dose of 10 mg/kg. A second application of DNFB was performed on the left ear 30 min after compound dosing. After 24 hours, left ear edema was measured by change in ear weight compared to the right ear, and levels of INF-γ in ear tissue homogenates were quantified by ELISA.

Results: Two synthetic macromolecules identified in this investigation, E-34935 and E-35018, were characterized by a competition ELISA with human IL17A, and determined to have a dissociation constant (Kd) = 2 nM. E-34935 and E-35018 were found to inhibit IL17A with EC50 of 2.0 and 2.1 μM in RASF, and 45 and 20 nM in HT29 cells, respectively. Both compounds were inactive (EC50 > 25 μM) in a battery of cellular assays for the human cytokines IL-1β, IL-6, IL22, and TNFα. A single i.p. dose of 10 mg/kg of E-34935 or E-35018 in the murine DTH model suppressed edema vs. vehicle control by 50 or 54% respectively (p < 0.05 vs. vehicle control). In comparison, a rat anti-mouse IL17A IgG1 (5 mg/kg, i.p.) resulted in 76% inhibition of edema. INF-γ levels in tissue homogenates were also suppressed by E-34935, E-35018, or anti-IL17A Ab vs. vehicle control by 72%, 62% or 75%, respectively (p < 0.05 for all groups vs. vehicle control group).

Conclusion: Our data provide evidence that synthetic macrocycles can be identified that bind potently and specifically to human IL17A, and act as inhibitors of IL17A-stimulated IL-6 production in RASF and HT29 cells. These compounds are also anti-inflammatory in an IL17-directed murine DTH model. Prior to this investigation, such specific inhibitors of the IL17A-IL17receptor interaction were limited to polypeptides.

Disclosure: **D. Livingston**, Ensemble Therapeutics, 3; **S. Alexander**, Ensemble Therapeutics, 3; **J. Bond**, Ensemble Therapeutics, 3; **T. Briggs**, Ensemble Therapeutics, 3; **A. Fraley**, Ensemble Therapeutics, 3; **S. Hale**, Ensemble Therapeutics, 3; **T. Landsman**, Ensemble Therapeutics, 3; **R. Martinelli**, Ensemble Therapeutics, 3; **K. Shortsleeves**, Ensemble Therapeutics, 3; **N. Terrett**, Ensemble Therapeutics, 3; **N. Walsh**, Nathan Walsh, 3.

1811

On the Origin of the Type I Interferon Signature in Rheumatoid Arthritis. T.D. de Jong[1], Saskia Vosslamber[1], Maija-Leena Eloranta[2], Lars Rönnblom[2], Kyra Gelderman[1], Mary von Blomberg[1], Irene Bultink[1], Alexandre Voskuyl[1] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Section of Rheumatology, Uppsala University, Uppsala, Sweden

Background/Purpose: Presence of a type I interferon (IFN) signature has been described for several autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). For SLE, it was shown that the IFN signature is induced by IFNα from plasmacytoid dendritic cells via specific immune complexes. Although the IFN signature in RA seems to be comparable to SLE, the source of IFN induction is yet unknown. This study aims to investigate the mechanism by which components of RA serum contribute to the IFN signature.

Methods: Healthy PBMCs were exposed to RA or SLE serum. IFNα protein production was measured in an immunoassay after 20h incubation with 5% patient serum. To study the involvement of immune complexes containing antinuclear antibodies, samples were co-cultured with necrotic or apoptotic cells (Lövgren et al., Arthritis Rheum. 2004 Jun;50(6):1861-72). Moreover, IFN response genes (IRG), IFNα and IFNβ mRNA induction were measured by quantitative PCR after 4h and 8h incubation with 25% patient serum. An IFN score is calculated as the average expression of 3 IRGs (RSAD2, IFI44L, MX1). To study the involvement of new protein synthesis on IRG induction, part of the samples were co-cultured with 2μg/ml cycloheximide (CHX).

Results: As expected, SLE serum induced more IFNα protein induction than healthy donor serum (NHS) (p=0.0006, Mann Whitney test), which even further increased with dead cell material (p=0.006, Mann Whitney test). RA serum did not induce significantly more IFNα protein production than NHS, although a small increase was observed in the absence of dead cell material (p=0.0516, Mann Whitney test).

With respect to IRG mRNA induction, both RA and SLE sera induced higher levels than NHS, though with different induction kinetics. SLE serum showed IRG mRNA induction already at 4h, which stayed present after 8h. CHX treatment even slightly increased IRG mRNA induction at 8h, suggesting that the IRG mRNA induction occurs independently of new protein synthesis and is probably mediated directly by IFNα, as described before. RA serum, on the other hand, showed only IRG mRNA induction after 8h. This IRG mRNA induction was downregulated upon CHX treatment, indicating an indirect IRG induction process. To study whether the IRG induction was preceded by IFN mRNA induction, IFNα en IFNβ mRNA expression was determined. The IRG induction by RA serum was positively correlated to IFNβ mRNA induction at 4h and 8h (Pearson correlations, 4h: r= 0.6873, p=0.0023; 8h: r=0.7173, p=0.013), but not to IFNα production.

Conclusion: RA serum did not induce IFNα protein production, and mRNA induction kinetics differed from those of SLE serum. Furthermore, the IRG mRNA induction by RA serum was preceded by IFNβ mRNA induction. Altogether, this indicates a different source of IRG induction in SLE and RA serum and thus possibly a different mechanism behind their type I IFN gene signature.

Disclosure: **T. D. de Jong**, None; **S. Vosslamber**, None; **M. L. Eloranta**, None; **L. Rönnblom**, None; **K. Gelderman**, None; **M. von Blomberg**, None; **I. Bultink**, None; **A. Voskuyl**, None; **C. L. Verweij**, None.

ACR/ARHP Poster Session C
Epidemiology and Health Services Research:
Rheumatic Disease Pharmacoepidemiology
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

1812

A Retrospective Evaluation of the Clinical and Economic Implications of Gout in Nursing Home Residents in Hawaii Treated with Allopurinol. Joy Higa[1], Gregory Reardon[2] and Gregory Tong[3]. [1]Long Term Care Research Center, Kaneohe, HI, [2]Informagenics, LLC, Worthington, OH, [3]Deerfield, IL

Background/Purpose: We describe patient characteristics, serum uric acid (sUA) levels while on allopurinol, and activities of daily living (ADL) in nursing home residents with gout.

Methods: On-site chart review of 14 nursing homes in Hawaii (Oct 2010-Mar 2011), including serum creatinine, sUA, the Minimum Data Set (MDS) and medication records. Eligible residents were >65 years of age, had been residents > 30 days, and had recent sUA and ADL assessments. Cases (n=202) were eligible residents with gout using allopurinol. Controls (2 per case, n=404) without gout were identified by simple random sampling from the same time frame. A global ADL score was calculated [BMC Geriatr 2006, 6:7] from the most recent MDS. Multiple regression separately estimated the independent association of gout with ADL score and the use of any opiate medication, adjusting for potentially related factors (eg, demographics, body mass index (BMI), renal function, and comorbid conditions).

Results: Of residents with gout, 69% had sUA ≥6mg/dl, despite allopurinol treatment. Compared with controls, cases were younger (39% vs. 53% <85 years of age; p<0.001) and more likely to be of Hawaiian ancestry (OR=7.3, p<0.001). BMI was 2.3 points higher for cases vs controls (p<0.001). Cases were more likely to have coronary artery disease (OR=4.0, p<0.001), diabetes (OR=3.6, p<0.001), previous myocardial infarction

(OR=7.3, p<0.001), and charted renal failure (OR=4.9, p<0.001). They had a mean Carpenter score of 25.2 (0–28; 28=total dependence) vs 17.1 for controls (p<0.001). Adjusted logistic regression models showed that gout was independently associated with a 7.26-point higher (worsened) Carpenter ADL score (p<0.001). Cases were more likely than controls to receive an opiate (adjusted OR=8.7, p<0.001).

Conclusion: In nursing home residents, gout is independently associated with worsened ADL scores and should be factored into pre-admission evaluation and considered in resident care management. In the institutionalized elderly, renal insufficiency is prevalent. Allopurinol, even when given at maximum renally-adjusted doses, may not be sufficient to achieve target sUA.

Disclosure: **J. Higa**, Takeda Pharmaceuticals America, Inc., 2; **G. Reardon**, Informagenics, Inc., 3; **G. Tong**, Takeda Pharmaceuticals America, Inc., 3.

1813

Accuracy of Veterans Affairs Database for Gout-Related Health Care Utilization. Jasvinder A. Singh. University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Gout outcome studies have used administrative and claims databases. It is unknown whether administrative-derived data are accurate for gout-related utilization. The goal of the study was to assess the accuracy of Veterans Affairs (VA) administrative and clinical claims databases for gout-related health care utilization.

Methods: This retrospective study utilized the VA administrative and clinical claims databases for the fiscal year 2006. A cohort consisting of randomly mixed sample of two types of visits was identified that included visits with gout as primary or secondary diagnosis versus other diagnoses. An experienced senior epidemiologist (JS) blinded to the database information related to the visit performed review of electronic medical records (EMR). The gold standard was medical record documentation of gout or gout-related terms (gouty arthritis. tophaceous gout, acute gout, chronic gout, podagra, urate renal stones) in the chief complaint, history of present illness or assessment and plan for the visit. This indicated that gout was the main reason or one of the main reasons for the visit. We assessed the accuracy of database-derived gout-related utilization by calculating sensitivity, specificity, and positive and negative predictive values (PPV and NPV).

Results: Of the 108 potential visits, 85 visits to a health care provider (in 85 patients: 84 men, 1 woman with mean age of 63 years) in one of the three settings (outpatient, inpatient or urgent care/emergency room), and retrievable data from medical records, constituted the analyzed dataset. According to the gold standard of chart documentation, 21 visits were related to gout and 64 were not. Administrative claims for visits related to gout were accurate with excellent PPV of 86%, sensitivity of 86%, specificity of 95% and NPV of 95%. There were three visits coded as gout-related visit in databases that did not have medical record documentation related to gout: one visit each to discuss blood pressure medication, for regular follow-up of multiple medical problems, and for increased blood sugar. Three visits coded as not related to gout in administrative databases were related to gout based on medical record documentation: one patient each with continuing acute gout flare, a new diagnosis with documentation of urate crystals in knee joint fluid, and chronic gout stable on allopurinol.

Conclusion: VA databases can be used to identify gout-related visits with good accuracy. This finding supports the use of VA databases for studies of health services outcomes to identify gout-related utilization. It remains to be seen if findings are generalizable to other clinical and/or claims databases.

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1814

Comparing Clinical Characteristics and Comorbidities of Gout Patients Treated with Allopurinol or Febuxostat. Michael A. Becker[1], Xiangyang Ye[2], Kasem S. Akhras[3], Rima H. Tawk[4], Sudhir Unni[2], Jason Young[2] and Carl V. Asche[5]. [1]University of Chicago, Chicago, IL, [2]University of Utah College of Pharmacy, Salt Lake City, UT, [3]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [4]University of Illinois at Chicago, Chicago, IL, [5]University of Illinois College of Medicine at Peoria, Peoria, IL

Background/Purpose: Gout is a common acute and potentially progressive disease affecting approximately 8 million Americans. Hyperuricemia (serum urate levels [sUA] >6.8mg/dL) is a major pathogenic factor in gout.

Urate-lowering therapy (ULT), aimed at maintaining sUA in the range <6.0 mg/dL, is the commonly recommended goal for managing the hyperuricemia in gout, with allopurinol (ALLO) being the first line therapy in the majority of patients. ALLO, however, has many limitations, including intolerance and dose-limitations in renally compromised patients. Febuxostat (FEB) is another xanthine oxidase inhibitor approved by the FDA in 2009 with favorable safety and tolerability profiles. Our aim was to compare baseline demographics and comorbid characteristics of gout patients receiving ALLO and FEB.

Methods: Retrospective cohort study using a U.S. ambulatory care-based electronic medical record database with health records of primary care pts. Pts ≥18 years with a prescription for ALLO or FEB from April 1, 2009 to July 31, 2011 and with 13+ months of database activity prior to and a minimum of 6 months of activity after index date were included. Pts prescribed ALLO or FEB with diagnosis of neoplasm or with prescriptions for 2 or more ULTs on index date were excluded. Baseline pt characteristics (age, gender, race, and payer status); gout disease features (duration, sUA, presence of tophi); and comorbidities, (obtained from clinical history and/or body mass index, blood pressure, fasting plasma glucose, estimated creatinine clearance (eCrCL), smoking status, and alcohol use) were recorded. Comorbid status was summarized by Deyo-modified Charlson Comorbidity Index (CCI) and concomitant medication variables. Descriptive statistics, including mean and standard deviation for continuous variables, counts and proportions for categorical variables were utilized to describe the characteristics of ALLO and FEB cohorts. T-tests were used for continuous variables and chi-square tests for categorical variables.

Results: The study identified 35,404 ALLO-treated pts (mean age 63.2($\pm$12.1) years; 77% male) and 2,837 FEB pts (mean age 61.7($\pm$13.1) years; 73% male). Mean baseline sUA was significantly higher in FEB than ALLO pts (8.28 mg/dL vs 6.93 mg/dL, p<0.0001) and more FEB pts had sUA ≥ 9.0 mg/dL (32.7% vs 12.9%, p<.0001). Majority of ALLO-treated pts (57.1%) were receiving 300mg/day and 37.3% were receiving 100mg/day. FEB-treated pts had greater numbers of comorbidities (CCI ≥3, 22.1% vs 17.05 %, p<0.0001), and higher mean CCI scores (1.65 vs 1.51, p=0.0002) than ALLO pts, and more severe renal disease (eCrCL <60 29.8.0% vs 19.4%, p<.0001), presence of tophi (2.22% vs 0.39%), heart failure (5.11% vs 3.01%, p<0.0001), hypertension (HTN) (18.26% vs 16.29%, p=0.0066), and coronary artery disease (CAD) (8.35% vs 7.05%, p=.0097) were also more common in FEB pts than in those receiving ALLO.

Conclusion: A real-world comparison of utilization patterns of ALLO and FEB, shows that ALLO remains the ULT most often used in patients with gout, while FEB is being used in more difficult to treat patients, including those with higher baseline sUA levels and with commonly associated co-morbidities.

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1815

Factors Associated with a Prolonged Hospital Length of Stay for Patients with Acute Gout. Rebecca Sharim[1], Meghan Musselman[2] and Marissa Blum[2]. [1]Temple University Hospital, Philadelphia, PA, [2]Temple University School of Medicine, Philadelphia, PA

Background/Purpose: Management of gout in the hospital setting has been poor. This study aimed to describe patient characteristics and the treatment patterns of acute gout for patients hospitalized with gout in a tertiary care hospital. We hypothesized that the effects of treatment for gout and diagnostic delays for those with acute gout would prolong hospital length of stay.

Methods: Medical records of patients hospitalized with a primary or secondary diagnosis of gout (ICD-9-CM: 274.9) were retrospectively reviewed from 2005–2011. Charts were abstracted for demographic data (age, sex, race, insurance status, primary language), co-morbid conditions, length of stay, day of musculoskeletal complaint, medications used to treat gout, day of rheumatology consultation, and day of diagnosis of gout. Bivariate analyses were performed using Fisher's exact tests for categorical variables, and t-tests and analysis of variance for continuous variables. Multivariable regression testing was performed to evaluate factors associated with length of stay after adjustment for age, race, sex, insurance status, Charlson comorbidity Index, diabetes, chronic kidney disease, heart disease, and history of gout. A follow up qualitative chart review was done to evaluate other factors contributing to length of stay for female and male patients.

Results: A total of 205 patients were included. 24.4% (n = 50) were females and 75.6% (n = 155) were males. 7.8% of patients were white, while 82.9% were black and 7.8% were Latino. 83.9% of patients had a prior diagnosis of gout. Co-morbid conditions included cardiac disease (58.5%), pulmonary disease (33.2%), diabetes (45.8%), and chronic kidney disease (44.8%). Rheumatology was consulted in 99.5% of admissions (n=204). 76.6% of patients were treated with intra-articular steroids (n = 157), 40.5% were treated with colchicine (n = 83), 37.1% were treated with systemic steroids (n = 76), and 6.8% were treated with NSAIDs (n = 14). In 45.4% of patients (n = 93), more than one treatment modality was used. Only 31 patients experienced side effects from medications used to treat gout. There was no significant association found between treatment side effects and length of stay. There was a significant association found between time to diagnosis and length of stay (median length of stay for diagnosis within 24 hours of symptom onset vs. greater than 24 hours: 9 vs. 12.5 days, p=0.001), and between sex and length of stay (median length of stay for females vs. males: 14 vs. 9 days, p=0.01). Multivariable regression of log length of stay revealed a diagnosis of gout made after 24 hours of symptom onset and female sex were each significantly associated with an increased length of stay (β-coefficient, p-value [0.49, p=0.000, and 0.29, p=0.02, respectively]). A follow up qualitative analysis revealed that females with longer length of stay had other medical complaints in addition to gout prolonging their length of stay.

Conclusion: In this retrospective cohort study, a later diagnosis of gouty arthritis and female sex were associated with an increased length of stay after controlling for potential confounders. These data should guide future management of gout to reduce length of hospitalization.

Disclosure: R. Sharim, None; M. Musselman, None; M. Blum, None.

1816

Relationship Between Race, Uric Acid Levels, Urate-Lowering Therapy and Resource Use in Patients with Gout. Kim Coley, Melissa Saul and Karen Pater. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Gout is a chronic inflammatory disease caused by the deposition of monosodium urate crystals in joints and soft tissues. The overall prevalence is increasing worldwide, with African-Americans (AA) being affected more than Caucasians. We evaluated the association between race, uric acid levels, urate-lowering therapy (ULT) and resource utilization in patients with gout in a large health system.

Methods: The study population was a cohort of African-American and Caucasian men and women with gout who had an inpatient or emergency department encounter at a large health system in Southwestern Pennsylvania between 10/1/2008 and 9/30/2011. To be included, subjects had to have an ICD-9-CM code for gout (274.xx) as a either primary or secondary diagnosis during the study timeframe. A mean uric acid (UA) level was calculated for each patient across the study period and categorized as either <6 or ≥ 6 mg/dL. ULT was identified during the hospitalization. All patient encounters where gout was listed as the primary diagnosis were collected to assess gout resource use. Chi-square and T-tests were used to compare categorical and continuous data, respectively. Logistic regression was conducted to determine the relationship between race, UA levels, and resource utilization.

Results: There were 8,483 patients who met study criteria: 5,998 (71%) were male and 7,073 (83%) were Caucasian. UA levels were available in 43% of patients; a higher percentage of AA had UA levels assessed compared to Caucasians (53% vs. 41%, p<0.001). After stratifying by sex, mean UA levels were similar for females, however AA men had higher mean UA levels than Caucasian men (7.9 vs. 7.1, p<0.001). Despite having higher UA levels, only 27% of AA received ULT compared to 39% of Caucasians (p<0.001). There were no differences between the sexes with respect to the use of ULT. Multivariate regression analysis revealed that patients with a UA level ≥ 6 mg/dL were more likely to be AA race (OR=1.5), male (OR=1.2), and have chronic kidney disease (OR=1.4) and less likely to be on ULT (OR=0.7). Additionally, after controlling for other variables, AA patients (OR=2.6) and those with high UA levels (OR=2.5) were more likely to have inpatient and emergency department visits for gout (p<0.001).

Conclusion: AA race is associated with higher UA levels and lower use of ULT. AA patients and those with high UA levels were more likely to have emergency department visits or be hospitalized for gout. Improving access to ULT may reduce the burden of gout in African-Americans and reduce overall healthcare costs.

Disclosure: K. Coley, None; M. Saul, None; K. Pater, None.

1817

The Role of Repeating Tuberculin Skin Tests During Biologic Therapy.
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OR

Background/Purpose: Prior to starting biologic therapy, it is recommended that all patients be screened for tuberculosis (TB).[1] However, for
patients who screen negative at baseline and then subsequently start biologic
therapy, the utility of repeating a tuberculin skin test (TST) is uncertain. This
retrospective study was conducted to evaluate the frequency of TST conversion among patients on biologic therapy in a low incidence region for TB
(1.4 cases per 100,000).[2]

Methods: We retrospectively reviewed records from a community
rheumatology practice in Boulder County, Colorado, to identify patients
screened for TB between March 2005 and August 2010. All patients planning
to start biologic therapy were screened with a TST at baseline. Those with
negative results were screened annually thereafter while on biologic therapy.
We defined ≥5mm induration as a positive TST and "conversion" as
induration of ≥5mm after an initial negative TST.

Results: Five hundred eighty-nine patients were screened prior to biologic therapy initiation. Most were female (n=353, 60%) and had rheumatoid
arthritis (n=359, 61%) or spondyloarthritis (n=198, 34%). Three hundred
twenty-seven patients (56%) underwent a total of 818 repeat TSTs, 9 (1.1%)
of which were positive. Five (56%) of the converters had no apparent risk
factors for TB exposure. All converters had negative chest radiographs. While
continuing biologic therapy, all but 1 completed 8–9 months of isoniazid
(INH). None have developed TB during a median follow-up period of 49
months (range 16 to 70).

Test	Patients tested with TST	Number (%) of +TSTs
TST #1	589	17 (2.9)
TST #2	327	5 (1.5)
TST #3	220	2 (0.9)
TST #4	147	2 (1.4)
TST #5	79	0
TST #6	31	0
TST #7	10	0
TST #8	4	0
TST #2–8	818	9 (1.1)
Overall	1407	26 (1.8)

Conclusion: In an area of low TB incidence, annual TST conversion
while on biologic therapy was rare. Checking yearly TSTs on all patients
being treated with biologic agents is of low yield. A small number of
converters were identified, but more than half had no apparent risk factors for
TB exposure. It is unclear if these conversions truly represent new infections,
but all were started on INH and none have developed TB.

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1818

**Latent Tuberculosis Detection and Tuberculosis Reactivation in Patients
Receiving Anti-TNFá Drugs: A Nationwide Italian Survey.** Fabrizio
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Background/Purpose: Anti-TNFα drugs are associated with an increased risk of tuberculosis (TB) and several recommendation sets for latent
tubercular infection (LTBI) detection and TB reactivation prevention are
available. Primary end-point of present Italian survey was to investigate the
behavior of Italian rheumatologists regarding LTBI detection and TB prevention. Secondary end-points were the occurrence of TB reactivation during
anti-TNF therapy despite LTBI screening and the association with different
anti-TNF agents.

Methods: An anonymous, 24-multiple-response questionnaire was completed by 393 rheumatologists operating in all Italian regions between January
and March 2012. The questionnaire encompassed several aspects of clinical
practice including the use of different recommendations, the availability of
tuberculin skin test (TST) and interferon-gamma release assay (IGRA), the
strategies to detect active TB in the case of positive LTBI, the type and
duration of TB prophylaxis, the number of patients currently treated with
anti-TNF at the date of March 31,2012 and the recorded active TB cases over
the previous 10 years expressed as total number and divided by the specific
anti-TNF drug.

Results: The Italian Society for Rheumatology recommendations were
used by 323/393 (82%) rheumatologists, other international sets by 60 (15%)
and occasionally by 10 (3%).However, local infectious disease experts were
always consulted by 81(21%) and occasionally by 73 (19%). TBST and
IGRA were available in 78% and 71% of the centers, respectively. LTBI
screening was made using chest radiograph (CR)+TST by 39%, CR+IGRA
by 28%, CR+TST+IGRA by 33%. Isoniazid (9-month course) for TB
reactivation prevention was employed by 324/393 (83%) of rheumatologists,
isoniazid+rifampicin for 4 months by 19/393 (5%), other strategies by 50
(12%). TB prevention was initiated in presence of positive TST by 134 (34%)
rheumatologists, positive TST+IGRA by 211 (54%), positive IGRA by 48
(12%). When TB prevention was indicated, anti-TNF was started 1 month
later in 63% of the cases, after 3 months in 28%, concomitantly in 9%. Over
a 10-year period, 39353 patients (pts) received at least one anti-TNF drug and
317 (0.8%) developed active TB. Active TB occurred during the anti-TB
prophylaxis period in 192 (60.6%) p., in 24 (7.6%) after anti-TB therapy
withdrawal, and in 101 (31.8%) with negative LTBI screening. Active TB
cases distribution by drug was: etanercept 51 (16%), adalimumab 98 (31%),
infliximab 137 (43.2%), golimumab 9 (2.8%),certolizumab 8 (2.5%), 14
(4.4%) in pts switched to multiple agents, with a significant lower frequency
in pts receiving etanercept compared to those treated with monoclonal
anti-TNF (χ^2= P<0.001).

Conclusion: The Italian rheumatologist attitude to detect LTBI and to
prevent TB reactivation in pts requiring anti-TNF is quite variable despite the
availability of multiple sets of recommendations. The elevated number of
active TB cases during anti-TB therapy and in pts with negative LTBI
screening indicate some defects of these procedures. Confirming other
studies, active TB occurrence seems significantly lower in pts receiving
etanercept compared to monoclonal anti-TNF drugs.

1819

**Predictors of Pneumococcal Vaccination in Patients with Rheumatoid
Arthritis and Systemic Lupus Erythematosus.** Anna Gramling[1], Kaleb
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Center, Omaha, NE

Background/Purpose: Patients with rheumatoid arthritis (RA) and
systemic lupus erythematosus (SLE) are at high risk for serious infection, including those caused by *Streptococcus pneumoniae*. Administration of 23-valent polysaccharide pneumococcal vaccination (23-PPV)
is recommended for patients with several co-morbidities and age >65 years.
EULAR recommends 23-PPV for all patients with autoimmune inflammatory rheumatic diseases and the ACR recommends it for all patients
with RA. Small observational studies suggest that administration of
23-PPV in RA patients is inadequate while none studied SLE. The
purpose of our study is to determine rates and predictors of 23-PPV
administration in US RA and SLE patients.

Methods: We surveyed patients across the US with RA, SLE, or osteoarthritis (OA) every 6 months from 2007 through 2011 about 23-PPV
along with their demographic and health status. We identified characteristics within each diagnosis that predicted administration of 23-PPV in a
subsequent 6-month period through the use of univariate logistic regression adjusted for sex and age > 65 years. Significant predictors were
combined in a multivariate logistic regression model and eliminated with
backward stepwise selection until all remaining predictors were significant
for an alpha of 0.05. We also selected a subset of cases who had never

received 23-PPV at baseline and used univariate Cox proportional hazards models controlling for diagnosis group to predict the timing of the first administration of 23-PPV. Significant predictors were combined in a multivariate Cox proportional hazards model and eliminated with backward stepwise selection until all remaining predictors were significant for an alpha of 0.05.

Results: A total of 15,954 patients participated in the study (11,952 RA, 1,773 SLE, and 2,229 OA). Among these groups 69.8%, 65.2%, and 67.8% of patients reported having ever received 23-PPV, respectively. SLE patients who reported receiving 23-PPV in the subsequent 6 months were more likely to be over 65 (OR 1.64, p=0.01), taking prednisone (OR 1.38, p=0.01), and to have chronic lung disease (OR 1.68, p<0.01). RA patients age > 65 (OR 1.70, p<0.01), male (OR 1.16, p=0.01), on biologic therapy (OR 1.18, p=0.03) or prednisone (OR 1.20, p<0.01), and suffering from chronic lung (OR 1.53, p<0.01) or heart disease (OR 1.20, p=0.03) were more likely to receive 23-PPV. Age > 65 was the strongest predictor of 23-PPV use in OA patients (OR 2.06, p<0.01). Patients were more likely to receive their first 23-PPV if they were over 65 (HR=2.05, p<0.01), male (HR=1.2, p=0.01), taking a non-biological DMARD (HR=1.32, p<0.01), taking a biological DMARD (HR=1.31, p<0.01), had chronic lung disease (HR=1.33, p<0.01), or had a lower SF36 PCS score (HR=0.99, p<0.01).

Conclusion: Despite current EULAR and ACR recommendations nearly a third of RA and SLE patients have never received a pneumococcal vaccination in a large, contemporary US cohort. Age greater than 65 years and chronic lung disease were the strongest predictors of 23-PPV administration. This is the first study to report that use of immunosuppressive drugs other than prednisone was not associated with pneumococcal vaccination in SLE patients.

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1820

Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Gardasil®) and Autoimmune Disorders: Safety Assessment Using the Pharmacoepidemiologic General Research Extension System. Lamiae Grimaldi-Bensouda[1], Michel Rossignol[2], Elodie Aubrun[1], Pamela Leighton[3], Didier Guillemot[4], Alfred Mahr[5], Jacques Benichou[6], Paul-Henri Lambert[7], Bertrand Godeau[8] and Lucien Abenhaim[9]. [1]LA-SER, Paris, France, [2]LA-SER, Centre for Risk Research, Montreal, [3]LA-SER Europe Ltd., London, United Kingdom, [4]Institut Pasteur (PhEMI)/ INSERM U657 & Université Paris-Ile de France Ouest, Paris, France, [5]Hospital Saint-Louis, Paris, France, [6]INSERM U657 Pharmacoepidemiology and evaluation of the impact of health products on human health, France, and Department of Biostatistics, University Hospital of Rouen, Rouen, France, Rouen, France, [7]Centre of Vaccinology & neonatal immunology, University of Geneva, Geneva, Switzerland, [8]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [9]LA-SER Europe Ltd, London, United Kingdom

Background/Purpose: This study investigated whether the human papillomavirus (HPV) vaccine [types 6, 11, 16, 18] is associated with a modified risk of autoimmune disorders (AIDs). It carried out a case-control study within the population targeted for HPV vaccination.

Methods: The following AIDs were studied: central demyelination, Guillain-Barré syndrome, connective tissue disorders (lupus, rheumatoid arthritis, myositis, dermatomyositis, undifferentiated connective tissue disorder), type 1 diabetes, autoimmune thyroid disorders (Graves' disease, Hashimoto's thyroiditis) and immune thrombocytopenia. A network of specialist centers (internal medicine, neurology, rheumatology, paediatrics, endocrinology, dermatology) throughout France recruited newly-diagnosed cases in females 14–26 years-old. Cases were diagnosed according to standardized criteria. Controls were recruited from general practice settings and matched to cases on age (within ± one, ± three, ± six or ± 12 months successively if no match was found for cases under 18 years-old, within ± 12 or ± 24 months for cases 18 years-old or older), region of residence (northern or southern France) and recruitment consultation date (within ± three or ± nine months). Vaccinations and other potential risk factors for AIDs were assessed in a standardized telephone interview of patients or their parents. The interviewers were blind to case/control status.

Results: Between December 2007 and April 2011, 113 specialist centers recruited 248 definite cases of AIDs which were matched to 1001 controls. 97.4% of reported vaccinations against HPV [types 6, 11, 16, 18]

were confirmed using medical records from the patients or their general practitioners. A smaller proportion of cases (26 or 10.5%) than controls (232 or 23.2%) received the HPV vaccine [types 6, 11, 16, 18] within predefined time windows up to 24 months before the index date but the difference was not statistically significant (adjusted odds ratio 0.72, 95% confidence interval 0.45, 1.18). No association was found when each AID was considered separately, although these analyses were based on small numbers of cases, or when considering various time windows prior to the index date, the inclusion of uncertain exposures to vaccination and unconfirmed cases. The specialist centers reported no important increase in incidence for any of the AIDs in the population eligible for HPV vaccination.

Conclusion: No evidence of an increased risk of the studied AIDs was observable following vaccination with HPV vaccine [types 6, 11, 16, 18] for the time window of study available. The study lacked the power to conclude on individual disorders taken separately. The study observed no unusual accrual, in a large series of centers specialized in AIDs, of incident cases of any of the diseases surveyed in young females, at a time when one-third of them were getting vaccinated against HPV, mainly by HPV vaccine types 6, 11, 16, 18.

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1821

Clinical Predictors of Methotrexate-Induced Liver Enzyme Elevation in Patients with Rheumatoid Arthritis in an Electronic Medical Record. Monica Ramirez[1], Bing Lu[1], Michelle A. Frits[1], Anne H. Fossel[2], Katherine P. Liao[1], Robert M. Plenge[1], Jonathan S. Coblyn[3], Nancy A. Shadick[4] and Elizabeth W. Karlson[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham & Womens Hospital, Boston, MA, [3]Brigham & Womens Hosp, Boston, MA, [4]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Methotrexate (MTX) use for the treatment of rheumatoid arthritis (RA) has been associated with hepatotoxicity, and requires monitoring of liver transaminases. However, elevations in liver transaminases may be transient and may not predict the development of cirrhosis or fibrosis. We aimed to identify clinically relevant factors associated with persistently elevated liver transaminases leading to discontinuation or dose reduction of MTX in RA patients.

Methods: The study population was derived from an EMR-based cohort of 5906 RA cases at a large academic medical center followed since 1992. We used a validated algorithm to identify patients with RA (PPV 94%). We extracted data on any MTX prescription, and any LFT elevation, defined as liver transaminases > 2 times the upper limit of normal (> 2X ULN). From the 1,040 RA patients identified as ever treated with MTX and with LFTs > 2X ULN, we randomly selected 500 patients for detailed chart review; 90 cases (18%) were confirmed as having LFT elevations while receiving MTX, with LFT elevations attributed to MTX. We abstracted data on risk factors for liver toxicity: age, sex, obesity, hyperlipidemia, MTX dose (2.5–7.5mg, 10.0– 17.5mg, or 20–25mg), alcohol use, NSAID use, and statin use. We defined our outcome as continuation of MTX versus discontinuation or dose reduction. We examined the univariable associations of the predictors with outcome and developed a multivariable adjusted logistic regression model to estimate odds ratios and 95% CI.

Results: In our cohort of 90 patients, MTX was discontinued or the dose was reduced in 55 (61%) of patients. The remainder of those that continued MTX had a single transaminase elevation that resolved. Among the patients in whom MTX was discontinued or the dose was reduced, 8 (15%) of patients had biopsies that showed fibrosis attributed to MTX use. In our univariable analysis, obesity was significantly associated with MTX discontinuation or dose reduction (**Table**). In our multivariable model we included age, sex, obesity and hyperlipidemia, and obesity remained significantly associated with MTX discontinuation or dose reduction, OR 2.60 (95% CI 1.01–6.66), p-value 0.05. Fifteen (27%) of obese patients had a clinical diagnosis of nonalcoholic fatty liver disease (NAFLD) in the MTX discontinuation or dose reduction group, and 2 (4%) obese patients had this diagnosis in the MTX continuation group.

Table. Univariable Analysis of Predictors of MTX Discontinuation or Dose Reduction

Predictors	Univariable OR (95% CI)	Univariable p-value
Age	0.99 (0.95–1.03)	0.57
Male sex	0.58 (0.16–2.17)	0.42
Obesity	2.89 (1.20–7.00)	**0.02**
Hyperlipidemia	1.92 (081–4.54)	0.14
Alcohol use	1.58 (0.59–4.25)	0.36
MTX dose		
2.5–7.5 mg (ref)	1.00 (ref)	*
10–17.5 mg	0.76 (0.22–2.64)	0.54
20–25 mg	1.01 (0.27–3.77)	0.76
NSAID use	0.95 (0.41–2.22)	0.90
Statin use	1.15 (0.43–3.12)	0.78

* p for trend = 0.85

Conclusion: In our cohort of RA patients with MTX-related LFT elevation, single LFT elevations resolved in 39% of patients. We found a significant association between obesity and LFT elevations that led to MTX discontinuation or dose reduction. This suggests a potentially heightened risk of hepatotoxicity among obese patients. Further studies are needed to determine whether NAFLD may be an underlying risk factor in this patient population.

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1822

Liver Toxicity Monitoring and Its Impact On Methotrexate Discontinuation in a National Cohort of Veterans. Gabriela Schmajuk[1], Yinghui Miao[2], Jinoos Yazdany[3], Mary Margaretten[1] and Michael Steinman[2]. [1]UCSF, San Francisco, CA, [2]San Francisco Veterans Affairs Medical Center, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA

Background/Purpose: The National Quality Forum recently endorsed a controversial quality measure that assesses liver toxicity monitoring for patients receiving oral methotrexate (MTX). Using national data from the Veterans Health Administration (VHA), we assessed the frequency of liver function testing (LFT) and rates of MTX discontinuation after minimally elevated LFTs among patients taking oral MTX.

Methods: We created a national cohort of incident MTX users $\geq$ age 65 using linked pharmacy and laboratory data from the VHA during fiscal years 2007–2008. Patients were included if they had $\geq$ 28-day supply of MTX dispensed and use of VHA services for a minimum of 180 days prior and 90 days after the index MTX prescription. Patients were excluded if they had any diagnosis of inflammatory bowel disease (ICD-9 codes 555.x, 556.x) or if they had evidence of having obtained care outside of the VHA (patients with any medical encounter billed to Medicare during the study period were removed from the sample). We defined performance on the MTX liver toxicity monitoring quality measure through 2 methods (Table). Using the value of the first abnormal LFT after the index MTX prescription, we assessed rates of MTX discontinuation (defined as lack of MTX dispensed for $\geq$ 90 days after the anticipated refill date).

Table. Performance on methotrexate liver toxicity monitoring quality measure in a national cohort of veterans

Definition	Description	Performance in national veteran incident user cohort
NQF technical specification	Proportion of patients in the population who were prescribed at least a 6-month supply of methotrexate during the measurement year that received a liver function test in the 120 days (3 months + 1 month grace period) following the earliest observed methotrexate prescription claim.	77%
Rolling interval method (Agnew-Blais 2009)	Mean of the "percent adherence" for each individual, calculated as the proportion of intervals (ranging in duration from 0–12 weeks) during the time when a patient was exposed to methotrexate in which a liver function test was documented.	65%

Results: 899 new users of MTX met inclusion and exclusion criteria for the study. 97% were male, mean age was 71 years (SD 6.3), and mean follow-up period was 267 days (SD 133). Mean MTX dose received was 11.4 mg weekly (SD 5.1). Performance on the quality measure is described in the Table. 148 (16.5%) patients did not have any LFT testing after MTX was initiated. 136/899 (15%) patients had any abnormality of AST or ALT during the follow-up period; 49/899 (5%) had an elevation of $\geq$ 1.5 $\times$ upper limit of normal (ULN). MTX was discontinued in 28/87 (32%) subjects with LFT elevations < 1.5 $\times$ ULN and 27/49 (55%) subjects with elevations $\geq$ 1.5 $\times$ ULN. Compared to patients with no LFT elevations during the follow-up period, patients with LFT elevations < 1.5 $\times$ ULN had 1.4 greater odds (95% CI 1.1, 1.8) of stopping MTX.

Conclusion: Despite many MTX users not receiving liver toxicity monitoring with the frequency intended by the National Quality Forum quality measure, one third of patients with mild LFT elevations may be having their MTX stopped unnecessarily. These findings suggest that there may be unintended negative consequences to a policy that encourages more frequent liver toxicity monitoring.

Disclosure: **G. Schmajuk**, None; **Y. Miao**, None; **J. Yazdany**, None; **M. Margaretten**, None; **M. Steinman**, None.

1823

Short Periods of Glucocorticoid Use Increase the Risk of Gastrointestinal Bleeding. Steven C. Vlad[1], David T. Felson[1], Donald R. Miller[2] and Yuqing Zhang[1]. [1]Boston University, Boston, MA, [2]Edith Nourse Rogers Memorial VA Hospital, Bedford, MA

Background/Purpose: Short term use of glucocorticoids (GCs) is thought to be relatively benign and most adverse events have been studied in chronic users; there is little if any published evidence about the safety of short term use. We aimed to examine whether short periods of GC use are associate with an elevated risk of gastrointestinal bleeding (GIB).

Methods: We used national US Veterans Administration data from fiscal year 1998 through 2008 to compare the risk for GIB during periods of GC use compared to periods of non-use using a self-controlled case series design. This is a case-only design which compares risks within persons, thus limiting confounding. Based on prescription records we first developed a cohort of subjects who had only used 'burst' GCs, defined as dispensed oral prescriptions of [2] 30 days with at least 42 days between consecutive prescriptions. We excluded persons who received GCs during their first 60 days of follow-up or who could have received GCs during a prior hospitalization so as to limit the amount of unmeasured GC use. From these subjects, we selected those who had a first GIB requiring hospitalization using previously validated ICD-9 codes; we excluded cases who had a GIB within the first year of follow-up (to limit the number with possible recurrences) and those using NSAIDs during the follow-up period so as to eliminate this as a potential confounder. We focused on the period in which each subject was using GCs, as well as 30 days before and after to account for confounding by indication and any residual GC effects. The risk of GIB in each of these periods was compared to that in the remaining period of follow-up time. We controlled for age in 5 year bands (18–24, 25–29, 30–34,..., > 80).

Results: There were 433 cases of GIB among burst GC users. 94.7% were men. Mean age at GIB was 65.2 (sd 11.9) years; 65.9 (11.5) in men, 53.6 (12.4) in women. 71.4% of subjects were white, 13.7% African American, 6.3% Hispanic, 8.6% other. All cases had only 1 GC prescription for a median duration of 8 (Q1, Q3: 1, 14) days and median average daily prednisone equivalent dose of 20 (17.5, 26.8) mg. The incidence rate ratio (IRR) of GIB while using GCs was 5 times that of the baseline risk period. See table.

	No. cases of GIB in risk period	Incidence rate ratio	95% CI
Total number of cases	433		
Reference period (no GC use)	406	1.0	-
1–30 days prior to GC prescription	11	2.0	1.1, 3.7
Time while GC was being used	8	5.1	2.5, 10.4
1–30 days after GC discontinuation	8	1.5	0.7, 3.0

Conclusion: Our results suggest that even short periods of GC use increase the risk of GI bleeding and that the risk corresponds to the time when the drug is being used.

Disclosure: **S. C. Vlad**, None; **D. T. Felson**, None; **D. R. Miller**, None; **Y. Zhang**, None.

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Do Statins Reduce the Incidence of Connective Tissue Disease? A Retrospective Cohort Study. Thomas W. Schmidt[1], Daniel F. Battafarano[1], Christopher R. Frei[2], Eric M. Mortensen[3] and Ishak Mansi[4]. [1]San Antonio Military Medical Center, San Antonio, TX, [2]University of Texas Health Science Center at San Antonio, San Antonio, TX, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]San Antonio Military Medical Center, San Antonio

Background/Purpose: Due to their anti-inflammatory effects, statins were proposed to lower the incidence of connective tissue diseases (CTD). The objective of this study is to determine if statin use is associated with a lower incidence of CTD in a healthcare setting where patients have similar access to care.

Methods: This was a retrospective analysis of adult patients (30–85 year-old) enrolled as Tricare Prime in a military medical facility. The study period was divided into baseline period (10/1/2003 to 9/30/2005), and follow up period (10/1/2005 to 3/5/2010). "Statin Users" received and dispensed a statin prescription of at least 90 days during the period from 10/1/2004 to 9/30/2005. "Non-users" did not receive a statin at any time during the study period. The outcome measure was the occurrence of any diagnosis code of the *International Classification of Diseases, 9th Revision, Clinical Modification*(ICD-9-CM) consistent with CTD (Rheumatoid arthritis and related disease, Systemic lupus erythematosus, and other connective tissue diseases as identified by the Clinical Classification Software of the Agency for Healthcare Research and Quality). We described comorbidities during the baseline period using the Charlson comorbidity score (CCS). We repeated the analysis in a prespecified subgroup of patients with CCS of 0 (no comorbidities).

Results: 46,488 patients were included: 13,640 statin-users and 32,848 non-users. Statin users were predominately male (58.3% vs 43.8%), older (60.4 years vs 44.8 years), smokers (9.0% vs 5.8%) and had a higher average CCS (1.2 vs 0.3) (p<0.0001). In the subgroup with no comorbidities, there were 6,137 statin users and 27,626 non-users. Regression analysis showed that statin users had a statistically significant lower incidence of connective tissue disease (adjusted odds ratio [OR]: 0.84; 95% confidence interval [CI]: 0.73–0.96; p-value=0.01). However, in the subgroup with no comorbidities, there was no difference between statin users and non-users in the incidence of CTD (adjusted OR: 0.83; 95% CI: 0.67–1.04; p-value=0.1).

Conclusion: Statin use is not associated with a lower incidence of CTD in patients without comorbidities. This finding may suggest that the beneficial effect of statins on CTD in many studies may be due to unadjusted baseline confounders or healthy user bias.

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1825

Work Disability and Work Limitations in Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis Are Equal and Increase with Comorbidities. Chanseok Rhee[1], Janet E. Pope[2], Andrew E. Thompson[3], Nicole G. H. Le Riche[4], Gina Rohekar[4] and Sherry Rohekar[4]. [1]Schulich School of Medicine and Dentisty, Western University, London, ON, [2]St. Joseph Health Care London, University of Western Ontario, London, ON, [3]St. Josephs Health Ctr, London, ON, [4]St. Joseph's Hospital, London, ON

Background/Purpose: Few studies directly compare work disability (WD) and work productivity losses in different forms of inflammatory arthritis (IA) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Also, the effect of comorbidities on WD in IA has not been thoroughly examined.

Methods: WD was defined as the inability to work or early retirement due to arthritis. Relationships between the Work Limitations Questionnaire (WLQ) scores, HAQ, Patient Global Assessment (PGA) and Functional Comorbidity Index (FCI) were analyzed in patients seen serially in a rheumatology clinic via standardized forms.

Results: 846 responded (65% response rate with 332 RA, 88 PsA, 58 AS) and 289 had WLQ data as they were working (139 RA, 51 PsA, 35 AS). The mean age was 51.7 (SD 14.5), 74.3% female and 11.3 years (SD 11.3) of disease duration. WD due to arthritis was 22.8% (RA), 29.9% (PsA), and 27.6% (AS) (between groups p <0.35). WD was associated with HAQ, PGA, fatigue, pain and sleep score in all three IA conditions. The average loss of the productivity from WLQ was 4.72% for IA overall and 4.47%, 4.71% and 5.77% for RA, PsA and AS, respectively (no difference between groups, p=0.405). Using Pearson correlation, the WLQ score was significantly correlated with HAQ (0.59; p<0.000), fatigue (0.51; p<0.000), pain score (0.57; p<0.000), sleep score (0.63, p<0.000), and with increasing number of comorbid conditions for all three IA conditions (RA:0.30; p<0.01, PsA:0.30; p=0.03 and AS:0.53; p<0.01) but not disease duration and gender.

Conclusion: WD and productivity loss were not different in RA, PsA and AS. WLQ scores were associated with patient factors in all IAs. Comorbidities increased the likelihood of work productivity loss and WD in all forms of IA, but the correlation was particularly strong in AS.

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1826

Intravenously Administered Golimumab Significantly Improves Health Related Quality of Life and Work Productivity in Patients with Rheumatoid Arthritis: Results of a Phase III, Placebo Controlled Trial. Rene Westhovens[1], Michael Weinblatt[2], Chenglong Han[3], Tim Gathany[3], Lilianne Kim[4], Michael Mack[4], Jiandong Lu[4], Daniel Baker[4], Alan Mendelsohn[4] and Clifton O. Bingham III[5]. [1]University Hospital KU Leuven, Leuven, Belgium, [2]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [3]Johnson & Johnson Pharmaceutical Services, LLC, Malvern, PA, [4]Janssen Research & Development, LLC, Spring House, PA, [5]Johns Hopkins University, Baltimore, MD

Background/Purpose: To evaluate the impact of intravenously (IV) administered golimumab (GLM) on health related quality of life (HRQoL) and work productivity in patients (pts) with rheumatoid arthritis (RA).

Methods: GO-FURTHER was a multicenter, randomized, placebo-controlled study. Adult pts with active RA despite MTX therapy (≥6 tender and swollen joints, CRP ≥1.0mg/dL, and RF and/or anti-CCP positive) were randomized to placebo + MTX (PBO group) or GLM (2mg/kg) plus MTX at week 0, 2, and every 8 week thereafter (GLM group). Pts in PBO group with <10% improvement in tender and swollen joint count from baseline at week 16 entered early escape (EE) and received a 2mg/kg GLM infusion at Weeks 16 and 20 and every 8 weeks subsequent. HRQoL was assessed using Short-Form of 36 items questionnaire (SF-36) and EQ5D. The EQ5D instrument consists of a five-item descriptive system of health states and a visual analog scale (EQ VAS, 0–100). Scores for the five health states were converted into a utility score (EQ5D index, 0–1, 0=dead and 1=full health) using the US D1 model. Impact of disease on daily work productivity was assessed using a visual analogue scale (VAS) of 0–10 (0=no affect at all, 10=affected very much). Clinically meaningful improvements were defined as a change of ≥5 points in SF-36 physical and medical component summary score (PCS and MCS) or a change in magnitude of half of standard deviation in EQ VAS and EQ5D index. Correlation of remission measured by disease activity score (DAS28 using CRP <2.6) with change in PCS and MCS, and productivity scores were analyzed. Comparisons between groups were performed using ANOVA on van der Waerden normal scores for continuous outcomes or Chi-square test for binary outcomes.

Results: At baseline, mean (SD) SF-36 PCS (30.8±6.95) and MCS (37.6±11.28) were notably below the US norm of 50. The impact of disease on daily work productivity was 6.4 (2.32). Compared to the PBO group, significantly greater changes were observed in the GLM-treatment group in SF-36 PCS (5.92 vs. 3.19), SF-36 MCS (4.91 vs. 1.46), EQ VAS scores (11.43 vs. 2.53) and EQ5D index (0.13 vs. 0.09) at week 12, which were sustained through week 16 and 24 (all p-values<0.01). Compared to the PBO group, a greater proportion of pts in the GLM group achieved clinically meaningful improvement in SF-36 PCS, SF36 MCS, EQ VAS and EQ5D index. Similarly, significantly greater improvements in all 8 SF-36 sub-scores for the GLM group, compared to the PBO group, were observed (all p-values<0.001). At week 24, mean change (improvement) from baseline in impact of disease of daily work productivity was significantly better in the GLM group than in the PBO group (−2.78 vs. −1.03, p<0.001). Change in SF-36 and work productivity score were correlated with change in DAS28 score, and those who achieved DAS28 remission had greater improvement in SF-36 PCS, MCS and productivity VAS scores than those who did not achieve remission.

Conclusion: Treatment with IV administered GLM significantly improved HRQoL and work productivity in pts with RA.

1827

Factors That Impact Work Productivity in the Preserve Trial: A Randomized Controlled Trial of Combination Etanercept-Methotrexate Therapy in Patients with Moderately Active Rheumatoid Arthritis. Vibeke Strand[1], Thomas V. Jones[2], Wenzhi Li[3], Andrew S. Koenig[3] and Sameer Kotak[4]. [1]Stanford University, Portola Valley, CA, [2]Pfizer, Inc, Collegeville, PA, [3]Pfizer Inc., Collegeville, PA, [4]Pfizer Inc., New York, NY

Background/Purpose: Active joint inflammation and structural damage in patients with rheumatoid arthritis (RA) often result in impaired physical function and ultimately work disability.[1,2] Lost productivity is associated with higher costs than direct expenditures in determining overall RA costs.[3] In a recent multinational database study, more than one third of patients working at the time of onset of RA symptoms reported work disability.[2] In a 2006 systematic review, two thirds of employed RA patients reported RA-related loss of productivity in the prior year.[4] Despite advances in RA treatment, work disability remains a persistent problem. The objective of the analysis presented here was to assess predictors of impairment in work productivity in patients with moderately active RA (3.2<DAS28≤5.1) enrolled in the randomized, double-blind period of the PRESERVE trial.

Methods: Patients achieving DAS28 low disease activity (DAS28 ≤3.2, avg wk 12–36 and at wk 36) following 36 wks of open-label treatment with etanercept (ETN) 50 mg QW + methotrexate (MTX; E50/M) were randomized to receive E50/M (n=202), ETN 25 mg QW + MTX (E25/M; n=202), or ETN placebo + MTX (P/M; n=200) as double-blind treatment for 52 wks. The Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI:RA) was administered at baseline (BL) and wk 88, after double-blind treatment. Correlation (Pearson's r) and linear regression analyses were conducted: the dependent variable was % of overall work impairment in WPAI:RA; independent variables were age, gender, and RA duration at BL, and HAQ score ≤0.5 vs >0.5, PtGA of disease activity, pain score, FACIT-Fatigue score, WPAI:RA score, and treatment at wk 36.

Results: No significant association was observed between patients' age and gender at BL or pain or FACIT-Fatigue scores at wk 36 and % overall work impairment at wk 88 (table). In contrast, disease duration at BL as well as HAQ score >0.5, PtGA of disease activity, and WPAI: RA score at wk 36 were significant predictors of work impairment (P<0.05). After controlling for other factors, in comparison with P/M, E50/M provided greater benefit in improving work productivity at wk 88 (P<0.05), whereas E25/M did not.

Table. Factors predicting WPAI:RA % overall work impairment at wk 88 in the PRESERVE trial

Predictor	Regression Coefficient (SE)	P-value
Age	−0.10 (0.13)	0.447
Female	−4.18 (3.18)	0.190
Disease duration	**0.51 (0.19)**	**0.008**
HAQ score >0.5 at wk 36	**8.19 (3.32)**	**0.014**
PtGA of disease activity at wk 36	**3.92 (1.52)**	**0.010**
Pain VAS score at wk 36	−0.34 (0.19)	0.086
FACIT-Fatigue score at wk 36	0.28 (0.21)	0.185
WPAI:RA at wk 36	**0.56 (0.11)**	**<0.0001**
E50/M treatment	**−11.51 (3.17)**	**0.0003**
E25/M treatment	−3.90 (3.00)	0.196

HAQ = Health Assessment Questionnaire; PtGA = patient global assessment; VAS = visual analog scale; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; WPAI:RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis; E50/M = etanercept 25 mg QW plus methotrexate; E25/M = etanercept 25 mg QW plus methotrexate

Conclusion: Disease duration, HAQ score >0.5, PtGA, and work impairment at baseline were significant predictors of work impairment at end of the study in this population of patients with moderately active RA. Significant improvement in the overall percentage of work productivity was evident in patients receiving etanercept 50 mg plus methotrexate compared with placebo plus methotrexate.

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1828

Smoking Is Associated with Worse and More Widespread Pain, Worse Fatigue, General Health and Quality of Life in a Swedish Population Based Cohort of Patients with Psoriatic Arthritis. Ann B. I. Bremander[1], Lennart TH Jacobsson[2], Stefan Bergman[3], Emma Haglund[4] and Ingemar F. Petersson[5]. [1]Halmstad University School of Business and Engineering, Halmstad, Sweden, [2]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [3]R&D Center Spenshult, Oskarström, Sweden, [4]Spenshult Hospital for Rheumatic Diseases, Halmstad, Sweden, [5]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden

Background/Purpose: Smoking has been found to be associated with an increased risk of developing psoriatic arthritis (PsA). The purpose of this study was analyse possible associations of smoking habits with self-reported clinical features in a large population based cohort of patients with a diagnosis of PsA.

Methods: All health care seeking subjects with a diagnose of PsA according to ICD 10 codes (given at least once by a rheumatologist/internist or twice by any other physician) were identified by a regional health care register during 2003–2007. In 2009 all identified subjects aged 18 years or older (n=2003) were invited to participate in a cross sectional questionnaire survey. The questionnaire included self-reported data on smoking (never smokers or ever smokers), age at disease onset, physical function (HAQ, 0–3 best to worst), pain, fatigue and global health (numerical rating scales 0–10 best to worst) health related quality of life (EQ-5D, 0–1 worst to best), and number of painful regions noted on a pain mannequin (0–16, best to worst). Linear regression analysis was performed and all data were controlled for sex and age.

Results: Response rate was 77% whereof 369 patients (18%) declined participation and 1185 (59%) returned the questionnaire, mean age 57.5 (SD 13.5) years and 58% were women. 1173 subjects responded to the smoking question whereof 448 (38%) were never smokers and 725 (62%) were ever smokers.

Mean age at disease onset was 42.3 (SD 13.4) years in never smokers vs. 46.0 (SD 13.2) in ever smokers. Never smokers vs. ever smokers had mean HAQ 0.59 (SD 0.6) vs. 0.71 (SD 0.6), mean pain 3.9 (SD 2.4) vs.4.4 (SD 2.5), mean fatigue 4.4 (SD 2.8) vs. 5.0 (SD 2.7), mean global health 3.9 (SD 2.4) vs. 4.4 (SD 2.3), mean EQ-5D 0.68 (SD 0.23) vs. 0.63 (SD 0.26) and mean no of painful regions were 7.2 (SD 4.0) vs. 7.9 (SD 4.3).

The regression analysis showed that ever smokers had worse pain with age-sex adjusted parameter estimates (B) = 0.38 (95% CI 0.09; 0.67), worse fatigue B = 0.34 (95% CI 0.02; 0.66), worse global health B = 0.36 (95% CI 0.09; 0.64), worse EQ-5D B = −0.04 (95% CI −0.07; −0.01) and an increased no of painful regions B = 0.54 (95% CI 0.02; 1.07) compared with never smokers.

Conclusion: In this population based PsA cohort, patients who were ever smokers reported worse clinical outcomes compared with never smokers. Further longitudinal studies are needed to better understand cause and effect. However, smoking cessation should be recommended due to general health perspectives and also due to disease specific issues.

1829

Cost of Etanercept, Adalimumab, and Infliximab in Patients with Rheumatoid Arthritis with Employer Provided Health Insurance.
Machaon Bonafede[1], Crystal Watson[2], George Joseph[2], Nicole Princic[1] and David J. Harrison[2]. [1]Thomson Reuters Healthcare, Cambridge, MA, [2]Amgen Inc., Thousand Oaks, CA

Background/Purpose: Tumor Necrosis Factor Inhibitors (TNFi) are the mainstay of treatment for rheumatoid arthritis (RA) in patients with moderate to severe disease. The three most commonly used agents, etanercept (ETN), adalimumab (ADA), and infliximab (INF), differ with respect to frequency of administration, dosing and the approved dose ranges. In addition, INF is administered as infusion by a healthcare professional, whereas ETN and ADA are self-administered subcutaneously. The goal of this study was to determine the annual TNFi drug and administration costs for RA patients on ETN, ADA, or INF.

Methods: The MarketScan Commercial Database was used to identify adult patients (18–64 years) with ≥1 claim for ETN, ADA, or INF between February 1, 2008 and July 5, 2010. Patients were required to have a diagnosis of RA and excluded if they had diagnoses for other conditions treated with TNFi (psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, or juvenile idiopathic arthritis) in the six months prior to the start of their index TNFi. The patient's first TNFi claim after 6-months of continuous enrollment was their index claim and defined their index TNFi. If they had at least one claim for the same agent in the 6-months pre-index they were defined as "continuing", otherwise they were "new". Patients were followed for 1 year and the cost of all TNFi used in that year were attributed to their index TNFi. Cost of TNFi was calculated based on total dose and the March 2012 wholesale acquisition costs and the Medicare Physician Fee Schedule was used to determine TNFi drug administration costs.

Results: There were 7,003 patients who met the inclusion and exclusion criteria. ETN was the most frequently used index TNFi agent (3,159) followed by ADA, 2,057 and INF 1,787. The mean age was similar across agents, (51.1 ETN and ADA and 52.0 INF). The majority of patients (77.8%) were female and 76.2% of the patients were continuing on therapy. Preferred provider organizations were the most common insurance type, 58.8%–63.2%. Across new and continuing patients combined, the annual TNFi cost per patient was highest for INF ($27,366), followed by $20,594 for ADA and $17,753 for ETN. The costs among continuing patients were higher than the new patients but the trends were similar across both groups.

Conclusion: TNFi costs differ meaningfully by index TNFi agent in the patients with employer provided health insurance. ADA cost 16% more than ETN and INF cost 54% more than ETN across new and continuing patients combined. The difference was greater in continuing compared to new patients.

1830

Drugs Are the Major Cost Driver of Rheumatoid Arthritis As Soon As the First Year of the Disease: An Economic Analysis Based On the Espoir Cohort Data.
Bruno Fautrel[1], Sandy Lucier[2], Georges Haour[2], Hassani Maoulida[2], Stephanie Harvard[1], Alain Saraux[3], Xavier Mariette[4], Francis Guillemin[5], Isabelle Durand-Zaleski[2] and Karine Chevreul[2]. [1]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [2]APHP - URC Eco, Paris, France, [3]Université Brest Occidentale, Brest, France, [4]Université Paris-Sud, Le Kremlin Bicetre, France, [5]Faculte de Medecin/BP 184, Vandoeuvre-les-Nancy, France

Background/Purpose: Many studies have explored the economic burden of established RA but few data are available about the determinants of costs in early rheumatoid arthritis (RA) cared in real life settings.

The present study aims to describe the determinants of medical costs of early RA during the first 4 years of the disease.

Methods: The ESPOIR cohort is a nationwide cohort that enrolled 813 patients with early arthritis, highly suspect of RA[1], between 2002 and 2005. Data were collected every six months during the first two years then every year. The health resource use was investigated using a validated questionnaire collecting consultations to medical doctors or health professionals, clinical workups, hospitalizations, and treatments. Costs of care (direct costs) were elicited using the national average prices (2007 euros).

After log-transformation of costs, their determinants were explored by multilevel modeling, using unconditional means models to test for structural effects. To investigate the impact of treatment strategies, patients were classified according to time of biologic initiation: "first-year" (n = 42), "later year" (n = 66) and "never" (n = 440). Univariate correlations were first tested (p ≤ 0.05) so as to preselect a set of variables for multivariate analyses. Then, a multilevel regression analysis was conducted to identify determinants of total direct costs during the first 4 years of follow-up.

Results: Complete data were available for 548 patients (mean age 56 yrs, female 77%, ACPA 46%, RF 50%, ACR/EULAR 2010 83%, mean DAS28 5.1, mean HAQ 1). Annual mean direct cost per patient was €3,648, with a range from €18 to €53,739. On average, RA drug costs represented 48% of the overall direct costs, and up to 76% for patients receiving biologics.

With respects to total costs, living with a partner and baseline physician certainty of RA diagnosis less than 50% were each associated with lower total costs. Higher baseline HAQ score, increase in HAQ score ≥ 0.25 between baseline and the 6-month study visit, and positive rheumatoid factor were associated with higher total costs. In addition, the greatest increases in total costs were associated with "first year" use and "later year" use with approximately 9 and 5-fold increases in total costs, respectively (Table below). Patient socioeconomic status had no impact on total medical costs.

Variables		Multiplicative factor	95% CI	p value
Age at baseline		1.07	1.002; 1.13	0.04
Living with a partner	No	1		
	Yes	0.79	0.79; 0.94	0.01
Rheumatoid Factor positivity at baseline	No	1		
	Yes	1.20	1.03; 1.40	0.02
HAQ score at baseline	0–0.5	0.47	0.34; 0.64	<0.001
	0.5–1	0.49	0.36; 0.66	<0.001
	1–2	0.72	0.56; 0.94	0.01
	2–3	1		
Variation in HAQ score ≥ 0.25 between baseline and 6 month visit	No	1		
	Yes	1.07	1.04; 1.12	<0.001
Biologic use	Never	1		
	First year	9.03	6.83; 11.95	<0.001
	Later year	5.30	4.21; 6.67	<0.001
Physician certainty for RA diagnosis < 50% at baseline	No	1		
	Yes	0.74	0.61; 0.90	<0.001
Intercept		10729€	6794; 16943€	<0.001

Conclusion: As in established RA, biologic use is the main cost driver in rheumatoid arthritis care within the first years of the disease.

1. Combe B and Al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007;74(5):440–5.

Evaluation of the Cost-Effectiveness of Rheumatoid Arthritis Treatment with Biologic Agents Using the IORRA Cohort Database.

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Background/Purpose: Rheumatoid arthritis (RA), a chronic inflammatory disorder, causes a significant decrease in quality of life. Recently developed biologic agents (BAs) have caused a considerable economic burden to society. Several previous studies have investigated the cost-effectiveness of specific BAs; however, they have not adequately considered BA utilization under real-life conditions. In actual clinical conditions, various individual patient-based factors influence BA utilization and timing of selecting, switching, or discontinuing agents. Previous studies on specific BAs considering only a few aspects of the conditions of RA patients in actual clinical practice were frequently based on controlled trials. In this study, we investigated the cost-effectiveness of selecting BAs followed by switching to other BAs or methotrexate (MTX) under actual clinical conditions using RA cohort database, the Institute of Rheumatology, Rheumatoid Arthritis (IORRA).

Methods: A Markov model-based probabilistic simulation from a societal perspective was conducted using a hypothetical population of 10,000 patients. Patients who had failed more than one disease-modifying antirheumatic drug (DMARD) and for whom BAs were selected started one of the four BAs (adalimumab, etanercept, infliximab, and tocilizumab) used in Japan in 2010, switched to other BAs or MTX, or discontinued all drugs comprised the BA group. Patients similar in background to the BA group who started MTX following discontinuation of all drugs comprised the comparator group (MTX group). Almost all model parameters were determined with respect to each group, except those related to effects and costs of the four BAs and MTX, based on clinical data extracted by the matching method from the IORRA. Health states in the model were defined on the basis of physical dysfunction levels stratified according to the Japanese version of the Health Assessment Questionnaire (J-HAQ), which corresponded to cost and utility. Lifetime costs, quality-adjusted life years (QALY), and incremental cost-effectiveness ratio (ICER) were calculated. The threshold ICER was assumed to be 5.0–6.0 million JPY (1 USD = 88 JPY in 2010). A lifetime horizon and a discount rate of 3% per year for both health benefits and costs were assumed. We also conducted a probabilistic sensitivity analysis.

Results: Clinical data from two groups of 454 patients each were used for calculating model parameters (percentages of patients in the BA group started adalimumab, etanercept, infliximab, and tocilizumab were 17.3%, 45.9%, 24.3%, and 12.5%, respectively). Lifetime costs in the BA and MTX groups were 34.8 and 24.1 million JPY and QALYs were 11.4 and 9.3, respectively. The average period with acceptable disability defined by J-HAQ <1.1 was longer in the BA group (15.8 years) than that in the MTX group (10.4 years). The ICER was 5.04 million JPY, with 75.8–89.1% probability of falling below 5.0–6.0 million JPY, respectively, according to probabilistic sensitivity analysis.

Conclusion: This study demonstrated that selecting BAs is cost-effective for RA patients who had failed more than one DMARD according to the analysis of data obtained from an observational cohort representing daily clinical practice in Japan.

Evaluating the Cost-Effectiveness of Personalized Treatment with Adalimumab Using Serum Drug Levels in Rheumatoid Arthritis Patients.

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Background/Purpose: The high costs of biologicals warrant a rational use of these drugs, preferably by tailoring them to the individual patient. The objective was to evaluate the cost-effectiveness of personalized biological treatment for rheumatoid arthritis (RA) using European League Against Rheumatism (EULAR) response and adalimumab drug level tests.

Methods: In 272 rheumatoid arthritis patients treated with adalimumab, Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire (HAQ) and biological use was measured over three years. A treatment algorithm for personalized care was defined in which EULAR response and drug levels at 6 months defined whether adalimumab treatment was continued or discontinued, dosing was altered or, in case of non response, a next biological treatment was started.

Using a patient level Markov model, outcome in terms of DAS28 and HAQ and biological use according to the treatment algorithm for a personalized care group was simulated and compared to the observed drug use and disease course. Mean total costs, Quality Adjusted Life Years (QALYs) (both based on DAS28 and HAQ) and the average Incremental Cost-Effectiveness ratio (ICER) with 95 percentile range were calculated.

Results: Effectiveness was higher in the simulated personalized care group and the average difference in QALYs was 3.67 (95 percentile range −6.09 to 13.33). Costs were saved in the personalized care group as compared to observed care group: mean total savings €2.595.557 (95 percentile range -€2.983.760 to -€2.211755). In total €2.562.494 was saved on biological drug costs and testing costs amounted to €10.872. This resulted in an average ICER of -€ 707.236 per QALY gained. In 77.6% of simulations personalized care saved costs and was more effective (dominant) and in 22.4% cost-saving and less effective. Additionally, scenario analyses were performed and these were all cost-saving with variable effectiveness.

	observed care	simulated care	difference		
	mean	mean	mean	2.5%	97.5%
direct costs	€4,263,470	€4,237,086	-€ 26,384	-€391,927	€334,886
productivity	€1,876,147	€1,850,595	-€17,552	-€163,925	€124,873
drug costs	€11,893,326	€9,330,832	-€2,562,494		
testing costs	€0	€10,872	€10,872		
total costs	€18,032,942	€15,437,385	-€2,596,557	-€2,983,760	-€2,211,755
QALYs	587.98	591.65	3.67	−6.09	13.33

Cost effectiveness plane
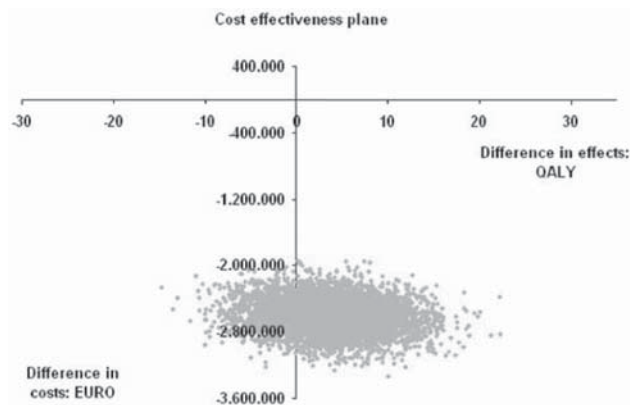
Conclusion: Tailoring biological treatment to individual RA patients using drug level tests to evaluate short-term outcomes is cost effective. Although specific for adalimumab, the results underline the potential cost-effectiveness for personalized biological treatment in RA.

1833

Healthcare Costs in Psoriatic Arthritis Patients Newly Initiated On a Biologic Disease-Modifying Anti-Rheumatic Drug or Methotrexate.
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Background/Purpose: Several treatment options are available for psoriatic arthritis (PsA) patients (pts). The healthcare cost associated with the management of PsA pts varies depending on the disease severity and treatments used by pts. Methotrexate (MTX) and biologics are commonly prescribed disease-modifying anti-rheumatic drugs (DMARDs) in PsA. Due to the safety concerns around these DMARDs, frequent monitoring is required during clinical practice. The objective of this study was to describe healthcare costs associated with the management of PsA in pts newly initiated on a biologic DMARD or on MTX, focusing on office care and monitoring costs.

Methods: Adult pts with $\geq$ 2 PsA diagnosis (from office visits) were selected from the MarketScan Commercial Claims database (2005–2009). The first biologic DMARD or MTX prescription date was defined as the index date. Biologic initiators were required to be biologic-naïve prior to the index date but may have used a non-biologic DMARD. MTX initiators were required to be both biologic and non-biologic DMARD naïve prior to index date. Pts with a diagnosis of ankylosing spondylitis prior to the index date were excluded. All patients were required to have continuous enrollment 6-month prior to and 12-month post index date. All-cause and PsA-related total healthcare costs were estimated during the 12-month study period from a payer perspective and expressed in 2011 USD. PsA-related medical costs were identified based on claims for medical services associated with a PsA diagnosis or costs associated with DMARD administration by healthcare professionals. Among medical costs, office care and monitoring costs were defined as the sum of costs for outpatient visits and other medical service costs (excluding costs for drugs administered by healthcare professionals) that were associated with a diagnosis of PsA. Urgent care cost was defined as the sum of costs for inpatient service and ER visits. PsA-related pharmacy costs were identified based on claims for a biologic or a non-biologic DMARD irrespective of a PsA diagnosis.

Results: A total of 1,217 MTX initiators and 3,263 biologic initiators met the eligibility criteria. Over the 12-month study period, MTX initiators had an average total healthcare cost of $14,329 and $6,065 were PsA-related. Pharmacy costs accounted for 80.4% ($4,878) of the PsA-related total costs; office care and monitoring costs ($986) accounted for 16.3%; urgent care costs accounted for 3.3% ($201). Biologic initiators had an average annual total healthcare cost of $30,282 and 67.5% were PsA-related ($20,439). Pharmacy costs accounted for 92.7% ($18,938) of the PsA-related total costs; office care and monitoring cost ($1,041) accounted for 5.1%; urgent care cost ($461) accounted for 2.2%.

Conclusion: PsA patients initiating on a DMARD are associated with substantial healthcare costs. Although pharmacy costs accounted for the majority of the PsA-related costs, office care and monitoring costs accounted for a significant part of the PsA-related costs.

Disclosure: F. Zhang, Celgene Corporation, 3; **R. Hiscock**, Celgene Corporation, 5; **J. Curtis**, Celgene, Roche/Genetech, UCB< Centocor, Corrona,Amgen, Pfizer, BMS, Crescendo, Abbott, 2, Celgene, Roche/Genetech, UCB< Centocor, Corrona,Amgen, Pfizer, BMS, Crescendo, Abbott, 5.

1834

Utilization and Expected Cost of Rheumatoid Arthritis Patients Treated with Golimumab: A Specialty Pharmacy Perspective.
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Background/Purpose: Golimumab is a 50 mg, once-monthly, patient-administered anti-tumor necrosis factor alpha (anti-TNF) therapy indicated for moderate to severe rheumatoid arthritis (RA), active psoriatic arthritis, or active ankylosing spondylitis. A substantial proportion of patients receive golimumab through a specialty pharmacy provider (SPP). The purpose of this study is to describe the utilization and expected golimumab cost for RA patients receiving golimumab from a SPP.

Methods: Pharmacy and eNAVIGATOR™ data were analyzed for adult patients with an ICD-9-CM diagnosis code for RA (714.X) who received $\geq$2 golimumab doses between 4/24/2009 and 8/24/2011. Utilization measures included the proportion of 50 mg dose fills and the proportion of compliant fills, defined as 21 to 38 days, corresponding to a 28 to 31 days supply $+/-7$ days. Descriptive statistics were employed. Mean refill interval and wholesale acquisition cost (WAC) for golimumab ($2,075.62 per 50 mg; 2/1/2012-Analysource; First Databank) were used to estimate the annual cost of golimumab.

Results: The study population included 126 golimumab patients and was predominantly female (79%) and aged >45 years (72%). The majority (71%) reported prior biologic use. Of the 109 patients with baseline Health Assessment Questionnaire II (HAQ-II) assessments, a score >1 was found in 62% (n=68). A total of 942 golimumab fills were dispensed during the study period. A 50 mg golimumab dose was dispensed in 100% of patients and 100% of fills. The mean ($\pm$SD) interval between golimumab doses was 35 $\pm$22days (median 30 days). The mean ($\pm$SD) refill interval of patients with prior-biologic use (bio-experienced) was 35 $\pm$25 days with a median of 30 days. The mean ($\pm$SD) refill interval for patients without prior biologic therapy (bio-naïve) was 34$\pm$15 days with a median of 31 days. Approximately 84% of all fills fell within the defined compliance window for the overall population and in bio-experienced and bio-naïve subgroups. Based upon a mean refill interval of 35 days, the average RA patient would have 11 golimumab fills per year at an estimated annual cost of $22,831.82.

Conclusion: In this SPP population over a period of slightly more than two years, golimumab consistently was used at a 50 mg dose with a median refill interval of 30 days and mean refill interval of 35 days. These findings correspond closely with dosing and administration recommendations in the golimumab product label. Overall refill compliance was observed in a high proportion of fills (greater than 80%). Based upon these utilization trends, the average annual cost of golimumab therapy was estimated to be $22,831.82.

Disclosure: L. Ellis, Janssen Scientific Affairs, LLC, 3; **S. Bolge**, Janssen Scientific Affairs, LLC, 3; **H. Hanna**, Janssen Scientific Affairs, LLC, 5; **C. White**, Janssen Scientific Affairs, LLC, 5; **P. Rice**, Janssen Scientific Affairs, LLC, 5.

1835

Prescription of Biologics in Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS) in 4 Norwegian Regions 2002–2011: A Study of Prescription Rates and Baseline Disease Activity.
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Background/Purpose: Biologics have constituted a major advance in the treatment of RA, PsA and AS. In Norway access to these therapies has been good since their introduction. With increasing focus on early and aggressive therapy, one could expect increasing use of biologics, including use in patients (pts) with moderate disease activity. The objectives were to examine if prescription rates of biologics in RA, PsA and AS continue to increase or have reached a plateau, and whether disease activity at initiation of therapy has changed over the years.

Methods: Data for this study were from the NOR-DMARD register. Prescriptions of biologics to biologics naïve pts with RA, PsA and AS between Jan 2002 and Nov 2011 in 4 centers covering regions in East- and Mid-Norway were studied. Population data were extracted from Statistics Norway (www.ssb.no). Prescription rates per 100,000 inhab. per year were calculated and adjusted for an estimated 15% incompleteness of the register. Numbers were also adjusted for incomplete data for 2 centers in 2002 and all centers in 2011. Further, we calculated rates as % of pts, based on published Norwegian disease prevalence data [0.45% for RA (2 studies), 0.20% for PsA, 0.26% for AS]. Baseline (BL) disease activity [CRP, DAS28 and ASDAS (from 2006)] was examined per diagnosis per year. Potential effects of prescription year were assessed by linear regression with BL variables as the dependent variable and year as a continuous (1–10) independent variable. CRP was Ln-transformed for the analyses.

Results: The material included 1961 prescriptions – 1026 in RA, 375 in PsA and 560 in AS. These were all TNF inhibitor (TNFi) prescriptions in AS, 2 non-TNFi in PsA and 38 non-TNFi in RA (32 rituximab, 3 abatacept, 3 tocilizumab). The population in the study area increased from 1.31 mill to 1.44 mill from 2002 to 2011. Prescription rates per year are shown in Table 1. There was a trend towards increasing prescription rates in AS throughout the study period. Fluctuations in the annual prescription rates were observed for RA and PsA. First biologic was since 2007 prescribed more frequently in AS and PsA together than in RA. (Table 1). BL levels of disease activity measures decreased significantly over time in all 3 diagnoses (Table 2).

Table 1. Prescription rates of biologics in biologics naïve patients 2002–2011

	Prescriptions per 100,000 inhabitants				Percent of patients*		
	Overall	RA	PsA	AS	RA	PsA	AS
2002	5.8	4.8	0.2	0.7	1.1%	0.1%	0.2%
2003	15.3	11.0	2.5	1.8	2.4%	1.3%	0.7%
2004	20.6	12.6	3.5	4.5	2.8%	1.8%	1.7%
2005	13.2	7.5	1.5	4.2	1.7%	0.8%	1.6%
2006	14.0	7.1	1.9	5.0	1.6%	1.0%	1.9%
2007	15.5	7.3	3.0	5.2	1.6%	1.6%	2.0%
2008	23.3	11.4	5.5	6.4	2.5%	2.8%	2.5%
2009	20.7	8.5	5.3	6.9	1.9%	2.7%	2.7%
2010	19.4	8.7	4.5	6.4	1.9%	2.3%	2.4%
2011	25.2	12.0	5.0	8.2	2.6%	2.6%	3.1%

*Based on est. prevalence of 0.45% for RA, 0.20% for PsA and 0.26% for AS.

Table 2. Baseline disease duration and disease activity levels

	RA		PsA		AS	
	DAS28 Mean (SD)	CRP Median (IQR)	DAS28 Mean (SD)	CRP Median (IQR)	ASDAS Mean (SD)	CRP Median (IQR)
2002	6.04 (1.15)	31 (11, 71.5)	4.75 (2.07)	NA	NA	38 (10, 91)
2003	5.45 (1.17)	22.5 (11, 42.75)	4.38 (1.26)	13.5 (4.25, 37.5)	NA	26.5 (15, 47.5)
2004	5.05 (1.28)	13 (6, 31)	4.40 (1.21)	8 (4, 22)	NA	14 (6.75, 35.25)
2005	5.34 (1.45)	15 (6, 31.5)	5.20 (1.16)	11.5 (5.5, 31.5)	NA	10 (5, 25)
2006	5.19 (1.48)	10 (3, 31)	4.63 (1.14)	14 (8, 39)	3.86 (1.16)	10 (3.5, 23.5)
2007	5.08 (1.46)	12.5 (7, 24)	4.27 (1.55)	12 (5, 34.5)	3.55 (0.91)	13.5 (6, 28.25)
2008	4.80 (1.48)	7.5 (4, 21.25)	3.89 (1.16)	6 (4, 12)	3.34 (0.90)	12 (5, 22.25)
2009	4.59 (1.51)	8 (3, 22)	3.93 (1.30)	7.5 (3, 15.75)	3.28 (0.84)	10 (5, 18)
2010	4.65 (1.43)	7 (2.5, 16.5)	3.63 (1.35)	5 (1, 15)	3.19 (0.90)	6 (3, 15)
2011	4.16 (1.23)	5 (3, 14.5)	3.91 (1.13)	5 (2, 12)	3.21 (0.92)	7 (3, 13.25)
P*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

NA = not applicable. *Linear regression.

Conclusion: The annual rate of first-time prescriptions of biologics to patients with RA, PsA and AS increased from 15 per 100,000 in 2003 to 25 per 100,000 in 2011. During recent years the increase was most pronounced in AS and prescriptions were more frequent in AS and PsA combined than in RA. Baseline disease activity levels at the start of treatment decreased gradually in all diseases, with a marked reduction in patients with RA.

1836

Early Versus Delayed Initiation of Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. Sharon Van Doornum[1], Lynden Roberts[2], Mark D. Reed[3] and Danny Liew[1]. [1]The University of Melbourne, Melbourne, Australia, [2]James Cook University, Townsville, Australia, [3]Sir Charles Gairdiner Hospital, Nedlands, Australia

Background/Purpose: Studies from a number of countries suggest that the time between symptom onset and initiation of DMARD therapy in RA patients is still longer than would be considered optimal, or even acceptable. We sought to assess the health economic impact of this delay in an Australian context.

Methods: Delay in initiation of DMARD therapy was estimated from a 2005 study of 96 Australian patients with RA referred to one public and four private rheumatology practices. RA-associated utilities and costs were sourced from published data. Patients not taking and taking DMARD therapy were assumed to have utilities of 0.443 and 0.543, respectively. The annual direct costs of RA, excluding DMARDs, was AUD $3780, and the annual cost of DMARD therapy was $2658. It was conservatively assumed that DMARD therapy did not reduce non-DMARD RA costs (that is, it was $3780 for all patients).

Results: In the 2005 study, the mean time from time of symptom onset to initiation of DMARD therapy was found to be 17.7 months, or 1.48 years. Over the 1.48 years, a mean of 0.65 QALYs would have been lived per patient and $5579 of direct healthcare costs incurred. Had DMARDs been commenced at the time of symptom onset, 0.80 QALYs would have been lived per patient, and $9503 of direct healthcare costs incurred. The differences of 0.15 QALYs and $3924 in direct healthcare costs equated to an incremental cost-effectiveness ratio (ICER) of $26,583 per QALY saved. Up to $4500 of additional costs could be spent per patient to reduce the time to initiation of DMARDs before the ICER breached the arbitrary cut-off of $50,000 per QALY saved. Our analysis was conservative in it did not consider the long-term health and cost savings associated with avoidance of permanent joint damage.

Conclusion: There is considerable delay in the initiation of DMARD therapy among patients with RA, which leads to significant health loss. Reducing the time to initiation of DMARDs represents a cost-effective means of reducing the burden of RA.

1837

Which Rheumatoid Arthritis, Ankylosing Spondylitis and Juvenile Idiopathic Arthritis Patients Initiate Anti-TNFá Therapy? Alain Saraux[1], Jacques Benichou[2], Chantal Deslandre[3], Loic Guillevin[4], Latifa Idbrik[5], Jean Sibilia[6], Marc Soudan[5], Daniel Wendling[7] and Francis Guillemin[5]. [1]CHU de la Cavale Blanche and Université Bretagne occidentale, Brest Cedex, France, [2]EA4438 Laboratoire Physiopathologie des Arthrites, Rouen, France, [3]Cochin Hospital, Paris, France, [4]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [5]Faculte de Medecin/BP 184, Vandoeuvre-les-Nancy, France, [6]EA4438 Laboratoire Physiopathologie des Arthrites, Illkirch-Strasbourg, France, [7]Minjoz University Hospital, Besancon, France

Background/Purpose: Comprehensive guidelines for anti-TNFα were proposed in 2005 by the French Society for Rheumatology (SFR) in France; they did not include any economic considerations and they remained only informative for rheumatologists. Although they were not endorsed by the governmental agency, anti TNF-α were available without reimbursement restriction to all patients fulfilling them. Only limited information is available about patients who are potential candidates for anti-TNFα therapy (anti-TNFα) as well as about the physicians' attitude towards initiation of anti-TNFα.The French authorities initiated the CORPUS (cohorte d'observation rhumatologique des pratiques et des usages) survey to evaluate how rheumatologists prescribe anti TNF in active inflammatory rheumatic disease in case of the eligibility to biologics.

Methods: Between 2007 and 2009, 102 rheumatologists, internists and paediatricians in French University Hospitals and private practice recruited patients having an active IRD [DAS28 > 3.2 despite methotrexate use for rheumatoid arthritis (RA), BASDAI≥4 despite NSAID use for spondyloarthritis (SA) and not responder to methotrexate for Juvenile idiopathic arthritis (JIA)] naïve of biologics. They were followed prospectively for one year.

Results: Overall, 543 RA, 287 SA and 53 JIA patients were included among whom 382 RA, 171 SA and 28 JIA patients had complete follow-up data available at one year. The activity of the disease evaluated by the DAS, BASDAI and CHAQ was elevated in all goups. Both disability and quality of life indicators attested of the severity of the diseases. Among patients with available data, 110/382 (28.8%) RA, 81/171 (47.4%) SA, and 26/28 (92.9%) JIA patients received at least one injection of anti TNF-α during the first year of follow-up. Younger age, smoking, corticosteroid use, previous X-ray progression, higher disease activity (VAS patients, morning stiffness, DAS), higher disability (HAQ) level and poorer quality of life (SF36) at baseline were associated with anti TNF-α initiation among RA patients; by multivariate analysis, only younger age and poorer quality of life remained associated with anti TNF-α initiation. In SA patients, disease activity (high BASDAI), X-ray progression, high handicap (HAQ) level and poor quality of life (SF36) were also associated with anti TNF-α use. According to the physicians, the main reason for non prescription of anti- TNF-α to RA or AS patients was the low level of disease. In only 10% of cases, the lack of prescription was due to patient's refusal and in 5% to contraindications.

Conclusion: In France, anti TNF-α, available without reimbursement restriction, was quite systematically prescribed to JIA patients not responder to methotrexate, to about one half of SA patients with BASDAI score ≥4, and to one third of RA patients with DAS28 score >3.2 despite methotrexate therapy.

1838

10-Year Trends in the Use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and Biologic Agents in Rheumatoid Arthritis: A National Veteran Affairs Study. Bernard Ng[1], Nancy Petersen[1], Hong-Jen Yu[1], Myrna Khan[1] and Maria E. Suarez-Almazor[2]. [1]Michael E. DeBakey VA Medical Center Health Services Research and Development Center of Excellence, Houston, TX, [2]University of Texas MD Anderson Cancer Center, Houston, TX

Background/Purpose: It is unclear how recommendations for disease modifying anti-rheumatic drugs (DMARDs) & biological agents in treatment of Rheumatoid Arthritis (RA) have influenced their use over the past decade. Using the department of Veterans Affairs (VA) as a model to represent a large multi-facility health care organization, we studied the trend of MTX dosing and the use of traditional DMARD/biologics in treating Veterans with RA over a 10-year period from 2000 to 2009.

Methods: Using various national administrative databases of the department of VA, we found an incident cohort of 13,254 RA patients with validated algorithms to identify RA. Descriptive statistics were used to characterize trends in MTX start and highest dose and changes in patterns of DMARDs and biologics usage over the study period.

Results: Use of biologics increased from 2.8% in 2000–2001 to 18.9% in 2008–2009. Between 2000 and 2001, etanercept was the main biologic available, and it represented 96.2% of all biologics used. Since the introduction of adalimumab in 2003, its use increased tremendously, and by 2008–2009, it became the most used biological agent for the treatment of RA in our study population (48.5%). For the first DMARD/biologic used in a DMARD-naïve RA patient, there was an increase in use of MTX over time from 39.8% to 52.1%. There was also a gradual decline in both hydroxychloroquine and sulfasalazine as first line agents. Use of biologics as first-line agents remained relatively unchanged over the study period at 1.3–3.6 %. For the subjects who had been on MTX monotherapy for 90 or more days (52.9% of 13,254), between 2001–2002 and 2008–2009, the mean MTX start dose increased slightly but significantly from 10.1 to 11.4mg per week (p<0.01) and the proportion who were started on MTX less than 10mg per week dropped from 43.2% to 22.1% (p<0.01). Over the same time period, the mean maximum MTX dose attained increased significantly from 15.6 to 17.8 mg per week (p<0.01) and the proportion attaining peak dose of MTX of less than 15mg/week dropped from 35.0% to 17.0% (p<0.01).

Conclusion: The use of DMARDs and biologics in treatment of RA has changed markedly over the past decade. The increased use of MTX as the first line agent is consistent with it becoming the anchor drug for RA treatment. Though the start and maximum MTX dose attained have increased significantly over the decade, the average maximum dose at the end of our study is still considered low compared with current standards. Biologics have been gaining acceptance and now play an important role in RA treatment. In the VA system, adalimumab has become the most common biologic used in 2008–2009.

Disclosure: **B. Ng**, UCB Pharmaceuticals, 5; **N. Petersen**, None; **H. J. Yu**, None; **M. Khan**, None; **M. E. Suarez-Almazor**, None.

1839

The Progression of the Rate of Biologic Initiation in Early Rheumatoid Arthritis Is Constant Over the First 5 Years in the Espoir Cohort. Stéphanie Emilie[1], Cécile Gaujoux-Viala[2], Benjamin Granger[3], Anne-Christine Rat[4], Bernard Combe[5] and Bruno Fautrel[6]. [1]Paris 6,Pierre and Marie Curie University, AP-HP, Pitié-Salpêtrière Hospital, Department of Rheumatology, Paris, France, [2]Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [3]Université Pierre et Marie Curie - Paris 6; AP-HP, Paris, France, [4]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F-54 000, Nancy, France, [5]Hopital Lapeyronie, Montpellier, France, [6]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France

Background/Purpose: The European League Against Rheumatism recommends tight control of rheumatoid arthritis (RA). However, tight control of RA may depend on several factors, including patient characteristics and disease activity, social and medico-economic parameters.

The purpose of our study is to determine which factors influence the time-to-introduction of first biologic agent in RA patients in the French ESPOIR (study and following of undifferentiated early stage arthritis) cohort.

Methods: Among the 813 ESPOIR patients, 641 RA patients satisfying the ACR/EULAR 2010 RA diagnostic criteria were followed over 5 years. Among them, we excluded patients participating in therapeutic trials, such that 619 RA patients were analysed.

The outcome variable was the delay between the first stable symptoms and the introduction of the first biologic agent. The potential explanatory variables tested were patients and disease characteristics as well as health care system characteristics (medical center of follow-up, time to first rheumatologist consultation, population of city of residence).

Survival rates were estimated using the Kaplan-Meier method. Cox proportional hazards models were used to determine independent predictors of introduction of the first biologic agent.

Results: Among the 619 RA patients (mean age 50.3 years, 50.6% Rheumatoid Factor positive and 43.3% ACPA positive, 27.1% with erosion on baseline X-rays), 121 (19.5%) had received a biologic agent at 5 years (TNF-blockers for most of them, rituximab and abatacept for 14 of them).

The mean time between the first stable symptoms to the introduction of the first biologic agent was 27.9 months (± 17.2), the median was 23.7 months (Q1 13.2, Q3 43.8).

The results of the Cox model are shown in figure 1.

Survival of the RA without any biologic agent
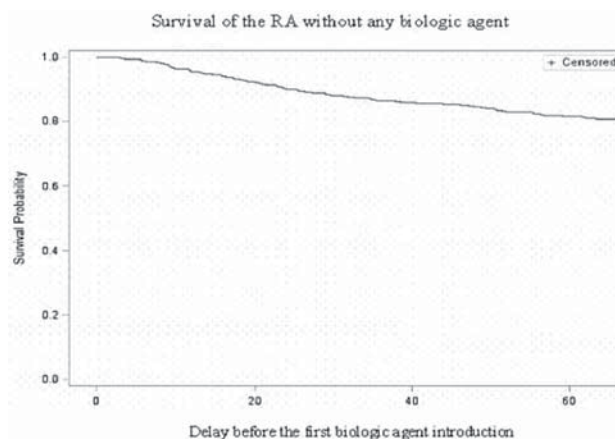
The time-to-introduction of first biologic was significantly decreased by the presence of ACPA (Risk ratio [RR]: 3.4; 95% confidence interval [CI]: 2.1–5.5), younger patient age (RR: 0.97; CI 0.95: 0.95–0.99) and by the use of a DMARD during the first year of evolution of the disease (RR: 2.2, CI 0.95: 1.4– 4.4). There was no protective effect of corticosteroids (RR: 2.5, CI 0.95: 1.5–4.1). The medical center of follow up was related to the time-to-introduction of first biologic (RR: 0.4, CI 0.95: 0.2–06). However, no influence of other socio-economics parameters such as professional activity, employment status, population of city of residence, or time to first rheumatologist consult was noted.

Conclusion: Our results suggest that there was no peak period in the distribution of a biologic agent's introduction in the first five years of follow-up of the ESPOIR cohort. However, the medical center of follow-up shown to have a large impact on the time-to-introduction of the first biologic agent. By contrast, the time to first rheumatologist consult or social parameters do not have any influence on the first biologic agent's start.

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1840

Treatment Patterns in Psoriatic Arthritis Patients Newly Initiated On Non-Biologic Disease-Modifying Anti-Rheumatic Drugs. Jeffrey Curtis[1], Genevieve Gauthier[2], Robert Hiscock[2] and Frank Zhang[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Analysis Group, Inc., Montreal, QC, [3]Celgene Corporation, Warren, NJ

Background/Purpose: Several treatment options are available for psoriatic arthritis (PsA) patients (pts). Oral disease modifying anti-rheumatic drugs (DMARDs) are often used as a first-line treatment when non-steroidal anti-inflammatory drugs (NSAIDs) failed to control the PsA symptoms. Few studies have reported the treatment patterns in current PsA management in real-world settings. The objective of this study was to describe treatment changes (i.e., discontinuations and therapy modifications) following the initiation of a non-biologic DMARD in PsA pts.

Methods: Adult pts with ≥2 PsA diagnoses from physician office visits were selected from the MarketScan Commercial Claims database (2005–2009). All pts were required to have continuous insurance coverage ≥6-month prior to and ≥12-month post index date. First prescription date of a non-biologic DMARD was the index date and the preceding 6 months defined the 'baseline'. Pts who used any biologic/non-biologic DMARDs or had a diagnosis of ankylosing spondylitis during the baseline were excluded. Treatment discontinuation was defined as a treatment interruption of ≥60 consecutive days between the end of days' supply of one prescription and the start of the next prescription for the index drug. Switch in therapy was defined as the initiation of a biologic/non-biologic DMARD (not used at the index date or during the baseline) within 60 days of the discontinuation date of the index DMARD. Therapy augmentation was defined as the use of a non-biologic or biologic DMARD (not used at the index date or during the baseline) concomitantly with the index non-biologic DMARD for ≥28 consecutive days after the index date. A treatment change was defined as either a switch in therapy or an augmentation to the index therapy. Treatment patterns were captured over the one-year study period following the index date. Since pts might have used different DMARDs during the study period, the 4 most frequent treatment sequences (excluding treatment interruption) were also reported.

Results: A total of 1,698 PsA pts met the selection criteria; 71.7% initiated on methotrexate, 17.5% on sulfasalazine. Over the 12-month study period, 72.5% of the pts had ≥ 1 therapy change (median time: 86 days). More specifically, 57.7% of pts discontinued the index non-biologic DMARD (median time: 89 days), 13.1% switched to a biologic DMARD (median time: 141 days), 9.3% switched to another non-biologic DMARD (median time: 111 days), 21.4% had a therapy augmentation with a biologic DMARD (median time: 119) and 7.4% had a therapy augmentation with another non-biologic DMARD (median time: 94). The most common treatment sequences observed were 1) pts used MTX only during the study period (42.5%), 2) pts used MTX and a biologic (22.0%), 3) pts used sulfasalazine only (9.8%), and 4) pts used MTX and sulfasalazine (4.2%). Among pts who initiated a biologic during the study period (N=513), 90.8% did not use other oral DMARDs, while 9.2% also initiated another oral DMARD either in combination or sequentially.

Conclusion: This study suggests that PsA pts newly initiated on a non-biologic DMARD do not remain on the index therapy for a long period of time. Most pts switched to or added on biologics quickly without using a second oral DMARD.

1841

Lower Than Expected Levels of DMARD Acquisition Immediately Pre and Post Biologic Initiation in Rheumatoid Arthritis Patients. Denis Choquette[1], Oliver Thomas[2] and Mark Arundine[2]. [1]University of Montreal, Notre-dame Hospital, Montreal, QC, [2]Roche, Toronto, ON

Background/Purpose: Reports suggest that a large proportion of patients who acquire and use biologic DMARD agents (biologics) to treat Rheumatoid Arthritis (RA) do not acquire or adequately consume traditional DMARDs (DMARDs)[1,2]. However acquisition rates of biologics and DMARDs at the point of biologic initiation remains to be determined. The primary objective is to explore the level of DMARD acquisitions in Canadian RA patients in the 6 to 12 months both immediately prior to and post-biologic initiation to quantify the levels of biologic monotherapy vs. biologic + DMARD combination consumption.

Methods: Biologic and DMARD concomitant therapy based on actual patient purchases was examined by tracking a cohort of 1,652 anonymous RA patient records from public and private drug plans in Canada (ON, QC) via unique drug plan identifier numbers (3rd party source).[3] All patients who were initiated on a biologic between August 2009 and July 2010 were tracked for a one-year period prior to and post their biologic initiation date. All cohort patients were compliant on biologics post initiation. Rheumatologist prescribing frequencies of RA therapies were assessed through randomly recruited surveys (n=100).[4]

Results: Physicians prescribed a biologic without a DMARD only 12% of the time[4]. 25% of cohort patients did not purchase any form of DMARD within the 6 months prior to starting a biologic (41% for MTX). 29% did not acquire DMARDs at any point in the 6 months post-biologic initiation (43% for MTX). Data 12 months pre-biologic initiation showed that 22% did not acquire DMARDs (37% for MTX). Data 12 months post-biologic initiation showed that 26% did not acquire DMARDs (41% for MTX).[3] Prescriptions supplied to 2–3 months worth of drug.[4]

Conclusion: A large proportion of Canadian patients do not acquire any form of DMARD in the 6–12 months prior to being initiated on a biologic for the first time. This may negatively influence compliance on DMARDs once a biologic is initiated. Six months post-biologic initiation, 29% do not acquire any form of DMARD (43% for MTX) despite the general physician prescribing rate of biologic monotherapy (12%).[3,4] These results are consistent with other registries, however this study isolates biologic monotherapy levels immediately prior to and post-biologic initiation.[1,2,3] Many patients report reluctance or refusal to take DMARDs due to side effects that include headache, GI discomfort, malaise, fatigue, nausea, hair loss, and lifestyle restrictions[4,5]. Close monitoring of DMARD intake is recommended and/or management of patients on monotherapy. Patient education is of prime importance as sustainability, clinical and radiological efficacy of biologic treatment may be compromised.

1842

Disease Activity and Treatment Strategies in Moderate Rheumatoid Arthritis Patient Population: Data From the Consortium of Rheumatology Researchers of North America. Sameer Kotak[1], Andrew S. Koenig[2], David H. Collier[3], Katherine C. Saunders[4], Ping He[5], Joel M. Kremer[6] and George W. Reed[7]. [1]Pfizer Inc., New York, NY, [2]Pfizer Inc., Collegeville, PA, [3]Amgen Inc., Thousand Oaks, CA, [4]CORRONA, Inc., Southborough, MA, [5]UMASS Medical School, Worcester, MA, [6]Albany Medical College and The Center for Rheumatology, Albany, NY, [7]University of Massachusetts Medical School, Worcester, MA

Background/Purpose: Studies on patients with severe rheumatoid arthritis (RA) are widely reported. However, limited data are available on patients with moderate disease activity (MOD). Recent evidence, including data from the PRESERVE trial, have highlighted the disease burden in MOD patients, and further warrant an understanding of disease progression/remission and impact of treatment strategies in this patient population from longitudinal clinical registries.

Methods: Patients enrolled in CORRONA (a large US multicenter, longitudinal database of RA patients) from March 2002 through April 2012, aged ≥18 years, who moved from LDA (CDAI≤10) to MOD (10<10CDAI<22) were included at baseline. Patients were followed over time to estimate the proportion with Low CDAI/Moderate CDAI/ Severe CDAI at the 6 month and 12 month follow up visit. Additionally proportion of patients accelerating between baseline and 6 month; and 6 month and 12 month follow up visit were reported. Accelerations were defined as (i) add/switch a DMARD (ii) increase dose only (iii) both add/switch DMARD and increase dose. Patients were excluded if (i) time between last LDA and first Moderate CDAI was > 1 year (ii) they moved from LDA to Severe CDAI before Moderate CDAI. We included patients with CDAI at all three visits (first moderate, 6 month follow up, and 12 month follow up).

Results: 4,118 RA patients met the inclusion criteria. At 6 months, the majority (2,451/4,118; 60%) were LDA, while 32% (1,298/4,118) remained MOD, and 9% progressed to severe (CDAI>22). Of those who were at LDA at 6 months (N=2,451), 76% remained at LDA at 12 months; while 46% of those who were MOD at 6 months actually improved to LDA at 12-months. Majority (69%) of those severe at 6-months had either improved to LDA or MOD at 12-months. Between baseline and 6-month visit, 39% (1,590/4,118) accelerated by adding/switching a DMARD (43%), increasing the dose (43%), or both (12%) and in spite of that, 10% patients had progressed to severe (160/1,590) at the 6-month visit. Eight percent of patients with no accelerations from baseline (2,528) worsened (209/2,528) at the 6-month visit. Between 6 and 12 month visit, patients initially accelerated but with LDA or MOD at 6-month did not receive high number of accelerations. Nearly half of those severe at 6-months were accelerated, although a quarter (25%) continued to demonstrate severe disease activity at the 12-month visit.

Conclusion: Patients identified with moderate disease activity (10<CDAI<22) from a longitudinal registry generally regress and progress disease activity levels over a 6-month and 12-month follow-up period. Patients with treatment accelerations were presumably more severe as evidenced in a higher proportion of patients with severe disease activity at the 6-month visit (10%) than those without accelerations (8%). In this patient population, for patients who move from LDA to moderate disease, even at one year there were still substantial numbers who had not moved to LDA. Data demonstrates transition potential and disease instability in an understudied population, even within a short follow-up window of 6-months to a year.

1843

Predictors of Starting and Stopping Disease Modifying Anti-Rheumatic Drugs for Rheumatoid Arthritis: A 23 Year Longitudinal Cohort. Daniel H. Solomon[1], Edward Yelin[2], Jeffrey N. Katz[3], Chris Tonner[4], M. Alan Brookhart[5], Seoyoung C. Kim[1], Bing Lu[1] and John Z. Ayanian[6]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of California San Francisco, San Francisco, CA, [3]Brigham & Women's Hospital, Boston, MA, [4]UCSF, San Francisco, CA, [5]University of North Carolina, [6]Brigham and Women's Hospital

Background/Purpose: DMARDs are the standard of care for rheumatoid arthritis (RA), however multiple studies find that not all patients use these agents. We examined predictors of DMARD stopping and DMARD starting among a large cohort of patients with RA.

Methods: Study participants were drawn from an open longitudinal cohort of 1,346 participants with RA recruited from rheumatologists' practices in Northern California. We examined patterns and predictors of DMARD stopping and starting, including non-biologic and biologic DMARDs, based on annual questionnaires. Stopping was defined as stopping ALL DMARDs and starting was defined as transitioning from NO DMARDs to any DMARD across consecutive years. Predictors were categorized as related to RA (disease duration, HAQ score, tender and swollen joints, and use of oral steroids), sociodemographics (age, gender, race/ethnicity, education, income), or comorbidities (index). Calendar year was also included. Generalized linear mixed regression models for binary outcomes were constructed that accounted for the non-independence of multiple pairs of years from individual participants, and model fit was assessed using the c-statistic.

Results: The analysis of determinants of starting DMARDs included 471 subjects with 1,974 pairs of years with no DMARD use in the first of two consecutive years from which 313 (16.3%) started DMARD use before year two. The analysis of determinants of stopping DMARDs included 1,026 subjects with 7,595 pairs of years with DMARD use in the first of two consecutive years from which 423 (5.6%) stopped DMARD use before year two. Over the 23 years of follow-up (1987–2009), the percent starting DMARDs between two consecutive years was stable at approximately 10%, but the percent stopping DMARDs from one year to the next decreased from 9% to 3%. In fully adjusted models, significant predictors of starting DMARDs included younger age (OR 0.85, 95% CI 0.75–0.95, per 5-year decrease), Hispanic ethnicity (OR 1.88, 95% CI 1.06–3.33), shorter disease duration (OR 0.90, 95% CI 0.80–1.00, per 5-year decrease), and the use of oral steroids (1.90, 95% CI 1.36–2.66). In separate fully adjusted models, predictors of stopping DMARDs included older age (OR 1.05, 95% CI 1.00–1.10, per 5-year increase), Hispanic ethnicity (OR 1.54, 95% CI 1.02–2.30), lowest annual income quartile (OR 1.83, 95% CI 1.13–2.96, compared with highest), and more tender joints (OR 1.03, 95% CI 1.00–1.07 per joint increase). The c-statistics for RA-related factors were 0.60 (stopping a DMARD) and 0.62 (starting a DMARD), suggesting that they were relatively weak predictors of stopping or starting a DMARD. Including sociodemographic factors and comorbidities in the fully adjusted models improved the model fit for both sets of models – c-statistics 0.68 (stopping a DMARD) and 0.69 (starting a DMARD).

Conclusion: Predictors of stopping and starting DMARDs include non-RA related factors as well as RA-related factors. More frequent starting and stopping of DMARDs in Hispanic subjects may reflect barriers to continued use. The significance of non-RA related factors such as race/ethnicity and income suggest that there are disparities in DMARD use despite clear clinical guidelines about their use.

1844

Inequities in Access to Biologic Disease-Modifying Anti-Rheumatic Drugs for Patients with Rheumatoid Arthritis Across 46 European Countries. Polina Putrik[1], Sofia Ramiro[2], Milena Pavlova[1], Tore K. Kvien[3], Tuulikki Sokka[4], Till Uhlig[3], Annelies Boonen[5] and Equity In Access To Treatment of RA Across Europe[6]. [1]Maastricht University, Maastricht, Netherlands, [2]Academic Medical Center, University of Amsterdam, The Netherlands and Hospital Garcia de Orta, Almada, Portugal, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [5]University Hospital Maastricht, Maastricht, Netherlands, [6]European Region

Background/Purpose: In the treatment of patients with RA, EULAR recommends to initiate biologic DMARDs after failing synthetic DMARDs. However, biologics are costly, and it is not known to what extent limited access to these drugs can hamper implementation of the EULAR recommendations. A poor ability to adhere to these recommendations might contribute to health disparities previously seen in RA patients across countries [1]. The purpose of the study was to explore access to biologics across Europe along the three dimensions of access: availability, affordability and acceptability.

Methods: Number of reimbursed drugs, prices of biologics, and data on cultural acceptability of biologics were collected by questionnaire sent to one representative rheumatologist in 49 countries of the European Region. To ensure comparability, national prices were converted into international dollars ($) to adjust for the countries' purchasing power parity (PPP). Data on socio-economic welfare (gross domestic product (GDP), health expenditure, median income and minimum wage) were retrieved from web-based sources. Data on RA health status (DAS28, HAQ, TJC, SJC, ESR) were retrieved from the literature (QUEST RA) [1]. Indicators of access in each axis were correlated with indicators of welfare and RA health status using Spearman correlations.

Results: In total, 46 countries (response rate 94%) provided data. With respect to *availability*, in 10 countries no biologics were reimbursed, while 5 or more were reimbursed in 27 countries. With respect to *affordability*, annual average prices per patient of all available biologics varied from €9,431 (Turkey) to €21,349 (Germany), corresponding to a price ratio of 2.3. However, after adjusting the prices for PPPs, prices ranged from int.\$14,446 to int.\$61,552 (price ratio 4.3). Cultural *acceptability* ranged from 0 to 10 (10 poorest acceptability). Number of reimbursed drugs showed moderate to very strong positive correlation with the economic welfare and inverse correlation with the RA health status. While national prices seemed to be slightly lower in low income countries, after adjusting to PPP prices were strongly inversely correlated with economic welfare and positively with RA health. The sum-score of the acceptability was negatively associated with the economic indicators, and positively with the RA health status (table).

	Range	Mean (SD)	Median	Correlations with GDP	Correlations with median income	Correlations with mean DAS28	Correlations with SCJ
Total number of biologics reimbursed	0–8	4.9 (3.3)	7	0.88	0.59	−0.78	−0.61
Average annual price of biologics, int.\$	14,446–61,552	28,548.1 (10,768.5)	27,632.13	−0.84	−0.75	0.75	0.72
Average acceptability score	0–10	5.1 (3.3)	2.5	−0.63	−0.37	0.69	0.71

Conclusion: European countries with lower socio-economic status seem to have less access to biologics in terms of lower availability, affordability and acceptability (more barriers), while health of RA patients is worse. This implies inequity in access for innovative care disfavoring patients in poorer societies.

Reference
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Inequalities Across 46 European Countries in Clinical Eligibility Criteria for the Start of A First (Reimbursed) Biologic in Patients with Rheumatoid Arthritis. Polina Putrik[1], Sofia Ramiro[2], Tore K. Kvien[3], Tuulikki Sokka[4], Till Uhlig[3], Annelies Boonen[5] and Equity in Clinical Eligibility Criteria for RA treatment[6]. [1]Maastricht University, Maastricht, Netherlands, [2]Academic Medical Center, University of Amsterdam, The Netherlands and Hospital Garcia de Orta, Almada, Portugal, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [5]University Hospital Maastricht, Maastricht, Netherlands, [6]European Region

Background/Purpose: In the treatment of patients with RA, strategies that include biologics have resulted in a better outcome for patients with regard to disease activity, need for surgery and work participation. Across the countries, reimbursement criteria and/or recommendations/guidelines have been formulated to regulate access to these costly treatments. The objective of this study was to explore clinical eligibility criteria for the start of a first reimbursed biologic in patients with RA and compare them across different European countries.

Methods: A questionnaire was sent via email to one representative rheumatologist in 49 countries of the European Region to collect data on the eligibility criteria for a first biologic in patients with RA, as of May 2011. First, rheumatologists were asked whether either reimbursement or clinical recommendations or both were mainly regulating prescription in clinical practice. Further information was collected on (a) minimal disease duration required, (b) number of previous DMARDs needed to be failed and (c) requirements for disease activity or severity, mandatory before the start of a biological. A simple score was developed to evaluate the level of restrictions in access to reimbursed biologics across the countries (table). This score varied between 0 and 5, the higher the score, the easier the access. Study results are presented using descriptive statistics.

Results: Forty-six countries (response rate 96%) provided data. In 10 countries (22%) no biologic was reimbursed. Among the remaining 36, Luxemburg had no regulation of access to reimbursed biologics, in 13 (36%) the reimbursement criteria were the major source of eligibility criteria, while in 7 (19%) the clinical recommendations predominated, and in 15 (42%) both reimbursement criteria and clinical recommendations were used (usually because they were similar).

Among those with at least 1 biologic reimbursed, 21 countries (58%) had no requirement for disease duration in order to initiate a biologic, and for the remaining countries a duration of 3 to 12 months was mandatory. The majority of the countries (47%) required a failure of 2 synthetic DMARDs to qualify for therapy with biologics. Thirty-one out of 36 countries specified a minimum level of disease activity that had to be fulfilled before treatment with biologics (table). Three countries (8%) had the maximum (5) eligibility score (most liberal), 19.5% had a score of 4, 19.5% a score of 3, 22% a score of 2, 28% of 1 and 3% (1 country) a score of 0 (more restrictive). Countries from Eastern Europe and former Soviet Union were more likely to be classified in the more restricted scores.

Criterion	Cut-off	Score for eligibility for biologics	Number of countries (%)
Disease duration	No limitation	1	21 (58%)
	Yes	0	15 (42%)
Disease activity	No requirement	2	5 (14%)
	DAS28≥3.2 or equivalent as major criteria	1	12 (33%)
	Stricter requirement than DAS28≥3.2	0	19 (53%)
Number of synthetic	≤1	2	15 (42%)
	2	1	17 (47%)
DMARDs to be failed>2	0	4 (11%)	

Conclusion: Clinical criteria for biologic therapy differ significantly across the countries, suggesting inequalities in access to treatment in RA. These findings should alert stakeholders to further strive for optimal standards of rheumatologic care and implement them across all European countries.

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Observation of Persistence Rates and Potential Costs Savings Associated with Certolizumab Pegol Treatment for Rheumatoid Arthritis in England, Wales and Northen Ireland Clinical Practice. Mike Russell[1], Jen Timoshanko[1], Graeme Duncan[2], Angela Spandley[1] and Samantha Roskell[3]. [1]UCB Pharma, Slough, United Kingdom, [2]Healthcare at Home Ltd, Burton on Trent, United Kingdom, [3]Rheumatology, Cannock Chase Hospital, Cannock, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) therapy in the UK is standardized by the National Institute for Health and Clinical Excellence (NICE). To be eligible for anti-TNF therapy RA patients (pts) must show inadequate response to 2 synthetic DMARDs (including methotrexate [MTX]) and high disease activity (DAS28>5.1). To continue therapy pts must show a change in DAS28>1.2 at 24 weeks (wks).[1] Certolizumab pegol (CZP) studies in RA have shown the majority of pts respond by Wk 12[2,3], and response at 12 wks is predictive of clinical outcome at 1 year[2–4]. Continued CZP therapy should be carefully reconsidered in pts who show no therapeutic benefit in the first 12 wks[5]. In the UK, CZP is available via a Patient Access Scheme (PAS), which provides the first 12 weeks of CZP free of charge. This analysis examines persistency and actual versus potential cost savings realized with a 12 wk decision with CZP.

Methods: This retrospective analysis used anonymised data from Healthcare at Home (HAH), the UK's largest home healthcare service provider. A crude unadjusted persistence rate was calculated for pts receiving CZP between March 2010 - March 2012. Persistence was defined as the percentage of pts continuing to receive deliveries of CZP with pts censored according to the date of first delivery. Treatment start was first delivery date and treatment status was determined as current or finished at specified time points (13, 26, 39, 52 weeks). Pts were defined as naive or switch (≥1 prior anti-TNF, according to HAH records). Pts who temporarily discontinued therapy were excluded. A cost analysis was performed by calculating a) the savings from the PAS and b) the potential reinvestment which could be made by removing non-responders at 12 wks versus 26 wks.

Results: This analysis included 2,737 pts receiving CZP (mean age 57 years). At 52 wks, the persistence rate was 64% in anti-TNF naive and 48% in switch pts (table). Analyzing first-line biologic drug costs only, the NHS would save ≤2,363.14 per pt in the first year if CZP were used in place of adalimumab, assuming similar persistence rates; largely due to the PAS. Stopping treatment for non-responders at Wks 12 (CZP) vs Wk 24 (adalimumab), could allow the UK NHS to re-invest ≤ 2145 per pt whilst avoiding unnecessary drug exposure.

Table. Persistence for Total population. Naive and Switch.

Duration of treatment	Persistence		
	TOTAL	Naive	Switch
13 wks	92% (N = 2,737)	93% (N = 2,032)	88% (N = 705)
26 wks	75% (N = 2,404)	78% (N = 1,717)	68% (N = 687)
39 wks	65% (N = 2,027)	69% (N = 1,392)	56% (N = 635)
52 wks	59% (N = 1,604)	64% (N = 1,030)	48% (N = 574)

Conclusion: In this UK cohort, CZP persistence was 64% at 52 wks in naive pts. Reinforcing a 12 wk treatment decision could result in more efficient spend on drugs as well as avoiding unnecessary drug exposure and delayed initiation of alternative treatment in non-responders.

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1847

Status of the Rheumatology Clinical Trials Portfolio: Data From Clinicaltrials.Gov. Ankoor Shah[1], Samuel Broderick[2], Karen Chiswell[2], Asba Tasneem[2] and John S. Sundy[1]. [1]Duke University Medical Center, Durham, NC, [2]Duke University Medical Center, Durham

Background/Purpose: In an effort to provide a comprehensive listing of clinical trials Congress initiated the creation of the ClinicalTrials.gov (CT-

.gov) registry in 1997. In 2007 the FDA Amendment Act mandated registration of most non-phase I interventional drug, biologic, and device trials. Until recently, there has been no systematic analysis of the clinical trial enterprise, either broadly or for rheumatologic diseases. As part of the Clinical Trials Transformation Initiative we analyzed the CT.gov database to describe the current state of clinical trials in rheumatology and compare these findings to other specialties.

Methods: A dataset of 96,346 studies was downloaded from CT.gov on 9/27/2010 and was restricted to 40,970 interventional studies registered between 10/2007 and 9/2010. Clinical specialists annotated medical subject heading terms and common disease terms for relevance to rheumatology. An initial dataset identified studies with ' 1 disease relevant term. Manual review of individual studies, and additional keyword searching yielded the final rheumatology study dataset (R). Studies were further divided into disease and sponsorship subcategories and comparisons were made between these sub-categories, and with non-rheumatology (NR) studies.

Results: 1,622 rheumatology trials were identified, representing 4% of the CT.gov dataset. Disease groups were classified as: osteoarthritis (24.4%), rheumatoid arthritis (19.4%), lupus/connective tissue disease (8.6%), spondyloarthritis (4.1%), scleroderma (2.3%), gout (2.2%), vasculitis (0.7%), and all others (38.2%). Median (quartiles) enrollment for R trials was 80 (35,200) compared to (64 (30,180)) for NR studies. The primary purpose was treatment in the majority of studies (86.8%). Prevention (5.0%) and diagnostic (2.3%) were less represented than in NR studies (11.1% and 4.0% respectively). 59.4% were industry-sponsored compared to 45.4% of NR studies. Biologics were used in 23.2% of R studies. There was double-blind masking in 49.0% and randomization in 75.2%, versus 32.4% and 68.6% for NR studies, respectively. 33.1% reported using a data monitoring committee (DMC) which was less than that among NR studies (40.9%). Industry sponsored studies were less likely to utilize a DMC compared to non-industry (26.1% v. 39.1%) and more likely to utilize a biologic and focus on treatment (compared to prevention and diagnosis). Only 3.6% of the rheumatology studies had posted results to the CT.gov website by date of download, compared to 2.2% among NR studies.

Conclusion: The rheumatology clinical trial enterprise represents a small number of trials in the CT.gov database between 10/2007 and 9/2010. Rheumatologic diseases with high prevalence and substantial unmet need are under represented relative to less common rheumatologic diseases. Half of clinical trials had enrollment of 80 participants or less. Double-blind masking and use of a DMC were employed in a minority of studies and only a small fraction of rheumatology studies have reported results. Our results indicate that there is an opportunity to improve the quality of clinical trials in rheumatology and initiate a policy discussion on whether resources are optimally focused on the highest priorities.

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1848

Impact of Biologics On Total Knee Replacement and Total Hip Replacement Rates in Rheumatoid Arthritis Patients: Results From US Marketscan Database. Andrew S. Koenig[1], Jack Mardekian[2] and Sameer Kotak[3]. [1]Pfizer Inc., Collegeville, PA, [2]Pfizer Inc, New York, NY, [3]Pfizer Inc., New York, NY

Background/Purpose: Joint replacement surgery patterns continue to change in patients with rheumatoid arthritis (RA), possibly reflecting the widespread adoption of disease modifying antirheumatic drugs, earlier intervention and better supportive care. In a study of a population based RA sample from Rochester, Minnesota, a decline in cumulative incidence of orthopedic surgery by decade of RA diagnosis was reported.(1) Previous analyses based on the Swedish Hip Arthroplasty Register demonstrated a decline in the proportion of total hip arthroplasties due to inflammatory joint disease from 5% during 1992–2002 to 2% in 2007.(2)

Methods: We performed a retrospective analysis of pharmacy and medical claims data from 2003–2010 in the United States utilizing the MarketScan database. Patients were required to be continuously enrolled preceding 1–3 years post RA diagnosis. We used a coding algorithm to identify all patients having a diagnosis of RA and no prior use of biologics ≤1 yr preceding the diagnosis. From this pool, we stratified patients who did

and did not receive a biologic within 6 months, 1, 2, and 3 yrs post diagnosis. We further coded the analyses to identify total hip or knee replacement events (THR/TKR) and mean days to THR/TKR in these sub-groups and estimated general population rates of THR/TKR.

Results: From 2003–2010, 90,545 patients were identified with a diagnosis of RA; mean age 56.5 yrs; majority were female (71%) with low comorbidity [Charlson Comorbidity Index (CCI) 0.77]. Of these, 10,492 (11.5%) initiated a biologic and nearly half (5,054/10,492; 48%) received the biologic ≤1 yr of diagnosis. No differences in age and other demographic variables between groups at baseline; however the biologic cohort had higher proportions of rheumatologic disease in the CCI. Proportions of THR/TKR in the non-biologic cohort were 7% vs. 11% in the more severe biologic cohort over the follow-up period (p<0.0001). In spite of the higher event rate, patients in the biologic cohort were event free for an additional mean 221 days compared to the non-biologic cohort (p<0.0001). THR/TKR event rates in the general population in MarketScan were 0.49% (484,107/98,414,730) compared to 6.91% (10,927/158,187) in the RA specific cohort (regardless of treatment).
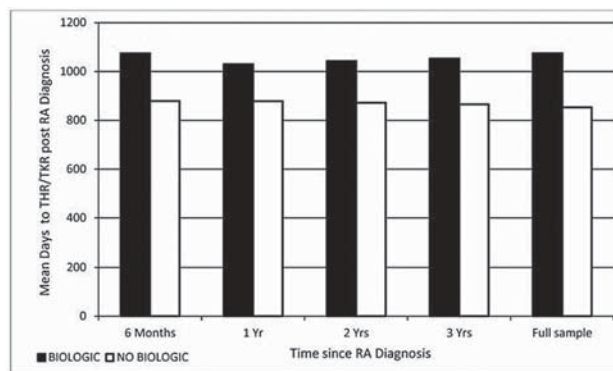
[1]da Silva E, Doran MF, Crowson CS, O'Fallon WM, Matteson EL: Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. Arthritis Rheum 2003, 49:216-220.
[2]Swedish Hip Arthroplasty Register. Annual Report 2007. Dept. of Orthopedics, Gothenburg University. [http://www.jru.orthop.gu.se/].

Conclusion: The rates of THR/TKR were slightly higher in the supposedly more severe RA population who initiated a biologic (CCI 0.88), as opposed to those who did not (CCI 0.76). The mean time to THR/TKR was significantly delayed in the biologic cohort by up to 7 months, despite the higher proportion of rheumatologic disease in CCI. These results are compatible with the extensive evidence for delayed peripheral joint damage in RA patients treated with TNF inhibitors. Results must be interpreted by acknowledging the non-randomized nature of the claims data and inability to adjust for RA severity at baseline due to lack of relevant database variables.

Disclosure: A. S. Koenig, Pfizer Inc, 3, Pfizer Inc, 1; **J. Mardekian**, Pfizer Inc, 3, Pfizer Inc, 1; **S. Kotak**, Pfizer Inc, 1, Pfizer Inc, 3.

1849

Value of Matrices Developed to Identify Early Rheumatoid Arthritis Patients with Rapid Radiographic Progression Despite Methotrexate Therapy: A Comparison of Their Performance in the Early Rheumatoid Arthritis Espoir Cohort. Bruno Fautrel[1], Benjamin Granger[2], Bernard Combe[3], Francis Guillemin[4], Alain Saraux[5] and Xavier Le Loët[6]. [1]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [2]Université Pierre et Marie Curie - Paris 6; AP-HP, Paris, France, [3]Lapeyronie Hospital, Montpellier, France, [4]Faculte de Medecin/BP 184, Vandoeuvre-les-Nancy, France, [5]Université Brest Occidentale, Brest, France, [6]Rouen University Hospital and Inserm U 905, Rouen, France

Background/Purpose: Rapid radiographic progression (RRP)—i.e., increase of the Sharp/van der Heijde score (vSHS) ≥ 5 points during the 1st year – is a marker of poor prognosis in early rheumatoid arthritis (ERA). The study aims to test the validity of five matrices have been proposed recently (ASPIRE[1], BEST[2], SWEFOT[3], ESPOIR[4], SONORA[5]).

Methods: Between 2002 and 2005, the ESPOIR cohort enrolled 813 patients with recent arthritis in at least 2 joints with 6 weeks to 6 months disease duration. During the 2 first years of follow-up, patient data were collected every 6 months and structural damage progression on X-ray was measured by the vSHS. For the purpose of the study, only patients treated

with methotrexate or leflunomide for $\geq$ 3 months within the 1st year of follow-up were selected. Baseline radiographic damage was assessed either by the present of RA erosions (at least 1 or more than 3) or vSHS value.

The validity of the different matrices, i.e., the capacity of the matrices to efficiently identify RRP patients at 1 year, was tested by Receiver Operation Curve (ROC) analysis in which the area under the curve (AUC) reflected the discriminating power of each matrix.

Results: 398 ESPOIR patients started MTX or leflunomide during the 1st year. Their main characteristics were: mean age 49.3 yrs, female 73.6%, FR+ or ACPA+ 62%, typical RA erosion 18.1% (central reading), ACR/EULAR 2010+ 86.4%, mean DAS28 5.35, mean swollen joint count 8.1, mean tender joint count 8.9, mean CRP 25.4 mg/L, mean HAQ 0.27. During the 1st year, the mean vSHS progression was 1.7 ±5.0 and 46 patients (11.6%) were classified RRP.

The performance of the ASPIRE and SWEFOT matrices displayed only moderate validity in the ESPOIR population, with AUC below 0.7 (Figure). The BEST matrix seems to perform optimally and its AUC was in the same range of the ESPOIR matrix, with an AUC of 0.79 and 0.75 respectively. The matrices using baseline vSHS value (ESPOIR+ and SONORA) displayed higher discriminating power than that using erosion information.

Figure: ROC analysis assessing the performance of the 4 matrices
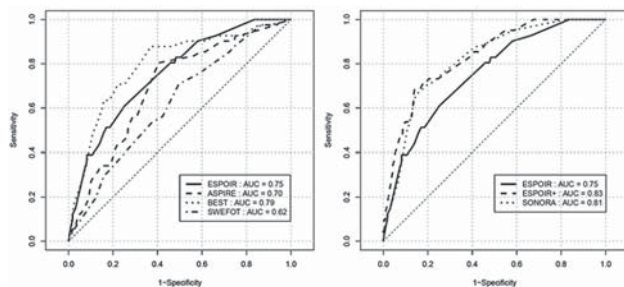
Conclusion: The BeSt matrix performs adequately in the ESPOIR cohort. However, the matrices using vSHS instead of erosion status seem to display higher discriminating power to identify ERA patients with RRP despite initial MTX or leflunomide therapy.

[1]Vastesaeger N. et al, Rheumatology(Oxford) 2009. [2]Visser K. et al, Ann Rheum Dis 2010. [3]Saevarsdottir S. et al, ACR 2011.(Abs 2513). [4]Fautrel B. et al, ACR 2011 (Abs 353). [5]Bombardier C. et al, ACR 2009.

Disclosure: **B. Fautrel**, None; **B. Granger**, None; **B. Combe**, None; **F. Guillemin**, None; **A. Saraux**, None; **X. Le Loët**, None.

1850

Association of Clinical Trial Characteristics with Positive Study Outcome Reporting in Randomized Controlled Trials of Rheumatoid Arthritis Therapy. Fatima M. Khan[1], Juan I. Lombeida[2], Horace Spencer[1], Karina D. Torralba[3], Winnie K. Pang[3] and Nasim A. Khan[4]. [1]University of Arkansas for Medical Sciences, Little Rock, AR, [2]Mercy Medical Center, Rogers, AR, [3]University of Southern California Keck School of Medicine, Los Angeles, CA, [4]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR

Background/Purpose: Randomized controlled trials (RCTs) are considered the best research design for assessing healthcare intervention. Concerns have been raised about the increased likelihood of positive RCT outcome (bias) with trial characteristics such as financial conflicts of interests (FCOIs) and inadequate methodological quality parameters reporting. Our objective was to assess whether reported trial characteristics are associated with outcome of RCTs of rheumatoid arthritis (RA) drug therapy.

Methods: We identified original, non-phase 1, parallel-group, drug therapy RCTs of RA published in English in the years 2002–3, 2006–7, and 2010–11 by searching Medline and CENTRAL databases. RCT efficacy was assessed for primary outcome as positive (statistically significant result favoring experimental intervention) or negative. RCT characteristics [experimental intervention (traditional anti-rheumatic drugs, biologics, small molecules, others), study phase (phase 2, non-phase 2), funding source (industry, non-profit), FCOIs of authors related to industry sponsor (honoraria/consultation fee, employment, research grant, stock ownership), number of subjects enrolled, study center (single, multiple), study duration, and placebo use], and reported methodological quality measures [adequate description of random sequence generation, allocation concealment, blinding, subject follow-up, intent-to-treat analysis] were assessed independently by two investigators. Univariable associations of trial characteristics and methodological quality measures with positive study outcome were assessed using Chi-square, Fisher's exact test, likelihood ratio, or t-test. Multivariable logistic regression (MLR) was performed by including funding source and all variables associated with positive outcome with P≤0.1

Results: 146 eligible RCTs were identified. Efficacy outcome could be assessed for 125 (85.6%) RCTs. Studies were excluded for the following reasons: primary outcome safety (11), no intervention declared experimental a priori(10). Positive outcome was noted in 86 (68.8%) RCTs. Non-phase 2, higher number of enrolled patients and author FCOI (honoraria/consultation fee) increased likelihood, while adequate random sequence generation description decreased this likelihood of positive outcome on univariable analysis. Author FCOI (honoraria/consultation fee), number of enrolled patients, and adequate description of randomization were independently associated with positive outcomes in MLR analysis (Table 1).

Table 1. Univariable and multivariable analysis of clinical trial characteristics and study outcome.

Variable	Referent	Univariable analysis		Multivariable analysis	
		OR (95% CI)*	P	OR (95% CI)*	P
Funding source, industry**	Non-profit	0.89 (0.40–1.97)	0.769	0.53 (0.18–1.53)	0.241
Honoraria/consulting fee receipt by author, yes	No	2.41 (0.99–5.88)	0.043	3.24 (1.06–9.88)	0.039
Non-phase 2	Phase 2	3.45 (1.41–8.45)	0.005	2.68 (0.88–8.11)	0.082
Number of patient enrolled***	Δ 1	1.59 (1.09–2.32)	0.013	1.73 (1.11–2.69)	0.016
Duration of study, months***	Δ 1	1.49 (0.95–2.32)	0.075	1.28 (0.78–2.10)	0.321
Adequate reporting of random sequence generation, yes	No	0.40 (0.18–0.89)	0.022	0.32 (0.13–0.78)	0.013

*OR: odds ratio; CI: confidence interval
*RCTs with partial or complete funding by industry were considered as industry funded, while those with explicit non-profit source or unspecified funding source were considered non-profit.
**log transformed

Conclusion: Certain trial characteristics (number of enrolled subjects, author's receipt of honoraria/consultation fee) and reported trial quality measure (random sequence generation description) were independently associated with positive outcomes of RA drug therapy RCTs.

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1851

Exploring the Relationship of Anti-Tumor Necrosis Factor Drugs and Methicillin Resistant Staphylococcus Aureus Nasal Colonization in Patients with Rheumatologic Conditions and Psoriasis. Daniel E. Kreutz[1], Santosh P. Reddy[1], Guy P. Fiocco[2], Colleen Colbert[1] and Juhee Song[1]. [1]Scott & White Healthcare/Texas A&M University, Temple, TX, [2]Scott & White Clinic, Temple, TX

Background/Purpose: Infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is a source of significant morbidity/mortality. Healthcare entities spend large amounts to prevent spread of MRSA. Most MRSA colonization literature is for surgical inpatients, with little exploration of the possible influence of immune-modifying drugs on colonization. These drugs are being used more commonly in treatment of chronic conditions, such as rheumatologic diagnoses. This study attempted to identify the influence of Tumor Necrosis Factor inhibitor (anti-TNF) drugs on MRSA carrier state in patients with diagnoses of psoriasis, psoriatic arthritis, rheumatoid arthritis, or ankylosing spondylitis.

Colonization with MRSA leads to greater risk of infection with MRSA.Screening and intervention decrease blood borne infections, leading to use of screening programs.Studies in various environments have attempted to describe the carriage rate for MRSA, now estimated to be 1.2–14%.

There has been some investigation into the relationship between MRSA colonization and immunosuppression, but it has been limited to transplant patients, cancer patients, and those with HIV.Currently there are no data on the relationship between immunosuppresive drugs and MRSA colonization in those being treated for rheumatologic conditions and psoriasis.

Methods: Medical records of patients admitted to two large referral hospitals between 1/1/07 and 3/31/10 were reviewed. All admitted patients 18 years and older with psoriasis, psoriatic arthritis, rheumatoid arthritis, or ankylosing spondylitis during this period were included for retrospective chart review (1001 persons). Of these, 436 were screened for nasal MRSA during the study period. Demographics, comorbidities and length of stay were noted

as was information on treatment of their conditions and MRSA screen result. The rate in this group was compared to known MRSA rate for all patients screened in the two hospitals for the period (6.7%).

Results: Records from 436 patients were used; 10 (2.3%) had psoriatic arthritis, 15 (3.4%) had ankylosing spondylitis, 72 (16.5%) had psoriasis, and 341 (78.2%) had rheumatoid arthritis. MRSA colonization was noted for 53 (12.2%) patients, which is much higher than the overall rate of 6.7% for adults. A TNF inhibitor was in the medical regimen for 54 (12.4%) patients. Of those prescribed anti-TNF drugs, 11.1% were MRSA positive. The study population with MRSA tended to have a longer length of stay (p = 0.0529), and come from a nursing home (27.5%). There was a strong association between nursing home residence and MRSA result (p = 0.0003).

Conclusion: Patients with psoriasis and rheumatologic conditions had a higher rate of MRSA colonization than the general patient population at these referral centers. Patients treated with anti-TNF drugs were no more likely than those being treated with traditional immune modulating agents to have a positive MRSA screen. Those patients coming to the hospital from a nursing facility were more likely to have a positive MRSA screen.

Disclosure: **D. E. Kreutz**, None; **S. P. Reddy**, None; **G. P. Fiocco**, None; **C. Colbert**, None; **J. Song**, None.

1852

Tumour Necrosis Factor-Alpha Antagonists and Alopecia: A Case/Non-Case Study in a Nationwide Pharmacovigilance Database. Johana Béné[1], Guillaume Moulis[2], Marine Auffret[1], Claire Fessier[1], Guillaume Lefevre[3] and Sophie Gautier[1]. [1]Lille University Hospital, Lille Pharmacovigilance Regional Centre, Lille, France, [2]Toulouse University Hospital, Clinical Pharmacology Department, University of Toulouse, UMR INSERM-UPS 1027, Toulouse, France, [3]Lille University Hospital, Internal Medicine Department, Lille, France

Background/Purpose: Cases of alopecia occurring on TNF-alpha antagonists have been described. Nevertheless, no epidemiological study has been conducted to assess the link between TNF-alpha antagonists exposure and occurrence of alopecia. The aim of this study was to describe the cases of TNF-alpha antagonist-related alopecia reported in the French Pharmaco-Vigilance Database (FPVD), and to assess the putative association.

Methods: All spontaneous reports of TNF-alpha antagonist-related alopecia recorded in the FPVD between January 2000 and April 2012 were described. We conducted disproportionality analyses (case/non-case method) to assess the link between alopecia and exposure to TNF-alpha antagonists. Cases were all reports of alopecia recorded during the study period. Non-cases were all other reports recorded during the same period. Exposure to TNF-alpha antagonists was searched in cases and non-cases. Reporting odds ratios (ROR) were calculated to assess the association. To assess the validity of the method we used exposure to docetaxel (well-known as alopecia inducer) as positive control and to acetaminophen as negative one.

Results: During the study period, 283 658 spontaneous reports were colligated in the FPVD, of which 4742 (1.7%) involved TNF-alpha antagonists. Among these 4742 reports, 51 (1.1%) were alopecia (mainly, alopecia areata): 18 involved infliximab, 17 adalimumab, 15 etanercept and 1 certolizumab. Male:female sex-ratio was 0.18 and mean age was 39 years. Seventeen patients were treated for rheumatoid arthritis, 13 for ankylosing spondylitis, 11 for Crohn disease and 6 for psoriasis. Mean delay from TNF-alpha antagonist introduction to alopecia onset was 11.3 months (extremes: 4 days–8 years). An improvement was observed in 12 cases after TNF-alpha antagonist withdrawal (available data for 24 reports). Association between TNF-alpha antagonist exposure and alopecia was significant for all TNF-alpha antagonists pooled (ROR=3.0; 95%CI [2.3–4.0]), as well as for infliximab, ROR=2.0; 95%CI [1.2–3.1], adalimumab, ROR=4.7; 95%CI [2.9–7.7] and etanercept, ROR=3.3; 95%CI [2.0–5.4]. The ROR with docetaxel was 29.9; 95%CI [25.3–35.5] and with acetaminophen was 0.3; 95%CI [0.2–0.4].

Conclusion: These results suggest a link between TNF-alpha antagonists exposure and occurrence of alopecia. A channeling bias cannot be excluded, but improvement in half of the cases after TNF-alpha antagonist withdrawal is a strong argument for the drug responsibility.

Disclosure: **J. Béné**, None; **G. Moulis**, None; **M. Auffret**, None; **C. Fessier**, None; **G. Lefevre**, None; **S. Gautier**, None.

1853

Rheumatoid Arthritis Patients' Experiences of Medication Side Effects and Subsequent Decision Making about Medications. Yomei Shaw[1], Ilinca D. Metes[2], Susan L. Zickmund[2], Dawn McBride[2], Kelly A. Reckley[2], Stephen R. Wisniewski[1], Larry W. Moreland[2], Mark S. Roberts[1] and Marc C. Levesque[2]. [1]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA

Background/Purpose: Medication adherence in rheumatoid arthritis (RA) patients can be influenced by their previous experiences with medication side effects. Negative experiences may lead patients to become fearful towards medications, increasing rates of non-adherence and rejection of physician recommendations to add medication therapy. To better understand how patients' experiences of adverse drug reactions affect perceptions of medication risk and subsequent decisions to take recommended medications, we conducted an analysis of patient narratives of their experiences with adverse drug reactions due to medications for RA. Our goal was to describe features of RA patients' experiences of medication side effects, and to compare narratives of patients who self-report discontinuing medications on their own or rejecting physician recommendations for medications ('Non-adherent' group) with narratives of patients who do not ('Adherent' group).

Methods: A qualitative analysis was conducted of transcripts from semi-structured interviews with 20 RA patients. Interviews were from a pilot study testing patient education materials for usage in the RA Comparative Effectiveness Research (RACER) registry (n = 1,000). Subjects were recruited from RACER enrollees treated at a participating clinic. During interviews, subjects were asked whether they had ever experienced side effects due to their medications for RA, and if so, to describe the side effects. Comments of all subjects describing any experiences of side effects were analyzed. A coding scheme was developed to index statements about: 1) medications in general, 2) the side effects experienced and relevant medications, 3) the patient-provider relationship, and 4) RA and treatment related information. The first 2 authors coded the interview transcripts separately, then discussed and reached a consensus on assignment of codes for each transcript. Codes for patients in the Non-adherent group were compared to the Adherent group.

Results: Fourteen of 20 patients reported side effects. The inter-observer agreement was high (mean kappa = 0.90). Among the 14 subjects with side effects, subjects in the Non-adherent group (n = 6) and Adherent group (n = 8) reported a similar mean number of side effects which they perceived as important (2.83 vs. 2.13) and non-important (0.67 vs. 1.25). However, patients in the Non-adherent group were more likely than patients in the Adherent group to discuss fear (66.7% vs. 12.5%), unacceptability of side effects (66.7% vs. 25%), unsatisfactory resolution of side effects (66.7% vs. 25%), and negative aspects of medications (83.3% vs. 25%).

Conclusion: Fear, viewing side effects as unacceptable, dissatisfaction with how side effects were resolved, and negative perceptions of medications played a more central role in the experiences of patients who discontinued medications on their own or rejected physician recommendations, compared to patients who did not. This suggests that interventions to address these patient concerns may be critical for improving patient adherence to medications.

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1854

The Safety of Anti-TNF Biologic Agents in Rheumatoid Arthritis - A Meta-Analysis of 35 RCTs. Tzuyu Lin[1], Tatyana Shamliyan[1], Hyon Choi[2], Young Hee Rho[2] and Karen Kuntz[1]. [1]Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, MN, [2]Boston University School of Medicine, Boston, MA

Background/Purpose: The objectives of this systematic review were to study and update the safety of anti-TNF agents. We examined whether etanercept (ETN), compared to the anti-TNF antibody therapies, infliximab (INF) and adalimumab (ADA), had an inverse impact on adult patients with rheumatoid arthritis (RA) in terms of malignancy, serious adverse events (SAEs), serious infection, and discontinuation due to adverse events (AEs).

Tuesday, November 13

Methods: We conducted a systematic-literature review of randomized controlled trials (RCTs) that studied one of the three biologics used for rheumatoid arthritis and reported on our pre-specified adverse outcomes of malignancy, SAEs, serious infections, and discontinuation due to AEs. We searched various databases including MEDLINE® via OVID and PubMed®, the Cochrane Library, Google Scholar, and ClinicalTrials.gov, and further mined the reference lists from systematic reviews and original publications to identify all English-language studies published from January 1, 1990 until September 30, 2011. In addition, we searched the US Food and Drug Administration (FDA) database to review drug approval reports that could provide eligible trials. The search strategy and data extraction processes were duplicated by independent reviewers. For the meta-analysis, we performed random effect inverse variance, maximum-likelihood estimation (MLE), arcsine transformed, and Bayesian models. We abstracted the studies with 0 events in both arms and used software default correction coefficients for 0 events or missing data. Furthermore, we compared the results from randomized trials with published large nationally representative cohort studies and administrative databases.

Results: Thirty-five trials met our inclusion criteria, including 5,524 patients who received anti-TNF biologic agent treatment and 3,257 patients who received MTX/placebo. The risk of malignancy in patients treated with INF was significantly higher than that among those treated with MTX (risk difference=0.02 [95% CI, 0.00 to 0.05]) in the arcsine transformed model. The risk of serious infections in patients treated with ADA or INF was significantly higher than that among those treated with MTX or placebo (OR=7.8 and 2.07; ARD=0.03 and 0.03), both in the Bayesian and arcsine transformed models (Table). In contrast, patients treated with ETN tended to have non-significant lower risks of SAEs, serious infections, and discontinuation (ORs=0.84, 0.71, and 0.84, respectively) (Table).

Table. GRADE evidence profile: Anti-TNF agents for adults with rheumatoid arthritis

No. of studies (Design)	Risk of bias	Inconsistency	Imprecision	Indirectness	Active arm	Control arm	Bayesian odds ratio (95% CI)	Arcsine transformed risk difference (95% CI)	Number needed to treat (NNT) (95% CI)	Attributable events (95% CI)	Strength of evidence
Serious adverse events											
3 (RCT)	Low	No serious inconsistency	No	No	Adalimumab 58/544	Placebo 21/220	1.1 (0.59, 2.06)	0.01 (−0.04, 0.06)	Not Sig.	Not Sig.	High
2 (RCT)	Low	No	No	No	Adalimumab + MTX 16/108	MTX 11/105	1.53 (0.48, 5.28)	0.12 (−0.04, 0.34)	Not Sig	Not Sig	High
2 (RCT)	Low	No	No	No	Etanercept + MTX 62/505	MTX 71/496	0.84 (0.40, 1.72)	0 (−0.04, 0.04)	Not Sig	Not Sig	High
5 (RCT)	Low	No	No	No	Infliximab + MTX 223/1897	MTX 89/902	1.06 (0.75, 1.51)	−0.01 (−0.04, 0.02)	Not Sig.	Not Sig.	High
Malignancy											
2 (RCT)	Low	No	No	No	Adalimumab 0/479	Placebo 2/157	0 (0.00, 7.59)	−0.01 (−0.01, 0.00)	Not Sig.	Not Sig.	High
2 (RCT)	Low	No	No	No	Adalimumab + MTX 4/301	MTX 4/289	1.07 (0.19, 7.59)	0.03 (−0.01, 0.18)	Not Sig.	Not Sig.	High
3 (RCT)	Low	No	No	No	Etanercept 14/861	MTX 5/673	2.28 (0.77, 7.71)	0 (−0.01, 0.01)	Not Sig.	Not Sig.	High
2 (RCT)	Low	No	No	No	Etanercept + MTX 10/321	MTX 5/327	2.18 (0.59, 9.37)	0 (−0.01, 0.02)	Not Sig	Not Sig	High
5 (RCT)*	Low	yes	No	No	Infliximab + MTX 10/1169	MTX 3/473	1.35 (0.35, 7.15)	0.02 (0.00, 0.05)	19 (0.48)	53 (21, 2.991)	Moderate
Serious infections											
2 (RCT)[a]	Low	No	No	No	Adalimumab 17/479	Placebo 1/157	7.8 (1.12, 198.6)	0.03 (0.00, 0.07)	30 (4, 72)	33 (14, 239)	High
2 (RCT)	Low	No	No	No	Adalimumab + MTX 20/475	MTX 7/356	2.21 (0.72, 7.77)	0 (−0.02, 0.02)	Not Sig.	Not Sig.	High
2 (RCT)	Low	No	No	No	Etanercept + MTX 30/321	MTX 37/327	0.71 (0.20, 1.90)	−0.02 (−0.06, 0.03)	Not Sig.	Not Sig.	High
5 (RCT)*	Low	No	No	No	Infliximab + MTX 96/1853	MTX 21/829	2.07 (1.18, 3.73)	0.03 (0.01, 0.04)	25 (9, 44)	40 (23, 115)	High
Discontinuation due to adverse events											
4 (RCT)	Low	No	No	No	Adalimumab 39/763	Placebo 10/276	1.5 (0.70, 3.46)	0.02 (−0.01, 0.05)	Not Sig.	Not Sig.	High
3 (RCT)	Low	No serious inconsistency	No	No	Adalimumab + MTX 51/703	MTX 17/335	1.24 (0.47, 2.68)	0.02 (−0.01, 0.08)	Not Sig	Not Sig	High
2 (RCT)	Low	No	No	No	Etanercept + MTX 82/638	MTX 60/445	0.76 (0.40, 1.38)	0.02 (−0.02, 0.07)	Not Sig.	Not Sig.	High
2 (RCT)	Low	No	No	No	Etanercept + MTX 20/321	MTX 24/327	0.84 (0.33, 2.14)	0.01 (−0.03, 0.05)	Not Sig	Not Sig	High
5 (RCT)	Low	No	No	No	Infliximab + MTX 103/1897	MTX 26/902	1.48 (0.65, 2.91)	0 (−0.01, 0.02)	Not Sig	Not Sig	High

Conclusion: The findings of this meta-analysis suggest potential differences in adverse outcomes among ADA-, INF-, and ETA-treated RA patients. The risk of malignancy may be increased among INF-treated RA patients, whereas the risk of serious infection may be increased ADA- or INF-treated patients. These findings call for further post-marketing surveillance to clarify these risks with longer term exposure.

1855

Prevalence of Potential Drug-Drug and Drug-Condition Interactions in Fibromyalgia Patients Newly-Initiating Pregabalin or Duloxetine.

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Background/Purpose: Drug-drug and drug-condition interactions (DDI/DCI) can present a significant challenge to the appropriate prescribing of drugs. The risk of DDI/DCI may be elevated in patients who are treated with polypharmacy or have many comorbid conditions, which is often the case in fibromyalgia (FM) patients. This study quantified the prevalence of potential DDI/DCI in FM patients newly-initiating either pregabalin or duloxetine.

Methods: Retrospective cohort study using a large U.S. administrative claims database. Studied patients had newly-initiated either pregabalin or duloxetine between 7/1/2008–10/1/2010 (initiation date=index), were aged ≥18 years at index, had continuous insurance enrollment for ≥12 months pre-index (pre-period) and ≥6 months post-index (post-period), and had ≥1 inpatient or ≥2 outpatient medical claims with a diagnosis of FM (≥1 of which was incurred ≤60 days prior to or on index). Patients were excluded if during the pre- to post-period they resided in a long-term care facility for ≥90 total days or had evidence of epilepsy, post-herpetic neuralgia, transplant surgery, or cancer.

Potential DDI were measured using software (DRUG REAX) which identified instances in which prescriptions that carry a potential for DDI with pregabalin or duloxetine were filled within 180 days before to 30 days after index, with days supply of the potentially interacting drug extending beyond index. Potential DCI were medical conditions listed in the Contraindications and Warnings and Precautions sections of the prescribing information for pregabalin and duloxetine. With the assistance of medical coders, each DCI was assigned an administrative claims-based identification algorithm. The presence of potential DCI was measured during the pre-period. Chi-squared tests compared the prevalence of potential DDI/DCI across the pregabalin and duloxetine initiators.

Results: Study sample comprised 7,751 pregabalin and 7,785 duloxetine initiators; mean age 49 years, 88% female. Among pregabalin initiators, 1.4% had ≥1 potential pregabalin DCI, the most common of which was dizziness (0.9% of patients); none had potential pregabalin DDI. Among duloxetine initiators, 67% had ≥1 potential duloxetine DDI/DCI, largely driven by concomitant drugs carrying a potential for major (45% of patients) or moderate (35% of patients) duloxetine DDI; the most common of which were with tramadol (19% of potential major DDI) and amitriptyline (16% of potential moderate DDI). The prevalence of potential DDI/DCI was significantly different across pregabalin and duloxetine initiators (p<0.001). Of the 107 pregabalin initiators with ≥1 potential pregabalin DCI, 17% had no potential duloxetine DDI/DCI. Of the 5,184 duloxetine initiators with ≥1 potential duloxetine DDI/DCI, 98% had no potential pregabalin DDI/DCI.

Conclusion: In FM patients initiating pregabalin or duloxetine, the prevalence of potential duloxetine DDI/DCI was substantially higher than that of pregabalin. Most duloxetine initiators with a potential duloxetine DDI/DCI had no potential pregabalin DDI/DCI. These findings may have implications to the appropriate prescribing of drugs for the treatment of FM.

1856

Burden of Adverse Events Associated with Immunosuppressant Therapy for the Treatment of Systemic Lupus Erythematosus: A Systematic Literature Review.

Alan Oglesby[1], Arthur Weinstein[2], Greg Dennis[3], Alissa Shaul[4], Tiffany Pokora[4], Clark Paramore[5], Lael Cragin[6] and Siva Narayanan[3]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]Washington Hospital Center, Washington, DC, [3]Human Genome Sciences, Inc., Rockville, MD, [4]United BioSource Corporation, Bethesda, MD, [5]United BioSource Corporation, Lexington, MA, [6]United BioSource, Bethesda, MD

Background/Purpose: Past systematic literature reviews on adverse events (AEs) associated with immunosuppressants in patients with systemic lupus erythematosus (SLE) focused mostly on cyclophosphamide (oral: CYC; IV: IVC) and mycophenolate mofetil (MMF). The aim of this research

is to quantify the incidence of AEs, identify discontinuation rates due to AEs and resource use and cost associated with AEs from CYC/IVC, MMF, azathioprine (AZA), methotrexate (MTX), and cyclosporine (CsA) in SLE patients.

Methods: A systematic review of English-language, MEDLINE- and EMBASE-indexed literature published between January 1980 and September 2011 was conducted using terms related to SLE, AEs, discontinuation, resource use and costs. After excluding case reports, case series, non-systematic reviews, studies of fewer than 50 patients, and articles without abstracts, 38 eligible non-review articles were identified (14 randomized controlled trials (RCTs) & 22 observational studies (OBS); results are presented here.

Results: The development of AEs ranged from 42.8% to 97.3%. Commonly noted AEs are shown in the table. Discontinuation rates due to AEs were 1.4–13% in short-term (<12 months) RCTs, 2.3–44.4% in long-term (>12 months) RCTs, and 0–21.8% in OBS. Eight studies reported resource use in terms of hospitalizations due to AEs; however, frequency measures used to report hospitalization varied among the studies resulting in an inability to make comparisons between studies. No studies reported costs associated with AEs.

Table. Summary of Commonly Reported AEs by Intervention

	>1 AE	Infections	GI	Amenorrhea and/or Ovarian Complications	Hematological	Death
AZA						
RCTs (n=7)	NA	2.4–42.4%	3.2–21.4%	8.0–36.0%	6.0–50.0%	0.0–25.0%
OBS (n=3)	NA	NA	1.3%	1.4–5.6%	16.7%	NA
IVC						
RCTs (n=8)	95.0%	11.8–77%	29.4–66.7%	2.2–56.3%	1.4–38.7%	2.7–20%
OBS (n=13)	57.5–65.0%	12.5–67.9%	18–58.8%	1.9–58%	2.5–7.7%	3.0–20%
Oral CYC						
RCTs (n=3)	NA	33–40%	3.2%	36.0–71.0%	25.8%	6.5–22.2%
OBS (n=5)	NA	26–61%	7.0%	28.0–37.0%	7.0%	NA
CsA						
RCTs (n=2)	NA	6.4–19.4%	17.0–30.6%	N/A	11.1–38.3%	4.3%
OBS (n=1)	62.5%	NA	3.9%	NA	NA	NA
NA: Not Available						
MTX						
RCTs (n=1)	93.0%	4.9%	56.1%	NA	26.8%	NA
OBS (n=0)	NA	NA	NA	NA	NA	NA
MMF						
RCTs (n=5)	96.2–97.3%	12.5–68.5%	9.1–61.4%	0–6%	0.0–21.7%	1.9–5.0%
OBS (n=5)	42.8–66.7%	3.9–44.4%	4.2–38.9%	NA	0.5–5.6%	NA

Conclusion: The development of AEs associated with immunosuppressant medications in SLE patients was consistently high as reported in the SLE literature, while discontinuation due to these AEs varied from 0% to 44%. Studies describing costs and resource use associated with these AEs were sparse and warrant further study.

Disclosure: A. Oglesby, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **A. Weinstein**, HGS, Genentech, Savient, Pfizer, 2, HGS, GSK, Pfizer, 5, HGS, GSK, 8; **G. Dennis**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **A. Shaul**, United BioSource Corporation, 3; **T. Pokora**, United BioSource Corporation, 3; **C. Paramore**, United Biosource Corporation, 3; **L. Cragin**, United BioSource Corporation, 3; **S. Narayanan**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3.

ACR/ARHP Poster Session C
Fibromyalgia and Soft Tissue Disorders
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

1857

Identifying Core Symptom Domains in the Fibromyalgia Impact Questionnaire: Principal Component Analysis of Data From Milnacipran Clinical Studies. Philip Mease[1], Robert M. Bennett[2], Robert H. Palmer[3] and Yong Wang[3]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Oregon Health & Science Univ, Portland, OR, [3]Forest Research Institute, Jersey City, NJ

Background/Purpose: The Fibromyalgia Impact Questionnaire (FIQ) is a multidimensional instrument that encompasses many of the core domains recommended by OMERACT for evaluation in fibromyalgia (FM) clinical trials, including pain, tenderness, fatigue, global wellbeing, functioning, sleep disturbance, depression, anxiety, and stiffness. In randomized clinical studies, significant decreases in FIQ total scores were found with milnacipran (MLN) vs placebo (PBO), indicating overall improvements in FM severity with this treatment. A Principal Component Analysis (PCA) of data from MLN clinical studies was conducted to determine which FIQ items may be most relevant to FM patients and to further evaluate the effects of MLN on these specific items.

Methods: FIQ data were pooled from 3 double-blind trials in which FM patients were randomized to MLN 100 mg/d (n=1139), MLN 200 mg/d (n=837), or PBO (n=1133). For the PCA analysis, correlations were performed among all FIQ items based on changes from baseline in all patients receiving either MLN or PBO. Principal components with optimally weighted variables were then extracted to identify groups of FIQ items that accounted for most of the variance in FIQ results. Mean changes in FIQ scores were analyzed to evaluate whether items in the extracted components discriminated the effects of MLN treatment in this study population.

Results: Three independent groups of FIQ items were identified by PCA: Component 1 ("Core Symptoms") primarily composed of FIQ items 2 (feel good), 4 (do job), 5 (pain), 6 (fatigue), 7 (rest), and 8 (stiffness); Component 2 ("Depression/Anxiety") primarily composed of FIQ items 9 (anxiety) and 10 (depression); and Component 3 ("Physical Function") primarily composed of FIQ items 1 (physical impairment) and 3 (work missed). Each FIQ item above represents a meaningful loading with at least a correlation of 0.4 with its component. Component 1 accounted for 37.3% of the total variance in the data, suggesting that this selected set of FIQ items has the strongest relevance in FM patients. Components 2 and 3 accounted for 17.5% and 17.2% of the total variance, respectively, also indicating clinical relevance. Mean changes in FIQ by treatment group indicated significant improvements with MLN ($p<.01$; both doses vs PBO) for all FIQ items in Components 1 and 2; discrimination of treatment effect was less consistent with the FIQ items in Component 3.

Conclusion: This PCA analysis of the FIQ resulted in 3 independent components of FM symptom domains. In the population of FM patients included in this analysis, improvements in FIQ scores were largely explained by core FM symptoms, including pain, fatigue, global wellbeing, and stiffness. Independent of these core symptoms, depression/anxiety, and physical functioning also explained a meaningful portion of the FIQ improvement. Additionally, treatment with MLN was associated with improvements in all of the items in these symptom groups.

Disclosure: P. Mease, Forest Laboratories, 2, Forest Laboratories, 5, Forest Laboratories, 8; **R. M. Bennett**, Forest Laboratories, 9; **R. H. Palmer**, Forest Laboratories, 3; **Y. Wang**, Forest Laboratories, 3.

1858

Hypervigiliance in Fibromyalgia. Robert S. Katz[1], Ben J. Small[2], Susan Shott[1] and Sharon M. Ferbert[3]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical School, Chicago, IL, [3]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL

Background/Purpose: Patients with fibromyalgia syndrome (FMS) experience severe chronic pain and usually are tender to touch. They are hyperactive to weather changes and stress. Do FMS patients perceive physical pain the way they are hypersensitive to their environment? Are FMS patients more likely to be hypervigilant? Hypervigilance is a symptom associated with post-traumatic stress disorder, experience an exaggerated sense of threat in their surroundings that is disproportionate to reality. They are easily set off and startled by mild stimuli and feel anxious in public.

Methods: 128 office patients with fibromyalgia (FMS) or rheumatoid arthritis (RA) (111 women, 17 men; mean age 51 ± 13) completed a questionnaire about hypervigilance symptoms. 100 patients had FMS and 28 had RA. The chi-square test of association and Fisher's exact test were used to compare the responses of FMS and RA patients, with a two-sided 0.05 significance level. As a part of an Internet survey administered by the volunteer community fibromyalgia organization AFFTER, 763 female self-identified FMS patients and 115 female controls without FMS responded to questions asking if they experience the symptoms common to hypervigilance. Only women's responses were analyzed to eliminate confounding by gender. Percentages were compared using the chi-square test of association with a 0.05 significance level.

Results: FMS patients were more likely than RA patients to report hypervigilance symptoms: waking up more than once during the nights, FMS 75.0%, RA 46.4% (p = 0.004); feeling uncomfortable in crowded places, FMS 57.6%, RA 25.0% (p = 0.002); feeling uncomfortable if people are standing behind them, FMS 33.0%, RA 10.7% (p = 0.021); and easily startled, FMS 59.4%, RA 29.6% (p = 0.006)

In the Internet questionnaire: The mean respondent age was 49.8 ± 11.4 years. 73.9% of FMS and 45.4% of controls were easily startled (p < 0.001).

57.4% of FMS and 30.2% of controls reported that they did not feel at ease around strangers (p < 0.001). 77.2% of FMS reported feeling uncomfortable in crowded places, versus to 42.7% of controls (p < 0.001). 44.9% of FMS and 16.5% of controls reported feeling uncomfortable if people are standing behind them (p < 0.001). For, easily "let their hair down", only 39.1% of FMS said yes, versus 66.0% of controls (p < 0.001). 32.7% of FMS and 15.5% of controls do not find it easy to trust people (p = 0.001). Easy for other people to pull the wool over their eyes, FMS responded yes (45.9%) more often than controls (32.0%) (p = 0.009). 32.5% of FMS and 11.3% of controls found themselves disliking people for no reason (p < 0.001). 75.0% of FMS and 21.6% of controls had trouble falling asleep(p < 0.001). 86.8% of FMS said they wake up more than once a night to 48.5% of controls (p < 0.001).

Conclusion: Results suggest that FMS patients are more aware of social and environmental stressors and more likely to be hypervigilant. They have trouble sleeping and are more easily startled. They are less likely to trust their surroundings. Hypervigilance might confer a survival advantage in threatening circumstances, but the hyper-reactivity associated with the condition could also be associated with the central sensitization of pain and dysesthesias, insomnia and other symptoms associated with FMS.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **S. Shott**, None; **S. M. Ferbert**, None.

1859

The Polysymptomatic Distress Scale and the Effect of Age On Polysymptomatic Distress and Fibromyalgia: A Survey in a Representative Population Sample. Winfried Häuser[1], Frederick Wolfe[2], Johannes Rasker[3], Elmar Brähler[4] and Heide Glaesmer[4]. [1]Technische Universität München, Munich, Germany, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]University Twente, Enschede, Netherlands, [4]University of Leipzig, Leipzig, Germany

Background/Purpose: Recent advances in the definition of the fibromyalgia syndrome (FM) have led to the development of the polysymptomatic distress (PSD) scale, providing a quantitative measure of the PSD continuum and an alternative definition of fibromyalgia. We examined PSD and FM in the general population.

Methods: We studied a representative random sample of 2,322 subjects from the German general population between the ages of 20 and 90 years. Patients completed the widespread pain index (WPI) and measures of fatigue, somatic symptom intensity, depressed mood and the Short Form Health Survey SF-12, including physical function, bodily pain, and vitality. The effect of age was assessed with quantile regression at the 25th, 50th, 75th and 95th percentiles, and the mediated effect of age with 2-stage least squares (2SLS) instrumental variable regression.

Results: The PSD score was substantially skewed to the right with a mean and median of 5.3 (SD 4.6) and 3.8. All FM-related variable scores worsened with age and with increases in PSD. Age explained 11% of the variance of PSD, but the effect of age was mediated through bodily pain. In quantile regression of PSD on age, PSD increased 50% faster in patients in the 75th and 95th percentiles of PSD than the 50th percentile. Abnormal somatic symptom intensity scores and widespread pain appeared at the 80th percentile of PSD, cutpoints for somatization and depressive distress at the 85th percentile, the WPI criterion for FM at the 90–95th percentile, and the PSD FM criteria and FM diagnosis at the 95th–100th percentile of PSD.

Table 1. Values of key covariates at percentiles of polysymptomatic distress (PSD).

Percentile of PSD	PSD	WPI	VAS Fatigue	SF12 PCS	SF12 PF	SF12 BP	Age	PHQ 15	PHQ9	FMS (%)	WP (%)
>0–5	0.2	0.0	0.0	57.0	99.7	98.7	41.1	0.4	0.3	0.0	0.0
>5–20	1.1	0.1	0.9	56.1	98.7	97.7	40.8	0.7	0.9	0.0	0.0
>20–35	2.0	0.3	1.7	55.3	97.3	94.8	45.2	1.2	1.1	0.0	0.0
>35–40	2.9	0.8	2.2	54.1	95.3	92.6	45.3	2.1	2.0	0.0	0.0
>40–50	3.8	1.3	2.7	52.4	90.9	88.8	47.1	2.8	2.1	0.0	0.0
>50–55	4.7	1.8	3.2	52.6	92.5	87.7	49.8	3.0	2.4	0.0	0.0
>55–65	5.6	2.1	3.9	51.6	89.8	86.2	49.6	3.6	2.9	0.0	0.0
>–65–70	6.5	2.6	4.4	50.8	87.3	83.5	51.5	4.6	3.5	0.0	0.0
>70–75	7.4	3.1	4.9	48.5	77.7	75.0	54.0	4.6	4.1	0.0	0.0
>75–80	8.3	4.0	5.0	49.0	78.2	77.5	53.2	*5.1*	4.5	0.0	*2.0*
>80–85	9.2	4.9	5.1	44.8	68.6	67.9	59.3	*6.3*	5.2	0.0	11.4
>85–90	10.5	5.9	5.5	44.6	64.0	64.1	57.6	6.7	5.8	0.0	24.1
>90–95	12.9	*7.9*	*6.2*	42.2	57.6	56.1	60.6	8.3	6.6	0.0	53.4
>95–100	*18.7*	13.8	6.6	37.8	46.0	43.1	64.3	11.3	8.2	*100.0*	100.0
Mean	5.2	2.5	3.0	51.6	86.8	84.7	48.9	3.4	2.8	4.2	8.8
Correlation With PSD	1.0	0.91	0.78	0.63	0.61	0.64	0.35	0.75	0.61		

Conclusion: The PSD scale supports the hypothesis that FM represents the end of a continuum of distress. Age is causally associated with PSD and FM, but is mediated primarily by pain. The effect of age on PSD and fibromyalgia is greatest in persons with more than average PSD.

Disclosure: W. Häuser, None; **F. Wolfe**, None; **J. Rasker**, None; **E. Brähler**, None; **H. Glaesmer**, None.

1860

Fibromyalgia and the Disease and Statistical Manual Classification As a Somatic Symptom Disorder. Frederick Wolfe[1], Brian T. Walitt[2] and Winfried Häuser[3]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Washington Hospital Center, Washington, DC, [3]Technische Universität München, Munich, Germany

Background/Purpose: Fibromyalgia was first defined by rheumatologists, and is often thought of as a disorder of widespread pain and decreased pain threshold. In the wider literature, however, including non-US studies, fibromyalgia is considered to be one of a series of "medically unexplained syndromes." These illnesses are sometimes called somatic symptom disorders (SSD) or functional somatic syndromes because the main symptoms, pain, fatigue, cognitive disturbance, and unrefreshed sleep, are somatic and have no clear etiological explanation. This definition, however, comes into conflict with the Diagnostic and Statistical Manual-5 (DSM) of SSD mental illnesses draft criteria of April–27–2012. DSM-5 defines a SSD as a mental illness when all of A and B are present chronically: A) one or more somatic symptoms that are distressing and/or result in significant disruption in daily life; B) persistently high level of anxiety about health or symptoms OR excessive time and energy devoted to these symptoms or health concerns.

Methods: We studied 13,229 rheumatic disease patients, including 3,657 who satisfied ACR 2010 criteria for fibromyalgia modified for survey research and 9,572 who did not meet criteria. We calculated the criteria Symptom Severity score (SS4) and omitted the non-somatic depression symptom of SS4. We defined patients as probably DSM-5 positive if they had at least one of the following symptoms, fatigue, cognitive disturbance, unrefreshed sleep present which was defined at a severity level of "Severe: continuous, life-disturbing problems." DSM-5 status was defined as definite if they had at least 2 of the 3 symptoms at a severe level or had an average SS4 of at least 10 of a possible 12.

Results: See Table 1. 35.0% of FM positive patients were positive at a definite level, 2.6% of non-FM criteria patients were positive. Probable DSM positivity in FM patients was indicated by 39.3% with severe fatigue scores, 42.2% with severe unrefreshed sleep, and 15.8% with severe cognitive problems.

Percent satisfying DSM-5 criteria

Category	Percent Positive
Possible DSM (+)	
Severe fatigue	39.3
Severe unrefreshed sleep	42.2
Severe cognitive problems	15.8
Definite DSM (+)	
At least 2 of 3 positive	33.6
At least 2 of 3 positive or SS4 score >=10	35.0

Conclusion: Using severity measures from survey modified ACR 2010 fibromyalgia criteria, we noted high rates of DSM-5 SSD positivity. At least 35% of FM patients would be classified as having an SSD mental disorder using our definitions. These results are inconsistent with clinical experience and call into question the use of proposed DSM criteria in clinical populations. Moreover, many, including us, would argue that all FM patients have an SSD, though not necessarily a mental disorder. Our results should be regard with caution because our definitions used *ad hoc* measures based on FM assessments, and it is possible that different levels of abnormalities might have been found using the Whitely Index mentioned in DSM-5. However, such an index is not used outside of psychiatric clinics and does not appear germane to FM symptoms. The DSM-5 continues to be revised.

Disclosure: F. Wolfe, None; **B. T. Walitt**, None; **W. Häuser**, None.

1861

Efficacy and Safety of Pregabalin in Japanese Patients with Fibromyalgia: A Randomized, Double-Blind, Multicenter, Placebo-Controlled Phase III Trial and Open-Label Extension Study. Hiroyoshi Ohta[1], Masayuki Ohkura[1], Makoto Suzuki[1], Hiroshi Oka[2], Chie Usui[3] and Kusuki Nishioka[4]. [1]Pfizer Japan Inc, Tokyo, Japan, [2]Tokyo Medical University Hachioji Medical Center, Tokyo, Japan, [3]Juntendo University Nerima Hospital, Tokyo, Japan, [4]Tokyo Medical University, Tokyo, Japan

Background/Purpose: Fibromyalgia (FM) is a common, chronic pain disorder, however, at the time of this study there was no approved medicine for FM patients in Japan. This study aimed to assess the efficacy and safety of the $\alpha_2\delta$ ligand pregabalin for the symptomatic relief of pain in Japanese patients with FM.

Methods: In a randomized, double-blind, multicenter, placebo-controlled phase III trial conducted at 44 centers in Japan, patients aged ≥18 years who had met the 1990 American College of Rheumatology criteria for FM were randomized to receive either pregabalin, starting at 150 mg/day and increasing to a maintenance dose of 300 or 450 mg/day, or placebo, for 16 weeks (3-week dose-escalation/optimization phase; 12-week fixed-dose treatment phase; 1-week taper phase). The primary endpoint was mean pain score at final assessment. Secondary endpoints included Patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire (FIQ), and measures of sleep (quality of sleep score and Medical Outcomes Study-Sleep Scale). Patients completing the double-blind study were eligible for a 53-week open-label extension study to evaluate the longer-term safety and efficacy of pregabalin (maintenance dose 300–450 mg/day).

Results: In total, 498 patients (89% female) were randomized to receive either pregabalin (n = 250; mean age 47.9 years) or placebo (n = 248; mean age 46.7 years). Pregabalin significantly reduced mean pain score at final assessment (p = 0.0046) and at every week during the study (p < 0.025). Key secondary endpoints were also significantly improved with pregabalin treatment compared with placebo, including PGIC (percentage of patients reporting symptoms "very much improved" or "much improved"; p = 0.0078); pain visual analog scale (p = 0.0013); FIQ total score (p = 0.0144); and quality of sleep score (p < 0.0001). The safety profile of pregabalin was consistent with previous clinical trials. Somnolence, dizziness, nasopharyngitis and increased weight were the most frequently reported adverse events; the majority of adverse events were mild to moderate in severity. A total of 106 patients completing the double-blind trial entered the open-label extension study. Total exposure to pregabalin in the open-label study was 100 person-years, with no new patterns in the type, incidence or severity of adverse events observed. Improvements in measures of pain, sleep and physical functioning were also maintained throughout the 53 weeks of the open-label extension study.

Conclusion: Pregabalin, at doses of up to 450 mg/day, was safe and efficacious for the symptomatic relief of pain when compared with placebo in the double-blind trial. Treatment also improved measures of sleep and physical functioning. Treatment was generally well tolerated and no new safety signals were observed over 53 weeks' treatment in the open-label extension study. Together, these results indicate that pregabalin is an effective treatment option for Japanese patients with FM.

1862

The 2012 Canadian Fibromyalgia Guidelines: Clinically Applicable Recommendations for the Management of Fibromyalgia. Mary-Ann Fitzcharles[1], Peter A. Ste-Marie[2], Don L. Goldenberg[3], John X. Pereira[4], Susan Abbey[5], Manon Choinière[2], Gordon Ko[5], Dwight Moulin[6], Pantelis Panopalis[7], Johanne Proulx[8] and Yoram Shir[1]. [1]McGill University, Montreal, QC, [2]University of Montreal, Montreal, QC, [3]Newton-Wellesley Hosp, Newton, MA, [4]University of Calgary, Calgary, AB, [5]University of Toronto, Toronto, ON, [6]University of Western Ontario, London, ON, [7]McGill University Health Center, Montreal, QC, [8]Patient Representative, Montreal, QC

Background/Purpose: The healthcare community remains challenged regarding the care of fibromyalgia (FM) patients. Previous guidelines have mostly addressed treatment options rather than provide an overall approach to FM care. With new evidence concerning pathogenesis and more diverse treatment strategies, updated direction for global care in FM is needed. These evidence-based guidelines for the diagnosis, management, and patient trajectory of persons with FM were developed taking into account these new advances and new ACR 2010 diagnostic criteria.

Methods: A needs assessment by structured consultation with 139 healthcare professionals from relevant disciplines across Canada generated 18 key questions. Questions drove a literature search to identify evidence, which was graded according to the classification system of the Oxford Centre for Evidence Based Medicine, and supporting recommendations were drafted. Recommendations were edited and appraised by an advisory panel to reflect meaningful clinical practice. The whole document was reviewed by an international expert.

Results: Sixty recommendations pertaining to the identification, evaluation, and management of persons with FM, incorporating new clinical concepts were drafted. The essence of the recommendations is as follows: FM represents a composite of symptoms, with body pain present as the pivotal symptom. There is a spectrum of severity which associates with functional outcome, with fluctuating symptoms over time. The diagnosis of FM is clinical, not one of exclusion, not needing specialist confirmation, and requires only limited laboratory testing. A physical examination is required to exclude other conditions presenting with body pain, but tender point examination is not required to confirm the diagnosis. There is no confirmatory laboratory test and excessive testing is strongly discouraged. Ideal care for most patients is in the primary care setting. Treatments should be multimodal, incorporating non-pharmacologic and pharmacologic strategies, with focus towards reduction of symptoms and improvement of function. Patients must be active participants in their healthcare and non-pharmacologic strategies are imperative. Patient-tailored management that is symptom-based is recommended. In the absence of an ideal pharmacologic treatment, an agent impacting multiple symptoms is desirable. Doses of medications lower than those used in clinical trials and combination of medications may facilitate adherence. Emphasis on proper lifestyle practices, periodic assessment of the need for continued medication, and evaluation of efficacy/side effects of ongoing treatments is recommended. New symptoms should be evaluated according to good clinical practice to exclude another illness without summarily attributing symptoms to FM.

Conclusion: These new Canadian guidelines for the care of patients with FM should provide the health community with more confidence in the global care of these patients and thereby improve patient outcome.

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Resetting the Naming Speed Clock with Methylphenidate (Ritalin). Robert S. Katz and Frank Leavitt. Rush University Medical Center, Chicago, IL

Background/Purpose: Abnormalities in naming speed are an unappreciated feature of cognitive dysfunction in fibromyalgia (FMS). Approximately 50% of FMS patients with memory problems name words at a rate that is 203 milliseconds slower than the norm. The connection between naming speed and memory loss in FMS is unclear. Stimulant medications like methylphenidate have been known to influence naming speed and could provide clues to the relationship between cognitive functioning and naming speed. The purpose of this paper is to determine if faster naming speed is connected to a positive change in cognitive functioning.

Methods: A word naming speed measure (Stroop Color and Word Test) and a measure of cognitive functioning (Mental Clutter Scale:MCS) were administered to 15 patients with FMS, before receiving methylphenidate and post methylphenidate. The FMS patients were female, met 2010 ACR criteria for FMS and had memory problems. Methylphenidate dosage was clinically determined and ranged from 10 to 30 mg. The median methylphenidate usage at retesting was 30 days. Naming speed was determined by the number of words named in a 45 second time period.

Results: The mean age of the FMS sample was 46.3±11.6 years with 14.1±2.1 years of education. Twelve of 15 FMS patients showed a significant reduction in time needed to name words post methylphenidate. Pre-methylphenidate, they read 77.4 words in 45 seconds or 605 milliseconds (45/77.4) per word. Post methylphenidate, they read 93 words in 45 seconds or 498 milliseconds (45/93) per word. This represents a 107 millisecond benefit from methylphenidate. The normative sample reads 108 words in 45

sec. or 417 msec. per word. Post methylphenidate changes on the Cognition and Mental Clarity subscales of the MCS are shown in Table 1. FMS patients showed a 17 point improvement with methylphenidate on Cognition, and a 19 point improvement on mental clarity. Both changes were significant at $p<0.01$.

Table 1. Pre-methylphenidate and Post-methylphenidate Scores on the Cognition and Mental Clarity Subscales of the Mental Clutter Scale

	Pre-methylphenidate	Post-methylphenidate
Cognition	52.8 ± 15.6	35.1 ± 11.3**[a]
Mental Clarity	48.1 ± 16.5	29.2 ± 13.6**

**$p<0.01$
[a]Lower scores represent improved performance

Conclusion: Methylphenidate appears to have short term benefits for naming speed and cognitive functioning in fibromyalgia. It quickly allows patients with FMS to operate at a more normal pace in naming words and broadly improves cognitive functioning. Elimination of the 107 millisecond time lag is thought to reset the neural clock in FMS so that word information is back in sync with other streams of neural information. The benefits of methylphenidate clearly show a connection between faster naming speed and improved cognition, however, it remains to be determined whether positive changes in cognition are brought on by faster neural transmission that likely underlies faster naming speed.

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Swimming Is As Effective As Walking for Treating Fibromyalgia: A Randomized Controlled Trial. Giovana Fernandes, Fabio Jennings, Michele V. Nery, Ana Leticia P. de Buosi and Jamil Natour. Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Background/Purpose: Fibromyalgia (FM) is a chronic widespread pain syndrome that causes deterioration of physical capacity. Exercises are fundamental in the treatment of FM and walking is the most common aerobic exercise studied. However, it is not known the effects of swimming in patients with FM. The purpose of this study was to evaluate the effects of swimming on pain, functional capacity, health-related quality of life, general quality of life and aerobic capacity in patients with FM, compared to walking.

Methods: Seventy-five women with diagnosis of FM according to ACR criteria with age between 18 and 60 years were selected. The patients were randomized to swimming group (SG) or walking group (WG). The SG performed swimming in front-crawl style and the heart rate (HR) training was defined by subtracting 10 beats from anaerobic threshold heart rate to compensate underwater horizontal position. The WG performed walking at anaerobic threshold HR. Exercise sessions had duration of 50 minutes and were performed three times a week for 12 weeks. The outcome measures were visual analogue scale (VAS) for pain, Time Up and Go Test (TUG) for functional capacity, Fibromyalgia Impact Questionnaire (FIQ) for health-related quality of life and SF 36 for general quality of life. Aerobic capacity was measured by an incremental cardiopulmonary exercise testing protocol by treadmill. The evaluations were done by a blinded assessor at baseline (T0), 6 (T6) and 12 weeks (T12) after randomization. It was used intention-to-treat analysis.

Results: Thirty-nine patients were randomized to SG and 36 to WG. The groups were homogeneous at baseline regarding clinical and demographic characteristics. Five patients (3 in SG and 2 in WG) withdrew after few exercise sessions because of pain worsening. After 12 weeks, both groups improved pain, functional capacity and quality of life (FIQ and SF 36) compared to baseline, however there were no differences between groups. Regarding aerobic capacity, both groups did not show changes over time. Tolerance to exercise, measured by adherence to programs, was similar in both groups (77.8% in SG and 72.2% in WG).

Conclusion: Swimming is as effective as walking in improving pain, functional capacity, health-related quality of life and general quality of life in patients with FM. In addition, swimming is well-tolerated by patients with FM. However, clinical improvements are not associated to aerobic capacity. More studies are necessary to define the mechanisms by with aerobic exercises lead to symptom improvements in FM.

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Emotional Pain and Catastrophizing Influence Quality of Life in Fibromyalgia. Neda Faregh[1], Peter A. Ste-Marie[2] and Mary-Ann Fitzcharles[1]. [1]McGill University, Montreal, QC, [2]University of Montreal, Montreal, QC

Background/Purpose: Fibromyalgia (FM) is a composite of symptoms with the pivot symptom of pain, traditionally measured as intensity with little attention to other qualities. Emotional pain is an important component of the global pain experience, although seldom measured in the clinical setting. The McGill Pain Questionnaire (MPQ) evaluates pain beyond intensity through subgroups of descriptor words. We have examined the associations of pain quality as measured by the subsections of the MPQ with quality of life, psychological status and function.

Methods: In a prospective cohort of FM patients attending a multi-disciplinary pain clinic, emotional pain was measured by the affective component of the McGill Pain Questionnaire (MPQ). The MPQ has 4 subsections, measuring sensory, evaluative, affective and miscellaneous pain. Other measures included pain intensity by a visual analog scale (VAS), patient global assessment (PGA), the Fibromyalgia Impact Questionnaire (FIQ), the Health Assessment Questionnaire (HAQ), the Pain Disability Index (PDI), the Pain Catastrophizing Scale (PCS), and the Arthritis Impact Measurement Scale (AIMS) for anxiety and depression.

Results: 229 FM patients (91% females, mean age and symptom duration, years, 48 and 11) had pain VAS 6.5, PGA 6.5 and MPQ 41. With the exception of unemployment, no demographic variable correlated with the MPQ. MPQ (total and subsections) was significantly correlated with pain VAS, PGA, FIQ, HAQ, PDI, PCS, and AIMS anxiety and depression. Stepwise hierarchical multiple regression analysis examining the association with the MPI total score retained FIQ, PCS, and HAQ. A MANOVA assessed if there were differences in measures (FIQ, HAQ, PGA, included on clinical judgement) based on a linear combination of MPI scores, while taking catastrophizing into account. The miscellaneous subsection correlated highly with the sensory subsection ($p <.001$) and was eliminated. A significant effect was found for the affective subscale (Wilks' Lambda $\Lambda=.941$, F= (3, 222) = 4.64, $p <.005$, multivariate $\eta^2=.06$), but not for evaluative or sensory subscales. The main effect of covariation for catastrophizing was significant (Wilks' lambda $\Lambda=.880$, F (3, 222) = 10.1, $p <.001$, multivariate $\eta^2=.12$). Follow-up ANOVAs indicate that affective scores contribute significantly to FIQ and PGA; evaluative scores contribute significantly to PGA, and the sensory scores contribute significantly only to HAQ. Catastrophizing contributes significantly to PGA and FIQ. Catastrophizing is the variable with the largest and significant Beta weights for each of the MPQ variables.

Conclusion: Higher scores on emotional pain and catastrophizing were predictors of poor quality of life, whereas sensory scores better predicted function. Emotional pain, especially when associated with high levels of catastrophization has important negative effects on well-being for FM patients. Psychological interventions targeting these aspects may offer additional benefits to the standard pharmacological management of pain.

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Association of Opioid Use with Symptom Severity and Quality of Life in Patients with Fibromyalgia. Terry H. Oh[1], Chul H. Kim[2], Connie A. Luedtke[1], Jeffrey Thompson[1], W. Michael Hooten[1] and Ann Vincent[1]. [1]Mayo Clinic, Rochester, MN, [2]Kyungpook National University, Daegu, South Korea

Background/Purpose: Chronic widespread pain is a cardinal symptom in patients with fibromyalgia. Current pharmacotherapies for fibromyalgia targets central neurochemical abnormalities and pain processing pathways. Analgesics and opioids are currently not standard of care for patients with fibromyalgia. Our objective was to evaluate the frequency of opioid use and clinical characteristics, symptom severity and quality of life (QOL) associated with opioid use in patients seen in a fibromyalgia treatment program (FTP) at a tertiary medical center.

Methods: We studied 971 patients (917 women and 54 men) with fibromyalgia who met the 1990 ACR clinical criteria for fibromyalgia. Comprehensive medication review was conducted when they were seen at the FTP. Opioid users and nonusers were compared with respect to demographic characteristics, numeric rating scale (NRS) for current pain, Fibromyalgia Impact Questionnaire (FIQ) and Short Form-36 Health Survey (SF-36) scores, and tender point count. Univariate logistic regression models were used to model the

endpoint of opioid use (Yes vs No). Variables significant at the alpha = 0.05 level were entered into a multivariable logistic regression model.

Results: Mean age of patients was 49 (SD, 12.8) years and mean duration of symptoms was 130 months (SD, 134.8). Two hundred thirty-six patients (24%) who presented to the FTP used opioids for pain. In a univariate analysis, the opioid users had higher rates of tobacco use ($p<0.001$), unemployment ($p<0.001$), tender point ($p=0.001$) and NRS scores ($P<0.0001$) and lower alcohol use ($p=0.009$), when compared to the nonusers. There were no significant differences in age, sex, race, marital status, abuse history, education level or BMI status between the 2 groups. The opiod users also had higher symptom severity as measured by the FIQ total ($p<0.001$) and all subscales ($p\leq0.01$) and worse QOL as measured by all SF-36 subscales ($p\leq0.04$) and physical and mental components ($p<0.001$). Multivariate analysis confirmed that opioid use was independently and significantly associated with increased tobacco use ($p=0.003$), unemployment ($p=0.002$), increased symptom severity ($p=0.009$) and worse SF-36 physical component score ($p=0.02$). However, no significant associations were found between opioid use and alcohol use, NRS scores, tender points or SF-36 mental component score.

Conclusion: The frequency of opioid use was 24 % in patients with fibromyalgia seen in the FTP at a tertiary medical center. Our results demonstrate that opioid use is associated with adverse social factors and worse symptom severity and physical health in patients with fibromyalgia. To better deal with this problem in clinical practice, factors that predispose to opiod use in patients with fibromyalgia need to be further investigated.

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Assessment of ART Therapy Program for Women with Fibromyalgia: Randomized, Controlled, Blinded Study. Andreia S. Baptista[1], Anamaria Jones[1], Fernanda P. Cardoso[1], Betina C. Schaffir[1], Elisa R. W. Coelho[1], Aline Orlandi[1] and Jamil Natour[2]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Fibromyalgia (FM) is a chronic non-inflammatory syndrome characterized by diffuse pain throughout the body, sleep disorder, stiffness, fatigue, depression and other psychological problems. Patients with FM feel incapable of performing the majority of activities of daily living. Medication offers only short-term benefits. Thus, it is necessary to include other measures for treatment, such as physical activity and patient education. Art therapy combine the field of psychology with artistic activities, working with therapeutic and instructive aspects as well as the potential for personal growth contained in all forms of art. The aim of the present study was to assess the effectiveness of an art therapy program for the treatment of pain and improvements in both quality of life and body image of patients with fibromyalgia.

Methods: A randomized, controlled study with a blinded evaluator and 20-week follow-up period was carried out involving 80 patients with fibromyalgia. A visual analog scale (VAS) pain and sleep the six-minute walk test, Fibromyalgia Impact Questionnaire (FIQ), Medical Outcome Survey Short Form 36 (SF-36), Beck Depression Inventory and Body Dysmorphic Disorder Examination (BDDE) questionnaire were used for the assessments, which were performed at baseline and after 10, 20 (end of intervention) and 40 weeks.

Results: The groups were homogeneous at baseline regarding clinical and demographic characteristics. The art group achieved statistically significant improvements in VAS for pain ($p=0.001$), VAS for sleep ($p=0.027$), FIQ ($p=0.001$), Beck Depression Inventory ($p=0.038$) and the physical functioning ($p=0.027$), role-physical, ($p<0.001$), bodily pain ($p=0.002$), vitality ($p=0.001$), role-emotional ($p=0.002$) and mental health ($p=0.010$) subscales of the SF-36. Regarding body image no differences between groups was found over time.

Conclusion: Art therapy can be used in the treatment of fibromyalgia, leading to a reduction in pain and improvements in degree of depression and quality of life.

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Clinical Outcome in Fibromyalgia Patients Treated with Milnacipran Is Largely Independent of Symptom Duration. Philip Mease[1], Robert M. Bennett[2], Robert H. Palmer[3] and Yong Wang[3]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Oregon Health & Science University, Portland, OR, [3]Forest Research Institute, Jersey City, NJ

Background/Purpose: Patients with fibromyalgia (FM) usually experience pain, fatigue, and other debilitating symptoms for years. In clinical studies ranging from 3 months to >3 years, treatment with milnacipran was found to improve these symptoms. A post hoc analysis of milnacipran study data was conducted to examine whether duration of FM symptoms affected treatment outcomes.

Methods: Data were pooled from 2 double-blind trials that included patients randomized to milnacipran 100 or 200 mg/day (n=1311) or placebo (n=910). Outcomes were assessed in patients categorized into subgroups based on duration of FM symptoms at study baseline. Outcomes included percentage of patients with pain response ($\geq30\%$ improvement in visual analog scale [VAS] recall pain scores) and composite response ($\geq30\%$ pain improvement plus Patient Global Impression of Change score ≤2), as well as mean changes from baseline in VAS pain, Multidimensional Fatigue Inventory (MFI), Fibromyalgia Impact Questionnaire (FIQ), and Beck Depression Inventory (BDI) scores. Analyses were conducted using descriptive statistics.

Results: The mean duration of FM symptoms at baseline was 10.2 years (range = ≤3 month to 55 years); 33% of patients had experienced symptoms for <5 years and 10.4% for >20 years. Baseline pain, FIQ, and MFI were similar across the range of symptom durations; BDI scores were slightly higher in patients with shorter (1–2 years) symptom duration. Examination of treatment response trends across symptom duration subgroups indicated that the placebo responses were remarkably similar, regardless of treatment duration. Consistent with the percentage of composite responders observed in FM duration subgroups (Figure), improvements in pain, FIQ, MFI, and BDI were generally greater with milnacipran versus placebo across symptom durations >1 year. The milnacipran response was generally smaller for pain, FIQ, MFI, and BDI for patients with very short symptom durations (≤1 year) when compared with patients in other symptom duration subgroups.
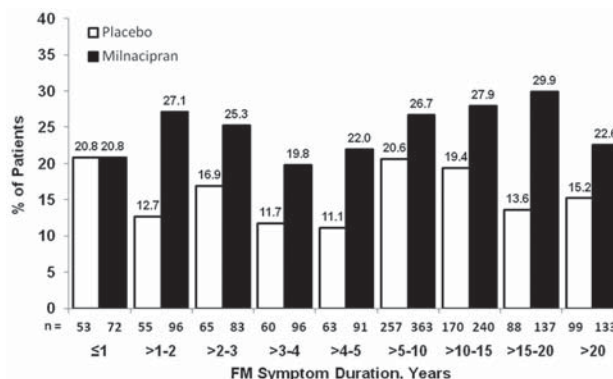
Figure. Percentage of patients with pain + global improvements by FM symptom duration.

Conclusion: Baseline levels of pain and other FM symptoms appeared to be largely independent of symptom duration. Treatment effects with milnacipran were relatively consistent across symptom duration for all symptom domains except for an unexplained smaller treatment effect size in patients with symptoms of shorter duration.

Disclosure: **P. Mease**, Forest Laboratories, 2, Forest Laboratories, 5, Forest Laboratories, 8; **R. M. Bennett**, Forest Laboratories, 9; **R. H. Palmer**, Forest Laboratories, 3; **Y. Wang**, Forest Laboratories, 3.

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Predictors of Fatigue in Fibromyalgia. Ann Vincent[1], Mary O. Whipple[1], Debra L. Barton[1], Daniel J. Clauw[2], David A. Williams[3], Terry H. Oh[1] and Loren L. Toussaint[4]. [1]Mayo Clinic, Rochester, MN, [2]University of Michigan, Ann Arbor, MI, [3]Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [4]Luther College, Decorah, IA

Background/Purpose: Previous research suggests that fatigue in chronic diseases is multifactorial and that fatigue in fibromyalgia is worse than fatigue

in rheumatoid arthritis or osteoarthritis. Although fatigue along with widespread pain is a cardinal symptom in patients with fibromyalgia, the predictors of fatigue in fibromyalgia have not been comprehensively assessed. Our objective was to examine the predictors of fatigue cross-sectionally in patients with fibromyalgia.

Methods: Measures of fatigue, mood, pain, sleep, and autonomic symptoms were gathered from a random sample of 1303 patients with fibromyalgia identified through an existing fibromyalgia registry. Validated self-report questionnaires were mailed which included the Multidimensional Fatigue Inventory (MFI-20), Brief Pain Inventory (BPI), Medical Outcome Study Sleep Scale (MOS), Profile of Mood States – Short Form (POMS-SF), and Autonomic Symptom Profile (COMPASS). Eight hundred fifty-eight (66%) patients returned completed questionnaires. Data were analyzed using multiple linear regression.

Results: The overall model fit was $R^2 = 0.44$. The most significant predictors of fatigue were depression/dejection ($\beta = -.326$, $p<.001$), sleep problems index ($\beta = .247$, $p<.001$), pain severity ($\beta = .182$, $p<.001$), BMI ($\beta = .148$, $p<.001$), and autonomic symptoms ($\beta = .126$, $p<.001$). Neither age ($p=.28$) nor tension/anxiety ($p=.88$) were significant predictors of fatigue.

Conclusion: Cross-sectional results indicate that depression, sleep, pain severity, BMI, and autonomic symptoms are significantly associated with fatigue in patients with fibromyalgia. Among predictors of fatigue identified in this study, depression was the strongest predictor. If these results can be replicated in a longitudinal study, improving mood, sleep, pain, etc. could all be potential targets to decrease fatigue.

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Financial Conflicts of Interest and Industry Sponsorship Are Associated with Positive Outcomes in Fibromyalgia Randomized Controlled Trials. Winnie K. Pang[1], Karen Yeter[1], Nasim A. Khan[2] and Karina D. Torralba[1]. [1]University of Southern California Keck School of Medicine, Los Angeles, CA, [2]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR

Background/Purpose: Fibromyalgia randomized controlled trials (RCTs) have become more common in the past 15 years, in part due to industry sponsorship. Recently, there has been growing concern that financial conflicts of interest (FCOIs) among authors and funding source may affect reporting of results in RCTs. These issues have not yet been adressed for fibromyalgia RCTs. The objective of this study was to determine the prevalence of pharmaceutical industry funding and and FCOIs among authors of RCTs of drug therapy for fibromyalgia and assess their association with study outcome.

Methods: MEDLINE and Cochrane Central Register of Controlled Trials databases were searched for fibromyalgia drug therapy RCTs published between 1997 and 2011. Eligible studies were original, randomized, parallel design drug trials with clinical efficacy as primary outcome. Two reviewers independently assessed each RCT for funding source (industry, non-profit, mixed), FCOI disclosure by author, and outcome [positive (statistically significant result favoring experimental drug for the primary outcome) or not positive]. RCTs with and without different types of FCOIs were compared using Chi-square, Fisher's exact or likelihood ratio test.

Results: Of 47 eligible RCTs, study sponsors were industry (25, 53.2%), non-profit (9, 19.1%), mixed (5, 10.6%), and unspecified (8, 17%). A higher likelihood of positive outcomes was associated with industry sponsorship (22/25, 88%) and unspecified funding (6/8, 75%) compared to other funding types [non-profit 4/9 (44.4), mixed 3/5 (60%); P = 0.073]. Industry funded RCTs were significantly associated with positive outcome compared to non-profit funded RCTs (P = 0.017). FCOIs among authors were reported in 30 (63.8%) RCTs. RCTs with author(s) employed by the industry sponsor or author(s) who received consultancy fee/honoraria from the industry sponsor had significantly higher likelihood of positive outcome (Table). All RCT's (15/15) of the three Food and Drug Administration-approved drugs (duloxetine, pregabalin, and milnacipran) were industry sponsored and all had positive outcomes. Adjustment for potential confounding factors, such as type of experimental drug, study duration, and number of enrolled patients, could not be performed due to small number of eligible RCTs.

Table. Association of positive study outcome with types of financial conflicts of interest

Relationship to drug industry	FCOI present n/N (%)	FCOI absent n/N (%)	p-value
Any FCOI	25/29 (86.2)	10/18 (55.6)	0.037
Employee status	19/19 (100)	16/28 (57.1)	0.001
Consultancy fees/honoraria	15/16 (93.8)	20/31 (64.5)	0.037
Stock ownership	10/11 (90.9)	25/36 (69.4)	0.244
Research grant	16/20 (80)	19/27 (53.8)	0.517

n: Number of RCTs with positive outcome within each group
N: Total number of RCTs in each group

Conclusion: Industry sponsorship and FCOIs are common in published fibromyalgia drug therapy RCTs and are more likely to be associated with positive outcomes. The small number of eligible trials precluded adjustment for potential confounders to assess whether these represent independent association with study outcome.

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Tender Point Count and Pressure Pain Threshold As Predictors of Chronic Widespread Pain and Health Status in a Seven Year Prospective Study. Emma Jacobsen[1] and Stefan Bergman[2]. [1]R&D center Spenshult, Oskarström, Sweden, [2]R&D Center Spenshult, Oskarström, Sweden

Background/Purpose: Chronic widespread pain is common in the general population with a prevalence ranging between 4.2% and 13.3%. It has been identified as a major health problem. The aim of this study was to evaluate the prognostic value of tender point count, pressure pain thresholds and pain group classification with regard to chronic widespread pain report and self-reported SF-36 quality of life measurements in persons with a history of chronic widespread pain.

Methods: A cohort of 303 individuals was identified as having self-reported chronic widespread pain in a cross-sectional survey with 3928 participants. 146 of the 303 individuals underwent clinical examination with palpation of tender points, dolorimeter pressure pain threshold examination and pain grouping (no chronic pain, chronic regional pain, and chronic widespread pain) based on a report of painful regions on a drawing of the body with predefined regions. Chronic widespread pain was evaluated according to the American College of Rheumatology 1990 criteria for fibromyalgia. Two and seven years later, pain classification and SF-36 quality of life assessments were collected from postal questionnaires. Sex and age adjusted OR were calculated for each clinical baseline factor separately.

Results: Having more than four tender points significantly (p<0.05) predicted a four time higher risk of reporting chronic widespread pain at the two (OR=4.33) and seven (OR=3.89) year follow up. Having 11– 18 tender points at baseline was superior to a report of chronic widespread pain in predicting a low SF-36 vitality score. Chronic widespread pain at baseline strongly predicted chronic widespread pain two and seven years later. Low pressure pain thresholds did predict chronic widespread pain and a low health status although the associations were subordinated the prognostic value of tender point counts and widespread pain classification.

Conclusion: Easy attainable anamnestic and clinical findings such as a report of chronic widespread pain and a tender point count above four can be used as prognostic signs in the clinical evaluation of patients with a history of longstanding pain.

Disclosure: E. Jacobsen, None; **S. Bergman**, None.

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Quality of Reporting in Pharmacological Randomized Controlled Trials for Fibromyalgia. Karen Yeter[1], Winnie Pang[1], Nasim A. Khan[2] and Karina D. Torralba[1]. [1]University of Southern California Keck School of Medicine, Los Angeles, CA, [2]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR

Background/Purpose: Randomized controlled trials (RCTs) are considered the gold standard for assessment of healthcare interventions. Recently, there have been growing concerns about the quality of reporting of results in RCTs. Factors such as pharmaceutical industry sponsorship and financial conflicts of interest among authors are may create bias and influence study quality. No studies have addressed these issues in fibromyalgia RCTs. Our

objective was to assess the quality of reporting in drug therapy randomized controlled trials (RCTs) of fibromyalgia and their effect on study outcome.

Methods: MEDLINE and Cochrane Central Register of Controlled Trials databases were searched to identify original fibromyalgia drug therapy RCTs published between 1997 and 2011. Eligible studies were identified by screening the title and abstract for original, randomized, parallel design drug trials with clinical primary outcome(s). Two reviewers independently assessed each RCT for study characteristics, outcome [positive (statistically significant result favoring experimental drug for the primary outcome) or not positive], and quality measures (sample size calculation, adequacy of randomization, allocation concealment, double-blinding, follow-up description, and intention-to-treat (ITT) analysis). RCTs with and without different types of quality measures were compared using Chi-square, Fisher's exact or likelihood ratio test.

Results: 47 eligible RCTs were identified. In 21 (44.6%) RCT's, random sequence generation and allocation concealment were described adequately. Statistical power calculation was reported in 28 (62.2%) RCTs (2 RCTs were excluded as they were phase 2 studies). Double-blinding was reported in 21 (44.6%) of trials. In 30 (63.8%) RCTs, ITT analysis and prospectively defined follow-up schedule were also described. There were no significant assocations between specific quality measures and study outcome (Table).

Table. Association of positive study outcome with types of study quality measures.

Study Quality Measure	Quality measure present n/N (%)	Quality measure absent n/N (%)	p-value
Sample Size Calculation	20/28 (71.4%)	14/17 (71.4%)	0.493
Randomization	18/21 (85.7%)	17/26 (65.4%)	0.179
Allocation concealment	16/20 (80.0%)	19/26 (70.4%)	0.517
Double-blinding	14/21 (66.7%)	21/26 (80.8%)	0.326
Description of follow-up	23/30 (76.7%)	12/17 (70.6%)	0.733
Intention-to-treat analysis	24/30 (80.0%)	11/17 (64.7%)	0.306

n: Number of RCTs with positive outcome within each group
N: Total number of RCTs in each group

Conclusion: Study quality measures are not consistently reported in fibromyalgia drug therapy RCTs. The presence of specific types of study quality measures in RCTs was not associated with higher likelihood of positive study outcome.

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Clinical Characteristics and Health Care Utilization Patterns Among Patients with Fibromyalgia Newly Prescribed Amitriptyline, Duloxetine, Gabapentin or Pregabalin: A Large Cohort Study. Seoyoung C. Kim[1], Joan E. Landon[1] and Daniel H. Solomon[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Background/Purpose: Patients with fibromyalgia (FM) tend to use a number of different medications and have high health care costs. Treatment for FM generally consists of symptom management. The objective of this study was to describe clinical characteristics and health care utilization patterns in patients with FM newly prescribed amitriptyline, duloxetine, gabapentin or pregabalin.

Methods: We conducted a large population-based cohort study using US health care utilization data (1/2007–12/2009). Adult patients were categorized into four groups if they were newly prescribed amitriptyline, duloxetine, gabapentin or pregabalin after their first diagnosis of fibromyalgia (ICD-9 code 729.1). A 180-day baseline period free of any of the four drugs was required prior to the first prescription date (index date). Demographic characteristics and comorbidities during the baseline period and their relationship with use of FM-related drugs and health care utilization patterns during the follow-up period were examined.

Results: The study population included a total of 74,378 patients with FM with a mean follow-up period of 141 to 195 days. The mean ages were 48 to 51 years and 72% to 81% were women, depending on the prescribed drug. Comorbidities were similar across the four groups ranging from a mean of 0.5 to 0.8 conditions. Back pain (48%–65%) was the most frequent comorbidity in all four groups and hypertension (29%–38%), headache (22%–30%), depression (11%–24%), sleep disorder (16%–19%) and inflammatory arthritis (10%–15%) were also common across the four groups. Median daily dose (in milligram) at both index date and the last day of follow-up was 25 for amitriptyline, 60 for duloxetine, 300 for gabapentin, and 75 for pregabalin. The mean number of physician visits ranged from 6.6 to 9.0 and mean number of prescription drugs were from 7.9 to 9.6 during the follow-up. **Table** shows a slight decrease in the use of various FM-related drugs after the index date across the four groups. Opioids and antidepressants were most commonly taken with drugs for FM.

Table. Use of fibromyalgia-related drugs before and after the index date (%)

	Amitriptyline (n=13, 404)		Duloxetine (n=18, 420)		Gabapentin (n=23, 268)		Pregabalin (n=19, 286)	
	Before	After	Before	After	Before	After	Before	After
Opioids	54	45	56	51	66	56	69	61
Anti-convulsants	10	19	13	23	40	100	39	100
Antidepressants	55	100	68	100	38	37	41	43
COX2/NSAIDs	34	26	33	28	38	29	42	33
Sleep disorder drugs	19	14	25	22	19	15	23	20
Muscle relaxants	30	24	31	27	36	28	40	32

Conclusion: Patients who were newly prescribed one of the four common drugs for FM similarly had multiple comorbidities, a great number of other medication use and high health care utilizations. Median daily dose for all four drugs remained the same during the follow-up.

1874

Genomic Categories of Fatigue in Women with Fibromyalgia. Nada Lukkahatai[1], Brian T. Walitt[2], Majors Benjamin[1], Gelio Alves[3] and Leorey Saligan[1]. [1]National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, [2]Washington Hospital Center, Washington, DC, [3]National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD

Background/Purpose: FM is the chronic experience of body-wide pain, fatigue, cognitive dysfunction, and disordered sleep that occurs in the absence of any clear cause. Fatigue is a cause of significant morbidity and disability in FM. Most genomic studies in the FM population focus on pain symptoms. Only a few studies had investigated the fatigue experience in FM and no genomic studies investigated FM-specific fatigue symptoms. The purpose of this study is to identify genomic categories of fatigue in fibromyalgia (FM) and describe behavioral characteristics of these fatigue categories.

Methods: Under an active Medstar Research Institute protocol, FM participants diagnosed by 2010 diagnostic criteria and pain-free, race, age, and gender-matched controls were enrolled in the study. Participants completed questionnaires. RNA from peripheral blood samples collected using Paxgene tubes® were analyzed for differential gene expression using microarray technology with Affymetrix GeneChip® human genome U133 Plus 2.0. Cluster analysis was used to determine genotypic categories. The differences of symptoms between two clusters were analyzed by the analysis of variance (ANOVA).

Results: Thirty one Caucasian women diagnosed with FM, experiencing significant fatigue (MFI-general fatigue $\geq$ 13) and 20 pain and fatigue free, age-, race-, gender-matched controls were enrolled. Microarray data showed differential upregulated expression of centromere protein K (CENPK) gene after the probesets passed filtering criteria of 1% false discovery rate (FDR) and a slope of $>$ log2 (over 2.0-fold change, $p <$ 0.05). This CENPK gene is related to centromere function. Cluster analysis was conducted on the expressed genes from FM subjects which revealed two distinct clusters. Forty nine genes were differentially expressed over 2-fold change ($p < 0.05$) between the two clusters. One cluster showed significantly higher pain interference ($p = 0.028$) and higher depression ($p = 0.027$). Genes that upregulated in the high pain interference and high depression cluster include genes related to immune response, iron absorption and GABA transport. Genes related to calcium iron binding were differentially expressed in the other FM cluster with lower pain interference and depression.

Conclusion: Within FM women with high fatigue, there appears to be two distinct patterns of gene expression. These genomic patterns correspond with differences in behavioral characteristics. Further investigation of these genomic patterns may provide some insights into the mechanisms behind the relationship of fatigue with other FM behavioral symptoms.

Disclosure: N. Lukkahatai, None; **B. T. Walitt**, None; **M. Benjamin**, None; **G. Alves**, None; **L. Saligan**, None.

1875

A Patient and Physician Survey of Impact and Management of Fibromyalgia Across Latin America and Europe. Patricia Clark. Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Background/Purpose: Differences in healthcare practices around the world have been reported; however any impact on management of chronic conditions is often unclear. We surveyed patients and physicians from three Latin American (LA) and six European countries to ascertain differences in journey to diagnosis and management of fibromyalgia (FM).

Methods: Data from 900 FM patients (300 LA; 600 Europe) and 1824 GPs/specialists (604 LA; 1220 Europe) were collected between 2008 and 2010.Patients and physicians completed separate questionnaires. which included questions on symptoms (14 common symptoms), management, and impact of FM. Patient interviews (face-to-face or via telephone; 25mins) were conducted in local languages (Spanish, Portuguese). Rating scales were used throughout. Data were analyzed using cross tabulations and descriptive statistics; no multivariate analysis. Significance determined at $P < 0.05$ (indicated by *).

Results: Patients from LA reported FM symptoms for longer time (100.8 vs 83.7* months), took longer to be diagnosed (42.3 vs 31.1* months), and saw more physicians to receive a diagnosis (5.4 vs 4.0*) vs European patients, respectively. FM was characterized by multiple symptoms in both regions, although a higher proportion of patients from LA vs Europe reported common FM symptoms, including widespread pain (92% vs 62%*), sleep problems (84% vs 49%*), and fatigue (88% vs 46%*). Patients from LA rated their pain higher on a 10-point scale vs European patients (8.0 vs 7.2*). Patients from both regions reported common FM symptoms as disruptive to their quality of life (pain: 86% vs 78%*; sleeping problems: 80% vs 76%; fatigue: 80% vs 75%). Patients from LA more often reported that FM had impacted their ability to work and/or earn an income vs patients from Europe. LA patients were managed by different healthcare professionals, while European patients were mostly treated by GPs (47% vs 96%*). Physicians principally considered widespread pain as a typical FM symptom and being disruptive to patient's. Although >50% of patients considered them common symptoms, <10% of GPs or specialists from either region considered problems sleeping or fatigue typical FM symptoms. Physicians from LA more often considered problems sleeping*, difficulty concentrating*, anxiety*, depression*, numbness/tingling*, and leg cramps* disruptive vs European physicians.

Conclusion: Differences between FM characteristics, treatment practices, and opinions were noted by physicians and patients from LA and Europe. Improved understanding of these complexities involved in FM in different healthcare settings may help target educational/training programs towards improving aspects of chronic care. Improving alignment between perception of FM from the patient and physician's perspective may also improve patient management.

Disclosure: P. Clark, Pfizer Inc, 5;

1876

The Assessment and Treatment of Nonsurgical Periarticular Post-Traumatic Soft Tissue Injuries of the Knee. Dan Nemes[1], Elena Amaricai[1], Liliana Catan[1], Daniel Popa[1], Simona Cerbu[2] and Paula Bicov[1]. [1]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania, [2]Telescan Imaging Centre, Timisoara, Romania

Background/Purpose: In spite of the fact that periarticular post-traumatic soft tissue injuries of the knee were considered less important than the knee joint pathology itself, they are disorders with a high risk of disability, with potential to affect functioning and quality of life causing thus important socioeconomic implications. The main objectives of our study are to point out the necessity of an ultrasonography score that can be correlated with a functional score (in order to quantify the evolution of nonsurgical periarticular post-traumatic soft tissue injuries of the knee) and to prove the importance of a long-term rehabilitation treatment of this pathology.

Methods: We included into 1-year randomized, prospective study a number of 159 patients diagnosed with different types of nonsurgical periarticular post-traumatic soft tissue injuries of the knee: soft tissues edema, quadriceps tendon lesions (tendinitis or partial tear), prepatellar or infrapatellar bursitis, bursitis of the pes anserinus, lesions of the patellar retinaculum (elongation or partial tear), lesions of the medial collateral ligament (elongation, partial or total tear) and lesions of the iliotibial band (friction syndrome with or without bursitis). Group A suffered traumatic events on healthy knee joint. Group B patients had pre-existing knee lesions. Group A_1 (41 patients) and B_1(38 patients) followed a medical treatment, while group A_2 (39 patients) and B_2 (41 patients) followed both medical and rehabilitation therapy. All patients were assessed initially, after 6 months and after 1 year using functional evaluation (KOOS: Knee injury and Osteoarthritis Outcome Score) and knee ultrasonography (quantified in a self-developed ultrasonography score).

Results: At the beginning of the study we found no statistically significant difference of total US scores and of total KOOS scores between group A_1 (US=6.95 ± 1.378; KOOS=143.71 ± 7.497) and A_2 (US=6.92 ± 1.403; KOOS=144.33 ± 8.358), and between group B_1 (US=8.58 ± 1.328; KOOS=187.26 ± 12.326) and B_2 (US=8.51 ± 1.287; KOOS=187.17 ± 10.89). At the final assessment group A_2 and B_2 had significant decrease both of total US scores ($p < 0.01$) and total KOOS scores ($p < 0.001$) (US=3.10 ± 1.142 and KOOS=57.44 ± 5.702, respectively US=4.54 ± 1.14 and KOOS=95.8 ± 9.988) in comparison to group A_1(US=3.76 ± 0.994; KOOS=95.15 ± 8.519), respectively B_1(US=5.32 ± 1.068; KOOS=130.89 ± 10.506). When compared to group B_2, group A_2 had statistically very significant decreased total US scores (U=311; z=-4.83; $p < 0.001$) and total KOOS scores (U=3; z=-7.70; $p < 0.001$). No statistic correlation between the two assessment scores (ultrasonography score and KOOS score) was revealed.

Conclusion: The best functional results were recorded in patients with post-traumatic soft tissue injuries on a healthy knee joint and that followed both a medical treatment and a long-term rehabilitation. We propose a self-ultrasonography protocol that can monitor the progression in time of this pathology. Both functional and ultrasonography assessment scores are necessary in evaluation of periarticular soft tissue injuries of the knee.

Disclosure: D. Nemes, None; **E. Amaricai**, None; **L. Catan**, None; **D. Popa**, None; **S. Cerbu**, None; **P. Bicov**, None.

1877

Is the Amount of T and B Lymphocytes, Natural Killer Cells and Macrophages in Biopsies From Non-Ruptured Chronic Tendinopathic Achilles Tendons Predictive for Long Term Outcome? A >3 Years Prospective Study of 37 Patients. Maja S. Kragsnæs[1], Ulrich Fredberg[2], Katrine Stribolt[3], Søren G. Kjær[1], Knud Bendix[3] and Torkell Ellingsen[1]. [1]Region Hospital Silkeborg, Silkeborg, Denmark, [2]Diagnostic Centre Region Hospital Silkeborg Denmark, 8600 Silkeborg, Denmark, [3]Aarhus University Hospital, Aarhus, Denmark

Background/Purpose: In biopsies from non-ruptured chronic tendinopathic Achilles tendons, presence of T and B lymphocytes, natural killer cells and macrophages has been reported. Whether the amount of these cells at baseline is predictive for long term outcome (>3 years) remains to be examined.

The purpose of this study was to evaluate the prognostic value of the amount of immune competent cells present at baseline in biopsies from non-ruptured chronic tendinopathic Achilles tendons.

Methods: 17 women and 20 men suffering from non-ruptured chronic Achilles tendinopathy were followed prospectively for more than 3 years. At baseline, a biopsy was obtained from each tendinopathic Achilles tendon (n=37). In addition to the following immunohistochemical cell markers: CD3, CD4, CD8, CD20, CD56, CD68(PG-M1), Granzyme-B and S100, the biopsies were stained with hematoxylin/eosin, Van Gieson, toluidin blue, Pearls Blue and NASDCL. The numbers/counts (n/c) of positive cells for each marker in each sample were determined and calibrated to a standard area in 4 μm thick slides (equals n/c in standard volume) using unbiased stereological techniques.

At follow-up, patients completed the Scandinavian (Danish) version of the VISA-A questionnaire in addition to a self-composed questionnaire evaluating presence of Achilles tendon symptoms.

The Mann-Whitney rank sum test and the Fishers exact test were used ($p < 0.05$ was considered significant).

Results: At baseline, the median age of the patients was 55 years (range: 32–69) and the median symptom duration was 12 months (range: 4–156). 18 patients (49%) had never received anti-inflammatory treatment.

Patients were instructed to perform Achilles tendon eccentric loading exercises and were followed for a median time of 6 years (range: 3–11). During this period, the majority of patients (n=31) received additional local tendon injections of steroid (n=12), sclerosis (n=6), TNF-α antagonist (n=6) or interleukin-1 receptor antagonist (n=6). 5 patients had an Achilles tendon operation.

At follow-up, the median VISA-A score was 75 (range: 41–94), and 15 patients (41%) reported having no Achilles tendon symptoms.

No differences in presence of symptoms at follow-up were observed between patients receiving different injection treatments during follow-up (p=0.81).

IMMUNOHISTOCHEMICAL CELL MARKERS AT BASELINE	ASYMPTOMATIC AT FOLLOW-UP N = 15	SYMPTOMATIC AT FOLLOW-UP N = 22	
	Cell numbers/count (median, (range))		*P*
CD3	12 (0–45)	27 (0–83)	0.16
CD4	10 (0–42)	18.5 (0–51)	0.63
CD8	1 (0–35)	2 (0–22)	0.67
CD20	0 (0–2)	0 (0–6)	0.31
CD56	5 (0–73)	0 (0–26)	0.07
CD68-PGM1	35 (0–158)	30.5 (0–84)	0.39
Granzyme-B	0 (0–2)	0 (0–14)	0.77
NASDCL	6 (0–31)	9 (0–50)	0.36
S100	13 (0–53)	5.5 (0–24)	0.28
Presence of iron *(yes/no)*	7/8	3/19	0.06

Conclusion: 37 patients suffering from non-ruptured chronic Achilles tendinopathy were followed for more than 3 years. At follow-up, 15 patients (41%) had no Achilles tendon symptoms. When comparing the asymptomatic group of patients (n=15) to the symptomatic group (n=22), no differences in numbers per count of baseline immune competent cells in standard volume of Achilles tendon biopsies were observed.

Thus, the amount of immune competent cells at baseline cannot predict long term outcome of chronic Achilles tendinopathy.

1878

Cognitive Manifestations of Fibromyalgia and Lupus. Robert S. Katz and Frank Leavitt. Rush University Medical Center, Chicago, IL

Background/Purpose: Similar cognitive complaints for patients with fibromyalgia and systemic lupus erythematosus (SLE) have been reported; however, inherently different deficits can share superficial similarities. The major purpose of this study is to determine if the two syndromes have deficits in cognitive functioning in common as measured by the new Mental Clutter Scale.

Methods: The Mental Clutter Scale is a new 16 item scales that focuses on 8 dimensions of the tradition cognitive skills such as memory and concentration, and 8 dimensions of disturbed mental clarity such as cluttered thinking and mental fog. The measure was administered to 52 patients who met ACR criteria for fibromyalgia and 35 patients who met ACR criteria for Lupus. The classification criterion for cognitive dysfunction was the upper boundary of the 95% confidence interval (CI) of the normative sample. This score provided prevalence rates of cognitive dysfunction in the two samples.

Results: The two groups were predominantly female (81.5% vs. 82.9%0), with those in the fibromyalgia group significantly older [mean ($\pm$SE) age (49.0 $\pm$ 12.7 vs. 32.2.3$\pm$ 10.6 p<0.001)]. Cognitive dysfunction was present in 63.5% (33/52) of the sample with FMS and in 28.6% (10/35) of the sample with Lupus. The differences were significant (p<0.001). Both the traditional cognitive symptoms (52.7$\pm$ 10.0 vs. 32.2$\pm$ 10.6; p<0.004) and the disturbance in mental clarity (45.5 $\pm$ 15.5 vs. 30.6$\pm$ 10.7; p<0.01) were more pronounced in fibromyalgia. Endorsement of the 16 subscales is shown in Table 1. As can be seen, patients with FMS report significantly higher severity on 5 of 8 cognitive scales, and 7 of 8 mental clarity scales.

Conclusion: The cognitive findings suggest that there is considerable difference in the cognitive functioning of people with fibromyalgia and Lupus. The majority of patients with FMS report cognitive dysfunction; whereas only a minority of patients with lupus report cognitive dysfunction. Among those reporting cognitive dysfunction, cognitive deficits are more pronounced in FMS. Fog like features as measured by the mental clarity scale

are more prominent in fibromyalgia, providing strong support for the notion of fibrofog. Fog like features play less of a role in lupus, providing weak support for the notion of brain fog in most lupus patients.

1879

Work Related Injuries Causing or Aggravating Fibromyalgia in the Medicolegal Arena: A Jurisprudential Analysis. Mary-Ann Fitzcharles[1], Peter A. Ste-Marie[2] and Yoram Shir[1]. [1]McGill University, Montreal, QC, [2]University of Montreal, Montreal, QC

Background/Purpose: Up to 40% of persons report onset of fibromyalgia (FM) following a "triggering event". Injuries, which may occur in the workplace, may be implicated in some, hence linking FM to compensation. In Ontario, Canada, work injury causing physical abnormality is compensated according to the American Medical Association guides, with apportionment for pain, whereas injury without body changes, ie soft tissue, is compensated according to a chronic pain policy. FM, without tissue damage, falls under this policy. The Workplace Safety and Insurance Appeals Tribunal (WSIAT) is the final level of appeal for workers who request compensation for a work-related injury as causation for FM, with decisions available in the public domain.

Methods: Between June 2006 and December 2011, 150 Tribunal decisions relevant to FM were examined by predetermined search protocol. Twelve did not meet inclusion criteria; FM was not the central issue in 4, and 8 were for increased awards. New onset FM was appealed in 123, and aggravation of pre-existing FM in 15. Information in the aggravation cases was limited.

Results: All injuries were of a soft tissue nature, without any persistent physical findings to explain continued symptoms. Of the 15 cases pleading *aggravation of FM* (14 female, mean age 50 $\pm$ 8 years), 5 were manual, 3 clerical, 7 health care or education workers. Thirteen injuries were acute, 2 occurred gradually, with low back or neck identified in 13, and the Tribunal accepted 10/15 (67%). In the 123 *new onset FM,* (104 female, mean age 52 $\pm$ 9 years), 60 were manual, 29 clerical, 30 health care or education workers, 4 unknown, with 32% reporting repetitive work activity. Time from injury to diagnosis of FM (available for 117) was 4.3 $\pm$ 4.1 years, with 6.3 $\pm$ 2.8 physicians cited for each worker. Previous psychological illness, injuries, neck pain or back pain were recorded as present for 17%, 22%, 10%, and 13% respectively, whereas there was no statement of previous health status for 39%. Injuries were a single event in 68%, and gradual in 32%, with location of injury in low back for 44%, and shoulder/upper limb in 40%. The FM diagnosis was based on report by a rheumatologist in 74%, and family physician in 13%, with 73 (59%) appeals accepted by the Tribunal.

Conclusion: Over half of appeals for aggravation or causation of FM following a work related soft tissue injury were upheld by the Tribunal. Claimants were demographically similar to other FM cohorts, although healthcare utilization was very high. Low back and upper limb injuries predominated as causation, with over two thirds reporting FM following a single incident. The attribution of causation of FM to a single workplace traumatic event is contentious and requires further examination.

1880

A Brazilian Portuguese Validation of the Revised Fibromyalgia Impact Questionnaire (FIQR). Eduardo S. Paiva[1], Roberto E. Heymann[2], Marcelo C. Rezende[3], Milton Helfenstein Jr.[4], José E. Martinez[5], José R. Provenza[6], Aline Ranzolin[7], Marcos Renato Assis[8], Vivian D. Pasqualin[9] and Robert M. Bennett[10]. [1]Universidade Federal do Paraná, Curitiba, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil, [3]Santa Casa de Campo Grande, Campo Grande, Brazil, [4]Universidade Federal de de São Paulo, São Paulo, Brazil, [5]Pontifícia Universidade Católica de São Paulo, Sorocaba, Brazil, [6]Pontifícia Universidade Católica de Campinas, Campinas, Brazil, [7]Universidade Federal de Pernambuco, Recife, Brazil, [8]Faculdade de Medicina de Marilia, Marilia, Brazil, [9]Pontifícia Universidade Católica do Paraná, Curitiba, Brazil, [10]Oregon Health & Science Univ, Portland, OR

Background/Purpose: General health evaluation questionnaires are important instruments in assessing the impact of disorders that affect multiple domains of a patient's life. The Fibromyalgia Impact Questionnaire (FIQ) was specifically developed to assess disease severity and functional ability in

fibromyalgia patients. Since its initial publication in 1991, it has been widely used in clinical trials and clinical practice, with many translated versions around the world. In 2009, a revised version of the FIQ was published, the FIQR; this attempted to correct some of the problems that had emerged in the use of the original FIQ over the ensuing 18 years in aiming to achieve a better balance among different domains (Function, Overall Impact, Symptoms) and provide an easier scoring system. Here we present the validity and reliability of the Brazilian version of the Revised Fibromyalgia Impact Questionnaire (FIQR).

Methods: Female fibromyalgia patients (n=106) completed an online survey consisting of demographic data, the SF-36 questionnaire, the original FIQ (both in validated Brazilian Portuguese Translation), and the Brazilian Portuguese FIQR, which was translated by a standard method. Validity was established with correlational analyses between FIQR, FIQ and SF-36 items. Three domains were established for FIQR (Function, Overall Impact, Symptoms) and their contribution for the SF-36 subscales was also scrutinized.

Results: The Brazilian Portuguese FIQR validation process showed that the questions performed in a very similar way to the English FIQR. Four new questions in the FIQR symptoms (memory, balance, tenderness and environmental sensitivity) showed strikingly similar results to the original FIQR, revealing a significant impact in FM patients. The Brazilian Portuguese FIQR demonstrated excellent reliability, with a Cronbach alpha of 0.96. The correlation with the original FIQ was also good (r=0.854, p<0.001). There was a gain the weight of the function domain, with little change of the overall impact domain, and a decrease of the symptom domain, leading to a better balance among FM domains. FIQR predicted a great number of SF-36 subscales, showing both convergent and discriminant validity.

Conclusion: The Brazilian Portuguese version of the FIQR was validated, and found to be a reliable and easy-to-use and score FM specific questionnaire that should prove useful in routine clinical practice and FM-related research.

1881

Increased Psychosocial Stress Is a Major Component of Fibromyalgia Triggers. Emma K. Guymer[1], Kathleen Elford[2] and Geoffrey O. Littlejohn[1]. [1]Monash Medical Centre and Monash University, Clayton, Victoria, Australia, [2]Monash Medical Centre, Clayton, Victoria, Australia

Background/Purpose: Fibromyalgia is a common, chronic pain disorder. Initial development of symptoms occurs under conditions unique to each patient. Psychological and physical triggers are recognized, however their frequency and contribution to illness onset is less defined.

The aim of this study was to examine fibromyalgia triggers and identify clinical features linked to specific triggering situations.

Methods: Fibromyalgia patients seen in a public outpatient clinic were questioned using a standardized interview regarding the circumstances of their symptom onset. Demographic and clinical data were collected, including the Widespread Pain Index (WPI), Symptom Severity Score (SSS) and the Fibromyalgia Impact Questionnaire (FIQ). Patients were divided into groups based on whether or not they reported a trigger for their fibromyalgia, and if this involved increased levels of psychosocial stress, physical illness or injury. These groups were then compared for differences regarding clinical and demographic features.

Results: Information was collected on 260 consecutive patients. 232 (89.2%) patients reported a specific triggering situation corresponding to the onset of their symptoms. 77 (29.7%) described a triggering situation of purely increased psychosocial stress and a further 107 (41.3%) described a physical illness or injury combined with increased psychosocial stress. 46 (17.8%) described a purely physical trigger. Patients with a trigger involving increased psychosocial stress had a higher number of coexisting fibromyalgia-associated conditions (e.g. irritable bowel syndrome, temporomandibular joint disorder, etc) (p<0.005), higher levels of anxiety (p<0.05) and depression (p<0.05) than those patients who did not. If patients who had a psychosocial stress component of their trigger were currently regularly exercising, they had significantly lower FIQ scores (p<0.05), better physical function (p<0.05), less reported pain (p<0.05),

less sleep disturbance (p<0.05), fewer positive tender points (p<0.05), and a lower WPI (p<0.05) and SSS (p<0.05) than those patients who were not regularly exercising. Patients without a trigger involving increased psychosocial stress who were regularly exercising had lower FIQ scores (p<0.05) and less anxiety (p<0.05) only. If patients with psychosocial stress triggers were currently using medications with proven benefit in fibromyalgia (amitriptyline, duloxetine or pregabalin), they had better reported physical function (p<0.05) than those patients not using these medications. There was no significant clinical difference found between those using pain management psychology and those who were not, in the group of patients who had reported increased psychosocial stress as part of their trigger.

Conclusion: Most patients report a specific trigger for their fibromyalgia. The majority of these involved increased levels of psychosocial stress, including those with injury or illness. Patients with an increased psychosocial stress component to their trigger had less severe clinical features if they regularly exercised.

1882

Predictors of a Favorable Outcome in Patients with Fibromyalgia: Results From the 1-Year Follow-up. Dong-Jin Park[1], Shin-Seok Lee[1], Seong-Ho Kim[2], Seong-Su Nah[3], Ji Hyun Lee[4], Seong-Kyu Kim[5], Yeon-Ah Lee[6], Seung-Jae Hong[6], Hyun-Sook Kim[7], Hye-Soon Lee[8], Hyoun Ah Kim[9], Chung-Il Joung[10] and Sang-Hyon Kim[11]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Inje University Haeundae Paik Hospital, Busan, South Korea, [3]Soonchunhyang University, South Korea, [4]Maryknoll Medical Center, Busan, South Korea, [5]and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu, South Korea, [6]Kyung Hee University, Seoul, South Korea, [7]Internal Medicine, Chosun University Hospital, Gwangju, South Korea, [8]Hanyang University Guri Hospital, Guri, South Korea, [9]Ajou University School of Med, Suwon, South Korea, [10]Konyang University Medical School, Daejeon, South Korea, [11]Dongsan Medical Center, Keimyung University, Daegu, South Korea

Background/Purpose: To determine the outcomes in Korean patients with fibromyalgia (FM) and identify the prognostic factors associated with improvement at 1-year follow-up.

Methods: Forty-eight patients with FM were enrolled and examined every 3 months for 1-year. We interviewed these patients using a structured questionnaire that included sociodemograhpic data, current or past FM symptoms, and current use of relevant medications at the time of enrollment. Tender point counts and scores were assessed by thumb palpation. Patients were asked to complete a Korean version of the Fibromyalgia Impact Questionnaire (FIQ), the Brief Fatigue Inventory, the SF-36, the Beck Depression Inventory, the State-Trait Anxiety Inventory, the Self-Efficacy Scale, and the Social Support Scale. During follow-up, tender points, FIQ, and current use of relevant medications were recorded during 1 year follow-up period.

Results: Of the 48 patients, 32 (66.7%) had improved FIQ scores 1 year after enrollment. The improved patients had higher baseline FIQ scores (68.4±13.9 vs 48.4±20.8, p=0.001) and higher Trait Anxiety Inventory scores (55.8±10.9 vs 11.5±11.5, p=0.022). The patients treated with pregabalin which was added during the follow-up period were more likely to be improved after 1-year (71.9 % vs 37.5 %, p=0.031). In multivariate logistic regression analyses, the additional use of pregabalin and higher Trait Anxiety Inventory scores at baseline were the predictor of improvement (p=0.026 and p=0.043) and this statistical significance persisted after adjustment for age, gender, and disease duration (p=0.016 and p=0.037).

Conclusion: Two-thirds of the Korean FM patients experienced some clinical improvement by 1-year after enrollment. The use of pregabalin and anxiety were shown to be important predictors of improved FM. Interventions, particularly medications, may be associated with good outcome in a significant number of these patients.

1883

Efficacy and Safety of Joint and Soft Tissue Injections; A Retrospective Study. Jenny Cabas-Vargas[1], Leah Alon[2], Nina Ramessar[2], Dimitre Stefanov[2], Jose B. Toro and Deana M. Lazaro[4]. [1]SUNY Downstate, Brooklyn, NY, [2]SUNY Downstate Medical Center, Brooklyn, NY, [3]Brooklyn VA, Brooklyn, NY

Background/Purpose: Despite wide use of corticosteroid injection in the treatment of soft tissue and articular disorders, there is little data about its efficacy. We conducted a retrospective study to evaluate the effectiveness of corticosteroid (CS) and local anesthetic (LA) injections for treatment of musculoskeletal disorders (MSD).

Methods: The study was conducted at VA NYHHS; Brooklyn facility. Patients 18–85 years old who underwent CS or LA injection for MSD were identified by billing codes. The patients were invited to participate in a 28-question telephone survey. Information was collected regarding informed consent, impact on pain using pain score (PS 0–10), patient global assessment (PGA 0–100, 0 very poor-100 very well), functional status (M-HAQ) and side effects. Additional data was obtained by chart review. Descriptive analysis of all data collected and comparison of PS and PGA before and after the procedure were conducted.

Results: 116 patients were included in the final analysis. The average patient age was 60 years old, 85.3% men and 14% women.

The procedures were performed by different specialties, Rheumatology (30.17%), Podiatry (28.45%), Orthopedics (17.24%), Physical Medicine and Rehabilitation (12.07%), and Pain Management (12.07%). The most common indications were knee osteoarthritis (20.68%), plantar fasciitis (15.92%), rotator cuff tendinitis/impingement (15.92%) and trigger finger (8.62%). LA were used in combination with CS in the majority of procedures (91.96%).

Patients' overall satisfaction with their procedure was 85%. The average PS prior to the procedure was 8.6; post-procedure average PS decreased to 2.8 (p<0.001Wilcoxon signed rank test). 69.93% of patients reported immediate relief after the injection. PGA before and after the procedure improved from an average 24 to 75 (p<0.001Wilcoxon signed rank test). 87.9% of patients reported that they experienced improvement in functional status; patients reported improvement in the ability to dress (34%), ability to get in and out of bed (45%), ability to lift a cup to their mouth (24%), ability to walk outdoors on flat ground (50%), ability to turn regular faucets (23%), ability to get in and out of a vehicle (49%). 57.76% of patients reported less analgesic use after the procedure; the average benefit of the injection was 6.18 months (range 0–24 months). 25.86% of the patients had a second injection and 12.93% of the patients underwent surgery for the same MSD. No serious adverse effects were reported; 3 patients reported bruising, 1 patient mild bleeding with the injection, 3 patients reported skin changes and 1 uncontrolled hypertension afer the procedure. No infections were reported.

Conclusion: This retrospective study found that CS injections for MSD are associated with significant self-reported reduction in pain and improvement in functional status. There was high reported satisfaction with the procedures and benefits were long-lasting (average 6 months). Corticosteroid injections should be considered an important tool for clinicians treating musculoskeletal conditions. This study is limited by recall bias and diversity of procedures.

Disclosure: J. Cabas-Vargas, None; **L. Alon**, None; **N. Ramessar**, None; **D. Stefanov**, None; **J. B. Toro**, None; **D. M. Lazaro**, None.

1884

Fibromyalgia Patients Who Meet the ACR 1990 Criteria Have More Severe Disease. Carmen E. Gota[1], Benjamin Nutter[2] and William Wilke[3]. [1]The Cleveland Clinic Desk A50, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland, OH

Background/Purpose: To compare the fibromyalgia patients who meet the 1990 ACR criteria for fibromyalgia with those who do not.

Methods: All new consecutive patients diagnosed with fibromyalgia that were seen in the Rheumatology Department at the Cleveland Clinic by two physicians between September 1st, 2008 and January 31st, 2011, were enrolled in the study.

Enrollment in the study was based on clinician's overall impression of patient suffering from fibromyalgia.

Three hundred and six patients were enrolled.

Data collected included: demographics, detailed fibromyalgia symptoms, physical examination findings (tender points, brisk deep-tendon reflexes and carotid artery tenderness on palpation), family history of fibromyalgia and

mood disorders and comorbidities. All patients were asked to complete the following questionnaires: Brief Patient Health Questionnaire Mood Scale (PHQ-9), Epworth Sleepiness Scale (ESS), Mood Disorders Questionnaire (MDQ), Fibromyalgia impact questionnaire (FIQ), Symptom Intensity Scale (SIS) and Health Assessment Questionnaire Disability Index (HAQ-DI).

Results: We compared 240 fibromyalgia patients who met the ACR 1990 criteria with the other 66 patients who did not (lacked widespread pain or had <11 tender points). Patients who met the ACR 1990 criteria, compared to the rest of the patients, had higher depression scores, PHQ-9 12 (7.75, 16) vs 9.5 (5, 14.7), p<0.03; higher regional pain scores 12 (9, 15) vs 9 (6, 12), p<0.001; higher VAS fatigue 8 (7, 9) vs 7.25 (5, 9), p =0.022; higher symptom intensity score SIS 7 (6.21, 8.25) vs 6.25 (5.25, 6. 75), p <0.001; higher FIQ score 69.03 (65.1, 80.8) vs 59.95 (46.11, 72.74), p =0.001; higher difficulty with daily activities involving large muscle groups - FIQ-1 score 16 (7, 24) vs 12 (7, 20), p 0.039; less days when they felt well in the course of a week - FIQ-2 score 1(0, 2) vs 2 (0, 3), p = 0.003.

Conclusion: Fibromyalgia patients who meet the ACR 1990 criteria represent a more severe subset, manifested by more disability, and higher depression scores.

Disclosure: C. E. Gota, None; **B. Nutter**, None; **W. Wilke**, None.

ACR/ARHP Poster Session C
Medical Education
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

1885

Rheumatologists' Ultrasound Confidence and Interpretation of Normal Anatomy Are Improved by a Cadaver Based Sonoanatomy Course. Iain Goff[1], David Wright[2] and Debra Patten[3]. [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Sunderland Royal Hospital, Sunderland, United Kingdom, [3]School of Medical Sciences Education and Development, Newcastle upon Tyne, United Kingdom

Background/Purpose: Correct interpretation of musculoskeletal ultrasound (MSUS) requires thorough knowledge of normal 3D anatomy, but several authors report deficiencies in anatomy skills among rheumatologists. Cadaver-based anatomy review courses improve clinical and injection skills, but the value of such courses in MSUS training is unclear. During 2010-12 we delivered two cadaver based, MSUS anatomy courses for the British Society of Rheumatology (BSR), and a self assessment questionnaire was devised to measure confidence to perform key MSUS learning objectives before and after the course.

Methods: The two day course in March 2012 consisted of orientation lectures with MR imaging; expert led, small group workshops handling cadaveric specimens; simultaneous access to real-time ultrasound on live models; and ultrasound practice on patients with pathological anatomy. Ten item confidence logs based on BSR core competency outcomes and ability to diagnose EULAR pathologies were completed by the delegates before, after and four weeks following the course. Standardised imaging protocols with anatomy checklists devised by tutors from the BSR ultrasound special interest group were used to guide scanning technique and to assess delegate ability to locate specific anatomic structures with ultrasound.

Results: Twenty delegates attended the course. Delegate feedback rated the course very highly (Overall mean satisfaction score = 4.25, 1=poor, 5=excellent). Confidence logs collected from all 20 delegates demonstrated low levels of confidence in core domains pre-course (mean 3.5/10), improving to mean 5.5/10 immediately post-course (paired t test p< 0.001) with significantly improved confidence at 4 weeks compared to baseline in 7/10 domains (paired t test p< 0.05, see table).

Competency outcome	Delegate Confidence (0–10)		
	Pre-Course	End of course (all p< 0.001)	Four Weeks (* p< 0.05)
Perform structured assessment of each anatomic area	3.3	6.0	5.7*
Identify, demonstrate and interpret anatomy	3.4	6.0	6.0*
Identify, demonstrate and interpret pathology	3.2	5.5	6.0
Use US to guide aspiration and injection	3.4	5.1	5.8*
Correlate US with other imaging modalities	3.2	5.7	6.5*
Prepare a written report and archive images	2.7	4.5	5.5
Understand clinical relevance and apply to patient management	5.3	6.3	7.8*
Correctly diagnose EULAR basic pathology	4.3	5.6	6.5
EULAR intermediate pathology	3.4	5.1	5.3*
EULAR advanced pathology	2.3	3.6	3.1*

Anatomy checklists were completed and returned by 13 delegates. Most structures were located at the shoulder, elbow, wrist, knee and ankle (68–72% of structures located) though fewer structures were visualised at the hip (44%).

Conclusion: This cadaver based anatomy review course produced significant improvement in confidence across a range of MSUS competencies including interpretation of normal anatomy, which was maintained after 4 weeks. Expert led, small group workshops handling cadaveric specimens with simultaneous practice of MSUS on live models is an effective model for MSUS anatomy training. This method of teaching was highly regarded by the delegates, and imaging protocols and checklists are a useful tool for self assessment.

Disclosure: I. Goff, None; **D. Wright**, None; **D. Patten**, None.

1886

Evaluation of a New Educational Tool: A Resident's Guide to Pediatric Rheumatology. Tania Cellucci and Ronald M. Laxer. The Hospital for Sick Children, Toronto, ON

Background/Purpose: "A Resident's Guide to Pediatric Rheumatology" was specifically designed to address a gap in pediatric rheumatology teaching resources. It was intended for medical students and residents who participate in pediatric rheumatology rotations as part of their training program. The aims of this study were to determine whether the Guide was reaching its target population and to evaluate its perceived utility, frequency of use, and user satisfaction.

Methods: The Guide was developed by rheumatology staff and fellows at The Hospital for Sick Children in 2011 and provides a summary of common pediatric rheumatology topics. It was distributed electronically at no cost to interested training programs. All individuals who requested a copy of the Guide were contacted via email to solicit their participation in an online survey. The survey collected information on: (1) participant demographics; (2) frequency and methods in which the Guide was used; (3) ratings of user satisfaction on a 5-point Likert scale (level 1 outcome of Kirkpatrick's evaluation model); and (4) identification of perceived positive and negative features of the Guide.

Results: An invitation was sent to 261 recipients of the Guide and 81 (31% response rate) completed the survey. Participants included 45 staff pediatric rheumatologists, 18 residents, 7 pediatricians, 5 pediatric rheumatology fellows, 3 adult rheumatology fellows, 2 occupational therapists, and 1 nurse practitioner. The Guide was used for teaching by 63% of participants and for learning by 48%. As expected, no staff physicians used the Guide as a learning tool; however, fellows and residents reported using the Guide to study as well as to teach. Most teachers (90%) provide the Guide to trainees to read independently during rotations, while a smaller group use the Guide to stimulate discussion (37%) or as part of case-based teaching (35%). Frequency of use was described as weekly (20%), monthly (30%), or every few months (30%). Overall, participants were satisfied with the Guide as a teaching resource (69% very satisfied, 20% somewhat satisfied) and learning resource (65% very satisfied, 22% somewhat satisfied). The most commonly cited positive features were its' free availability, and balance between comprehensive and concise information.

Conclusion: The Guide appears to fill an identified gap in pediatric rheumatology resources for non-rheumatology trainees. Uptake of the Guide as a learning tool was broader than the intended audience since fellows report using it for teaching and learning. Further study is required to determine if the Guide increased knowledge in non-rheumatology trainees (Kirkpatrick level 2 outcome) and changed teaching behaviours by pediatric rheumatology teachers (Kirkpatrick level 3 outcome).

Disclosure: T. Cellucci, None; **R. M. Laxer**, None.

1887

Facebook Support Groups in Systemic Lupus Erythematosus: Content Analysis. Evelyne Vinet[1], William Shihao Lao[2], Christian A. Pineau[1], Ann E. Clarke[3] and Sasha Bernatsky[4]. [1]McGill University Health Centre, Montreal, QC, [2]McGill University, Montreal, QC, [3]MUHC, Montreal, QC, [4]Research Institute of the McGill University Health Ctre, Montreal, QC

Background/Purpose: Facebook is the most important social network site, with over 600 million registered users worldwide. Many disease-specific groups exist on Facebook, offering a convenient way to exchange information and support, particularly for patients affected with a rare disease such as systemic lupus erythematosus (SLE). However, no one has explored the content of SLE-related groups on Facebook. We aimed to evaluate the purpose of the SLE-related groups on Facebook, and assess the patterns of use and the information shared on the groups dedicated to support.

Methods: We searched Facebook groups using the term "lupus", from 10/08/2011 to 01/04/2012. We selected groups related to SLE, operating in English or French, and publicly accessible. We extracted information on the purpose of the group and its administrator, as well as on the number and type of user-generated contributions. We analyzed the content of support groups using a previously developed coding scheme.

Results: We found 173 SLE groups on Facebook containing a total of 42 240 members. Half (49%) of the groups were created for support, while 32% were for disease awareness and 14% for fundraising. The largest group included 30 972 members and was intended for awareness. 3469 members were found in support groups, representing 31% of the overall membership (when excluding the largest group), and the median number of members was 11 (interquartile range, IQR, 39). The most frequent support group locations of origin were the United States (46%), Canada (10%), and United Kingdom (10%). In support groups, the total number of user-generated contributions was 1932, including wall posts (54%), comments (32%), discussion posts (10%), and discussion threads (4%), while the median number of user-generated contributions was 5 (IQR 20).

Conclusion: Support groups represent a substantial proportion of Facebook groups dedicated to SLE. Given their convenience, accessibility, and potential audience, Facebook support groups might represent an efficient way to reach patients with SLE and improve their wellbeing. Further research should evaluate the effect of this type of support groups on patients with SLE.

Disclosure: E. Vinet, None; **W. S. Lao**, None; **C. A. Pineau**, None; **A. E. Clarke**, None; **S. Bernatsky**, None.

1888

Immunology for Rheumatology Residents: Working towards a National Curriculum Consensus. Shirley L. Chow[1], Dharini Mahendira[2], Sari Herman-Kideckel[3] and Heather McDonald-Blumer[4]. [1]University of Toronto, Toronto, ON, [2]St Michael's Hospital, Toronto, ON, [3]University of Toronto, North York, ON, [4]Mt. Sinai Hospital, Toronto, ON

Background/Purpose: Immunologic mechanisms play an integral role in the understanding of rheumatic conditions. Currently, there is limited access to standardized formal instruction in immunology for trainees across Canada. A comprehensive immunology curriculum is essential for adult rheumatology trainees to meet the competencies required for practice and mandated by the national accrediting body.

The purpose of this project is to review the current immunology curriculum amongst adult rheumatology training programs across Canada. We will compare the self identified learning needs of rheumatology residents with the perceived learning needs of rheumatology program directors and will seek to integrate these needs into a focused nationwide immunology curriculum for rheumatology training programs

Methods: Rheumatology trainees and program directors from rheumatology programs across Canada were asked to complete an online questionnaire and rank a comprehensive list of immunology topics. A modified Delphi approach was used to obtain consensus on topics to be included in the curriculum.

Results: 38 rheumatology trainees and 15 program directors were contacted between March 1 to May 31 2012. 42% of trainees and 66% of program directors responded, with a total 49% response rate. Of the rheumatology trainees, 67% had prior experience in immunology, which consisted of undergraduate and graduate courses. Teaching formats and formal teaching hours varied between sites. Only 31% of trainees and 42% of program directors felt the current method of teaching immunology was effective. Preliminary results reveal high concordance between the majority of topics ranked by Trainees and Program Directors. However, discordance was seen with the topics of diagnostic laboratory immunology and therapeutics, immunomodulators and immunosupressants.

Conclusion: There is a need to improve immunology teaching in rheumatology training programs. Preliminary results show a high concordance between the majority of topics ranked by trainees and program directors, however discordance is seen with others. Final completion of the Delphi will allow for a national consensus and more definitive conclusions. This study provides the groundwork for development of future national immunology curricula.

Disclosure: **S. L. Chow**, None; **D. Mahendira**, None; **S. Herman-Kideckel**, None; **H. McDonald-Blumer**, None.

1889

The Effects of Physical & Mental Health Rehabilitation Program (PMHRP) for Hemophilic Arthritis Patients. Won Sook BAK[1], Myung Chul Yoo[1], Nam Su Cho[1], Sang Hack Lee[1], Yoon Hee Kim[2] and Ki Young Yoo[1]. [1]Kyung Hee University Hospital at Gangdong, Seoul, South Korea, [2]Seoul, South Korea

Background/Purpose: Most of the rehabilitation program for patients with hemophilic arthritis are focused on only the improvement of physical activities. However, the actual hemophilic arthritis patients are accompanied by mental problems as well as physical disabilities, so a rehabilitation program to improve physical and mental problems simultaneously is needed. PMHRP was developed to solve these problems through increasing the interpersonal relationship, developing each potentials, self-development and understanding others. PMHRP was analysed by two different groups to verify the clinical effectiveness.

Methods: This study used a nonequivalent control group quasi-experimental research based on data acquired through a pre-post test. The subjects for this study were a total of 53 patients with hemophilic arthritis who underwent lower extremity joint surgeries at the orthopedic. The experimental group(n=24)was attended PMHRP 5 times(4hours/time) for 4 weeks, and the control group(n=29) was not given any physical & mental health rehabilitation program. The measurement tools of this study were Numerical Rating Scale for 100mm Pain VAS, 100mm Fatigue VAS, self efficacy, self esteem, quality of life, SCL-90-R(Symptom Checklist-90-Revision) and WOMAC Scale. The data was analyzed with X^2-test and t-test using SPSS/Win18.0.

Results: After PMHRP application, self efficacy score increased significantly in the study group and self esteem score also increased (p<.001). On the contrary, these scores decreased after 4 weeks in the control group. 100mm Pain VAS & 100mm Fatigue VAS, and quality of life scores improved significantly in the study group(p<.001). SCL-90-R scores decreased significantly after the program (p<.001). Although there were no statistically significant differences in WOMAC scores between two groups, however, the average score was changed from pre-treatments(M=36.51) to post-treatment(M=30.08) and it revealed the alleviation of arthritic symptoms and improvement of activities.

Conclusion: In conclusion, PMHRP showed much more satisfactory results than the simple physical therapy to treat the physical and mental disabilities including psychosocial stresses in patients with hemophilic arthritis by increasing the self esteem and quality of life by themselves. These results suggest that PMHRP is highly recommended as a distinguished method of rehabilitation for patients with hemophilic arthritis.

Disclosure: **W. S. BAK**, None; **M. C. Yoo**, None; **N. S. Cho**, None; **S. H. Lee**, None; **Y. H. Kim**, None; **K. Y. Yoo**, None.

1890

The Current State of Mentoring Among Pediatric Rheumatology Fellows and Junior Faculty in the United States and Canada. Meredith P. Riebschleger[1], Eyal Muscal[2], Matthew M. Davis[3], Hermine Brunner[4], B. Anne Eberhard[5], C.J. Inman[6], Marisa S. Klein-Gitelman[7], Lakshmi N. Moorthy[8], Marc D. Natter[9], Sampath Prahalad[10], Rayfel Schneider[11] and Peter A. Nigrovic[12]. [1]University of Michigan Health System, Ann Arbor, MI, [2]Baylor College of Medicine, Houston, TX, [3]University of Michigan, Ann Arbor, MI, [4]Cincinnati Children's Hospital Medical Center and PRSCG, Cincinnati, OH, [5]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [6]University of Utah, Salt Lake City, UT, [7]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [8]Robert Wood Johnson-UMDNJ, New Brunswick, NJ, [9]Children's Hospital Boston, Boston, MA, [10]Emory Children's Center, Atlanta, GA, [11]The Hospital for Sick Children, Toronto, ON, [12]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Prior studies have shown that mentoring increases professional success among physicians. Many pediatric rheumatology (PR) divisions are small, which may limit options for mentoring. The ACR/Childhood Arthritis and Rheumatology Research Alliance (CARRA) Mentoring Interest Group (AMIGO) is a new collaborative effort to promote professional development within PR via cross-institutional mentoring. In this study, we describe the pre-AMIGO state of mentoring among PR fellows and junior faculty in the US and Canada.

Methods: A cross-sectional web-based survey of all pediatric rheumatologists in the US and Canada was conducted Nov 2011-Jan 2012. The survey was distributed via ACR, CARRA, and McMaster PR email lists. Where possible, survey items were drawn from validated scales. For this study, the analysis cohort was limited to include fellows and junior faculty, as AMIGO targets those groups. Independent variables included respondent demographics; dependent variables included the reported presence and location of mentors and overall satisfaction with mentoring received on a 5-point Likert scale. Chi square tests were used to assess associations.

Results: 135 respondents were included in the analysis cohort. 42% of the analysis cohort were fellows (estimated subgroup response rate 64%) and 58% were junior faculty (estimated subgroup response rate 70%). 74% of the analysis cohort were female; 95% were employed in academic institutions; and 96% were fellowship-trained. Most respondents had a clinical mentor, while fewer had mentors for important career-related tasks such as identifying funding sources, defining career goals, and understanding how to achieve career goals (Figure 1). Fellows and junior faculty were equally likely to have clinical mentors, but fellows were more likely to have research mentors; 5% of fellows and 26% of junior faculty reported no research mentoring (p<.01). Both fellows and junior faculty reported finding mentors outside their home PR divisions.

Figure 1: Location of Mentors

Do you have a mentor who you go to for:
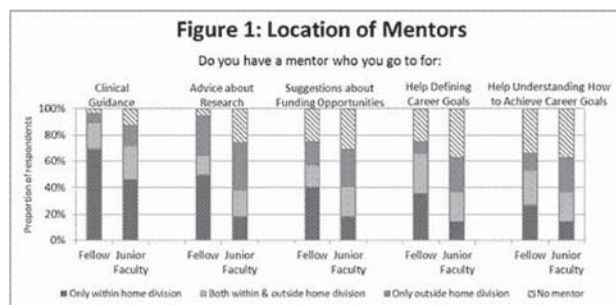
Overall, 74% of fellows and 64% of junior faculty were somewhat or very satisfied with the mentoring they receive. The presence of a mentor in any domain was associated with an increased likelihood of satisfaction with mentoring (all p<.01). This association was strongest for having a mentor who helped respondents understand how to achieve their career goals; 84% of those with a mentor in this domain were satisfied with mentoring, compared to only 17% of those without (p<.001).

Conclusion: Many PR fellows and junior faculty members lack mentors in specific areas of career development. Programs such as AMIGO may have a role in providing cross-institutional mentors in critical career-related domains. Future studies will assess changes in mentee satisfaction and academic achievement for pediatric rheumatologists engaged in the AMIGO program and for the PR community at large.

Disclosure: **M. P. Riebschleger**, None; **E. Muscal**, None; **M. M. Davis**, None; **H. Brunner**, None; **B. A. Eberhard**, None; **C. J. Inman**, None; **M. S. Klein-Gitelman**, None; **L. N. Moorthy**, None; **M. D. Natter**, None; **S. Prahalad**, None; **R. Schneider**, None; **P. A. Nigrovic**, None.

1891

Teaching Medical Students Principles of Chronic Disease: Medicine of the 4th and 5th Dimension At Weill-Cornell. Michael D. Lockshin[1], Greg McDermott[2], Lester Zambrana[2] and Alana B. Levine[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill-Cornell Medical College, New York

Background/Purpose: Medical students learn about acute illness and sometimes have experience with longitudinal care, but they do not encounter concepts specific to the management of chronic, non-lethal, intermittent, disabling illness, such as the rheumatic diseases. Here we describe a novel curriculum designed to address this gap.

Methods: We initiated a pilot course on chronic illness at Weill-Cornell Medical College, Medicine of the 4th and 5th Dimension (time and communication). The course did not focus on biology or treatment. Each of 7 seminar sessions focused on one or more of the following themes: *time scales* (making decisions for immediate, short-term, and long-term needs); *communication* (patient priorities, hearing the unsaid, seeing the unseen, physician arrogance); *living with disability*; *managing co-morbidity*; *decision-making when the evidence is incomplete* or the patient disagrees; *working with other medical personnel*; attending to *externalities* (family, insurers, society); and *maintaining an identity* other than that of a person with a chronic illness. At the conclusion of the course students submitted essays on strengths and weaknesses of the course; patients were interviewed separately.

Results: Two first-year and one fourth-year students, one rheumatology fellow, one parent-patient advocate, one parent, and 9 patients participated. Patients had lupus, scleroderma, Sjogren's with and without cryoglobulinemia, Wegener's, kidney transplant, and undefined autoimmune illnesses. Patients were 17–60 years old, female, and of Caucasian, Hispanic, and Asian ethnicities (two African-Americans initially volunteered to participate but did not). All patients, recruited from rheumatology practices, were articulate and well-informed about their illnesses.

Students particularly valued the ability to learn *from* rather than *about* patients. They noted that: there is a distinction between "staying healthy" and "getting well"; patients are not defined by their disease; fear of future pain can be worse than current pain; humble and arrogant physicians have different effects on patients; lectures on empathy do not substitute for hearing a patient's words and observing her body language; not all problems have right answers; external influences affect patients' decisions.

Students asked for more didactic instruction on how to speak to a patient when knowledge is uncertain. They asked for a session how to manage stalled progress (keeping up patients' hope) in a chronic illness. Because the patients had been selected for reliable attendance and for articulateness, students felt they did not get a sense of managing a patient across language, cultural, socioeconomic or intellectual barriers. They felt that video-taped interviews or on-line exercises would not substitute for face-to-face interviews.

Conclusion: This pilot program identified important needs of students with regard to learning about chronic illness. With a larger program (more students, more time per year, more years in medical school, broader patient base) these needs can be met.

Disclosure: M. D. Lockshin, None; G. McDermott, None; L. Zambrana, None; A. B. Levine, None.

1892

Impact of a Lupus Patient Education Event On Knowledge about Systemic Lupus Erythematosus. Mithu Maheswaranathan[1], Melissa A. Cunningham[2], Sharon Wolf[1] and Diane L. Kamen[3]. [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC, [3]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC

Background/Purpose: There is a need for educational interventions to boost chronic disease management skills among patients. To address this need, we created a lupus patient education event comprised of a panel of multidisciplinary experts to provide information to lupus patients. The study objectives were (1) to survey the local lupus population regarding their lupus-related questions and (2) to assess the impact of this event on patient knowledge about lupus.

Methods: A planning team including representatives from the community, medical school, and rheumatology division oversaw the creation and execution of the event. Patients with lupus (n=550) who had given permission to be contacted were invited to the event and those who registered were sent a pre- and post-event lupus knowledge survey via email. Rheumatologists presented topics including a lupus overview, cardiovascular health, reproductive health and contraception for teens and adults, clinical research trials, and answered questions submitted from the audience. A motivational speaker discussed ways to overcome challenges in managing a chronic disease, and a nurse educator presented material on speaking to your doctor about lupus.

Results: 91 individuals attended the Lupus Patient Education Event in October 2011. The pre- and post-event surveys were sent via email to all attendees, of which 39 individuals responded to the pre-test and 22 individuals responded to the post-test. The mean age of responders was 39 +/−14 years. 81% of total responders were lupus patients. Respondents had limited awareness about belimumab as an FDA-approved medication for lupus (59% pre, 86% post), meaning of a positive ANA (64% pre, 73% post), malar rash

as a symptom of lupus (67% pre, 91% post), and age groups most at risk (74% pre, 86% post).

The knowledge questionnaire demonstrated an increase in patients' knowledge about lupus after attending the event, especially regarding risk factors and knowledge about the disease state. Overall patients had less awareness about the meaning of a positive ANA, biologic medications (e.g. belimumab) and some of the characteristics of lupus including symptoms and risk factors prior to the event, with scores improving after attending the event (Table 1).

Table 1. Pre-test and post-test results from participants

Theme	Question	Pre-Test (% Correct)	Post-Test (% Correct)	p value
Etiology	how lupus damages body	100	100	NS
Etiology	what is the cause of lupus?	100	95	NS
Knowledge/Acuity	what SLE stands for	100	100	NS
Knowledge/Acuity	meaning of a positive ANA	64	73	0.472
Knowledge/Acuity	medications safe in pregnancy	89	86	NS
Knowledge/Acuity	FDA-approved medication	59	86	0.036
Knowledge/Acuity	malar rash	67	91	0.036
Knowledge/Acuity	protein in urine	97	100	NS
Risk Factors	age group most at risk	74	86	0.275
Risk Factors	risk in men vs. women	90	86	0.6375
Risk Factors	African Americans and SLE	90	100	0.125
Comorbidities	comorbidities (CVD, Vit D)	92	95	NS

*NS = non-significant

Of 48 individuals who responded to the post-event evaluation, 91.3% said they felt we achieved the goal of providing information and education about lupus which will impact disease management and overall health.

Conclusion: The improvements in scores suggests efficacy of the patient education event in increasing awareness and knowledge about lupus in those who attended. The interactive nature of a symposium enables quality information to be disseminated to patients and families, and for patient questions to be answered. Future events will emphasize topics suggested by participants and provide more interactive sessions.

Disclosure: M. Maheswaranathan, None; M. A. Cunningham, None; S. Wolf, None; D. L. Kamen, None.

1893

Eliciting Prescribing Choices of Anti-Tumour Necrosis Factor Therapy From Rheumatology Trainees. Rodney A. Hughes[1] and Alison J. Carr[2]. [1]St. Peters Hospital, Chertsey Surrey, United Kingdom, [2]Hamell Communications, London, United Kingdom

Background/Purpose: A rheumatologist's choice of anti-TNF prescription is likely to be influenced by a number of factors. Doctors believe their prescribing to be evidence-based, rational and justifiable. With greater understanding of health behaviour, it is likely that prescribing decisions about anti-TNF will involve conscious and sub-conscious factors. We conducted a clinical decision exercise with senior rheumatology trainees to try better to understand these influences and whether all doctors take into account patient perceptions and preferences.

Methods: 12 trainees were each given an IPad with details of 30 individual simulated patients, based on real patients with RA. For each individual 'iPad' patient doctors were asked to decide whether to start anti-TNF and which brand they would prescribe if they did. Each doctor was in training at a different hospital with different local anti-TNF guidelines for therapy although all purported to follow UK national guidelines for anti-TNF drug therapy. IPad patients differed in gender, age, disease duration and disease activity score, previous drug history and symptoms of stiffness and function. Work status varied as did quality of life measures and aspects of patient choice. iPads were coded to allow attribution of answers and data were analysed anonymously by a third party from the recorded iPad answers at a later time and place.

Results: The analysis of results indicated that doctors could be fitted broadly into one of two categories; Evidence-based decision makers (EBDs) and Intuitive patient-focused decision makers (IPDs) according to the way that doctors in these two groups made decisions. Prescribing choice appeared independent of the background of the doctor and geographical area of training and extent of rheumatological experience.

EBD's stuck rigidly to guidelines for initiation of anti-TNF therapy and took no account of subjective data or patient specific concerns of preferences. EBD's were rigid in their choice of anti-TNF and chose the same product for all patients who were going to be initiated onto anti-TNF. EBD's appeared not

to feel that patients could make informed decisions or choices about treatment. EBD's did not think that adherence would be a problem with ant-TNF therapy. In contrast IPD's ignored guidelines around the threshold for starting anti-TNF in cases where they felt that patients would benefit from anti-TNF. With IPD's patient factors were important in driving treatment decisions – quality of life and impact of RA on the ability to work strongly influenced decisions. IPD's responded to patient requests, concerns and preferences in making prescribing choices and were more likely to tailor their choice to fit best with patient-specific characteristics. IPD's felt that patients could and should make informed decisions about their treatment and recognised that adherence was potentially a problem even with anti-TNF drugs.

Conclusion: As with many health care decisions there appear to be strong sub-conscious influences on anti-TNF prescribing that introduce variance into treatment decisions. Recognition of different groups of prescribers suggests that information given to doctors might be processed differently by different groups.

Disclosure: R. A. Hughes, None; **A. J. Carr**, None.

1894

Factors Associated with Confidence Level of Rheumatology Fellows in Joint Procedural Skills. Tara J. Rizvi, Min Xu and Nancy Searle. Baylor College of Medicine, Houston, TX

Background/Purpose: Rheumatology fellowship programs in the U.S. lack clear standardized criteria to train fellows in joint procedural skills. More recently, some programs are utilizing joint simulated anatomical models (JSM); some are introducing musculoskeletal ultrasound (MSUS) modalities. We sought to determine whether these instructional modalities, and/ or other factors were associated with fellow's confidence level in procedural skills. The purpose of our study is to determine factors associated with overall level of confidence of rheumatology fellows in the United States, in joint procedural skills.

Methods: An online survey was sent to junior and senior fellows enrolled in rheumatology programs in the United States. Survey included questions pertaining to: fellowship year, training on joint simulated models, training with musculoskeletal ultrasound, other instructional methods employed for procedural skills, attending physician supervision during procedures, number of times 25 individual procedures were performed, fellow's confidence level in 25 individual procedures and overall confidence level in procedural skills. Statistical analysis including chi-square test and spearman correlation coefficiency were performed using SPSS10.0.

Results: Data was obtained from 139 respondents: 63 junior and 76 senior fellows. 80 out of 103 accredited fellowship programs responded, so sample was representative of the majority of adult fellowship programs. 39/ 139 (28%) and 50/139 (36%) fellows reported being trained on JSM and MSUS respectively. Factors associated with fellow's overall confidence level for joint procedural skills are: years of fellowship training and training on joint simulated anatomical models (Table 1). Confidence levels for individual joints significantly correlated with the number of times procedure had been performed (p<0.01). MSUS training, other instructional modalities, and attending physican supervision were not significantly associated with overall confidence level.

Table 1. Factors associated with overall confidence level

ASSOCIATION WITH CONFIDENCE LEVEL	CHI-SQUARE	P-VALUE
Year of fellowship*	15.451	0.004
Joint simulation models*	11.995	0.017
Musculoskeletal ultrasound	6.283	0.179
Videos	7.713	0.103
Cadavers	3.585	0.465
Demonstration on patients	2.186	0.702
Attending physician presence	24.146	0.086

Conclusion: Factors associated with higher confidence level of rheumatology fellows in joint procedures include: training on joint simulated models, year of fellowship training and the number of opportunities to perform individual procedures. To improve fellow's level of confidence and hence improve procedural training, it may be suggested that training authorities encourage use of joint simulated models, and set standarized criteria to ensure adequate exposure for all fellows to procedures thought to be necessary for graduation.

Disclosure: T. J. Rizvi, None; **M. Xu**, None; **N. Searle**, None.

1895

Safety Competences Knowledge and Behavioural Skills of Patients Treated by Biologics in Rheumatology. Anne-Christine Rat[1], Bruno Fautrel[2], Elisabeth Flipon[3], Laure Gossec[4], Benoit-Damien Caritey[5], Laurent Marguerie[6], Henri Nataf[7], Beatrice Pallot Prades[8], Rose Marie Poilvert[9], Valerie Royant[10], Fathia Sadji[11], Christelle Sordet[12], Corinne Thevenot[13] and Catherine Beauvais[14]. [1]Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, F-54 000, Nancy, France, [2]APHP-Pitie Salpetriere Hospital/UPMC, Paris, France, [3]Cochin hospital, Paris, France, [4]Paris-Descartes University, Cochin Hospital, Paris, France, [5]Université de lorraine, Nancy, France, [6]Institut Calot, Berck, France, [7]Mantes-la-Jolie, Mantes-la-Jolie, France, [8]Saint Etienne university hospital, Saint Etienne, France, [9]Saint Antoine Hospital, Paris, France, [10]Chartres, Chartres, [11]Victor Jousselin Hospital, Dreux, France, [12]Strasbourg University Hospital, Strasbourg, France, [13]Laon hospital, Laon, France, [14]Saint Antoine, Paris, France

Background/Purpose: Biologics are known to entail specific risks; therefore teaching patients safety skills, appropriate behaviours in situations of risks and what decisions to take in these situations is necessary. The level of knowledge of safety competences are not well known in patients treated by biologics.The objective of the study was to describe the safety competences of patients treated by biologics for inflammatory arthritis and to determine the factors associated with a lower level of competences.

Methods: Data were obtained from a national cross-sectional survey. To be as representative as possible of the patients treated by biologics, rheumatologists were randomly sampled from the national directory. They were invited to include 3 to 5 consecutive patients treated by biologics whatever their inflammatory arthritis diagnosis.All patients completed a 55-item questionnaire (*BioSecure**) assessing patients' self-care safety skills and sociodemographic characteristics, type of information received, quality of life and coping style data. Rheumatologists completed personal and practice data.The questionnaire measuring knowledge and skills regarding biologics was developed by health professional and patients using 3 steps: elaboration of an exhaustive list of competences, selection via a Delphi technique then elaboration of a questionnaire for the 26 competences selected. The questionnaire includes a series of multiple-choice questions on knowledge and on clinical situations grouped in dimensions.

Results: Of the 671 patients included, 67% were women, 62% had RA and 38% spondylarthritis, 63% were treated by subcutaneous antiTNF. The mean age was 53 ± 13 years old. Patients received information during a medical consultation (90%), a consultation with a nurse (30%), with a written booklet (59%) and during a therapeutic education program (11%). The median total score (percentage of right items) was 73 (interquartile 60–82). Knowledge items had not higher percentages of correct answers than behavioural skills items. Scores and number (%) of patients with a number of correct answers lower than 50% are described in the table. In multivariate analysis, several patients' factors were associated with a lower level of competences: living alone, a lower education level, living in a big city, not to be employed and having not received written information or therapeutic education. Rheumatologists treating more than 80 patients with biologists had an increased risk of having their patients in the moderate skills group compared to the high skills group.

		N° items	Median	Q1	Q3	Patients with a n° of wright items < 50% N	Patients with a n° of wright items < 50% %
Biologics management		11	**100.0**	90.9	100.0	12	**(1.8)**
	General knowledge	4	**100.0**	75	100.0	24	**(3.6)**
	Communication	4	**100.0**	100	100	17	**(2.5)**
When to consult		15	**73.3**	53.3	86.7	145	**(21.4)**
	Fever	11	**81.8**	54.5	90.9	127	**(18.8)**
	Infectious symptoms	4	**75.0**	25	100	188	**(27.8)**
Specific situations		19	**73.7**	52.6	84.2	128	**(18.9)**
	Vaccination. Injuries	8	**62.5**	50	87.5	167	**(24.7)**
	Dental care	2	**100.0**	50	100	79	**(11.7)**
	Surgery	7	**85.7**	57.1	100	86	**(12.7)**
	Planning child conception	2	**50.0**	0	100	336	**(49.6)**
Sub-cutaneous injection		3	**66.7**	66.7	66.7	245	**(36.2)**

Conclusion: Safety competences can be improved, especially competences needed to deal with infectious symptoms, vaccinations, planned surgery and planning child conception. These results provide also elements to

help identifying patients who need therapeutic education or to adapt the messages given.

*L Gossec. Ann Rheum Dis 2010;69(Suppl3):476

1896

Variation in US Pediatric Rheumatology Fellowship Training. Anjali Patwardhan[1], Michael Henrickson[2], Sandy D. Hong[3], Laura Laskosz and Charles H. Spencer[1]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]U of Iowa Children's Hosp, Iowa City, IA

Background/Purpose: Pediatric rheumatology (PR) became an American Board of Pediatrics subspecialty in 1990. This is the first survey to examine training differences between the 31 US PR fellowship programs. We hypothesize that there is infinite variation in the Pediatric Rheumatology Fellowship Training across North America.

Methods: Members of the American Academy of Pediatrics (AAP) Section of Rheumatology and its Executive Committee conducted this cross-sectional study. We developed the survey instrument through extensive literature research and the Delphi consensus technique. Following institutional human subjects research review and approval, we distributed the survey to PR trainees (n=82).

Results: We obtained a 57% response rate (n=47). Respondents' training level followed a normal distribution: initial (8%); completion of 1st year (16%), 2nd year (34%), 3rd year (37%) and 4th year (5%). Their clinical commitments involved the following half-day sessions per week: 1 (28%), 2 (43%), 3 (13%), 5 (11%), and 6 (4%). Sixty percent provided care for either 4 (30%) or 5 (30%) patients per session. Procedural experience included joint injections and musculoskeletal ultrasound. Respondents' average number of joint injections per month comprised 0–1 (55%), 2–4 (37%), and ≥ 5 (7%); 20% received formal ultrasound training. On-call experience at home involved nights and weekends; the latter also included inpatient rounds for 98% of respondents. The range of nights on-call was 0–15, distributed as: 0 (2%), 3 (16%), 7 (27%), 10 (14%) and 15 (7%). The range of weekends on-call was 1–4, distributed as: 1 (37%), 2 (39%), 3 (9%) and 4 (9%). Educational session hours attended varied among trainees: 2 (13%), 3 (35%), 4 (29%) and ≥ 5 (22%). Sessions included journal club presentations (range=1–8/year), trainee-presented PR lectures (97%), resident education (88%), and attendance at specialty conferences with adult rheumatology (81%), radiology (59%), nephrology (48%) and histopathology (43%). Respondents' research activity hours per week (range= 20 to > 60) varied: ≤ 20 (43%), 21–40 (43%), 41–60 (11%), > 60 (2%). Respondents presented abstracts at regional or national academic meetings in a range of 1 (32%) to 8 (6%). Regarding published papers, 41% had one, while 59% had none.

Table. Please indicate the average number of patients you have seen in each group during your fellowship

Disease Groups	'Number of patients seen' subgroup (numbers in italics denote % of responders)						Range of exposure
	0–5	6–10	11–20	>20	Never observed/qatreated	Response Count	
Existing Diagnosis of SLE	11.3	13.6	31.8	43.1	0	44	43.1% of responders see >20 & Only 11.3% responders saw less than 5 of previously diagnosed SLE patients
SLE Nephritis	20.4	25	27.2	27.2	0	44	27.2% of responders saw >20 while 20.4% responders saw <5 patients with SLE nephritis
New Case of SLE	29.5	34	31.8	4.5	0	44	29.5% responders saw <5 cases while only 4.5% responders saw >20 cases of newly diagnosed SLE
Existing Diagnosis of WG	68.1	22.7	4.5	0	4.5	44	68.1% of responders saw < 5 patients while 4.5% responders never saw a patients with previously diagnosed WG
New WG	86.3	6.8	0	0	6.8	44	86.3% of responders saw < 5 patients while 6.8% responders never saw a patients with newly diagnosed WG
Scleroderma	47.7	29.5	20.45	5	0	44	47.7% of responders saw < 5 patients while no one saw <20 patients with scleroderma
Sjogren's Syndrome	62.7	23.2	4.6	0	9.3	43	62.7% of responders saw < 5 patients while 9.3% responders never saw a patients with Sjogren's
Existing Diagnosis of JDM	56.8	29.5	25	13.6	2.2	44	56.8% of responders saw < 5 patients while 2.2% responders never saw a patients with previously diagnosed JDM
New JDM	56.8	29.5	4.5	2.2	6.8	44	56.8% of responders saw < 5 patients while 6.8% responders never saw a newly diagnosed JDM patients
CNS Vasculitis	72.7	18.1	0	0	9	44	72.7% of responders saw < 5 patients while 9% responders never saw a patients with CNS Vasculitis
PAN	65.9	2.2	0	0	31.8	44	65.9% of responders saw < 5 patients while 31.8% responders never saw a patients with PAN
MPA	68.1	6.8	0	0	25	44	68.1% of responders saw < 5 patients while 25% responders never saw a patients with PAN
Poly JIA	4.5	6.8	13.6	75	0	44	4.5 % of responders saw < 5 patients while 75% saw >20 Poly JIA patients
Oligo JIA	5	0	15.9	81.8	0	44	5% of responders saw < 5 patients while 81.8% saw >20 patients with Oligo JIA
Spondyloarthropathies/ERA	6.8	15.9	25	52.2	0	44	6.8% responders saw <5 cases while 52.2% responders saw >20 cases of Spondyloarthropathies/ERA
SOJIA	15.9	46.5	27.9	9.3	0	43	15.9% responders saw <5 cases while only 9.3% responders saw >20 cases of SOJIA
MAS	61.3	29.5	2.3	2.3	0	43	61.3% of responders saw less than 5 cases while 2.3 % saw >20 cases of MAS
Other ANCA related Vasculitis	75	9	27.7	0	13.5	44	75% of responders saw less than 5 cases while 13.5 % saw >20 cases of Other ANCA related Vasculitis
Churg-Strauss syndrome	52.2	0	0	0	47.7	44	52.2% of responders saw less than 5 cases while 47.7% never saw a cases of Churg-Strauss syndrome
Behcet's syndrome	77.4	13.6	2.2	0	6.8	44	77.4% of responders saw less than 5 cases while 6.8% never saw a cases of Behcet's syndrome
Streptococcal Syndromes/RF/Reactive arthritis/PANDA	20.4	38.6	36.6	4.5	0	44	20.4% of responders saw less than 5 cases while 4.5 % saw >20 cases of Streptococcal Syndromes
Kawasaki Disease	20.4	45.4	18.1	13.6	2.2	44	20.4% of responders saw less than 5 cases while 13.6% saw >20 cases while 2.2% never saw a case of Kawasaki Disease
Resistant to treat HSP	53.4	29.5	9.3	0	6.9	43	53.4% of responders saw less than 5 cases while 6.9% never saw a Resistant to treat case of HSP
Chronic Recurrent multifocal Osteomyelitis (CRMO)	59	29.5	4.5	2.2	4.5	44	59% of responders saw less than 5 cases while 2.2 % saw >20 cases of CRMO. 4.5% responders never saw a case of CRMO
Pain Enhancement Syndrome	2.2	15.9	18.1	59	4.5	44	2.2% of responders saw less than 5 cases while 59% saw >20 cases of Pain Enhancement Syndrome. White interestingly 4.5% never saw such case
Sarcoidosis	60.4	23.2	4.6	0	11.6	43	60.4% of responders saw less than 5 cases while 11.6% never saw a case of Sarcoidosis
Periodic Fever Syndromes	29.5	31.8	27.2	11.3	0	44	29.5% of responders saw less than 5 cases while 11.3% saw >20 cases of Periodic Fever Syndromes
Antiphospholipid Antibody Syndrome (APLS)	63.6	25	6.8	2.2	2.2	44	63.6% of responders saw less than 5 cases while 2.2% saw >20 cases of APLS while 2.2% responders never saw a case of APLS

Other (please specify) Others:
Neonatal SLE −4.5%
MCTD −6.8%
Neurosarcoid −2.2%
Takayasu arteritis −2.2%   2
answered question   44
skipped question   3

Conclusion: Both clinical and research experience varies widely between US PR fellowship programs. Our survey data may identify areas for programmatic improvements, best practice benchmarks, and policy development for future training recommendations & workforce development. We hope programs will accomplish similar standards of excellence through the use of comparison data.

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Pregnancy and Contraception in Adolescents and Teens with SLE: Are pediatric rheumatologists adequately Screening and Educating Their Patients?. Deirdre I. De Ranieri[1], Karen Onel[1], Linda Wagner-Weiner[2] and Melissa S. Tesher[1]. [1]University of Chicago, Chicago, IL, [2]University of Chicago Hospital, Chicago, IL

Background/Purpose: Pregnancy in patients with systemic lupus erythematosus (SLE) is often complicated by both disease flares and risks to the fetus. It is important that young women with SLE be educated on both the risks of pregnancy and on safe and effective methods of contraception. We aimed to evaluate how often pediatric rheumatologists discuss sexual activity and contraception with their young female patients with SLE. We also aimed to assess the perception of our knowledge and how we educate our patients on both pregnancy risks and contraception in SLE. We compared these responses with those of a small cohort of providers in other medical fields.

Methods: All general pediatricians and nurse practitioners at the University of Chicago, all adult rheumatologists and trainees in Chicago who are registered with the American College of Rheumatology (ACR), and all pediatric rheumatologists and trainees in the United States who are registered with the ACR were identified. An online survey was sent to these providers to evaluate how often they take sexual histories in their adolescent and young adult female patients (ages 11–21) with SLE, the frequency with which they educate their patients on the risks of lupus in pregnancy, and if they offer contraceptive guidance.

Results: Responses were received by 56 pediatric rheumatologists, including 12 trainees, 12 nurse practitioners, 9 general pediatricians, and 7 adult rheumatologists, including 1 trainee. Relatively few pediatric rheumatologists consistently discuss sexual activity, pregnancy risks, or contraception with patients. 32% of pediatric rheumatologists were "very comfortable" taking a sexual history, compared to 16.7% of adult rheumatologists. 88.9% of general pediatricians reported taking a sexual history during at least 75% of adolescent visitis, compared to pediatric rheumatologists (26.5%). Adult rheumatologists reported obtaining sexual histories the least often among those surveyed. Only 58.8% of pediatric rheumatologists surveyed discussed the risks of pregnancy in their young female patients with active lupus, although the majority expressed adequate knowledge of these risks. Only 50% of pediatric rheumatologists reported discussing contraception with patients on teratogenic medications during at least 75% of their clinic visits despite reporting adequate familiarity with medications that can cause birth defects. Written and web-based educational resources were identified as useful tools in educating patients about pregnancy and contraception in women with lupus.

Conclusion: This preliminary survey identified a discrepancy in pediatric rheumatologists' knowledge of the complications of pregnancy in SLE, teratogenic drugs, and contraceptive methods, and their communication of this knowledge to their young female patients with SLE. Implementing tools to help these providers feel more comfortable discussing these important topics is indicated in order to better serve this population. Surveyed physicians identified both online resources and paper handouts explaining the risks of pregnancy in young women with SLE and different methods of contraception as useful tools.

Disclosure: **D. I. De Ranieri**, None; **K. Onel**, None; **L. Wagner-Weiner**, None; **M. S. Tesher**, None.

1898

A Competence-Based Model for Teaching Rheumatology in Undergraduate Medical Students in Pontificia Universidad Católica De Chile: A Five Years Experience. Pamela Díaz, Carolina Cuellar, Miguel Gutiérrez and Marcela Cisternas. Pontificia Universidad Católica de Chile, Santiago, Chile

Background/Purpose: Several reports have demonstrated that Rheumatology disorders are increasingly arising. In USA, for example, three of the top eight primary diagnosis groups presenting to ambulatory care visits in 2007 were for musculoskeletal disorders.

In the meanwhile, medical student's surveys have consistently demonstrated their lack of confidence in diagnosing and managing musculoskeletal problems.

Until 2005 the rheumatology teaching in our School of Medicine was predominantly based in lecture classes, some seminars and a written multiple choice test. Since then, in order to improve the rheumatology teaching, we introduced new learning objectives in this field with three domains of learning: knowledge, attitudes, and skills.

To achieve these domains, we added a program consisting of small group tutorials, the use of one-way-mirror offices to direct observation, personalized feedback, formative evaluations and objective structured clinical examinations (OSCEs).

The aim of this study was to describe this novel assessment method, and evaluate the acquisitions of rheumatology teaching domains in undergraduate students with this program.

Methods: We implemented seven consultation offices with one-way mirror, with special audio and video systems.

The students are organized in small groups of six, with a rheumatology professor, and during two weeks they review the most common rheumatology problems: musculoskeletal diseases, osteoarthritis, rheumatoid arthritis, systemic lupus erytemathosus, laboratory test and radiology.

Each day starts with a session discussion about the different diseases, then one student performed a real rheumatology patient evaluation being observed for the group, who is also filling a summary sheet of the interview with special emphasis in the attitudes and the skills observed. After a complete evaluation, the entire group discussed relevant aspects of the interview and of the patient's disease, and gives feedback.

To determine the acquisitions of the contents and competences, we introduce a formative test at the beginning and the end of the program, and an OSCE. Also, each student completes a survey about the program and the methodology.

Results: In the last five years, over 500 students have completed this new curriculum program.

The student's surveys about this methodology showed a high level of satisfaction. They estimated the objectives achievement in more than 90%, and evaluate the overall program with a mean score of 6.8 over 7 (range 6.6–7).

Three hundred and seventy one students filled the formative test at the beginning of the program, and 361 at the end. At the beginning, the percentage of correct answers was 62% vs 92% at the end of the program ($p < 0.01$). In the first formative test, there were 10% of non-respond answers, vs 0.5% at the second test ($p < 0.01$).

In the final OSCE, all the students had a good performance being all approved with over 60% of achievement in the three different domains evaluated.

Conclusion: This new assessment in rheumatology teaching is highly appreciated for the students, and it seems to be a good methodology to the acquisition of knowledge and trainee in competences in rheumatology patient's evaluation.

Disclosure: **P. Díaz**, None; **C. Cuellar**, None; **M. Gutiérrez**, None; **M. Cisternas**, None.

1899

Factors Contributing to Non-Publication of Abstracts Presented At the American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting. Jennifer M.P. Woo[1], De Furst[2], Deborah K. McCurdy[1], Olivia I. Lund[3], Rotem Eyal[3], Cijin Piao[3] and Gil Amarilyo[1]. [1]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [2]University of California at Los Angeles, Los Angeles, CA, [3]David Geffen School of Medicine at UCLA, Los Angeles, CA

Background/Purpose: The American College of Rheumatology/ Association of Rheumatology Health Professionals (ACR/ARHP) Annual Scientific Meeting (ASM) provides a premier forum for the rapid dissemination of novel clinical and basic science research in the fields of rheumatology and immunology. We recently investigated the publication outcomes of abstracts presented at the 2006 ACR/ARHP ASM in Washington, D.C. (November 12–16, 2006). We estimated that 59.1% of all abstracts presented at the meeting were published as full-length peer-reviewed manuscripts within 5 years of presentation. In order to assess the reasons behind non-publication of the remaining research, we administered a survey to a cross-section of authors who we previously identified as presenting abstracts that remained unpublished.

Methods: Of 2156 abstracts presented at the 2006 ACR/ARHP ASM, we classified 879 abstracts as "not published" following an extensive PubMed search for potential publication matches. Primary authors of non-published abstracts were anonymously surveyed via an internet questionnaire to identify factors that prevented presented research from reaching full-length publication status.

Results: A total of 713 primary authors had at least one abstract presented at the 2006 ACR/ARHP ASM that did not result in publication as a full-length manuscript. Abstracts that described studies in rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis constituted approximately 39.7% of all presented abstracts and included 38.6% of all unpublished abstracts (non-publication rates: 38, 43, and 41%, respectively). A cross-section of 459 authors, who served as primary author on 599 unpublished abstracts, was surveyed. Sixty-five authors (14.2%) responded to the questionnaire, reflecting 117 abstracts (19.5%). At the time of the survey, 10 abstracts (8.5%) were reported as being published as full-length manuscripts within the 5 years following their presentation and were supported by corresponding citations. Three additional abstracts were confirmed as being published, but reached this status during the period between January-June 2012, which was outside of the defined search period. The primary reasons reported for non-publication included: 1) Insufficient time to prepare manuscript (35.2%); 2) a co-author was responsible for authoring the manuscript (29.6%); and 3) the study was still ongoing (16.7%).

Conclusion: Although most of the abstracts presented at the 2006 ACR/ARHP ASM were eventually published in peer reviewed journals, data indicates that the lack of subsequent publication was related to the presence of time constraints or deferred responsibility for authorship rather than the quality of the data.

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Mormed Project: A New 21st Century Web Platform for Multilingual Communication in systemic Lupus Erythematosus and Antiphospholipid Syndrome. Oier Ateka-Barrutia[1], Adriane Rinsche[2], Maria Laura Bertolaccini[1], Munther A. Khamashta[1] and MORMED consortium[3]. [1]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [2]Language Technology Center Ltd., Kingston, United Kingdom, [3]EU

Background/Purpose: The internet is used nowadays as the preferred repository where people search for, access and publish information on any topic. However, language barriers prevent efficient international information exchange. This problem is further exacerbated by the fact that information for restricted and highly focused communities, e.g. communities with an interest in rare diseases, is not easily available or easy to find. An example of such a focused community is the community of individuals and stakeholders interested in lupus or antiphospholipid syndrome (Hughes Syndrome).

Language barriers impede the dissemination of interesting information and the exchange of valuable experiences between people from diverse cultures and backgrounds. Thus communication channels between the various stakeholders, e.g. between researchers and general practitioners (GPs), between specialists and GPs, and between GPs and patients, are cumbersome or even non-existent across countries due to language barriers of national languages and specific terminology.

Methods: MORMED (Multilingual Organic Information Management in the Medical Domain, www.mormed.eu) is a European Union-funded project that proposes a multilingual community platform combining Web 2.0 social software applications with semantic interpretation of domain-relevant content, enhanced with automatic translation capabilities and fine-tuned for a specific medical domain. It has been under development since March 2010 and piloted upon the community interested in lupus and Antiphospholipid Syndrome (Hughes Syndrome), involving researchers, medical doctors, general practitioners, patients and patient support groups, since spring 2012.

Organisations involved in this project include: King's College London (UK); Language Technology Centre Ltd. (UK); South East European Research Centre (Greece); Medical and Health Science Centre, University of Debrecen (Hungary); Institute for Clinical Chemistry and Laboratory Medicine, University Hospital Mainz (Germany); Hospital Clinic Barcelona (Spain).

Results: The project promotes online collaboration, where people contribute content and evaluate and exchange information resources, and it supports the diffusion of knowledge within multilingual social networks and online communities. Efficient machine translation, supported by interactive computer-aided human post-editing ensures that all content is seamlessly offered in English, Spanish, German and Hungarian, and at a high quality. Thus, new and innovative translation methods, tools and processes emerge, which set the service offerings of the MORMED service provider apart from those of other providers. A trial version of the platform is available at http://lupus.mormed.eu. The final version of the platform will be released by autumn 2012.

Conclusion: The MORMED platform is a multilingual web-based platform focused on the lupus and antiphospholipid syndrome community. High quality translation tools and resources in four languages (English, Spanish, German and Hungarian), along with social-network applications, are proposed as a new tool for information and experience exchange for clinicians, researches and patients involved in this field.

ACR/ARHP Poster Session C
Metabolic and Crystal Arthropathies
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Chronic Gout. Improvement According to Outcome Meaures in Rheumatology Domains in Daily Clinical Practice. Janitzia Vazquez-Mellado[1], Betsabé Serrano[1], Jaime Mendoza[2], Sergio Garcia-Mendez[1], V. Chantal Hernández[1], Virginia Pascual Ramos[2], Ruben Burgos-Vargas[1] and Marina Rull-Gabayet[2]. [1]Hospital General de Mexico, Mexico city, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Background/Purpose: OMERACT has proposed domains to evaluate the effect of treatment in patients with acute and chronic gout. Their frequency, time to improve and percentage of change have not been evaluated in chronic gout patients under conventional treatment.

Methods: This is a prospective, longitudinal and observational cohort study. Since July 2010, we included all patients with Gout diagnosis (ACR criteria), attending for the 1st time to 2 Rheumatology departments. All signed informed consent and were evaluated by a rheumatologist in each visit. Variables: Demographic, clinical/biochemical related to gout and associated diseases, previous treatments. Individualized, regular treatment was prescribed in 1st visit as recommended (Life style modifications, NSAID, ULT, prophylaxis and treatment for associated diseases). Response to treatment evaluations: Number of: painful, swollen, limited to motion joints, tophi and flares/6mo. Main tophi size, VAS pain, general health (patient and physician), HAQ and uricemia. Statistical analysis. Chi square and paired t test.

Results: 178 Gout patients had been included in this prospective study. This report includes 93 patients with baseline and 6 mo evaluations. Males 97%, mean ± SD age, age at onset and duration of the disease: 49.7 ± 11.68; 35.82 ± 12.84 and 13.7 ± 10.46 years respectively; in 40%, disease duration was <3 ys. Tophaceous gout: 61% (29%, ≥ 5 tophi). Most had been irregularly treated, 58% previous auto-prescribed glucocorticoids. More frequent associated diseases: Hypertrygliceridemia 53%, hypertension 52% and obesity 30%. Allopurinol prescribed doses were: 341.9 ± 280.7 and 382.4 ± 215.9 mg/day (baseline and 6mo respectively); although, at 6 mo 69% had uric acid >6 mg/dL, the group improved significantly in 7/11 outcome domains (see table).

Response to treatment

Variable, mean ± SD	Baseline	6mo	P	>25% improvement (%)
Flares/6mo	2.6 ± 3.6	0.6 ± 1.2	0.000	72
Painful joints	2.4 ± 4.5	2.2 ± 4.7	NS	29
Swollen joints	0.53 ± 1.2	0.25 ± 0.8	0.025	21
Limited joints	4.2 ± 7.9	3.5 ± 7.01	0.000	23
Tophi	5.8 ± 8.75	5.8 ± 8.5	NS	10
Main tophi size, cm	3.6 ± 4.06	3.0 ± 3.7	0.004	22
HAQ	0.45 ± 0.6	0.29 ± 0.5	0.012	39
Serum uric acid, mg/dL	7.9 ± 2.2	7.1 ± 1.9	0.001	34
VAS pain	4.6 ± 3.2	3.7 ± 3.2	0.024	36
VAS health, patient	3.8 ± 2.9	3.3 ± 2.9	NS	39
VAS health, physician	3.7 ± 2.6	3.6 ± 2.3	NS	47

Variables according to OMERACT domains.

Conclusion: Before uricemia is controlled and as soon as the first 6 months, patients with longstanding and severe disease under regular treatment, improve significantly in 7/11 OMERACT domains, particularly acute flares and HAQ score.

What Factors Are Associated with Target Serum Urate Concentrations in Patients with Gout? Nicola Dalbeth[1], Meaghan House[1], Anne Horne[1], Keith J. Petrie[1], Fiona M. McQueen[1] and William Taylor[2]. [1]University of Auckland, Auckland, New Zealand, [2]University of Otago, Wellington, New Zealand

Background/Purpose: Long term serum urate (SU) lowering to a target of <6mg/dL is recommended for effective gout management. However, many studies have reported low achievement of SU targets. The aim of this study was to examine the clinical and psychological factors associated with SU targets in patients with gout.

Methods: Patients with gout for <10 years were recruited from primary and secondary care settings. SU target was defined as SU concentration <6mg/dL at the time of the study visit. Both clinical and psychological factors associated with SU target were analysed. The relationship between SU target and measures of gout activity including flare frequency in the preceding three months was also analysed.

Results: Of the 273 patients enrolled into the study, 89 (32.6%) had SU concentration <6mg/dL. Urate-lowering therapy (ULT) use was strongly associated with SU target ($p<0.001$). In those patients prescribed ULT (n=181), allopurinol dose, patient confidence to keep SU under control, female sex, and ethnicity were independently associated with SU target (Table). Other patient psychological factors and health-related behaviours, including adherence scores, were not independently associated with SU target in those taking ULT. Creatinine clearance, diuretic use, age, and body mass index were not associated with SU target. Patients at SU target reported lower gout flare frequency, compared with those not at target (p=0.03).

Table 1. Forward stepwise logistic regression analysis of factors associated with SU target in those taking ULT. Model included all factors with p<0.15 between groups in univariate analysis

Variable	OR	95% CI	p	Model
Female sex	4.34	1.65–11.44	0.003	Adjusted R^2=0.35, p<0.001
Mβori or Pacific ethnicity	0.19	0.07–0.52	0.001	
Allopurinol dose (per every 100mg/day)	2.22	1.43–3.44	<0.001	
Confidence to keep serum urate under control (per every point on 0–10 Likert scale)	1.025	1.007–1.044	0.006	

Excluded from model: adherence score, secondary care treatment, age, confidence to have blood tests at recommended frequency, confidence to take gout medications regularly, Brief Illness Perception Questionnaire (BIPQ) treatment control score, BIPQ understanding score.

Conclusion: ULT prescription and dosing are key modifiable factors associated with achieving SU target. These data support interventions focusing on improved use of ULT to optimise outcomes in patients with gout.

Disclosure: N. Dalbeth, None; **M. House**, None; **A. Horne**, None; **K. J. Petrie**, None; **F. M. McQueen**, None; **W. Taylor**, None.

Oxidation of Urate to Allantoin by Myeloperoxidase in Gout. Lisa K. Stamp, Irada Khalilova, Mei Zhang, Rufus Turner and Anthony Kettle. University of Otago, Christchurch, Christchurch, New Zealand

Background/Purpose: Hyperuricaemia is critical for the development of gout and may play a pivotal role in the pathophysiology of hypertension, metabolic syndrome, and cardiovascular disease. Urate is a substrate for the neutrophil enzyme myeloperoxidase (MPO) and is oxidized to reactive intermediates that breakdown to allantoin. Monosodium urate (MSU) crystals promote a painful and acute inflammatory response within joints. Our hypothesis is that during inflammation MPO will be released from neutrophils and oxidize urate to reactive intermediates that will contribute to the adverse effects of hyperuricaemia. The aims of this study were to determine whether MPO is released from neutrophils and urate is oxidized in patients with gout and if these effects are attenuated by allopurinol.

Methods: 50 patients with gout and 37 healthy controls were recruited. 10/50 gout patients were commencing allopurinol and had samples collected at baseline and after 4 weeks of allopurinol. 33 of the remaining 40 patients were receiving allopurinol and these 40 patients had samples collected on one occasion only. Serum urate (SU) and plasma oxypurinol (OXYH) were measured by HPLC. Plasma MPO activity was measured by ELISA and allantoin by mass spectrometry.

Results: 43/50 gout patients were male, mean age was 58.2 years (30–91). Mean SU was 6.6mg/dl (3.0–10.6mg/dl). Mean allopurinol dose was 275.8mg/d (50–500mg/d). Plasma MPO activity was significantly higher ($p<0.001$) in patients with gout not receiving allopurinol (12.9 ng/nl IQR 10.5–41.2; n=18) compared to healthy controls (7.5 ng/ml IQR 4.7–9.4; n=37). Plasma allantoin concentrations were significantly higher ($p<0.001$) in patients with gout not receiving allopurinol (5.5 μM IQR 3.3–7.3; n=18) compared to healthy controls (2.0 μM IQR 1.4–3.5; n=37) (**Figure**). There was a significant correlation between MPO activity and plasma allantoin concentrations (r=0.54, $p<0.0001$; n=54). In the ten patients starting allopurinol there was a significant reduction after four weeks in SU (571 ± 48 μM vs. 480 ± 55 μM; $p<0.001$) and plasma allantoin (4.1 ± 1.6 μM vs. 2.9 ± 1.3 μM; $p<0.001$). Those patients receiving allopurinol with plasma OXYH concentrations >50μmol/l had significantly lower MPO protein (18.6 ng/ml IQR 12.3–33.2, n=31 vs. 30.9 ng/ml IQR 19.3–39.2, n=27; p=0.027) but paradoxically higher allantoin (9.9 μM IQR 6.0–12.5, n=31 vs. 4.6 μM IQR 2.9–6.5, n=29; $p<0.001$) compared to those with OXYH <50μmol/l.
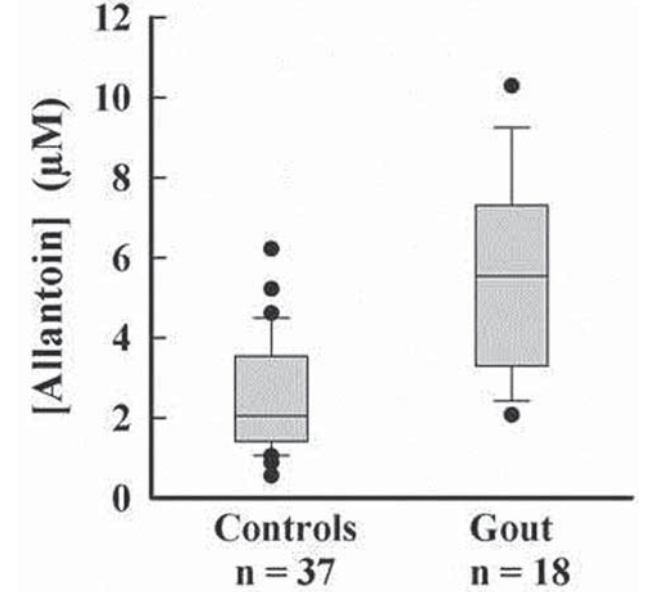
Conclusion: During episodes of gout neutrophils release MPO which oxidizes urate. The interaction of MPO and urate will exacerbate oxidative stress in inflamed joints. At low concentrations, oxypurinol should dampen oxidative stress by lowering MPO and urate but at high concentrations it will increase oxidative stress presumably because hydrogen peroxide is also produced when allopurinol is metabolised by aldehyde oxidase.

Disclosure: L. K. Stamp, None; **I. Khalilova**, None; **M. Zhang**, None; **R. Turner**, None; **A. Kettle**, None.

Patterns of Gout Treatment and Related Outcomes in US Community Rheumatology Practices: the Relation Between Gout Flares, Time in Treatment, Serum Uric Acid Level and Urate Lowering Therapy. Max I. Hamburger[1], John RP Tesser[2], John L. Skosey[3], Allan H. Morton[4] and Karl M. Kilgore[5]. [1]Rheumatology Associates, Melville, NY, [2]AZ Arthritis Rheum Assoc, Paradise Valley, AZ, [3]Illinois Bone & Joint Institut, Chicago, IL, [4]Warren, MI, [5]Cetus Group, LLC, Hunt Valley, MD

Background/Purpose: Study patterns of gout treatment and related outcomes in US community rheumatology practices, specifically the relation between likelihood and severity of gout flares, time in treatment with current physician, serum uric acid (sUA) level and urate lowering therapy (ULT, which included, at any dosage level, allopurinol, febuxostat, pegloticase, probenecid).

Methods: Fifty practices completed retrospective chart abstraction on their 25 most recently seen patients with gout. Data, abstracted from all visits in 2010–2011 using standardized case report forms, included demographics, gout history, co-morbidities, sUA, gout treatment, and visit type (flare-related or follow-up). This report includes all data from the subset of the total cohort which was available at time of abstract submission. Final dataset will comprise 1,250 patients.

Data were analyzed using logistic regression, with visit type (coded as severe flare, mild/moderate flare, non-flare related) as an ordinal response variable, and 3 predictor variables: time in treatment with current rheumatologist at start of chart abstraction (TxTime: new patient vs. $\geq$ 2 months), ULT (absence vs. presence at time of visit) and sUA ($\geq$ 6.0 vs. < 6.0).

Results: The study population consisted of 479 gout patients from 21 sites, 79% male, 77% Caucasian, mean age 62 years, median disease duration 5.5 years.

Patients had a total of 2,460 visits during study period. Of these, 1,465 (59.6%) included all analysis variables and constitute the analysis sample. 273 (18.6%) of visits were flare-related. All 3 main effects were significant. Increased likelihood of a flare was associated with 1) shorter TxTime, 2) absence of ULT, and 3) higher sUA. Data are summarized in the table.

| | | | Type of Visit (%) | | | |
		n	Flare-Related: Severe	Flare-Related: Mild/ Moderate	Not Flare-Related	Any Flare vs. Non-Flare *p-value* OR (95% CI)
TxTime	NewPt.	565	9.6	16.6	73.8	<.001
	>2 mos.	900	5.2	8.7	86.1	1.62 (1.22–2.15)
ULT	Absent	277	18.1	29.2	52.7	<.001
	Present	1188	4.3	7.7	88.0	4.79 (3.52–6.52)
sUA	$\geq$ 6.0	729	9.9	15.9	74.2	.004
	<6.0	736	3.9	7.6	88.5	1.64 (1.21–2.22)

The only significant interaction effect was ULT by TxTime (p <.01). Patients who were already on ULT when referred to the current rheumatologist were no more likely to flare than the physician's current ULT patients. For patients not on ULT, however, new patients had triple the odds of flaring compared with current patients (OR=3.04, 95%CI=1.86–4.95).

Conclusion: Data depict aspects of current usage of gout therapy in US community practices and underscore importance of managing sUA levels. All patients regardless of sUA levels or treatment had some risk of flare, but risk was greatly mitigated by ULT therapy. These data suggest that failure to treat hyperuricemia in gout patients is associated with a greatly increased likelihood of a flare.

1905

Increase of Thyroid Stimulating Hormone in Patients On Febuxostat Treatment. Fernando Perez-Ruiz[1] and Ana M. Herrero-Beites[2]. [1]Hospital Universitario Cruces, Baracaldo, Spain, [2]Hospital de Gorliz, Gorliz, Spain

Background/Purpose: to evaluate whether TSH increases during febuxostat treatment and factors that could be implicated.

Methods: before starting febuxostat, patients had analysis at baseline and month 3 and 6 including serum urate, estimated glomerular filtration, liver function test, and TSH at baseline and 6-month visit. General characteristics and previous urate-lowering drugs, and concomitant diseases were registered. Patients with altered TSH at baseline were included if T4 was within normal range. All patients showing TSH out of the normal range (0.5–5.0 mU/ml) had to undergo T4 determination while on febuxostat and febuxostat was to be withdrawn if T4 was found not within normal limits. Results are shown as median and interquartile range. Febuxostat was started 80 mg eod for the first month and then all patients escalated to 80 mg/d until the 3-month visit. Febuxostat was then regulated to 80 mg eod for patients showing Sur <3 mg/dl and non-tophaceous gout and to 120 mg/d in patients with serum urate > 6 or > 5 and tophaceous gout.

Results: sixty-eight patients were included, mean age 62 years (51–73), time from onset 8 years (2–15), 59% with tophi present, serum urate 9.5 mg/dl (8.7–10.4) glomerular filtration 78 ml/min (52–101), TSH 2.34 U/ml (1.39–2.89). Three (4.4%) patients showed baseline TSH > UNL, but T4 was

within normal range. At 6-month 5, 3 patients were on 80 mg eod, 5 on 120 mg/d, and 60 on 60 mg/day, 62/68 (91%) showing serum urate < 6 mg/dl. TSH increased from 2.34 to 2.71(1.51–3.27, p<0.001), 5 (7.3%) showing TSH > UNL ranging from 5.56 to 8.92. None of these patients showed altered T4 levels or any symptom related to hypothyroidsm. There was a close correlation between baseline and final TSH (r2=0.75) (Figure 1). Multivariant analysis showed a that baseline TSH and the dose of febuxostat at 6-month visit were independently associated with TSH levels at 6-month visit (model R2=0.855), and with the change in TSH from baseline to 6-month (model R2= 0.396). No patient with baseline TSH < 3 showed TSH above UNL.
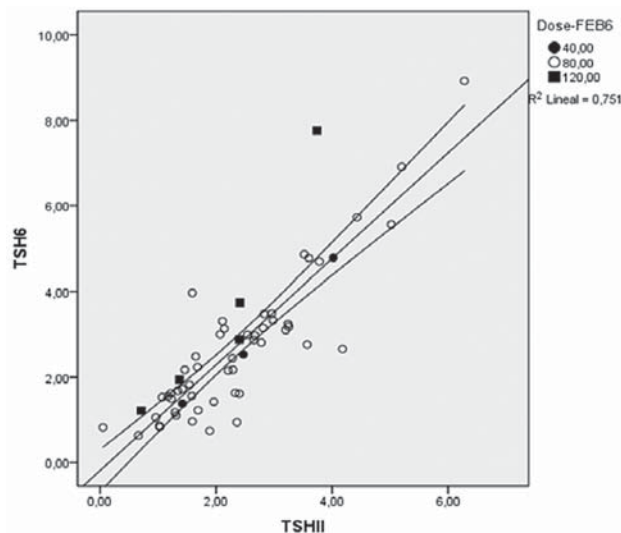
Figure 1. Correlation between baseline and final TSH

Conclusion: febuxostat increases TSH levels, both baseline TSH and febuxostat dose being associated with the increase. No patient with TSH above UNLs showed altered T4 levels or symptoms of thyroid dysfunction.

1906

Changes in Gout patient's Clinical Profile in the Last Two Decades. Fernando Perez-Ruiz[1] and Ana M. Herrero-Beites[2]. [1]Hospital Universitario Cruces, Baracaldo, Spain, [2]Hospital de Gorliz, Gorliz, Spain

Background/Purpose: to assess whether changes in the clinical profile of gout are observed in a large cohort of gout patients over the last 20 years.

Methods: a total number of 904 patients have been prospectively included in a cohort of patients with gout from June 1992 to June 2012 with a gout-specific dataset (time from onset, joints involved, flares per year, X-ray involvement, presence of tophi, previous urate-lowering therapy-ULT, ongoing ULT, average serum urate while on therapy) in addition to general characteristics of subjects (age, gender, body mass index), and comorbidities (diabetes, chronic kidney disease, hypertension, hyperlipidemia, renal lithiasis, previous vascular events). For statistical analysis, patients have been stratified in two decades, from 1992 to 2002 (349 patients) and from 2002 to 2012 (555 patients).

Results: As for the second decade, an statistically significant increase in age (57±12 vs. 61±13 years), in the number of flares (2.8±0.1 vs. 4.0±1.2 per patient-year), in BMI (27.5±3.2 vs. 28.2±4.2 kg/sqm) were observed. Serum urate at baseline and time from onset of gout to referral were not statistically different. Polyarticular–> 4 joints–involvement (29.8 vs. 39.5%) and presence of subcutaneous tophi (26.6 vs. 36.4%) were significantly more frequent in the second decade, although the percentage of patients naive to ULT (63.8 vs. 59.3%) or allergic to allopurinol (4.9 vs. 5.7%) were similar. Hypertension (33.4 vs. 51.9%), diuretic prescription (17.8 vs. 30.8%), and previous vascular events (20.7 vs. 31.8%) were significantly more common in the second decade. Although the mean clearance of creatinine were not statistically different, the percentage of patients with CKD stages 3–5 was close to significance (20.1 vs. 25.6%, p=0.059.

Interestingly, while the mean baseline serum urate was numerically higher, the mean reduction and the percentage reduction from baseline were greater in the second decade (3.4 vs. 3.7 mg/dl and 38 vs. 45%, respectively), so that the percentage of patients averaging serum urate < 6 mg/dl while on follow-up remained pretty good (87 and 89%, respectively). This can reflect a trend to more intensive therapy due to more severe disease in the second decade.

Conclusion: the profile of patients with gout seems to have changed over the last two decades as they are older, more commonly hypertensive, on diuretics, with a previous vascular event, and they show more commonly tophaceous and polyarticular gout.

Disclosure: F. Perez-Ruiz, Menarini, 5, Ardea Biosciences, 5, Novartis Pharmaceutical Corporation, 5, Savient, 5, Menarini, 8, Ardea Biosciences, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8; **A. M. Herrero-Beites**, None.

1907

Pharmacological Management of Gout in Italy in the Years 2005–2009: A Nationwide, Population-Based Study. Lorenzo Cavagna[1], Gianluca Trifirò[2], Roberto Caporali[3], P. Morabito[2], C. Ferrajolo[4], S. Pecchioli[5], M. Simonetti[5], G. Medea[6], C. Cricelli[7], A. Caputi[2], G. Mazzaglia[5] and Carlomaurizio Montecucco[8]. [1]University and IRCCS Foundation Policlinico S. Matteo, Pavia, Italy, [2]University of Messina, Italy, [3]Division of Rheumatology, IRCCSPoliclinico S. Matteo Foundation, Pavia, Italy, [4]Second University of Naples, Naples, Italy, [5]Italian College of General Practitioners, Italy, [6]Italian college of General Practitioner, Italy, [7]Italian college of General Practitioner, Pavia (Italy), Italy, [8]University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Background/Purpose: Despite the increasing interest on gout, only few nationwide drug utilization studies have been conducted on this topic. The aim of this study was to investigate the Italian prescribing pattern of medications for gout in the years 2005–9

Methods: The data source of the study was the national Database of the Italian College of General practitioner, covering about 1.5 million patients from all around Italy. Patients with incident gout (years 2005–9) were identified using specific ICD9-CM codes and related key words for free text search. In this cohort of patients, we measured the yearly prevalence of use of the following drugs: allopurinol (ATC: M04AA01); colchicine (M04AC01); NSAIDs (M01A*). Moreover, systemic corticosteroids (H02*) were taken into account, because frequently used during acute attacks. Drugs not marketed in Italy, or not reimbursed by National Health System (probenecid, sulfinpirazone and benzbromarone) were not taken into account. For allopurinol rate and predictors of persistence and adherence to the treatment have been evaluated too.

Results: During the study period, 3,069 patients with incident gout were identified. Allopurinol prescription in these patients decreased from 45.2% in 2005 to 41.1% in 2009. Among drugs for the acute attack of gout, NSAIDs (from 41.9% in 2005 to 39.8% in 2009) were significantly more prescribed than colchicine (from 4.5% in 2005 to 4.9% in 2009). Corticosteroids were prescribed in a significant proportion of patients (from 12.3% in 2005 to 12.4% in 2009) during the whole study period. Only 22.7% of patients continued allopurinol after three months from the beginning of the therapy (6.6% after 6 months, 1.6% after one year). For allopurinol, the proportion of days covered (PDC) was on average equal to 39%. The proportion of patients with high adherence to the treatment (PDC >80%) increased with advancing age and was significantly higher in males. Hypertension, obesity, cerebrovascular diseases, congestive heart failure and sUA levels > 9mg/dl, enhanced allopurinol treatment adherence

Conclusion: to our knowledge, this is the first drug-utilization study on pharmacological management of gout in Italian general population. Our results were quite similar to that recently described in US population, although in this study the prevalence of colchicine (16.7%) and corticosteroids (21%) prescription was higher than those we observed. Our data show very low levels of persistence and adherence to allopurinol treatment; non-adherence was particularly common in younger patients, with lower serum urate levels and burden of comorbidities, as suggested in a recent survey. Clinicians should motivate low risk patients to increase the level of adherence to the treatment for the prevention of gout

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1908

Multinational Evidence-Based Recommendations for Diagnosis and Management of Gout: Integrating Systematic Literature Research and Expert Opinion of a Broad Panel of Rheumatologists in the 3E Initiative. Mariano Andres[1], Francisca Sivera[2], Alison Kydd[3], John Moi[4], Rakhi Seth[5], Melonie K. Sriranganathan[6], Caroline van Durme[7], Irene AAM van Echteld[8], Ophir Vinik[9], Mihir D. Wechalekar[10], Daniel Aletaha[11], Claire Bombardier[9], Rachelle Buchbinder[12], Loreto Carmona[13], Christopher J. Edwards[14], R. Landewe[15] and Désirée van der Heijde[16]. [1]Hospital General Universitario de Alicante, Alicante, Spain, [2]Hospital General de Elda, Alicante, Spain, [3]University of British Columbia, Vancouver, BC, [4]Royal Melbourne Hospital, Melbourne, Australia, [5]University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [6]St. Mary's Hospital, Isle of Wight, United Kingdom, [7]Maastricht University Medical Centre, Maastricht, Netherlands, [8]Atrium Medical Center, Heerlen, Netherlands, [9]University of Toronto, Toronto, ON, [10]Flinders University School of Medicine, Adelaide, Australia, [11]Medical University of Vienna, Vienna, Austria, [12]Monash Department of Clinical Epidemiology at Cabrini Hospital, Department of Epidemiology and Preventive Medicine, Monash University, Malvern, Australia, Malvern, Victoria, Australia, [13]Universidad Camilo José Cela, Villanueva de la Cañada, Spain, [14]University Hospital Southampton, Southampton, United Kingdom, [15]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [16]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The 3e (Evidence, Expertise, Exchange) Initiative is a multinational collaboration that aims to promote evidence-based medicine in rheumatology. The 2011–12 3e Initiative aimed to develop evidence-based recommendations for the diagnosis and management in patients with gout by integrating evidence and the expert opinion of a broad international panel of rheumatologists.

Methods: 474 rheumatologists from 14 countries participated. Using a formal voting process, a panel of 78 rheumatologists developed a list of 10 clinical questions, 9 regarding the diagnosis and management of gout, and 1 focused on the management of asymptomatic hyperuricaemia. Bibliographic fellows undertook a systematic literature review for each clinical question. A literature search was performed using MEDLINE, EMBASE, Cochrane CENTRAL, and abstracts from 2010–11 EULAR and ACR meetings. Relevant studies were retrieved for data extraction and synthesis, and assessment of risk of bias. Using this evidence, rheumatologists from each country developed a set of national recommendations. Finally, multinational recommendations were formulated and assessed for agreement among the participants and the potential impact on clinical practice.

Results: In total, 42,823 references were identified, from which 325 studies were included in the systematic reviews. Combining this evidence and clinical expertise, the initial questions led to a set of 10 recommendations. Oxford Levels of Evidence were applied to each recommendation. One recommendation related to the potential role of clinical and laboratory data for the diagnosis of gout in the absence of crystal identification. Two recommendations considered screening for, and the management of cardiovascular and renal co-morbidities. Six recommendations focused on different aspects of the management of gout, with one recommendation considering a suitable treatment target and how to monitor patients. The last recommendation regarded the management of asymptomatic hyperuricaemia in order to prevent gout and renal and cardiovascular outcomes. The level of agreement by participants with the recommendations ranged from 8.1 to 9.2 (mean 8.7) on a 1–10 point scale with 10 representing full agreement. 17% (range 7.5–31.5%) of rheumatologists reported that the final set of recommendations would change their practice, and 79% (range 60.8–88.7%) felt that these recommendations were in accordance with their current practice.

Conclusion: Ten recommendations on the diagnosis and management of gout were established. They are evidence-based and supported by a large panel of rheumatologists from 14 countries, thus enhancing their utility in clinical practice.

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1909

Use of Uric Lowering Therapies within a Large Health Care System.
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Background/Purpose: Guidelines for initiating urate lowering therapy (ULT) in the treatment of gout recommend treatment to a target serum urate (SUA) level of ≤6mg/dl with monitoring of SUA.

Methods: We reviewed the use of ULT with allopurinol (allop) or febuxostat (febux) in a large health care system between June 2010 and April 2012. Eligible subjects were >18 years at ULT initiation, had a diagnosis of gout, and had ≥ two outpatient prescriptions for a ULT after June 1, 2010. Demographics, ULT dose, prescribing providers, diagnosis, and SUA levels were collected from our *EPIC* EMR using Explorys Inc. proprietary software. A study author checked agreement of data between the subjects EMR and the Explorys data in random cases within the study population. Cleveland Clinic IRB approval was obtained.

Results: 1,870 subjects were eligible for inclusion: 74.1% male, mean age 62.8 (SD 14.2). Study subjects had been prescribed allop alone (82.5%, n=1543), febux alone (5.9%, n=188), or both (11.6%, n=217). Following initiation of ULT, 68.8% of subjects (n=1286) had a repeat SUA within our health system: 56.1% within 6 months and 65.4% within 12 months of their initial prescription. After initiation of ULT, 45.9% of subjects achieved a level of ≤6mg/dl, 22.0% had levels between 6.1–7.0mg/dl, and 32.1% never had a level ≤7.0mg/dl. There were 523 subjects on allop with SUA measurements ≥7.0mg/dl, yet only 2.3% were prescribed a daily dose of >300mg. Subjects treated by a rheumatologist (60.6%) vs non-rheumatologist (42.0%) were more likely to achieve a SUA ≤6mg/dl, odds ratio 2.1 (95% CI 1.7–2.7). The starting dose of allop was <100mg (1.0%), 100mg (59.6%), 101–300mg (38.8%). For subjects prescribed allop the maximum daily dose was ≤ 100mg in 32.4% and 101–300mg in 65.0% of subjects. Maximum dose of allop was greater than 300mg in 2.7% of subjects seen by a rheumatologist and 2.6% of non-rheumatologists. The starting dose of febux was ≤ 40mg in 87.9% of subjects. Of those who did not achieve a SUA level ≤6.0mg/dl, 38.4% had ULT adjusted to a higher dose (ULT adjustment to target may not have been completed by the time of analysis). Only 11.3% of subjects started on febux had documented allop intolerance. A statistically significant difference was found in the mean creatinine level closest to the initiation of ULT (1.3 allop vs 1.5 febux p<0.001) which may indicate renal insufficiency as a perceived reason for febuxostat.

Conclusion: Only 45.9% of patients started on ULT achieved recommended SUA levels, only 38.4% of those not meeting target had a documented dose adjustment and > 97% of patients on allop were on < 300mg per day. This demonstrates a persistent care gap in the treatment of gouty arthritis.

1910

Regulation of Microrna 223 Expression in a Gouty Arthritis.
Gianina Statache[1], Ashleigh-Ann Rainey[1], Seth Masters[2], Andra Balanescu[3], Iain B. McInnes[1] and Mariola Kurowska-Stolarska[4]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Trinity College Dublin, Dublin, United Kingdom, [3]University of Medicine and Pharmacy, Bucharest, Romania, [4]Institute of Infection,Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom

Background/Purpose: Gout is an inflammatory chronic disease caused by deposition of uric acid crystals in the joint and connective tissues causing pain and disability. Current data suggest that gout is mediated by IL-1b that is produced due to the activation of the inflammasome pathway by uric acid crystals. In addition, neutrophil influx in the joint is the key initiator of a gout flare. miR-223 has been identified as a masterswitch molecule limiting neutrophil activation. In addition, we showed previously that this miR negatively regulates NLRP3 (an inflammasome component) and IL-1b production in human macrophages. To investigate miR-223 expression and regulation in monocytes and neutrophils of gout patients.

Methods: CD14+ cells and neutrophils were isolated from gout patients (n=10) and healthy donors (n=6) peripheral blood using CD14 microbeads and polylymphoprep gradient buffer, respectively. CD14+ from healthy donors were stimulated with LPS (10 ng/ml) IL-1beta (100–10ng/ml), IL-6 (100 ng/ml), TNF alpha (10–100ng/ml) or monosodium urate crystals MSU (1mg-1ug/ml) for different time points (24–72h). Cells were harvested and miRNA extracted. Expression of miR-223 and endogenous control snRNA U1 was assessed by qPCR.

Results: miR-223 expression in peripheral blood monocytes of patients with chronic gout was lower compared to healthy controls. This suggest that overproduction of IL-1b in chronic disease might be partially mediated by low levels of miR-223. In vitro studies revealed that MSU, IL-1b, TNFa and IL-6 significantly inhibited miR-223 expression in monocytes in all time points (24–72h). In contrast, IL-10 strongly increased miR-223 expression. Interestingly, the levels of miR-223 in peripheral blood neutrophils were higher in gout patients compared to healthy controls

Conclusion: A decrease in miR-223 expression in monocytes of chronic gout patients may contribute to uric acid crystals induced inflammasome activation and chronicity of disease. Upregulation of miR-223 expression in gout neutrophils may reflect the activation of mechanisms that limits neutrophils activation and lead to the resolution of gout flares.

1911

Efficacy and Safety of Canakinumab Vs Triamcinolone Acetonide in Patients with Gouty Arthritis Unable to Use Nonsteroidal Anti-Inflammatory Drugs and Colchicine, and On Stable Urate Lowering Therapy (ULT) or Unable to Use ULT.
T. Bardin[1], A. So[2], R. Alten[3], M. Bloch[4], M. R. John[5], G. Krammer[5], J. M. Nebesky[5], A. Tao[6] and N. Schlesinger[7]. [1]Service de Rhumatologie, Hôpital Lariboisière, Paris, France, [2]Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland, [3]Charité Univ Medicine, Berlin, Germany, [4]Holdsworth House Medical Practice, Sydney, Australia, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

Background/Purpose: The primary treatment goals for gouty arthritis (GA) are rapid relief of pain and inflammation during acute attacks, and long-term hyperuricemia management. A *post-hoc* analysis of 2 pivotal trials was performed to assess efficacy and safety of canakinumab (CAN), a fully human monoclonal anti-IL-1β antibody, vs triamcinolone acetonide (TA) in GA patients unable to use NSAIDs and colchicine, and who were on stable urate lowering therapy (ULT) or unable to use ULT.

Methods: In these 12-week, randomized, multicenter, double-blind, double-dummy, active-controlled studies (β-RELIEVED and β-RELIEVED II), patients had to have frequent attacks (≥3 attacks in previous year) meeting preliminary GA ACR 1977 criteria, and were unresponsive, intolerant, or contraindicated to NSAIDs and/or colchicine, and if on ULT, ULT was stable. Patients were randomized during an acute attack to single dose CAN 150 mg s.c. or TA 40 mg i.m. and were redosed "on demand" for each new attack. Patients completing the core studies were enrolled into blinded 12-week extension studies to further investigate on-demand use of CAN vs TA for new attacks. The subpopulation selected for this *post-hoc* analysis was (a) unable to use NSAIDs and colchicine due to contraindication, intolerance or lack of efficacy for these drugs, and (b) currently on ULT, or contraindication or previous failure of ULT, as determined by investigators. Subpopulation comprised 101 patients (51 CAN; 50 TA) out of 454 total.

Results: Several co-morbidities, including hypertension (56%), obesity (56%), diabetes (18%), and ischemic heart disease (13%) were reported in 90% of this subpopulation. Pain intensity (VAS 100 mm scale) was comparable between CAN and TA treatment groups at baseline (least-square [LS] mean 74.6 and 74.4 mm, respectively). A significantly lower pain score was reported with CAN vs TA at 72 hours post dose (1st co-primary endpoint on baseline flare; LS mean, 23.5 vs 33.6 mm; difference −10.2 mm; 95% CI, −19.9, −0.4; P=0.0208 [1-sided]). CAN significantly reduced risk for their first new attacks by 61% vs TA (HR 0.39; 95% CI, 0.17–0.91, P=0.0151 [1-sided]) for the first 12 weeks (2nd co-primary endpoint), and by 61% vs TA (HR 0.39; 95% CI, 0.19–0.79, P=0.0047 [1-sided]) over 24 weeks. Serum urate levels increased for CAN vs TA with mean change from baseline reaching a maximum of +0.7 ± 2.0 vs +0.1 ± 1.8 mg/dL at 8 weeks, and +0.3 ± 2.0 vs +0.2 ± 1.4 mg/dL at end of study (all had GA attack at baseline). Adverse Events (AEs) were reported in 33 (66%) CAN and 24 (47.1%) TA patients. Infections and infestations were the most common AEs, reported in 10 (20%) and 5 (10%) patients treated with CAN and TA respectively. Incidence of SAEs was comparable between CAN (gastritis,

gastroenteritis, chronic renal failure) and TA (aortic valve incompetence, cardiomyopathy, aortic stenosis, diarrohea, nausea, vomiting, bicuspid aortic valve) groups (2 [4.0%] vs 2 [3.9%]).

Conclusion: CAN provided superior pain relief and reduced risk of new attack in highly-comorbid GA patients unable to use NSAIDs and colchicine, and who were currently on stable ULT or unable to use ULT. The safety profile in this *post-hoc* subpopulation was consistent with the overall β-RELIEVED and β-RELIEVED II population.

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Colchicine, As Assessed by Target Joint Pain Scores, Is Effective At 16 Hours in Patients with Acute Gout Flares. Suman Wason, Thomas Lauterio, Steve Crockett and Matthew W. Davis. URL Pharma, Philadelphia, PA

Background/Purpose: The management of patients with gout remains suboptimal, leading to increasing frequency and severity of recurrent flares that eventually lead to joint destruction and deformity, with patients experiencing a severely compromised quality of life. Colchicine is considered the standard of care in the treatment and prophylaxis of patients with gout flares. The AGREE (Acute Gout Flare Receiving Colchicine Evaluation) trial established that low-dose (LD) colchicine is as effective as high-dose (HD) colchicine in achieving flare control, by reducing the median time to 50% joint pain reduction (HD colchicine 24.5 hrs; LD colchicine 24 hrs). Patients in both colchicine grps also achieved significant reductions ($\geq$2 units) in mean pain scores relative to placebo (PBO) at 24 and 32 hrs after the initial dose. This post-hoc analysis from AGREE examined improvement in target joint pain scores at 16 hours after the initial dose versus PBO, time-to-response, and use of rescue medication.

Methods: 184 patients experiencing an acute gout flare (ACR criteria) were randomly assigned to HD colchicine (4.8 mg: 1.2 mg initially, then 0.6 mg q1hr × 6; n=52), LD colchicine (1.8 mg: 1.2 mg initially, then 0.6 mg at 1 hr; n=74), or PBO (n=58). Mean baseline pain scores were 6.8 for PBO and 6.9 for both HD and LD colchicine (0 to 10 Likert scale)After confirmation of gout flare, pain intensity scores, as well as adverse events (AEs), were recorded over the next 72 hrs. Rescue medications, such as NSAIDs, were permitted if intolerable pain continued after taking at least 1 dose of study drug. Uric acid–lowering therapy was not to be discontinued at the onset of flare.

Results: At 16 hrs there was a significant treatment response in the LD colchicine grp (1.7 unit reduction from baseline in target joint pain score; P=0.0366) versus PBO. After 24 hours, reductions in target joint pain scores were consistently superior to PBO (mean 2.0 and 2.2 unit reductions in the HD and LD colchicine grps, respectively; 0.7 unit reduction for PBO). For time-to-response, the median time to 50% reduction from baseline in target joint pain score was 32 hrs for HD colchicine and 24.5 hrs for the LD colchicine grp. An insufficient number of patients in the PBO grp achieved this target. A significantly greater number of patients (P=0.0273) assigned to placebo used rescue medication through the 24 hour post-dose assessment compared to those received LD colchicine (50% and 31.1%, respectively). The time to the use of rescue medication was also earlier in the PBO grp (24 hrs) versus 36.5 hrs for LD colchicine). Rates of AEs were similar between LD and PBO grps, but greater than PBO in the HD grp.

Conclusion: This study establishes that LD colchicine provides significant pain relief as soon as 16 hr after dosing. By contrast, NSAIDs commonly prescribed for gout flares (Naprosyn, Indomethacin) have shown significant pain reduction by 48 hrs at the earliest. In addition, in this study, use of rescue medication was significantly lower in LD vs.PBO grps while the safety profile for LD colchicine was comparable to PBO. These results further support the use of low dose colchicine for treatment of acute gout flares.

1913

Complete Tophus Response in Patients with Chronic Gout Initiating Pegloticase Treatment. Michael A. Becker[1], Neil J. Gonter[2], Janet E. Pope[3], Raymond L. Malamet[4] and Herbert S. B. Baraf[5]. [1]University of Chicago, Chicago, IL, [2]Rheumatology Associates of North Jersey, Teaneck, NJ, [3]Univ of Western Ontario, London, ON, [4]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [5]Arthritis & Rheumatism Associates, Wheaton, MD

Background/Purpose: Pegloticase, a recombinant modified mammalian uricase that acts via enzymatic degradation of uric acid to allantoin, is approved in the US for the treatment of refractory chronic gout (RCG). Of 212 patients with RCG enrolled in two 6-month randomized, placebo-controlled trials (RCTs) of q2wk or q4wk pegloticase therapy, 155 (73%) had baseline tophi. All tophi were assessed during RCT and subsequent open-label treatment (OLE; up to 2.5 additional years) with regard to the time course of complete resolution by serial, quantitative digital photography evaluated by blinded and experienced central readers. Patients treated with placebo during the RCTs provided an additional opportunity to evaluate long-term tophus response upon initiation of pegloticase in the OLE study.

Methods: Photographs of patients' hands and feet (and up to 2 other sites of tophi) were made at baseline, at weeks 13, 19 and 25 of RCT treatment, and at weeks 13, 25, 53, 77, 101 and final visit of the OLE. Each patient had up to 5 measurable tophi and 2 additional tophi tracked. A complete response (CR) was defined as 100% decrease in the area of the target tophus (or complete disappearance of the additional tophi) in the absence of any new or enlarging tophi.

Results: CR of at least one tophus was significantly more frequent among patients receiving pegloticase q2wk vs. placebo at 13 weeks of treatment and at all subsequent times of measurement in the RCTs. Tophus CR was achieved by 40% of patients after 6 months of q2wk pegloticase (vs. 7% with placebo; p=0.002). Although more patients treated with q4wk pegloticase had tophus CR (21%) vs placebo (7%) at the final RCT visit, this difference was not statistically significant. During the RCTs, 21 patients showed a new incident tophus (all among patients manifesting baseline tophi). New tophi were seen in 6% (4/62), 11% (7/64) and 35% (10/29) of patients receiving biweekly pegloticase, monthly pegloticase, and placebo treatment, respectively.

After 1 year in the OLE study, CR of at least one tophus was recorded for 74% (50/68) of patients receiving q2wk pegloticase. The Kaplan Meier curve below shows the time to first tophus CR for patients treated with placebo during the RCT followed by pegloticase in the OLE study. Despite receiving no urate-lowering therapy during the 6 months of RCT enrollment, approximately one-half of placebo-treated patients had a tophus CR within 6 months of initiation of q2wk pegloticase treatment in the extension study.

Graph: Time to tophus CR for patients who received placebo during the blinded trials and initiated pegloticase (Q2 week and Q4 week) in the OLE study
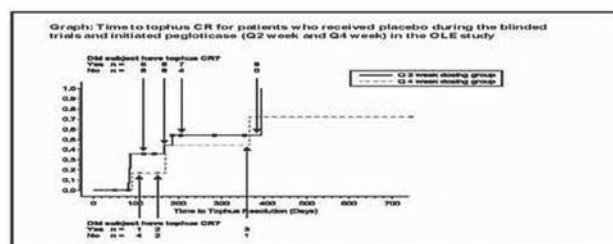
Conclusion: A significant rate of CR of at least one baseline tophus was achieved for patients treated with biweekly pegloticase within 13 weeks (compared with placebo treatment). Tophus CR rates over time are consistent and rapid for patients initiating pegloticase in both the RCTs and OLE study. The proportion of patients with a tophus CR continued to increase over time for up to 2.5 years of additional pegloticase treatment.

1914

The Diagnosis and Management of Gout in 2012: Survey of US and Canadian Rheumatologists. John J. Cush[1] and Robert T. Keenan[2]. [1]Baylor Research Institute, Dallas, TX, [2]Duke University, Durham, NC

Background/Purpose: The introduction of novel treatment modalities for gout has escalated interest and education on this topic. Although gout is the most common inflammatory arthropathy encountered, it still remains a diagnostic and therapeutic challenge for many. We surveyed a large cohort of North American Rheumatologists (Rheums) for their views, practices and treatment of gout.

Methods: 2401 adult Rheums from the USA and Canada (138) were invited (via emails) to partake in an online survey in early 2012. The survey included 39 questions regarding respondent demographics, practice type, diagnosis of gout, choice of therapy and safety concerns. On-line responses were tabulated using the CSV file downloads to Excel spreadsheets and verify data combing for outliers.

Results: There were 318 respondents (13.2% response), 78.8% male; with a mean age of 57.7 yrs. Responses came from private practice (56%), academic (31%), government (4%); with an overall mean of 25 years in practice (52% > 25 yrs). They see an average of 5.3 gout patients per week and follow 86.4 gout patients in their practice, with 62% seen every 3–6 months. 92% can see an acute gout referral in less than 1 week. Only 8% are followed for asymptomatic hyperuricemia. 22% for acute gout/flare, 70% for intercritical or chronic inactive gout. 78% are PCP referred, 2/3 for acute gout and 24% for hospitalized gout. 37% view gout a metabolic disorder and 34%as a uric acid overload disorder. For the diagnosis of gout, Crystal ID (98%) and clinical hx (96%) were most important and alcohol and family history (40%) least important. 77% have a polarizing microscope and 96% routinely follow urate levels. Indications for urate lowering therapy (ULT) included tophi (72%), >2 attacks/yr (71%) or gouty erosions (68%). Uricosurics were seldom chosen (<20%) and allopurinol therapy predominated (>95%). Surprisingly 28% felt no allopurinol dose adjustments were needed with creatinine levels of 2.5–3.5mg/dl. When initiating ULT, prophylaxis with colchicines (90%) was preferred over NSAID (43%) or prednisone (16%). The primary goal of Rx is attack prevention (94%) more so than urate level < 6.0 (66%). However, acute gout is preferably managed with steroids (86%), NSAIDs (82%) over colchicine (65%). 57% use less Colcrys and 47% use more NSAID and prednisone. Febuxostat is indicated with allopurinol failure/intolerance (93%) or sensitivity (82%). Pegloticase is indicated for allopurinol failure/sensitivity (69%/44%), febuxostat failure/intolerance (65%) or multiple tophi or attacks (58%/46%). Overall, 76.5% achieve a urate < 6.0 and 23% have tophi. Most disappointing is patient noncompliance (78%), management by nonrheumatologist (54%) and confusion between hyperuricemia and gout (41%). The greatest safety concerns were for NSAID or colchicine with renal dz (98% or 54%) and allopurinol with azathioprine (86%). While cherries, febuxostat and allopurinol were ranked as safest, NSAIDs and pegloticase had the most safety concerns.

Conclusion: Tradition continues to dominate Rheum practice standards in gout with the majority relying on MSU crystal ID and clinical features for diagnosis. Prevention of attacks, targeting urate < 6.0, and reliance on ULT continue to guide management.

1915

Elevated Serum Homocysteine Levels Were Related Not with Serum Uric Acid Levels but with Decreased Renal Function in Chronic Gouty Patients. Sang Tae Choi[1], Jung-Soo Song[2], Jin Su Kim[1], Eun-Jin Kang[3], Kwang-Hoon Lee[4] and You-Jung Ha[5]. [1]Chung-Ang University School of Medicine, Seoul, South Korea, [2]Chung-Ang University College of Medicine, Seoul, South Korea, [3]Busan Medical Center, Busan, South Korea, [4]Dongguk University Ilsan Hospital, Goyang, South Korea, [5]Kwandong University college of Medicine, Goyang, South Korea

Background/Purpose: Hyperhomocysteinemia, which is related with cardiovascular diseases and metabolic syndrome, is regarded as one of the important factors in endothelial cell damage processes. It is well known that Gout is associated with metabolic syndrome, and cardiovascular diseases are major causes of mortality that are found in gouty patients. However, there are few reports about the serum homocysteine levels in gouty patients, and

moreover their results showed discrepancy. In this study, we investigated whether or not serum homocysteine levels are elevated in the patients with chronic gout and which factors are associated with the elevated homocysteine levels.

Methods: This cross-sectional study included 91 male patients with chronic gout and 97 age-matched healthy male controls. The averages of age were 51.19 ± 15.08 and 51.57 ± 17.01 years old, respectively. Serum homocysteine, uric acid (UA), blood urea nitrogen (BUN), creatinine (Cr) and other laboratory findings were tested for all participants. Serum homocysteine levels were measured by a competitive immunoassay using direct chemiluminescent (Siemens Centaur Immunoassay Systems, USA). The estimated glomurular filtration rate (eGFR) was uptained using modification of diet in renal disease (MDRD) formula, then the stages of chronic kidney disease (CKD) were classified according to eGFR levels as follows; stage 1, more than 90 mL/min/1.73m^2: stage 2, 60–89 mL/min/1.73m^2: stage 3, 30–59 mL/min/1.73m^2: stage 4, 15–29 mL/min/1.73m^2: stage 5, less than 15 mL/min/1.73m^2.

Results: The chronic gout group were not significantly different from the control group in serum uric acid levels (6.15 ± 2.23 mg/dL vs 5.82 ± 1.22 mg/dL, $p = 0.224$). However, the patients with chronic gout showed much higher serum homocysteine levels than healthy controls (13.96 ± 4.05 μmol/L vs 12.67 ± 3.52 μmol/L, $p = 0.021$). Serum homocysteine levels showed the positive correlations with serum BUN and Cr levels, and the negative correlation with eGFR ($r = 0.429, p < 0.001; r = 0.435, p < 0.001; r = -0.413, p < 0.001$, respectively) in the chronic gouty group. However, serum homocysteine levels are uncorrelated with serum uric acid levels or cholesterol profiles. The patients at stages 1 or 2 of CKD had significantly lower serum homocysteine levels than the patients at stage 3 of CKD (12.99 ± 4.81 μmol/L, 13.17 ± 2.97 μmol/L, and 17.45 ± 4.68 μmol/L, $p < 0.001$). Serum homocysteine levels were not different between the groups that are treated with allopurinol and with benzbromarone. In multiple linear analyses, serum homocysteine level was affected by eGFR ($\beta = -0.385, p < 0.001$), however, was not affected by the serum uric acid level.

Conclusion: Serum homocysteine levels were higher in the male patients with chronic gout than in the healthy male controls. Hyperhomocysteinemia in gouty patients could be related not with serum uric acid levels, but with decreased renal function. Types of uric acid lowering agents did not affect the serum homocysteine levels.

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Serum Uric Acid As a Biomarker for Mitigation of Infusion Reactions in Patients Treated with Pegloticase for Refractory Chronic Gout. Herbert S. B. Baraf[1], Robert A. Yood[2], John S. Sundy[3], Faith D. Ottery[4] and Michael A. Becker[5]. [1]Arthritis & Rheumatism Associates, Wheaton, MD, [2]Reliant Medical Group, Worcester, MA, [3]Duke University Medical Center, Durham, NC, [4]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [5]University of Chicago, Chicago, IL

Background/Purpose: Using data pooled from the randomized, placebo-controlled trials (RCTs) of pegloticase, post-hoc analyses of urate-lowering, antibody titers and the patterns of infusion-related reactions (IRs) were carried out to evaluate predictors of risk for IRs. These analyses eventually led to guidance on monitoring uric acid (UA) levels as a biomarker of response to therapy[1]. Here we describe the basis and outcomes of these risk mitigation analyses.

Methods: The 2 RCTs enrolled patients at 56 centers in the US, Mexico and Canada. Patients were > 18 yrs of age, had baseline UA ≥8 mg/dL and at least one of the following: ≥3 self-reported gout flares during the prior 18 mos; ≥1 tophi; or gouty arthropathy; and contraindication to allopurinol or failure to normalize UA during ≥3 mos of treatment at the maximum appropriate dose. Pegloticase was administered as 8 mg infusions q2wks or q4wks; plasma UA was sampled at baseline and immediately preceding each q2wk infusion. All patients received prophylaxis for IRs and flares. A responder was defined by plasma UA <6 mg/dL for 80% of time during mos 3 and 6. IR was defined as any adverse event occurring during or within 2 hours after infusion.

Results: IRs were experienced by 26% and 42% of patients receiving pegloticase q2wks and q4wks, respectively. Post-hoc assessments revealed that the majority of these IRs (91% of IRs with q2wk dosing and 71% with q4wk dosing) occurred when UA exceeded 6mg/dL--suggesting that loss of urate-lowering response was predictive of risk for IRs. This relationship was

not apparent to investigators during the 6 mos of RCT treatment because they were blinded to the pre-infusion UA levels.

Multiple benefit/risk scenarios were tested using UA concentration cut points and IRs to determine the most effective stopping rule for maximizing both safety and efficacy. The Table shows the number of patients reaching the two endpoints in the pooled trial population (no stopping rules) and the number of patients that would have reached these 2 endpoints if the specific stopping rule had been applied to the RCT population. Among the options tested, discontinuation of drug when patients had 2 consecutive serum UA levels >6 mg/dL appears to reduce the proportion of patients with IRs from 26% (observed) to 14% (estimated) with little impact on efficacy.

Table. Risk mitigation scenarios for patients treated with q2wk pegloticase in Phase 3 placebo-controlled trials

Stopping Rule	Observed Number of Pts with IRs Pooled N=85n (%)	Observed Number of Pts Meeting Responder Criteria Pooled N=85n (%)
No Stopping Criteria	22 (26%)	36 (42%)
One SUA >6 mg/dL	7 (8%)	31 (36%)
One SUA >7 mg/dL	7 (8%)	32 (38%)
One SUA >8 mg/dL	9 (11%)	33 (39%)
Two consecutive SUA >6 mg/dL	12 (14%)	35 (41%)
Two consecutive SUA >7 mg/dL	12 (14%)	35 (41%)
Two consecutive SUA >8 mg/dL	13 (15%)	36 (42%)

Conclusion: Post-hoc assessments from the 2 RCTs provided valuable information on the relationship between UA levels and IR risk that was not available during the trials. Multiple benefit/risk analyses informed the recommendation that patients discontinue pegloticase when serum UA is >6 mg/dL, particularly at 2 consecutive time points. Ongoing post-marketing surveillance will be important to assess the risk of IRs in clinical practice and adherence to these recommendations.

1.Sundy et al. *JAMA*. 2011;306:711–20.

ACR/ARHP Poster Session C
Miscellaneous Rheumatic and Inflammatory Diseases
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Long-Term Follow-up of IgG4-Related Diseases Presenting with Lacrimal and Salivary Gland Involvement. Hiroki Takahashi[1], Motohisa Yamamoto[1], Tetsuya Tabeya[1], Chisako Suzuki[1], Yasuyoshi Naishiro[1], Yasuhisa Shinomura[1] and Kohzoh Imai[2]. [1]Sapporo Medical University School of Medicine, Sapporo, Japan, [2]The University of Tokyo, Tokyo, Japan

Background/Purpose: IgG4-related disease (IgG4-RD) is a recently recognized disease entity that is characterized by tumefactive and hyperplastic lesions in various organs including the lacrimal and salivary glands, pancreas and kidneys. Because patients with IgG4-RD have elevated serum IgG4 levels and characteristic histopathological features including dense infiltration of IgG4-positive plasma cells and storiform fibrosis, such lesions are assumed to have a common etiology and pathogenesis. Organ dysfunction is rarely severe in patients with IgG4-RD at diagnosis and responsiveness to corticosteroid therapy is frequently positive. Although the prognosis of IgG4-RD seems favorable, no long-term follow-up study has been reported. Data regarding the prognosis of IgG4-RD is essential when considering the introduction of intensive immunosuppressive therapy. We describe the clinical characteristics and prognosis of patients who have had IgG4-RD for ≥10 years.

Methods: This retrospective study at Sapporo Medical University Hospital analyzed clinical data at onset, involved organs during the clinical course and prognosis of 15 patients (5 men, 10 women) who had lived with IgG4-RD for ≥10 years. They were basically diagnosed according to the diagnostic criteria for IgG4-related Mikulicz's disease determined by the Japanese Society for Sjögren's syndrome.

Results: The average age at onset was 59 years and the average disease duration was 158 months. The lacrimal and salivary glands were the most frequently involved organs at onset in 12 of the 15 patients. Other initially involved organs included the mammary glands, pancreas and optic nerve. Only the lacrimal and salivary glands were affected in 6 patients during the clinical course (Mikulicz type). The others had multiple lesions (systemic type) of the retroperitoneum (n = 4), pancreas (n = 3), kidney (n = 2), lung (n = 2), liver (n = 1) and pituitary gland (n = 1). However, other lesions developed within 5 years in most patients with the systemic type and autoimmune pancreatitis developed in 1 patient 19 years after onset. The average levels of serum IgG4 at diagnosis in the Mikulicz and systemic types were 703 and 1,111 mg/dL, respectively. All patients initially responded well to corticosteroid therapy. Two patients required additional immunosuppressants due to recurrence during corticosteroid tapering. None of the patients died, progressed to end-stage organ failure or developed malignant lymphoma during the clinical course.

Conclusion: Patients with IgG4-RD presenting with lacrimal and salivary lesions at onset often developed other involved lesions within 5 years. However, only the lacrimal and salivary glands remained affected in a third of the patients over a period of about 10 years. Because the prognosis in terms of both life and function for patients with IgG4-RD is favorable when supported by corticosteroid therapy, careful consideration is required before introducing intensive immunosuppressive therapy.

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Cluster Analysis of Organ Involvements Patients with Serum IgG4 Elevation; IgG4–related Disease Is a Distinct Subtype of Patients with Hyper-IgG4. Masamitsu Tatewaki, Kazuhiro Kurasawa, Ayae Tanaka, Junya Nagasawa, Satoko Arai, Reika Maezawa, Takayoshi Owada and Takeshi Fukuda. Dokkyo Medical University, Mibu, Tochigi, Japan

Background/Purpose: IgG4-related disease (IgG4-RD) is a multi-organ affecting disease characterized by fibroinflammatory lesions with a abundant IgG4-positive plasma cells infiltration. This disorder includes many conditions such as autoimmune pancreatitis, Mikulicz disease and retroperitoneal fibrosis. Elevation of serum IgG4 levels is frequently found and is a key clue for diagnosis of IgG4-RD. However, there are patents who do not have fibrotic-sclerotic lesions, characteristics of IgG4-RD, but revealed elevation of serum IgG4. To determine whether IgG4-RD is a distinct subtype of diseases with hyper-IgG4, we conducted cluster analysis of patients with elevation of serum IgG4 levels and examined clinical features of each cluster.

Methods: Subjects were 86 patients with elevation of serum IgG4 (>100mg/dl) among 350 patients whom received IgG4 examination for diagnosis of mass lesions or inflammation. Cluster analysis of organ involvements of the patients were performed through Ward's method. Clinical features of patients in each cluster were e4xamined through reviewing medical records retrospectively.

Results: Through cluster analysis, 5 clusters were identified: cluster1; patients with multiple organ involvements including salivary glands, eyes, pancreas and retroperitoneum (typical IgG4 RD), cluster 2; patients with autoimmene pancreatitis alone (a subset of IgG4-RD), cluster 3; patients with lung involvement alone, cluster 4; patients with pleuritis alone, and cluster 5; patients without specific organ involvements. Renal involvement was found in patients in cluster1; generalized lymphadenopathy was detected in those in cluster 1, and pulmonary involvement was seen in those in cluster 1. Serum IgG4 level were significantly high in patients in cluster 1 compared to those in other clusters. In addition, serum IgG4 levels were increased in correlation with numbers of affected organs in cluster 1. Hypergammaglobulinemia occurred frequently in cluster 1. Serum CRP elevation was not found in cluster 1 and 2. IgG4 plasma cell rich infiltration was found in some biopsy samples from patients in all clusters. Glucocorticoid was effective on inflammatory lesions and systemic inflammation in most cases of all clusters.

Conclusion: Typical IgG4-RD (cluster1) is a distinct subtype of diseases with serum IgG4 elevation, which is characterized by multiple organ involvements, particularly salivary glands, eyes and retroperitoneum, generalize lymphadenopathy, marked IgG4 elevation with hypergammaglobulinemia and absence of systemic inflammation.

Disclosure: **M. Tatewaki**, None; **K. Kurasawa**, None; **A. Tanaka**, None; **J. Nagasawa**, None; **S. Arai**, None; **R. Maezawa**, None; **T. Owada**, None; **T. Fukuda**, None.

1919

Regulatory T Cells in IgG4-Related Disease Patients Presenting with Sclerosing Sialadenitis and Dacryoadenitis. Winnie K. Pang, Ya Liu, Julie Wang, Song Guo Zheng, Kiran Qidwai, Russell K. Brynes and Francisco P. Quismorio Jr., University of Southern California Keck School of Medicine, Los Angeles, CA

Background/Purpose: IgG4-Related Disease (IgG4-RD) is characterized by inflammation and fibrosis of various organ systems. Its diverse clinical presentations include autoimmune pancreatitis, retroperitoneal fibrosis, sialadenitis, and dacryoadenitis. The etiology and pathogenesis are not well understood; however, the role of regulatory T cells (Treg) has been suggested. We evaluated the phenotype and function of Tregs in IgG4-RD patients with lacrimal and salivary gland involvement.

Methods: Three untreated IgG4-RD patients with chronic lacrimal and salivary gland enlargement underwent clinical evaluation at the Los Angeles County Medical Center Rheumatology clinic. Peripheral blood mononuclear cells were obtained from healthy controls and the untreated IgG4-RD patients. Treg subsets were identified with a combination of monoclonal antibodies (anti-CD4, -CD25, -CD45RA, -Foxp3, -CCR7) conjugated to different fluorochromes. Intracellular cytokine production (IL-2, IL-4, IL-5, IL-17A, IFN-g) was assessed in T cells by flow cytometry after PMA/Ionomycin stimulation in vitro. Statistical analysis was performed using Mann-Whitney or Wilcoxon tests.

Results: The patients, initially referred to rheumatology for Sjogren's Syndrome, had clinical and histopathologic features consistent with IgG4-RD. Patient 1 was a 50-year-old Caucasian female with submandibular and lacrimal gland swelling for 3 years. She also had an enlarged right submandibular gland excised in 1989. Patient 2 was a 60-year-old African American female with bilateral parotid and lacrimal gland swelling since 2007. Patient 3 was a 33-year-old Filipino male with a history of hemimandibulectomy for ameloblastoma in 1989 who presented with painless enlargement of the lacrimal and parotid glands for 18 months. All patients underwent PET-CT scan, which showed diffuse lymphadenopathy and metabolically active, enlarged lacrimal and salivary glands. Excisional biopsies were performed. Histopathologic evaluation excluded lymphoma but revealed diffuse fibrosis, lymphocytic infiltration, and elevated IgG4/IgG plasma cell staining ratio (>50%) consistent with the diagnosis of IgG4-RD. Serum IgG4 levels were elevated in two patients.

Compared to healthy controls, the frequency of Treg (CD4+CD25+ FOXP3+) cells was remarkably decreased in IgG4-RD patients, whereas naïve Treg cells (population with naïve phenotype, CCR7+CD45RA+) were increased. IgG4-RD patients were also characterized by increased circulating Th2 (including CD4+IL-4+, CD4+IL-5+) cells compared to healthy controls, while Th1 (CD4+IFN-g) and Th17 (CD4+IL17+) cells did not differ significantly.

Conclusion: IgG4-related sclerosing dacryoadenitis and sialadenitis may mimic Sjogren's Syndrome, prompting referral to rheumatologists. Histopathologic evaluation is essential for diagnosis. Untreated IgG4-RD patients were found to have a higher percentage of Th2 and a lower percentage of Treg, suggesting that correcting the balance of Treg/Th2 cells may be a potential therapeutic approach.

Disclosure: **W. K. Pang**, None; **Y. Liu**, None; **J. Wang**, None; **S. G. Zheng**, None; **K. Qidwai**, None; **R. K. Brynes**, None; **F. P. Quismorio Jr.**, None.

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Spectrum of IgG4-Related Disease and Diagnostic Value of Serum IgG4 Determinations. Emma Kotisalmi[1], Tom Pettersson[2], Aaro Miettinen[3], Johanna Arola[4] and Martti Färkkilä[2]. [1]University of Helsinki, Helsinki, Finland, [2]Helsinki University Central Hospital, Helsinki, Finland, [3]Huslab, Helsinki, Finland, [4]University of Helsinki and Huslab, Helsinki, Finland

Background/Purpose: IgG4-related disease is a recently described systemic inflammatory and fibrosing condition that may mimic various other systemic rheumatic diseases. We studied the occurrence of IgG4-related disease over a one year period at a university hospital serving a population of 1.5 million, and assessed the diagnostic significance of a serum IgG4 concentration higher than the upper level of the reference interval.

Methods: Files were scrutinized for a diagnosis of IgG4-related disease over a one year period (May 2010 to May 2011). The diagnosis rested on the combination of a clinical picture consistent with IgG4-related disease and histopathological features showing a characteristic appearance with a dense lymphoplasmacytic infiltration, a pattern of fibrosis, and variable numbers of IgG4 positive plasma cells. In addition, the files of all patients with a serum IgG4 concentration higher than 1.40 g/l, determined for various reasons during the same time period, were examined and the diagnoses were recorded. IgG subclasses in serum were analysed with a BN II nephelometer using N AS IgG1, N AS IgG2, N Latex IgG3, and N Latex IgG4 reagents (Siemens, Marburg, Germany). The reference interval for IgG4 at our laboratory is 0.08–1.4 g/l.

Results: 14 patients (12 men and 2 women, mean age 61 years, range 40–78 years) were diagnosed with IgG4-related disease during the one-year study period. In 3 patients the disease was confined to a single organ, whereas the other 11 had multiorgan involvement. The presenting features and major manifestations were autoimmune pancreatitis in 10, autoimmune cholangitis in 10, Mikulicz disease in 3, Riedel's thyroiditis in 2, retroperitoneal fibrosis in 1, and mediastinal fibrosis in 1. Three had a diagnosis of bronchial asthma. Median serum IgG4 concentration at diagnosis was 7.75 g/l with a range of 1.66–18.20 g/l. No patients with a diagnosis of IgG4-related disease and normal serum IgG4 concentrations were identified. Major diagnoses suspected at referral included pancreatic carcinoma, liver disease, primary Sjögren's syndrome, sarcoidosis, lymphoma, and vasculitis. Over the same time period no less than 238 additional patients with a serum IgG4 concentration higher than 1.40 g/l (median 2.22 g/l, range 1.41–11.50 g/l) were recorded. The most common diagnoses among these patients were bronchial asthma, chronic sinusitis and various allergic conditions, but high values were observed in a wide range of other diseases including sclerosing cholangitis, inflammatory bowel disease, and vasculitis.

Conclusion: We confirmed previous observations that IgG4-related disease occurs predominantly in middle aged or elderly men. Awareness of this newly recognized condition is essential since it constitutes a major differential diagnosis against various systemic inflammatory diseases and other diseases including lymphoma and other neoplasia. In our series a high serum IgG4 concentration was a regular finding among patients with IgG4-related disease. However, serum IgG4 concentrations higher than normal also occurred in a great variety of other diseases.

Disclosure: **E. Kotisalmi**, None; **T. Pettersson**, None; **A. Miettinen**, None; **J. Arola**, None; **M. Färkkilä**, None.

1921

Diagnostic Utility of Serum IgG4 in IgG4-Related Disease. Mollie Carruthers[1], Tamara Augustin[2], John H. Stone[1] and Arezou Khosroshahi[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Internal Medicine, Northshore Medical Center, Salem, MA

Background/Purpose: IgG4-related disease (IgG4-RD) is a recently recognized fibro-inflammatory disease with multi-organ system involvement, often but not always characterized by elevated serum IgG4 concentrations. The aim of this study was to determine the sensitivity, specificity, and positive and negative predictive values of serum IgG4 levels for the diagnosis of IgG4-RD.

Methods: This study was approved by the Institutional Review Board of our hospital. We searched the Massachusetts General Hospital database using the Research Patient Data Registry tool. Since March, 2001, 193 serum samples from unique patients were found to have elevated serum IgG4 concentrations (normal < 135 mg/dL). We reviewed the electronic medical record to determine the reason for the serum IgG4 assay and the underlying diagnosis in every case. The diagnostic criteria of IgG4-RD were determined according to the IgG4-RD international symposium consensus guidelines. In addition, we randomly selected 193 separate patients with normal serum IgG4 concentrations (from a pool of 3360 patients with normal results) in order to evaluate the test characteristics of IgG4 measurement.

Results: Among the 386 patients analyzed, 73 had either probable or definitive diagnoses of IgG4-RD. Sixty-six of these 73 patients had elevated serum IgG4 concentrations (mean: 404 mg/dL), for a sensitivity of 90%. In contrast, 313 (82%) of the patients analyzed did not have IgG4-RD diagnoses. Among those, 127 had elevated IgG4 concentrations (mean: 232 mg/dL; p <0.0001), for a specificity of 59%. The non-IgG4-RD diagnoses associated

with elevated serum IgG4 levels are shown in the **Figure**. Common causes of false-positive results were chronic sinusitis, recurrent pneumonia, and connective tissue diseases such as lupus, Sjögren's, and vasculitides. The negative predictive value of a serum IgG4 assay was 96%, but the positive predictive value was only 34%.
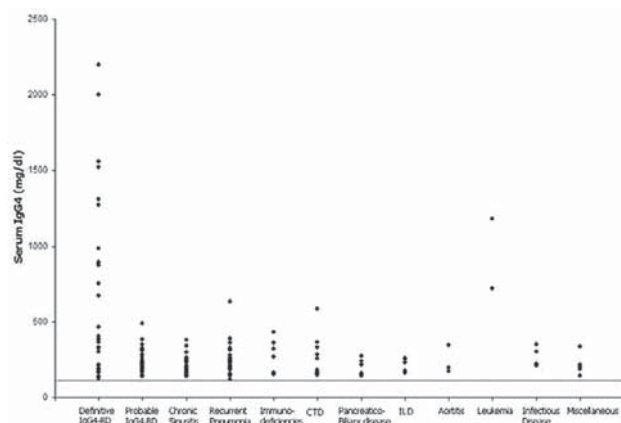
Figure 1. Diagnoses Associated with Elevated Serum IgG4 Concentrations

Conclusion: With regard to the diagnosis of IgG4-RD, both the sensitivity and the negative predictive value of serum IgG4 assays are high. However, multiple non-IgG4-RD conditions can also be associated with elevated serum IgG4 concentrations, leading to poor specificity and a low positive predictive value for this test.

Disclosure: **M. Carruthers**, None; **T. Augustin**, None; **J. H. Stone**, Genentech, 5; **A. Khosroshahi**, None.

1922

Articular Involvement in Relapsing Polychondritis: A Case Series. Laura O. Damian[1], Linda Ghib[1], Ioana Felea[2], Alma Maniu[3], Nadia Radics[1], Simona Falaus[1], Ileana Filipescu[4], Siao-pin Simon[3] and Simona Rednic[4]. [1]Emergency County Clinical Hospital Cluj Napoca, Cluj Napoca, Romania, [2]Emergency County Clinical Hospital Cluj Napoca, Cluj-Napoca, Romania, [3]University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, Cluj Napoca, Romania, [4]University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, Cluj-Napoca, Romania

Background/Purpose: Relapsing polychondritis (RP) is a relatively rare, but progressive disease with predilection for cartilage, with few data available regarding the arthritis in this setting. Purpose: To assess the type of articular involvement and its clinical associations of RP.

Methods: Systematic retrospective analysis of all patients diagnosed with RP in the Rheumatology Department, a tertiary care facility, over a 12-year period (2000 to 2012) using the hospital and outpatient databases. The McAdam diagnostic criteria for RP were employed. The patients were interviewed by the rheumatologist using a standard protocol. Patients self-taking pictures of the ear, eye or other involved organs during the painful episodes was encouraged.

Results: We identified 34 patients (67% women), age of onset 44.8 ± 16.9 years. The mean time to diagnosis was 36 months (1–168), after consultations of 4 other specialists (1–8). Most frequent autoimmune disease associated were vasculitis (10 cases, 2 with Behcet's /MAGIC syndrome), SLE (5), Sjogren's syndrome (2) and psoriatic arthritis (2). Hematological malignancies were seen in 5 cases. The arthritis was present in 30/34 (88%) cases and was intermittent, but symmetric in 17 (56%) cases and asymmetric in 13 (43%), mimicking microcristalline arthritis in 9/30 (30%) cases. Mutilating arthritis was seen in 3 patients (2 with dissecting osteochondritis) and avascular necrosis in 3. Chondrosternal and manubriosternal arthritis were noted in 61% (21/34) and 44% (15/34) cases, respectively; when inaugural, pointed to a diagnosis of Tietze or SAPHO syndrome. In 3 patients signs of vertebral chondritis were present, mimicking ankylosing spondylitis or vertebral chondrocalcinosis. Three patients diagnosed with Lyme disease had acute intermittent arthritis attributed initially to borreliosis, before the appearance of chondrosternal arthritis and later of the ENT involvement. The symmetric arthritis was associated with a shorter time from onset to diagnosis (2.43 vs 4.3 yr, p=0.03) than the asymmetric one. Symmetric arthritis was also correlated with more serious ENT involvement, auricular deformities (p=0.028) and also with ocular inflammation (p=0.03), pericarditis (p=

0.02), leukopenia (p=0.02) and glomerulonephritis (p=0.02). Rheumatoid factor was present in only 4 cases, rather reflecting the presence of cryoglobulinemia or hematological malignancies.

Conclusion: Even in the presence of auricular or nasal chondritis, RP could still be a tricky diagnosis, several consultants being seen before diagnosis. In our series symmetric arthritis was associated with a more complicated disease course, possibly reflecting the underlying pathology. The diagnosis of RP should be considered in recurrent paroxistic chest pain and also in vertebral acute relapsing pain. The instruction of patients to self-report and to document by pictures an evanescent inflammation could add to a better recognition of disease.

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1923

Biologics in Relapsing Polychondritis: A Single Center Case-Series. Guillaume Moulis[1], Laurent Sailler[2], Grégory Pugnet[3], Leonardo Astudillo[1] and Philippe Arlet[1]. [1]Toulouse University Hospital, University of Toulouse, Toulouse, France, [2]Toulouse University Hospital, University of Toulouse, INSERM UR 1027, Toulouse, France, [3]Toulouse University Hospital, University of Toulouse, INSERM UMR 1027, Toulouse, France

Background/Purpose: First-line treatment for relapsing polychondritis (RP) is costicosteroids (CS). Dapsone and methotrexate have been proposed as second-line therapies. Only few reports have been published on the use of biologics in RP. There may be a publication bias favouring successful issues. This work was aimed at colligating and describing the effects of biologics in RP patients in our Department.

Methods: Diagnosis codes are given and registered in a computerized medical file for each patient treated in our department since 1993. We performed the extraction of all cases encoded as "RP". The diagnosis was confirmed using Damiani's McAdam-modified criteria. All patients treated with biologics were evaluated for efficacy and adverse drugs reactions until the 20th June 2012 (last follow-up date).

Results: Among 22 patients encoded "RP", 17 fulfilled Damiani's criteria. Among them, 8 were exposed to 19 biologics as CS-sparing drugs. Mean age at diagnosis was 45.7 years and male:female sex-ratio was 1:4. All patients had chondritis and seronegative polyarthritis, 4 had cochlear or vestibular dysfunction and 2 had ocular inflammation. Biologics were used at the same doses as in rheumatoid arthritis. Seven patients were treated with TNF-alpha antagonists (adalimumab, n=7, etanercept, n=3, infliximab, n=2, certolizumab, n=1), 2 with anakinra, 2 with abatacept and 2 with tocilizumab. Treatments used before biologics were CS (all patients), methotrexate (n=3), dapsone (n=2), hydroxychloroquine (n=4), azathioprine (n=1). In 3 cases (patients 4, 6 and 8), biologics were used because of a cortico-dependant and severe disease (tracheal inflammation). Mean delay from diagnosis to first biologic use was 9.75 months. Outcomes are described in table 1. Seven adverse drug reactions were considered as drug-related: reactions at injection site occurred in 2 patients (1 on anakinra, 1 on adalimumab), and infections in 3 patients (1 pneumonia on adalimumab, sinusitis and otitis followed by herpes zoster on tocilizumab, 1 cellulitis on abatacept).

Table 1. Outcomes of the 19 biologic therapies

Patients	Drug	Efficacy	Duration (months)	Reason for withdrawal, if any
1	Etanercept	Partial	3	Insufficient efficacy
	Adalimumab	Partial	3	Insufficient efficacy, pain at injection sites
2	Adalimumab	Yes	15	Loss of efficacy
	Infliximab	No	0.5	Systemic reaction
	Anakinra	No	3	Inefficacy
	Abatacept	Partial	12	Insufficient efficacy
	Tocilizumab	Yes	2	Ongoing
3	Etanercept	Yes	12	Loss of efficacy
	Adalimumab	Yes	26	Inactive disease
4	Etanercept	Yes	9	Loss of efficacy
	Adalimumab	Partial	6	Loss of efficacy
	Infliximab	Yes	10	Loss of efficacy
	Anakinra	No	1.5	Inefficacy
	Abatacept	Yes	33	Minor loss of efficacy
	Certolizumab	No	3	Inefficacy
	Abatacept again	Yes	10	Ongoing
5	Tocilizumab	Yes	5	Ongoing
6	Adalimumab	Yes	20	Inactive disease
7	Adalimumab	Yes	60	Ongoing
8	Adalimumab	Yes	1	Ongoing

Conclusion: All biologics but anakinra and certolizumab in one patient had a consistent effect. Loss of efficacy occurred frequently. Switching from a TNF-alpha antagonist to another TNF-alpha antagonist was frequently efficacious and may be proposed before switchting to abatacept or tocilizumab. The benefit-to-risk ratio of biologics compared with immunosuppressive drugs should be evaluated prospectively in RP.

1924

What Do Patients with Polmyalgia Rheumatica Mean When They Describe Stiffness? A Qualitative Study. Rodney A. Hughes[1], Sarah Mackie[2], John R. Kirwan[3], Colin T. Pease[4], Margaret Walsh[1] and Marianne Morris[5]. [1]St. Peters Hospital, Chertsey Surrey, United Kingdom, [2]University of Leeds, Leeds, United Kingdom, [3]Bristol Royal Infirmary, Bristol, United Kingdom, [4]Leeds Teaching Hospitals NHS Trust, Harrogate, United Kingdom, [5]University of the West of England, Bristol, United Kingdom

Background/Purpose: Patients with PMR report significant symptoms of pain and stiffness. Stiffness has usually been included in diagnostic criteria for PMR but has never been clearly defined. Stiffness can prove difficult to measure and to distinguish from pain. To try to establish both a definition and a clearer understanding of stiffness in PMR we have performed a qualitative study designed to elicit appropriate patient experience and perception of stiffness.

Methods: We have conducted 8 focus groups in 3 rheumatology centres in the UK involving 50 patients with PMR. We included one city and two semi-urban units in three regions in the UK to try to explore differences in language or communication across areas. Patients all had English as a first language. Each focus group ran for 1.5 hours, data were transcribed and thematically analysed into codes, sub-themes and themes. Two expert patients with PMR were included in the research from the start of the study. Sample size was designed to reach saturation of themes.

Results: Themes have emerged in response to direct questioning that relate specifically to definitions of stiffness and measurable outcomes for PMR (deductive thematic anaysis). Through inductive analysis additional themes have emerged; that pain and stiffness were inextricably linked, the use of metaphors to describe PMR symptoms, and an in depth understanding of the cognitive and behavioural impact of polymyalgia.

PMR emerges as a disease of 'two halves' with a very close relationship between pain and stiffness. For some, stiffness appears before pain is experienced and can serve as a warning of pain should the person move—'freezing up in anticipation of pain'. From the data set it appears that patients are dominated either by pain, fatigue or stiffness but there is always a background of stiffness. Metaphorical descriptions of disease relating to stiffness have included 'tin soldier', 'rusty hinge', '2 bricks cemented on my shoulders' and being 'trapped in a coffin'. Patients report stiffness in association with sleep disturbance, loss of confidence, mood and stress disorders and a clear temporal variation of symptoms worse at night and in the early morning 'my 24 hour problem', 'a cycle'. Although patients report a very significant improvement in stiffness and pain after treatment with corticosteroids data suggest that they almost always continue to experience stiffness although they may not report this to their physicians. Stiffness both before and after treatment impacts on function, independence and social and working life.

A thematic model of stiffness in PMR
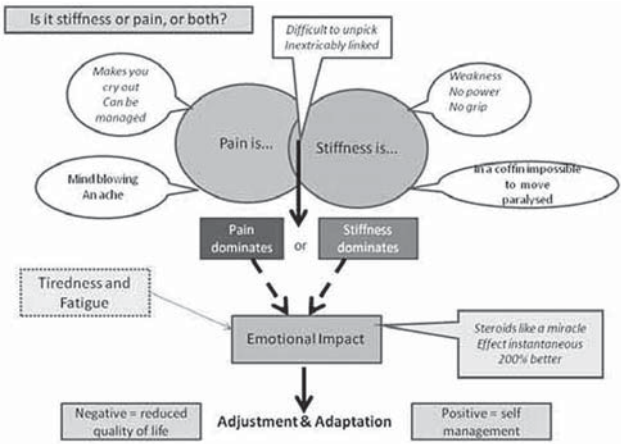
Conclusion: This work has led us towards a clearer definition of the meaning, experience and impact of stiffness. We have devised an initial thematic model of symptoms in polymyalgia that emerges from our work that will enable us to proceed further towards an adequate definition of stiffness ways of measuring it.

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Patient Satisfaction and Experience with Golimumab, Adalimumab, and Etanercept for the Treatment of Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis. Susan Bolge[1], Helen Eldridge[2], Dilesh Doshi[1], Lorie Ellis[1], Barbara Roland[3] and John Woelfel[3]. [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Janssen Pharmaceuticals, Inc, Titusville, NJ, [3]The Dominion Group, Reston, VA

Background/Purpose: Golimumab (GLM), adalimumab (ADA), and etanercept (ETN) are subcutaneous (SQ) anti-TNF therapies available for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). The purpose of this study was to explore satisfaction with effectiveness and injection experience with GLM, ADA, and ETN from the patient perspective.

Methods: In 2012, RA, PsA, and AS patients currently receiving SQ biologic therapy participated in telephone interviews. Patients rated satisfaction with current SQ therapy on a 7-point Likert scale ($1=$ extremely dissatisfied and $7=$ extremely satisfied). Patients also described their most recent injection experience. Propensity weights were applied to adjust for differences in duration of therapy and past intravenous (IV) biologic use of GLM patients vs. ADA and ETN patients.

Results: A total of 69 GLM, 143 ADA, and 181 ETN patients participated in the study. Before adjustment, GLM patients had shorter duration of therapy than ADA and ETN patients (less than one year GLM: 51% vs. ADA: 21%, $p<0.05$ and ETN: 17%, $p<0.05$). Also, a greater proportion of GLM patients had prior IV biologic exposure (GLM: 41% vs. ADA: 14%, $p<0.05$ and ETN: 13%, $p<0.05$). When propensity weights were applied to adjust for differences in duration of therapy and prior IV biologic experience, GLM patients reported high satisfaction with effectiveness (6–7 on 7-point scale) at similar rates to ADA and ETN patients for prevention/treatment of condition (GLM: 55%, ADA: 55%, ETN: 56%), symptom relief (GLM: 45%, ADA: 51%, ETN: 57%), and time to onset (GLM: 44%, ADA: 42%, ETN: 50%). GLM patients reported lesser degrees of discomfort, pain, stinging, and burning during injection than ADA or ETN patients.

Table 1. Most Recent Injection Experience (Adjusted using Propensity Weights)

		GLM	ADA	ETN
Discomfort	None	49%	32%*	18%*
	Moderate	10%	23%†	23%*
Pain	None	49%	44%	28%*
	Moderate	7%	23%*	15%
Stinging	None	41%	16%*	12%*
	Moderate	4%	28%*	26%*
Burning	None	58%	41%†	40%*
	Moderate	9%	20%†	24%*

*$p<0.05$ compared to GLM; †$p<0.10$ compared to GLM

Conclusion: Patient reported satisfaction with effectiveness is comparable among patients treated with GLM, ADA and ETN, and less discomfort, pain, burning, and stinging with injection is reported by GLM patients. Patient injection experience may be an important consideration in selection of biologic treatment. Future research should explore potential effects of patient injection experience on treatment adherence and patient outcomes.

1926

Evaluation of Strategies to Taper Anti-TNF Drugs in Patients with Inflammatory Rheumatic Disease (Rheumatoid Arthritis, Ankyloing Spondylitis, Psoriatic Arthritis, Adult-age Juvenile Idiopatic Arthritis) in Long-Term Remission. Jakub Zavada, Katarina Hviscova, Katerina Jarosova, Sarka Forejtova, Jiri Stolfa, Liliana Sedova, Dana Tegzova, Jiri Vencovsky and Karel Pavelka. Institute of Rheumatology, Prague, Czech Republic

Background/Purpose: While abrupt discontinuation strategies of anti-TNF drugs have been shown to result in frequent disease flares, tapering of dose may be a feasible option for patients with inflammatory rheumatic disease in long-term remission. We aimed to assess the feasibility to taper anti-TNF drugs (either by dose reduction or by prolongation of dosing interval) in patients with inflammatory rheumatic disease (RA, AS, adult-age JIA, PsA) in long-term remission

Methods: Patients with RA, AS, PsA or adult-age JIA in long-term remission of the disease (>6 months) were eligible for this prospective observational cohort study. Baseline and 3-monthly follow-up visits data concerning medication and activity of the disease were recorded prospectively by a questionnaire. The desicions whether and how to taper (or increase in case of flare) anti-TNF therapy were left solely to the discretion of the treating physician, without any pre-specified protocol. Survival analyses, performed using a Cox proportional hazards model, were used to assess the predictors of failure of the tapering strategies (failure was defined as reinstitution of the usual/baseline dose of the anti-TNF drug).

Results: 132 patients (AS: 55, RA: 45, adult-age JIA: 22, PsA: 10) with at least one follow-up visit after tapering of anti-TNF therapy (corresponding to 176 patient-years of follow-up) have been analyzed. Median time of follow-up per analyzed patient was 189 days (IQR 98–343 days). 70 (53%) patients were treated by etanercept, 37 (28%) by adalimumab, and 25 (19%) by infliximab. 50% fraction (or less) of the baseline dose was reached in 81 (62%) patients. Within respective diagnoses, 50% fraction (or less) of the baseline dose was reached in 34 (62%) pts with AS, 17 (77%) with JIA, 5 (50%) with PsA, and 25 (56%) with RA. In 25 (19%) patients the subsequent flare of the disease activity required increase of the anti-TNF drug back to the baseline dose (i.e. the tapering strategy failed). Within the diagnoses, failures were observed in 7 (13%) of pts with AS, 1 (5%) with adult-age JIA, 3 (30%) with PsA, and 14 (31%) with RA. In univariate survival analyses, the risk of the tapering strategy failure was numerically higher in RA patients (HR 2.39, 95%CI 0.96–5.97), PsA pts (HR 2.38, 95%CI 0.62–9.24), and lower in JIA pts (HR 0.32, 95%CI 0.04–2.60) as compared to AS patients (referent); the risk of failure was also numerically greater in pts treated with infliximab (HR 2.49, CI95% 0.95–6.58) as compared to etanercept (referent), or adalimumab (HR 1.41, CI95% 0.55–3.58).

Conclusion: This observational study from one academic center on patients with inflammatory rheumatic disease (RA, AS, PSA, adult-age JIA) in long-term remission showed, that after tapering of the anti-TNF drug dose (or prolongation of the dosing interval) 19% of pts required reinstitution of the usual/baseline dose of the anti-TNF drug within the limits of the relatively short-term follow-up

Disclosure: J. Zavada, None; K. Hviscova, None; K. Jarosova, None; S. Forejtova, None; J. Stolfa, None; L. Sedova, None; D. Tegzova, None; J. Vencovsky, None; K. Pavelka, None.

1927

Inflammatory Meningeal Involvement in Patients with Rheumatic Diseases Responsive to Rituximab. Jane Park[1], Eyal Kedar[1], Ingeborg Sacksen[1], John Henson[2] and Gregory C. Gardner[1]. [1]University of Washington, Seattle, WA, [2]Swedish Neuroscience Institute, Seattle, WA

Background/Purpose: Inflammatory meningeal involvement can be idiopathic or associated with a variety of inflammatory rheumatic diseases such as ANCA associated vasculitis (AAV), rheumatoid (RA) arthritis, sarcoidosis or the recently described IgG4 related diseases. Clinical symptoms can include headache, cranial neuropathies, cognitive changes, seizures, and encephalopathy. Case reports have described successful therapy with steroids, methotrexate, mycophenolate, cyclophosphamide, and rituximab. We present five cases of inflammatory meningitis unresponsive to various doses of steroids and other immunosuppressive agents treated successfully with rituximab**.**

Methods: All 5 patients with inflammatory meningeal disease seen in rheumatology clinic over the last 5 years and treated with rituximab were reviewed.

Results: The current series consisted of 3 women and 2 men with an age range of 49–84 years. Underlying diseases included 3 patients with AAV (1 localized AAV the other 2 with systemic AAV), 1 patient with RA, and 1 patient with idiopathic disease (possible GCA). Major symptoms and signs included headaches in 4, hearing loss in 2, vision loss in 2, and significant cognitive changes in 2 patients. MRI showed pachymeningeal thickening/enhancement in 4 patients and leptomeningeal in 1. Four of the 5 patients had meningeal biopsies and all showed granulomatous inflammation, a finding not seen with IgG4 disease. All patients had received steroids. Other immuno-suppressants used included methotrexate, azathioprine, leflunomide, myco-phenolate, and abatacept.

Rituximab was used due to continued meningeal symptoms and because it was indicated for the underlying diseases (AAV, RA). The initial rituximab doses were 1000–2000 mg repeated every 6 months. Two patients continued on methotrexate in addition to rituximab. Three of 5 patients had rapid and dramatic reversal of most if not all of the symptoms referable to the meningeal inflammation. One patient with localized GPA has significant improvement allowing the reduction of prednisone from 40–60 mg/day to 5 mg per day. One patient had improvement without resolution of headache and hearing loss but has received only 1 dose. Repeat MRI scans were available on 4 patients and results ranged from complete resolution of MRI changes in 1 patient and improvement in 3. In 1 patient with the shortest treatment course, no MRI improvement has been noted to date. No side effects occurred that are referable to rituximab treatment.

Conclusion: Rituximab is a useful agent in the treatment of refractory inflammatory meningeal disease whether idiopathic or associated with another inflammatory rheumatologic illness

Disclosure: J. Park, None; E. Kedar, None; I. Sacksen, None; J. Henson, None; G. C. Gardner, None.

1928

Evaluating the Therapeutic Effects of B Cell Depletion Therapy with Rituximab in a Longitudinal Cohort of Mixed Connective Tissue Disease Patients. Ragnar Gunnarsson, Inge-Margrethe Gilboe, Torhild Garen and Øyvind Molberg. Oslo University Hospital Rikshospitalet, Oslo, Norway

Background/Purpose: Even though 40 years have passed since MCTD was defined as a distinct disorder, there is still no evidence based therapy available. The choice of treatment is based on data from related connective tissue diseases. Biological agents have been used in a few patients with disease resistant to conventional immune-modulating drugs. Tumor necrosis factor alpha (TNFα) inhibitors have had limited efficacy and/or adverse effects (1, 2). B cell depletion therapy with rituximab (RTX) has only been reported in three MCTD patients, two of these responded to the treatment (3, 4), whereas the last had a treatment related complications (5).

Methods: A retrospective chart review of all the MCTD patients who were treated with RTX at the Rheumatology unit at the Oslo University Hospital from the 1st of June 2006 to the 15th of June 2012 and fulfilled at least one of the four MCTD criteria sets (Kasukawa's, Alarcón-Segovia's, Kahn's and/or Sharp's criteria) were performed.

Results: Four female MCTD patients, all fulfilling all the four MCTD criteria sets, were treated with RTX according to the rheumatoid arthritis protocol with two 1,000 mg RTX infusions two weeks apart. Two of these patients were retreated with RTX after 10 and 21 months. At the start of the RTX treatment, the patient's mean age was 44 years (37 to 65) and their mean disease duration was 8.7 (5 to 12) years. The mean observation time was 46 (23 to 70) months. So far, no adverse effects have been identified

Patient details;

Patient 1: Therapy resistant thrombocytopenia over years. Normalization of platelets 15 weeks after RTX and currently uses low dose prednisolone (GC).

Patient 2: Therapy resistant myositis with high serum creatinine kinase (CK, max 4605 U/L); reduced proximal muscle strength and increased signal intensity on MRI (STIR and T1).

After RTX, normalization of CK and reduced MRI changes and was able to reduce GC dose. She had two minor relapses, the first 12 months after RTX and is currently treated with methotrexate (MTX) and low dose GC.

Patient 3: Therapy resistant myositis with; high CK (max 7076 U/L); MRI changes and reduced muscle strength. Two courses of RTX, ten months apart, with the background of MTX, GC, Hydroxychloroquine (HCQ) led to normalization of CK and increased muscle strength.

Patient 4: MCTD/RA overlap, therapy resistant, destructive arthritis. Non-responder to two TNFα-inhibitors. RTX with a background therapy of MTX, GC & HCQ, led to a complete remission of arthritis and significant relief in Raynaud's phenomenon for 18 months. A recent relapse was treated with a new round of rituximab.

Conclusion: During the observation period, four MCTD patients received B cell depletion therapy with RTX. The treatment was well tolerated and had significant clinical effects on thrombocytopenia, myositis and arthritis. Randomized controlled trials are needed to further evaluate the effects of RTX in MCTD.

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1929

Pernicious Anemia and Vitamin B-12 Deficiency in Autoimmune Disease: Neglecting the Feet Will Lead You Astray. Michael R. Lovy Desert Oasis Healthcare, Palm Springs, CA

Background/Purpose: The occurrence of multiple autoimmune disorders in individual patients is commonly observed. Rarely, this is explained by recently recognized genetically based autoimmune polyendocrine syndromes. Pernicious anemia accompanies other autoimmune disorders both in patients with and without these discrete syndromes. The purpose of this study was to detect possible underlying vitamin B-12 (B-12) deficiency or pernicious anemia in a rheumatology clinic based on a simple neurologic exam of the feet.

Methods: Patients seen in a rheumatology clinic over a six month period were examined for evidence of peripheral neuropathy. If typical findings of stocking sensory loss at the ankle level were found a B-12 level was obtained. If B-12 levels were low anti parietal cell and intrinsic factor antibody titers were obtained. Methylmalonic acid (MMA) levels were obtained in patients without either antiparietal cell or intrinsic factor antibodies. Clinical features of antibody positive patients as well as those with B-12 deficiency and elevated MMA levels were reviewed.

Results: 38 patients with low B-12 levels were positive for antiparietal cell or intrinsic factor antibodies. An additional 10 patients with low B-12 and elevated methylmelanic acid levels were indentified. Diagnosis among antibody positive patients included: rheumatoid arthritis 9-including one with vitiligo. one with Grave's disease, 2 with Hashimoto's; lupus 5; primary Sjogren's 3-including one with stiff man syndrome; primary Raynaud's 4; polyarticular CPPD 3; tophaceous gout 3; vasculitis 2; ankylosing spondylitis 1; and pyoderma gangrenosum 1. Diagnosis among antibody negative patients included osteoporotic fracture 4, osteoarthritis 4, lupus 2, rheumatoid 2, ankylosing spondylitis 2, tophaceous gout 1, CPPD 1. Among the lupus and Sjogren's patients there were 2 positive for both SS-A and SS-B, 3 for SS-A, 1 for SS-B, 3 with anticardiolipin antibody, and 3 with false positive VDRL. Paraproteinemia was present in 3 patients. Among the 15 male patients, 7 were being treated for hypogonadism. Four patients had 25-OH vitamin D levels below 10 ng/ml, 9 patients had thyroid disease, 7 had diabetes, and 13 had a positive family history for either diabetes or an autoimmune disease. The MCV level and hemoglobin level was normal in all but 1 patient who drank alcohol excessively.

Conclusion: Pernicious anemia and B-12 deficiency was observed in a wide spectrum of autoimmune and arthritic diseases, especially SS-A and SS-B positive individuals. Other components of autoimmune polyendocrine syndrome including diabetes, thyroid disease, male hypogonadism, and low vitamin D levels, suggesting the possibility of celiac disease, occurred frequently in this study group. Recognition of pernicious anemia should alert the clinician to the possible presence of other components of autoimmune polyendocrine syndrome and vice versa. Also, B-12 deficiency can cause elevated MCV, foot complaints, constitutional symptoms, neuropathy that could be mistaken as a complication of the underlying disease or its therapy, and is associated with osteoporotic fractures. A simple 30 second neurologic exam can lead to the diagnosis of this potentially treatable deficiency.

Disclosure: M. R. Lovy, None;

1930

Progranulin Plays a Protective Role in the Pathogenesis of Inflammatory Bowel Disease. Fanhua Wei[1], Jinlong Jian[1], Yuying Zhang[1], Jiqiang Lin[1], Juan Lafaille[2], Michael Dustin[3], Lloyd Mayer[4] and Chuanju Liu[5]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]New York, NY, [3]NYU School of Medicine, New York, NY, [4]Mount Sinai Medical Center, New York, NY, [5]New York University, New York, NY

Background/Purpose: Progranulin (PGRN) is a growth factor with multiple functions. We recently reported that PGRN and its derived engineered protein Atsttrin directly bound to TNF receptors, inhibited TNF-α activity and exhibited potent anti-inflammatory effect in inflammatory arthritis models (Tang, W., et al, *Science*, 2011 Apr 22;332(6028):478–484). TNF-α is also known to play a critical role in the pathogenesis of inflammatory bowel disease (IBD), and blockage of TNF-α represents an effective therapeutic option in the treatment of IBD. Thus the objective of this project is 1) to examine the expression profiling of PGRN in the course of IBD, 2) to define the role of endogenous PGRN in IBD, and 3) to determine whether recombinant PGRN or its derivatives represents novel therapeutic interventions for IBD.

Methods: The expression of PGRN in the course of IBD was detected using immunohistochemistry. To elucidate the effects of endogenous PGRN on the initiation and progression of colitis, various colitis models, including DSS- and TNBS-induced colitis model, CD4+CD45Rb^{hi} T cell transfer model were established with WT and PGRN-deficient mice. To determine the therapeutic effect, recombinant PGRN or Atsttrin at a dosage of 5mg/kg body weight was injected into various experimental colitis models. Body weights were recorded and the colon tissues were collected for histological and immunohistochemical assays.

Results: PGRN was highly expressed in the epithelial cell layer and smooth muscle of colon in WT mice, and its expression was significantly induced in the course of DSS- or TBNS-induced colitis. PGRN KO mice suffered from accelerated body weight loss, and exhibited more severe transmural inflammation with extensive ulceration and necrosis compared to WT mice. Transfer of PGRN$^{-/-}$CD4+ CD45RB^{hi} T cells into RAG1$^{-/-}$ recipient mice led to an accelerated onset of disease and to more severe signs of inflammation. In addition, all mice died 35 days after T cell transfer in this group, whereas all mice were still alive following T cell transfer from WT donor mice up to 56 days. These results indicate that CD4+ CD45RB^{hi} T cells-derived PGRN is critical for the augmented inflammation of IBD. Importantly, injection of recombinant PGRN, or its derived engineered molecule Atsttrin, was able to effectively ameliorate the symptoms of colitis, as revealed by significantly delayed body weight loss and less tissue inflammation. In addition, the application of PGRN restored the survival rate in the T cell transfer model.

Conclusion: PGRN plays a protective role in the pathogenesis of inflammatory bowel disease. PGRN, specially its derived engineered molecules, may be used as new anti-TNF/TNFR therapeutic interventions for inflammatory bowel disease.

Disclosure: F. Wei, None; **J. Jian**, None; **Y. Zhang**, None; **J. Lin**, None; **J. Lafaille**, None; **M. Dustin**, None; **L. Mayer**, None; **C. Liu**, None.

1931

Influence of Trough Serum Drug Level and Immunogenicity On the Lack of Response to Adalimumab Therapy in Inflammatory Bowel Disease Patients. Shui Long Wang[1], Scott Hauenstein[1], Linda Ohrmund[1], Reshma Shringarpure[1], Douglas C. Wolf[2], Isam A. Diab[3], Jared Salbato[1], Rukmini Reddy[1], Kevin McCowen[1], Shawn Shah[1], Steven Lockton[1], Emil Chuang[1] and Sharat Singh[1]. [1]Prometheus Laboratories, San Diego, CA, [2]Atlanta Gastroenterology Associates, Atlanta, GA, [3]Paramount Medical Research & Consulting, Middleburg Heights, OH

Background/Purpose: Anti-TNF-α therapy is effective for the treatment of inflammatory bowel disease (IBD). Nevertheless, over 30% of IBD patients fail to respond to anti-TNF-α therapy and approximately 60% of the patients who respond initially to the therapy will lose the response over time and will need to either dose escalation or switch to another agent to maintain response. Low serum drug levels and/or anti-drug antibody (ADA) generation may play a role for the failure and, recent data suggest monitoring of patients for serum drug and ADA levels is an important strategy for optimal patient management. Here, we report the application of the homogeneous mobility shift assay (HMSA) method for monitoring of adalimumab (ADL) and

human antibodies-to-adalimumab (ATA) in serum samples from patients who lost response to ADL treatment.

Methods: Serum samples were collected from 100 patients who initially responded to ADL therapy for at least three months but were beginning to lose response. ATA and ADL levels in the serum samples were measured by ATA- and ADL-HMSA as described previously, except that in the ATA-HMSA Alexa Fluor 488 labeled ADL (ADL-488) was used as antigen and rabbit anti-ADL serum as standard. Full analytical method validation of both the ATA- and the ADL-HMSA was performed, and cut points for ADL and ATA levels were established with 100 drug-naïve healthy controls. The relationship of the ADL drug level and ATA generation in these patients was analyzed.

Results: Validation of the ATA- and ADL-HMSA revealed a lower limit of detection to be 0.026 U/mL for ATA and 0.018 μg/mL for ADL in the serum samples. The intra-assay and inter-assay precision determination yielded a coefficient of variation of less than 15%, and the accuracy of the assay is within 20% for both assays. ADL drug tolerance in ATA HMSA is up to 40 μg/ml in the test serum. Serum samples from 100 drug-naïve healthy subjects were tested to set up the cutoff point of 0.55U/mL (Mean+3.0xSD) for ATA and 0.66 μg/mL for ADL. Analysis of 100 serum samples from patients who were losing response showed that 36% of the patients had an ADL level < 3 μg/mL, of these 58.3% were ATA positive. However, only 18% of the patients (4/22) had ATA when their ADL level was over 20 μg/mL. Overall, 40% of the patient (40/100) were positive for ATA.

Conclusion: Analysis of ADL and ATA levels in non-responding IBD patients showed a high incidence of ATA generation and the ADL levels were inversely correlated with the level of ATA generation. Drug and ADA levels are important determinants of patient response to the therapy.

1932

Clinical Features of an Aromatase Inhibitor Associated Syndrome Presenting As Rheumatoid Arthritis Ronald J. Anderson, MD, Brigham &Women's Hospital. Ronald J. Anderson. Brigham & Womens Hospital, Boston, MA

Background/Purpose: The aromatase inhibitors (AI); anastrozole, letrozole and exemestane are used in the treatment of postmenopausal women with estrogen receptor positive breast cancer. Arthralgias occur in close to 30% of patients taking these agents and are a major reason for their discontinuation. Published reports on these arthralgias are primarily in the oncology literature and describe the prevalence of these symptoms but not their clinical features.

Methods: During the five year period, 2005–2010, all new patients taking AI presenting to the practice of the author, a rheumatologist practicing in an academic medical center, were prospectively analyzed. Fourteen out of a total of 1,149 new patients were taking AI. The source of referral was: oncologists (8), internists (4) and rheumatologists (2). Diagnostic studies were performed on the basis of clinical care needs. The diagnosis of a joint abnormality was based on a physical exam which demonstrated soft tissue swelling and limitation of motion. Tenderness, alone, was used as a sign of involvement only in the MTP joints. If the cause of a joint deformity could not be explained by physical exam, radiographs were obtained to exclude osteoarthritis or other structural abnormalities.

Results: The ultimate diagnoses in this group of 14 patients were as follows: osteoarthritis (2), idiopathic frozen shoulder (2), bilateral palmar flexor tenosynovitis (2), fibromyalgia (1), Charcot joints (1) and previously undiagnosed chronic rheumatoid arthritis (RA) (1). The remaining 5 patients presented with a unique syndrome of morning stiffness, joint swelling, limited motion and dysfunction in a pattern consistent with early RA. All 5 patients met both the 1987 ACR and the 2010 ACR/EULAR Classification Criteria for RA. All were negative for ANA and CCP. One patient had a borderline positive RF. ESRs were normal and only one patient had an elevated CRP. Joints involved were wrists and MCPs (5),

MTPs (4), shoulder and elbows (3), hips (2) and the knee in one patient. No joint effusions sufficient for aspiration were seen in this group of patients. All patients with this syndrome were followed for at least one year. Four of the five patients stopped the AI and underwent a complete remission in 3 months. The remission persisted in the 2 patients who did not resume an AI. Two patients restarted another AI and both developed a similar RA syndrome within 3 months. Of these 2 patients, one remitted on stopping the second AI and the other elected to stay on the agent with persistence of the syndrome. One of the five patients chose to stay on the original AI and has had persistent mild disease for over 2 years. The 5 patients had used AI for a mean of 3 months prior to the onset of symptoms. Remissions occurred within 3 months of stopping the drug.

Conclusion: A syndrome with clinical features resembling RA may be seen in association with the use of AI. The patients described in this study fulfilled both the 1987 ACR and 2010 ACR/EULAR criteria for RA. The condition may remit on stopping the agent but can recur on switching to another agent in the same class.

1933

Incidence and Early Detection of Retinal Toxicity in Patients Treated with Chloroquine and Hydroxichloroquine in Rheumatology Practice. Sandra Soro Marin[1], Ana del Carmen Haro Martínez[1], Deseada Palma Sanchez[1], María del Rocío Gonzalez Molina[1], Marta Mayor Gonzalez[2] and Elena Rubio Velazquez[3]. [1]Rafael Mendez Hospital, Spain., Lorca (Murcia), Spain, [2]Rafael Mendez Hospital, Lorca (Murcia), Spain, [3]Rafael Mendez Hospital, Lorca (Murcia)

Background/Purpose: The antimalarial drugs are considered safe and well tolerated, with low risk of side effects. Hydroxychloroquine is considered safer but less effective than chloroquine, although the choice remains a matter of discussion and it generally depends on the experience. Both can cause ocular toxicity by corneal and retinal deposition which produces irreversible visual disturbances and the patient may not perceive its presence at an early stage. The American Academy of Ophthalmology recommendations for screening of chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy recommend to use more sensitive test than fundus exam such as Spectral Domain Optical Coherence Tomography (SD-OCT) to detect early retinal toxicity. The objective was to study the incidence of retinal toxicity in patients treated with antimalarials in a Rheumatology Unit and to evaluate the effectiveness of SD-OCT in the screening of hydroxichloroquine and chloroquine toxicity

Methods: Descriptive study evaluating 39 patients treated with antimalarials who were referred to ophthalmology to study retinal toxicity during 2011. Data collection included demographic data of patients, type of antimalarial prescribed, daily and cumulative doses, rheumatic disease, corticosteroid use, associated morbidity, visual acuity, examination of the anterior pole, fundus exam, visual field, SD-OCT and, in case that it shows any sign of toxicity, multifocal electroretinogram. Fluorescein angiography (FAG) was made to patients that showed macular disturbances.

Results: Three patients were treated with CQ and 36 with HCQ. Five of 39 patients had alterations in the SD-OCT, two of them had typical fundus appearance and three didn't show significant changes in visual acuity or retinal imaging. Visual field and electroretinogram helped to confirm early toxicity. Among the patients with retinopathy, three (100%) had been treated with CQ and two (5.5%) with HCQ. The average duration of treatment in these patients was 2.37 +/−1.37 years and the mean cumulative dose of CQ was 559 g and 172.5 g for HCQ. There was no statistically significant association between retinal toxicity and sex, age, rheumatic disease, duration or dose of treatment with p value greater than 0.05.

Conclusion: The incidence of retinal toxicity in our patients treated with antimalarial drugs was 12.8%. Despite the small sample size to prove statistical significance, CQ was the antimalarial that caused most of cases of retinopathy and the SD-OCT was the most sensitive test to detect it. It is essential a fluent communication between Rheumatology and Ophthalmology to have a proper follow-up of the patients treated with CQ and HCQ and an early detection of retinopathy.

1934

Improvement in Cryoglobulin Detection Employing a Temperature Controlled Sample Transporter. W. Winn Chatham, Moon Nahm and William H. Benjamin Jr., University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Optimal conditions for detecting serum cryoglobulins in patients with suspected vasculitis requires drawn blood samples remain at 37 degree F or higher temperature until the sample has clotted and the serum is removed. Failure to maintain these temperature conditions during sample transport to the processing laboratory may lead to failure to detect cryoglobulins and false negative test results. We determined the utility of a custom-designed sample transporter for optimizing the quality of blood samples submitted for cryoglobulin detection.

Methods: A quality study was undertaken in a hospital-based clinical immunology laboratory to assess the frequency of samples sent to the lab for cryoglobulin analysis that were deemed acceptable for optimal cryoglobulin analysis (sample temperature at or greater than 37 degrees C). Following the study, a specially designed blood tube carrier (Cryocab) containing a 300 gram 1:1 mixture of n-docosane and n-eicosane was developed for use in the hospital/clinic pneumatic tube transport systems. The mixture in the carrier melts at 38 degrees C, with a high heat of fusion when solidifying and maintaining a temperature of 38°C for several hours as the material undergoes phase transition. Following implementation of Cryocab use, a subsequent study to determine the frequency of acceptable samples arriving to the clinical immunology lab was undertaken.

Results: During a ten month time period prior to routine use of the Cryocab, only 146/226 (34%) of samples arriving in the clinical immunology lab for cryoglobulin assessment had a temperature at or exceeding 37 degrees C. During a four month time frame following implementation of routine Cryocab use by the hospital and clinic phelebotomy services, the percentage of samples arriving to the clinical immunology lab at 37 degrees or higher improved dramatically—;87/90 (97%).

Conclusion: Use of a gel-based transporter to maintain blood samples at temperatures conducive to optimal detection of cryoglobulins can dramatically improve the quality of samples arriving to the analyzing lab, and may improve cryoglobulin detection rates.

Disclosure: **W. W. Chatham**, None; **M. Nahm**, None; **W. H. Benjamin Jr.**, None.

ACR/ARHP Poster Session C
Muscle Biology, Myositis and Myopathies:
Genetics, Autoantibodies and other Molecular Aspects of
Idiopathic Inflammatory Myopathies and Models
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Longitudinal Peripheral Blood Lymphocyte Subsets Correlate with Decreased Disease Activity in Juvenile Dermatomyositis. Floranne C. Ernste[1], Cynthia S. Crowson[2], Consuelo Lopez de Padilla[2], Molly Hein[2], Abigail B. Green[2] and Ann M. Reed[2]. [1]Mayo Clinic Rochester, Rochester, MN, [2]Mayo Clinic, Rochester, MN

Background/Purpose: Perturbations in peripheral blood lymphocyte (PBL) subsets in juvenile dermatomyositis (JDM) are variably and inconsistently reported in active and inactive disease. Decreased PBL CD8+ T cells and increased CD4+ T cells, and CD19+ B cells have been correlated with disease activity in JDM. Increased numbers of CD56+ NK cells have been found in inflamed muscle of JDM patients. Untreated JDM patients have decreased levels of CD3-CD16+, CD54+ (ICAM-1), CD56+ (NK) and CD3+CD8+ T suppressor cells, suggesting that they are contributing to pathogenesis. We sought to determine the subsets of PBLs which correspond with improved disease activity in JDM.

Methods: Peripheral blood mononuclear cell (PBMC) samples from 24 patients with definite JDM were collected between 2007–2011 in two visits, 3–6 months apart. Frozen PBMC samples were analyzed using fluorescence activated cell sorting and flow cytometric analysis. Childhood myositis activity tools validated by the International Myositis Assessment & Clinical Studies Group (IMACS) for the assessment of disease activity were used including visual analog scores (VAS). Spearman correlation methods were used.

Results: The mean age was 9.5 (min: 3, max: 19) years and 15 (63%) were female. The figure shows significant correlations between the change in VAS scores between visits and change in percentage of lymphocyte subsets. The change in the percentage of CD3+ CD69+ T cells was positively correlated with the change in global VAS (p=0.037). The change in the percentage of HLA-DR- CD11c+ myeloid dendritic cells (mDCs) was positively correlated with change in extramuscular VAS (p = 0.040). The change in the percentage of HLA-DR- CD123+ plasmacytoid dendritic cells (pDCs) cells negatively correlated with change in muscle VAS (p=0.028). Although the results did not reach statistical significance, some trends were noted. The change in the percentage of HLA-DR- CD11c+ mDCs was positively correlated to the change in muscle VAS (p=0.08) and global VAS (p=0.08). The change in the percentage of CD16-CD56+ NK cells and of HLA-DR- CD86+ mDCs was positively correlated with the change in extramuscular VAS (p=0.08, and p=0.09, respectively). In addition, the change in percentage of CD16+ CD56- NK cells was inversely correlated to the change in global VAS (p=0.09).
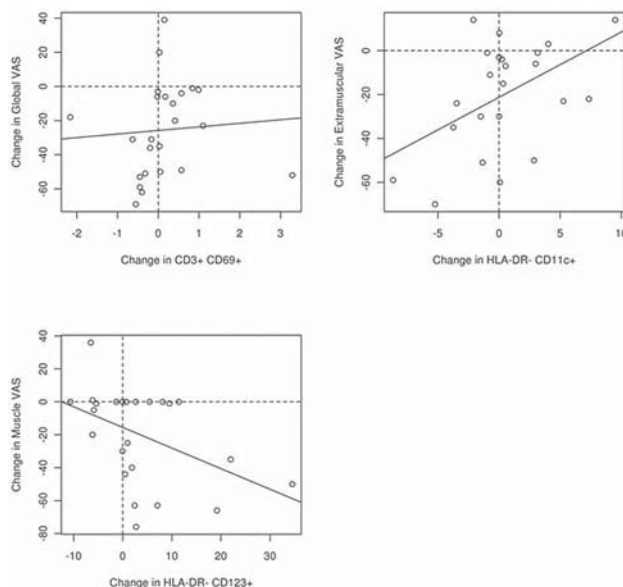
Figure. Change between visits in peripheral lymphocyte cell subsets vs. change in VAS scores.

Conclusion: This is the first prospective study in JDM patients to identify the relationship of disease activity with PBL subsets: CD3+ CD69+ T cells, HLA-DR- CD11c+ mDCs, and HLA-DR- CD123+ pDCs. Additionally, our findings suggest that NK cells do not correlate with disease activity level in JDM. There is a trend toward decreased levels of CD3-CD16-CD56+ NK cells with decreased extramuscular VAS, and increased CD 16+CD56- NK cells with decreased global VAS.

Disclosure: **F. C. Ernste**, None; **C. S. Crowson**, None; **C. Lopez de Padilla**, None; **M. Hein**, None; **A. B. Green**, None; **A. M. Reed**, None.

1936

The human leukocyte antigen DRB1*13:02-DQB1*06:04-DPB1*04:01 haplotype isclosely associated with dermatomyositis patients with Anti-CADM-140 (melanoma differentiation-associated protein 5: MDA5) Antibody. Yuji Hosono[1], Chikashi Terao[2], Ran Nakashima[1], Yoshitaka Imura[1], Naoichiro Yukawa[1], Hajime Yoshifuji[1], Motomu Hashimoto[1], Koichiro Ohmura[1], Takao Fujii[1] and Tsuneyo Mimori[1]. [1]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Kyoto University, Kyoto, Japan

Background/Purpose: Recent studies have revealed that anti-CADM-140 (MDA5/IFIH1)-antibody positive dermatomyositis (DM) patients frequently develop acute or subacute progressive interstitial pneumonia (A/SIP) with poor prognosis. However, genetic background of anti-CADM-140-antibody positive DM is currently unclear. Here, we intended to analyze the relationship between specific human leukocyte antigen (HLA) alleles in anti-CADM-140-positive DM patients.

Methods: Anti-CADM-140-antibody positive DM patients (CADMs, N=20) and healthy controls (HCs, N=2972) were enrolled in this study.

Autoantibodies were screened using immunoprecipitation with [^{35}S]methionine-labelled HeLa cells. HLA class I (A, B, and C) and class II (DRB1, DQA1, DQB1, and DPB1) genotyping was carried out with a high-throughput, high-resolution genotyping method (WAKFlow WAKUNAGA) by combining PCR and sequence-specific oligonucleotide probe protocols with the Luminex 100 xMAP flow cytometry dual-laser system to quantify fluorescently labelled oligonucleotides attached to colour-coded microbeads.Allele frequency was compared between CADMs and HCs by chi-square test or Fisher's exact test. Haplotypes with frequency more than 10% in CADMs were analyzed for comparison between CADMs and HCs with chi-square test.

Results: No specific HLA class I alleles show significant associations with CADMs.CADMs demonstrated higher allele frequencies of DRB1*1302 (15% vs 5.5%; with OR=2.73,0.0854), DQB1*0604 (12.5% vs 5.5%; with OR=2.5,P= 0.0114), and DPB1*0401 (12.5% vs 5□G with OR=2.5,P= 0.03469) than HCs. However, no specific HLA alleles reached significant difference between CADMs and NCs due to lack of power. The observed distribution of HLA class II alleles among patients and controls suggested the notion that specific combinations of alleles at the DRB1, DQB1, and DPB1 loci are associated with the risk for CADMs. Haplotype analysis showed the frequency of the haplotype DRB1*13:02-DQB1*06:04-DPB1*04:01 was higher in CADMs than NCs (12.5% vs 3.6%;OR 3.79, 95%CI 1.47–9.76, P = 0.0030).

Conclusion: HLA-DRB1*13:02-DQB1*06:04-DPB1*04:01 haplotype is closely associated with CADMs, suggesting that the production of anti-CADM-140 may be associated with a certain immunogenetive background.

Disclosure: Y. Hosono, None; **C. Terao**, None; **R. Nakashima**, None; **Y. Imura**, None; **N. Yukawa**, None; **H. Yoshifuji**, None; **M. Hashimoto**, None; **K. Ohmura**, None; **T. Fujii**, None; **T. Mimori**, Medical & Biological Laboratories, Co., Ltd., 2, Medical & Biological Laboratories, Co., Ltd, 8.

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HLA-DRB1*0101/*0405 Is Associated with Susceptibility to Anti-MDA5 Antibody-Positive Dermatomyositis in the Japanese Population. Takahisa Gono[1], Yasushi Kawaguchi[1], Masataka Kuwana[2], Tomoko Sugiura[1], Takefumi Furuya[1], Kae Takagi[1], Hisae Ichida[1], Yasuhiro Katsumata[1], Masanori Hanaoka[1], Yuko Okamoto[1], Yuko Ota[1], Sayuri Kataoka[1] and Hisashi Yamanaka[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Keio University School of Medicine, Tokyo, Japan

Background/Purpose: The complication of interstitial lung disease (ILD) is associated with the anti-aminoacyl tRNA synthetase antibody (ARS ab) or the anti-melanoma differentiation-associated gene 5 antibody (MDA5 ab) in polymyositis (PM)/dermatomyositis (DM). Anti-MDA5 ab is associated with clinically amyopathic DM (C-ADM) and fatal outcome due to rapidly progressive ILD (RP-ILD) in Asia. The association between genetic factors and anti-MDA5 ab-positive DM has remained unclear. We investigated the HLA-DRB1 genotype in anti-MDA5 ab-positive DM. In addition, we compared genetic differences in HLA between anti-MDA5 ab-positive DM, anti-ARS ab-positive PM/DM and PM/DM without the anti-ARS ab or ILD.

Methods: This retrospective study included patients admitted to Tokyo Women's Medical University Aoyama Hospital or Keio University Hospital from August 1992 to February 2010. Medical records were obtained from 142 and 57 patients diagnosed as having DM and C-ADM, respectively. The anti-MDA5 antibody was detected in 31 patients. DNA samples were obtained from 17 patients with the anti-MDA5 antibody, and all of these patients were enrolled in this study. All of the enrolled patients suffered from skin rashes, myopathy, or respiratory symptoms (or a combination thereof) upon admission. These patients were diagnosed as having DM or CADM based on the criteria of Bohan and Peter or Sontheimer, respectively. To investigate the characteristics of the HLA-DRB1 genotype in anti-MDA5 ab-positive DM, we compared the genetic differences among 17 patients with anti-MDA5 ab-positive DM, 33 patients with anti-ARS ab-positive PM/DM, 33 PM/DM patients without anti-ARS ab or ILD and 265 healthy controls (HCs).

Results: The HLA-DRB1*0101 and DRB1*0405 alleles were identified in 5 (29%) patients and 12 (71%) patients, respectively, which were higher than the frequencies in HCs (10% and 25%, respectively). The HLA-DRB1*0101 or *0405 allele was identified in 16 (94%) of the 17 patients. No patients had homo alleles of HLA-DRB1*0101 or DRB1*0405. One patient had both DRB1*0101 and DRB1*0405. With respect to the clinical phenotype, 16 patients had C-ADM. ILD complication was observed in all of the patients. Moreover, the frequency of RP-ILD was high (65%). No patients

had RA or other connective tissue diseases as complications.The frequency of the DRB1*0101 or 0405 allele was significantly higher in anti-MDA5 ab-positive DM patients compared with PM/DM patients without anti-ARS ab or ILD (P = 1.1e-05, odds ratio 42.7, confidence interval [CI] 4.9–370.2) or anti-ARS ab-positive PM/DM patients (P = 4.5e-03, odds ratio 13.3, CI 1.6–112.6).

Conclusion: HLA-DRB1*0101/*0405, which were defined as 'shared epitope' alleles in RA, is associated with susceptibility to anti-MDA5 ab positive-DM in the Japanese population. These alleles were also associated with ILD complication in PM/DM.

Disclosure: T. Gono, None; **Y. Kawaguchi**, None; **M. Kuwana**, N/A, 9; **T. Sugiura**, None; **T. Furuya**, None; **K. Takagi**, None; **H. Ichida**, None; **Y. Katsumata**, None; **M. Hanaoka**, None; **Y. Okamoto**, None; **Y. Ota**, None; **S. Kataoka**, None; **H. Yamanaka**, None.

1938

A New Enzyme-Linked Immunosorbent Assay System for Detecting Autoantibodies to Aminoacyl-tRNA Synthetases: Clinical Usefulness in Myositis and Interstitial Pneumonia. Ran Nakashima[1], Yoshitaka Imura[2], Minae Seto[3], Akihiro Murakami[3], Yuji Hosono[2], Kizuku Watanabe[4], Tomohiro Handa[4], Michiaki Mishima[4], Michito Hirakata[5], Tsutomu Takeuchi[6], Keishi Fujio[7], Kazuhiko Yamamoto[8], Hitoshi Kohsaka[9], Yoshinari Takasaki[10], Noriyuki Enomoto[11], Kingo Chida[11], Toshihiro Nukiwa[12] and Tsuneyo Mimori[1]. [1]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Kyoto University Graduate School of Medicine, Kyoto, Japan, [3]Medical & Biological Laboratories Co., Ltd., Ina, Japan, [4]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, Kyoto, Japan, [5]Keio University, Tokyo, Japan, [6]Keio University School of Medicine, Tokyo, Japan, [7]Graduate school of Medicine, The University of Tokyo, Tokyo, Japan, [8]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [9]Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [10]Division of Rheumatology, Department of Internal Medicine, Juntendo University, Tokyo, Japan, [11]Hamamatsu University School of Medicine, Hamamatsu, Japan, [12]Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Background/Purpose: Autoantibodies to aminoacyl-tRNA synthetases (ARS) are the most frequent myositis-specific antibodies and they are useful in the diagnosis and management of polymyositis (PM)/ dermatomyositis (DM) and interstitial pneumonia (IP). However, routine detection of all of them at once is not available. We developed an enzyme-linked immunosorbent assay (ELISA) system using a mixture of recombinant ARS antigens to detect them easily and simultaneously. We tested the usefulness of this system for diagnosing PM/DM and IP in the multicenter study.

Methods: We prepared 6 recombinant ARS antigens; GST-Jo-1, His-PL-12, His-EJ and GST-KS expressed in *Eschericha coli*, and His-PL-7 and His-OJ expressed in Hi-5 cells. After confirming antigenic activity of all the recombinant proteins except His-OJ, using immunoblotting or ELISA, we made an ELISA system mixing the five recombinant ARS antigens. Efficiency was confirmed using the sera from 549 Japanese patients with various connective tissue diseases (PM/DM 273, systemic lupus erythematosus (SLE) 91, systemic sclerosis (SSc) 70, rheumatoid arthritis (RA) 75, Sjögren's syndrome (SS) 27 and other diseases 13), 170 idiopathic IP (IIP) and 30 healthy controls collected from 8 institutes. IIP was classified into two groups according to the radiologic pattern, usual interstitial pneumonia (UIP) (n=36) and non-UIP (n=132). **Results** were compared with those of the standard RNA immunoprecipitation assay.

Results: All of the ELISA results were consistent with those of the immunoprecipitation assay, except for one false-positive sample. Sensitivity and specificity were 100% and 99.8%, respectively when compared with the RNA immunoprecipitation. Anti-ARS antibodies were detected in 34.8% of PM/DM, 2.2% of SLE, 2.9% of SSc, 4% of RA, 0% of SS and 10.6% of IIP. None of the healthy controls were positive for anti-ARS antibodies. The frequency of each anti-ARS antibodies was compatible with previous reports. Anti-ARS-positive PM/DM patients had IP much more frequently than anti-ARS-negative PM/DM patients (87.3% vs. 48.6% respectively, p<0.001). In IIP, anti-ARS antibodies were positive in 5.6% of UIP and 12.1% of non-UIP. Anti-ARS-positive IIP patients were younger and more frequently treated with corticosteroids and/or immunosuppressants than anti-ARS-negative patients.

Conclusion: A newly established anti-ARS ELISA system detected anti-ARS antibodies as efficiently as RNA immunoprecipitation. This system will enable the easier and wider detection of anti-ARS antibodies in patients with PM/DM and IP in daily practice.

Disclosure: **R. Nakashima**, None; **Y. Imura**, None; **M. Seto**, Medical & Biological Laboratories, Co., Ltd., 3; **A. Murakami**, Medical & Biological Laboratories, Co., Ltd., 3; **Y. Hosono**, None; **K. Watanabe**, None; **T. Handa**, None; **M. Mishima**, None; **M. Hirakata**, None; **T. Takeuchi**, None; **K. Fujio**, None; **K. Yamamoto**, None; **H. Kohsaka**, Chugai Pharma, Ajinomoto Pharma & Teijin Parma, 5; **Y. Takasaki**, None; **N. Enomoto**, None; **K. Chida**, None; **T. Nukiwa**, None; **T. Mimori**, Medical & Biological Laboratories, Co., Ltd., 2, Medical & Biological Laboratories, Co., Ltd, 8.

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Overexpression of Ankyrin Repeat Domain Containing Protein 1 Gene (*ANKRD1*) in Dermatomyositis Muscle Biopsies Is Correlated to Hypoxia and Perifascicular Atrophy. Samuel K. Shinjo, Sueli M. Oba-Shinjo, Miyuki Uno and Suely K. N. Marie. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: *ANKRD1* codes for ankyrin repeat domain containing protein 1, which belongs to the muscle ankyrin repeat protein family involved in a mechano-signaling pathway that links myofibrillar stress response to muscle gene expression. In addition, *ANKRD1* has an important role in transcriptional regulation, myofibrillar assembly, cardiogenesis, myogenesis and also possibly in angiogenesis. Microvasculopathy is considered as a cornerstone and early pathological change in dermatomyositis (DM), leading to hypoxia, capillary necrosis and muscle perifascicular atrophy. These alterations could upregulate genes involved in myogenesis and angiogenesis like *ANKRD1*. Therefore, we analyzed *ANKRD1* expression in muscle biopsies of DM patients and correlated with other hypoxia parameters.

Methods: RNA was extracted from frozen muscle biopsies samples of 30 untreated adult DM patients (Bohan and Peter's criteria, 1975). As a control group, we analyzed 20 muscle biopsies with no histological change from untreated adult patients with non-inflammatory myopathy diseases. The gene coding for hypoxia-inducible factor 1, alpha subunit (*HIF1A*) was analyzed to estimate hypoxia degree. The *ANKRD1* and *HIF1A* transcript expression levels were determined by quantitative real time PCR using Sybr Green method. Perifascicular atrophy was analyzed histologically by semi-quantitative method of HE stained biopsies. Expression and localization of ANKRD1 and HIF1a in muscle biopsies was accessed by immunohistochemistry.

Results: Higher *ANKRD1* and *HIF1A* expressions levels were observed in DM relative to control group ($p<0.001$ and $p<0.001$). In addition, the expression levels of both genes were correlated (r=0.703, $P=0.001$). We also observed a positive correlation of both genes to perifascicular atrophy (r=0.420, $p=0.023$ and r=0.404, $p=0.030$, respectively). However, *ANKRD1* and *HIF1A* expression levels did not correlate to demographic, clinical and laboratory features ($p>0.05$). Immunohistochemistry showed that ANKRD1 and HIF1a were expressed mainly by atrophic muscle perifascicular cells.

Conclusion: Our results demonstrated *ANKRD1* is overexpressed, correlated to *HIF1A* in perifascicular atrophic fibers of DM muscle specimens. *ANKRD1* involvement in myogenesis and angiogenesis mechanism will be further investigated.

Disclosure: **S. K. Shinjo**, Federico Foundation, 2; **S. M. Oba-Shinjo**, None; **M. Uno**, None; **S. K. N. Marie**, None.

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A Comprehensive Study of Novel Serum Markers of ILD Associated with Inflammatory Myopathies. Fang Chen, Xiaoming Shu, Xin Lu and Guochun Wang. China-Japan Friendship Hospital, Beijing, China

Background/Purpose: To investigate and compare the association between serum markers and Interstitial Lung Disease (ILD) in patients with inflammatory myopathies(IIM).

Methods: Serum levels of KL-6, anti-melanoma differentiation-associated gene 5(MDA5), monocyte chemotactic protein-1 (MCP-1),Surfactant protein-A,D (SP-A, SP-D) were detected by ELISA in 119 adult IIM patients and 50 healthy controls. The association between serum levels and clinical signs of ILD in patients with IIM was analyzed.

Results: Serum KL-6, anti-MDA5,MCP-1,SP-A, SP-D were significantly elevated in IIM patients with ILD(all $P<0.05$). KL-6 showed the highest value (sensitivity 90.9% and specificity 80.6%) for diagnosing ILD. Anti-MDA5 could effectively diagnose acute/subacute interstitial pneumonia (A/SIP) in DM patients (sensitivity 88.2%, specificity 94%). Patients with elevated KL-6 showed more frequently ground glass opacity than those with normal KL-6(all $P<0.05$). Inverse correlations were found between serum KL-6/SP-A/SP-D and lung function parameters such as DLCO% and FVC (all $P<0.05$). KL-6 (OR 1.032, 95%CI 1.006–1.059, $P=0.016$) and anti-MDA5 (OR = 8.46, 95% CI 1.77–40.36, P = 0.007) are independent risk factors predicting unfavorable prognosis in IIM patients with ILD.

Conclusion: Serum KL-6, anti-MDA5,MCP-1,SP-A, SP-D are useful markers for ILD in IIM patients, of which KL-6 presented highest diagnosing value. Anti-MDA5 may be a useful marker for A/SIP in patients with DM. these biomarkers can help diagnosing ILD and predicting prognosis in IIM patients with ILD though they cannot replace conventional diagnosing procedure.

Disclosure: **F. Chen**, None; **X. Shu**, None; **X. Lu**, None; **G. Wang**, None.

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Clinical Evaluation of Anti-Aminoacyl tRNA Synthetase Antibodies in Japanese Patients with Connective Tissue Diseases. Masakazu Matsushita, Toshio Kawamoto, Ken Yamaji, Naoto Tamura and Yoshinari Takasaki. Juntendo University School of Medicine, Tokyo, Japan

Background/Purpose: Anti-Jo-1 antibody is an autoantibody specifically detected in sera of patients with polymyositis/dermatomyositis (PM/DM). The antigen corresponding to this autoantibody is histidyl-tRNA synthase, being an aminoacyl-tRNA synthase (ARS), which occurs in the cytoplasm of eukaryotes. Many autoantibodies directed to other ARS have been identified in recent years, and the condition of patients positive for these antibodies is currently termed anti-ARS antibody syndrome in that such condition is characterized by clinical features of pulmonary lesions and cutaneous manifestations. This study was performed to evaluate the clinical usefulness of determination of serum anti-ARS antibody levels in patients with PM/DM or other connective tissue diseases.

Methods: The study included 197 outpatients with connective tissue diseases at this hospital. Of them, 62 patients had PM/DM, 39 had systemic lupus erythematosus (SLE), 31 had rheumatoid arthritis (RA), 21 had Sjögren's syndrome (SjS), 12 had progressive systemic sclerosis (SSc), 11 had mixed connective tissue disease (MCTD), 7 had vasculitis syndrome, 5 had Behçet's disease, 4 had adult-onset Still's disease, and 5 had other diseases. Determination of anti-ARS antibodies was carried out using Myositis Profile 3 Euroline Blot Test Kit commercially available from EUROIMMUN (Lubeck, Germany), in accordance with the manufacturer's instructions. For each clinical entity concerned, anti-ARS antibody positivity rate, antinuclear antibody staining pattern, the presence/absence of concurrent interstitial pneumonia (IP), and dose levels of the corticosteroids or immunosuppressants used were assessed.

Results: Anti-ARS antibodies were detected with a significantly higher frequency among PM/DM patients with concurrent IP. Positivity for anti-ARS antibodies was observed even among RA patients with clinical signs of IP. Patients with PM/DM in whom cytoplasmic stain with antinuclear antibody was evident were frequently positive for anti-ARS antibodies other than anti-Jo-1 antibody even if they had negative results for this antibody. In patients negative for cytoplasmic staining, however, no other anti-ARS antibodies were detected. In patients with PM/DM complicated by IP positive for anti-ARS antibodies, the dosage of corticosteroids and percentage of patients receiving immunosuppressant therapy tended to be higher as compared with those negative for anti-ARS antibodies.

Conclusion: The present data suggest that the determination of serum anti-ARS antibody levels is clinically useful even in patients with IP-complicated connective tissue disease other than PM/DM. A strong association of the autoantibodies with pulmonary lesions was noted particularly in RA patients. The results also suggest that determination of serum anti-ARS antibody levels may be less necessary in myositis patients showing no positive cytoplasmic staining in the antinuclear antibody test using HEp-2.

Disclosure: **M. Matsushita**, None; **T. Kawamoto**, None; **K. Yamaji**, None; **N. Tamura**, None; **Y. Takasaki**, None.

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Increased Levels of Eotaxin and MCP-1 in Juvenile Dermatomyositis Median 17 Years After Diagnosis; Associations with Disease Activity, Duration and Organ Damage. Helga Sanner[1], Thomas Schwartz[2], Berit Flatø[1], Maria Vistnes[2], Geir Christensen[2] and Ivar Sjaastad[1]. [1]Oslo University Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway

Background/Purpose: Juvenile dermatomyositis (JDM) is a systemic vasculopathic disease of childhood affecting skeletal muscle, skin and other organs. Increased abundance of pro-inflammatory cytokines has been shown in JDM patients in the active phase of the disease. We now wanted to compare cytokine profiles in JDM patients after medium to long-term follow-up with matched controls, and to examine associations between cytokine levels and disease activity, disease duration and organ damage in JDM.

Methods: Inclusion criteria were a probable or definitive diagnosis of Dermatomyositis (DM) according to the Bohan/Peter criteria for DM, disease onset before 18 years and minimum 24 months disease duration. A retrospective inception cohort of JDM patients was established; 54 patients were clinically examined median 16.8 years (range 2–38 years) after disease onset and compared with 54 age- and sex-matched controls (randomly drawn from the Norwegian population register). Concentrations of 26 cytokines in plasma were quantified by Luminex technology or ELISA. In patients, disease activity score (DAS), myositis damage index (MDI) and other disease parameters were collected by clinical examination (at follow-up) or chart review (from one year post-diagnosis).

Results: Serum levels of eotaxin, monocyte chemoattractant protein 1 (MCP-1) and interferon inducible protein 10 (IP-10) were higher in JDM patients compared to controls (31.5%, 37.2% and 43.2%, respectively, all P < 0.05). Levels of eotaxin and MCP-1 correlated with disease duration ($r_s = 0.47$ and $r_s = 0.64$, both P < 0.001) and age in patients, but not with age in controls. MCP-1 levels were associated with MDI, DAS, physical health and cumulative prednisolone dose at follow-up (standardized β = 0.43, 0.29, 0.28 and 0.33 respectively, all P ≤ 0.020), after adjusting for disease duration and sex in a multivariate linear regression model. High MDI 1 year post-diagnosis predicted high levels of eotaxin and MCP-1 at follow-up (standardized β = 0.24 and β = 0.29, both P < 0.05) after adjusting for disease duration and sex.

Conclusion: Patients with JDM had higher eotaxin, MCP-1 and IP-10 levels than controls after median 17 years follow-up. High eotaxin and MCP-1 was predicted by early disease parameters and MCP-1 was associated with disease activity and damage at follow-up. It is not clear whether eotaxin and MCP-1 per se cause sustained inflammation; they might also be markers for disease damage as a result of disease activity caused by other unknown mechanisms. Either way, the novel knowledge on these substances can improve insight and treatment modalities of JDM.

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Autophagy Expressions Were Decreased in Circulating T Cells in Inflammatory Myopathies Patients. Fang Chen, Xiaoming Shu, Xin Lu and Guochun Wang. China-Japan Friendship Hospital, Beijing, China

Background/Purpose: The autophagy in circulating lymphocytes in IIM patients has not been clarified yet. Our research is aimed to study the autophagy in circulating T cells in IIM patients and to explore the possible role of aberrant autophagy contributing to the pathogenesis of IIM.

Methods: circulating T cells were isolated from 27 IIM patients and 19 normal controls. The expressions of protein and mRNA level of autophagy-related molecules (LC3, Beclin1) were examined by western blot and quantitative PCR. Transmission electron microscope was applied to detect the formation of autophagosome in circulating T cells.

Results: The formation of autohagosome in circuiting T cells of IIM patients was decreased than those of normal controls (P<0.01). The expression of LC3 and Beclin 1 proteins and mRNA level in circulating T cells of IIM patients (Beclin protein: 0.34±0.08; LC3 protein: 0.08±0.03; Beclin mRNA: 0.014±0.007; LC3 mRNA: 0.11±0.046) were both significantly lower in IIM patients than those in healthy controls (Beclin protein: 0.52±0.13; LC3 protein: 0.13±0.05; Beclin mRNA: 0.021±0.01; LC3 mRNA: 0.17±0.095) (all p<0.05).

Conclusion: Autophagy expression was decreased in circulating T cells in IIM patients. Further study is needed to explore the possible role of aberrant autophagy contributing to the pathogenesis of IIM☐B

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Expression of Human Leukocyte Antigen-G in Polymyositis or Dermatomyositis. Xiaolan Tian, Xiaoming Shu, Xin Lu, Qinglin Peng and Guochun Wang. China-Japan Friendship Hospital, Beijing, China

Background/Purpose: Human leukocyte antigen-G is a non-classical MHC--I molecule that may be involved in the pathogenesis of autoimmune diseases, but the significance of HLA-G in polymyositis/dermatomyositis (PM/DM) remains to be determined. The aim of this study was to determine HLA-G expression in patients with PM/DM.

Methods: Consecutive cryosections of muscle biopsies obtained from 30 PM/DM patients(22 DM, 8 PM)and 8 healthy controls were detected by immunohistochemical analysis. Serum soluble HLA-G (sHLA-G) levels of 96 patients (26 PM, 70 DM) and 35 matched healthy controls were measured by ELISA. The relationship between sHLA-G levels and clinical or laboratory variables in PM/DM patients was analyzed.

Results: HLA-G had a higher expression in 18 of 30 cases of PM/DM (60%) than that in 0 of 8 healthy controls (P =0.000). Serum level of sHLA-G in PM/DM patients were significantly higher than healthy controls [(43.96±70.20)U/ml vs (4.22±5.13)U/ml, P= 0.000]. Importantly, serum sHLA-G levels in non-treated PM/DM patients (75.75±99.07 U/ml) were significantly higher than that in treated patients (33.94±51.97) U/ml, P=0.021]. Spearman rank correlation analysis showed serum sHLA-G levels were negatively correlated with CD3+Tcells (r=−0.233, P=0.047) and CD4+Tcells (r=−0.287, P=0.015) in peripheral blood in patients with PM/DM.

Conclusion: HLA-G was found to be highly expressed in muscle tissues and sera from patients with PM/DM. Serum sHLA-G is increased in PM/DM patients and is associated with lower level of CD3+T cells and CD4+T cells. These data support the notion that HLA-G overexpression has a role in the progression of PM/DM through T cells.

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Anti-Transcription Intermediary Factor 1-Gamma (TIF1-γ) Autoantibody Detection by ELISA and Immunoprecipitation in a Prospective Myositis Cohort: Predictive Value for Cancer Associated Myositis. Rohit Aggarwal, Noreen Fertig, Danielle Goudeau, Chad Stephans, Qi Zengbiao, Diane Koontz, Mary Lucas, Marc C. Levesque and Chester V. Oddis. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Myositis [particularly dermatomyositis (DM)] is associated with cancer and anti-transcription intermediary factor-1 gamma (TIF1γ) is a serologic risk factor for cancer associated myositis (CAM). Anti-TIF1γ detection by immunoprecipitation is costly, time-consuming and research-based. We used a validated anti-TIF1γ ELISA to determine the frequency of this marker in a large prospective myositis cohort, to compare it with the identification of TIF1γ by IP and to determine whether quantitative anti-TIF1γ levels could identify CAM patients.

Methods: We analyzed a prospectively collected computer and serum database of adult myositis (n=856) patients to identify CAM patients with a non-skin (basal/squamous cell) cancer within 3 years (CAM3) or 5 years (CAM5) (before or after) the myositis diagnosis. A control group of polymyositis (PM), DM and overlap myositis (OM) patients without CAM matched 2:1 by gender and age (+/−10 years) and with a minimum 5 year follow up was selected. Serum was assessed for anti-TIF1γ by ELISA and IP.

Results: Using anti-TIF1γ detection by IP as the gold standard, the ELISA had 91% sensitivity, 96% specificity, 93% positive predictive value (PPV) and 95% negative predictive value (NPV) for anti-TIF1γ detection. There were 34 and 22 PM CAM5 and CAM3 cases (26F/8M), respectively, and 69 PM (53F/16M) controls, who were anti-TIF1γ (−) by IP (n=32) and ELISA (n=22). Six OM CAM5 cases (4F/2M), 3 being CAM3, were also anti-TIF1γ (−) by IP and ELISA (n=5) and 15 OM controls were anti-TIF1γ (−) by IP (n=13) and ELISA (n=14) except for 1 SSc-PM overlap patient. Of 45 CAM3 DM patients (31F/14M), 34 (24F/10M; mean age 58) had anti-TIF1γ IP and ELISA testing along with 95 DM controls (59F/36M; mean age 47). Anti-TIF1γ by IP was (+) in 47% CAM3 and 23% controls with

47% sensitivity, 82% specificity, 50% PPV and 80% NPV. By comparison, anti-TIF1γ by ELISA showed similar test characteristics at a low (+) cutoff (6 units/ml) while higher specificity (98%) was noted with a high (+) (>100 units/ml) cutoff but with a loss of sensitivity (35%). The odds of CAM3 was 3–4x higher in patients with TIF1γ positivity by IP or ELISA, but 25x higher in patients with a high (+) ELISA. Similar results were seen for CAM5 DM. Most DM-CAM patients were diagnosed within 1 year (31/34) before or after the myositis diagnosis and 3 females with high (+) anti-TIF1γ ELISAs decreased markedly after cancer treatment on longitudinal follow up. A high (+) ELISA (>50units/ml) was common in breast, ovarian and lung cancers (13/24) and in CAM within 1 year of myositis diagnosis (6/12).

Conclusion: This is the first case-control study in CAM using anti-TIF1γ by IP and ELISA. Anti-TIF1γ was not seen in PM or OM with or without cancer, but was highly specific for DM. Anti-TIF1γ was also seen in non-CAM DM (23–32% depending on detection method) contrary to previous studies showing a specificity of >90% in DM-CAM. Moreover, ELISA has similar test characteristics to IP for anti-TIF1γ detection with greater specificity and likelihood (i.e. odds) to identify cancer in a myositis patient with high levels of anti-TIF1γ. Finally, longitudinal follow up of anti-TIF1γ by ELISA may be useful prognostically.

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Effect of Immunosuppressive Treatment On Gene Expression in Patients with Polymyositis and Dermatomyositis. Ingela M. Loell[1], Yi-Wen Chen[2], Marina Korotkova[1], Kanneboyina Nagaraju[3] and Ingrid E. Lundberg[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Children's National Medical Center, Washington, [3]Children's National Medical Center, Washington, DC

Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) muscle tissue is characterized by infiltrating T cells, macrophages and dendritic cells, as well as cytokines and chemokines. In addition, the muscle fibers express major histocompatibility complex (MHC) class I. Patients are treated with high doses of glucocorticoids in combination with additional immunosuppressive drugs. However, remaining signs of inflammation in the muscle tissue, such as T cells, MHC class I and cytokines, as well as sustained muscle impairment are common even after prolonged treatment. Our aim was to investigate how the gene expression in pathways of inflammation and muscle remodeling is affected by immunosuppressive treatment in patients with PM and DM.

Methods: Six newly diagnosed, untreated patients (2 PM/4 DM, 2 men/4 women) with biopsies from *m.vastus lateralis* before and after a median of 10 (8–16) months of immunosuppressive treatment were analyzed using microarray.

Results: Alterations in a number of genes coding for immune responses and muscle tissue remodelling were observed.

Affy accession #	Gene	Gene ID	Fold	P-value
Immune response				
1554519_at	CD80	CD80	−2, 2	0, 034
210895_s_at	CD86	CD86	−2, 6	0, 013
222868_s_at	interleukin 18 binding protein	IL18BP	−1, 9	0, 032
206295_at	interleukin 18	IL18	−2, 2	0, 041
205992_s_at	interleukin 15	IL15	−1, 5	0, 027
216598_s_at	chemokine (C-C motif) ligand 2	CCL2	−5, 9	0, 004
1555759_a_at	chemokine (C-C motif) ligand 5	CCL5	−3, 1	0, 003
1405_i_at	chemokine (C-C motif) ligand 5	CCL5	−3, 0	0, 043
206978_at	chemokine (C-C motif) receptor 2	CCR2	−2, 3	0, 004
206991_s_at	chemokine (C-C motif) receptor 5	CCR5	−2, 8	0, 027
204533_at	chemokine (C-X-C motif) ligand 10	CXCL10	−5, 6	0, 020
210163_at	chemokine (C-X-C motif) ligand 11	CXCL11	−6, 3	0, 005
211122_s_at	chemokine (C-X-C motif) ligand 11	CXCL11	−5, 6	0, 015
215313_x_at	MHC class I, A	HLA-A	−1, 1	0, 012
211911_x_at	MHC class I, B	HLA-B	−1, 7	0, 010
208812_x_at	MHC class I, C	HLA-C	−2, 6	0, 013
211991_x_at	MHC class II, DP alpha 1	HLA-DPA1	−2, 2	0, 046
203290_at	MHC class II, DQ alpha 1	HLA-DQA1	−2, 8	0, 036
211656_x_at	MHC class II, DQ beta 1	HLA-DQB1	−2, 2	0, 038
209312_x_at	MHC class II, DR beta 3	HLA-DRB3	−1, 7	0, 027
204806_x_at	MHC class I, F	HLA-F	−2, 4	0, 018
Muscle structure				
206891_at	actinin, alpha 3	ACTN3	3, 4	0, 037
200930_s_at	vinculin	VCL	1, 9	0, 022
207145_at	growth differentiation factor 8	MSTN	2, 3	0, 041
204802_at	Ras-related associated with diabetes	RRAD	−3, 4	0, 013
204560_at	FK506 binding protein 5	FKBP5	3, 2	0, 016
206394_at	myosin binding protein C, fast type	MYBPC2	1, 9	0, 031
206304_at	myosin binding protein H	MYBPH	−6, 9	0, 036
208148_at	myosin, heavy polypeptide 4	MYH4	2, 2	0, 020
202724_s_at	forkhead box O1A	FOXO1	2, 2	0, 033

Conclusion: This data indicates that transcriptional alterations in genes involved in muscle tissue structure are taking place during immunosuppressive treatment. The treatment down-regulates the muscle inflammation to some extent but the local milieu might be accountable for the preserved expression of inflammatory cells and mediators seen in treated PM/DM patients.

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Muscle Wasting in HTNFtg Mice, an Animal Model for Rheumatoid Arthritis, Due to Increased Cathepsin L and LC3B Expression. Martin Willburger[1], Birgit Niederreiter[1], Ewald Unger[1], Josef S. Smolen[2], Kurt Redlich[1] and Silvia Hayer[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: To investigate the impact of systemic inflammation on skeletal muscles in human tumor necrosis factor transgenic (hTNFtg) animals.

Methods: We isolated triceps surae, quadriceps, tibialis anterior as well as rectus abdominis muscles from hTNFtg animals at different time-points of disease starting at week 4 after birth. Muscle weight and body weight were assessed from these animals. Age and sex-matched wildtype (wt) animals served as controls. We performed quantitative real-time PCR for Cathepsin L, B, S, H, D, LC3-B, MMP-9 and Interleukin (IL)-1 and IL-6 from mRNA isolated from muscle tissues of hTNFtg and wt animals. Moreover, hTNFtg animals were treated for 5 weeks with anti-TNF ab (Infliximab, 10mg/kg, 3x per week, i.p.) starting either at week 6 or week 10 after birth. Muscle tissue sections were also stained for macrophages, neutrophils, T cells and B cells. Mobility of animals was assessed by video-analysis using Ethovision Software (from Noldus, The Netherlands). Functionality of triceps surae muscle was evaluated by electro-stimulation.

Results: We could demonstrate that hTNFtg mice significantly lost muscle weight when compared to sex- and age matched wt animals. Reductions in muscle weight became already manifest at early stages of the disease, at week 4, and continuously progressed until week 16. Bodyweight was also significantly lower in hTNFtg animals compared to their wt littermates. Next, we found significantly increased mRNA expression levels of Cathepsin L, a lysosomal endopeptidase responsible for muscle protein degradation, in muscles from hTNFtg compared to their wt littermates. In contrast, other proteases such as cathepsin B, S, H, D did not significantly increased differ. In addition, we also found LC3B, an enzyme for autophagy-lysosome-mediated proteolysis, to be upregulated in hTNFtg mice compared to wt animals. Moreover, proinflammatory cytokines such as IL-1 and IL-6 were also significantly upregulated in muscles from hTNFtg mice. Interestingly, we observed an increased presence of macrophages and granulocytes in the muscle vascular system but no accumulation of inflammatory cells into the muscle tissue. We also investigated the rectus abdominis muscle, which is not located between inflamed articular joints, and found elevated levels of Cathepsin L and LC3B in this muscle, indicating that hTNFtg mice suffer from a systemic muscle proteolysis due to systemic inflammation. In addition, functionality of muscles was impaired as observed by markedly reduced maximal strength and faster fatigue in triceps surae from hTNFtg mice compared to wt animals. Remarkably, mobility of hTNFtg animals was already significantly reduced at week 6 indicating reduced use of muscles at early stage of TNF driven disease. TNF blockade at both early and late time points could completely rescue mobility to wildtype levels, whereas muscle atrophy could not be prevented by treatment at late stage of arthritis.

Conclusion: Despite spontaneous development of chronic inflamed, erosive arthritis, chronic overexpression of TNF leads to skeletal muscle atrophy due to increased tissue-degrading cathepsin L and LC3B and reduced mobility starting at early phase of arthritis disease in hTNFtg animals.

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Decreased C4A Gene Copy Numbers in Children with Juvenile Dermatomyositis: Association with Decreased C4 Protein and Lower Absolute Number of CD3 Negative CD16/56+ Natural Killer Cells.

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Background/Purpose: Juvenile Dermatomyositis (JDM), a systemic vasculopathy, is member of the family of autoimmune diseases. In 56% of untreated JDM, a decrease in the absolute number of natural killer cells reflects immune activation and increased disease activity. JDM is also associated with *B*08*, *DRB1*03*, *DQA1*0501*, *C4B1*, *C4AQ0 (null),* and *TNFA*-308A polymorphism, in linkage disequilibrium on chromosome 6. In the families of children with JDM, there is a significant increase in the history of systemic lupus erythematosus (SLE). Patients with SLE, have an overrepresentation *of C4A* null alleles, with associated decreased levels of the C4 protein. The frequency of *C4A deficiency* in children with JDM is unknown.

Objective: To determine the association of C4 protein and other clinical parameters with C4A gene copy number in JDM.

Methods: A cross-sectional cohort of children, n=91, with definite/probable JDM (overlap syndromes excluded) were enrolled (IRB# 2008–13457). There were 78% (71/91) girls, 96.7% (88/91) White, mean age of 5.06 yrs, and 35% (32/91) were untreated at time of first visit. Genomic DNA was assessed for gene copy number (GCN) for total *C4*, *C4A* and *C4B* by real time qPCR; EDTA-plasma was used to determine C4A and C4B polymorphisms and validate genotype data. Data for C4 protein concentrations, disease activity scores (DAS) for skin involvement and muscle weakness were obtained, along with nailfold capillary end row loop number, and absolute cell count of CD3negative, CD56/16 positive natural killer (NK) cells at time of first visit. NHANES normative data obtained from 523 subjects for C4A gene copy number were used as a comparator.

Results: Patients with JDM have lower *C4A* GCN than the general population (30% vs. 17% with 0–1 copy, p=0.009, Chi-square test). The level of C4 protein was significantly associated with the *C4* total gene copy number, p<0.001; the C4 protein levels increases by 3.61 unit/one *C4* copy number. The C4 protein concentration was not significantly associated with any of the following: nailfold capillary end row loop number, DAS skin or DAS muscle. However, there was a significant association of the *C4A* GCN with the absolute number of circulating CD3negative NK cells in JDM (p=0.02).

Conclusion: Children with JDM have decreased levels of C4 protein as a function of significantly decreased GCN of *C4*. Although the decreased C4 was not associated with nailfold capillary end row loop numbers, or clinical disease activity markers, the *C4A* GCN appeared to be associated with the absolute levels of circulating NK cells, suggesting a locus of control on chromosome 6. We speculate that the decrease in C4 as a consequence of *C4A* GCN may contribute to the pathogenetic mechanisms of damage in JDM.

1949

Anti-Transcription Intermediary Factor 1-Gamma (TIF1-γ) Autoantibody ELISA Development and Validation.

Rohit Aggarwal, Chester V. Oddis, Noreen Fertig, Danielle Goudeau, Diane Koontz, Chad Stephans, Zengbiao Qi and Marc C. Levesque. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Anti-transcription intermediary factor 1-gamma (TIF1-γ) autoantibody is disease-specific for myositis and identifies a subset of dermatomyositis patients at risk of cancer. Currently non-quantitative immunoprecipitation (IP) is used to identify anti-TIF1-γ. IP has several limitations and development of a quantitative ELISA would improve anti-TIF1-γ detection, especially for cancer screening in myositis. Our aim was to develop and validate a quantitative anti-TIF1-γ ELISA.

Methods: The ELISA utilizes recombinant purified full length human TIF1-γ (Origene Technologies, Rockville MD) coated on the solid surface of a high-binding ELISA plate (Costar, Corning, NY). Patient serum (dilution ≥1:100) was incubated with TIF1-γ coated ELISA plates and a horseradish peroxidase conjugated secondary antibody that binds human IgG detected anti-TIF1-γ binding. 3,3′,5,5′-tetramethylbenzidine was the horseradish peroxidase enzyme substrate, and the optical density of the resulting chromagen was measured. Units/ml of anti-TIF1-γ were determined using a standard serum sample. Values below the detection range (< 4 U/ml) were considered negative and were assigned a value of 2. Assay validation utilized lP results as the gold standard for anti-TIF1-γ. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), ROC curve and area under the curve (AUC) were evaluated. Mann-Whitney tests were used to compare levels of anti-TIF1-γ. Agreement between ELISA and IP was tested. Test-retest reliability was measured. Myositis patients with positive and negative anti-TIF1-γ by IP and non-myositis patients (scleroderma, lupus and RA) and healthy samples were analyzed.

Results: We identified 55 myositis patients with anti-TIF1-γ by IP and 111 myositis patients without anti-TIF1-γ from our connective tissue disease database. Anti-TIF1-γ positivity by ELISA significantly correlated with IP results (p<0.001) with strong agreement between both methods (kappa 0.867). Median (IQR) anti-TIF1-γ levels in patients with (+) and (−) anti-TIF1-γ IP results was 42 (16–95) and 2 (2–2) units/ml, respectively (p<0.001) (figure 1). The sensitivity, specificity, PPV, NPV and overall accuracy of the anti-TIF1-γ ELISA was 91%, 96%, 93%, 95% and 94%, respectively. The AUC of a ROC curve was 0.938. Test-retest reliability was strong (Pearson r = 0.913, p<0.001). Inter-assay CV: 19.5%

Figure 1.   Anti-TIF1-γ antibody levels by ELISA.

Conclusion: We developed a quantitative ELISA for detecting anti-TIF1-γ autoantibodies and validated the assay using serum samples from patients with myositis and other autoimmune disorders. The anti-TIF1-γ ELISA is simple, sensitive and highly specific. The availability of a validated, quantitative ELISA should improve the detection of anti-TIF1-γ antibodies in myositis and malignancies in these patients.

1950

Anti-Signal Recognition Particle Autoantibody ELISA Development and Validation: Utility in Patients with Necrotizing Myopathy. Rohit Aggarwal, Chester V. Oddis, Danielle Goudeau, Chad Stephans, Noreen Fertig, Qi Zengbiao, Diane Koontz and Marc C. Levesque. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Anti-signal recognition particle (SRP) autoAb identifies a myositis subset with a necrotizing myopathy and poor prognosis. Currently, immunoprecipitation (IP) is used to identify anti-SRP. Our aim was to develop and validate a quantitative anti-SRP ELISA to streamline anti-SRP detection.

Methods: The anti-SRP ELISA utilized recombinant purified full length human SRP54 (Diarect AG product number 18401) coated on a high-binding ELISA plate (Costar, Corning, NY). Patient (pt) serum (dilution $\geq$1:100) was incubated with ELISA plates and a horseradish peroxidase conjugated secondary antibody that binds human IgG quantified anti-SRP binding. Units/ml of anti-SRP were determined using a standard serum sample. Values below the detection range ($<$4 U/ml) were considered ($-$) and assigned a value = 2. Values $>$128 U/ml were assigned a value = 128. Assay validation utilized lP as the gold standard. The following test characteristics were evaluated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, ROC curve and sensitivity analysis, and area under the curve (AUC). Mann-Whitney tests compared anti-SRP levels and kappa statistics tested agreement between ELISA and IP. Controls included a) anti-SRP ($+$) and ($-$) myositis pts by IP, b) scleroderma (SSc) and lupus pts, and c) other SRP ($-$) necrotizing myopathy pts. Serial samples from 7 SRP ($+$) pts by IP were also tested.

Results: We identified 26 SRP ($+$) myositis pts by IP. 77 SRP ($-$) myositis pts by IP were evaluated as controls (including 37 pts with necrotizing myopathy). Non-myositis control pts included SLE (n=4) and SSc (n=7). Anti-SRP positivity by ELISA correlated with IP results (p$<$0.001) with strong agreement between both methods (kappa 0.94). Median (IQR) anti-SRP levels in pts with ($+$) and ($-$) anti-SRP by IP was 113.3 (15.6–128) and 2 (2–2) units/ml, respectively (p$<$0.001). The sensitivity, specificity, PPV, NPV and accuracy of the ELISA was 88%, 100%, 100%, 96% and 97%, respectively. The AUC of a ROC curve was 0.94. Serial samples showed that anti-SRP levels decreased consistent with clinical improvement in 3 pts, were unchanged at low levels in 2 pts with stable disease, and increased in 1 pt with a myositis flare. Inter-assay coefficient of variance (CV) was 23%.
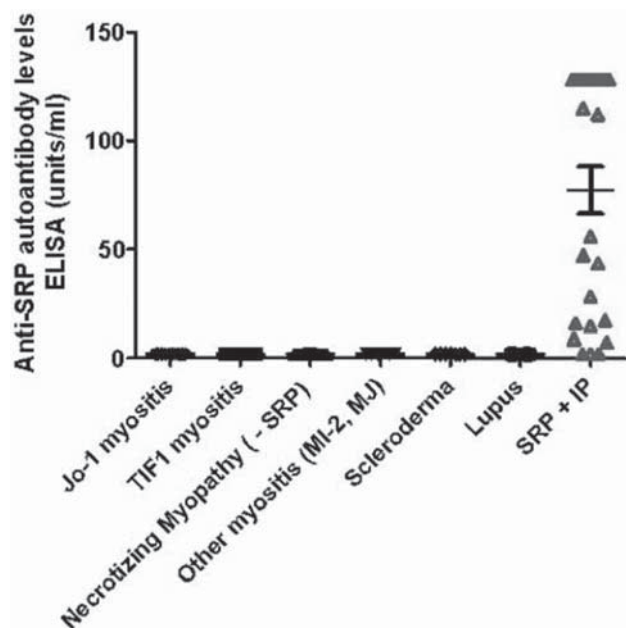
Figure 1. Anti-SRP antibody ELISA levels in different myositis subsets.

Conclusion: We developed a quantitative ELISA for anti-SRP autoAbs, validating the assay in myositis and other rheumatic disease pts including a group of SRP ($-$) necrotizing myopathy pts. The ELISA is simple to perform, sensitive and highly specific. The availability of a validated, quantitative, easy to perform ELISA should improve anti-SRP autoAb detection in myositis pts facilitating early identification of pts with a refractory necrotizing myopathy necessitating aggressive therapy.

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1951

Elevated Level of Tumor Necrosis Factor-Like Weak Inducer of Apoptosis in Patients with Polymyositis or Dermatomyositis. Qinglin Peng, Xin Lu, Ning Zu, Lu Zhang and Guochun Wang. China-Japan Friendship Hospital, Beijing, China

Background/Purpose: TNF-like weak inducer of apoptosis (TWEAK), a member of the tumor necrosis factor (TNF) family, has emerged as a cytokine that regulates multiple cellular responses, including proinflammatory activity, angiogenesis and cell proliferation. Increased levels of TWEAK were observed in many types of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus. However, information about TWEAK in polymyositis and dermatomyositis is limited.The aim of the present study was to investigate the expression of TWEAK in patients with polymyositis and dermatomyositis.

Methods: Twenty four patients with polymyositis, twenty two dermatomyositis patients and twenty four healthy controls were recruited in the study. Serum levels of TWEAK were measured by ELISA. TWEAK messenger RNA (mRNA) expression in skeletal muscle from 19 out of 46 PM/DM patients and 11 healthy controls was detected by relative quantification RT-PCR. The results of two groups were compared using unpaired t test.

Results: Serum levels of TWEAK in PM/DM patients were significantly higher compared to healthy controls [(555.34$\pm$124.05) pg/ml vs (346.22$\pm$146.29) pg/ml, $P<0.05$]. However, there was no statistically significant difference between PM patients and DM patients [(533.34$\pm$119.67) pg/ml vs (579.25$\pm$127.06)pg/ml,$P>0.05$]. TWEAK mRNA in skeletal muscle showed a higher level in skeletal muscle of PM/DM patients than healthy controls, using GAPDH gene as reference gene.

Conclusion: The present study shows that serum levels and mRNA expression of TWEAK were elevated in patients PM/DM. TWEAK may possibly be enrolled in pathogenesis of PM/DM.

Disclosure: **Q. Peng**, None; **X. Lu**, None; **N. Zu**, None; **L. Zhang**, None; **G. Wang**, None.

1952

The Effect of CXCL10 Blockade in C Protein-Induced Myositis. Jinhyun Kim[1], Jiyong Choi[2], Sung Hae Chang[3], Ki Chul Shin[2], Sung-Hye Park[2], Hye Won Kim[4], Hye Jin Oh[2], Myeong Jae Yoon[4], Bong Seung Ku[5], Eun Young Lee[2], Eun Bong Lee[3], Hiroshi Kawachi[6], Hitoshi Kohsaka[7] and Yeong Wook Song[3]. [1]Chungnam National University School of Medicine, Daejeon, South Korea, [2]Seoul National University College of Medicine, Seoul, South Korea, [3]Seoul National University Hospital, Seoul, South Korea, [4]Department of Internal Medicine, School of Medicine, Seoul National University, Seoul, South Korea, [5]Department of Internal Medicine, School of Medicine, Seoul National University Hospital, Seoul, Korea, Seoul, South Korea, [6]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [7]Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

Background/Purpose: CXCL10 (also called interferon-γ-inducible protein 10 [IP-10]) is a chemokine that plays a critical role in the infiltration of T cell in autoimmune disease such as RA and SLE. CXCL10 is reported to be expressed in muscle tissue of polymyositis, thus we investigated the role of CXCL10 and the effect of CXCL10 blockade in C protein-induced myositis, an animal model of polymyositis.

Methods: C protein-induced myositis model was induced with human skeletal C protein fragment in 8-week-old female C57BL/6 mice. Immunohistochemistry was performed to detect CXCL10 and CXCR3, its receptor in muscle tissue. CXCR3 in mouse splenocyte was investigated by flow cytometry. Migration assay of mouse splenocyte was performed with 5 μm pore transwell system. Mice with C protein-induced myositis were treated with anti-CXCL10 antibody or control IgG 8 days after the induction of myositis and the inflammation in muscle tissue was assessed 3 week after the induction.

Results: Immunohistochemistry showed the expression of CXCL10 and CXCR3 in the muscle of C protein-induced myositis. Flow cytometry demonstrated increased CXCR3+CD4+ T cells (normal mice, 14.14%±1.09% vs. C protein-induced myositis, 37.50%±5.63%) and CXCR3+CD8+ T cells (normal mice, 35.55±2.41% vs. C protein-induced myositis, 79.00%±0.89%) in C protein-induced myositis. Migration of splenocyte was increased in response to CXCL10 (chemotactic index=1.91±0.45). Treatment with anti-CXCL10 antibody (n=10) showed less inflammation score in muscles than treatment with control IgG (n=10; median [range], anti IP-10, 0.75 [0.25–2.00] vs. control IgG, 1.43 [1.125–4.25], p=0.045).

Conclusion: CXCL10 was expressed in the inflammation of C protein-induced myositis model and its blockade suppressed inflammation in muscle.

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1953

Antibodies to NXP-2 and Transcriptional Intermediary Factor-Gamma Identify Patients with Cancer-Associated Dermatomyositis. David Fiorentino[1], Lisa Christopher-Stine[2], Lorinda Chung[3], Bharathi Lingala[4], Andrew L. Mammen[5], Antony Rosen[6] and Livia Casciola-Rosen[2]. [1]Stanford University School of Medicine, Redwood City, CA, [2]Johns Hopkins University, Baltimore, MD, [3]Stanford Univ Medical Center, Palo Alto, CA, [4]Stanford University, Redwood City, CA, [5]Johns Hopkins, Baltimore, MD, [6]The Johns Hopkins University, Baltimore, MD

Background/Purpose: Dermatomyositis (DM) is known to be associated with internal malignancy, and identifying patients at high risk is a high priority. Recently, several groups have shown that patients with circulating autoantibodies directed against transcriptional intermediary factor (TIF) isoforms are at increased risk of malignancy. In these studies, anti-TIF antibody positive patients were identified by immunoprecipitation of 140 kD and/or 155 kD proteins from radiolabeled cell lysates. However, this methodology can have suboptimal sensitivity and specificity. This might explain why the sensitivity and specificity of such assays for detecting those patients with cancer-associated DM varies widely in the literature. We wished to use novel sensitive assays to test if anti-TIF-g (or other) autoantibodies were associated with malignancy.

Methods: We designed, optimized and validated novel, sensitive, and highly specific assays to detect antibodies, including those against TIF-g and NXP-2. To detect TIF-g antibodies, HeLa cells were transiently transfected with the appropriate cDNA, resulting in expression levels 33–62 fold above endogenous levels. Immunoprecipitations were performed using these transfected lysates, electrophoresed on SDS-polyacrylamide gels, transferred to nitrocellulose and immunoblotted with an anti-TIF-g monoclonal antibody. NXP-2 antibodies were assayed by immunoprecipitation using ^{35}S-methionine labeled NXP-2 generated by *in vitro* transcription-translation as source material. Patient sera from two DM cohorts seen at the Stanford University Dermatology Outpatient Clinic (n = 111) and the Johns Hopkins University Myositis Center (n = 102) were tested for antibodies against TIF-g and NXP-2 using these assays. We used logistic regression to estimate odds ratios for cancer.

Results: The cohorts were similar in terms of age, gender, ethnicity distribution, as well as proportions of clinically amyopathic patients, and frequency of antibodies against NXP-2 and TIF-g. In the combined group, 17.3% and 36.2% of patients had antibodies against NXP-2 and TIF-g, respectively. Cancer was associated with DM in 35/213 (16.4%) of patients. In the group of 35 cancer patients, 11 (31.4%), 16 (45.7%) and 8 (22.9%) had antibodies against NXP-2, TIF-g, or neither. Thus, reactivity against either NXP-2 or TIF-g identified 77% of patients with cancer-associated DM. On univariate analysis, the odds ratios for cancer in patients with antibodies to NXP-2, TIF-g, or either were 2.6 (95% CI 1.1–6.0, p=0.022), 1.6 (95% CI 0.77–3.3, p=0.212), and 3.6 (95% CI 1.6–8.5, p=0.0027), respectively. This association between cancer and having either NXP-2 or TIF-g antibodies remained significant on multivariate analysis when corrected for other variables (age, gender, ANA, rash on back) that were associated with cancer in univariate analyses.

Conclusion: In this study using 2 large, well defined adult DM cohorts, and novel, highly specific assays to detect antibodies against TIF-g and NXP-2, we show that both of these antibody specificities are associated with an increased risk for cancer in patients with DM.

Disclosure: **D. Fiorentino**, None; **L. Christopher-Stine**, None; **L. Chung**, Gilead and Actelion, 5, Gilead, Actelion, Pfizer, United Therapeutics, 2; **B. Lingala**, None; **A. L. Mammen**, anti-HMGCR antibody test,; **A. Rosen**, None; **L. Casciola-Rosen**, None.

1954

Immune Responses to NXP-2 and TIF-g Are Associated with Distinct Clinical Phenotypes and Prognosis for Skin Disease in Dermatomyositis Patients. David Fiorentino[1], Lorinda Chung[2], Lisa Zaba[1], Bharathi Lingala[3], Antony Rosen[4] and Livia Casciola-Rosen[5]. [1]Stanford University School of Medicine, Redwood City, CA, [2]Stanford Univ Medical Center, Palo Alto, CA, [3]Stanford University, Redwood City, CA, [4]The Johns Hopkins University, Baltimore, MD, [5]Johns Hopkins University, Baltimore, MD

Background/Purpose: Myositis-specific antibodies have been proposed as tools for disease classification as they are correlated with certain clinical and genetic features. Recently, two new DM-specific autoantigens have been described—;TIF-g and NXP-2. Detection of autoantibodies to these proteins has largely been assayed by immunoprecipitation from radiolabeled cell lysates, and thus may not have characterized the patients' immune responses with maximal sensitivity and specificity. We hypothesized that development of sensitive assays for detection of these specificities would enable us to see different patterns of skin and systemic disease associated with these antibodies when applied prospectively to a large DM cohort.

Methods: We designed, optimized and validated novel, sensitive, and highly specific assays to detect antibodies against TIF-g and NXP-2. To detect TIF-g antibodies, HeLa cells were transiently transfected with the appropriate cDNA, resulting in expression levels 33–62 fold above endogenous levels. Immunoprecipitations were performed using these transfected lysates, electrophoresed on SDS-polyacrylamide gels, transferred to nitrocellulose and immunoblotted with an anti-TIF-g monoclonal antibody. NXP-2 antibodies were assayed by immunoprecipitation using ^{35}S-methionine labeled NXP-2 generated by *in vitro* transcription-translation as source material. Patient sera from a large DM cohort at the Stanford University Dermatology Outpatient Clinic (n = 111) were tested for antibodies against TIF-g and NXP-2 using these assays. In order to maximize stringency and clinical utility, we compared the features of patients with a specific autoantibody to those without the antibody (as opposed to those with another antibody). Dichotomous variables were evaluated using Fisher exact tests. We used unpaired t tests (two-tailed) to evaluate differences between continuous variables.

Results: Antibodies to TIF-g and NXP-2 were detected in 37% and 14% of patients, respectively. When compared to those without antibodies to TIF-g, anti-TIF-g patients were associated with female sex, positive ANA, absence of arthralgia, "V" sign, and difficulty with controlling skin inflammation. Antibodies to NXP-2 were associated with male sex, internal malignancy, calcinosis cutis, absence of alopecia/ulceration/Gottron's papules/elbow and knee rash, positive response to hydroxychloroquine, and satisfactory control of skin disease. In the non-amyopathic subgroup, patients with antibodies to TIF-g were significantly associated with lower maximal CK values than those without (488 vs 3467, respectively, p=0.05).

Conclusion: Over 50% of our Stanford DM cohort can be typed by antibodies to either NXP-2 or TIF-g. NXP-2 antibodies are associated with calcinosis cutis, malignancy, and a benign course of skin disease, while TIF-g antibodies are characterized by absence of arthralgia, "V" sign, relatively low CK values, and skin inflammation that is difficult to control.

Disclosure: **D. Fiorentino**, None; **L. Chung**, Gilead and Actelion, 5, Gilead, Actelion, Pfizer, United Therapeutics, 2; **L. Zaba**, None; **B. Lingala**, None; **A. Rosen**, None; **L. Casciola-Rosen**, None.

1955

Is the Pattern of Capillary Deposition of Complement Membrane Attack COPMLEX Useful in the Differential Diagnosis of Inflammatory? Patrick Gordon[1], Nuria Villagra[2], Istvan Bodi[2], Andrew King[2], Stefan Buk[2], Tibor Hortobagyi[2] and Safa Al-Sarraj[2]. [1]Department of Rheumatology, King's College London, London, United Kingdom, [2]Department of Clinical Neuropathology, King's College Hospital, London, United Kingdom

Background/Purpose: Inflammatory myopathies are a heterogeneous group of diseases. We investigated if the location and pattern of deposition of complement membrane attack complex (MAC) can be used in the differential diagnosis of inflammatory myopathies.

Methods: We reviewed histological sections of 227 cases of muscle biopsies in which MAC was requested for diagnosis and analysed 145 cases with clear clinical and pathological diagnosis; 88 inflammatory myopathies, 31 muscular dystrophies and 26 controls. We reviewed the immunohistochemical location of MAC, HLA Class I, utrophin, neo-myosin, together with the standard histological sections of the muscle biopsies.

Results: MAC deposition was demonstrated in 86.2% of dermatomyositis (DM), 86.5% of inclusion body myositis (IBM) and about 50% of patients with

polymyositis (PM) and mixed connective tissue disease (MCTD). Most of the DM cases (55%) showed continuous solid and strong staining pattern in the capillary wall (pattern 1) with clear tendency of perifascicular deposition but with no sarcolemmal labelling. Samples from muscles with IBM, PM and MCD showed lighter granular segmental staining (pattern 2) in the capillaries, which is frequently associated with frequent granular staining in sarcolemma of muscle fibres across the fascicles. About 31% of DM biopsies showed a mixture of patterns 1 and 2.

There were infrequent granular and infrequent granular deposits in the capillaries in about 13% of muscular dystrophies and 11% in control cases.

Conclusion: Pattern 1 deposition of MAC in capillaries appears to be more frequent in DM and could contribute to the diagnosis, in addition to other criteria. This pattern of deposition may indicative of primary humoral mechanism involving capillaries in DM. Pattern 2 deposition of MAC in capillaries and sarcolemma of other inflammatory diseases, such as IBM and PM, could suggest complement system activation secondary to the inflammatory process and muscle necrosis.

1956

A New Linked Set of Autoantibodies in Dermatomyositis: Anti-Mi-2 and Anti-Transcription Intermediary Factor (TIF) 1alpha. Minoru Satoh[1], Jason YF Chan[1], Yi Li[1], Monica Vázquez-Del Mercado[2], Marcelo Petri[3], Luis J. Jara[4], Miguel A. Saavedra[5], Claudia Cruz-Reyes[6], Eric S. Sobel[1], Westley H. Reeves[1], Angela Ceribelli[1] and Edward K.L. Chan[1]. [1]University of Florida, Gainesville, FL, [2]Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico, [3]Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico, [4]Hospital de Especialidades Centro Medico La Raza, México City, Mexico, [5]Centro Medico La Raza Instituto Mexicano del Seguro Social Mexico D.F., México D.F., Mexico, [6]Centro Medico La Raza Instituto Mexicano del Seguro Social Mexico D.F., Mexico D. F., Mexico

Background/Purpose: Myositis specific autoantibodies (MSA) produced in patients with polymyositis/dermatomyositis (PM/DM) are clinically useful biomarkers in diagnosis and management. Anti-Mi-2 antibodies that recognize nucleosome remodeling deacetylase complex are classic marker of DM. Anti-p155/140 (transcription intermediary factor 1 gamma and alpha, respectively) antibodies are one of the new MSA that have been studied actively because of their tight link to cancer-associated DM. A well known but poorly explained characteristic in MSA production is the rare coexistence of more than one MSA in each individual patient. We here report frequent coexistence of anti-Mi-2 and anti-TIF1 alpha antibodies as an exception for this concept.

Methods: Sera of patients with PM/DM from United States, Mexico, Italy, and Japan were screened for their autoantibody specificities by immunoprecipitation (IP) of ^{35}S-labeled K562 cells extract. Sera with anti-Mi-2 and anti-p155/140 were further characterized by IP-western blot (IP-WB) using monoclonal antibodies to TIF1alpha and TIF1gamma. Antibodies to TIF1alpha, gamma, and Mi-2 were also tested by ELISA using recombinant proteins. Clinical information was from the database and chart review.

Results: Forty-one anti-Mi-2 and 18 anti-p155/140 positive sera were identified and their characteristics are summarized in Table. Anti-Mi-2 positive sera immunoprecipitated a 140kD protein that comigrates exactly with TIF1alpha. This protein was determined as TIF1alpha that was immunoprecipitated by coexisting autoantibodies to TIF1alpha in majority of human anti-Mi-2 sera based on 1) disappearance of the 140kD protein from human anti-Mi-2 IP by preincubation of cell extract with anti-TIF1alpha mAb, 2) mAb to Mi-2 and rare human sera with anti-Mi-2 do not IP the 140kD protein, 3) human anti-Mi-2 sera were positive for TIF1alpha by IP-WB, and 4) human anti-Mi-2 sera were positive in anti-TIF1alpha ELISA. Autoantibodies to TIF1gamma in human anti-Mi-2 sera appeared uncommon based on 1) the 155kD protein that comigrates with TIF1gamma is not seen in human anti-Mi-2 IP, 2) lack of anti-TIF1gamma reactivity in ELISA, 3) although many human anti-Mi-2 sera were also positive for TIF1gamma, the levels of TIF1gamma immunoprecipitated by human anti-Mi-2 sera are very little compared with those by human anti-p155/140 sera, suggesting that they are via co-IP by TIF1alpha.

Table 1. Reactivity of anti-Mi-2 and p155/140 sera

	Anti-Mi-2	Anti-p155/140	control
n	41	18	5
^{35}S-IP-TIF1alpha	88%	100%	0%
^{35}S-IP-TIF1gamma	0%	100%	0%
TIF1alpha ELISA	88%	83%	0%
TIF1gamma ELISA	2%	83%	0%
TIF1alpha-IP-WB	88%	100%	0%
TFI1gamma-IP-WB	80%	100%	0%

Conclusion: Majority of human sera with anti-Mi-2 also have antibodies to TIF1alpha but not TIF1gamma. This is a new linked set of autoantibodies in DM and an exception of the rare coexistence of MSA in individual patient. This finding will affect identification and classification of PM/DM based on serology and may require reevaluation of clinical significance of anti-TIF1 alpha antibodies as anti-TIF1alpha coexisting with anti-Mi-2 has not been considered in the past.

ACR/ARHP Poster Session C
Osteoporosis and Metabolic Bone Disease
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

1957

Prevalence and Associated Factors of Vitamin D Insufficiency and Deficiency in 4,793 Japanese Patients with Rheumatoid Arthritis. Takefumi Furuya[1], Takayuki Hosoi[2], Eiichi Tanaka[1], Ayako Nakajima[1], Atsuo Taniguchi[1], Shigeki Momohara[1] and Hisashi Yamanaka[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]National Center for Geriatrics and Gerontology, Aichi, Japan

Background/Purpose: Vitamin D (25[OH]D) insufficiency and deficiency is reported to be common in patients with rheumatoid arthritis (RA) and is associated with increased disease activity of RA, although there are limited reports of Japanese RA patients in the literature. Among osteoporosis patients treated with bisphosphonates, vitamin D status and concomitant use of active vitamin D3 analogs are both reported to affect the increase in bone mineral density (BMD). Our purpose was to define the prevalence and associations of 25(OH)D insufficiency and deficiency with clinical characteristics in Japanese patients with RA.

Methods: Serum 25(OH)D levels, laboratory data, and clinical data were obtained from 4,793 patients with RA (4,075 women, 718 men, mean age 59.7 years) who participated in the Institute of Rheumatology Rheumatoid Arthritis (IORRA) observational cohort study in April and May of 2011. Their serum vitamin D levels were evaluated using radioimmunoassays. Insufficiency was defined as a concentration < 20 ng/mL and deficiency as < 10 ng/mL. Associations of 25(OH)D insufficiency and deficiency with patient characteristics were examined using multivariate logistic regression.

Results: The mean (SD) serum 25(OH)D level was 16.9 (6.1) ng/mL. The prevalence of 25(OH)D insufficiency and deficiency among all the patients in the study were 71.8% and 11.5%, respectively. Serum 25(OH)D levels were significantly different ($P < 0.05$) between the patients with (n = 507, 10.6%) and without active vitamin D3 analogs. Among the patients treated with bisphosphonates (n = 1,130), insufficiency and deficiency were 71.5% and 10.4%, respectively. In multivariate analyses, female gender (odds ratios [OR] 2.38, 95 confidence interval [CI] 1.88–2.92 and OR 2.01, 95% CI 1.41–2.91), age (per 10 years, OR 0.72, 95% CI 0.68–0.77 and OR 0.67, 95% CI 0.62–0.73), Japanese health assessment questionnaire (J-HAQ) disability scores (OR 1.20, 95% CI 1.07–1.36 and OR 1.63, 95% CI 1.40–1.92), serum total cholesterol levels (per 10 mg/100mL, OR 0.96, 95% CI 0.94–0.98 and OR 0.95, 95% CI 0.92–0.98), serum alkaline phosphate level (per 10 IU/L, OR 1.01, 95% CI 1.00–1.02 and OR 1.02, 95% CI 1.00–1.03), and use of non-steroidal anti-inflammatory drugs (NSAIDs) (OR 1.27, 95% CI 1.11–1.46 and OR 1.25, 95% CI 1.02–1.54) were associated ($P < 0.05$) with vitamin D insufficiency and deficiency, respectively. Body mass index (BMI) and use of active vitamin D3 analogs (OR 0.96, 95% CI 0.93–0.99 and OR 0.69, 95% CI 0.48–0.97, respectively) were significantly associated with vitamin D deficiency alone. The Disease Activity Score including 28 joints (DAS28) was not significantly associated with either vitamin D insufficiency or deficiency in this patient population.

Conclusion: Vitamin D insufficiency and deficiency are common in Japanese patients with RA, as previously reported for patients of other ethnicities. Female gender, younger age, high HAQ disability score, serum levels of total cholesterol and alkaline phosphate and NSAID use appear to be associated with both vitamin D insufficiency and deficiency in Japanese patients with RA. Low BMI and disuse of active vitamin D3 analogs, however, appear to correlate only with vitamin D deficiency in Japanese patients with RA.

1958

Bone Mineral Density in Lupus Erythematosus Women One Year After Rituximab Therapy. Claudia Mendoza-Pinto[1], Mario Garcia-Carrasco[1], Mario Jiménez-Hernández[1], Alma Rodríguez-Gallegos[2], Socorro Méndez-Martínez[1] and Aurelio Lopez-Colombo[3]. [1]HGR 36 CMN Manuel Ávila Camacho, Instituto Mexicano del Seguro Social, Puebla, Mexico, [2]Laboratorios Clínicos de Puebla, Puebla, Mexico, [3]Delegación Estatal, Instituto Mexicano del Seguro Social, Puebla, Mexico

Background/Purpose: Low bone mineral density (BMD) and osteoporosis may be significant complications in patients with systemic lupus erythematosus (SLE). Recent studies have shown that biologic therapy could arrest general bone loss, however, the role of rituximab on BMD in SLE patients has not been analyzed. The aim of this prospective study was to assess the effects of rituximab on BMD at the lumbar spine and femoral neck in women with SLE, one year after rituximab therapy.

Methods: Thirty active female SLE patients treated with rituximab were compared with control SLE women not treated with rituximab. In those patients, rituximab 1 g was administered on days 1 and 15 in addition to current immunosuppressive treatment, which was maintained until disease remission. Since all patients were using steroids when rituximab therapy began, they were all taking calcium and vitamin D. Historical controls included forty-six SLE women with similar lupus activity treated with conventional therapy azathoprine, methotrexate, mycophenolate mofetil, leflunomide and cyclophosphamide) without rituximab therapy. BMD at the femoral neck and lumbar spine was measured using dual energy x-ray absorptiometry before initiating conventional and biologic therapy and after one year.

Results: Seventy-six patients were studied. The mean age was 38.5 ± 2.1 SD, median disease duration was 7 years (range 1 to 26). Thirty patients received rituximab and forty- six controls received conventional treatment. Baseline BMD measurements were higher in the rituximab group. In the rituximab group, after 1 year of follow up femoral neck BMD decreased from 0.980 ± 0.130 g/cm2 to 0.809 ± 0.139 g/cm2 (-17.4%; p = 0.001). Similarly, lumbar spine BMD decreased from 1.062 ± 0.137 g/ cm2 to 0.893 ± 0.194 g/ cm2 (-15.8%; p= 0.001). In controls, femoral neck BMD decreased from 0.914 ± 0.193 g/cm2 to 0.890 ± 0.135 g/cm2 (-2.6%; p= 0.001) and lumbar spine BMD decreased from 0.926 ± 0.128 g/cm2 to 0.867 ± 0.139 g/cm2 (-6.2%; p= 0.09). BMD loss was higher in postmenopausal rituximab patients than in postmenopausal controls (0.324 ± 0.128 g/cm2 vs 0.138 ± 0.099 g/cm2). There was a significant difference in BMD at the femoral neck between responders and nonresponders (p = 0.014) but not in BMD at the lumbar spine.

Conclusion: After one year of follow up, SLE patients had lower BMD at both the femoral neck and lumbar spine, but the loss was greater in patients receiving rituximab than in patients receiving conventional treatment, and in postmenopausal women. Postmenopausal candidates for rituximab should be evaluated closely to prevent further BMD loss.

1959

Low Fracture Incidence Is Maintained in Postmenopausal Women ≥75 Years with Osteoporosis with Long-Term Denosumab Treatment. Socrates Papapoulos[1], Michael R. McClung[2], Nathalie Franchimont[3], Jonathan D. Adachi[4], Henry G. Bone[5], Claude-Laurent Benhamou[6], Jordi Farrerons[7], JC Gallagher[8], Johan Halse[9], Kurt Lippuner[10], Salvatore Minisola[11], Ove Törring[12], Nadia Daizadeh[3], Andrea Wang[3], Rachel B. Wagman[3] and Steven Boonen[13]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Oregon Osteoporosis Center, Portland, OR, [3]Amgen Inc., Thousand Oaks, CA, [4]Charlton Medical Centre, Hamilton, ON, [5]Michigan Bone and Mineral Clinic, Detroit, MI, [6]EA 4708 University Orleans, Orleans, France, [7]Hospital de la Santa Creu I Sant Pau, Barcelona, Spain, [8]Creighton University Medical Center, Omaha, NE, [9]Osteoporoseklinikken, Oslo, Norway, [10]University Hospital, Bern, Switzerland, [11]Sapienza, Università di Roma, Rome, Italy, [12]Karolinska Institutet Sodersjukhuset, Stockholm, Sweden, [13]Leuven University, Leuven, Belgium

Background/Purpose: In the pivotal fracture trial, FREEDOM, denosumab increased bone mineral density (BMD) and reduced the incidence of new vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis (Cummings SR et al, *NEJM* 2009). Denosumab reduced the risk of hip fracture in high-risk subgroups, including a 62% reduction in patients ≥75 years old (Boonen S et al, *JCEM* 2011). The effects of long-term denosumab treatment up to 10 years are being evaluated in the FREEDOM extension study. As fracture incidence increases with age, and in particular, hip fracture in women ≥75, we have further characterized the fracture incidence and BMD gains in women ≥75 who have been treated with denosumab for a total of 6 years.

Methods: During the extension, each woman has received 60 mg denosumab every 6 months and supplemental calcium and vitamin D daily. We evaluated the fracture incidence and BMD gains in women who completed 6 years of denosumab treatment (overall long-term group) and in the subset of these women who were ≥75 at FREEDOM baseline (higher-risk group).

Results: The FREEDOM baseline characteristics for the overall long-term denosumab group (N=2343) and the higher-risk group (N=662) were similar except that those subjects in the higher-risk group were older (mean age: 72 years for overall and 78 years for higher-risk), and had a lower mean total hip BMD T-score (–1.9 for overall and –2.1 for higher-risk). Despite the increase in age of the subjects, denosumab treatment during years 4 to 6 continued to be associated with a low incidence of new vertebral, nonvertebral, and hip fractures. Furthermore, the incidence of fractures in the higher-risk group during years 4 to 6 was similar to what was originally observed in years 1 to 3 in women ≥75 treated with denosumab (Figure).
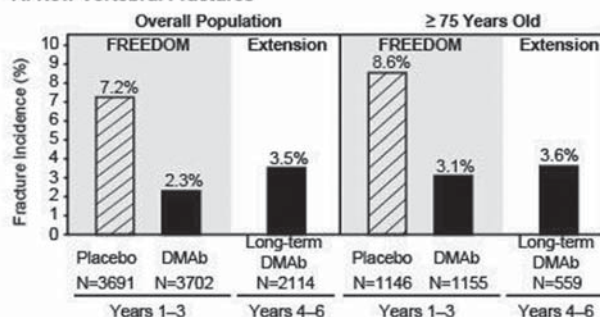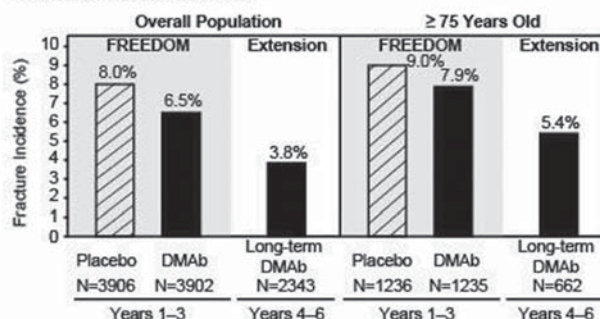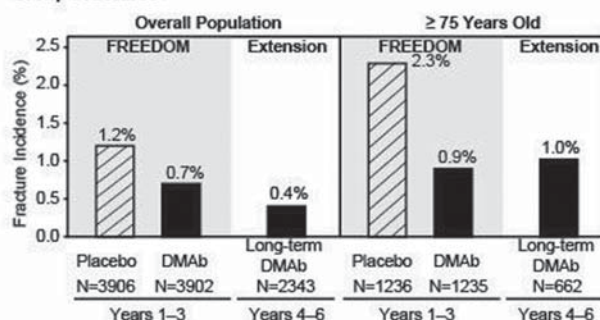
Fracture incidence is based on crude incidence rate for panel A and Kaplan-Meier estimate for panels B and C.
N=number of subjects in the respective primary efficacy analysis set.

Figure. Subject incidence of fractures in the FREEDOM and extension trial.

BMD progressively increased over 6 years at the lumbar spine and total hip and was similar in women ≥75 compared with women in the overall long-term group. Despite advanced age, adverse events (AEs) and serious AEs in the higher-risk group in the extension were similar to the higher-risk group from FREEDOM, and these events did not increase over time with denosumab treatment.

Conclusion: Patients aged ≥75 are at higher risk of fracture than younger patients. Denosumab is a therapeutic option for the women ≥75 in whom the high risk of hip fracture is of particular concern. These results amplify the robust and consistent anti-fracture efficacy and safety profile of continued denosumab treatment over 6 years.

1960

Initiation of Tumor Necrosis Factor Alpha (TNFα) Antagonists and Risk of Fractures in Patients with Selected Rheumatic and Autoimmune Diseases.

Vivian K. Kawai[1], Carlos Grijalva[1], Patrick Arbogast[1], Jeffrey R. Curtis[2], Daniel H. Solomon[3], Elizabeth S. Delzell[2], Lang Chen[2], Lisa Herrinton[4], Liyan Liu[4], Edward F. Mitchell Jr.[1], C. Michael Stein[5] and Marie Griffin[1]. [1]Vanderbilt University, Nashville, TN, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [4]Kaiser Permanente, Oakland, CA, [5]Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Inflammation mediates bone resorption, in part through TNFα. In experimental models TNFα antagonists reduce inflammation-mediated bone resorption; however, the effect of this class of drugs on fracture risk in patients is unknown. We tested the hypothesis that initiation of TNFα antagonists reduced the risk of fractures compared to nonbiologic comparators in patients with RA.

Methods: Using four large administrative databases we assembled a retrospective cohort of patients with RA from 1998 to 2005 enrolled in Tennessee's Medicaid Program (TennCare), Kaiser Permanente Northern California (KPNC), Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE), and multi-State Medicaid programs (MAX) and identified patients who initiated either a TNFα antagonist (n=20,814) or a non biologic disease modifying anti-rheumatic drug (DMARD): hydroxychloroquine (HCQ), sulfazalasine (SSZ) and/or leflunomide (LEF) (n=8,964). We used baseline covariate data to calculate propensity scores (PS) to match treatment groups, and Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). We compared the risk of the first fracture (hip, radius/ulna, humerus, or pelvic); first hip fracture; and first clinical vertebral fracture between PS-matched cohorts of new users of TNFα antagonists and non biologic DMARDs.

Results: We identified 9,020 new PS matched episodes of TNFα antagonist and non biologic DMARD use. The risk of fractures was similar between new users of TNFα antagonists and non biologic DMARDs: HR:1.17, 95%CI [0.91–1.51] for combined fracture outcome (Figure 1); HR:0.87, 95%CI [0.60–1.27] for hip fracture (Figure 2); and HR:0.71, 95%CI [0.43–1.19] for clinical vertebral fracture (Figure 3). The risk of the combined fracture outcome was associated with an average daily dose of prednisone equivalents >10 mg/day at baseline compared with no glucocorticoid (HR: 1.54, 95%CI [1.03, 2.30]).

Figure 1

Figure 2

Figure 3
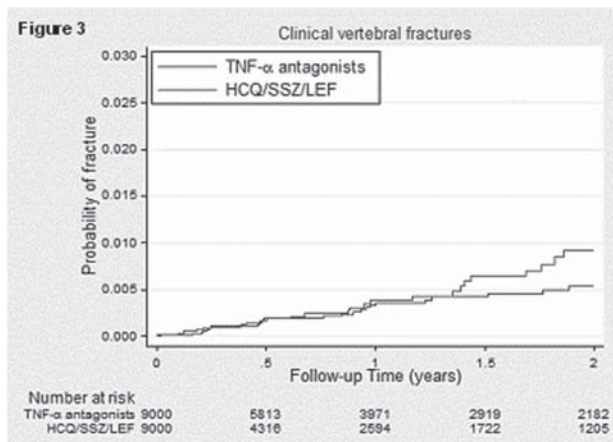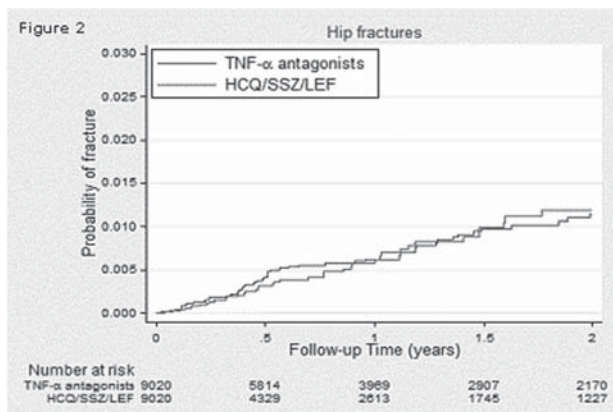
Conclusion: The risk of fracture did not differ between new users of TNFα antagonists and non biologic DMARDs in patients with RA. The use of >10mg/day of prednisone equivalents at baseline increased the fracture risk.

1961

In Postmenopausal Women with Osteoporosis, Denosumab Significantly Improved Trabecular Bone Score (TBS), an Index of Trabecular Micro-architecture. Michael R. McClung[1], Kurt Lippuner[2], Maria Luisa Brandi[3], Jean-Marc Kaufman[4], Jose R. Zanchetta[5], Marc-Antoine Krieg[6], Henry G. Bone[7], Roland Chapurlat[8], Didier Hans[6], Andrea Wang[9], Jang Yun[9], Carol Zapalowski[9] and Cesar Libanati[9]. [1]Oregon Osteoporosis Center, Portland, OR, [2]University of Berne, Berne, Switzerland, [3]University of Florence, Florence, Italy, [4]University Hospital of Ghent, Ghent, Belgium, [5]Instituto de Investigaciones Metabólicas and University of Salvador, Buenos Aires, Argentina, [6]Lausanne University Hospital, Lausanne, Switzerland, [7]Michigan Bone and Mineral Clinic, Detroit, MI, [8]Hôpital Edouard Herriot, Lyon, France, [9]Amgen Inc., Thousand Oaks, CA

Background/Purpose: The trabecular bone score (TBS), a novel gray-level texture index determined from lumbar spine DXA scans, correlates with 3D parameters of trabecular bone microarchitecture known to predict fracture. TBS may enhance the identification of patients at increased risk for vertebral fracture independently of bone mineral density (BMD) (Boutroy *JBMR* 2010; Hans *JBMR* 2011). Denosumab treatment for 36 months decreased bone turnover, increased BMD, and reduced new vertebral fractures in postmenopausal women with osteoporosis (Cummings *NEJM* 2009). We explored the effect of denosumab on TBS over 36 months and evaluated the association between TBS and lumbar spine BMD in women who had DXA scans obtained from eligible scanners for TBS evaluation in FREEDOM.

Table. Lumbar Spine TBS and BMD Percentage Change From Baseline Over Time and Pearson Correlation Between TBS and BMD

	Placebo (N = 128)			Denosumab (N = 157)		
Month	TBS % Change	BMD % Change	Pearson Correlation	TBS % Change	BMD % Change	Pearson Correlation
12	0.0	−0.1	0.0036	1.4[a,b]	5.7[a,b]	0.0256
24	0.2	0.1	0.0004	1.9[a,b]	7.8[a,b]	0.0225
36	−0.7	0.0	0.0324	2.4[a,b]	9.8[a,b]	0.0529

N = number of randomized subjects who enrolled in the DXA substudy and had observed TBS data at baseline and ≥1 post-baseline visit. [a]$p \leq 0.0144$ compared with placebo. [b]$p \leq 0.0003$ compared with baseline.

Percentage Change From Baseline in Lumbar Spine TBS

[a]$p \leq 0.0144$ compared with placebo
[b]$p \leq 0.0003$ compared with baseline
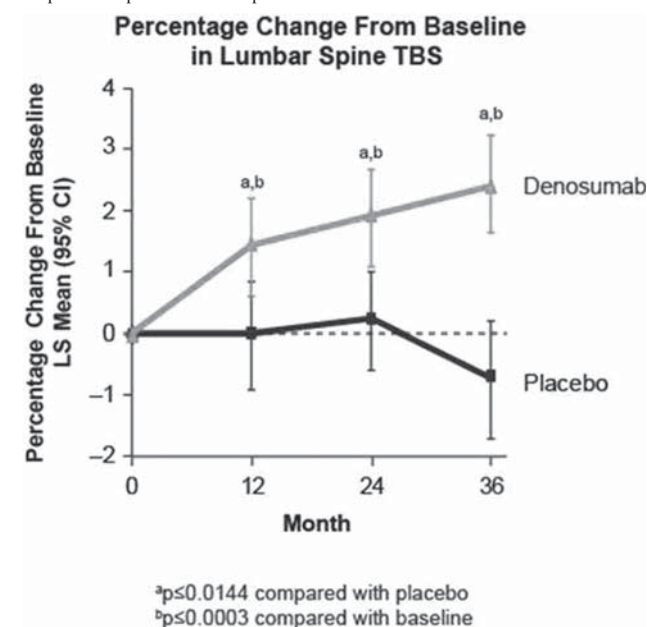
Methods: FREEDOM was a 3-year, randomized, double-blind trial that enrolled postmenopausal women with a lumbar spine or total hip DXA T-score < -2.5, but not < -4.0 at both sites. Women received placebo or 60 mg denosumab every 6 months. A subset of women in FREEDOM participated in a DXA substudy where lumbar spine DXA scans were obtained at baseline and months 1, 6, 12, 24, and 36. We retrospectively applied, in a blinded-to-treatment manner, a novel software program (TBS iNsight® v1.9, Med-Imaps, Pessac, France) to the standard lumbar spine DXA scans obtained in these women to determine their TBS indices at baseline and

months 12, 24, and 36. From previous studies, a TBS >1.35 is considered as normal microarchitecture, a TBS between 1.35 and >1.20 as partially deteriorated, and ≤ 1.20 reflects degraded microarchitecture.

Results: There were 285 women (128 placebo, 157 denosumab) with a TBS value at baseline and ≥ 1 post-baseline visit. Their mean age was 73, their mean lumbar spine BMD T-score was -2.79, and their mean lumbar spine TBS was 1.20. In addition to the robust gains in DXA lumbar spine BMD observed with denosumab (9.8% at month 36), there were consistent, progressive, and significant increases in TBS compared with placebo and baseline (Table & Figure). BMD explained a very small fraction of the variance in TBS at baseline ($r^2 < 0.07$). In addition, the variance in the TBS change was largely unrelated to BMD change, whether expressed in absolute or percentage changes, regardless of treatment, throughout the study (all $r^2 < 0.06$); indicating that TBS provides distinct information, independently of BMD.

Conclusion: In postmenopausal women with osteoporosis, denosumab significantly improved TBS, an index of lumbar spine trabecular microarchitecture, independently of BMD.

1962

The Specific Role of Glutaredoxin2 Isoform b (Glrx2b) in RANKL-Induced Osteoclastogenesis Through Activation of the p38-MAPK Signaling Pathway. Chang-Hoon Lee[1], Wan-Hee Yoo[2], Jin-Jung Choi[3], Myong-Joo Hong[2], Ji-Min Kim[4] and Jeong-Tae Yeon[5]. [1]Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [3]CHA University Hospital, Seongnam, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, South Korea, [5]Department of anatomy, school of medicine, Wonkwang university, Iksan, Chonbuk, South Korea

Background/Purpose: Recently, reactive oxygen species (ROS) and antioxidant enzymes were shown to be closely associated with RANKL-mediated osteoclast differentiation. Although glutaredoxin2 (Glrx2) plays a role in cellular redox homeostasis, its role in RANKL-mediated osteoclastogenesis is unclear.

Objectives: The aim of this study was to examine the effect of Glrx2 on osteoclast differentiation

Methods: Osteoclast formation was evaluated in bone marrow cells (BMC) in specific condition with over-expression of Glrx2 or down-regulation of Glrx2 during receptor activator of NF-κB ligand (RANKL)-mediated osteoclastogenesis. The expression of c-fos and NFATc1 mRNA in osteoclast precursor were assessed by RT-PCR. The levels of c-fos and NFATc1 protein were assessed by western blot. Also the mitogen-activated protein (MAPK)s pathways were measured using Western blot analysis.

Results: We found that Glrx2 isoform b (Glrx2b) expression is induced during RANKL-mediated osteoclastogenesis. Over-expression of Glrx2b strongly enhanced RANKL-mediated osteoclastogenesis. In addition, Glrx2b-transduced BMMs enhanced the expression of key transcription factors c-Fos and NFATc1, but pre-treatment with SB203580, a p38-specific inhibitor, completely blocked this enhancement. Conversely, down-regulation of Glrx2b decreased RANKL-mediated osteoclastogenesis and the expression of c-Fos and NFATc1 proteins. Also, Glrx2b down-regulation attenuated the RANKL-induced activation of p38.

Conclusion: Taken together, these results suggest that Glrx2b enhances RANKL-induced osteoclastogenesis via p38 activation. It may be very useful information for treatment of bone-resorbing disorders, such as rheumatoid arthritis and osteoporosis.

1963

Fracture Sites, Frequencies and Causes in 9,720 Japanese Patients with Rheumatoid Arthritis: A Prospective Observational Cohort Study. Kensuke Ochi, Takefumi Furuya, Eisuke Inoue, Katsunori Ikari, Atsuo Taniguchi, Shigeki Momohara and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Although rheumatoid arthritis (RA) is a risk factor for osteoporosis and fracture, limited data exist in the literature concerning fracture site and frequency in patients with RA. We previously reported clinical risk factors for both incident vertebral and nonvertebral fractures in Japanese RA patients using our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study. Herein we expanded our previous study to evaluate fracture sites, frequencies, and causes in Japanese RA patients.

Methods: The IORRA is a prospective observational cohort study of Japanese RA patients at the Institute of Rheumatology, Tokyo Women's Medical University (Tokyo, Japan) that was started in 2000. A total of 9,720 patients (82% female; mean age, 56 years) with RA were enrolled in the IORRA cohort study from 2000 to 2010. All participants self-reported whether they had a fracture event within the previous 6 months, the site of fracture (ankle, arm, cervical spine, clavicle, elbow, femoral neck, foot, hand, knee, leg, nose, pelvis, rib, shoulder, thoracic spine, lumbar spine, wrist, and others), and the reasons for fracture (accident, fall, spontaneous event, or sports injury) every 6 months from October 2000 to October 2010. We then analyzed the sites, frequencies, and causes of the fractures to clarify the epidemiology of fractures in Japanese RA patients.

Results: During a mean (SD) duration of 5.2 (3.3) years, 1357 patients reported a total of 2076 incident fractures. Among them, 837 (61.7%) reported a single fracture, 520 (38.3%) reported two fractures, 303 (22.3%) reported three fractures, and 217 (16.0%) reported more than three fractures. Overall, 287 (13.8%) vertebral fractures and 1789 (86.2%) nonvertebral fractures (head: n=35, 1.7%; trunk: n=504, 24.3%; upper limb: n=508, 24.5%; and lower limb: n=742, 35.7%) were reported. The most frequent fresh nonvertebral fracture was rib (n=368, 20.6%), followed by toe (n=276, 15.4%), femoral neck (n=178, 9.9%), ankle (n=132, 7.4%), wrist (n=122, 6.8%), hand (n=117, 6.5%), shoulder (n=105, 5.9%), arm (n=86, 4.8%), knee (n=84, 4.7%), elbow (n=78, 4.4%), pelvis (n=71, 4.0%), leg (n=57, 3.2%), clavicle (n=56, 3.1%), and head including nose (n=35, 2.0%). Causes of overall fractures were fall in 55.5% of patients, followed by spontaneous events in 33.2%, accident in 7.8%, and sports injury in 1.0%; the major causes of vertebral fractures were spontaneous events (63.5%) and fall (27.4%), while fall (60.0%) and spontaneous events (28.3%) were the major causes of nonvertebral fractures.

Conclusion: Fourteen percent of Japanese patients with RA reported one or more incident fractures within a mean duration of 5.2 years. Unlike non-RA elderly subjects, spontaneous events were a major cause of fractures. Differences between RA patients and non-RA subjects should be at least in some part due to the significant osteoporosis seen in RA patients.

1964

Rolofylline, an Adenosine A1R Antagonist, Acts As an Inverse Agonist to Inhibit Osteoclast Differentiation. Wenjie He[1] and Bruce N. Cronstein[2]. [1]NYU, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Previous work from our laboratory has uncovered a critical role of adenosine A1 receptor (A1R) in osteoclast formation both in vivo and in vitro. Adenosine may be generated by hydrolysis of extracellular adenosine nucleotides including ecto-nucleoside triphosphate diphosphohydrolase 1 (CD39), ecto-5′-nucleotidase (CD73) and nucleotide pyrophosphatase phosphodiesterase 1 (NPP-1). Interestingly selective A1R agonists neither affect basal osteoclast formation nor do they reverse A1R-mediated inhibition of osteoclast formation. In this study, we determined whether ectonucleotidase-mediated adenosine production was required for osteoclast formation and, when we saw no effect, determined whether the A1R was constitutively activated and the antagonist was acting as an inverse agonist to mediate its effects on osteoclast formation.

Methods: Osteoclasts were generated from bone marrow mononuclear cells (BMMs) extracted from wildtype, CD39KO, CD73KO and NPP-1KO mice using differentiation factors macrophage colony-stimulating factor (M-CSF) and RANKL. The A1R specific antagonist, Rolofylline, was added to the culture media. TRAP+ staining was performed and Acp5 and Ctsk mRNA expression were examined to study osteoclast differentiation. Intracellular cAMP concentration was determined by ELISA.

Results: A1R blockade inhibits osteoclast differentiation of BMMs derived from wildtype mice in a dose-dependent manner ($IC_{50}=1\mu M$ p<0.05, n=3). A1R blockade similarly inhibits osteoclast formation by marrow precursors from CD73KO, CD39KO and NPP-1KO mice in a dose-dependent manner ($IC_{50}=1\mu M$, and $1\mu M$, and $0.1\mu M$, respectively, p<0.05 for all, n=3) for all three knockouts, although baseline osteoclast formation was significantly less (310 in CD73 KO vs 91 in wildtype, p<0.05, n=3) in precursors from CD73KO mice. Moreover, in the absence of agonist, A1R antagonist, rolofylline ($1\mu M$) caused an increase of cAMP content of BMMs by 9.9 fold (p<0.05, compared with control: M-CSF + RANKL, n=3). Similarly, rolofylline ($1\mu M$) leads to increased cAMP production in human healthy BMMs by 3.6 fold (n=1, compared with control: M-CSF+ RANKL), which is consistent with our findings that A1R blockade by rolofylline inhibits human BMMs-derived osteoclast formation (p<0.001, n=3; $IC_{50}=$ 1nM).

Conclusion: Based on these findings we hypothesize that the A1R is constitutively activated in osteoclast precursors, thereby diminishing basal adenylate cyclase activity, and that the A1R antagonist acts as an inverse agonist to release the A1R-mediated inhibition of basal adenylate cyclase activity. The constitutive activity of A1R promotes osteoclast formation and downregulation of this activity blocks osteoclast formation.

1965

Adenosine Regulates Bone Metabolism Via A_1, A_{2A} and A_{2B} Receptors in Bone Marrow Cells From Normal and Patients with Multiple Myeloma. Wenjie He[1], Amitabha Mazumder[2] and Bruce N. Cronstein[3]. [1]NYU, New York, NY, [2]NYU Cancer Center, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Multiple myeloma is a haematologic malignancy that is characterized by osteolytic bone lesions, wherein coupled bone remodeling is disrupted with increased osteoclast activation and decreased osteoblast differentiation. In this study, we examined the effect of adenosine on osteoblast and osteoclast differentiation derived from multiple myeloma (MM) patients.

Methods: Human bone marrow was collected from multiple myeloma patients. Bone marrow stromal cells (BMSCs) and bone marrow derived mononuclear (BMMs) cells were isolated and osteoblasts and osteoclasts were cultured, respectively. Adenosine A1 receptor agonist CHA and antagonist Rolofylline, A_{2a} receptor agonist CGS and antagonist ZM, and A_{2b} receptor agonist BAY and antagonist MRS 1754, A_3 receptor agonist IB-MECA and antagonist MRS 1191; and dipyridamole, a nucleoside transport inhibitor, were added to the culture media. Alkaline phosphatase (ALP) activity assay was used to quantitate the osteoblast differentiation. In vitro osteoblast calcification was determined by alizarin red staining. TRAP+ staining was used to examine the osteoclast differentiation and bone resorption assay was used to study the osteoclast activity.

Results: We found that $A1_R$ blockade by rolofylline and $A_{2a}R$ ligation by CGS21680 inhibited differentiation of both normal and MM BMMs into TRAP+ multinucleated cells ($IC_{50}=$ 1nM for A1R, $IC_{50}=$ 10μM for A2aR; p<0.001, n=3 for both). The A_{2A} receptor antagonist completely reversed the effects of CGS21680 on osteoclast differentiation. Moreover, enhanced adenosine accumulation in the presence of dipyridamole ($0.5\mu M$) and $A_{2b}R$ activation promoted the differentiation of BMSCs into osteoblasts shown by Arlizarin red staining and ALP activity assay (by 1.8 ± 0.41 and 1.57 ± 0.26 fold, respectively, p<0.05, compared with osteogenic media only, n=3 for both).

Conclusion: These results indicate that adenosine receptors may be useful targets for the treatment and prevention of MM-induced bone disease.

1966

Cost-Effectiveness of Bazedoxifene Compared with Raloxifene in the Treatment of Postmenopausal Osteoporotic Women. Mickaël Hiligsmann, Wafa Ben Sedrine and J.-Y. Reginster. University of Liege, Liege, Belgium

Background/Purpose: Bazedoxifene is a novel selective estrogen receptor modulator (SERM) in development for the prevention and treatment of osteoporosis. In addition to the therapeutic value of a new agent, evaluation of the cost-effectiveness compared with relevant alternative treatment(s) is an important consideration to facilitate health-care decision making. This study evaluated the cost-effectiveness of bazedoxifene compared with raloxifene for the treatment of postmenopausal women with osteoporosis.

Methods: The cost-effectiveness of treatment for 3-years with bazedoxifene was compared with raloxifene using an updated version of a previously validated Markov microsimulation model. Analyses were conducted from a healthcare payer perspective and, the base-case population was women (aged 70 years) with bone mineral density T-score ≤ -2.5. The effects of bazedoxifene and raloxifene on fracture risk were derived from the 3-year results of a randomized, double-blind, placebo- and active-controlled study, including postmenopausal women with osteoporosis.

Results: The cost-effectiveness analysis based on efficacy data from the overall clinical trial indicated that bazedoxifene and raloxifene were equally cost-effective. When the results were examined based on the subgroup analysis of women at higher risk of fractures, bazedoxifene was dominant (lower cost for higher effectiveness) compared with raloxifene in most of the simulations. Sensitivity analyses confirmed the robustness of the results, which were largely independent of starting age of treatment, fracture risk, cost and disutility. In addition, when the cost of raloxifene was reduced by half, bazedoxifene remained cost-effective, at a threshold of €35,000 per quality-adjusted life-years gained, in 85% of the simulations.

Conclusion: Under the assumption of improved anti-fracture efficacy of bazedoxifene over raloxifene in women with high risk of fractures, this study suggests that bazedoxifene can be considered cost-effective, and even dominant, when compared with raloxifene in the treatment of postmenopausal osteoporotic women.

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1967

Hypophosphatemic Osteomalacia Induced by Tenofovir in Patients with Human Immunodeficiency Virus Infection. Beatriz Tejera[1], Lourdes Mateo-Soria[1], Susana Holgado[1], Luisa Mariñoso[2], Ricard Pérez[1], Anna Bonjoch[1], Melania Martínez-Morillo[1], Dolors Grados[1] and Alejandro Olivé[1]. [1]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [2]Hospital del Mar, Barcelona, Spain

Background/Purpose: treatment of human immunodeficiency virus (HIV) infection has dramatically changed survival prognosis of these patients.New drugs included in antiretroviral therapy are much more effective. Tenofovir disoproxil fumarate (TDF) was approved for the treatment of HIV infection in highly active antiretroviral therapy (HAART) combinations in 2001. Increasing evidence has emerged relating TDF use and the development of kidney proximal tubular dysfunction, Fanconi syndrome and renal insufficiency.

Objective: to describe 4 cases of Tenofovir induced hypophosphatemic osteomalacia.

Methods: we describe 4 cases of tenofovir-treated HIV patients from HIV Section setting University Academic Hospital reference area 800.000 inhabitants, who were refered to Rheumatology Service. All patients were having by multilple disabling bone pain. We present clinical manifestations, laboratory and imaging studies, and the results of iliac bone biopsy performed in 3 cases, after labeling with tetracycline.

Results: Four patients, 2 men and 2 women, mean age of 48,2 years, mean duration of HIV infection of 20.2 years. All patients were on Tenofovir in combination therapy with a median duration of 7 years. All patients complained of severe and increasing pain of the lower extremities with considerable functional impairment and inability to walk without assistance during the last 8–24 months (mean symptom duration 14 months) The general characteristics are shown on the Table. In all cases a marked hypophosphatemia with elevated alkaline phosphatase (ALP) and deficiency of vitamin D 25-OH were in 3 patients. Bone scan and MRI showed multiple insufficiency fractures. Histopathological study of iliac bone biopsy (patients 1, 2 and 3) showed increased bone formation and an increased osteoid thickness (more than 5 slides) with laminar structure. There were few osteoblasts, and resorption was diminished with no presence of osteoclasts. The diagnosis was osteomalacia in all patients. The clinical diagnosis was hipophosphatemic osteomalacia induced by tenofovir. In all patients, tenofovir was stopped. This was supplemented with oral vitamin D and calcium supplements. Two patients required oral phosphate salts. A few weeks after starting treatment showed gradual resolution of bone pain (6–8 weeks) and normalization of walking without support. Furthermore, 8–12 weeks later, blood test were strictly normal in all patients.

	Gender	Age	HIV diagnosis (years)	Duration of symptoms (months)	Bone pain	Fractures	Duration of treatment tenofovir (years)	Calcium (mg/Dl) (mmol/L) (N 8.8–10.6) (N 2.2–2.65)	Phosph (mg/dl) (mmol/L) (N 2.5–4.5) (N 0.81–1.45)	FA U/L	25-OH-Vit D (ng/ml)	PTH (pg/ml)
Case 1	M	64	24	8	Hips, ankles	Distal femur, metatarsal	6	10	1.28	355	16.5	39.6
								2.51	0.41			
Case 2	W	46	19	12	Hips, ankles, rib cage	Bilateral femoral neck, rib, sacral	5	8.8	1.83	170	5.9	54
								2.2	0.59			
Case 3	W	41	20	24	Hips, ankles, knee, rib cage	Rib, subtrochanteric, distal tibial epiphysis bilateral, calcaneus	10	8.6	1.36	158	20	28
								2.15	0.44			
Case 4	M	42	18	12	Hips, thoracic-lumbar spine	Subcapital femur, thoracic and lumbar spine	7	8.7	0.99	295	46	15

Conclusion: We described an uncommon complication of HIV patients treated with tenofovir. A high index of suspicion is required to diagnose hipophosphatemic osteomalacia. Serum P and ALP should be monitored to prevent the development of osteomalacia.

Disclosure: B. Tejera, None; **L. Mateo-Soria**, None; **S. Holgado**, None; **L. Mariñoso**, None; **R. Pérez**, None; **A. Bonjoch**, None; **M. Martínez-Morillo**, None; **D. Grados**, None; **A. Olivé**, None.

1968

The Specific Role of Vesicle-Associated Membrane Protein-Associated Protein B/C(VapB) As a Regulator of Osteoclastogenesis Via Modulation of Phospholipase Cã(PLCã2-Ca2+-NFAT Signaling. Chang-Hoon Lee[1], Wan-Hee Yoo[2], Jin-Jung Choi[3], Myong-Joo Hong[2], Ji-Min Kim[4] and Sik-Won Choi[5]. [1]Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [3]CHA University Hospital, Seongnam, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, South Korea, [5]School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea

Background/Purpose: Recently, Vesicle-Associated Membrane Protein-Associated Protein B/C(VapB) has been shown to regulate calcium homeostasis in myotrophic lateral sclerosis. Calcium signalingis also important in metabolic bone diseases, but the role of VapB in the generation of osteoclasts for bone resorption during osteoclastogenesis is not known. Therefore, we investigated the role of VapB in RANKL-induced osteoclast differentiation

Methods: Osteoclast formation was evaluated in bone marrow cells (BMC) in specific condition with over-expression of VapB or down-regulation of VapB during receptor activator of NF-κB ligand (RANKL)-mediated osteoclastogenesis. The expression of c-fos and NFATc1 mRNA in osteoclast precursor were assessed by RT-PCR. The levels of c-fos and NFATc1 protein were assessed by western blot. Also the mitogen-activated protein (MAPK)s pathways were measured using Western blot analysis.

Results: We found that VapB is induced during osteoclastogenesis, and regulates osteoclast differentiation by modulating NFATc1. The results suggest that VapB regulates osteoclastogenesis via of Phospholipase Cγ (PLCγ)2-Ca2+-NFAT signaling. The involvement of PLCγ2-Ca2+-NFAT signaling in VapB-regulated osteoclastogenesis was confirmed by a pharmacological study.

Conclusion: Taken together, these results indicate that VapB positively regulates RANKL-mediated osteoclastogenesis via PLCγ2-Ca2+-NFAT signaling and may provide a basis for exploring the therapeutic potential of VapB silencing for metabolic bone diseases, such as osteoporosis and rheumatoid arthritis

Disclosure: C. H. Lee, None; **W. H. Yoo**, None; **J. J. Choi**, None; **M. J. Hong**, None; **J. M. Kim**, None; **S. W. Choi**, None.

1969

Correction of Vitamin D Insufficiency with the Fixed Daily Combination Strontium Ranelate 2 g/Vitamin D$_3$ 1000 IU Over 12 Months. René Rizzoli[1], Bess Dawson-Hughes[2], Jean-Marc Kaufman[3], Patrice Fardellone[4], Maria Luisa Brandi[5], Bruno Vellas[6], Julien Collette[7] and Jean-Yves Reginster[8]. [1]Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland, [2]Bone Metabolism Laboratory, Tufts University, Boston, MA, [3]University Hospital of Ghent, Ghent, Belgium, [4]Hôpital Nord, C.H.U. d'Amiens, Amiens, France, [5]University of Florence, Firenze, Italy, [6]CHU La Grave, Toulouse, France, [7]Labo RIA, CHU Sart Tilman, Liege, Belgium, [8]University of Liege, Liege, Belgium

Background/Purpose: To assess the efficacy and safety over 1 year of a daily oral administration of the fixed combination of strontium ranelate (SrRan) 2 g/vitamin D$_3$ (vitD$_3$) 1000 IU on the correction of vitamin D insufficiency in the treatment of osteoporotic men and postmenopausal women.

Methods: Prospective, international study, with a 6-month double blind SrRan/vitD$_3$ vs SrRan parallel group period (ratio 4:1), followed by a 6-month open-SrRan/vitD$_3$ extension period in a subgroup of patients. All patients were supplemented with calcium 1 g/d during the whole study. Men and postmenopausal women included were osteoporotic (BMD T-score ≤ −2.5 SD). 80% of the patients had to present insufficient levels of 25-hydroxyvitamin D (25-OHD), i.e.]22.5–50 nmol/L[, and 20% ≥50 nmol/L. 25-OHD level was assessed at 3 months (primary endpoint) and 6 months among assessable patients according to intent-to-treat principle, and in the group of patients treated 12 months with SrRan/vitD$_3$. Other criteria were: BMD, falls, PTH, 1,25-(OH)$_2$D and safety.

Results: 518 patients were randomized: 413 to SrRan/vitD$_3$, 105 to SrRan. Of these, 257 patients continued at M6 in the 5 countries selected into the extension period M6-M12: 53 patients switched from SrRan to SrRan/vitD$_3$ while 204 remained on SrRan/vitD$_3$. 242 patients completed the study at M12. Baseline characteristics were similar between groups. At inclusion, mean age (±SD) was 66.8 ± 8.3 years, mean L1-L4 T-score BMD was −2.85 ± 0.86 and mean 25-OHD was 44.1 ± 14.6 nmol/L.

The proportion of patients with 25-OHD ≥ 50 nmol/L at END (i.e. last post-baseline value over M0-M3) was significantly higher in SrRan/vitD$_3$ group than in SrRan group: 83.8% vs 44.2% (p<0.001). Adjusted odds ratio was 6.7 (95% CI [4.2; 10.9]). Mean 25-OHD reached 65.1 vs 49.5 nmol/L at M3, and 66.9 vs 45.4 nmol/L at M6, in SrRan/vit D$_3$and SrRan groups respectively.

The correction of vitamin D insufficiency was maintained over 12 months of SrRan/vitD$_3$treatment (N = 198) with an increase in the proportion of patients with 25-OHD ≥ 50 nmol/L from 21.2% at baseline to 81.1% at M12. The mean concentration of 25-OHD increased from baseline (44.3 ± 13.8 nmol/L) to M3 (64.3 ± 14.6 nmol/L), then remained stable until M12 (60.8 ± 13.9 nmol/L).

BMD significantly increased at all assessed sites in patients treated with SrRan/vitD$_3$during one year (+5% at L1-L4, +4% at femoral neck and +3% at total hip), consistent with annual BMD changes reported with SrRan in previous studies.

There was a trend to fewer patients falling with SrRan/vitD$_3$ (16.5%) as compared to SrRan (20.2%) at M6. PTH evolution over time was inversely correlated with 25-OHD. Increase in mean 1,25-(OH)$_2$D was higher in SrRan/vitD$_3$ than in SrRan group. Safety of SrRan/vitD$_3$was good, comparable to that of SrRan over M0-M6 and in accordance to that expected with SrRan over M6-M12.

Conclusion: The study demonstrates the efficacy and safety of the fixed combination of SrRan 2 g and vitD$_3$ 1000 IU on the correction of vitamin D insufficiency in osteoporotic men and postmenopausal women aged ≥50 years. The efficacy observed after 3 months was maintained after 6 and 12 months of treatment.

1970

Utility of Spine Bone Mineral Density in Fracture Prediction within the Fracture Risk Assessment Tool (FRAX). Tristan Blackburn[1], Diantha Howard[2] and Edward S. Leib[1]. [1]Fletcher Allen Health Care, University of Vermont College of Medicine, Burlington, VT, [2]Vermont Center for Clinical and Translational Science, Burlington, VT

Background/Purpose: Predicting which individuals are at risk to experience a fracture and modify that risk is important in preventative health. The WHO's Fracture Risk Assesment (FRAX) defines osteopenia and osteoporosis in terms of the femoral neck T-score and allows use of total proximal femur, but the lumbar spine site is frequently used in clinical practice and its use in diagnosis is supported by the International Society of Clinical Densitometry and the National Osteoporosis Foundation. Our study aim is to quantify the impact of spine bone mineral density (BMD) on fracture risk prediction and determine the positive predictive value of fracture prediction by using the lowest BMD value at the femoral neck, total hip, or lumbar spine and compare this to the femoral neck alone.

Methods: We performed a retrospective cross-sectional analysis of our database of 15,033 post-menopausal women combining clinical risk factors (CRF) and bone density (BMD) results collected over 9.2 years utilizing a GElunar densitometer. We validated our database by showing that age, low BMD and CRFs in our population correlate with presence of fracture. We performed a logistic regression to assess the contribution of age, BMI, number of CRFs, T-score, and WHO osteoporosis classification category to the presence of fracture. T-scores were differentiated as femoral neck, total hip, and lumbar spine.

Results: The percent of subjects with fracture was lower than that reported in other studies. In individuals with normal BMD at the femoral neck, there were few who were osteoporotic at the lumbar spine (0.7%) and more who were osteopenic at the femoral neck and osteoporotic at the lumbar spine (9.7%). In patients whose T-scores are 1 or 2 osteoporosis categories lower at the lumbar spine than femoral neck, there is an approximately 30% increased risk of fracture when compared with the femoral neck alone. For patients less than 60 years old, the odds ratio of having a fracture based on presence of lumbar spine osteoporosis was greater than the odds ratio based on femoral neck osteoporosis. This reversed for those ≥ 65 compared with those <65 years old. For each age category, the presence of osteoporosis measured at the total hip correlated best with presence of hip fracture and was better than taking the lowest T-score at any of the three sites (femoral neck, total hip, or lumbar spine).

Conclusion: It is most important to measure BMD at the lumbar spine in younger, post-menopausal women for fracture prediction. In our population total hip BMD is the best predictor of fracture. The spine BMD appears to be a better predictor of fracture than femoral neck in women 60 years and younger. When using the WHO Fracture Prediction Tool (FRAX), we recommend that the 10 year fracture prediction be adjusted when the lumbar spine T-score is 1–2 osteoporosis categories lower than the femoral neck T-score.

1971

Resolution of Effects On Bone Turnover Markers and Bone Mineral Density After Discontinuation of Long-Term Bisphosphonate Use. Kenneth G. Saag[1], Claude-Laurent Benhamou[2], Tobias De Villiers[3], C. Conrad Johnston Jr.[4], Bente Langdahl[5], Andrew Denker[6], Annpey Pong[6], John P. McGinnis[6], Elizabeth Rosenberg[6] and Arthur Santora[6]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]EA 4708 University Orleans, Orleans, France, [3]Mediclinic Panorama, Cape Town, South Africa, [4]Indiana University School of Medicine, Indianapolis, IN, [5]Aarhus University Hospital, Aarhus, Denmark, [6]Merck Sharp & Dohme Corp., Whitehouse Station, NJ

Background/Purpose: While bisphosphonates (BP) have been well studied in long-term trials of up to 4 years' duration, relatively less is known about the immediate consequences of continuing vs. interrupting long-term treatment. This report describes changes in bone turnover and BMD in a 1-year trial of the calcium-sensing receptor antagonist MK-5442 in postmenopausal women who, after taking BP for ≥3 years, were randomized to continued alendronate (ALN) 70 mg weekly, switch to placebo (PBO), or switch to MK-5442. Primary results for MK-5442 are presented separately.

Methods: 526 postmenopausal women who had taken ALN for ≥12 months preceding the trial and an oral BP for ≥3 of the 4 years before the trial, with spine or hip BMD T-scores ≤−2.5 (or '−1.5 with ≥1 prior

fragility fracture) and ≥ -4.0, were recruited into a dose-finding study of MK-5442. Statistical tests of within-group changes and comparison between the PBO and ALN groups were performed post-hoc.

Results: At baseline, women switched from ALN to PBO (n=88) or continued on ALN 70 mg weekly (n=87) were of mean age 67 years and had mean T-scores at lumbar spine of -2.5 and total hip of -1.6, and mean baseline urine NTX/Cr= 26.6 nmolBCE/mmolCr and serum P1NP= 26.0 ng/mL. Median length of previous BP use was 5.2 years. After 1 month, women switched from ALN to PBO experienced increases from baseline in urine NTX/Cr (28.4% vs. continued ALN, p<0.0001), while serum P1NP was unchanged. Both NTX/Cr and P1NP increased by 3 months (33.7% and 37.8%, respectively vs. ALN, both p<0.0001). After 12 months of PBO, least squares mean concentrations of NTX/Cr and P1NP rose to 42.2 nmol BCE/mmolCr and 40.1 ng/mL (both p<0.0001, Table). The markers were unchanged from baseline with continued ALN. After 12 months, the women who continued ALN had an increase in lumbar spine BMD while those switched to PBO experienced no change; total hip BMD did not change in those remaining on ALN but was reduced in women switched to PBO. BMD at both sites was significantly lower in women who switched to PBO vs. those who stayed on ALN (Table).

12 Month Least Squares Mean % Change from Baseline (95% CI)

	uNTX/Cr	sP1NP	Lumbar Spine BMD	Total Hip BMD
Continued Alendronate 70 mg	2.3 (-9.2, 15.3)	-5.5 (-16.7, 7.3)	1.5 (0.3, 2.6)	0.4 (-0.4, 1.3)
Switch to Placebo	66.3 (47.3, 87.7)	69.2 (48.6, 92.6)	-0.2 (-1.3, 0.8)	-1.4 (-2.2, -0.6)
p-value*	<0.0001	<0.0001	0.0137	0.0002

* Continued alendronate 70 mg weekly versus switch to placebo.

Conclusion: Discontinuation of alendronate after a median of 5 years resulted in an increase in NTX/Cr as early as 1 month and P1NP by 3 months. After 1 year, both bone turnover markers returned to levels similar to those expected in untreated postmenopausal women. These increases were accompanied by significantly lower spine and total hip BMD vs. continued treatment with ALN.

Disclosure: K. G. Saag, Amgen, 2, Eli Lilly and Company, 2, Merck Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Amgen, 5, Eli Lilly and Company, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5, Horizon Pharma (formerly Nitec Pharma, 5; **C. L. Benhamou**, Merck Pharmaceuticals, 6; **T. De Villiers**, None; **C. C. Johnston Jr.**, Merck Pharmaceuticals, 9; **B. Langdahl**, Merck Pharmaceuticals, 2, Merck Pharmaceuticals, 8, Merck Pharmaceuticals, 6; **A. Denker**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; **A. Pong**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; **J. P. McGinnis**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; **E. Rosenberg**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; **A. Santora**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3.

1972

Assessment of Fracture Risk in Postmenopausal Women with Rheumatoid Arthritis. Sina Esmaeilzadeh, Nurten Eskiyurt, Ekin Sen and Merih Akpinar. Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Background/Purpose: The aim of this study is to determine the risk of osteoporotic fracture in postmenopausal women with rheumatoid arthritis (RA) and to examine the effect of glucocorticoids (GCs) use on osteoporotic fracture.

Methods: A total of 51 postmenopausal women with RA who referred to the outpatient clinics and met the eligibility criteria were included in this research. The socio-demographic characteristics and risk factors for secondary osteoporosis were assessed at baseline. The ten-year probability of major osteoporotic fracture and hip fracture were estimated with the World Health Organization Fracture Risk Assessment (FRAX®) tool designed for Turkey. Lateral X-rays of the thoracic and lumbar spine were examined with visual semi-quantitative method to detect the presence of osteoporotic fracture. The FRAX® scores were compared between the patients with radiographic fracture and the patients without it, also between the patients who had a history of GCs use and the patients without it. The data were analyzed with nonparametric tests.

Results: The mean age of the patients was 63.9 ± 9.6 (46–87) years and the mean of body mass index was 27.0 ± 3.5 (20.9–35.4) kg/m². Forty-nine percent of the patients had at least one osteoporotic fracture in the thoracic or lumbar spine radiographic assessment according to the visual semi-quantitative method. Secondary causes of osteoporosis were identified in 33% of patients. Sixty-eight percent of the patients had GCs use and 54% had radiographic fracture on X-ray assessment. The 10-year probability of major osteoporotic fracture risk was 16.2% for the patients treated with GCs and 8.1% for those without it, and the risk of major osteoporotic fracture in the patients treated with GCs was significantly higher than the patients without it.

Moreover, the 10-year probability of hip fracture was 7.4% for the patients treated with GCs and 2.5% for those without it, and the risk of hip fracture in the patients treated with GCs was significantly higher than those without it. The 10-year probability of major osteoporotic fracture and hip fracture were 16.2% and 7.9% for the patients with vertebral fracture, as well as 11.2% and 3.9% for those without it, respectively. There was no significant difference between the patients who had radiographic fractures and those without it with regard to FRAX® scores.

Conclusion: These findings suggest that GCs use increased the risk of osteoporotic fracture in postmenopausal women with RA. Although our data do not support the use of FRAX® scores to predict the presence of vertebral osteoporotic fracture in clinical practice, further large-scale research is needed to confirm these results.

Disclosure: S. Esmaeilzadeh, None; **N. Eskiyurt**, None; **E. Sen**, None; **M. Akpinar**, None.

1973

Effect of Adalimumab On the Serum Level of Undercarboxylated Osteocalcin (ucOC), Bone Biochemical Markers and Bone Mineral Density. Yoshitada Sakai[1], Akira Hashiramoto[1], Takaichi Okano[1], Yoshiko Kawasaki[1], Nao Shibanuma[2] and Masahiro Kurosaka[3]. [1]Kobe University Hospital, Kobe, Japan, [2]The Center for Rheumatic Diseases, Kobe University Hospital/Departmant of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan, [3]Kobe University Graduate School of Medicine, Kobe, Japan

Background/Purpose: The osteoporotic fracture in patients with rheumatiod arthritis (RA) is caused by systemic osteoporosis as well as periarticular osteoporosis, On the other hand, the serum level of undercarboxylated octeocalcin (ucOC) has been recognized as being a sensitive marker of vitamin K deficiency in bone. A prospective large cohort study showed that increasing the serum level of ucOC predicted hip fracture risk independently of femoral neck bone mineral density (BMD).

Treatments with Adalimumab, a biologic TNF-alfa inhibitor, reduced the hand bone loss of RA patients (PREMIER study), however, the effect of adalimumab on systemic bone metabolism is still unknown.

In this study, we have evaluated the effect of adalimumab on serum ucOC, bone biochemical markers and bone mineral density in patients with RA.

Methods: 20 patients with RA were enrolled; 6 females, 4 males, average age 54.5 ±19.2 yrs, average stage 2.4 ± 1.3 and average class 2.1 ± 0.3. Serum levels of ucOC, cross-linked N-teropeptide of type1 collagen (NTx), bone alkaline phosphatase (BAP) and osteocalcin (OC) were evaluated at 0, 12, 24, 48 weeks after the administration of adalimumab. BMD were also examined by using dual energy X-ray absorptiometry (DXA) with lumbar spine and femoral neck. Patients' disease activities were evaluated by DAS-28 score and mHAQ. The statistical analysis was performed using one-way repeated measures ANOVA followed by Turkey's post hoc test.

Results: The serum levels of ucOC and OC were increased time-dependently and significantly by the administration of adalimumab.(ucOC: p=0.018; 0w vs. 24w, 0w vs. 48w, 12w vs. 48w, OC: p=0.001; 0w vs. 48w, 12w vs. 48w) The serum levels of NTx was decreased significantly by the administration of adalimumab (p=0.048), whereas the serum levels of BAP (p=0.221) and bone mineral density (L-spine: p=0.334, Femoral neck: p=0.069) did not changed (Table 1). Variability of disease activity, DAS28 and mHAQ scores did not correlate to bone biochemical markers.

Table 1.

	0w	12w	24w	48w	p-value
ucOC(ng/ml)	3.3 ± 2.1	3.7 ± 2.4	4.4 ± 2.3	5.2 ± 2.7	0.018
OC(ng/ml)	5.3 ± 1.6	6.0 ± 2.3	6.1 ± 2.7	7.5 ± 2.5	0.010
NTx(nmol BCE/l)	16.7 ± 5.3	15.9 ± 3.9	15.4 ± 5.5	14.9 ± 3.2	0.038
BAP(U/l)	13.8 ± 7.2	12.9 ± 5.9	14.7 ± 8.4	15.3 ± 6.8	0.221
DXA L-Spine(g/cm3)	1.007 ± 0.306	n/a	0.852 ± 0.313	0.837 ± 0.328	0.334
DXA F-Neck(g/cm3)	0.732 ± 0.097	n/a	0.726 ± 0.117	0.724 ± 0.109	0.069

Conclusion: Treatments with adalimumab increased the serum levels of OC, decreased NTx and thus arrested the systemic bone loss at 48 week. The increased serum ucOC is caused by the increase of the Vitamin K demand in the bone, presumably due to up-regulation of OC production. Therefore, during treatments with adalimumab, the vitamin K supplementation is required especially in cases with increased serum ucOC.

Disclosure: Y. Sakai, None; **A. Hashiramoto**, None; **T. Okano**, None; **Y. Kawasaki**, None; **N. Shibanuma**, None; **M. Kurosaka**, None.

1974

Incidence of Atypical Femur Fractures Associated with Bisphosphonate Use for Osteoporosis: A Systematic Review of the Literature. John N. Mecchella[1], John A. Batsis[1], Robin J. Larson[2] and Gautham Suresh[1]. [1]Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH

Background/Purpose: Reports of a link between bisphosphonate use in patients with osteoporosis and atypical femoral fractures--those occurring in subtrochanteric or diaphyseal locations--have generated significant concern among patients and providers. Attempts to estimate the degree of increased risk have varied widely with OR's ranging from 1 to 46. In addition, clinicians and patients may be overestimating the absolute risk of atypical fracture when considering these highly effective drugs. To obtain better estimates of these rates and assist clinicians in determining the risk versus benefits, we systematically identified and summarized studies reporting rates of atypical femoral fractures in subjects receiving bisphosphonates for osteoporosis.

Methods: With assistance of a reference librarian, we searched MED-LINE (1948–2012), and the Cochrane Library (2012) for studies that reported incidence of atypical femoral fractures among subjects exposed to bisphosphonates for osteoporosis. We also reviewed reference lists and consulted with experts. We excluded studies evaluating bisphosphonates in malignancy. We used no language restrictions. Two reviewers independently extracted data. Disagreements were resolved through consensus. Fracture rates were summarized according to study characteristics.

Results: Of 257 initial studies identified, 12 met all inclusion criteria and included three randomized controlled trials, six retrospective cohorts, and three population-based case-control studies. Among a total of 205,466 subjects followed over a range of less than 1 to 10 years of bisphosphonate exposure, there were 1440 subtrochanteric or diaphyseal fractures identified by ICD-9 or 10 coding, of which 160 were also confirmed radiographically. The incidence of atypical femoral fractures per 1000 patient-years of treatment with a bisphosphonate for osteoporosis ranged from 0.02 to 1 in studies that required radiographic verification of atypical nature, 0.23 to 3.4 in observational studies or randomized controlled trials, and 1.55 to 3.4 in studies of secondary prevention.

Conclusion: Currently available evidence suggests the incidence of atypical femoral fractures among patients receiving bisphosphonates for osteoporosis is low. In addition, even at the highest reported estimate of 3.4 per 1000 patient-years, the rate is considerably lower than estimates for recurrent osteoporotic fractures, which occur at approximately 100 per 1,000 patients per year. Discussions regarding bisphosphonate therapy should put both benefits and harms in appropriate context so that decisions are driven by evidence, not fear.

Disclosure: **J. N. Mecchella**, None; **J. A. Batsis**, None; **R. J. Larson**, None; **G. Suresh**, None.

1975

Mortality After Fragility Hip Fracture in Middle Aged and Elderly Men and Women in Southern Norway. Andreas P. Diamantopoulos[1], Mari Hoff[2], Marc C. Hochberg[3] and Glenn Haugeberg[1]. [1]Hospital of Southern Norway HF, Kristiansand, Norway, [2]and St Olavs Hospital, Trondheim, Norway, [3]University of Maryland, Baltimore, MD

Background/Purpose: The mortality of the fragility hip fracture patients has been reported to be higher compared to the general population for both men and women, and higher in men than in women. The highest incidence of fragility hip fracture has been reported from Norway. Our aim was to study mortality rates in patients with fragility hip fracture in Southern Norway after 1 and 5 years and compare them with the general background population.

Methods: The hip fracture patients were identified in the two most southern counties in Norway, Vest-Agder and Aust-Agder County. Six percent of the Norwegian population (4.9 million) lives in this geographic area. Individuals over 50 years resident in the two counties who had a fragility hip fracture between 1 January 2004 and 31 December 2005 were included. The hospital electronic diagnosis registers were used to identify all hip fracture patients in the two year period coded as S72.0–2 according to the International Classification of Diseases 10th Revision (ICD-10). Data on age, gender, date of hip fracture and death date up to five years after the fracture date were collected in all patients. The follow-up time for one person was from the month the fracture occurred to death or the censoring date in January 1, 2009 and 2010. For each fracture patient 3 age and gender matched controls from the same geographic area was randomly selected from Norway's national register. Standardized mortality ratio (SMR) was calculated comparing with mortality rates in the Norwegian population using the SPSS version 17.0 (SPSS, Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results: In the two year period, the final number of fragility hip fractures in the geographic area was 951 (271 men and 680 women). Mean age for all included patients was 81.2 years (men 80.0 years and women 81.8 years). The SMR for men and women compared to the Norwegian population for the 1st year was 2.78 (95% CI 2.24–3.31) and 2.08 (95% CI 1.77–2.38) and after 5 years 3.10 (95% CI 2.21–3.98) and 1.82 (95% CI 1.41–2.22) respectively. The overall mortality rates for patients with a fragility hip fracture older than 80 years at the end of 1st year were 29.4% (44.6% for men and 24.0% for women, $p < 0.005$) and at the end of 5th year 69.2% (85.4% for men and 63.5% for women, $p < 0.005$). The mortality rates in patients with a fragility hip fracture after one year were higher in men than in women (men 32.1% and women 19.0%, $p < 0.005$). The corresponding figures for the controls were 6.5% for men and 5.0% for women ($p < 0.1$). After 5 years the mortality rate was 69.9% for men and 54.3% for women ($p < 0.005$) with a fragility hip fracture and for the controls 24.0 % for men and 21.5 % for women ($p < 0.1$).

Conclusion: Mortality rates in patients with a fragility hip fracture are elevated compared to matched controls and the background population at the first year and continues to be elevated after 5 years, especially in men. Future research should focus on identifying risk factors for this increased mortality in hip fracture patients.

Disclosure: **A. P. Diamantopoulos**, None; **M. Hoff**, None; **M. C. Hochberg**, None; **G. Haugeberg**, None.

1976

Treatment Satisfaction in Postmenopausal Women Previously Treated with Bisphosphonates Who Transitioned to Denosumab Vs Ibandronate Therapy in an Open-Label Study. Santiago Palacios[1], Giovanni Iolascon[2], Irene Agodoa[3], Hema Viswanathan[3], Prayashi Ghelani[4], Irene Ferreira[5], Cynthia O'Malley[3], Rachel B. Wagman[6] and Sydney Bonnick[7]. [1]Instituto Palacios, Madrid, Spain, [2]Seconda Universita di Napoli, Naples, Italy, [3]Amgen Inc, Thousand Oaks, CA, [4]Ovatech Solutions, London, United Kingdom, [5]Amgen Inc., Cambridge, United Kingdom, [6]Amgen Inc., Thousand Oaks, CA, [7]Clinical Research Center of North Texas, Denton, TX

Background/Purpose: Higher treatment satisfaction is associated with greater persistence with osteoporosis therapy in postmenopausal women (Barrett-Connor *OI* 2012). Greater satisfaction has been reported with subcutaneous injections of denosumab compared with oral alendronate tablets in a randomized, cross-over study where subjects received both treatments (Freemantle *OI* 2012). In this open-label trial, we evaluated treatment satisfaction in postmenopausal women with low bone mineral density (BMD) who were sub-optimally treated with prior bisphosphonate therapy and were transitioned to denosumab or ibandronate.

Methods: This was a multicenter, randomized, open-label, parallel-group study in which postmenopausal women aged 55 and older were randomized 1:1 to receive open-label denosumab 60 mg subcutaneously every 6 months or ibandronate 150 mg orally every month for 12 months. The treatment satisfaction questionnaire for medication (TSQM) version 1.4 was given at baseline and months 6 and 12 or at time of early termination. TSQM is a validated tool that measures the subject's perception of the 4 domains of treatment satisfaction: the medication's effectiveness, convenience, side effects, and global satisfaction (Atkinson *Health Qual Life Outcomes* 2004). Each TSQM domain score is between 0 and 100 and a higher score indicates a more preferred health status. Treatment comparisons of change in TSQM from baseline to months 6 and 12 were analyzed using an ANCOVA model fitted with treatment group and adjusted for baseline TSQM domain score.

Results: The study population included 833 women (417 denosumab; 416 ibandronate) with a mean (SD) age of 66.7 (8.0) years and mean (SD) BMD T-scores of –1.8 (0.7) at the total hip, 2.1 (0.7) at the femoral neck, and –2.5 (0.8) at the lumbar spine. Compared with the TSQM scores at baseline, subjects in both treatment groups reported greater satisfaction in all domains of the TSQM at month 6 and at month 12. However, subjects who transitioned to denosumab therapy had significantly greater improvements among all domains than did subjects who transitioned to ibandronate therapy at month 6 ($P \leq 0.0004$ in all domains; data not shown) and at month 12 ($P \leq 0.0003$ in all domains; Table 1).

Table 1. TSQM Change From Baseline to Month 12

TSQM Domain	Treatment	n	LS Mean	95% CI	P-value*
Effectiveness	Ibandronate	332	17.9	15.6, 20.2	<0.0001
	Denosumab	378	24.1	22.0, 26.3	
Convenience	Ibandronate	338	16.7	14.9, 18.6	<0.0001
	Denosumab	384	26.3	24.6, 28.0	
Side Effects	Ibandronate	337	4.2	2.7, 5.8	0.0003
	Denosumab	385	8.1	6.7, 9.6	
Global Satisfaction	Ibandronate	337	14.9	12.8, 17.1	<0.0001
	Denosumab	382	26.4	24.4, 28.4	

n = number of subjects with non-missing TSQM domain at baseline and at month 12. LS = least squares. CI = confidence interval. *P-value from treatment comparison based on an ANCOVA model fitted with treatment group and adjusted for baseline TSQM domain score.

Conclusion: In summary, postmenopausal women with low BMD who were sub-optimally treated with prior bisphosphonate therapy reported greater satisfaction if they transitioned to denosumab vs ibandronate in an open-label study. Greater treatment satisfaction may lead to better adherence to therapy and thus improvements in treatment efficacy.

Disclosure: S. Palacios, Amgen Inc., 2; **G. Iolascon**, Merck Italia, 8; **I. Agodoa**, Amgen, 1, Amgen, 3; **H. Viswanathan**, Amgen Inc., 1, Amgen Inc., 3; **P. Ghelani**, Amgen Inc., 3; **I. Ferreira**, Amgen Inc., Bristol Myers-Squibb, Novartis, 1, Amgen Inc., 3; **C. O'Malley**, Amgen Inc., 1, Amgen Inc., 3; **R. B. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **S. Bonnick**, Amgen Inc., Takeda, Merck, Wyeth, 2, Amgen Inc., Novartis, 8.

1977

Relationship Between Baseline Bone Turnover Marker Levels and Bone Mineral Density Changes in Men with Low Bone Mineral Density Receiving Denosumab or Placebo. Eric Orwoll[1], Ugis Gruntmanis[2], Steven Boonen[3], Yu-Ching Yang[4], Rachel B. Wagman[4], Jesse W. Hall[4] and Paul D. Miller[5]. [1]Oregon Health and Science University, Portland, OR, [2]Dallas Veterans Affairs Medical Center and University of Texas Southwestern Medical Center, Dallas, TX, [3]Leuven University, Leuven, Belgium, [4]Amgen Inc., Thousand Oaks, CA, [5]Colorado Center for Bone Research, Lakewood, CO

Background/Purpose: Denosumab, a fully human monoclonal antibody to RANKL, has been shown to increase bone mineral density (BMD) in postmenopausal women with high or low bone turnover,[1] and reduce the risk for new vertebral, non-vertebral, and hip fractures.[2] ADAMO evaluated denosumab in men with low BMD and demonstrated increases in BMD at all measured skeletal sites and reductions in serum CTX (sCTX).[3] We assessed the efficacy of denosumab to increase BMD in men across a range of baseline bone turnover levels in ADAMO.

Methods: ADAMO was a multicenter, randomized, double-blind, placebo-controlled study. Subjects were randomized 1:1 to receive either 60 mg denosumab or placebo administered subcutaneously once every 6 months over a 12-month period. Subjects were included if they were aged 30 to 85 years; had a BMD T-score ≤ -2.0 and ≥ -3.5 at the lumbar spine or femoral neck, or had a prior major osteoporotic fracture and a T-score ≤ -1.0 and ≥ -3.5 at the lumbar spine or femoral neck. Subjects received ≥ 1000 mg calcium and ≥ 800 IU vitamin D supplementation daily. Percentage change in sCTX was assessed at day 15. Percentage change in BMD from baseline to month 12 at the lumbar spine, total hip, femoral neck, trochanter, and 1/3 radius was assessed according to baseline tertile of sCTX.

Results: A total of 242 subjects (121, placebo; 121, denosumab) were enrolled. As previously reported, 12 months of denosumab treatment significantly increased BMD from baseline at the lumbar spine, total hip, femoral neck, trochanter, and 1/3 radius compared with placebo (all $p < 0.02$, adjusted for multiplicity). Denosumab reduced sCTX by 81% from baseline vs 7% for placebo at day 15. For each tertile of baseline sCTX, subjects treated with denosumab, compared with placebo, demonstrated greater gains in lumbar spine and total hip BMD at month 12 (Figure). Subjects in the highest tertile of baseline sCTX had the numerically greatest gains in BMD when compared with subjects in the lowest tertile, although differences were not statistically significant. Associations between baseline sCTX and 12-month BMD improvements were weaker at the femoral neck and 1/3 radius, sites with greater variability in BMD measurements.[4]
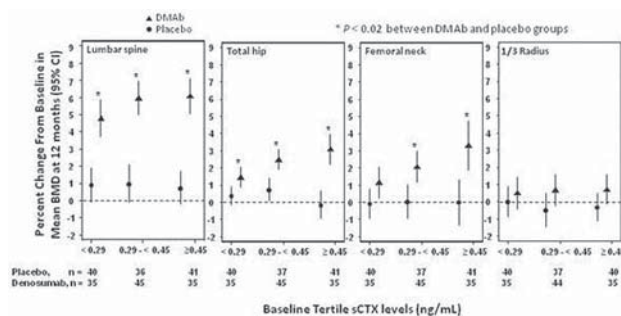
Figure 1. Percent Change From Baseline in Mean BMD at 12 Months by Tertiles of Baseline sCTX

Conclusion: Independent of baseline sCTX, men with low BMD treated for one year with denosumab, compared with placebo, demonstrated greater gains in BMD at key skeletal sites routinely used to diagnose and manage patients with osteoporosis, suggesting that men at all levels of bone turnover may benefit from denosumab therapy.

1. Bone, *JCEM* 2008
2. Cummings, *NEJM* 2009
3. Gruntmanis, *ENDO* 2012
4. Brown, *ASBMR* 2009

Disclosure: E. Orwoll, Amgen, Eli Lilly, Merck, 2, Amgen, Eli Lilly, Merck, Wright Medical Technology, 5; **U. Gruntmanis**, Amgen Inc., 2; **S. Boonen**, Amgen Inc., 2, Amgen Inc., 5; **Y. C. Yang**, Amgen Inc., 1, Amgen Inc., 3; **R. B. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **J. W. Hall**, Amgen Inc, 3, Amgen Inc, 1; **P. D. Miller**, Procter and Gamble, Sanofi Aventis, Roche, Eli Lilly, Merck, Novartis, Amgen, Takeda, Radius, GE, 2, Warner Chilcott, Merck, Eli Lilly, Amgen, Novartis, Roche, GSK, Baxter, Wright, 5, Warner Chilcott, Amgen, Novartis, Roche, 8.

1978

A Web-Based Intervention Aimed to Improve Bone Health Among Individuals On Chronic Glucocorticoids. Amy H. Warriner[1], Ryan C. Outman[1], Nathan Markward[2], Ronald Aubert[2], Jeffrey R. Curtis[3], Robert Epstein[2], Felix Freuh[2], Julia McEachern[2], David T. Redden[1], Monika M. Safford[1], Eric Stanek[2], Amy Steinkellner[2] and Kenneth G. Saag[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Medco, Bethesda, MD, [3]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Despite a significant associated fracture risk, previous population-based studies document low osteoporosis treatment rates for individuals treated with chronic glucocorticoids (GCs) at risk for glucocorticoid-induced osteoporosis (GIOP). We evaluated the influence of a direct-to-patient web-based educational video on the rates of anti-osteoporosis prescription medication use among chronic GC users who filled GCs online.

Methods: Using integrated medical and pharmacy data, we identified members of a pharmacy benefits management company who were prescribed ≥ 5 milligrams of prednisone (or an equivalent) for ≥ 90 days, but not prescribed GIOP therapies in the prior year. We developed an online video of osteoporosis risk-factors, treatment options, and real-life patient stories. Through an interrupted time series design, the video was automatically shown for 45 days to GC users following completion of an online GC refill. During the subsequent 45-day period, the video was inactivated. Those refilling GCs during the initial 45-days were the exposure group ("Video On") and those refilling GCs during the second 45-day period were the comparison group ("Video Off"). For 3 months following the completion of two Video On/Video Off cycles, the incidence of GIOP prescription use was assessed. Multivariable logistic regression was used to examine the influence of the video on GIOP prescription rates.

Results: Of the 4,659 patients that refilled their GC during the study, 3017 had the potential to view the intervention video. Among these, 59% had measurable video viewing time and 3% self-initiated the video. Most patients were between the ages of 50–70 (53.6%) and were male (56.8%). Commonly associated medical conditions in these patients included gastrointestinal illness (37.6%), history of organ transplant (29.9%), rheumatoid arthritis (17.5%), anxiety or depression (10.7%), and gout (9.2%).

During the 3-month follow-up, the overall GIOP prescription rate in the exposure group was 2.9% compared to 2.7% for the control group. GIOP prescription rates were slightly higher in those patients that self-initiated the video rather than in the automated manner (5.7%, p = 0.1). GIOP prescription rates were higher among older patients (50–70 years old: OR 2.1, 95% CI 1.3 – 3.5 and >70 years old: OR 1.8, 95% CI 1.0–3.2) when compared to those <50 years old and were lower among men (OR 0.2, 95% CI 0.2–0.4) when compared to women.

Conclusion: Among high-risk individuals, GIOP treatment rates were not affected greatly by an online educational video presented at the time of glucocorticoid refill. Women and persons aged 50–70 years old were more likely to be initiated on GIOP medications during the study period. This novel method of approaching patients may be more accepted by certain populations and further tailoring of the intervention could improve effectiveness.

Disclosure: A. H. Warriner, Amylin, 2, NIH, 2, AHRQ, 2; **R. C. Outman**, None; **N. Markward**, Medco, 3, Medco, 1; **R. Aubert**, Medco, 1, Medco, 3; **J. R. Curtis**, Roche/Genetech, UCB, Centocor, CORRONA, Amgen Pfizer, BMS, Crescendo, Abbott, 5, Roche/Genetech, UCB, Centocor, CORRONA, Amgen Pfizer, BMS, Crescendo, Abbott, 2; **R. Epstein**, Medco, 1, Medco, 3; **F. Freuh**, Medco, 1, Medco, 3; **J. McEachern**, Medco, 1, Medco, 3; **D. T. Redden**, None; **M. M. Safford**, None; **E. Stanek**, Medco, 1, Medco, 3; **A. Steinkellner**, Medco, 1, Medco, 3; **K. G. Saag**, Amgen, 2, Eli Lilly and Company, 2, Merck Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Amgen, 5, Eli Lilly and Company, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5.

1979

Care Gap in the Treatment of Patients with High Risk for Fractures in a Single Canadian Academic Center.

Arthur N. Lau[1], Michael Branch[2], Robert Bensen[3], Jonathan D. Adachi[4], Alexandra Papaioannou[1], William Wong-Pack[5] and William G. Bensen[6]. [1]McMaster University, Hamilton, ON, [2]CEO, Inovex, Oakville, ON, [3]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [4]Charlton Medical Centre, Hamilton, ON, [5]Hamilton, ON, [6]St. Joseph's Hospital and McMaster University, Hamilton, ON, Hamilton, ON

Background/Purpose: A number of clinical prediction tools are available to stratify patients into low, moderate and high risk for fractures in future. These tools are valuable in determining which patients should be initiated on an anti-resorptive agent. Bone Destiny is a validated tool which can accurately predict a patient's 10 year fracture risk. Patients are stratified into colours (green, yellow, orange, red and purple) which range from low to high 10 year risk. Patients in the purple and red range are deemed to be at very high and high risk respectively (10 year fracture risk >20%), and should be treated with an anti-resorptive agent. The goal of this study is to assess if a care gap exists in patients deemed at high risk of fractures using the Bone Destiny tool, and also if a similar gap exists in patients with a T-score in the osteoporosis range.

Methods: At a large single academic center in Hamilton, Canada, all patients who received a BMD from May 1, 2011 to April 30, 2012 were assessed using the Bone Destiny assessment tool and assigned a colour according to their fracture risk. All prevalent fragility fractures were recorded. We also assessed for the percentage of patients in each colour group being treated with either Prolia, Actonel, Fosavance, Evista, Aclasta or Forteo.

Results: At our center, 26,213 patients received a DXA scan and a Bone Destiny assessment. 3,643 patients were in the purple group, 4,501 patients were in the red group. Overall, 1805/3643 (49.5%) patients in the purple group and only 1817/4501 (40.4%) patients in the red group were on treatment. The younger patients (age<60 years) in the purple group were less likely to be started on treatment compared to older patients in this group (32.5% in age<60 years, while 46.1% in age 60–69 years, 53.9% in age 70–79 years, and 51.7% in age>80 years). The same trend was seen in the patients in the red group, where 32.9% of patients <60 years were on treatment, 41.4% in age 60–69 years, 44.3% in age 70–79 years, and 41.4% in age>80 years.

When we sorted patients in the database based on BMD T-scores, we found 3,367 patients with a T-score between −2.5 to −3.0. Only 1579/3367 (46.9%) patients were being treated with one of the listed agents. A similar trend was noticed, as younger patients were less likely to be on appropriate therapy. Only 33.8% of patients with age<60 years were on treatment, compared with 46.5% in age 60–69 years, 53.6% in age 70–79 years, and 53.7% in age>80 years.

Conclusion: It is important for clinicians to use a risk assessment tool to predict which patients are at high risk for fractures and start them on appropriate treatment. At our center; only 49.5% of patients in the purple group were on appropriate treatment and only 40.4% of patients in the red group. This is quite alarming, as the 67% (2443/3643) of patients in the purple group, and 33.4% (1502/4501) in the red group have a prevalent fragility fracture. This study suggests that a care gap indeed exists in patients at high risk for fractures, despite having the Bone Destiny tool to identify which patients require treatment. These results suggest more education is required to educate physicians and other healthcare providers about the availability and usefulness of such tools.

Disclosure: A. N. Lau, None; **M. Branch**, None; **R. Bensen**, None; **J. D. Adachi**, Amgen, Eli Lilly, GSK, Merck, Novartis, Procter & Gamble, Roche, Sanofi Aventis, 2, Amgen, Eli Lilly, GSK, Merck, Novartis, Procter & Gamble, Roche, Sanofi Aventis, Warner Chilcott, 5, Amgen, Eli Lilly, GSK, Merck, Novartis, Procter & Gamble, Roche, Sanofi Aventis, Warner Chilcott, 8; **A. Papaioannou**, None; **W. Wong-Pack**, None; **W. G. Bensen**, Abbott, Amgen, AstraZeneca, BMS, Merck-Schering, Janssen, Lilly, Novartis, Pfizer and Wyeth, Proctor and Gamble, Roche, Sanofi-Aventis, Servier, UCB, Warner Chilcott, 2, Abbott, Amgen, Astra-Zeneca, BMS, Merck-Schering, Janssen, Lilly, Novartis, Pfizer and Wyeth, Proctor and Gamble, Roche, Sanofi-Aventis, Servier, UCB, Warner Chilcott, 5, Abbott, Amgen, AstraZeneca, BMS, Merck-Schering, Janssen, Lilly, Novartis, Pfizer and Wyeth, Proctor and Gamble, Roche, Sanofi-Aventis, Servier, UCB, Warner Chilcott, 8.

1980

Intermittent Nitrate Use and Risk of Hip Fracture.

Devyani Misra[1], Christine Peloquin[1], Hyon Choi[1], Tuhina Neogi[2] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA

Background/Purpose: Nitrates are commonly used anti-anginal medications which have also been found to promote bone formation and decreases bone resorption. Intermittent nitrate use has been associated with increased bone mineral density; however, its effect on fracture risk has been conflicting. Because of potential tachyphylaxis with frequent use and challenge of defining regular vs. intermittent use in an observational study, we conducted a cohort study to examine the relation of incident short-acting nitrate use, a proxy for intermittent use, to the risk of hip fracture among older subjects with ischemic heart disease.

Methods: The Health Improvement Network (THIN) is an electronic medical records database containing anonymized clinical and prescription data entered by general practitioners in the UK. We included participants from THIN followed between 1986–2010 who were ≥ 60 years old with ischemic heart disease, without history of hip fracture prior to prescription of short-acting nitrates, no concomitant long-acting nitrate use, and continuously enrolled in the database for ≥12 months. Intermittent nitrate use was defined by incident nitrate use of short-acting formulations only (Glyceryl Trinitrate sublingual/spray/patch or Isosorbide Dinitrates injection/sprays) using Drug Codes, with ≥2 prescriptions in 1 year. Each intermittent nitrate user was matched by age, sex and enrollment year with a non-user (Never nitrate use). Follow-up started 1 year after the first nitrate prescription. Hip fractures were identified using Read Codes. We plotted Kaplan-Meier survival curves to determine cumulative incidence rate for hip fracture by intermittent nitrate use. Hazard ratios (HR) of incident hip fracture related to intermittent nitrate use was also estimated using Cox proportional hazards regression models, adjusting for BMI, recurrent falls, heart failure, smoking, alcoholism, use of beta-blockers, bisphosphonates, diuretics, estrogens and glucocorticoids.

Results: Included were 14 925 intermittent nitrate users (median # prescriptions in 1 year: 3.0) and 14 925 non-users (mean age 73±7.6, 41% women for each cohort). Hip fracture occurred in 267 intermittent nitrate users and 332 non-users, respectively. Cumulative incidence of hip fracture increased rapidly among non-users compared with intermittent nitrate users (Fig 1). Compared with non-users, rate of hip fracture was 30% lower and did not change substantially after adjusting for other potential confounders (adjusted HR=0.69, 95% CI 0.55–0.86, p=0.001).
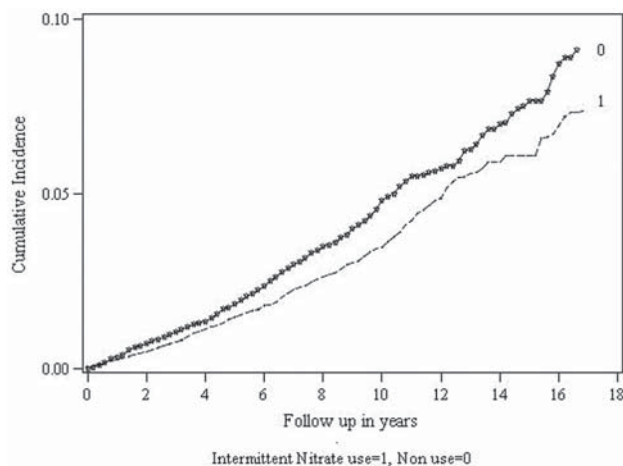
Figure 1. Cumulative incidence of hip fracture by nitrate use.

Conclusion: In this large population-based cohort study, we found that intermittent (short-acting) nitrate use was associated with significant reduction in hip fracture risk among older adults with ischemic heart disease. Future studies are warranted, given the potential for nitrates to be inexpensive and readily available anti-osteoporotic agents.

Disclosure: **D. Misra**, None; **C. Peloquin**, None; **H. Choi**, None; **T. Neogi**, None; **Y. Zhang**, None.

1981

Low Body Mass Index, Medication Use and Social Factors Such As Smoking but Not Secondary Medical Disorders or Older Age May Be More Prevalent in Males with Low Bone Mineral Density. Vandana J. Vedanarayanan, Allison V. Jones and Vikas Majithia. University of Mississippi Medical Center, Jackson, MS

Background/Purpose: Osteoporosis (OP) in Males is prevalent and frequently under-recognized. There are a number of known demographic factors such as age, race and BMI as well as secondary causes of low bone mineral density (BMD) i.e. osteopenia and OP. The effect of these on the prevalence of low BMD has not been well quantified. This study aims to describe the prevalence of the demographic factors and SC in men with low BMD and also assess their impact on the prevalence.

Methods: Retrospective chart review of men who underwent DEXA scan performed at UMC from 2005– 2009 was done. Data regarding BMD, demographics i.e. age, race, height, weight, BMI, secondary medical causes, medications, social factors such as smoking and alcohol use was abstracted, tabulated and analyzed using STATA software. Statistical significance was assessed using T-test and Odds ratio as appropriate.

Results: A total of 237 charts were analyzed. There were 158 whites (W), 79 African-Americans (AA) 66 patients had normal BMD. Low bone density was prevalent and seen in 171 patients (75.9%). Amongst these 61 had T-score < -2.5 (osteoporosis) and 110 had T-score > -2.5 and <-1.0 (osteopenia) BMD. There were no racial differences in prevalence of low BMD and was seen in 77.21 % of AA and 69.62 % of W males tested. The prevalence results are presented in the table with significant differences highlighted.

	NORMAL BONE DENSITY	LOW BONE DENSITY (T-score <−1) includes both osteopenia & Osteoporosis	OSTEOPOROSIS (T-Score <−2.5)	
DEMOGRAPHICS				
AGE (mean)	60.06 years	62.97 years	59.42 years	p-NS
BMI (mean)	31.53	27.28*	26.03*	*p<0.001
SECONDARY MEDICAL DISORDERS (%)				
ANY Disorder	69.69 %	73.09 %	80.32 %	p=0.11
Thyroid Disorders	13.63 %	13.45 %	16.39%	p-NS
Hyperparathyroidism	4.54 %	2.33 %	3.27 %	p-NS
Diabetes	28.78 %	25.14 %	16.39%	p-NS
Asthma/COPD	4.54 %	14.03 %*	18.03 %*	*p<0.05
Rheumatoid Arthritis	10.6 %	12.28 %	16.66 %	p-NS
Other Connective tissue Disorders	7.57 %	11.11 %	13.11 %	p-NS
Malignancy	18.18 %	19.29 %	22.95 %	p-NS
MEDICATIONS				
Any Relevant	42.42 %	60.81 %*	68.85 %*	*p<0.05
Steroids >5 mg	24.24 %	33.91 %	32.78 %	p-NS
SOCIAL FACTORS				
Smoking	15.15 %	32.74 %*	36.06 %*	*p=0.01
Alcohol Use	0	2.92 %	1.63 %	—

In this cohort of patients undergoing DEXA scan, a number of underlying factors are present with low BMD. Amongst these, low BMI, overall medication use, smoking and respiratory disorders were found to be significantly more prevalent than others. No difference was found with older age or race but there was significantly higher prevalence of low BMI with low BMD. Secondary medical disorders were prevalent in the cohort (>70%). But, there was no difference in their prevalence except for asthma/COPD among those with low versus normal BMD. Similarly, medication use was common and was significantly more prevalent with low BMD. Steroid use (>5 mg) was more frequent with low BMD but not statistically significantly. Smoking was significantly more prevalent with low BMD and alcohol use could not be quantified due to small numbers. The results suggest that low BMI, smoking and overall medication use may be better associated with low BMD and potentially better predictors than race, older age and secondary medical disorders. Limitations of this study include its retrospective design and small sample size. Nonetheless these results highlight that the effect of these underlying factors needs to be better quantified in population studies, so that males at risk of OP may be better identified and screened earlier.

Conclusion: Low BMI, asthma/COPD, smoking and overall medication use were found to be more prevalent in the male patients with low BMD as compared to those with normal BMD in patients undergoing bone mass measurement. This may have significant implications on decision to consider screening for OP in males.

Disclosure: **V. J. Vedanarayanan**, None; **A. V. Jones**, None; **V. Majithia**, None.

1982

Five Years of Treatment to Target in Early Active Rheumatoid Arthritis: Prevalence and Predictors of Vertebral Fractures. L. Dirven[1], M. van den Broek[1], A.J. Peeters[2], N. Riyazi[3], P.J.S.M. Kerstens[4], T.W.J. Huizinga[1], C.F. Allaart[1] and W. F. Lems[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Reinier de Graaf Gasthuis, Delft, Netherlands, [3]Haga Hospital, The Hague, Netherlands, [4]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [5]VU University medical center, Amsterdam, Netherlands

Background/Purpose: Vertebral fractures (VFs) are more common in patients with rheumatoid arthritis (RA) compared to the general population. It is suggested that an appropriate control of disease, generally more effectively achieved with disease activity score (DAS)-steered treatment strategies, may prevent the development of vertebral fractures. The prevalence of vertebral fractures after 5 years of DAS-steered treatment in patients with early active RA was determined and the association of VFs with disease activity, functional ability and bone mineral density (BMD) over time was investigated.

Methods: Five-year radiographs of the lateral thoracic and lumbar spine of 275 patients in the BeSt study, a randomized trial comparing four treatment strategies, were available. Treatment adjustments were made every 3 months aiming at a DAS≤2.4. Vertebral fractures were assessed using the Genant method, with a fracture defined as loss of height reduction >20% in one vertebra. BMDs of the spine and hip were measured with dual energy X-ray absorptiometry. With linear mixed models, DAS and Health Assessment Questionnaire (HAQ) scores over 5 years were compared for patients with and without VFs. With GEE the association between BMD and VFs was determined.

Results: At baseline patients were on average 54 years old and most were female (67%), of whom 18% were postmenopausal. Mean DAS was 4.4 and mean HAQ score was 1.3. After 5 years of DAS steered treatment, VFs were observed in 41/275 patients (15%). No difference in prevalence was found when stratified for gender, treatment with prednisone and menopausal status. Disease activity over time was higher in patients with VFs, with a mean difference of 0.20 (95% CI:0.05–0.36). HAQ scores were higher in patients with VFs, independent of disease activity, with a mean difference of 0.12 (95% CI:0.02–0.2). Although values were slightly lower over time in patients with vertebral fractures, mean BMDs in the spine and hip over time were not independently associated with VFs (OR 0.99, 95%CI:0.78–1.25 and 0.94, 95%CI: 0.65–1.36, respectively). Higher age was independently associated with VFs (OR 1.06, 95%CI:1.02–1.09).

Conclusion: After 5 years of DAS-steered treatment, 15% of these RA patients had vertebral fractures (VFs). Higher age was associated with the presence of VFs, but mean BMDs in the hip and spine were not. VFs are associated with more disability, independent of disease activity. Patients with VFs have a slightly higher disease activity over time, suggesting that optimal disease activity suppression may prevent VFs.

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1983

Comparative Risk of Fracture in Men and Women with Human Immunodeficiency Virus. Lydia Gedmintas[1], Elizabeth Wright[2], Jeffrey N. Katz[3], Elena Losina[3] and Daniel H. Solomon[4]. [1]Brigham's Women's Hospital, Boston, MA, [2]Orthopedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Background/Purpose: A growing body of evidence suggests that HIV-positive patients have an increased risk of osteoporosis compared to HIV-negative patients, with some studies suggesting a higher risk of fracture as well. Antiretroviral therapy (ART) is thought to contribute to this increased risk as certain therapies are linked to decreased bone mineral density, but the etiology of the higher risk of osteoporosis in HIV-positive patients is likely multifactorial. Expert recommendations suggest screening for osteoporosis in HIV-positive patients starting at age 50, in both men and women. However there is a insufficient evidence as to whether HIV-infected men have fracture rates similar to HIV-infected women.

Methods: We identified HIV-positive adult patients who had been prescribed ART and were seen at least annually at two large tertiary hospitals. An institutional electronic patient registry was used to identify these patients, as well as to identify the outcome of interest - fracture at any site – indicated by diagnosis code or the patient problem list. We reviewed 50 medical records of patients identified by the patient registry as having fracture in order to assess the positive predictive value (PPV) of the algorithm for identifying fracture in the registry database. We estimated the IR per 1,000 person-years for fractures for the entire cohort as well as the IR for fractures occurring at sites associated with osteoporosis (hip, wrist, vertebrae) and the IR for all other fractures. IR of fracture was then calculated stratified by age and gender. As well, IR ratios between men and women were calculated.

Results: We identified a cohort of 3,182 HIV-positive patients prescribed ART (883 women and 2,299 men) with a total of 15,317 person-years of follow-up. 696 total fractures were found in this population. The PPV of a fracture identified in the electronic patient registry was 90% (95% CI 78–97%) as compared with medical record review. The IR of fractures occurring at osteoporotic sites among men of all ages was 15.9 (95% CI 13.6– 18.4) compared with women which was 12.2 (95% CI 9.1–15.9), giving an incidence rate ratio of 1.3 (95% CI 0.95–1.80) (see Table). Men had similar or higher incidence rates of fractures at osteoporotic sites than women across most age groups until age 66, when women had higher rates, although this difference was not statistically significant. In addition, IR of fracture at all other sites were similar in men (IR 29.4, 95% CI 26.4–32.8) and women (IR 33.6, 95% CI 28.4–39.4), with IR ratio of 0.88 (95% CI 0.72–1.07).

	Men, Number of fractures	Men, IR of fracture/ 1000 person-years [95% CI]	Women, Number of fractures	Women, IR of fracture/ 1000 person-years [95% CI]	Incidence rate ratio (men/women) [95% CI]
All fractures, all age groups					
	497	45.3 [41.4–49.4]	199	45.8 [39.8–52.4]	0.99 [0.84–1.17]
Fractures occurring at osteoporotic sites (hip/femur, wrist/forearm, vertebral/spine)					
All age groups	174	15.9 [13.6–18.4]	53	12.2 [9.1–15.9]	1.30 [0.95–1.80]
Age ≤ 35	16	15.4 [8.8–24.9]	8	9.1 [3.9–17.8]	1.70 [0.69–4.60]
Age 36–45	48	11.8 [8.7–15.6]	12	7.1 [3.7–12.4]	1.66 [0.87–3.43]
Age 46–55	64	16.0 [12.3–20.3]	22	16.4 [10.3–24.7]	0.97 [0.59–1.66]
Age 56–65	35	23.0 [16.1–31.9]	7	20.6 [8.3–42.1]	1.12 [0.49–2.99]
Age ≥66	11	34.0 [17.1–60.0]	4	44.2[14.8–105.0]	0.77 [0.23–3.31]
Fractures occurring at all other sites (all other fracture sites)					
All age groups	323	29.4 [26.4–32.8]	146	33.6 [28.4–39.4]	0.88 [0.72–1.07]
Age ≤ 35	18	17.4 [10.3–27.3]	29	32.9 [22.1–46.9]	0.53 [0.28–0.98]
Age 36–45	100	24.5 [20.0–29.7]	42	24.8 [17.9–33.4]	0.99 [0.68–1.45]
Age 46–55	144	35.9 [30.3–42.1]	58	43.2 [33.0–55.5]	0.83 [0.61–1.15]
Age 56–65	47	30.9 [22.8–40.9]	11	32.4 [16.3–57.3]	0.95 [0.49–2.04]
Age ≥66	14	43.2 [23.6–72.5]	6	66.2 [24.3–144.1]	0.65 [0.24–2.07]

Conclusion: Fractures in HIV-positive patients on ART occur at similar rates in men and women. Recent expert recommendations suggest screening all HIV patients for osteoporosis including men. Our data offer support for this recommendation and can be used to further refine evidence-based recommendations for osteoporosis screening in HIV.

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1984

Orally Administered Parathyroid Hormone Analog Tablets in a Randomized Phase 2 Study Demonstrated Consistent Exposure and Increased Bone Mineral Density. Morten Asser Karsdal[1], Nozer M. Mehta[2], William Stern[2], Amy M. Sturmer[2], Sheela J. Mitta[2], Roxanne Tavakkol[2], Ali Bolat[2], Jenna Giacchi[2], Kim Henriksen[1], Lorraine A. Fitzpatrick[3], Claus Christiansen[4], Jeffrey A. Wald[3], Antonio J. Nino[3], Peter Alexandersen[4], Bente J. Riis[5], Jeppe Andersen[1], Ivo Valter[6], Bettina Nedergaard[4], Christence Teglbjaerg[4], Felicia Cosman[7] and John M. Trang[8]. [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Unigene Laboratories, Inc., Boonton, NJ, [3]GSK, King of Prussia, PA, [4]CCBR, Ballerup, Denmark, [5]Nordic Bioscience, Herlev, Denmark, [6]Ctr for Clinical & Basic Rsrch, Tallinn, Estonia, [7]Helen Hayes Hospital, West Haverstraw, NY, [8]PK/PD International Inc., Tucson, AZ

Background/Purpose: PTH is a potent anabolic agent for bone, but patient acceptance is difficult due to the need for daily injections. A solid dosage enteric-coated formulation has been developed that enables oral peptide delivery by a unique mechanism that includes an organic acid as a protease inhibitor and an acylcarnitine as a permeation enhancer. Based on results from phase 1 studies, we tested a 5 mg tablet dose of a differentiated $PTH(1–31)NH_2$ in a Phase 2 proof-of-concept study.

Methods: The Phase 2 study was a 24-week double blind, randomized, repeat dose parallel group study of $rhPTH(1–31)NH_2$, or placebo tablets, compared to open label Forsteo® [teriparatide, PTH(1–34)OH] in 97 post-menopausal women with osteoporosis. The primary endpoint was to characterize percent change from baseline in BMD by DXA at lumbar spine (LS) after 24 weeks of once daily oral treatment of $PTH(1–31)NH_2$ and the secondary endpoint was to determine the effect on bone markers. Plasma samples were collected to characterize the PK profiles of the tablets and the Forsteo®after the first dose and at the end of treatment. Blood samples were collected prior to and at intervals up to 5.75 hr after tablet administration and up to 2 hr after injection.

Results: The trial met the primary endpoint with an increase of 2.2% in LS BMD with $PTH(1–31)NH_2$ compared to baseline (p=0.004). Placebo LS BMD decreased by −0.17% (p=NS) and LS BMD for teriparatide increased by 5.1% (p<0.001). There were statistically significant increases from baseline in the total hip BMD for $PTH(1–31)NH_2$ and teriparatide, with no significant differences between these two groups. CTx-1, a marker of bone resorption, increased by 12.7% (p=NS) in the $PTH(1–31)NH_2$ group and by 124.6% in the teriparatide group at week 24. The increase in the bone formation marker P1NP was fairly modest for the $PTH(1–31)NH_2$group, whereas osteocalcin, another formation marker, increased 23.3% (p=0.015) compared to baseline. This is in contrast to 4.9% (p=0.87) in placebo and 169.3% (p<0.0001) in the teriparatide group at week 24. No clinically significant hypercalcemic events or elevated urine calcium were seen in the oral $PTH(1–31)NH_2$ arm. The PK profile for $PTH(1–31)NH_2$ showed a pulsatile peak with durations of at least 1 hr but less than 5 hr, which is consistent with the requirement for bone anabolic activity. The mean C_{max} of $PTH(1–31)NH_2$ measured at weeks 0 (n=32) and 24 (n=28) was 295 pg/mL and 207 pg/mL, respectively. The mean C_{max} at for patients receiving Forsteo® at weeks 0 and 24 was 120 pg/mL. Thus, the 5 mg dose resulted in higher mean C_{max} values than Forsteo®. The median C_{max} and AUC values were equivalent to those of Forsteo®. The most common adverse event in the oral PTH and placebo arms was GI pain or distress, and these events were mostly mild or moderate.

Conclusion: The efficacy data and safety profile in this study demonstrate that orally delivered $PTH(1–31)NH_2$ offers the potential for a bone anabolic treatment with greater physician and patient acceptance, and warrants evaluation in further late stage clinical studies.

Disclosure: M. A. Karsdal, Nordic Bioscience Diagnostic, 4; **N. M. Mehta**, Unigene Laboratories, Inc., 3; **W. Stern**, Unigene Laboratories, 3; **A. M. Sturmer**, Unigene Laboratories, Inc., 3; **S. J. Mitta**, Unigene Laboratories, Inc, 3; **R. Tavakkol**, Unigene Laboratories, Inc., 3; **A. Bolat**, Unigene Laboratories, Inc., 3; **J. Giacchi**, Unigene Laboratories, Inc., 3; **K. Henriksen**, None; **L. A. Fitzpatrick**, None; **C. Christiansen**, Nordic, Bioscience A/S, CCBR/Synarc, Roche, Eli Lilly, Novartis, Novo Nordisk, Proctor and Gamble, Groupe Fournier, Besins EscoVesco, Merck Sharp and Dohme, Chiesi, Boehringer Mannheim, Pfizer, GlaxoSmithKline, Amgen., 5; **J. A. Wald**, None; **A. J. Nino**, None; **P. Alexandersen**, None; **B. J. Riis**, None; **J. Andersen**, None; **I. Valter**, None; **B. Nedergaard**, None; **C. Teglbjaerg**, None; **F. Cosman**, Lilly, Novartis, 2, Lilly, Merck, Amgen and Unigene, 5; **J. M. Trang**, Unigene laboratories, Inc, 5.

1985

The Effect of Calcium and Vitamin D On Bone Loss in an Epileptic Population. Philip Dussault[1], Samuel Davis Jr.[1] and Antonio A. Lazzari[2]. [1]Boston VA HCS, Boston, MA, [2]Boston VA Medical Center, Boston, MA

Background/Purpose: Accelerated rate of bone loss leading to osteopenia and osteoporosis is a well recognized adverse effect of long term anticonvulsant use, particularly phenytoin, phenobarbital, sodium valproate or carbamazepine. Futher, compared to the general population, epileptics experience a two-fold increase in the incidence of vertebral and non-vertebral fractures.

In this trial, we sought to evaluate whether a bisphosphonate in addition to calcium and vitamin D supplementation can prevent bone loss and fractures in an epileptic population chronically treated with phenytoin, phenobarbital, sodium valproate or carbamazepine.

Methods: This was a phase IV randomized, two year double blinded, placebo-controlled trial of an epileptic male population of veterans. This study involved 80 patients with various types of seizures who were being treated with phenytoin, phenobarbital, sodium valproate or carbamazepine for a minimum of two years. At initial visit, patients underwent DXA scan on 5th generation GE IDXA. Subjects who had a T-score > -2.5 at AP spine or hip were randomized into two one of two groups. Group R received calcium and vitamin D supplementation along with risedronate 35mg weekly, while Group P received calcium and vitamin D supplementation along with a matching placebo tablet weekly. We excluded those subjects who had were found to be osteoporotic according to WHO criteria (BMD T-score < -2.5 at spine or hip) or were found to be vitamin D deficient.

BMD of bilateral proximal femur, LVA, A-P lumbar spine, total body and forearm were evaluated utilizing a GE Lunar Bone Densitometer or an iDXA instrument and had measurements of 25-OH Vit D, NTX, serum calcium and blood chemistries.

Results: 80 patients were randomly enrolled in either the B or P groups. Baseline characteristics of both groups were similar. Average age was $60+/-13$ years. Average bilateral total proximal femur mean BMD was $0.991+/-0.122$ for the B group and $0.992+/-0.213$ g/cm2 for the P group. Lumbar spine baseline BMD was $1.284+/-0.190$ for the B group and $1.237+/-0.249$ g/cm2 for the P group. Total body BMD was 1.229 $+/-0.107$ for the P group and $1.185 +/-0.110$ for the B group. A total of 56 patients competed the study. At the end of the study 12 out 28 patients from group B and 10 out 28 patients from group P had a significant increase of BMD as determined at the total proximal femur which was above the LSC for our site; further, 18 out 28 of group B and 22 out of 28 on group P demonstrated a significant increase of BMD at the L-Spine. Improvement of BMD at different sites was observed in more than 78% of patients who completed the study taking calcium and vit D both in the P or B groups. Five new vertebral fractures were observed only on the P group.

Conclusion: In this cohort, supplementation with calcium and vitamin D or use of calcium, vitamin D and bisphosphonates decrease rate of bone loss and at the same time increased bone mass associated with chronic treatment with phenytoin, phenobarbital, sodium valproate or carbamazepine. Prevention of new vertebral fractures was not observed in the group receiving only calcium and vitamin D.

Disclosure: **P. Dussault**, None; **S. Davis Jr.**, None; **A. A. Lazzari**, None.

1986

Impaired Endothelial Function in Post-Menopausal Women with Osteoporosis. Auleen M. Millar[1], Aaron McCann[2], Vivian McClenaghan[2], Paul Hamilton[2], Caroline Bleakley[2], Kristopher Lyons[2] and Gary McVeigh[2]. [1]Musgrave Park Hospital, Belfast, United Kingdom, [2]Belfast, United Kingdom

Background/Purpose: Although traditionally viewed as separate disease entities that increase in prevalence with aging, accumulating evidence indicates that similar pathophysiological mechanisms may underlie cardiovascular disease and osteoporosis. Endothelial dysfunction is the initial step in the atherosclerotic process. The aims of this study were to determine if women with post-menopausal osteoporosis have impaired endothelial function.

Methods: We used non-invasive Doppler ultrasound to assess endothelial function in sixty women with post-menopausal osteoporosis and compared results to 30 age, sex matched controls. After measurement of traditional cardiovascular risk factors, we measured flow mediated dilation (FMD) of the brachial artery in subjects. Flow mediated dilation is a dynamic assessment of endothelium-dependent and -independent dilation of an artery. Subjects were further assessed using radial artery tonometry. Isoprostane levels, which are a marker of oxidative stress, were compared between groups.

Results: Groups were equally matched for age, weight, blood pressure, cholesterol profile and smoking history. Results from radial artery tonometry indicated that cardiac output (p=0.03), large artery elasticity index (p=0.03) and small artery elasticity index (p=0.03) readings were significantly higher in the healthy control group. Systemic vascular resistance (p=0.005) and total vascular impedance (p=0.032) was statistically significantly higher in patients with osteoporosis compared to controls. Flow mediated dilatation of the brachial artery showed a statistically significant better dilatation of the brachial artery post cuff deflation in healthy controls (p=0.006), although there was no difference in endothelium-independent dilation ie. brachial artery dilation after administration of GTN. Isoprostane levels were statistically significantly higher in the osteoporosis group

Conclusion: The differences in flow mediated dilatation between healthy controls and post-menopausal women with osteoporosis may indicate impaired endothelial function and reflect the local distensibility of the brachial artery or the distal microcirculation's response to the ischaemic stimulus. Radial artery tonometry results also support a difference in endothelial function between groups. Changes in vascular reactivity are likely to be multi-factorial but may be related in part to differences in levels of oxidative stress between groups. This study demonstrates that further work is required on the assessment of potential structural remodelling in small arteries and vascular beds that may precede clinically detectable cardiovascular disease in women with post-menopausal osteoporosis. Further work is also required on the complex interaction of common risk factors and genetic or molecular determinants of both conditions.

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1987

A Comparison of Unilateral and Bilateral Hip BMD. Steven C. Schaub[1], Edward S. Leib[1] and Diantha Howard[2]. [1]U of Vermont College of Med, Burlington, VT, [2]Vermont Center for Clinical and Translational Science, Burlington, VT

Background/Purpose: The utility of bilateral hip dual energy x-ray absorptiometry scanning for identifying low bone mineral density has been a cause of debate. Intraperson differences in density at the hip can affect categorization of a patient as osteoporotic. Our study was designed to assess the correlation between sides of the hip in individual patients and to compare different sites of the hip for osteoporosis categorization.

Methods: Bilateral hip measurement data on postmenopausal women over age 40 from a single facility scanned on a GELunar Prodigy or Prodigy Advance were retrospectively reviewed. Data included patient demographics, bilateral scan BMD and T-score, presence of historical fragility fractures and data to determine clinical risk.

Results: Scans were evaluable for both proximal femurs in 12,741 women. We found lower density values, reported as T-scores, on the right side of the hip at all regions of interest that were statistically significant. Agreement in osteoporosis categorization between sides of the hip ranged by anatomic site from 82.7%–87.6%. Mean values showed improved agreement (91.0%–93.5%) over the lowest obtained T-score at each hip site. The total hip had the highest correlation in categorization and the closest association to previous fracture at each region of interest. Those categorized as osteoporotic by the mean value were as or more likely to have had a fracture than those with the lowest BMD. Using logistic regression models the adjusted odds ratio for fracture was 3.00 in the osteoporosis category compared to normals. Bilateral scanning effectively eliminated significant differences within an individual patient, but values were minimally divergent from unilateral measurements.

Conclusion: Our study demonstrates that, although there is a small difference between WHO classification of osteoporosis comparing the mean values of the hip to the lowest, the use of the mean value was as good as or better for predicting fractures as the lowest value. This supports the use of bilateral hip scanning for diagnosis of osteoporosis and identifying individuals at risk for fractures.

Disclosure: **S. C. Schaub**, None; **E. S. Leib**, None; **D. Howard**, None.

1988

Zoledronate Efficacy and Safety in Active Paget's Disease Long-Term Follow-up and Retreatment in Clinical Practice. Elsa Vieira-Sousa[1], Ana M. Rodrigues[1], Joana Caetano-Lopes[2], Susana Capela[3], Filipa Ramos[3], Ricardo Figueira[3], Joaquim Polido-Pereira[1], Cristina Ponte[1], Raquel Campanilho-Marques[1], Rita Barros[3], JC Romeu[3] and José A. Pereira da Silva[3]. [1]Rheumatology and Metabolic Bone Diseases Department, Hospital de Santa Maria, CHLN and Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [2]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [3]Rheumatology and Metabolic Bone Diseases Department, Santa Maria Hospital,CHLN, Lisbon, Portugal

Background/Purpose: Bisphosphonates are first line therapy in the treatment of Paget's disease (PD). Zoledronate, a third generation bisphosphonate, has showed high efficacy in the inhibition of bone resorption. The objective of this observational study was to assess short and long-term efficacy and safety of zoledronate in the treatment of active PD, in clinical practice.

Methods: Patients with active PD treated with zoledronate 5 mg were consecutively recruited between 2005 and 2011 and followed prospectively. Clinical (bone and joint pain attributed to PD) and laboratory parameters (alkaline phosphatase (ALP), bone specific alkaline phosphatase (BSALP), procollagen type 1 N-terminal propeptide (P1NP), collagen type 1 beta C-terminal telopeptide (b-CTX), seric and urinary calcium and phosphorus and parathormone levels) were determined before, at 3 and then every 6 months after treatment, up to a maximum of 60 months of follow-up. Remission was defined as normalization of ALP. Retreatement was considered when ALP levels increased more than 25% of the upper limit of normal or of the nadir achieve, in cases of non normalization of ALP. Adverse events were registered according to clinical protocol.

Results: 60 patients (60% males), with a mean age of 68 ± 11 years and a mean disease duration of 11 ± 9 years were included. 69% had polyostotic disease and the mean percentage of skeletal involvement (Howarth table) was of $10.8\pm7.6\%$. 68% were symptomatic: 71% of those referring bone and 54% joint pain attributed to PD. 54% were receiving analgesic or non steroidal anti-inflammatory drugs. 48.3% had been previously treated with parental pamidronate, with a cumulative dose of 234 ± 209mg. The mean follow-up period after zoledronate infusion was of 37 ± 13 months (minimum of 12 and maximum of 60). Only 4 patients (6.6%) required retreatment, on average 30 months after the first zoledronate infusion. A marked reduction of ALP ($261,6\pm152,5$ U/L at baseline) was observed at 3 ($70\%;79,6\pm42,6$) and 6 months ($74\%;67,0\pm22,1$) after zoledronate administration, being maximal at 12 months ($75\%;66,3\pm22,2$) ($p<0.001$). The difference of the mean values of ALP between 3 and 6 months was also significant ($p<0.05$). At 3 and 6 months, 95% and 96% of patients respectively, achieved remission. Maximum effect was obtained at 12 months after treatment with 98% of patients being in remission. Significant reductions of the mean levels of BSALP, P1NP, and b-CTX ($p<0.001$) were also verified at 3, 6 and 12 months after treatment. 47% of patients reported pain improvement: 89% at 3 months, 7% at 6 months and 4% at 12 months. Transitory side effects were registered in 15 patients, 18% referred flu-like symptoms, 10% showed asymptomatic hypocalcaemia and 30% asymptomatic hypophosphoremia.

Conclusion: This study confirms the efficacy and safety of zoledronate in a Portuguese population of patients with active Paget's disease. Biochemical remission was achieved in 98% of patients at 12 months and improvement of pain in 47%, the majority 3 months after treatment. Furthermore these benefits were long-term sustained with only 6.6% of patients requiring retreatment during an average follow-up of 37 months.

1989

Risk Factors for Vertebral Fractures in Patients with Rheumatoid Arthritis - the Tomorrow Study -. Tadashi Okano, Tatsuya Koike, Masahiro Tada, Kenji Mamoto, Yuko Sugioka, Atsuko Kamiyama and Hiroaki Nakamura. Osaka City University Medical School, Osaka, Japan

Background/Purpose: Rheumatoid arthritis (RA) is one of the causes for secondary osteoporosis. Osteoporosis as a multifactorial disease might be derived from comorbidity itself, poorer physical activity, treatment with glucocorticoids, or postmenopausal status. Accelerated generalized bone loss often leads to an increased risk of vertebral fractures. The purpose of this study is to determine the prevalence and the risk factors for vertebral fractures in patients with RA.

Methods: We started a 10-year prospective cohort study named TOMORROW (TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOWer morbidity and mortality, clinical trial registration number: UMIN000003876) in 2010. This study included 208 patients with RA (biological agents, n = 112; conventional therapy, n = 96) and 205 age- and sex-matched volunteers (total, n = 413). We evaluated the prevalence of vertebral fractures using thoracolumbar spine X-rays and analyzed the factors associated with vertebral fractures. Evaluation of existing vertebral fractures was used for a quantitative assessment of each vertebra from T4 to L4 as a first assessment and a semiquantitative visual assessment of each vertebra considered existing vertebral fractures by first assessment.

Results: The prevalence of vertebral fractures was 45.5% and 30% in the RA and volunteer groups, respectively. Significantly more RA patients than volunteers had semiquantitative (SQ) grade 2 or more (15.2% vs. 5%). Bone mineral density, urine pentosidine, homocysteine and bone specific alkaline phosphatase (BAP) significantly correlated with vertebral fractures among the patients and urinary pentosidine levels in the RA patients with fractures were significantly higher than without fractures. Patients using bisphosphonates was 33.3% in patients with rheumatoid arthritis. Bone mineral density was lower and more vertebral fractures was found in patients using bisphosphonates than in patients without bisphosphonates.

Vertebral fractures	Volunteers (n = 205)	RA (n = 208)
N = 0	70%	54.5%
N = 1	14.5%	10.1%
N = 2	8%	9.6%
N = 3	7.5%	25.8%
SQ grade = 2	5%	15.2%
Thoracic spine BMD	0.750 ± 0.126	0.701 ± 0.125
Lumbar spine BMD	0.930 ± 0.163	0.896 ± 0.164

Conclusion: The incidence of vertebral fractures was higher in patients with RA than in volunteers. Bone quality markers and vertebral fractures are closely linked with RA. We will continue to prospectively investigate the incidence of new vertebral fractures and the progression of osteoporosis in patients with RA.

1990

Risk of Falling Is Equivalent Between Patients with Rheumatoid Arthritis and Healthy Individuals—the Tomorrow Study. Kenji Mamoto, Tatsuya Koike, Tadashi Okano, Atsuko Kamiyama, Yuko Sugioka, Masahiro Tada and Hiroaki Nakamura. Osaka City University Graduate School of Medicine, Osaka, Japan

Background/Purpose: Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at increased risk of falling. The present study prospectively determines the incidence of falls and their risk factors in patients with RA who participated in the TOMORROW (TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOW er morbidity and mortality; clinical trial registration number: UMIN000003876) study that was started in 2010.

Methods: We evaluated anthropometric parameters, muscle volume, bone mineral density (BMD), disease activity, general health status and the occurrence of falls for a period of two years in 202 patients with RA (mean age: 58.4 years, 54% administered with biological agents) and 202 age- and sex-matched healthy volunteers (HV, mean age: 57.4 years).

Results: Among the patients with RA and HV, 29.6% and 26.7% respectively reported one or more falls during two years. These values did not significantly differ in the two groups. The fall group had higher age, lower BMD ($p<0.01$), higher whole % Fat mass ($p<0.01$) and tended to have induced walking time. After adjusting for risk factors of falls such as age, gender, smoking and BMI, multiple logistic regression analysis identified that a history of falls was the most significant parameter associated with falls

(odds ratio: 2.39, p=0.001) (Table 1). The RA group also had lower whole muscle volume (37.2 vs. 39.6 kg; p = 0.001), leg BMD (0.967 vs. 1.031 mg/cm^{3}; p < 0.001) and shorter exercise periods than HV, but none of these were associated with rates of falling. Furthermore, fall risk did not significantly and linearly increase with disease duration, disease activity score and physical status among the patients with RA.

Conclusion: We concluded that the fall rate is not higher in patients with RA than in healthy volunteers and that only a history of falls plays a role in increasing the risk of falls.

1991

Effects of Odanacatib On the Distal Radius and Tibia in Postmenopausal Women: Improvements in Cortical Geometry and Estimated Bone Strength. Roland Chapurlat[1], K. Brixen[2], A.M. Cheung[3], Sharmila Majumdar[4], B. Dardzinski[5], A. Cabal[6], N. Verbruggen[7], S. Ather[6], Elizabeth Rosenberg[5] and A. de Papp[5]. [1]Hôpital Edouard Herriot, Lyon, France, [2]University of Southern Denmark, Odense, Denmark, [3]University of Toronto, Ontario, [4]University of California San Francisco, San Francisco, CA, [5]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [6]Merck Sharp & Dohme Corp., Whitehouse Station, [7]MSD Belgium, Brussels, Belgium

Background/Purpose: The cathepsin K inhibitor odanacatib (ODN), a novel antiresorptive that preserves bone formation, is currently in phase 3 development for postmenopausal osteoporosis. In a phase 2 study, 5 years of ODN 50 mg once weekly progressively increased areal BMD at the lumbar spine and total hip (11.9 % and 8.5% from baseline, respectively). ODN reduced bone resorption markers while preserving bone formation markers. In an OVX primate model, ODN has been shown to increase cortical thickness and periosteal bone formation at the central femur and femoral neck.

Figure. Distal Radius HR-pQCT Endpoints in Postmenopausal Women at Month 24
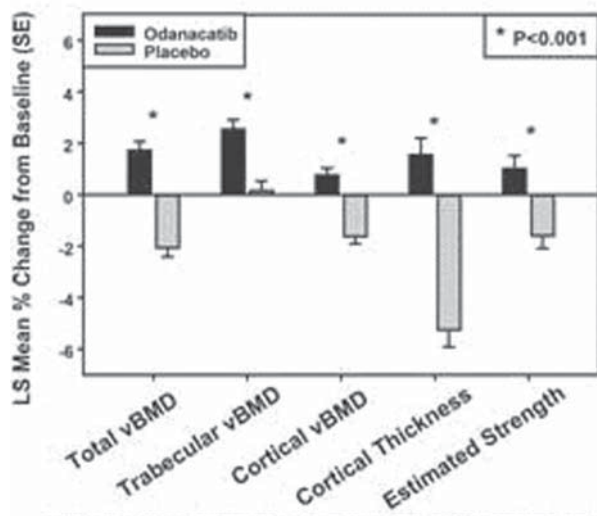
NOTE: HR-pQCT endpoints were exploratory and there was no adjustment for multiplicity.
vBMD=volumetric bone mineral density

Methods: In order to determine the effect of ODN on cortical geometry and to estimate bone strength, we conducted a randomized, double-blind placebo-controlled trial, using high resolution quantitative computerized tomography (HR-pQCT) of the distal radius and distal tibia. A total of 214 postmenopausal women, of mean age 64.0 ±6.8 years and baseline lumbar spine T-score −1.81 ±0.83, were randomized to oral ODN 50 mg or PBO weekly for 2 years.

Results: Lumbar spine areal BMD % change from baseline at 1 year (primary endpoint) was statistically significantly greater for ODN than PBO (3.49% treatment difference, p<0.001). After 2 years, there were significantly greater improvements with ODN than PBO in total, trabecular, and cortical volumetric BMD; cortical thickness; and estimated strength (failure load) of the distal radius using HR-pQCT-based finite element analysis (exploratory endpoints, FIGURE). At the radius, odanacatib attenuated the increase in cortical porosity that was seen in the placebo group (treatment difference in least squares mean % change from baseline −7.68, p=0.066). At the distal tibia, changes in volumetric BMD and cortical thickness were similar to changes at the radius. Safety and tolerability were similar between treatment groups.

Conclusion: Odanacatib increased cortical and trabecular density and improved cortical thickness of the distal radius and distal tibia, and improved the estimated bone strength in the distal radius compared to placebo.

1992

Anti-TNF Therapies Improve Bone Mineral Density At the Lumbar Spine of RA Patients by Decreasing Disease Activity and Suppressing Serum RANKL Levels. Allen P. Anandarajah[1], Jennifer Hossler[2], Kate Burns[2], Kelly Callahan[2], Yahui Grace Chiu[2] and Jennifer H. Anolik[2]. [1]Univ of Rochester Medical Ctr, Rochester, NY, [2]University of Rochester, Rochester, NY

Background/Purpose: Generalized bone loss (osteoporosis or osteopenia) is more common in patients with rheumatoid arthritis (RA) than in the general population. Recent studies suggest that inflammation in RA is a main contributor to this form of bone loss. Inflammation is mediated in turn by multiple cytokines with tumor necrosis factor (TNF) being a key player. Few studies, however, have described the effects of anti-TNF therapies on generalized bone loss.

Objective: To study the effects of anti-TNF therapies on the bone mineral density (BMD) of early RA patients and to correlate the BMD measurements with serum receptor activator of NFkB ligand (RANKL) and osteprotegerin (OPG).

Methods: This is a single center study of 40 subjects with active RA (disease activity scores of 3.2 or more) that are naïve to anti-TNF therapy and receiving stable doses of disease-modifying drugs. Patients were treated with adalimumab 40 mg every other week or etanercept (25 mg twice a week or 50 mg once a week). Subjects were allowed to be on a maximum daily dose of 10 mg of prednisone or an equivalent dose. Subjects did not require or were not willing to take medications for osteoporosis. DAS28 assessments were done at baseline, 12 and 24 weeks. Bone mineral density (BMD) measurements of the lumbar spine (LS) and hips were done using a Lunar Prodigy x-ray absorptiometer prior to the first dose of anti-TNF therapy and at week 52. Serum RANKL and OPG levels were measured by ELISA at baseline and at weeks 24 and 52.

Results: The 8 subjects (females, 5; males, 3) who have completed 1 year of anti-TNF therapy had a mean age of 57 years. The mean DAS28 score improved from 4.8 at baseline to 3.5 at 24 weeks. Five patients had a good DAS28 response, 2 had a moderate response, and 1 was a non-responder. The BMD at the LS increased in 5, decreased in 2, and did not change in 1. The mean BMD for the group as a whole did not change with treatment (1.22g/cm^{2} to 1.21g/cm^{2}) between baseline and week 52. Among the 5 patients with an increase in BMD, 4 had had a good DAS28 response and one had a moderate DAS28 response; whereas, among the 2 patients with a decrease in BMD, 1 was a DAS28 non-responder and 1 had had a good DAS28 response. The patient with no significant change in BMD had a moderate DAS28 response. Serum RANKL levels decreased significantly with treatment from 2381 pg/ml (+/−3025) at baseline to 921 pg/ml (+/−1630) at week 52 (p=0.03). Interestingly, at 24 weeks, the serum RANKL was decreased in those with improved BMD (mean RANKL 1994.4 pg/ml at baseline and 1298.2pg/ml at week 24), but was essentially unchanged in those with decreased/ unchanged BMD (mean RANKL 3025.7 pg/ml at baseline and 3029.7 pg/ml at week 24). In the 5 subjects with increased BMD, RANKL levels were decreased in 4 of the subjects and

increased in 1 subject. Among the 2 patients with a decrease in BMD, 1 had an increase and 1 had a decrease in RANKL levels. The remaining subject with no change in BMD also had no change in RANKL level. No relationship was noted between BMD at the LS and OPG levels.

Conclusion: Anti-TNF therapy improves BMD at the lumbar spine in a subset of RA patients. The increase in BMD is associated with a decrease in disease activity and may be mediated by a suppression of serum RANKL levels.

1993

Contribution of Lifestyle Factors to Healthy-Adherer Bias in Prevalent Users of Osteoporotic Drugs. Mitsuyo Kinjo[1] and Daniel H. Solomon[2]. [1]Okinawa Chubu Hospital, Uruma City Okinawa, Japan, [2]Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Background/Purpose: Adherence to drug therapy may be a surrogate marker for overall healthy behaviors leading to healthy-adherer bias in epidemiologic studies. This might be particularly emphasized in osteoporosis supplements and medications. However, individual factors contributing to healthy-adherer effects and their quantitative impacts are not well described. We assessed the association between prevalent use of and adherence to osteoporotic supplements or medications and healthy lifestyle factors in a population-based sample from the National Health and Nutrition Examination Survey, 1999–2008.

Methods: We identified subjects who used calcium plus vitamin D supplements and/or osteoporotic medications (bisphosphonate, calcitonin or raloxifene). We estimated the magnitude of association between prevalent use of these osteoporotic drugs and demographic, lifestyle and comorbid illness factors. Demographic, lifestyle, and comorbid factors of interest included body mass index, exercise, smoking, alcohol consumption, self-reported health status, comorbidities (cancer, coronary artery disease, COPD and diabetes), and steroid use. We also examined the subset of subjects with a history of fracture in the hip, wrist or spine, or those with osteoporosis who were advised to take treatments.

Results: Among 25,290 subjects, 1,529 were users and 23,761 were nonusers of calcium, vitamin D or an osteoporosis medication. Users and nonusers were similar in age (mean age 57 years), but were more likely to be women (64% vs 52%; $P<.05$). After adjustment for age, prevalent female users 50 years or older had significantly less severe obesity (odds ratio 0.7, 95% CI: 0.6, 0.9), current or past smoking (OR 0.8, 95% CI: 0.5, 1.0), more moderate exercise (OR 1.4, 95% CI:1.1, 1.8), lower self-reported poor health (OR 0.8, 95% CI: 0.7, 0.9), less diabetes (OR 0.7, 95% CI:0.6, 0.9) and acute coronary syndrome (OR 0.8, 95% CI:0.7, 1.0). Among subjects with previous fracture or osteoporosis, a similar trend was seen between users and nonusers.

Conclusion: In a large representative US population, prevalent use or adherence to osteoporotic drugs was associated with healthier lifestyle factors. The results suggest that healthy user or adherer can be explained, in part, by the healthier lifestyles in prevalent users or adherers in the elderly.

1994

The Influence of Percentage Body Fat On Bone Mineral Density in Thin Patients. Andrew Blanshard[1] and Marwan Bukhari[2]. [1]Lancaster University, Lancaster, United Kingdom, [2]Royal Lancaster Infirmary, Lancaster, United Kingdom

Background/Purpose: Low Body Mass Index (BMI) is associated with low Bone Mineral Density (BMD) and subsequent risk of fragility fracture. Percentage body fat (%BF), which is measured by most DEXA scanners, has a correlation with BMD, however the relative contribution of %BF on osteoporosis has not been examined in detail. A higher %BF may be associated with a higher BMD when BMI is accounted for. Previous work from this unit has shown that the threshold for poor bone health is a BMI of 22.

Our aim was to determine the relationship between %BF and BMD in a population at risk of fracture.

Methods: Patients with a BMI of less than 22 were identified from a total population of 25896 who had been referred for Dual-Energy X-Ray Absorptiometry (DEXA) scanning between June 2004 and August 2010. The relationship between %BF (as measured by DEXA) and the mean BMD at both the femoral neck and lumbar spine were analysed using Stata 9.0 for Windows. Linear regression was used to determine the relationship between %BF and the BMD at both the lumbar spine and the femoral neck, adjusting for BMI.

Results: 2634 patients were included in the analysis which consisted of 2333 females; 88.6% of the population. Although there was a correlation between %BF and BMI (coeff, 0.06; 95% CI, 0.05, 0.07), the variance explained was low (adjusted-R squared value 0.07). When examining %BF and BMD and adjusting for BMI, there was a statistically significant negative association at the lumbar spine (coeff, -0.004; 95% CI, -0.006, $-.004$) and the femoral neck (coeff, -0.005; 95% CI, -0.007, $-.004$). This relationship was also observed in an only female cohort. A sensitivity analysis was performed using %BF alone, which still showed a negative correlation.

Conclusion: BMD was negatively influenced by %BF in this population with a low BMI, after adjusting for baseline BMI. A possible hypothesis is that body fat in this group has a paradoxical effect on bone health. Further work investigating this relationship in patients with a higher BMI will be performed.

1995

What Are the Most Clinically Relevant and Feasible Pragmatic Osteoporosis Clinical Trial Designs? Nicole C. Wright[1], Ana Oliveira[1], Amy H. Warriner[1], Jeffrey Curtis[1], Neil Binkley[2], Steven R. Cummings[3], Marc C. Hochberg[4], Andrea LaCroix[5], E. Michael Lewiecki[6], John T. Schousboe[7], Daniel H. Solomon[8], Robert B. Wallace[9] and Kenneth G. Saag[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Wisconsin, Madison, WI, [3]San Francisco Coordinating Center, CPMC Research Institute, San Francisco, CA, [4]University of Maryland, Baltimore, MD, [5]Fred Hutchinson Cancer Research Center, Seattle, WA, [6]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, [7]Park Nicollet Health Services, Minneapolis, MN, [8]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA, [9]University of Iowa, Iowa City, IA

Background/Purpose: Pragmatic clinical trials (PCTs) allow for study of real world patients using efficient study designs, facilitating comparative effectiveness research in resource constrained settings. Although the need for osteoporosis PCTs is clear, it is unclear what study questions will most impact the field.

Methods: We conducted a Delphi meeting with 9 experts in osteoporosis trial design and patient care to consider PCT designs with aims of understanding the relative efficacy and safety of osteoporosis drugs. We asked the expert panel to review 2 osteoporosis PCT concepts in a practice-based setting with pre-specified study arms and drugs of interest including 1) active comparator osteoporosis initiation PCT that included 3-arm and 2-arm studies, and 2) osteoporosis therapy discontinuation/switching PCTs that included 2-arm and 3-arm designs among chronic bisphosphonate (BP) users (Table). The primary outcome of both concepts was non-vertebral fracture risk reduction. Participants ranked the clinical significance and feasibility (four domains) of each design (Table). Initial rankings were cast after independent review of the scenarios followed by a webinar discussion and re-ranking of each design.

Results: Rankings associated with initiation studies did not change appreciably pre and post discussion. With 1 being the least and 5 being the most clinically significant, experts ranked the design that compared the fracture reduction of alendronate (ALN), zoledronic acid (ZA), and denosumab (Dmab) as the most clinically significant initiation PCT. The median score was 5 compared to 3.5 for comparing ALN to two strategies of ZA administration (single dose once vs. annual dosing for 3 years), and 3.0 for comparing any oral BP to ZA (Table). Although clinical significance was lower, the panel ranked designs that did not incorporate Dmab as more feasible for recruitment, and human ethics and regulatory approvals (Table). The panel ranked the clinical significance of discontinuation studies with 2-arms higher than designs that incorporated switching (Table). In consideration of switching designs, the panel ranked switching to Dmab more clinically significant than other switching designs. The median recruitment feasibility scores ranged from 2.5–4, lowest designs associated with switching to teriparatide and highest associated with 2-arm studies. The panel ranked human ethics and regulatory concerns greater with switching designs and felt these designs would require more site training and monitoring than 2-arm designs.

Table. Study Arms for Potential Osteoporosis PCTs and Median Likert Scores Rankings on Significance and Feasibility

Initiation Study

Study Arm 1	Study Arm 2	Study Arm 3	Clinical Significance[A]	Recruitment[B]	IRB[C]	Feasibility FDA[C]	Monitoring[C]
ALN	ZA	Dmab	5	3	3	2.5	2.5
ALN	ZA (single dose)	ZA (3 annual doses)	3.5	4	3.5	4	3
Any oral BP	ZA	–	3	3.5	3.5	4	3

Discontinuation/Switching Study among Long Term Bisphosphonate Users*

Study Arm 1	Study Arm 2	Study Arm 3	Clinical Significance[A]	Recruitment[B]	IRB[C]	Feasibility FDA[D]	Monitoring[E]
Continue any BP	Discontinue BP	–	4	4	4	4	5
Continue ALN	Discontinue ALN	–	4	4	4	4.5	5
Continue ALN or ZA	Discontinue ALN or ZA	–	3	4	4	4	4
Continue any BP	Discontinue BP	Switch to Dmab	3	3	3	3	3
Continue any BP	Discontinue BP	Switch to Dmab or TPTD	3	2.5	2.5	3	3
Continue any BP	Discontinue BP	Switch to Dmab, TPTD, or other BP	2	2.5	2	3	3

Likert Scales: [A]Clinical Significance: 1 Least Significant – 5 Most Significant; [B]Recruitment: 1 Least Feasible – 5 Most Feasible; [C]IRB, FDA, Site Training and Monitory: 1 Most Concerns – 5 Fewest Concerns ALN-alendronate; ZA-zoledronic acid; Dmab –denosumab; BP-bisphosphonate; TPTD-teriparatide; IRB-Institutional Review Board; FDA–Food and Drug Administration

Conclusion: The study designs with the highest clinical significance included the 3-arm initiation PCT comparing ALN, ZA, and Dmab and the 2-arm discontinuation PCT that compared continuing any BP or ALN to discontinuing therapy. The 2-arm discontinuation PCTs were also ranked the most feasible, whereas feasibility was higher in other initiation designs.

Disclosure: N. C. Wright, Amgen, 2; **A. Oliveira**, None; **A. H. Warriner**, Amylin, 2, NIH, 2, AHRQ, 2; **J. Curtis**, Roche/Genetech, UCB< Centocor, Corrona,Amgen, Pfizer, BMS, Crescendo, Abbott, 2, Roche/Genetech,UCB, Centocor, CORRONA, Amgen, Pfizer, BMS, Crescendo, Abbott, 5; **N. Binkley**, Merck, Amgen, Lilly, Tarsa, 5, Merck, Amgen, Tarsa, 2; **S. R. Cummings**, None; **M. C. Hochberg**, Abbott Laboratories, Astra-Zeneca, Bioiberica S.A., Eli Lilly Inc., Genentech/Roche, Merck Inc., Novartis Pharma A.G., Pfizer Inc., Stryker LLC, Xoma., 5; **A. LaCroix**, None; **E. M. Lewiecki**, None; **J. T. Schousboe**, None; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2, Eli Lilly and Company, 2, Pfizer Inc,; **R. B. Wallace**, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5; **K. G. Saag**, Amgen, 2, Eli Lilly and Company, 2, Merck Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Amgen, 5, Eli Lilly and Company, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5.

1996

Are Changes in Bone Mineral Density Different Between Groups of Early Rheumatoid Arthritis Patients Treated According to a Tight Control Strategy with or without Prednisone, If Osteoporosis Prophylaxis Is Applied? Marlies C. van der Goes[1], Johannes W.G. Jacobs[1], Maud S. Jurgens[1], Marije F. Bakker[1], Maaike J. van der Veen[2], Jacobine H. van der Werf[3], Paco M.J. Welsing[1] and Johannes W.J. Bijlsma[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]St. Jansdal hospital, Harderwijk, Netherlands, [3]Diakonessenhuis, Utrecht, Netherlands

Background/Purpose: To describe effects on bone mineral density (BMD) of treatment according to EULAR guidelines with a methotrexate-based tight control strategy including 10 mg prednisone daily versus the same strategy without prednisone in early rheumatoid arthritis (RA) patients, who received preventive therapy for osteoporosis.

Methods: Early RA patients were included in the CAMERA-II trial: a randomized, placebo-controlled, double-blind two-year trial, in which effects of addition of 10 mg prednisone daily to a methotrexate-based tight control strategy were studied. All patients received calcium, and a bisphosphonate. Disease activity was assessed every four weeks. X-rays of hands and feet and dual-energy X-ray absorptiometry of lumbar spine and left hip were performed at baseline, and after one and two years of treatment.

Results: The BMD increased significantly over time in both treatment groups at the lumbar spine with a mean of 2.6 percent during the first year ($p < 0.001$), but not at the hip; at none of the time points the BMD differed significantly between the prednisone and placebo group. Higher age and lower weight at baseline, and higher disease activity scores during the trial, but not glucocorticoid therapy, were associated with a lower BMD at both the lumbar spine and the hip in mixed model analyses.

Conclusion: Addition of 10 mg prednisone daily to a methotrexate-based tight control strategy does not lead to bone loss in early RA patients on bisphosphonates. A small increase in lumbar BMD during the first year of treatment was found, regardless of the use of glucocorticoids.

Disclosure: M. C. van der Goes, None; **J. W. G. Jacobs**, None; **M. S. Jurgens**, None; **M. F. Bakker**, None; **M. J. van der Veen**, None; **J. H. van der Werf**, None; **P. M. J. Welsing**, None; **J. W. J. Bijlsma**, None.

1997

Safety and Efficacy of Denosumab Vs Ibandronate in Postmenopausal Women Sub-Optimally Treated with Daily or Weekly Bisphosphonates: A Randomized, Open-Label Study. Michael A. Bolognese[1], Edward Czerwinski[2], Henry G. Bone[3], Sydney Bonnick[4], Neil Binkley[5], Alfred Moffett Jr.[6], Suresh Siddhanti[7], Irene Ferreira[8], Prayashi Ghelani[9], Rachel Wagman[7], Jesse W. Hall[7] and Chris Recknor[10]. [1]Bethesda Health Research Center, Bethesda, MD, [2]Krakow Medical Center, Krakow, Poland, [3]Michigan Bone and Mineral Clinic, Detroit, MI, [4]Clinical Research Center of North Texas, Denton, TX, [5]University of Wisconsin, Madison, WI, [6]OB-GYN Associates of Mid Florida, PA, Leesburg, FL, [7]Amgen Inc., Thousand Oaks, CA, [8]Amgen Inc., Cambridge, United Kingdom, [9]Ovatech Solutions, London, United Kingdom, [10]United Osteoporosis Centers, Gainesville, GA

Background/Purpose: Denosumab, a fully human monoclonal antibody that specifically targets RANKL to inhibit osteoclast formation, function, and survival, reduces risk for vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis.[1] In subjects who were treatment naïve or previously treated with alendronate, denosumab was associated with greater gains in bone mineral density (BMD) and decreases in bone turnover markers when compared with alendronate-treated subjects.[2,3]The purpose of this open-label trial was to compare the safety and efficacy of denosumab with ibandronate over 12 months in postmenopausal women with low BMD who were sub-optimally treated with prior bisphosphonate therapy.

Methods: This was a multicenter, randomized, open-label, parallel-group study in which postmenopausal women age 55 years and older were randomized 1:1 to receive open-label denosumab 60 mg subcutaneously every 6 months or ibandronate 150 mg orally every month for 12 months. Percent change from baseline in total hip (primary endpoint), femoral neck, and lumbar spine BMD at month 12; percent change from baseline in serum CTX (sCTX) at 1 and 6 months; and safety were assessed.

Results: Randomized subjects (n=833; 417, denosumab; 416, ibandronate) had a mean (SD) age of 66.7 (8.0) years and mean (SD) BMD T-scores of −1.8 (0.7), −2.1 (0.7), and −2.5 (0.8) at the total hip, femoral neck, and lumbar spine, respectively. Denosumab significantly increased total hip BMD compared with ibandronate at 12 months (2.2% vs 0.9%, respectively; $p<0.0001$). Denosumab also significantly increased BMD compared with ibandronate at the femoral neck (1.7% vs 0.5%) and lumbar spine (4.1% vs 2.1%), $p<0.0001$ for both sites. Denosumab significantly decreased sCTX at 1 month with a median change from baseline of −81.1% compared with −35.0% for ibandronate ($p<0.0001$), and sCTX remained decreased through 6 months of treatment. In this open-label study, overall adverse events were similar between groups. Reports classified as serious adverse events (SAEs) were more frequent in subjects treated with denosumab than with ibandronate. No organ system accounted for a preponderance of these reports. The incidences of SAEs involving infection and malignancy were similar between groups.

Conclusion: Denosumab treatment resulted in greater increases in BMD at all measured skeletal sites compared with ibandronate. No new safety risks were identified in this open-label study.

[1]Cummings, et al. *NEJM* 2009;361:756
[2]Brown, et al. *JBMR* 2009;24:153
[3]Kendler, et al. *JBMR* 2010;25:72

Disclosure: M. A. Bolognese, Amgen Inc., 8; **E. Czerwinski**, Amgen Inc., 2, Amgen Inc., 9; **H. G. Bone**, Amgen Inc., 2, Amgen Inc., Merck, Zelos, Tarsa, GSK, 5, Amgen Inc., 8; **S. Bonnick**, Amgen Inc., Merck, Wyeth, Takeda, 2, Amgen Inc., Novartis, 8; **N. Binkley**, Merck, Amgen, Lilly, Tarsa, 5, Merck, Amgen, Tarsa, 2; **A. Moffett Jr.**, None; **S. Siddhanti**, Amgen Inc, 3, Amgen Inc., 1; **I. Ferreira**, Amgen Inc., 3, Amgen Inc., 1; **P. Ghelani**, Amgen Inc., 3; **R. Wagman**, Amgen Inc., 3, Amgen Inc., 1; **J. W. Hall**, Amgen Inc, 3, Amgen Inc, 1; **C. Recknor**, Amgen, Takeda, Novartis, Eli Lilly, 5.

Relationship Between Changes in Bone Mineral Density and Incidence of Fracture with 6 Years of Denosumab Treatment.

Michael A. Bolognese[1], Paul D. Miller[2], Jean-Yves Reginster[3], Nathalie Franchimont[4], Gerolamo Bianchi[5], Roland Chapurlat[6], Federico G. Hawkins[7], David L. Kendler[8], Beatriz Oliveri[9], Jose R. Zanchetta[10], Nadia Daizadeh[4], Andrea Wang[4], Rachel B. Wagman[4] and Socrates Papapoulos[11]. [1]Bethesda Health Research Center, Bethesda, MD, [2]University of Colorado Health Sciences Center and Colorado Center for Bone Research, Lakewood, CO, [3]University of Liège, Liège, Belgium, [4]Amgen Inc., Thousand Oaks, CA, [5]Azienda Sanitaria Genovese, Genoa, Italy, [6]Hôpital Edouard Herriot, Lyon, France, [7]Hospital Universitario, Madrid, Spain, [8]University of British Columbia, Vancouver, BC, [9]Laboratorio Enfermedades Metabólicas Oseas, Hospital de Clínicas, INIGEM UBA-CONICET, Buenos Aires, Argentina, [10]Instituto de Investigaciones Metabólicas and University of Salvador, Buenos Aires, Argentina, [11]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: During the first 3 years of denosumab treatment in FREEDOM, there were continued increases in bone mineral density (BMD) and a robust reduction in fracture risk (Cummings et al., *NEJM* 2009). The changes in total hip BMD explained a considerable proportion of the reduction in new or worsening vertebral and nonvertebral fracture risk (Austin et al., *JBMR* 2011). Here, we conducted a BMD responder analysis and explored if the progressive BMD gains with 6 years of denosumab therapy continued to relate to the observed fracture incidence.

Methods: The long-term efficacy and safety of denosumab for up to 10 years is being investigated in the open-label extension of the 3-year FREEDOM trial. During the extension, all participants receive 60 mg denosumab every 6 months. For the analyses presented here, women from the FREEDOM denosumab group received 3 more years of denosumab for a total of 6 years. The percentages of women treated with denosumab who achieved BMD increases from FREEDOM baseline at the lumbar spine, total hip, and femoral neck were determined. A logistic regression model was used to examine the relationship between change in total hip BMD and new or worsening vertebral fracture. A comparable approach was employed for nonvertebral fracture using the Cox proportional hazards model.

Results: For women who received 3 additional years of denosumab treatment (N=2343 enrolled), further significant increases in BMD occurred for cumulative 6-year mean gains of 15.2% (lumbar spine), 7.5% (total hip), and 6.7% (femoral neck). At year 6, almost all women treated with denosumab had gains in BMD at the lumbar spine (98%), total hip (96%), and femoral neck (91%). Additionally, 99% of women had gains in BMD at any of these sites, and of these, the gains were >3% in 98% of women and >6% in 95% of women. Fracture incidence remained low during the extension. The relationships between total hip BMD gains and new or worsening vertebral and nonvertebral fractures with 6 years of denosumab treatment are shown in Figures 1 and 2, respectively.

Figure 1.
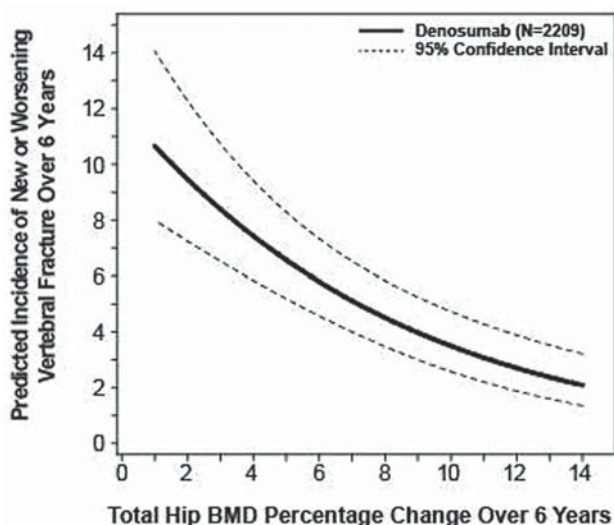
Figure 2.
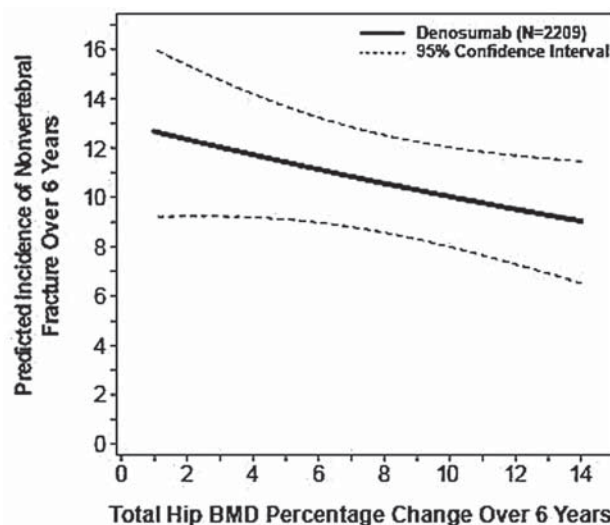
The predicted fracture incidence was estimated corresponding to the 5th through the 95th percentiles of the observed total hip BMD percentage changes over 6 years. N=number of subjects with an observed BMD value at FREEDOM extension baseline and at ≥1 follow-up visit.

Conclusion: Almost all women who received 6 years of denosumab treatment had gains in BMD at the lumbar spine, total hip, or femoral neck; and those gains were >6% in 95% of them. While on denosumab treatment, the risk of new or worsening vertebral fracture and nonvertebral fracture decreased with increasing percentage change in total hip BMD over 6 years. This association provides clinical relevance to the progressive and continued BMD gains reported with denosumab over time.

ACR/ARHP Poster Session C
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis and Other Pediatric Rheumatic Diseases
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

Immunogenicity and Safety of Two Doses of Influenza A H1N1/2009 Vaccine in Young Autoimmune Rheumatic Diseases Patients Under 9 Years Old.

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Background/Purpose: In 2010 the Advisory Committee on Immunization Practices from the CDC recommended that all children should receive the

trivalent seasonal influenza vaccine containing the A/California/7/2009 (H1N1)-like virus with a specific protocol of two doses in subjects under 9 years old. There is, however, no data regarding this vaccine immunogenicity and safety in young children with autoimmune rheumatic diseases (ARD).

Methods: 42 ARD patients and 12 healthy controls were initially recruited. One juvenile idiopathic arthritis patient had typical uncomplicated febrile seizure after first dose and did not receive the second dose and 3 patients and one control did not complete the study. Therefore, 38 ARD patients [25 juvenile idiopathic arthritis, 5 juvenile dermatomyositis, 3 juvenile systemic lupus erythematosus, 3 juvenile scleroderma and 2 primary vasculitis] and 11 healthy children completed the study and received two doses of a non-adjuvanted preparation of influenza A/California/7/2009 (H1N1) virus-like vaccine. They were clinically evaluated before and 21 days after the second dose of vaccination and serology for anti-H1N1 antibody was performed by hemagglutination inhibition (HI) assay. Seroprotection and seroconversion rates, geometric mean titres (GMT) and factor increase (FI) in GMT (ratio of the GMT after vaccination to the GMT before vaccination) were calculated. Adverse events were also evaluated.

Results: Current age (7 vs. 7.8 years, p=0.55) and female gender (76.3 vs. 63.6%, p=0.45) were comparable in ARD patients and controls. Five (13.2%) patients were not receiving any drug, 18 (47.4%) patients were under non-steroidal anti-inflammatory drugs and 11 (28.9%) under prednisone, with a median current dose of 15mg (4–40). Twenty-three (60.5%) were taking methotrexate, 6 (15.8%) cyclosporine, one (2.6%) azathioprine and 7 (18.4%) anti-TNF agents. Pre-vaccination seroprotection rates (p=1.0) and GMT (p=0.63) were comparable between patients and controls. Three weeks after immunization seroprotection (81.6 vs. 81.8%; p=1.0), seroconversion rates (81.6 vs. 90.9%; p=0.66), GMT (151.5 vs. 282.1, p=0.26) and the FI in GMT (16.7 vs. 36.3; p=0.226) were similar in patients and controls, with both groups achieving adequate response according to the European Medicines Agency and Food and Drug Administration standards. The analysis of the possible factors influencing seroconversion showed no difference in demographic data, leukocytes and lymphocytes count or frequency of immunosuppressive drugs use (including prednisone, methotrexate, cyclosporine, azathioprine and anti-TNF agents) between seroconverted and non-seroconverted patients (p>0.05). No severe adverse events were observed.

Conclusion: Two doses of the non-adjuvanted influenza A H1N1/2009 vaccination induced an effective antibody response in young children with ARD independent of demographic characteristics, lymphocytes count and immunosuppressive treatment. Adverse events were rarely observed suggesting vaccine recommendation for this group of patients. (ClinicalTrials.gov, #NCT01151644)

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2000

Whole Body Magnetic Resonance Imaging in Evaluation of Enthesitis in Spondyloarthropathy. Hemalatha Srinivasalu[1], Suvimol C. Hill[2], Gina A. Montealegre Sanchez[1], April D. Brundidge[1], Michael M. Ward[1] and Robert A. Colbert[1]. [1]NIAMS NIH, Bethesda, MD, [2]NIH Clinical Center, Bethesda, MD

Background/Purpose: Enthesitis is a characteristic feature of spondyloarthritis (SpA). Tenderness at enthesial points constitutes clinical enthesitis. However, this may not always correlate with actual inflammation at entheses. We assessed the agreement between enthesitis by clinical exam and whole body MRI (WB MRI).

Methods: Patients enrolled in an observational study on SpA who had undergone WB MRI and clinical exam for enthesitis were included. Patients had one of the following conditions: enthesitis related arthritis (ERA), psoriatic arthritis (PsA) (ILAR criteria); undifferentiated SpA (Amor or ESSG criteria); axial SpA (ASAS criteria); juvenile ankylosing spondylitis (AS) or adult AS (Modified NY criteria). Patients underwent detailed clinical exam including manual palpation of 34 enthesial sites by one of 2 examiners. Patients underwent WB MRI without contrast. Criterion for enthesitis by WB MRI was an increased signal on STIR sequence or presence of bony erosions or bone marrow edema at the sites of tendon attachments to bones. Four healthy volunteers also underwent clinical enthesial exam and WB MRI. Median, IQR calculations were performed for descriptive statistical analysis. Kappa statistics were used to assess agreement between enthesitis by clinical exam and WB MRI.

Results: Thirteen patients had WB MRI (66% were younger than 16 years at symptom onset; 66% male; 100% Caucasian). The median disease duration was 36 months (IQR 17.5–108). Inflammatory back pain by ESSG criteria was present in 92%; Median Schober test was 5 cm (IQR 4.15–6.25). Median ESR was 8 mm/hr (IQR 5–21.5) and CRP was 0.52 mg/L (IQR 0.16–26.72). Seventy seven percent of patients satisfied ILAR criteria for ERA (N=8) or PsA (2); 46% satisfied criteria for axial SpA (6). One patient had AS. All patients had at least one tender enthesis on exam; 77% had more than 4 tender entheses. A total of 108 enthesial sites were present among patients. The most common tender enthesial sites were medial epicondyle (N=7), L5 spinous process (6), anterior superior iliac spine (7), plantar fascia insertion to MTP (8), and 1st costosternal junction (7). None of the patients had tender Achilles insertion. Two patients had any evidence of enthesitis by WB MRI. Greater trochanter (2) and iliac crest (1) were the most common sites of enhancement on MRI.

There was poor agreement between WB MRI and clinical exam for enthesitis when evaluated for all enthesial sites (kappa=0). Agreement at individual sites including Achilles insertion, plantar fascia insertion to calcaneus and MTP; greater trochanter; upper and lower poles of patella; and iliac crest was also poor (k range −0.23 to 0.24). Only one enthesial site in one patient was positive both on WB MRI and clinical exam. Among 4 healthy controls, a total of 4 enthesial sites were positive by clinical exam and none were positive by WB MRI.

Conclusion: There is poor agreement between enthesitis by clinical exam and WB MRI in young patients with SpA. Clinical examination may overestimate enthesitis, or non-contrast WB MRI may have limited sensitivity to detect enthesitis.

Disclosure: H. Srinivasalu, None; S. C. Hill, None; G. A. Montealegre Sanchez, None; A. D. Brundidge, None; M. M. Ward, None; R. A. Colbert, None.

2001

Methotrexate and Injectable Tumor Necrosis Factor Alpha Inhibitor Adherence and Persistence in Children with Rheumatic Diseases. Sarah Ringold[1], Shannon Grant[2], Charmaine Girdish[3], Carol A. Wallace[4] and Sean Sullivan[5]. [1]Seattle Children's Hospital, Seattle, WA, [2]Axio Research LLC, Seattle, WA, [3]CVS Caremark, Scottsdale, AZ, [4]Seattle Childrens Hospital, Seattle, WA, [5]University of Washington, Seattle, WA

Background/Purpose: Medication adherence and persistence have been demonstrated to have important implications for treatment effectiveness, cost, and safety. Methotrexate is one of the most commonly prescribed medications for the treatment of pediatric rheumatic diseases. Two injectable tumor necrosis factor alpha inhibitors (iTNFα), etanercept and adalimumab, are approved by the US Food and Drug Administration (FDA) for use in JIA, and recent data suggest that the prevalence of anti-TNFα medication use for JIA is now approaching that for adult rheumatoid arthritis. While JIA is the most common indication for these medications, they are also used in the treatment of additional rheumatic and inflammatory conditions. Despite their frequent use and established efficacy in clinical trials, few studies have examined children's adherence and persistency with these medications.

The objective of this study was to measure adherence and persistence among children who were prescribed methotrexate and the injectable tumor necrosis factor alpha inhibitors (iTNFα) etanercept and adalimumab by an adult or pediatric rheumatologist.

Methods: Data were obtained from CVS Caremark®, a large pharmacy benefits manager. Children were included if they were < 18 years of age, and had ≥ 1 prescription claim between January 2009 and December 2010 for methotrexate or an iTNFα that was prescribed by an adult or pediatric rheumatologist. The medication possession ratio (MPR) was calculated for each medication, with MPRs ≥ 80% indicating good adherence. MPRs were compared by route of administration, age, and by new users versus continuing users. Persistence was measured for new users of each medication from initiation until discontinuation, or for a maximum of one year.

Results: 1,964 children were included. The majority of children had MPRs < 80%. Children taking subcutaneous methotrexate had the lowest mean MPR (46.9%; median 44.9%; IQR 23%–69.6%) and the lowest persistence, with 26% of children continuing the medication at one year. Mean MPR was highest for iTNFα (65.7%; median 70.1%; IQR 46%-89.3%), as was persistence, with 52% of children continuing the medication at one year. Children receiving oral methotrexate had higher MPRs and persistence than those receiving subcutaneous methotrexate. Children < 13 years tended to have higher MPRs, but this was statistically significant only for oral methotrexate (61.1% versus 54.9%; p=0.02).

Conclusion: Adherence and persistence in this cohort varied by medication and route of administration. Both outcomes are important considerations for physicians prescribing these medications in routine clinical care and for the assessment of treatment effectiveness in the research setting.

2002

Randomized Clinical Trial in Pediatric Rheumatology: Are Parents and Patients in Equipoise? Petra C.E. Hissink Muller[1], Bahar Yildiz[1], Cornelia F. Allaart[1], Danielle M.C. Brinkman[2], Marion A. J. Van Rossum[3], J. Merlijn Van den Berg[4], Lisette W.A. Van Suijlekom-Smit[5], Rebecca Ten Cate[1] and Martine C. de Vries[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rijnland Hospital, Leiderdorp, Netherlands, [3]Emma Children's Hospital / Academic Medical Center and Reade Institute, Amsterdam, Netherlands, [4]Emma Children's Hospital / Academic Medical Centre and Reade Institute, Amsterdam, Netherlands, [5]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands

Background/Purpose: It is an ethical requirement for setting up a randomized controlled trial (RCT) that the physician-investigator must have genuine uncertainty about the therapeutic options. This is called equipoise. Ideally patient-participants should also be in equipoise. In pediatric rheumatology, there are no data on whether this uncertainty also consists among parents and patients or if they have a specific preference for a particular treatment strategy. We conducted an interview study on the preferences of parents and children and the influence of the informed consent procedure on preferences in the setting of a randomized clinical trial in Juvenile Idiopathic Arthritis patients.

Methods: Semi-structured interviews with parents (n = 23, 1 father and 22 mothers) and patients aged 12 and older (n = 7) participating in the BeSt for Kids study, a randomized clinical trial with three treatment strategies (arm 1: initial monotherapy with sulfasalazine or methotrexate, arm 2: initial combination therapy with methotrexate and prednisone and arm 3: initial combination therapy with etanercept and methotrexate) in selected categories of newly diagnosed juvenile idiopathic arthritis patients.

Results: All parents had a preference for a particular treatment strategy, 65% had a preference for the combination therapy with etanercept and methotrexate (arm 3). Five parents and two patients participated in the study to have a chance to be initially treated with etanercept, as initial treatment with etanercept in daily practice is currently neither possible nor reimbursed. The preference of parents and patients for arm 3 was based on their idea that etanercept is the best treatment for juvenile arthritis. The parents indicated that these beliefs were mainly based on knowledge they had gained through the internet and from experiences from people in their environment. Four parents had a preference for a non-prednisone arm. Aversion for prednisone was primary due to the fear for side-effects, such as weight gain. According to four parents, the physician-investigator had a preference for arm 3, but the vast majority of parents (n = 19) stated that the physician-investigator had no preferred strategy. Similar results emerged from the interviews with children.

Conclusion: A large part of parents and children in the BeSt for Kids study are not in equipoise. In this study this is not caused by an assumed preference of the physician-investigator but by information on the various treatment possibilities obtained from other sources. The question is whether the absence of equipoise in parents and patients indicates that randomization is unethical or that this equipoise is not feasible in medical research.

2003

Colchicine As a Therapeutic Option in Periodic Fever Aphtous Stomatitis, Pharingitis Syndrome. and Cervical Adenitis (PFAPA). Yonatan butbul Aviel[1], Sameh Tatour[2], Ruth Gershoni[3] and Riva Brik[4]. [1]Rambam Medical center, Haifa, Israel, [2]Rambam Medical Center, Israel, [3]Rambam, Israel, [4]Rambam Medical center

Background/Purpose: PFAPA syndrome is episodic disease characterized by periodic episodes of high fever, aphthous stomatitis, pharyngitis, and cervical adenitis, so far no therapy was shown to be effective in preventing the attacks.

The aim of our study was to evaluate the efficacy of colchicine in reducing attacks of PFAPA.

Methods: We carried a randomized control study among patients diagnosed with PFAPA in the pediatric Rheumatology clinic- Rambam Medical center, Israel.

The patients were randomized into two groups followed for 6 months. In months 1–3 both groups were followed without preventive therapy; In months 4–6, group 1 continued to be followed in the same manner, patients in group 2 received colchicine for three months in a standard dose. During the study patients and physician recorded all PFAPA episodes, in a log book. DNA analysis for the common FMF mutation was done for all patients.

Results: 14 patients 5.8±1.9 years old were evaluated(8 in group 1, 6 in group 2).

The number of episodes in the first 3 months were 3.5±1.3 in group 1 and 4.9±2.45 in group 2 (p=0.187), the number of episodes in group 2 under colchicine therapy were 1.7±1 compared to 4.9±2.4 in the period without therapy (p=0.01).

Seven patients were found to be carrier of one FMF mutation;(4 in group2 and 3 in group1). Patients with PFAPA who carry one mutation for FMF responded to colchicine therapy (6.1±2 episodes before and 2±1.4 after therapy p-0.03).

Conclusion: Colchicine therapy might be effective in increasing intervals between episodes of PFAPA. Larger studies are needed to confirm these findings.

2004

Do We Need a Minimum Standards in Care for Children with Localized Scleroderma- Result of the Consensus Meeting in Hamburg Germany On the 11th of December 2011. Part I. Diagnosis and Assessment of the Disease. Ivan Foeldvari[1], Tamás Constantin[2], Peter Hoeger[3], Monika Moll[4], Clare Pain[5], Dana Nemcova[6], Kathryn S. Torok[7], Lisa Weibel[8] and Philip J. Clements[9]. [1]Hamburger Zentrum Kinder-und Jugendrheumatologie, Hamburg, Germany, [2]Semmelweis Egyetem, AOK, II.sz. Gyermekgyogyaszati Klinika, Budapest, Hungary, [3]Kinderkrankenhaus Wilhelmstift, Hamburg, Germany, [4]University Children's Hospital, Tübingen, Germany, [5]University Children's Hospital, Liverpool, United Kingdom, [6]University Children's Hospital, Prague, Czech Republic, [7]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [8]University Children's Hospital, Zurich, Switzerland, [9]UCLA School of Medicine, Los Angeles, CA

Background/Purpose: Juvenile localised scleroderma (jlSc) is an orphan disease. There are currently no guidelines regarding diagnosis, follow up and treatment. In the frame of the PRES scleroderma working group this consensus meeting was set up to gain consensus regarding these issues.

Methods: Members of the PRES scleroderma working group were invited to participate. Two pediatric dermatologists were invited to reflect the multidisciplinary care for these children. P. Clements was invited to moderate the meeting. A nominal group technique was used. 75% consensus was defined as agreement.

Results: The following agreements were reached regarding diagnosis and follow up:

1. Diagnosis is based on clinical grounds by a rheumatologist or dermatologist, preferably pediatric, with a biopsy as a confirmatory measure if it is unclear based on clinical findings.
2. If a biopsy is needed, a punch biopsy is appropriate. In the case of deep involvement, a deep biopsy is needed.
3. Since progression to systemic sclerosis is unlikely, an evaluation for internal organ involvement, such as HRCT and echocardiogram, is unnecessary.
4. There are no laboratory studies needed to confirm the diagnosis.
5. The group agrees there is no clear evidence for a pathogenic role of Borrelia, therefore we do not recommend investigation for Borrelia infection.
6. In patients with sclerodermatous skin changes of the head (face and/or scalp) the following are suggested:

1. MRI of the brain, preferably with contrast.
2. In the absence of clear evidence, the group suggested to screen every 6 months for uveitis with slit lamp examination for the first 4 years of the disease.
3. Dental assessment is strongly suggested, especially if the lesion crosses the maxilla and mandible.
4. Temporomandibular joint assessment by a pediatric rheumatologist every 6 months is suggested.
5. In the absence of clear evidence, the group suggested to screen every 12 months for uveitis with slit lamp examination for the first 4 years of the disease, if the lesion does not involves the face.
6. All patients besides superficial circumscribed localised scleroderma (plaque morphea), especially those with linear disease, are suggested to be seen at baseline and every 12 months by both a pediatric rheumatologist and pediatric dermatologist, ideally in combined clinic.
7. The group suggested using the LoSCAT (Localized Scleroderma Cutaneous Assessment Tool) to assess cutaneous activity and damage measures, because this is the only validated tool currently available according the OMERACT criteria for LS.
10. There is a need to assess the quality of life of jLS patients and the group suggests using the CDLQI, a generic skin disorder quality of life measure. This is one of the most widely used skin QOL instrument and is validated in most European languages.
11. The group suggested to assess the patients global assessment of disease severity on a VAS scale from 0 to 100.

Conclusion: Although there are no solid guidelines currently present as the 'standard of care' for jLs, these suggestions are part of routine care for most physicians specializing in the care of pediatric localized scleroderma and are non-invasive measures.

2005

Clinical Course and Outcomes of Children with Juvenile Idiopathic Arthritis-Associated Uveitis and Idiopathic Uveitis. Sheila T. Angeles-Han[1], Steven Yeh[1], Courtney McCracken[1], Larry B. Vogler[1], Kelly Rouster-Stevens[2], Christine W. Kennedy[2], Matthew Kent[1], Kirsten Jenkins[3], Scott Lambert[1], Carolyn Drews-Botsch[4] and Sampath Prahalad[2]. [1]Emory Univ School of Medicine, Atlanta, GA, [2]Emory Children's Center, Atlanta, GA, [3]Children's Healthcare of Atlanta, Atlanta, GA, [4]Emory University School of Public Health, Atlanta, GA

Background/Purpose: Uveitis can lead to vision loss and blindness. Few studies focus on the outcomes of children with both juvenile idiopathic arthritis-associated uveitis (JIA-U) and idiopathic uveitis (I-U). The determination of risk markers for uveitis development and disease severity is important in examining the long-term outcomes of this population. Our objective is to characterize the epidemiology and clinical outcomes of children with JIA-U and I-U in a cohort of children in an urban tertiary care center in the Southeast.

Methods: Children with JIA, JIA-U, and I-U participated. Medical record reviews were performed. Questionnaires were completed on overall quality of life (QOL) (Pediatric QOL Inventory - PedsQL), physical function (Childhood Health Assessment Questionnaire - CHAQ), and visual function (Effects of Youngsters' Eyesight on QOL - EYE-Q).

Results: Our 132 patients were primarily female (72%), non-Hispanic (89.4%) and Caucasian (74.2%). Compared to JIA, children with JIA-U were more frequently African American, diagnosed with oligoarticular extended JIA and had a younger age of arthritis onset (Table 1). There were no significant differences in gender, ANA, RF or HLA-B27. Children with I-U were more frequently HLA-B27 (+) (p=0.023), had worse visual acuity (p=0.005), and more band keratopathy (p=0.028), cystoid macular edema (p=0.032) and cataract extractions (p=0.032).

There were significant differences in the EYE-Q scores in children with uveitis compared to JIA (p=0.043), significant differences in the CHAQ and PedsQL Physical scale scores in children with arthritis compared to I-U (p=0.046), and no differences in PedsQL total and psychosocial QOL scores in all groups (p=0.045, p=0.023) (Table 2).

Table 1. Characteristics of children with JIA-associated uveitis, JIA alone, and idiopathic uveitis

	JIA alone N = 104	JIA-U N = 19	I-U N = 9	P-value 1[a] All groups	P-value 2[b] JIA vs. JIA-U	P-value 3[c] JIA-U vs. I-U
Demographic Characteristics						
Age, mean years ±SD	11.6 ± 4.8	10.5 ± 4.5	11.7 ± 4.9	0.669	0.38	
Gender, female, N (%)	74 (71.8)	16 (84.2)	5 (55.6)	0.269	0.283	
Hispanic, N (%)	10 (9.7)	4 (22.2)	0 (0)	0.159	0.221	
Race, N (%)				0.245	0.296	
Caucasian	81 (77.9)	12 (70.6)	5 (55.6)			
African American	13 (12.5)	5 (29.4)	4 (44.4)		0.026*	
Other[+]	10 (9.6)	0 (0)	0 (0)			
Disease characteristics						
Age at arthritis onset, mean years ±SD	7.4 ± 4.5	4.0 ± 4.6			0.004*	
Age at uveitis onset, mean years ±SD		6.8 ± 5.1	8.0 ± 4.4			0.594
Duration of JIA, mean years ±SD	3.99 ± 3.51	6.48 ± 3.74			0.008*	
Duration of uveitis, mean years ±SD		3.68 ± 3.56	3.65 ± 3.12			0.985
JIA subtype, N (%)						
Oligo persistent	27 (26.2)	15 (79.0)			<0.0001*	
Oligo extended	6 (5.8)	0 (0)			0.589	
Poly RF (+)	6 (5.8)	0 (0)			0.589	
Poly RF (−)	24 (24.3)	1 (5.3)			0.072	
Psoriatic	7 (6.8)	1 (5.3)			1	
Systemic	9 (8.74)	0 (0)			0.352	
ERA	9 (8.74)	2 (10.5)			1	
Undifferentiated	2 (1.94)	0 (0)			1	
Labs, N (%)						
ANA	32 (36.0)	9 (47.4)	1 (12.5)	0.226	0.437	
RF	12 (13.4)	0 (0)	0 (0)	0.126	0.12	
Anti-CCP	9 (10.1)	0 (0)	0 (0)	0.238	0.212	
HLA-B27	6 (6.8)	2 (10.5)	3 (37.5)	0.023*	0.63	
Ophthalmology exam, most recent	N = 34	N = 15	N = 7			
LogMarVA mean±SD, worse eye	0.17 ± 0.24	0.24 ± 0.22	0.74 ± 0.98	0.005*	0.347	
Intraocular pressure, worse eye	11.5 (7.8)	19.0 (7.5)	18.7 (8.6)	0.057	0.029*	
Slit lamp exam, worse eye						
Cells, N				0.015*	0.002*	
0(<1 cell in field)	34	11	4			
0.5+(1–5 cells in field)	0	2	2			
1+(6–15 cells in field)	0	1	0			
2+(16–25 cells in field)	0	2	0			
3+(26–50 cells in field)	0	0	0			
4+(>50 cells in field)	0	0	0			
Complications, N (%)		N = 17	N = 9			
Cataracts		5 (29.4)	6 (66.7)			0.103
Glaucoma		0 (0)	2 (22.2)			0.111
Synechiae		6 (36.3)	7 (77.8)			0.097
Band keratopathy		2 (11.8)	5 (55.6)			0.028*
Cystoid macular edema		0 (0)	3 (33.3)			0.032*
Other complications		3 (17.7)	4 (57.1)			0.188
Surgeries, N (%)						
Cataract extraction		0 (0)	3 (33.3)			0.032*
Periocular steroid injection		2(11.8)	3 (33.3)			0.302
Other ocular surgeries		1 (5.9)	2 (22.2)			0.529

ANOVA, Chi-square, * p-value <0.05
[a] P value 1: comparison of all groups, [b]P value 2: comparison of JIA and JIA-U, [c]P value 3: comparison of JIA-U and I-U
[+] Other races: American Indian, Asian, and unreported/unknown

Table 2. Mean scores on quality of life and function measures

	JIA N = 104	JIA-U N = 19	I-U N = 9	P value
EYE-Q[a] (range 0–4)**	3.64 ± 0.44	3.31 ± 0.44	3.37 ± 0.79	0.043*
CHAQ[b] (range 0–3)[++]	0.59 ± 0.61	0.72 ± 0.67	0.00 ± 0.00	0.046*
PedsQL[c] Physical scale (range 0–100)**	70.3 ± 24.4	60.47 ± 24.7	91.5 ± 5.3	0.023*
PedsQL Psychosocial scale	74.5 ± 18.8	69.0 ± 17.9	81.8 ± 18.4	0.334
PedsQL Total scale	73.1 ± 19.5	65.98 ± 18.90	85.31 ± 18.89	0.102

ANOVA , *p-value <0.05
[a] Effects of Youngsters Eyesight on QOL; [b]Childhood Health Assessment Questionnaire; [c]Pediatric Quality of Life Inventory
** Greater scores indicate better QOL; [++]Greater scores indicate worse QOL
Note: The sample size in each group varies by scoring tool.

Conclusion: Children with I-U may have a poorer visual outcome compared to JIA-U. Race, HLA-B27 (+), age of arthritis onset, and JIA subtype may be important risk factors for developing uveitis, whereas gender, ANA, and RF may not be as significant. As expected, visual disability was worse in uveitis, and physical disability was worse in arthritis. Hence, compared to JIA and I-U, children with JIA-U have more components of disability. All children had similar psychosocial and overall QOL probably secondary to having a chronic illness.

To improve the assessment of outcomes in JIA-U, a comprehensive approach incorporating all aspects of disability should be considered. Likewise, the determination of risk markers leading to poor outcomes in children with uveitis is crucial. Longitudinal studies examining the outcome of children with uveitis are ongoing.

2006

Sexual Health and Substance Abuse in Adolescents with Rheumatic Conditions. Sara M. Stern, Rhina Castillo, Katherine AB Marzan, Jennifer Jackson, Mona Desai, Ellen Iverson, Leslie F. Clark and Diane Tanaka. Children's Hospital Los Angeles, Los Angeles, CA

Background/Purpose: Adolescence is a unique stage with pubertal maturation, individuation from parents and peer group identification. The impact of a rheumatic condition can affect social, emotional and sexual development. We sought to examine the risky behavior of youth with rheumatic conditions, compare it to their unaffected peers, and identify differences between infusion (INF) and non-infusion (OP) patients (pts).

Methods: 50 pts with a rheumatologic diagnosis (RHEUM) from the rheumatology clinic and the ambulatory infusion center at a tertiary children's hospital were surveyed with the Audio Computer-Assisted Self-Interview (ACASI) system to assess their substance use and sexual health. Data from the RHEUM pts was compared to the Youth Behavior Surveillance – United States – 2011 (YRBS) for the region, and between INF and OP pts. The YRBS assesses the prevalence of health-risk behaviors in youth grades 9–12.

Results: 50 pts (42F: 8 M) aged 15–20 yrs were primarily Latino (74%). Diagnoses included arthritis (15), systemic lupus erythematosus (15), mixed connective tissue disease/ overlap syndrome (MCTD) (8), dermatomyositis (4), vasculitis (3) and unidentified (5). OP (n=26) and INF (n=24) pts were almost equal.

RHEUM patients reported lower percentage (%) of alcohol use (28% vs 65.1% CI 62.2–67.9%), binge drinking (10% vs 17.9% CI 15.5 – 20.5%), cigarette use (26% vs 39.2% CI 34.8 – 43.7%) and marijuana use (26%42.4% CI 37.0 – 47.9%) when compared to YRBS. INF and OP pts did not differ significantly in alcohol (63% vs 54%, p = 0.40) and marijuana use (25% vs 27%, p = 0.957), but cigarette use was more prevalent in INF than OP (21% vs 31%, p = 0.54). 14% of RHEUM pts gave health reasons for MJ use and 4% of INF pts had a medical MJ card. 12% of RHEUM pts had tried other street drugs (INF-4% vs OP 12% p=0.12). Prescription drug misuse was similar for RHEUM pts (14%) and YRBS (12.1% CI 10.0 – 14.5%) as well as INF and OP pts (17% and 12%) (p = 0.61).

RHEUM pts and YRBS had similar rates of first sexual experience (42% vs 38.9% (CI 32.4 – 45.7%), with equal results in INF and OP 42% (p = 0.96). RHEUM pts had a slightly higher % of current sexual activity than YRBS (28% vs 25.7% CI 20.1 – 32.1%) with higher % in the INF pts than the OP (33% vs 23%) (p = 0.432).

Of the 14 sexually active RHEUM pts, 57% used condoms, 75% INF vs 33% OP (p = 0.26). Condom use during last sexual intercourse (SI) was similar between RHEUM pts and YRBS (64.3% vs 61.1% CI 55.2 – 66.7%), with 14% of RHEUM pts using other forms of birth control (BC) during last SI vs 10.9% YRBS (CI 7.2 – 16.2).

70% of RHEUM pts had future plans for children but only 46% had discussed this with their rheumatologist. 50% felt that their condition or medication could interfere with a pregnancy with higher % in the INF than OP pts (58% vs 42%, p = 0.014).

Conclusion: Adolescents and young adults in a primarily Latino pediatric rheumatology population participate in risky sexual and substance use behaviors at rates similar to their unaffected peers with no statistically significant difference between INF and OP sub-groups. Routine screening and counseling by healthcare providers is important to decrease morbidity.

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2007

Radiological Peripheral Involvement At Hands, Feet and Hips in Young Adults with Polyarticular Idiopathic Juvenile Arthritis. Muriel Elhai[1], Ramin Bazeli[2], Veronique Freire[2], Antoine Feydy[2], Andre Kahan[1], Chantal Job-Deslandre[1] and Julien Wipff[1], [1]Rheumatology A, Paris Descartes University, Cochin Hospital, APHP, Paris, France, [2]Radiology B, Paris Descartes University, Cochin Hospital, APHP, Paris, France

Background/Purpose: Radiographic damage was recently considered to be a feature of poor prognosis in cases of polyarticular juvenile idiopathic arthritis (pJIA). However, most radiographic studies did not differentiate pJIA from other subtypes of JIA and did not include a control group. Furthermore little is known about radiographic damages in pJIA persisting into adulthood. The objective of our study was to describe structural peripheral involvement in pJIA persisting into adulthood and compare observed lesions to those seen in rheumatoid arthritis (RA) using a cross-sectional observational study.

Methods: All consecutive pJIA followed in a transition program were included. Age, sex, disease duration, medical or surgical treatments were collected. Laboratory tests (ESR, CRP, Rheumatoid Factor (RF) and anti-CCP) and standard radiographies of the hands and wrists, feet and hip were performed. A RA control group (<55years), matched for sex and disease duration, was recruited. Radiographs were analyzed by two independent radiologists blinded to the diagnosis. Structural lesions on the hands and feet were assessed by the modified version of Larsen's scoring method. The hands and feet scores range from 0 to 110 and from 0 to 50, respectively. Hips were assessed for presence of coxitis. Student and Fischer exact test were used.

Results: 58 pJIA (48 females/10 males) and 59 RA (52/7) were included. Respectively, mean age was 23.5±10.0 years and 43.2±9.6 years and mean disease duration 13.1±11.1 and 12.2±7.1 years. 60% and 80% were RF positive and 57% and 78% were anti-CCP positive (p=0.02). The inter-observer concordance coefficient kappa was 0.614 between the two investigators. Radiographs showed hand lesions in 45/58 (78%) pJIA and 50/58 (86%) RA-patients, feet lesions in 39/58 (67%) pJIA and 47/59 (80%) RA-patients and coxitis in 16/54 (30%) pJIA and 8/47 (17%) RA-patients (p=NS for all comparisons). Mean hands and feet scores were 17.9±21.8 and 7.7±10.8 in pJIA and 18.5±17.6 and 9.9±11.3 in RA, respectively (p=NS). Specificities to juvenile forms were a lower frequency of proximal inter-phalangeal joints involvement and a higher risk of bilateral coxitis (81% vs. 25% (p=0.007, OR=13 [1.701–99.375]) than adult RA. RF-positive patients differed from RF-negative patients only by a shorter disease duration (10.4±9.3 vs. 17.3±12.6, p=0.02). Comparison between RF positive and negative hand showed a trend for more frequent hand and feet lesions with a higher carpal score in RF-positive patients. There were less coxitis (5/31 vs. 11/23) in RF-positive subgroup (p= 0.01). In pJIA, presence of radiographic damage correlated with a more severe disease phenotype.

Conclusion: Structural peripheral damages are frequent in young adults with pJIA and correlated with a more severe disease. A specific feature to pJIA seems to be a high risk of bilateral coxitis. This requires a particular following and monitoring of pJIA patients with unilateral hip involvement to prevent bilateralization.

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2008

Initial Evaluation of a Localized Scleroderma (LS) Clinical Activity Measure. Suzanne C. Li[1], Kathryn S. Torok[2], Christina Kelsey[2], Mara L. Becker[3], Fatma Dedeoglu[4], Robert C. Fuhlbrigge[5], Gloria C. Higgins[6], Sandy D. Hong[7], Maria F. Ibarra[3], Ronald M. Laxer[8], Thomas G. Mason II[9], Marilynn G. Punaro[10], Elena Pope[11], Egla C. Rabinovich[12] and Katie G. Stewart[10],. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Children's Mercy Hospital, Kansas City, MO, [4]Boston Childrens Hosp, Boston, MA, [5]Childrens Hospital, Boston, MA, [6]Nationwide Childrens Hosp, Columbus, OH, [7]U of Iowa Children's Hosp, Iowa City, IA, [8]The Hospital for Sick Children, Toronto, ON, [9]Mayo Clinic Rochester, Rochester, MN, [10]Texas Scottish Rite Hospital, Dallas, TX, [11]Hospital for Sick Children, Toronto, ON, [12]Duke University Medical Center, Durham, NC

Background/Purpose: LS commonly causes severe morbidity for the growing child. Optimal therapy is not known and the lack of an agreed-upon standard for assessing disease state and monitoring treatment response has hindered treatment comparison. To work towards conducting comparative effectiveness studies, an LS-focused Childhood Arthritis and Rheumatology Research Alliance subgroup developed a clinical disease activity measure (LS Activity Score, Arthritis Care Res 2012 DOI: 10.1002/acr.21687), based upon LoSSI and LOCUS studies (J Rheumatol 2008;35:640; Arthritis Rheum 2011;63 Suppl:S955). The LS Activity Score scores for 7 parameters (erythema, violaceous color, waxy or white lesion, skin thickness of lesion edge, lesion warmth, new lesion, change in lesion size) in affected anatomic sites, with body divided into 19 sites.

Objective: To evaluate the validity and reliability of the LS Activity Score.

Methods: A two-day workshop meeting was conducted in which 13 pediatric rheumatologists and a pediatric dermatologist reviewed LS clinical measures and conducted a reliability of scoring study. The 14 raters evaluated 13 juvenile LS (jLS) patient volunteers with the LS Activity Score in a random order twice in one day. For each patient, raters were told which anatomic sites to assess (1–2/patient); new lesion and lesion size change were not scored because they require prior patient evaluation. Raters scored Physician Global Assessment (PGA, 0–100 mm) of disease activity (DA) and

PGA of disease damage (DD) for each patient based upon evaluated anatomic sites. We hypothesized the LS Activity Score would have moderate to high correlation with PGA-DA (convergent validity) and low correlation with PGA-DD (divergent validity). Spearman's rho was calculated to assess level of correlation, and intraclass correlation coefficients (ICC) calculated to assess intra- and inter-rater reliability (0.20–0.39 considered low, 0.40–0.59 moderate, >0.60 high).

Results: Mean age of jLS patients was 13.2 years, most common subtype was linear scleroderma (4 limb, 4 head). Mean patient LS Activity Scores ranged from 0.50 to 9.28 (4–52% of maximum possible score), mean PGA-DA from 4.0 to 59.6. There was a high correlation between LS Activity score and PGA-DA ($\rho=0.94$), and low with PGA-DD ($\rho=-0.121$). Raters showed moderate inter-rater reliability for LS Activity Score and PGA-DA, with nearly all showing moderate to high intra-rater reliability for these scores (Table). Among the different parameters, violaceous color and lesion warmth had the lowest inter-rater reliability.

Table. Inter-rater and intra-rater reliability of LS Activity score

Domains	Round 1 ICC (95% CI)	Round 2 ICC (95% CI)
LS Activity Score:		
Inter-rater reliability	0.564 (.38, .79)	0.628 (.43, .83)
Intra-rater reliability (median)		0.804 [range 0.464–0.910]
PGA-DA:		
Inter-rater reliability	0.566 (.38, .79)	0.516 (.33, .76)
Intra-rater reliability (median)		0.734 [range 0.369–0.955]
LS Activity Score parameters: inter-rater reliability		
Erythema	0.392 (.25, .59)	0.483 (.33, .67)
Violaceous color	0.187 (.09, .36)	0.140 (.06, .29)
Waxy or white lesion	0.429 (.29, .63)	0.518 (.37, .70)
Lesion warmth	0.197 (.10, .37)	0.148 (.07, .30)
Skin Thickness of lesion edge	0.407 (.26, .60)	0.307 (.18, .50)

Conclusion: We demonstrate initial construct validity for LS Activity score, and found moderate inter-rater reliability. Additional studies are needed to fully evaluate this measure's validity. More training for the violaceous color and lesion warmth parameters may improve the measure's reliability.

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2009

Does Breastfeeding Influence the Presentation of Juvenile Idiopathic Arthritis? Results From the Childhood Arthritis Prospective Study. Hannah Pickford[1], Eileen Baildam[2], Alice Chieng[3], Joyce Davidson[4], Helen E. Foster[5], Janet Gardner-Medwin[4], Lucy R. Wedderburn[6], Wendy Thomson[1] and Kimme L. Hyrich[1]. [1]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [2]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [3]Manchester Children's Hospital, Manchester, United Kingdom, [4]Royal Hospital for Sick Children, Glasgow, United Kingdom, [5]Musculoskeletal Research Group, Newcastle upon Tyne, United Kingdom, [6]University College London (UCL), London, United Kingdom

Background/Purpose: There is extensive research into the association between breastfeeding (BF) and the occurrence of autoimmune diseases, although results have been conflicting. Studies have suggested that BF may influence the presentation of juvenile idiopathic arthritis (JIA), with a higher prevalence of BF among children with polyarticular presentation. The aim of this analysis was to study the influence of BF on the presentation of JIA in a large prospective inception cohort of children with childhood-onset arthritis.

Methods: The Childhood Arthritis Prospective Study (CAPS) recruits children $\leq$ 16 years old with new onset ($\geq$2 weeks) inflammatory arthritis from five tertiary hospitals in the United Kingdom. At presentation to pediatric rheumatology, a physician performs an examination and completes a Physician Global Assessment (PGA). Families also complete a Childhood Health Assessment Questionnaire (CHAQ) including a Parent General Evaluation (PGE) and pain visual analogue scale (VAS). Detailed demographic data is collected including age at onset, gender, ethnicity, and household factors including parental education and income. Families were also asked if the child was BF and for how long. Baseline characteristics were compared between those children who were and were not BF using descriptive statistics. The association between BF and a high CHAQ score (>0.75) at presentation were determined using multivariate logistic regression, adjusted for age at onset, symptom duration, ILAR subtype, hospital, ethnicity

and socioeconomic status (SES). Using postcodes, SES was determined by calculating the Index of Multiple Deprivation score and categorised into three groups: low, medium and high.

Results: 927 children (65% female) were included in the analysis: median age at onset 6.4 years. Overall, 54% were breastfed, although the majority for <6 months. BF children reported a lower median age at onset (5.7 vs 7.5 years; p<0.001), a lower CHAQ score, lower PGE and lower pain at baseline (see Table). There was a trend towards a higher proportion of BF children with rheumatoid factor negative polyarthritis but lesser enthesitis related and psoriatic arthritis. There was a statistically significant inverse association between BF and high CHAQ (OR 0.62, 95% CI 0.41, 0.95) which was no longer significant after adjustment (OR 0.66, 95% CI 0.41, 1.07).

Characteristic, median (IQR) or n(%)	Never Breastfed	Breastfed	p-value
n	424 (45.7)	503 (54.3)	
Duration of breastfeeding (months)	–	3.6 (1.4, 6.9)	
Age at onset of symptoms (years)	7.5 (3.4, 10.7)	5.7 (2.0, 10.1)	<0.001
Symptom duration (months)	5.4 (2.8, 12.1)	4.9 (2.4, 10.3)	0.308
Caucasian	394 (92.9)	441 (87.7)	0.008
ILAR Subtype			0.009
Systemic	23 (5.4)	26 (5.2)	
Oligoarthritis	224 (52.8)	264 (52.5)	
Polyarthritis RF negative	81 (19.1)	135 (26.8)	
Polyarthritis RF positive	11 (2.6)	16 (3.2)	
Enthesitis-related	34 (8.0)	18 (3.6)	
Psoriatic	38 (9.0)	30 (6.0)	
Undifferentiated	13 (3.1)	14 (2.8)	
CHAQ (n=677)	0.88 (0.25, 1.63)	0.63 (0.13, 1.25)	<0.001
Physician Global Assessment	31 (18, 54)	28 (15, 50)	0.057
Parent Global Evaluation	29 (6, 53)	18 (4, 45)	0.006
Pain score	39 (10, 64)	23 (5, 50)	<0.001
Active joint count	2 (1, 5)	2 (1, 5)	0.747
Limited Joint Count	1 (1, 3)	1 (1, 3)	0.151
ESR, mm/hr	18 (6, 45)	21.5 (7, 53)	0.088
Hospital			<0.001
Liverpool	187 (44.1)	195 (38.8)	
Manchester	86 (20.3)	88 (17.5)	
Glasgow	68 (16.0)	71 (14.1)	
Newcastle	31 (7.3)	20 (4.0)	
London	52 (12.3)	129 (25.7)	
Index of Multiple Deprivation Category (n=475)			<0.001
Low	28 (12.6)	61 (24.1)	
Medium	93 (41.9)	123 (48.6)	
High	101 (45.5)	69 (27.3)	

Conclusion: There is an association between breastfeeding and an earlier and less severe presentation of JIA, although this could be explained in part by socioeconomic factors. Further work to elucidate the association between breastfeeding and later presentation of autoimmune diseases is required.

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2010

Administration of Routine Preventative Vaccinations in Children with Juvenile Idiopathic Arthritis Receiving Adalimumab. Neelufar Mozaffarian and Vipin Arora. Abbott, Abbott Park, IL

Background/Purpose: Adalimumab, a fully human monoclonal antibody to tumor necrosis factor-alpha (TNF) has been shown to be safe and effective in juvenile idiopathic arthritis (JIA), and is approved for this use in several countries.[1] Patients with JIA are candidates for routine childhood vaccinations. This post hoc report describes the observed use of vaccines in JIA patients receiving adalimumab for up to 3 years in a clinical trial setting.

Methods: Patients with active JIA were enrolled in one of the following trials: M10–444 (ages 2–4 or $\geq$ age 4 weighing <15 kg in US, EU), M10–240 (ages 4–17 in Japan), or DE038 (ages 4–17 in US, EU). Patients received treatment with ADA (weight-based dosing) every other week, either with or without methotrexate use. Any vaccinations administered were based on the judgment of the study investigators. Descriptive statistics were used to summarize all vaccinations, including influenza vaccine. Adverse events (AEs) related to active influenza virus infection were collected by a pre-

defined MedDRA Query, and events occurring within 270 days of influenza vaccination were identified.

Results: A summary of all vaccinations is presented in the **Table**. Among the different types of vaccines, the most frequently administered were: influenza virus vaccine polyvalent in DE038 and M10–240 (n=59 and 63 vaccinations, respectively), and pneumococcal in M10–444 (n=28 vaccinations). In DE038 and M10–240, 2 patients each received >5 vaccinations and in M10–444, 10 patients received >5 vaccinations. The majority of vaccinated patients in each study received >1 type of vaccination. Among those who were never vaccinated for influenza, 12/137 patients (9%) in DE038, 1/5 patients (20%) in M10–240, and 2/28 patients (7%) in M10–444 reported influenza infection-related AEs. In those who received influenza vaccination, 4/34 patients (12%) in DE038, and 3/20 patients (15%) in M10–240 reported influenza infection-related AEs within 270 days of vaccination; none (0%) reported influenza infection-related AEs in M10–444.

Table. Summary of Vaccination Data Among JIA Patients

All Vaccinations	DE038	M10-240	M10-444
Total patients vaccinated, n/N	40/171	20/25	20/32
Females vaccinated, %	83	75	85
Mean age, yrs (SD)	12 (3.6)	14 (3.3)	3 (0.7)
Total vaccinations, n	82	67	122
Patients with >1 vaccination, n	23	17	18
Patients with >1 type of vaccination, n	11	2	18
Different types of vaccinations, n	9	3	29
Mean time to 1st vaccination, days	714	187	96
Mean age at 1st vaccination, yrs[a]	13	14	3
Mean JIA duration at 1st vaccination, yrs[a]	NA	4.5	1.02
Influenza Vaccinations	**DE038**	**M10-240**	**M10-444**
Total patients vaccinated, n/N	34/171	20/25	4/32
Females vaccinated, %	79	75	75
Total vaccinations, n	59	63	6
Patients with >1 vaccination, n	17	17	1
Mean time to 1st vaccination, days	688	189	96

NA=not available. [a]Data for mean age at 1st vaccination and mean time to 1st vaccination are the same for "Influenza Vaccinations" for each study.

Conclusion: These data support the idea that JIA patients treated with adalimumab can be safely immunized with routine, inactive, preventative vaccines, including influenza vaccine.

Reference

1 Lovell DJ, et al. *NEJM* 2008;359:810–820.

Disclosure: N. Mozaffarian, Abbott Laboratories, 1, Abbott Laboratories, 3; **V. Arora**, Abbott Laboratories, 1, Abbott Laboratories, 3.

2011

ACR Criteria, Providers' Global Rating of Change and Role of Patient Self-Report in Evaluating Change in Disease Over Time: A Patient Reported Outcomes Measurement Information System Study. Bin Huang[1], Jennifer Farrell[1], Adam Carle[1], Stacey Niehaus[1], Hermine Brunner[2], Alexei A. Grom[1], Michael Henrickson[1], Jennifer L. Huggins[1], D. J. Lovell[3], Tracy V. Ting[1] and Esi M. Morgan DeWitt[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center and PRSCG, Cincinnati, OH, [3]Cincinnati Children's Hospital, Cincinnati, OH

Background/Purpose: As part of a longitudinal study of Juvenile Idiopathic Arthritis (JIA), providers completed clinical outcomes assessments and patients (pt) completed self-report measures at clinic visits. In addition to measuring ACR Pediatric response based on the 6 core variables (CHAQ, active joint count, loss of motion, ESR, physician global assessment (PGA), and pt's well-being), providers rated the pt's global change of overall health (GRC-health) and JIA (GRC-JIA) between visits on a scale from 1 (very much worse) to 7 (very much better). Pt's report of pain and health-related quality of life (HRQoL) are not part of the core measures. Study Aims: 1) To assess the relationship between JIA improvement at the ACR-Ped70 level with the provider's GRC-health and GRC-JIA ratings; 2) To evaluate whether pain and HRQoL as assessed by the PedsQL Core and Rheumatology modules are associated with the provider's GRC-health and GRC-JIA ratings.

Methods: Inclusion criteria were diagnosis of JIA, age 8–18 yrs at enrollment, and English fluency. Study visits occurred 3–4 times/yr concomitantly with scheduled clinic visits. Analyses considered baseline data and 2nd assessments.

Results: Data on 113 JIA pts was available (mean age=13.1±2.7 yrs; range=8.1–18.4 yrs). Majority (86) were female (71%); 72 had polyarthritis (63.7%), 18 oligoarthritis (16%), 11 systemic JIA (9.7%) and 12 other (10.6%). Mean age at diagnosis was 9.0±4.4 yrs. The GRC-health (N=95) and the GRC-JIA (N=106) were highly correlated (r = 0.73, P <.0001). At 2nd assessment, 10.6% (n=12) achieved an ACR-Ped70 treatment response from baseline. ACR-Ped70, 50 and 30 improvements were all moderately correlated with GRC ratings (r range:.32-.43, P<.001). ACR-Ped70 responders significantly differed from others in their GRC-health (4.1±1.2 vs. 5.8±1.1; P<.001) and GRC-JIA ratings (4.4±1.1 vs. 6.3±0.97; P <.001). All ACR-Ped70 responders had GRC-health and GRC-JIA ratings >4. Both GRC ratings were significantly (P<.05) correlated with ACR core measures except ESR (P<.12) (r range:.18-.46), and with pt's pain (r = 0.4,.45; P<.0001). PedsQL Core and Rheumatology Module total and domain scores were significantly correlated with both GRC ratings and ACR-Ped response levels. The final GRC-health multivariable model included ACR-Ped70, gender, ACR-Ped70 by gender interaction, JIA subtype, active joint count and pt's pain; none of the PedsQL scores remained significant. Age was not significant. The final GRC-JIA model includes PGA as a significant predictor, in addition to those included in the GRC-health model.

Conclusion: Provider's ratings of overall health and JIA change are closely related to the level of improvement as measured by the ACR-Ped Criteria. Provider's GRC are significantly influenced by patient's pain rating, and takes account of the active joint count over and beyond the ACR-Ped70 response level. Nonetheless, in comparison to the ACR-JIA Response Criteria the provider's GRC can serve as a valid measure to assess patient's change over time, but with differential gender effect. This study also suggests that patient reported pain should be considered in the assessment of disease progression.

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2012

Pediatric Rheumatology Productivity: Results of the American Academy of Pediatrics 2010 Workforce Survey. Michael Henrickson[1] and Laura Laskosz[2]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]The American Academy of Pediatrics, Elk Grove Village, IL

Background/Purpose: Relative value units (RVUs) are a payer-neutral measure of clinical work. The federal government uses a multi-component formula to convert this measure into reimbursement. The Association of Administrators in Academic Pediatrics (AAAP) surveys its practitioners to derive benchmark RVU data, aided by its affiliation with a leading medical management group (MMG). No other benchmarks exist for pediatric rheumatologists (PRs). While PRs largely practice at academic centers, they also work in a variety of settings. PR reimbursement follows a number of models, lacking uniformity or national consensus for practice diversity. Reimbursement estimates may also derive from adjusted adult rheumatology (AR) or various MMG putative standards. Providers can use RVU data to advocate for additional PR clinical support. Through a cross-sectional survey of all board-certified US PRs administered by the American Academy of Pediatrics (AAP), this study's objective was to determine clinical productivity through annual RVU data, obtain demographic and CPT coding data, and establish national benchmarks independent of an MMG.

Methods: An IRB-approved survey asked PRs (N=206) to provide data about their annual RVUs for fiscal year 2008-09, and detailed demographics including clinical full time equivalent (FTE) status. Statistical analysis included the two-sample Kolmogorov-Smirnov test for distribution and t-test for comparison of means.

Results: The overall response was 65% (n=133); 60% of respondents (80/133) provided RVU data including one high volume outlier. AAAP RVU data obtained from 38 centers in the same survey year served as controls (n=79). AAP and AAAP RVU data were normally distributed (p=0.129); but, their means were significantly different (p=0.013) [Table]. AAP demographic data revealed: median FTE=0.6 (0.1–1); 99% PR and 8% AR board certification; median practice years=16.2 (range by 5-yr intervals: <5 to >30); median patients/week=25; median work weeks/year=48.5 (range by intervals: <30 to 52); academic location: 66% (n=69); states represented=34 of 42 supported by PRs (incl. DC); median salary=$158,000; median initial access to care=6 weeks (1–32), previously 2 weeks (2005 AAP survey). Asked if their institution uses the RVU model to measure clinical productivity, 76% affirmed (n=90); 8% did not know (n=10).

Table. Annual RVUs

Quartile	AAP	AAAP
1st	1000	2073
2nd	1737	3310
3rd	2616	4700
Total	8377	7943
Interquartile range	1616	2627
N	80	79

Conclusion: AAAP RVUs sample only academic sites, limiting generalizability. Further, AAAP adjusts RVUs from partial to full FTE, uniformly inflating data. This practice and AAAP alignment with a commercial MMG preclude its role as the best available PR benchmark. AAP RVUs are normally distributed, representing 81% of the states where PRs practice, with mature demographics and wide practice diversity; they serve as a national benchmark. During the latter half-decade, the shift from a 2 to 6 week wait to access initial PR care is concerning and indicative of the pressing need for sustained workforce advocacy.

2013

Cross-Sectional and Longitudinal comparison of Bone Mass Status, Using pQCT, in a Large Cohort of Juvenile Idiopathic Arthritis and Juvenile Onset Systemic Lupus Erythematosus Patients. Fernanda Falcini[1], Stefano Stagi[2], Loredana Cavalli[3], Giulia Carnesecchi[4], Federico Bertini[1], Laura Masi[3], Marco Matucci-Cerinic[5] and Maria Luisa Brandi[3]. [1]Department of Internal Medicine, Rheumatology Section, University of Florence, Florence, Italy, [2]Mugello's Hospital, Borgo San Lorenzo, Firenze, Italy, [3]University of Florence, Firenze, Italy, [4]University of Florence, Florence, Italy, [5]Univ Florence, Firenze, Italy

Background/Purpose: A small number of prospective data have been published on the use of pQCT in large groups of pts with JIA and JSLE. Moreover, few studies have compared in groups of JIA an JSLE pts, homogenous for age and sex, the parameters of bone status using pQCT. Our aim is to evaluate**,** cross-sectionally and longitudinally, the prevalence of reduced bone mass and density and the differences on the biomechanical parameters, using pQCT, in two cohorts of patients with JIA and JSLE homogenous for age and sex.

Methods: 154 JIA pts (127 F, 27 M, median age 20.3 $\pm$ 7.9 yrs: 84 oligoarticular, 33 polyarticular, 10 systemic, 27 enthesitis-arthritis (ERA) onsets, and 56 JSLE pts (46 F, 10 M, median age 21.5 $\pm$ 6.1 yrs) have been studied. The obtained data have been compared with age and sex matched control groups.

Results: JIA pts do not show any difference in comparison to controls as regard to cortical density (CrtBMD), except for systemic pts ($p <$ 0.0001) while JSLE pts have a higher CrtBMD than controls and JIA pts ($p <$ 0.005). Analyzing bone trabecular density (TrbBMD), all JIA pts regardless of type onsets (except for ERA), and JSLE pts have significant reduced values than controls, with no differences between JIA and JSLE. In addition, JIA pts show a significant reduced muscle area (muscle CSA) than JSLE and controls ($p <$ 0.001). The difference is significant in systemic and polyarticular JIA pts, but no in oligo and ERA subsets. Conversely, fat area (fat CSA) is significantly increased in both JIA and JSLE pts when compared to controls ($p <$ 0.001), with no differences in the two groups. The same results are observed evaluating the polar resistance to stress (SSIp). On longitudinal evaluation, the difference of CrtBMD, TrbBMD, muscle CSA e fat CSA are unchanged; in JSLE pts, SSIp is stable in comparison to JIA and controls without any difference among JIA pts and controls.

Conclusion: The pQCT evaluation of the main parameters of bone density and structure in adolescents and young adults with JIA and JSLE highlights significant differences between the two groups and JIA subtypes. These data might indicate a different pathogenesis of bone damage in the two entities, and suggest a different diagnostic and therapeutic approach to improve the bone mass peak in these patients.

2014

Serum 25(OH)D Levels in Adolescents and Young Adults with Juvenile Idiopathic Arthritis and Juvenile Onset Systemic Lupus Erythematosus: Prevalence and Association with Disease Activity. Fernanda Falcini[1], Stefano Stagi[2], Loredana Cavalli[3], Giulia Carnesecchi[1], Federico Bertini[1], Laura Masi[3], Marco Matucci-Cerinic[1] and Maria Luisa Brandi[3]. [1]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Florence, Italy, [2]Pediatric Unit, Mugello's Hospital, Borgo San Lorenzo, Firenze, Italy, [3]Department of Internal Medicine, Endocrinology Unit, University of Florence, Firenze, Italy

Background/Purpose: Numerous data are available in literature on 25 (OH)D serum levels in general population, few and contradictory in Juvenile Idiopathic Arthritis (JIA), and scarce in Juvenile onset Systemic Lupus Erythematosus (JSLE) pts. Our goals are: 1- to evaluate the serum 25(OH)D status in a large cohort of JIA and JSLE pts; 2- to correlate the 25(OH)D levels with the variables associated with JIA and JSLE. 3.To compare the pts results with healthy controls.

Methods: 144 JIA pts (122 F, 22 M, median age 15.5 $\pm$ 7.2 yrs: 78 oligo, 30 poly, 12 systemic and 24 Entesitis-arthritis [ERA]) onsets, and 46 JSLE pts (38 F, 8M, median age 16.9 $\pm$ 6.8 yrs) were studied after informed consent and Ethical approval. In all, serum 25(OH)D, serum intact parathyroid hormone (PTH), calcium, phosphorus, and bone alkaline phosphatase were measured. 100 sex-matched healthy subjects acted as controls.

Results: No significant difference of 25(OH)D levels has been detected in JIA and JSLE pts in comparison to controls as regard the percentage of those with VD deficiency and insufficiency. Of note, in JIA and JSLE pts with deficiency or insufficiency, a significant difference in comparison to controls with deficit or insufficiency, as regard the percentage of subjects with increased PTH and alkaline bone phosphatase levels ($p <$ 0.0001) was detected. In addition, among 25(OH)D levels and JIA subtypes, the lowest levels were found in systemic and poly than in oligo and ERA onsets. Moreover, systmic and poly pts have a significant lower increase of 25 (OH)D levels after supplementation than oligo, ERA pts, and controls with a high percentage of those who remains with insufficiency ($p <$ 0.001). The same results have been observed in JSLE pts who showed a high percentage of insufficiency, despite supplementation, of 25(OH)D than controls. The persistent low 25 (OH)D levels, despite supplementation, are significantly higher in patients with persistent active disease.

Conclusion: Serum 25 (OH) D levels and the percentage with persistent VD insufficiency seem to correlate to type of disease and disease activity. These preliminary results suggest a higher consumption and a higher request of 25(OH)D in patients with active JIA and JSLE.

2015

Recognizing Two Distinct Clinical Phenotypes in Muckle-Wells Syndrome. J B. Kuemmerle-Deschner[1], Samuel Dembi Samba[1], Isabelle Kone-Paut[2], Isabelle Marie[2], Pascal N. Tyrrell[3] and Susanne M. Benseler[3]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]CHU Bicêtre, Paris, France, [3]The Hospital for Sick Children, Toronto, ON

Background/Purpose: The diagnosis of Muckle-Wells syndrome remains challenging due to the variable and often non-specific clinical presentation**.** The aim of this study was to identify key variables associated with time to diagnosis in patients with MWS.

Methods: A cohort study of consecutive patients with a clinical diagnosis of MWS plus genetic evidence of an *NLRP3*-mutation was conducted at two centres for autoinflammatory diseases. Demographic information, mutation subtype, clinical phenotype, detailed access to care data, and information about duration of symptoms and preclinical evaluation were collected. Presenting variables were compared between groups of patients with a diagnosis in childhood compared to adulthood.

Results: A total of 34 patients were included (16 males, 18 females), the median age at diagnosis of MWS was 31.5 years (0.5–75). Patients diagnosed during childhood most commonly complained of musculoskeletal symptoms (62%), fever (54%), headache (46%) and abdominal pain (31%), while those diagnosed as adults had musculoskeletal symptoms (86%), hearing loss (52%) and decreased performance (29%). Data

driven clustering strategies identified two distinct clinical phenotypes of MWS: the "inflammatory phenotype", most commonly found in patients diagnosed in childhood was associated with fever, rash, headache and abdominal pain. Patients diagnosed as adults showed a more "organ –disease" phenotype characterized by musculoskeletal symptoms, skin rash, hearing loss and eye disease.

Conclusion: Two distinct clinical phenotypes may be identified in patients with MWS. These are closely related to the time of diagnosis. The presence of these two distinct clinical phenotypes has to be considered when developing diagnostic criteria for MWS.

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2016

Primary Raynaud's Phenomenon in a Multicenter Cohort of Italian Children and Adolescents: Which Prognostic Relevance for Serological Tests? Fernanda Falcini[1], Valentina Denaro[1], Federica Cuoco[2], Giorgia Martini[3], Susanna Cappelli[1], Antonella Petaccia[2], Fabrizia Corona[2], Giulia Carnesecchi[1], Francesco La Torre[4], Marco Matucci-Cerinic[5] and Donato Rigante[6]. [1]Department of Internal Medicine, Rheumatology Section, University of Florence, Firenze, Italy, [2]Department of Pediatrics, University of Milan, Milan, Italy, [3]University of Padua, Padua, Italy, [4]DIMIMP-University, Rheumatologic Section, Bari, Italy, [5]University of Florence, Florence, Italy, [6]Università Cattolica Sacro Cuore, Rome, Italy

Background/Purpose: Raynaud's phenomenon (RP) is an episodic vasospasm of the peripheral arteries, causing pallor followed by cyanosis and redness with pain and sometimes paraesthesia or rarely ulceration of the fingers and toes. Primary RP (pRP) occurs without an underlying disease, while secondary RP occurs in association with an underlying connective tissue disease (CTD), mostly systemic lupus erythematous, juvenile dermatomyositis and systemic scleroderma. Predictors of a favorable outcome are still unraveled in pRP: the causative role of various autoantibodies remains to be elucidated mostly for pRP starting in childhood or adolescence. Our objective is to identify the potential predictors of outcome in a multicenter cohort of children and adolescents with pRP.

Methods: We performed a prospective data collection of demographic, clinical, laboratory and treatment features of 82 Italian children/adolescents with pRP (58 females, 24 males, median age at disease onset: 13.5 years, median age at diagnosis: 14.8 years), managed in 4 pediatric rheumatologic Units and 1 transition clinic during the last three years. Demographic characteristics included sex, age and ethnicity. The evaluation included clinical pictures, eventual disease associations, pubertal status, laboratory data and nailfold videocapillaroscopy (NVC) at baseline and at regular 6-month-follow-up. Laboratory examinations included erythrosedimentation rate, C-reactive protein, transaminases, serum creatinine, hemoglobin, complement fractions C4 and C3, renal and thyroid function and specific serum autoantibodies (anti-nuclear antibodies [ANA], anti-DNAds, anti-ENA, anti-cardiolipin, anti-Scl-70 and anti-centromere antibodies). Screening for coeliac disease was performed at the first evaluation. Treatment details included the eventual specific drug used, its dosage and overall treatment duration. Out of 82, 20 patients were treated with hydroxicloroquine, 10 with calcium blockers, 1 with low-dose aspirin, 3 with iloprost, while the remaining 48 did not receive any drug. A forward stepwise multiple logistic regression analysis was used to find any association among sex, pubertal status, inflammatory parameters, NVC abnormalities, all serum autoantibodies and the risk of developing a CTD at baseline and at 36-month-follow-up. The software used was STATA 10. A p-value <0.05 was considered significant.

Results: ANA positivity at baseline was significantly associated with the risk of developing a CTD ($p <0.05$). No NVC abnormalities was related to specific patients' outcome**.** No patient was positive at the screening for coeliac disease.

Conclusion: Our data show that ANA positivity appears as the only potential predictor of poor outcome and even progression to CTD in children and adolescents with pRP.

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2017

Orthopaedic Treatment of Temporomandibular Joint (TMJ) Damage in Adolescents with Juvenile Idiopathic Arthritis (JIA): Longitudinal Evaluation. Fernanda Falcini[1], Daniela Melchiorre[1], Giulia Carnesecchi[1], Federico Bertini[1], Katia Biondi[2], Mario Bosco[3] and Marco Matucci-Cerinic[4]. [1]Department of Internal Medicine, Rheumatology Section, University of Florence, Florence, Italy, [2]Department of Odontostomatologic Sciences, University of Pavia, Pavia, Italy, [3]Pavia, Italy, [4]University of Florence, Florence, Italy

Background/Purpose: TMJ involvement has been reported in all subsets of JIA. The prevalence of radiographic changes of TMJs varies from 30% to 65%, and 50–80% of children with JIA will have evidence of TMJ arthritis by MRI and by sonographic exam (SE) (effusions, synovial enhancement, condylar flattening and/or erosions, thickness of masseter muscle) before evidence of X-ray damage. At disease onset local injections with steroids or/and anti-TNF alpha blockers are recommended, but when joint damage is late recognized orthopedic treatment is suggested. Our aim is to evaluate the efficacy and safety of orthopedic treatment in a cohort of adolescents and young adults with JIA.

Methods: Our study population included 102 consecutive pts (76 F and 26 M, mean age 14.5±4.4 yrs), mean age at JIA onset 7.9±5 yrs, mean disease duration at first orthodontic evaluation 7.7±5.2 yrs, fulfilling the ILAR criteria for JIA, all treated at Transition clinic of Rheumatology Department between December 2009 and December 2011. Out of 102 pts, 53 had oligo (O-JIA), 34 polyarticular (P-JIA), 4 systemic (S-JIA), 11 enthesitis-related arthritis (ERA-JIA) onsets. The diagnosis of TMJ disease was performed on the presence of at least one Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) diagnosis. The anamnestic and functional data were collected in a medical record used by orthodontists of University of Pavia, Italy. 69/102 pts (68 %) showed recurrent pain localized in the temporomandibular area, crepitation, and jaw stiffness or fatigue. All TMJs were examined by panoramic X-ray, teleradiography with latero-lateral and anteror-posterior view, and by SE by Esaote MyLAB 70 (Genoa Italy linear probe 8–13 MHz). At first orthodontic evaluation 75 pts showed dento-skeletal malocclusions leading to a Class II caused by skeletal retrognathia, post-mandibular rotation, lower height of the mandibular body and ramus that can determine asymmetries in the frontal and/or in the sagittal plane.

Results: 51 pts (50%) undergone to orthopedic therapy with an activator order to help mandibular growth. After orthopedic therapy these pts had worn a bite. 31 pts (30.3%) wore a bite without orthopedic therapy. 20 pts (20%) did not receive any treatment. After two years from first orthodontic evaluation 58/ 75 pts (77.3%) showed improvement in occlusion, masticatory function and cranio-facial morphology. In 69 pts the thickness of masseter muscle, detected by SE after therapy, was similar on left and right side (mean value 7.6 mm) at rest and after contraction (p<0.001). In all pts SE showed bone remodeling of the condyle head, and in 62/102 (61%) pts monolateral erosions were present.

Conclusion: Our data confirm that early diagnosis and treatment should prevent the severe and often intractable damage in TMJ of JIA patients. The irreversible damage as micrognathia, aberrations in mandibulofacial development, and facial asymmetry may compromise the growth cartilage and rapidly progress into bone erosion of the condylar head. In our study, the results suggest that in case of delayed diagnosis and severe destruction of TMJs, an orthopedic treatment may be helpful in reducing the progression of bone injury.

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2018

Juvenile Idiopathic Arthritis in Adulthood: Evaluation of Disease Activity, Damage and Quality of Life. Alessandra Salmaso[1], Lorenzo Ceri[2], Serena Capannini[2], Francesco La Torre[3], Maurizio Gattinara[1], Irene Pontikaki[1], Pier Luigi Meroni[4], Fernanda Falcini[2] and Valeria Gerloni[1]. [1]Pediatric Rheumatology, G. Pini Institute, Department and Chair of Rheumatology, Milan, Italy, [2]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Firenze, Italy, [3]DIMIMP-University, Rheumatologic Section, Bari, Italy, [4]Division of Rheumatology, Istituto G. Pini, University of Milan, Milano, Italy

Background/Purpose: Health outcomes in Juvenile Idiopathic Arthritis (JIA) have been a very active area of research in the past several years. Altogether, the available data indicate that a considerable number of patients

with JIA enters adulthood with persistently active disease and a significant proportion of them may develop severe physical disability. In general children with polyarticular course are more likely to have erosive radiological damage on follow-up. The comparison of earlier studies with those published in the last decade shows a decline in the frequency of patients with severe physical disability over the years; however, patients who enter adulthood with active disease do not seem to be diminished. The purpose of this study is to evaluate in patients with JIA in adulthood the functional and anatomic damage and the quality of life.

Methods: All consecutive JIA patients aged >18 yrs, afferent to three different paediatric rheumatology centres in the last year, were assessed with: HAQ; SF36; active joint count; VAS (0–100 mm) for pain, patient and physician global health assessment; radiological evaluation (Steinbrocker classification).

Results: 347 patients with JIA in adulthood, age >18 yrs, were enrolled. The collected data are shown in the following table

Table. JIA in adulthood, age >18 yrs

	JIA all	Syst	Poly RF+	Poly RF-	Oligo pers	Oligo ext	Psor	ERA
# pts	347	41	22	60	122	50	14	38
Mean age	27 (17–52)	30 (18–52)	26 (18–42)	27 (18–51)	26 (18–44)	28 (18–46)	28 (19–44)	25 (18–39)
Mean disease duration	19 (3–51)	21 (3–48)	15 (4–30)	18 (3–51)	19 (6–40)	22 (6–43)	22 (6–43)	14 (3–31)
Active arthritis (%)	40	46	43	48	38	38	29	32
Mean VAS pain	24 (0–100)	36 (0–100)	25 (0–70)	24 (0–88)	22 (0–82)	21 (0–88)	22 (0–62)	22 (0–84)
Mean patient GH	71 (0–100)	62 (0–100)	77 (30–100)	70 (0–100)	74 (24–100)	72 (10–100)	65 (40–90)	72 (20–100)
Mean VAS physician	15 (0–100)	22 (0–100)	19 (0–75)	17 (0–90)	12 (0–70)	15 (0–50)	17 (0–94)	12 (0–60)
% anatomic class III–IV	45	72	71	53	25	60	50	30
% pts with protesis	11	49	10	12	1	15	21	0
Mean HAQ	0, 5 (0–3)	0, 8 (0–3)	0, 4 (0–2)	0, 4 (0–3)	0, 2 (0–1, 6)	0, 3 (0–1, 3)	0, 4 (0–1, 8)	0, 1 (0–0, 8)
Mean SF36 physical health	62 (1–99)	50 (1–97)	62 (25–97)	62 (11–99)	65 (13–99)	66 (15–99)	50 (22–80)	59 (12–98)
Mean SF36 mental health	63 (12–100)	61 (12–93)	63 (22–99)	62 (11–99)	64 (13–100)	68 (20–100)	51 (21–90)	60 (30–98)

Conclusion: this hospital-based study clearly shows a selection bias toward the most serious cases, but underlines the high rate of JIA patients with disease still active in adulthood, confirming the need of a more aggressive and precocious treatment, to improve outcome in the future.

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2019

A Novel MRI Scoring System for the Evaluation of Early-Stage Disease Activity of the Wrist in Juvenile Idiopathic Arthritis. Charlotte M. Nusman[1], Robert Hemke[1], Taco W. Kuijpers[2], Eline E. Deurloo[1], Dieneke Schonenberg[2], J. Merlijn Van den Berg[3], Koert M. Dolman[4], Marion A.J. Van Rossum[3] and Mario Maas[1]. [1]Academic Medical Center, Amsterdam, Netherlands, [2]Emma Children's Hospital / Academic Medical Center (AMC), Amsterdam, Netherlands, [3]Emma Children's Hospital / Academic Medical Center and Reade Institute, Amsterdam, Netherlands, [4]St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands

Background/Purpose: Evidence that early therapeutic intervention prevents structural damage in juvenile idiopathic arthritis (JIA) patients requires focus on early-stage disease activity scores. Most outcome measures in JIA, such as the validated paediatric-targeted MRI scoring system (PTMRIS)[1], are based on adult equivalents with extensive focus on late-stage structural damage. Using our recently validated juvenile arthritis MRI scoring system (JAMRIS) for the knee[2], we have developed a similar analysis tool for the wrist to assess disease activity at an early stage. This focus shift to early-stage disease activity is achieved through extending soft tissue structure scores and specifying the grading of bone items affecting <25% of the bone. The objectives of this study were (1) to assess the intra- and interreader reliability of the JAMRIS system for the evaluation of early-stage disease activity in the wrist and (2) to compare the reliability of JAMRIS and PTMRIS.

Methods: MRI datasets from 20 JIA patients with wrist involvement were evaluated independently by three readers using JAMRIS and PTMRIS. JAMRIS for the wrist comprises synovial hypertrophy (6 locations, grading from 0–3), tenosynovitis (2 locations, grading from 0–1), bone marrow changes (15 locations, grading from 0–3) and bone erosions (15 locations, grading from 0–3) as scoring items. The intraclass correlation coefficient (ICC) or Cohen's kappa was used to assess inter- and intrareader reliability. The ICC of each JAMRIS scoring item was compared with the ICC of its equivalent in PTMRIS.

Results: The interreader reliability (ICC or Cohen's kappa) of JAMRIS varied from 0.62 to 0.89. Interreader reliability for tenosynovitis score was low (0.24 to 0.48). Intrareader reliability (ICC or Cohen's kappa) of JAMRIS

varied with from 0.28 to 0.95 for reader 1 and from 0.41 to 0.97 for reader 2. JAMRIS and PTMRIS showed similar results of interreader reliability.

Conclusion: Early-stage JIA disease activity in the wrist can be reliably evaluated with three-out-of-four JAMRIS scoring items. JAMRIS, especially focussed on early-stage disease presentation, has comparable reliability to PTMRIS. Correlating clinical disease assessment and responsiveness to change will be needed to validate JAMRIS for the wrist as outcome measure and disease monitoring tool.

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2020

Assessment of Procedure Safety and Cannula Position in Temporomandibular Joint Puncture Evaluated by Cone Beam Computerized Tomography. Thomas K. Pedersen[1], Kasper D. Kristensen[1], Per Alstergren[2], Peter Stoustrup[1], Annelise Küseler[1] and Troels Herlin[3]. [1]University of Aarhus, Aarhus C, Denmark, [2]Karolinska Institutet, Huddinge, Sweden, [3]Aarhus University Hospital Skejby, Aarhus N, Denmark

Background/Purpose: Temporomandibular joint (TMJ) arthritis frequently occurs in juvenile idiopathic arthritis (JIA). Only sparse information is available concerning the inflammatory activity and the underlying biology and course of arthritis in the TMJ in JIA patients, although it is known to cause severe growth disturbances of the dentofacial complex. Studies evaluating the synovial fluid may lead to a better understanding of the interaction between synovial inflammation, cartilage condition, and the influence on condylar bone formation. TMJ synovial fluid sampling and intraarticular steroid injections are procedures useful to elucidate this issue and to control inflammation. However, the TMJ is also known to be a vulnerable joint where functional disorders also can cause growth disturbances when mandibular function is impaired. Therefore, it is crucial that no or only transient side effects occurs from intervening procedures. The aim of this study was to evaluate safety issues in relation to a synovial sampling technique and to determine the variation in needle position by cone beam computerized tomography (CBCT).

Methods: Twenty healthy, adult volunteers were examined for TMJ dysfunction and mandibular movements were assessed before and after a sample of synovial fluid were taken in local anesthesia using the push-pull technique described previously (1). Samples were obtained from both TMJs and a CBCT-scanning was done to evaluate the needle position in the upper joint compartment. The study was approved by the ethical committee.

Results: All volunteers reported slight TMJ pain after sampling (mean 13.0 on a VAS-scale (from 0–100)). Pain disappeared in all participants after 1–2 days maximum. Objectively, mandibular range of motion was not affected by the procedure. The cannula was clearly visible in 3D in relation to the osseous tissues on the CBCT. The scanning showed a large variety in cannula position. The CBCT scanning lasted approximately 20 sec.

Conclusion: The synovial fluid sampling technique was found to be safe resulting in only minor, transient symptoms. However, the technique visualized in 3D is applicable in studies on TMJ pathology responsible for dentofacial growth abnormalities in growing individuals. A considerable variation was found in needle position and as a therapeutic approach, injection of steroids should be done with caution. CBCT confirmation of cannula position can be advised to substitute medical CT thereby greatly reducing patient radiation exposure.

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The Schedule of Administration of Canakinumab in Cryopyrin Associated Periodic Syndrome Is Driven by the Phenotype Severity Rather Than the Age. Roberta Caorsi[1], Loredana Lepore[2], Francesco Zulian[3], Maria Alessio[4], Achille Stabile[5], Antonella Insalaco[6], Martina Finetti[1], Antonella Battagliese[4], Giorgia Martini[3], Chiara Bibalo[2], Alberto Martini[1] and Marco Gattorno[1]. [1]G. Gaslini Institute, Genova, Italy, [2]Ospedale-Infantile Trieste, Trieste, Italy, [3]University of Padua, Padova, Italy, [4]Federico II Hospital, Napoli, Italy, [5]DipartimentoPediatria, Policlinico Gemelli, Roma, Italy, [6]Ospedale Pediatrico Bambino Gesù, Roma, Italy

Background/Purpose: to identify the optimal regimen for the treatment with Canakinumab in CAPS patients and, in patients receiving both Anakinra and Canakinumab during their disease course, to compare the two drugs in term of the efficacy and impact on the quality of life.

Methods: 13 CAPS patients (10 paediatric, 3 adults) treated with Canakinumab were followed for 12 months; 12 patients were previously treated with Anakinra. Clinical and laboratory parameters were collected at each visit and health-related quality of life (HRQoL) was recorded at month 12.

Disease activity, doses of IL-1 inhibitors and HRQoL were analyzed at the time of the last administration of Anakinra and after 12 months of treatment with Canakinumab.

Results: 7 patients were classified as CINCA, 4 patients as Muckle-Wells syndrome (MWS) while 2 patients displayed an overlapping MWS/CINCA phenotype.

Nine modifications of the schedule were necessary in 6/7 CINCA patients, while a single modification was performed in two MWS and MWS/CINCA patients only.

At the last follow-up during Canakinumab treatment 4 patients (2 MWS, 1 MWS/CINCA and 1 CINCA patients) were treated with a stable dose of 2 mg/kg (or 150 mg if weight was higher than 40 Kg) every 8 weeks, all of them displaying a complete response. Two CINCA and one MWS patients were treated with the dose of 2 mg/kg (or 150 mg) every 7, 6 and 6 weeks respectively, with a complete response. Four patients (3 CINCA and 1 MWS/CINCA patients) were treated with the dosage of 300 mg with a frequency of 7, 6, 5 and 4 weeks. All of them displayed a partial response. One MWS patient, in light of the persistent good control of the disease, discontinued the treatment with the aim to use the drug on demand, with a subsequent complete wellbeing for the following 6 months. One CINCA patients withdrew Canakinumab due to incomplete response and poor compliance.

At the last administration of Anakinra the patients were treated with a mean dose of 1,38 mg/kg/day (range 0,66-2). Seven patients (3 CINCA, 1 MWS/CINCA and 2 MWS) displayed a complete response while a partial response was observed in 5 patients (4 CINCA, 1 MWS/CINCA patients), due to a slight increase of acute phase reactants.

The number of complete responders at the last follow up in Canakinumab (8/13) was comparable to that registered at the moment of Anakinra discontinuation (6/12). The evaluation of the quality of life with the CHQ-PF50 questionnaire did not reveal a significant difference of the impact of the two drugs on physical concepts (Phs 51.88 during Anakinra, 51.55 during Canakinumab), while Canakinumab determined a significant amelioration of psychosocial concepts (p < 0.03, Wilcoxon Pairs Test)

Conclusion: the long-term use of Canakinumab is associated with a satisfactory control of disease activity but needs a progressive dose adjustments in more severe patients. CAPS phenotype, rather than the age, represents the main variable able to determine the need of more frequent administrations of the drug at higher dosage. We propose that pediatric MWS patients should be treated with the proposed schedule of 2 mg/kg every 8 weeks. Conversely, patients with a severe CINCA phenotype should be more aggressively treated since the beginning with a monthly administration of 4 mg/kg as the starting dose.

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Individual Disease Burden in Children and Adolescents with Chronic Musculoskeletal Pain—Multilevel-Analysis of a Nationwide Prospective Longitudinal Observation Study. Kerstin Gerhold[1], Rebecca Muckelbauer[2], Jacqueline Müller-Nordhorn[2], Angelika Thon[3], Thomas Müller[4], Gerd Ganser[5], Martina Niewerth[1] and Kirsten Minden[6]. [1]German Rheumatism Research Center, a Leipniz Institute, Berlin, Germany, [2]Charité - Universitätsmedizin Berlin, Berlin, Germany, [3]Kinderklinik der Medizinischen Hochschule Hannover, Hannover, Germany, [4]Universitätsklinikum Halle (Saale), Halle (Saale), Germany, [5]Sankt Josef Stift, Sendenhorst, Germany, [6]German Rheumatism Research Center, a Leibniz Institute, Berlin, Germany

Background/Purpose: Chronic musculoskeletal pain was described to be a frequent complaint in children and adolescents with assumed relevant impairment of health-related quality of life (HRQoL) as crucial indicator of individual disease burden. Since only a few epidemiological data are available, we investigated the course of single dimensions of patient-assessed HRQoL in children and adolescents with either chronic idiopathic musculoskeletal pain (CIMP) or juvenile idiopathic arthritis (JIA) as two entities of chronic musculoskeletal pain.

Methods: The national pediatric database is an ongoing nationwide prospective observation study on health care of patients with rheumatic-inflammatory or other musculoskeletal diseases referring to pediatric rheumatology departments in Germany. Patients diagnosed with CIMP or JIA enrolled between 2000 and 2008 with a minimal observation period of two years were included in the present analyses. They evaluated annually single generic dimensions of HRQoL on numeric rating scales (NRS, 0–10, 0 best): pain severity, physical capability, limitation in daily life activities, and capability of disease coping. The method of linear multi-level analysis was used to predict two-year courses of these patient-reported outcome measures. Each statistical model was adjusted for sex, age at disease onset, disease duration, calendar year of documentation, and medical care level of recruiting departments (private practice, general children's hospital, university children's hospital).

Results: Data of 318 CIMP patients (70% females, age (mean $\pm$ sd) 12.0 ± 3.8 years, disease duration 2.4 ± 2.6 years) and 6,103 JIA patients (65% females, age 9.5 ± 4.5 years, disease duration 2.7 ± 3.1 years) were included. At baseline (t_0), CIMP patients assessed all single generic dimensions of HRQoL with poorer scores than JIA patients: pain severity by plus 1.5 NSR points, limitation in daily life activities by plus 0.9, physical capability and disease coping by plus 0.5 NSR points each, and global health state by plus 0.7 NSR points. Compared to t_0, values of single HRQoL dimensions decreased only in JIA up to one (t_1) und two years (t_2) of follow-up, but not in CIMP patients (t_1 versus t_0 p<0.001; t_2 versus t_0 p<0.001). CIMP patients evaluated single generic dimensions of HRQoL persistently worse than JIA patients; this group difference increased for all scales between t_0 and t_2(p<0.05).

Conclusion: Consistently poorer estimates of all investigated measures of HRQoL in children and adolescents with CIMP over the two-year observation period, compared to children with JIA, are first hints for a relevant and long-term burden of disease in these patients. These results may implicate the need for improving medical care conditions for these patients in Germany in order to avoid a possible long-lasting disease career beyond childhood and adolescence.

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Should Joint Ultrasound Contribute to Therapeutic Decisions in Juvenile Idiopathic Arthritis? Marie Halbwachs, Geraldine Durand. Caroline Robin, Catherine Gambert Abdel Rahman, Pierre Ingrand and Elisabeth Solau-Gervais, University Hospital, Poitiers, France

Background/Purpose: Over several years, numerous studies have been published on the interest of joint ultrasound in juvenile idiopathic arthritis. Several authors have demonstrated that ultrasonography is more sensitive in synovitis detection than clinical examination. As of today, we do not know whether or not joint ultrasonography has an impact on therapeutic decisions. The objective of this study is to determine the interest of joint ultrasonography in therapeutic management of juvenile idiopathic arthritis.

Methods: This was a monocentric, open cross-sectional study, conducted on twenty-seven outpatients with JIA between March 2010 and January 2012. Ultrasound (US) evaluations were always carried out by the same rheumatologist, who had been trained in joint US. The ultrasound scanner was an EsaoteMylab 60. The wrists, hands and feet were systematically analysed, as was any painful joint. Therapeutic decisions were taken following clinical

examination and joint ultrasound. In the second step of the study, all of the consultations with ultrasound evaluation were summarized in the form of scenarios and submitted to clinicians, without the US results. Three physicians then expressed their therapeutic decisions (no modification, treatment enhancement or reduced treatment), which were subsequently compared with and without ultrasound data.

Results: Among the twenty-seven children followed, US was carried out in thirteen. 53.8% of the thirteen children had oligoarticular JIA and the other 46.2% had polyarticular onset. Between March 2010 and January 2012, 34 ultrasounds were carried out on thirteen children and thirty-four scenarios were elaborated. Subclinical synovitis was found in 94.1% of the US with a mean of $4.82+/-3.46$. Treatment enhancement ensued after 52.8% of the consultations with ultrasound evaluation, with a mean subclinical synovitis of $5.11+/- 3.31$. Divergent decisions (29.4%) were found when comparing consultation with ultrasound and scenario without ultrasound. Whether there were more than 2 clinical instances of synovitis or none, the decision remained similar. The divergent decisions came about either when children were symptomatic but with no more than two clinical instances of arthritis or asymptomatic with no clinical synovitis.

Conclusion: This study strongly confirms the interest of joint ultrasound in therapeutic decision-making. It establishes a usable therapeutic tool by means of accurate articular evaluation and suggests its interest in the therapeutic management of JIA children, especially when the clinical data are not sufficiently explicit.

2024

Articular Symptoms in Cryopyrin-Associated Periodic Syndrome: Retrospective French Study. Laetitia Houx[1], Pierre Quartier[2], Isabelle Kone-Paut[3], Xavier Guennoc[4], Pascal Pillet[5], Thierry Lequerre[6], Irene Lemelle[7], Mohamed Hamidou[8], Gilles Grateau[9], Eric Hachulla[10], Jean-Marie Berthelot[11], Benedicte Neven[12], Christophe Richez[13], Anne Pagnier[14], Veronique Hentgen[15] and Valerie Devauchelle-Pensec[16]. [1]Brest, France, [2]Necker-Enfants Malades Hospital,, Paris, France, [3]Hospital Kremlin Bicêre, Kremlin-Bicêtre, France, [4]Hopital de Saint Brieuc, France, [5]Paediatry, CHU, Bordeaux, France, [6]Rouen, France, [7]Paediatry, CHU, Nancy, France, [8]Hôtel Dieu, Hôpital Universitaire de Nantes, Nantes, France, [9]Hopital Tenon, Paris, France, [10]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [11]Nantes University Hospital, Nantes, France, [12]Inserm U768, Paris, France, [13]Hôpital Pellegrin and Université Victor Segalen Bordeaux, Bordeaux, France, [14]Service de pediatrie, Grenoble, France, [15]Paediatric Unit, Le Chesnay, France, [16]Brest Occidentale university, Brest, France

Background/Purpose: The cryopyrin-associated periodic syndrome (CAPS) is a rare inherited inflammatory disease associated with a mutation in the NLRP3 gene. Articular symptoms are often described in CAPS, but their frequency has been poorly investigated. Our objective was to describe the type and frequency of articular symptoms present in a cohort of pediatric and adult patients followed for a CAPS in France.

Methods: We conducted a retrospective study concerning articular manifestations (articular symptoms bone and muscle) in patients with CAPS [the familial cold autoinflammatory (FCAS), the Muckle-Wells syndrome (MW), and the neonatal-onset multisystem inflammatory disorder (NOMID or chronic infantile neurologic, cutaneous and articular syndrome (CINCA)] by contacting their referring physicians in the adults or paediatrician departments. Medical data were collected using a standardized questionnaire and radiographs were analyzed when present in the records.

Results: 88 patients were included (16 FCAS, 55 MW, 12 CINCA / NOMID and 5 unclassified). 50% were women, 56 patients were adults (mean age 33 ± 18.4 years) and 32 children (10.8 ± 4.4 years). The onset age is on average about 4.35 ± 7.8 years, and age of diagnosis is delayed to 20 ± 16 years. The first symptoms are usually: a cutaneous manifestation (68%), fever (26%), articular (22%) or neurological manifestation (11%). 65 patients (74%) have a family history of CAPS and 11 patients have a CAPS without genetic mutation. During follow-up, only 17 patients (23%) showed no joint symptoms. 53 patients (60%) had arthralgia and 55 patients (63%) had synovitis. The most affected joint were respectively: knees (65%), ankles (60%), wrist (47%), hands (40%) and feet (20%). Tendinopathy occurred in 13 patients (15%) and myalgia in 29 cases (33%). Only two patients had arthropathy with a typical non-inflammatory enlargement of the growth plates and epiphyses of long bones. Contractures and joint limitations (2%) or synovial masses are rare (2%). 24/88 (27%) were treated with anakinra and 55/88 (62.5%) with canakinumab. When reported delay in statural growth was -2DS for children before anti-IL1 treatment.

Conclusion: Articular symptoms encountered in CAPS are very common and found in 82% of patients with arthralgia and synovitis in knees and ankles. These symptoms are considered predominant for 20% but rarely explored by imaging. Pseudo tumor are rare. Delay of growth is frequent. Most patients benefit from treatment with anakinra or Canakinumab which allows almost complete regression of joint symptoms.

2025

Clinical Characteristics and Therapy Response in a Large Single-Centre Cohort of Patients with Periodic Fever with Aphtous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome. Francesca Ricci[1], Antonella Meini[1], Lucio Verdoni[1], Laura Dotta[1], Marta Bolis[1], Marco Berlucchi[2], Gianfranco Savoldi[3] and Marco Cattalini[1]. [1]Pediatric Immunology and Rheumatology Unit, Brescia, Italy, [2]Department of Pediatric Otorhinolaryngology, Brescia, Italy, [3]Angelo Nocivelli Institute of Molecular Medicine, Brescia, Italy

Background/Purpose: PFAPA (Period Fever with Aphtous stomatitis, Pharyngitis and cervical Adenitis), is a periodic syndrome described for the first time in 1987 by Marshall et al. It is characterized by regular recurrence of fever which associates with aphtous lesions, pharyngitis and cervical adenitis. In 1999 the criteria for diagnosis of PFAPA were formulated by Thomas. PFAPA is considered peculiar to the pediatric age, but in the recent literature there are a few case reports of this syndrome in adults.

Methods: We reviewed medical records of 239 children meeting clinical criteria for PFAPA syndrome.

Results: in our cohort (136 males and 103 females) fever began at a mean of 2.1 ± 2 years of age. The majority of the children had a symptoms onset before the fifth year of life but 9% of the patients had a later onset. Since all the other clinical criteria but age were met in these latter patients, the diagnosis of PFAPA was confirmed. In 37% of the patients' family history there was at least one first- or second-degree relative who underwent tonsillectomy for recurrent fevers or suffered from recurrent fevers in childhood. The PFAPA episodes lasted a mean of 4 ± 2 days, with an interval between episodes of 28.3 days. Fever was accompanied by pharyngitis (98%), cervical adenitis (64%), aphtous stomatitis (39%) and abdominal pain (33%). The parents reported in 10% of their children that some symptoms (irritability, nausea, headache) appeared 24–48 hours before fever onset and the parents learned to interpret these symptoms as prodromes of the PFAPA attack. All the patients were treated with oral steroids, using a single somministration of 1mg/kg of prednisone equivalent the first day of fever. All the patients had a prompt response to steroid treatment and only 12% of the patients experience a free-interval shortening.

In 57% of our patients the disease resolved spontaneously, after a mean period of 3 years. Medium age at PFAPA resolution was $5,7 \pm 3$ years of age.

Among patients who underwent tonsillectomy (25%) only a single patient didn't have complete resolution. Mutation analysis for FMF, HIDS and TRAPS in this patient was negative.

When clustering our population for age at onset (less than 1 yr, 1–5 years, more than 5 years) we observed that patients with onset within the first year had a significantly longer duration of disease ($p<0.00002$).

Conclusion: our study indicates that the 5 years of age cut-off is too strict for considering PFAPA diagnosis and that the onset before the first year of life predicts a longer disease duration. As previously reported abdominal pain are a relevant feature in PFAPA, almost as common as aphtous stomatitis. We also observed "prodromic symptoms" quite commonly. A significant proportion of family histories is indicative of possible PFAPA Syndrome in the first or second degree relatives of our patients. In our experience prednisone in a single given dose is highly efficacious in managing patients with PFAPA, and the free interval reduction happens in a minority of patients. Finally, even though limited to few patients, tonsillectomy had a very high rate of success in our experience, probably due to very strict selection of patients undergoing tonsillectomy.

2026

High Prevalence of Cervical Spine and Temporomandibular Joint Involvement in Patients with Juvenile Idiopathic Arthritis. Nikolay Tzaribachev[1], Catrin Tzaribachev[1] and Bernd Koos[2]. [1]Center for Rheumatic Diseases, Bad Bramstedt, Germany, [2]University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

Background/Purpose: Detection of involvement of temporomandibular joints (TMJ), which are frequently affected by juvenile idiopathic arthritis (JIA), is only possible on Gadolinium enhanced MRI (GdMRI). A comparative X-ray study on adults with JIA and RA showed a more frequent involvement and destruction of the dens axis in JIA patients. The aim of the retrospective study was to evaluate the involvement of the cervical spine (CS) in children with JIA.

Methods: The first GdMRI TMJ examinations of consecutive patients with defined JIA from our center were re-evaluated for involvement of the cervical spine (dens axis, DA). Clinical parameters were recorded – CS pain on motion, CS limited range of motion (LOM), peripheral disease activity (PDA, peripheral active, painful and LOM joints) and medication. MRI examinations were re-evaluated for TMJ and dens axis arthritis defined as synovitis and synovial hypertrophy.

Results: 40 children (29 female) were included. 21 patients had RF neg. polyarthritis, oligoarthritis was present in 11, ERA and PsA in 4 children equally. Median age at GdMRI was 14 (7–18) years. Median disease duration was 36 (4–192) months. At first GdMRI 47% were on NSAIDs with a median duration of 10 (1–36) months, 49% were on MTX (sc 10–15 mg/m^2) with a median duration of 12 months and 13 patients were on TNF Alpha inhibitors with a median duration of 3 (2–12) months. 10 patients showed no PDA but of these only one had no inflammation in DA and TMJ on GdMRI. 34 patients had arthritis in DA (25) or TMJ (33) and 25 patients had arthritis in both DA and TMJ. Out of all patients only 8 had pain and/or LOM of the CS, which were always correlated with arthritis in TMJ and DA on GdMRI. In all other patients CS involvement was silent. Current medication was not able to control disease activity.

Conclusion: considering that long-term sequels of CS arthritis in adults with JIA tend to be more severe than in RA patients, the high frequency of silent CS arthritis should be kept in mind, where GdMRI is the only tool to detect the extent of disease activity of the cervical spine and help with a proper monitoring of the treatment effect.

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2027

Chronic Nonbacterial Osteomyelitis of the Mandible in Children: a Tertiary Center Experience. Daniela S. Ardelean[1] and Ronald M. Laxer[2]. [1]Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON

Background/Purpose: Chronic nonbacterial osteomyelitis (CNO) of the mandible is a rare osseous autoinflammatory disease. Diagnosis is based on characteristic clinical, laboratory and imaging features. Our aim was to describe the phenotype and response to treatment in children diagnosed at our center.

Methods: We conducted a retrospective chart review of the patients diagnosed and followed for at least 6 months from 1988–2012. Parameters recorded at the last 2 visits (within 6 months interval): pain, abnormal ESR/CRP, imaging features, including bone and/or soft tissue edema, bone enhancement, ongoing medication and/or surgery. For each of these parameters, an average score was calculated based on the presence (1) or absence (0) of that feature; 0.5=presence at 1 visit, absent/unknown at the 2nd visit. Mean and SEM were reported. Statistical comparison between 2 groups was performed with t-test. P<0.05 was considered statistically significant

Results: 11 patients (8F:3M) with CNO of the mandible were reviewed (Table). Mean age at diagnosis was 8.4 years (3–11 yrs.); follow-up, 67±13 months (9–155 mos). 6/11 (55%) children were followed primarily/exclusively by rheumatologists and 5, by dental surgeons. 9/11 (82%) had isolated CNO of the mandible; the last 2, each had 1 additional femoral lesion. 3/11 children (27%) had other immune manifestations: insulin resistance and antibodies against insulin receptors, autoimmune neutropenia and bilateral granulomatous uveitis. Mandibular biopsies were performed in 10/11 patients (91%); all were consistent with CNO. Blood and bone cultures were negative in all patients tested. All patients were prescribed antibiotics. 5/11 (45%) children underwent surgical interventions. 6/6 patients followed by rheumatologists received NSAIDs; 1/6 (17%), also received biphosphonates. No patient was treated with steroids or biological therapy. The patients followed by surgeons had pain at the last 2 visits (0.62±0.13), vs those followed by rheumatologists (0) (P=0.02).

Table. Demographic, clinical, laboratory, imaging features and treatment approaches in pediatric CNO of the mandible

	Demographics			Treatment					Last 2 visits		
Pt #	Gender	Age at dx (years)	FU (ms)	Medication	# of surgeries	Pain	Abnormal ESR/CRP	Radioogical signs of inflammation	Treatment	Type of treatment	Primary specialist
1	F	11	28	0	1		uk	uk	0	None	Dentist
2	F	10	144	Naproxen prn	5	1	uk	uk	0.5	Surgery; None	Dentist
3	F	6	86	0	2	0.5	uk	0.5	0.5	Surgery; None	Dentist
4	F	10	123	0	4	0.5	uk	uk	0	Surgery; None	Dentist
5	M	5	9	0	1	uk	uk	uk	0.5	Surgery; None	Dentist
6	M	13	73	Naproxen	4	0	0.5	0.5	1	NSAID	Rheum
7	F	10	24	Indocid	0	0	uk	uk	0	None	Rheum
8	F	10	58	Naproxen	0	0	1	0	1	NSAID	Rheum
9	M	3	39	Naproxen	0	0	1	uk	0	None	Rheum
10	F	5	95	Indocid;Pamidronate	0	0	0	0.5	1	NSAID	Rheum
11	F	10	55	Naproxen, then Indocid	0	0	1	uk	0	None	Rheum

FU=follow-up; dx=diagnosis; uk=unknown.

Conclusion: Pain at the last 2 follow-ups is common in patients that received only operative treatment. A major shift in the therapeutic approach of CNO of the mandible occurred in the last two decades, from exclusive surgical interventions to anti-inflammatory therapy and rheumatologic follow-up. CNO of the mandible can be associated with other immune manifestations.

Disclosure: D. S. Ardelean, None; **R. M. Laxer**, None.

2028

Medication Adherence and Quality of Life in Children with Rheumatic Disease. Stacey E. Tarvin[1], Lisa M. Macharoni[2], Christine M. Raches[1] and Nicole M. Taylor[2]. [1]Riley Hospital for Children, Indianapolis, IN, [2]University of Indianapolis, Indianapolis, IN

Background/Purpose: Children with rheumatic diseases are often prescribed complex medication regimens. Medication side-effects may have a negative impact on physical appearance and subsequently impact adherence. In children with rheumatic disease, non-adherence can lead to serious consequences such as decreased physical function, increased symptomology, and hospitalizations requiring more invasive and costly treatment. The purpose of this study is to examine parent and child report of medication adherence in children with rheumatic disease ages 8–18 years. Additionally, this study examines the extent to which health related quality of life (HRQOL) is associated with medication adherence. Adherence will also be examined for its relationship to other psychosocial variables, risk of depression and pain.

Methods: One hundred fifty children with rheumatic disease followed at a Midwest children's hospital were recruited at an outpatient rheumatology appointment. Each parent-child pair completed measures assessing adherence to the child's medication regimen, demographic variables, HRQOL assessed using the Pediatric Quality of Life Rheumatology module (PedsQLRM), depressive symptoms assessed using the Childhood Depression Inventory, and reported pain as assessed by visual analog scale and individual items from the aforementioned standardized measures. Appropriate parametric statistics were completed to determine statistical significance of demographic variables. MANOVAs were used to determine the relationship between HRQOL, pain, risk of depression and medication adherence. Data was analyzed using SPSS 16.0.

Results: Eighty-seven percent of the children in the sample were prescribed medication for their illness. Parent and child report of medication compliance showed significant correlation (r=.229, p<.009). Twenty percent of parents reported that their child missed two or more doses of medication within the prior week. One third of patients reported missing two or more doses of medication within the past week, with 8.6% reported missing 4 or more doses. One-third of the sample reported complete compliance with medications. Demographic variables that were significantly related to medication compliance were parent marital status (p<.032), parent employment (p<.043), gender (p<.038), and child age (p<.034). Medication non-adherence was associated with trouble sleeping (p<.032), report of side effects (p<.011), worry (p<.013) and total quality of life score (p<.046) based on child report. Neither risk of depression nor pain, as reported on the PedsQLRM, were found to be significantly related to medication compliance.

Conclusion: Rates of medication non-adherence in this population are high, and while children and their parents report a moderate correlation, results suggest that parents underestimate their child's medication adherence. A better understanding of key demographic, psychosocial and HRQOL variables associated with adherence may allow the physician to address non-adherence directly with at risk patients.

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2029

Reliability of Scoring a Disease Damage Measure for Juvenile Localized Scleroderma. Kathryn S. Torok[1], Suzanne C. Li[2], Christina Kelsey[1], Mara L. Becker[3], Fatma Dedeoglu[4], Robert C. Fuhlbrigge[5], Gloria Higgins[6], Sandy D. Hong[7], Maria F. Ibarra[3], Ronald M. Laxer[8], Thomas G. Mason II[9], Marilynn G. Punaro[10], Elena Pope[11], Egla C. Rabinovich[12] and Katie G. Stewart[10], [1]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [3]Children's Mercy Hospital, Kansas City, MO, [4]Boston Childrens Hosp, Boston, MA, [5]Childrens Hospital, Boston, MA, [6]PRCSG-Cincinnati Children's Hospital Medical Center, Columbus, OH, [7]U of Iowa Children's Hosp, Iowa City, IA, [8]The Hospital for Sick Children, Toronto, ON, [9]Mayo Clinic Rochester, Rochester, MN, [10]Texas Scottish Rite Hospital, Dallas, TX, [11]Hospital for Sick Children, Toronto, ON, [12]Duke University Medical Center, Durham, NC

Background/Purpose: In order to more accurately capture disease activity and damage in juvenile Localized Scleroderma (jLS) and to develop an accepted outcome measure for treatment protocols, an LS-focused Childhood Arthritis and Rheumatology Research Alliance subgroup developed clinical disease activity and damage measures. The objective of this abstract is to discuss the assessment of the reliability and validity of the LS Damage Score in jLS. The LS Damage Score includes four domains (dermal atrophy, subcutaneous atrophy, dyspigmentation hyper/hypo pigmentation, and skin thickness of lesion center) which are scored for all affected sites.

Methods: Thirteen pediatric rheumatologists and a dermatologist attended a 2-day workshop meeting to review LS clinical measures. Raters ranked 13 jLS patients on damage domains at 2 time points. Patients were presented to raters in random order in efforts to reduce recall bias. For each patient, raters were told which anatomic sites to assess (1–2/patient). Physicians also completed Physician Global Assessment of Disease for Activity and Damage (PGA-A; PGA-D). To examine construct validity, we hypothesized that the LS Damage Score would have a moderate correlation to PGA-D and a low correlation to PGA-A. Spearman's rho was calculated to quantify the relationship with clinical parameters, and intraclass correlation coefficients (ICC) were examined to determine inter/intra rater reliability (0.20–0.39 low, 0.40–0.59 moderate, 0.60–0.79 high).

Results: Median age of LS patients was 13 years (IQR = 9.5–17) and the most common subtype was linear scleroderma (4 limb, 4 head). Mean LS Damage Scores ranged from 3.96 to 16.46 (max score 24); PGA-D ranged from 14.54 to 53.48 (max score 100). There was a low correlation between the LS Damage Score and both PGA-D and PGA-A (ρ =.11, ρ =.14). Raters demonstrated moderate/high inter and intra-rater reliability for the LS Damage score, and low/moderate inter and intra-rater reliability for PGA-D. Among the domains, hypopigmentation showed the lowest inter-rater reliability (Table 1).

Table 1. Inter-rater and intra-rater reliability of LS Damage score

Domains	Round 1 ICC (95% CI)	Round 2 ICC (95% CI)
LS Damage Score:		
Inter-rater reliability	**0.56** (.37, .79)	**0.63** (.43, .83)
Intra-rater reliability *(median, [range])*	*0.81* [0.53–0.93]	
PGA-D:		
Inter-rater reliability	**0.19** (.08, .44)	**0.28** (.14, .54)
Intra-rater reliability *(median, [range])*	*0.51* [0.09–0.75]	
LS Damage Score parameters: inter-rater reliability		
Dermal Atrophy	**0.37** (.23, .58)	**0.48** (.33, .67)
Subcutaneous Atrophy	**0.42** (.28, .62)	**0.51** (.36, .70)
Dyspigmentation:		
Hyperpigmentation	**0.66** (.52, .81)	**0.71** (.58, .84)
Hypopigmentation	**0.22** (.12, 40)	**0.24** (.13, .42)
Skin Thickness of lesion center	**0.61** (.46, .77)	**0.53** (.39, .73)

Conclusion: The LS Damage Score had moderate-high reliability between and among raters, with hyperpigmentation, skin thickness center, and dermal atrophy contributing most to the total score. Overall, the inter-rater agreement of damage components increased in session 2. The PGA-D performed well within the rater's repeat assessment, but poorly in regards to inter-rater reliability. The poor correlation between PGA-D and LS Damage Score may reflect MD inclusion of extracutaneous manifestations (ECM), such as facial disfigurement. In post-hoc analysis, when patients with facial linear scleroderma were removed, the correlations of PGA-D with LS Damage Score increased (ρ =.317). Additional studies are needed to fully evaluate this measure.

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2030

A Multi-Modal Amplified Musculoskeletal Pain Treatment Program: Associations of Previous Pharmacotherapy with Subsequent Outcomes. Cara M. Hoffart[1], Pamela Weiss[1], David D. Sherry[2], Chris Feudtner[3] and Margaret Stineman[4]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, [3]Division of General Pediatrics, Children's Hospital of Philadelphia; University of Pennsylvania Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA, [4]The University of Pennsylvania, Philadelphia, PA

Background/Purpose: Management of Amplified Musculoskeletal Pain (AMP) in children (i.e. juvenile primary fibromyalgia, complex regional pain syndrome, neuropathic pain, central sensitization) remains controversial. Common practice includes the combination of potent medications with physical and behavioral therapy. We hypothesize that functional restoration and pain reduction in patients with AMP does not require potent medications. The objective of this study is to describe a cohort of children with AMP treated with a non-pharmacological highly structured protocol and to test whether previous utilization of pharmacotherapy (as a marker of initial severity) predicts subsequent treatment program outcomes.

Methods: We conducted a retrospective inception cohort study of children with AMP treated with a non-pharmacological multidisciplinary program at The Children's Hospital of Philadelphia between January 2008 and December 2011. All pain medications were discontinued prior to program entry. The primary outcome, function, was measured with the Functional Disability Inventory (FDI) and Bruce Treadmill Score. We tested whether previous utilization of pharmacotherapy predicted treatment outcomes using mixed effects linear regression.

Results: We identified 168 individuals with AMP treated over 4 years. The median age was 14 (IQR: 13, 16 years), and three-quarters of the patients were females. The median pain duration was 18 months (IQR: 9, 36 months) and the median pain score 0–10 at program entry was 7 (IQR: 5, 8). Previous pharmacologic drug therapy exposure included opioids (N=53, 32%), immunosuppressants (N=15, 9%), neurotropics (N=35, 21%), and psychotherapeutics (N=32, 19%). Median FDI at baseline and program completion were 22 (IQR: 15, 30) and 5 (IQR: 3, 18), respectively. Median Bruce Treadmill Score at baseline and program completion were 586.5 (IQR: 415.5, 712.5 seconds) and 796 (IQR: 750, 908 seconds), respectively. Median pain score at program completion was 4 (IQR: 0, 7), which is significantly improved from baseline (P=0.01). Change in FDI and Bruce Treadmill Score from start to finish of the program were significantly improved (P<0.001). After adjustment for patient characteristics, there was no significant variation in functional outcomes associated with previous exposure to pharmacotherapy (P=0.43).

Conclusion: These results suggest that in comparison to those children whom were medication naïve and "less severe", those children with "more severe" disease who were receiving potent pain medications prior to the start of the program were as likely to have restoration of function. Additionally, these results demonstrate that regardless of treatment before program entry, children with AMP have successful restoration of function without pharmacotherapy. Prospective studies are warranted to determine long-term efficacy and effectiveness of this multi-disciplinary program.

Disclosure: **C. M. Hoffart**, None; **P. Weiss**, None; **D. D. Sherry**, None; **C. Feudtner**, None; **M. Stineman**, None.

2031

Safety and Efficacy of Anakinra in Patients with Deficiency of Interleukin-1 Receptor Antagonist.

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Background/Purpose: Deficiency of interleukin-1 receptor antagonist (DIRA) is a neonatal-onset autoinflammatory syndrome caused by mutations in *IL1RN* gene and clinically characterized by a perinatal onset of pustular dermatosis, aseptic multifocal osteomyelitis and marked elevation of acute phase reactants. Individual reports have been shown that these patients present a prompt response to the recombinant human IL-1 receptor antagonist (IL1Ra) anakinra. However, long-term efficacy and safety of anakinra treatment in DIRA patients have not been assessed. Thus, the objectives of this study were to assess the clinical and laboratory findings of patients with DIRA followed at the NIH and enrolled in a natural history study to assess long-term outcomes in autoinflammatory syndromes patients.

Methods: Eight patients with a genetically confirmed diagnosis of DIRA were followed longitudinally. Demographic, clinical and laboratory findings and response to treatment variables were collected for each patient at the enrollment and subsequent clinical visits. Statistical analyses were performed using unpaired t- test with Welch's correction.

Results: Four (50%) patients were female. Age at disease onset ranged from 1 to 15 days of life and age at anakinra starting was 11 (2–114) months. Five patients had been receiving anakinra 4 to 54 months prior to the study enrollment. Before IL1Ra was started, 5 patients presented with intermittent fever; all 8 patients had mild to severe pustular rashes and 5 had nail abnormalities. Various degrees of multifocal osteomyelitis were observed in all patients and 3 had odontoid non-fusion. Unspecific lung disease was observed in 3 patients, 2 patients presented thrombotic events and 2 had vasculitis. Laboratory findings prior to anakinra showed mild to severe anemia and increased white blood cell (WBC) count in all 8 patients and thrombocytosis in 5. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated in all 8 patients. At the last follow-up visit (6 to 48 month), time on anakinra was 35 (20–102) months and anakinra doses ranged from 2.1 to 5.1 (median: 3.5) mg/kg/day. At that time, none of the patients had developed new osteomyelitis lesions, nor pustular skin manifestations and CRP and ESR were 0.21 (0.016–0.579) mg/dL and 7 (3–13) mm/h, respectively. All patients fulfilled criteria for inflammatory and clinical remission, except for one patient that had CRP of 0.579mg/dL. While acute phase reactants had almost normalized at the time of the first NIH visit, a decrease in the platelets (502 $\pm$ 180.0 vs. 273 $\pm$ 32.3 $\times$ 10^3cells/mm^3, p=0.016) and in the WBC (15.96 $\pm$ 6.56 vs. 8.44 $\pm$ 1.98 $\times$ 10^3cells/mm^3, p=0.023) was seen and took longer to normalize. Three serious adverse events were observed: rash and pneumonia in one patient and subarachnoid bleed in one patient. Anakinra was considered well tolerated and an increase of opportunistic or recurrent infections was not observed within the enrolled patients.

Conclusion: DIRA patients on treatment with anakinra for 20–102 months presented with a sustained clinical and laboratory response and no patient developed novel inflammatory lesions while on treatment. Anakinra is well tolerated and none of the patients has discontinued therapy.

2032

Results From a Multicentre International Registry of Familial Mediterranean Fever: Impact of Genetic and Environment Factors On the Expression of a Monogenic Disease in Children.

Seza Ozen[1], Erkan Demirkaya[2], Gayane Amaryan[2], Isabelle Koné-Paut[2], Adem Polat[2], Turker Turker[2], Patricia Woo[2], Yosef Uziel[2], Consuelo Modesto[2], Martina Finetti[2], Pierre Quartier[2], Efimia Papadopoulou-Alataki[2], Sulaiman Al-Mayouf[2], Giovanna Fabio[2], Romina Gallizzi[2], Luca Cantarini[2], Joost Frenkel[2], Susan Nielsen[2], Michael Hofer[2], Antonella Insalaco[2], Huri Ozdogan[2], Nicolino Ruperto[2] and Marco Gattorno[2]. [1]Hacettepe University, Ankara, Turkey, [2]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Familial Mediterranean Fever (FMF) is an auto-inflammatory disease caused by mutations in a single gene, the *MEFV* gene. The disease is very frequent among patients with an eastern European ancestry but may occur in much lesser frequencies in other ethnic groups as well. We present the disease characteristics in patients living in the eastern Mediterranean and how they compare to the eastern Mediterranean patients living in western Europe and to the Europeans.

Methods: The data was extracted from the Eurofever project, that accomplished a multicenter registry for the autoinflammatory diseases in Europe and neighboring countries. From this registry 346 FMF patients whose diagnosis was confirmed were the subjects of this study. We developed a disease severity score that was modified from and harmonized the existing scores in the literature.

Results: The disease manifestations such as fever, abdominal pain, acute phase reactants were similar in all patients. The genetics and demographic features with increased acute phase reactants were similar among eastern Mediterranean patients whether they lived in their countries or western European countries. The mutation distribution of the European patients displayed differences and they were diagnosed later. On the other hand when features suggesting a severe disease expression were analysed, the eastern Mediterranean patients living in Europe were significantly different than those living in their countries and were similar to European patients and displayed milder phenotypic manifestations, with less attacks, less arthritis and less chest pain. When multivariate analysis was applied to assess the effect of residence, not ethnicity but the country of residence positively influenced the severity of disease presentation. Other independent variables were the presence of M694V (also on a. single allele), a positive family history together with disease delay.

Conclusion: We clearly demonstrate the actual impact of environment and genetic factors on the expression of a monogenic disease. We suggest that since FMF is the disease of the innate immune system and since the mutated protein is a component of the inflammasome triggered by microbial products, environmental factors including diet have a significant effect. Epigenetic studies are now in order.

2033

Infliximab Is an Effective Therapy in Pediatric Renal Sarcoidosis.

Elisa Wershba, Laura Lewandowski, Heather Van Mater and Egla C. Rabinovich, Duke University Medical Center, Durham, NC

Background/Purpose: Renal sarcoidosis is an unusual form of a rare multisystem disease, and there is little data to guide therapy. The cytokines implicated in chronic sarcoidosis include IL-8, IL-12, and TNF-α, suggesting potential role of treatment with an anti-TNF-α monoclonal antibody. There are case reports of the use of infliximab in refractory sarcoidosis in adults, and one report in a child with renal sarcoid. There are no current studies investigating infliximab as a steroid sparing agent in pediatric sarcoidosis.

Methods: We identified 3 pediatric patients with an established diagnosis of sarcoidosis based on systemic manifestations, non-caseating granulomas on biopsy, and exclusion of other granulomatous diseases. They had biopsy proven renal manifestations and were treated with infliximab. A retrospective chart review was conducted to evaluate the disease course. All patients had failed a steroid taper prior to initiation of

infliximab. Creatinine levels and concurrent steroid doses were plotted in relation to initiation of infliximab. IRB exemption was granted prior to the start of chart review.

Results: In all 3 patients, a linear plot demonstrates that infliximab allowed for successful tapering of steroids without flare, and stabilization/improvement of serum Cr.

Patient 1 was diagnosed with sarcoidosis at 14 years with an elevated ACE and hepatic biopsy revealing multiple non-caseating granulomas. She was treated with corticosteroids. During an attempt to taper, she developed acute renal failure warranting a renal biopsy showing granulomatous interstitial nephritis. After failure with mycophenolate mofetil and IV methylprednisolone pulses, she was treated with infliximab. IV steroids were weaned over the next 4 months then discontinued. Four months later, her oral steroids were weaned completely. She remains stable on infliximab and mycophenolate mofetil.

Patient 2 was diagnosed at 10 years with sarcoid based on systemic manifestations and lymph node granulomas. She developed renal manifestations 4 years later. She failed chronic steroids and methotrexate. After initiation of infliximab, her steroids were weaned, her creatinine stabilized. After developing renal cell carcinoma, infliximab was discontinued, with an increase in daily oral steroid and eventual renal failure.

Patient 3 was diagnosed with sarcoidosis at 12 years based on elevated serum ACE level, uveitis, and conjunctival biopsy with non-caseating granulomas. His serum Cr was 2 mg/dL prior to initiation of steroids and methotrexate. Methotrexate was an ineffective steroid sparing agent. After initiation of infliximab, he was able to wean on his oral steroids, with stabilization of serum Cr. His Cr rose when infliximab was held for cellulitis and returned to baseline when reinitiated.
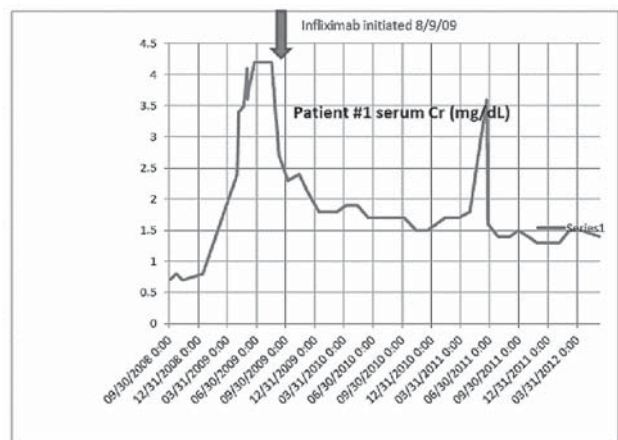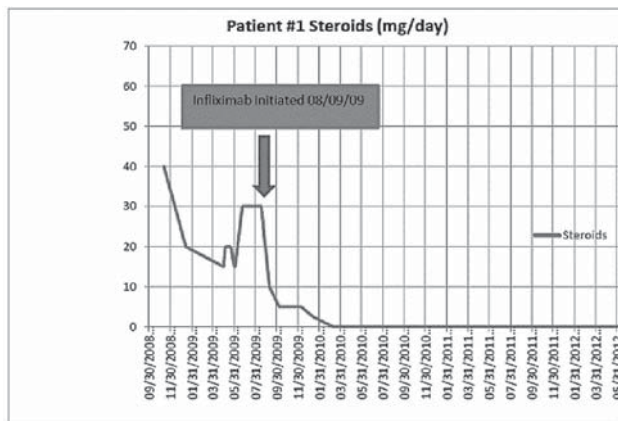
Conclusion: Infliximab is an effective steroid sparing agent in our pediatric patients with renal sarcoidosis.

2034

Magnetic Resonance Imaging Is a Reliable Tool to Monitor Chronic Non-Bacterial Osteomyelitis in Children.
Grazia Minardo[1], Giulia Zanon[1], Simone Corradin[1], Pietro Zucchetta[1], Giorgia Martini[1], Fabio Vittadello[1] and Francesco Zulian[2]. [1]University of Padua, Padua, Italy, [2]University of Padua, Padova, Italy

Background/Purpose: Chronic non-bacterial osteomyelitis (CNO) is a rare condition characterized by inflammatory bone lesions with no detectable infectious agents. It may be unifocal (U-CNO) or multifocal (M-CNO) and have a monophasic or relapsing course. Various laboratory or imaging parameters have been proposed as possible outcome measures but none has been validated, yet.

The present study was aimed to define the role of laboratory parameters and imaging tools (MRI and bone scinti-scan, BS) in detecting disease activity in patients with CNO.

Methods: Patients with CNO, lasting longer than 6 months, were followed every 3–4 months. Laboratory inflammatory parameters (ESR, CRP, WBC, Hb, PLT, SAA), MRI and BS were performed at diagnosis, at the time of clinical relapse or at least yearly in all patients. Clinically, active disease was considered in presence of bone pain needing analgesics or second line therapy. Bone lesions were considered active on MRI in the presence of bone marrow edema (BME) associated to soft tissue inflammation (STI) including perilesional effusion and edema. As resulted in recent sport medicine studies (1), BME alone was not considered a parameter of activity (3). Disease activity at BS was defined by signal intensity, number and extension of hyperactive sites. A single radiologist and nuclear medicine practitioner, blinded on patients' clinical status, reviewed all MRI and BS independently. Sensitivity, specificity and positive and negative predictive value (PPV, NPV) for disease activity detection of laboratory markers, MRI and BS were calculated by comparing data with clinical status of the patients at different time points.

Results: 16 CNO patients entered the study. 9 had UF-CNO, 7 had MF-CNO, mean age at disease onset 10,8 years (range 2.33–18.5), 54% were female. Disease duration at diagnosis was longer in patients with UF-CNO (14.2 vs 10.1 months). Localized bone pain was the leading symptom at onset in all patients; systemic symptoms, such as fever and fatigue, were more frequent in MF-CNO. At onset WBC was normal, CRP and ESR were elevated in 69.2%, especially in MF-CNO. After median 3 years follow up, 43.7% of patients had no symptoms and were off-therapy. At disease onset, all patients were evaluated by MRI and BS then, during the follow-up, 11 patients repeated BS once (T1), 13 patients repeated MRI once (T1) and 8 twice (T2). At disease onset, all 16 MRI showed BME with STI. Of the 21 follow up MRIs, 5 (23%) completely normalized, 7 (33%) showed only BME, 9 (42%) showed pathological changes. At disease onset all BS showed active lesions with mean 2.1 hyperactive sites (range 1–5). Of the 12 follow-up BS, 5 showed total remission, 3 partial remission and 4 persistent disease activity.

MRI sensitivity ranged between 0.83 and 1.00, specificity 1.00, PPV was 1.00, NPV ranged between 0.86 and 1.00. BS sensitivity was 0.83, specificity 0.74, PPV 0.76, NPV 0.80. Laboratory parameters correlated poorly with disease clinical status.

Conclusion: MRI is a reliable tool for monitoring CNO in pediatric patients. BS overestimates disease activity, especially in UF-CNO. Laboratory inflammatory parameters are of limited utility. A validation study in a larger patients' cohort is needed to confirm these preliminary findings.

2035

Performance of Icbd (International Criteria for Behcet's Disease) in Iranian Children with Behcet's Disease.
Nahid Shafaie, Bahar Sadeghi Abdollahi and Fereydoun Davatchi. Shariati Hospital-Tehran Univ, Tehran, Iran

Background/Purpose: ICBD is the new international criteria for diagnosis/classification of Behcet's Disease, created in 2006. The scoring system for ICBD depends on 2 points for ocular lesions and genital ulcers each, and 1 point for each of oral aphtosis; skin manifestations; vascular manifestations; and positive-pathergy test. Three or more points are required to consider the patient as a case of Behcet's Disease. The validity of the criteria has been confirmed for Iranian patients in 2010. To determine the performance of ICBD in Iranian children with Behcet's Disease (Diagnosed

before the age of 16), the sensitivity of ICBD is compared with 4 most commonly used diagnosis/classification criteria (Revised Japan, O'Duffy, International Study Group [ISG] and Classification Tree).

Methods: According to the data registry for Behcet's Disease patients in Rheumatology Research Center, Tehran University of Medical Sciences, Iran, all the patients diagnosed before the age of 16 (during 1975–2011) are included in the study. The fulfillment of each of the 5 criteria is evaluated for each patient and the sensitivity of different sets of criteria in childhood BD is calculated.

Results: 180 children out of 6813 BD patients (2.64 %, CI: 0.4) are selected (86 male and 94 female). The mean age was 10.7 years (SD: 3.4, CI: 0.5), mean duration 8.2 years (SD: 6.7), mean follow up 5 years (SD: 6.2) and the diagnosis delay 3.2 years (SD: 2.7).

I) 174 patients fulfilled the ICBD criteria (sensitivity 96.66%); 171 patients met Classification Tree criteria (sensitivity 95%); 156 patients for Revised Japan criteria (sensitivity 86.66%); 126 patients met ISG criteria (sensitivity 70%) and 103 patients fulfilled O'Duffy criteria with sensitivity of 57.2%.

II) Although the majority of the patients met all 5 sets of criteria, some of the patients could fulfill different combinations of criteria sets as described below.

88 patients (48.88%) met all 5 criteria; 30 patients (16.66%) fulfilled ICBD, Japan and Classification Tree; 26 patients (14.44%) met all the assessed criteria except for O'Duffy; 7 patients (3.9%) met all the assessed criteria except for ISG; 6 patients (3.33%) could meet only ICBD and Classification Tree; 6 patients (3.33%) met ICBD, Classification Tree and ISG; 5 patients (2.77%) met all the assessed criteria except for Japan; 3 patients (1.66 %) fulfilled ICBD and Japan Criteria; 2 patients (1.1 %) fulfilled ICBD, O'Duffy and Classification Tree; 2 patients (1.1 %) fulfilled ICBD, Japan and O'Duffy; 1 patient (1.1%) met ISG and Classification Tree and 4 patients (2.22 %) could not meet any of the 5 assessed criteria.

Conclusion: The most sensitive criteria for Iranian children with Behcet's disease was ICBD, followed by Classification Tree, Japan and ISG and O'Duffy. The higher sensitivity in ICBD, Classification Tree and Japan criteria may be explained by the prominence of the eye involvement in children and the importance of ocular lesions in these criteria sets.

Disclosure: N. Shafaie, None; **B. Sadeghi Abdollahi**, None; **F. Davatchi**, None.

2036

Children's Hospital of Pittsburgh Pediatric Onset En Coup De Sabre and Parry-Romberg Syndrome Cohort. Kristin M. Brown[1], Darren Smith[2], Christina Kelsey[3], Katherine Kurzinski[4] and Kathryn S. Torok[3]. [1]University of Pittsburgh, Pittsburgh, PA, [2]university of Pittsburgh Division of Plastic and Reconstructive Surgery, Children's Hospital of Pittsburgh, Pittsburgh, [3]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [4]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

Background/Purpose: Localized scleroderma is an autoimmune disease characterized by disfiguring thickening and fibrosis of the skin and underlying soft tissues; the majority of cases have onset in childhood. Multiple subtypes exist, including linear scleroderma, which is most common in children. Linear scleroderma involving the face and scalp is known as En Coup de Sabre (ECDS) and hemifacial atrophy that is often associated with ECDS or occurs alone is known as Parry Romberg Syndrome (PRS). Extracutaneous features are often associated with ECDS and PRS, including neurological, eye and dental abnormalities.

Methods: The patients and their associated disease characteristics of our Children's Hospital pediatric onset ECDS/PRS cohort were evaluated from years 2002–2012. This included demographic features, lesion characteristics, laboratory characteristics, extracutaneous manifestations, quality of life, family history, and response to medical and surgical treatment. Descriptive statistics were employed.

Results: Twenty patients in our ECDS/PRS cohort were identified, with mean age onset 5.9 years (± 4.5), time to diagnosis 1.9 years (± 2.3), female to male ratio (3:2), and majority were Caucasian (85%). The majority of patients had features of both cutaneous disease (ECDS) and hemifacial atrophy (PRS). The most common symptom at presentation was hyperpigmentation (65 %), followed by skin and subcutaneous depression (50%). Erythema or violaceous discoloration was common in patients presenting with active disease (55%). Antibody positivity for ANA, ss-DNA and histone ranged from 25–44%. Seven patients (35%) had neurological manifestations including the following: a pontine lesion associated with chronic ataxia, dysarthria, and cognitive dysfunction; a cerebral infarction; and white matter lesions on MRI ipsilateral to cutaneous lesion. One-third of the cohort patients had either an ophthalmologic or dental complication. Autoimmune thyroiditis was the most common familial autoimmune disease (20% 1st degree, 35% 2nd degree).

The majority of cohort patients were treated with prednisone and methotrexate; treatment was successful in halting disease and reversing a few active features, though less successful in reversing chronic disease damage. Mean follow-up of cohort 30.2 months (± 19.4). Four patients underwent surgical repair with lipoaspirated fat injection for volume restoration. Stereophotogrammetry 3-D imaging was used to objectively quantify facial morphology to assess patients' response to both surgical and medical therapy.

Conclusion: Our ECDS and PRS cohort demonstrated similar clinical findings of disease and associated ECM compared to other studies. Screening with brain MRI, ophthalmologic and dental evaluations for associated complications is reasonable in light of one-third of our cohort having neurologic, ophthalmologic, or dental involvement, some of which had a serious impact on daily living and QOL.

Disclosure: K. M. Brown, None; **D. Smith**, None; **C. Kelsey**, None; **K. Kurzinski**, None; **K. S. Torok**, None.

ACR/ARHP Poster Session C
Quality Measures and Innovations in
Practice Management and Care Delivery
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Poor Quality of Gout Care Is Strongly Associated with Higher Gout-Related Health Care Utilization. Jasvinder A. Singh[1] and Joshua Richman[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]UAB School of Medicine, Birmingham, AL

Background/Purpose: Proponents of improving quality of gout care have suggested various gout quality indicators, but no study to date has shown the link between good quality care and improved outcomes. The aim of the study was to assess whether appropriate good quality care for gout, including uninterrupted urate-lowering therapy (ULT) and achievement of target serum urate <6 mg/dl, is associated with reduced gout-related utilization.

Methods: This retrospective study utilized the Veterans Affairs (VA) administrative and clinical databases claims from fiscal years 2002 to 2010, using the presence of an International Classification of Diseases, ninth revision (ICD-9) code, 274.xx in a VA outpatient or inpatient visit to define the gout cohort. A 90-day or longer filled VA prescription for allopurinol, probenecid or febuxostat in a patient with gout was considered as exposure to ULT. The two independent predictors of interest were Medication Possession Ratios (MPRs) for each ULT and achievement of target sUA < 6 mg/dl. The MPR denominator was the number of days from index to the exhaustion of the last prescription and the numerator was days of medication supplied over that period from first to last prescription. We used regression analyses with a quasi-Poisson distribution given the type of data, limiting the analyses to patients with >=1-year of follow-up. The outcome was counts of visits with an offset for the number of years in the cohort.

Results: The gout cohort consisted of 376,421 patients with mean age 70 years, 99% were male and 61% were married. Their exposure to various medications for the treatment of gout was as follows: allopurinol, 70%; febuxostat, 0.3%; and probenecid, 3%. Mean follow-up was 6.2 years (standard deviation, 2.9). Higher MPRs for allopurinol, febuxostat, and probenecid were associated with significantly lower outpatient, urgent care, emergency room and overall visits (all p-values <0.0001; **Table 1**). Achievement of target sUA < 6 mg/dl was associated with significantly lower gout-related outpatient, inpatient, urgent care and emergency room visits (all p-values <0.012; **Table 1**). Conversely, a higher proportion of sUA levels >=6 mg/dl was associated with higher gout-related outpatient, inpatient, urgent care and emergency room visits (all p-values <0.00001).

Table 1. Association of MPR for three ULTs and of achievement of target sUA < 6mg/dl with future gout-related health care utilization

	Incidence rate ratio* [p-value]				
	Any visit	**Outpatient visit**	**ER visit**	**Urgent care**	**Inpatient**
Adherence to ULT					
Allopurinol MPR (n=231,131)	**0.50 [p<0.00001]**	**0.50 [p<0.00001]**	**0.32 [p<0.00001]**	**0.38 [p<0.00001]**	**0.80 [p=0.00005]**
Febuxostat MPR (n=759)	**0.64 [p=0.0031]**	**0.66 [p=0.0074]**	**0.38 [p=0.00073]**	**0.28 [p=0.0078]**	0.85 [p=0.661]
Probenecid MPR (n=10,514)	**0.47 [p<0.00001]**	**0.47 [p<0.00001]**	**0.45 [p<0.00001]**	**0.40 [p=0.00374]**	0.89 [p=0.63]
Achieving target sUA					
Any sUA <6 mg/dl (n=161,069)	0.99 [p=0.11]	**1.02 [p=0.0116]**	**0.79 [p<0.00001]**	**0.57 [p<0.00001]**	**0.90 [p=0.0105]**
Proportion of sUA levels >=6 mg/dl (n=161,069)	**1.72 [p<0.00001]**	**1.62 [p<0.00001]**	**2.43 [p<0.00001]**	**4.05 [p<0.00001]**	**2.87 [p<0.00001]**

*Incidence rate ratio for each outcome is for patients with MPR of 1 versus 0

Conclusion: This is the first study to find evidence of association of poor quality of care (lower ULT MPR and non-achievement of target sUA) with greater gout-related health care utilization, especially for emergency room and urgent care visits. Improvement in quality of gout care may reduce expensive gout-related utilization of emergency room and urgent care resources.

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Expanding Access in Rheumatology Specialty Care in New Mexico Via an Innovative Community Outreach Program. Arthur Bankhurst[1], Sanjeev Arora[1], Summers Kalishman[1], Jeannie F. Boyle[1], Cynthia Olivas[1], Rebecca Monette[1], Dara Som[2] and Yolanda Hubbard[1]. [1]University of New Mexico School of Medicine, Albuquerque, NM, [2]University of New Mexico School of Medicine, Albuquerque

Background/Purpose: The main objective of this innovative program is to provide training to Primary Care Clinicians (PCCs) in rural communities so they can provide best practice care to patients with rheumatologic disorders.

Methods:: The Rheumatology TeleECHO Clinic uses state-of-the-art technology to link PCCs with the Rheumatology Specialist here at University of New Mexico (UNM). Weekly clinics consist of short didactics, patient case presentations, and open discussions. In order to evaluate the effectiveness of the program, PCCs were given a pre and post self- efficacy survey. Eligibility criteria to participate in the survey included: attend three or more rheumatology TeleECHO clinic sessions or attend an on-site training session with Rheumatology clinic staff, participant completed 50% of questions on either the pre or post survey, and participant is not a TeleECHO clinical facilitator.

Results: Participation in the Rheumatology TeleECHO clinic has improved access to care for patients with rheumatologic disorders as well as improved self-efficacy of PCCs providing specialty rheumatologic care. There was a small but significant increase in overall self-efficacy from pre to post survey evaluation.

Conclusion: Since the induction of the program, 18 Centers of Excellence for Rheumatology have been established throughout New Mexico. A Center of Excellence is defined as a PCC who attends the two-day clinical training at UNM Rheumatology Clinic, who presents 10 individual cases to the Project ECHO™ Rheumatology TeleECHO Clinic and who is recognized in their local communities as a PCC with competence in rheumatologic care. To date, there have been 99 clinics held, with 1,265 attendees, and 644 patient case presentations. In addition, 28 primary care clinicians have attended the two day training program at UNM Rheumatology Clinic. In partnership with the American College of Rheumatology, providers were given the opportunity to enroll in the Advanced Rheumatology Course (ARC). A total of 25 providers have enrolled. As of today, 16 providers have graduated; nine other clinicians are actively working to complete the 16 modules. Project ECHO's TeleECHO Rheumatology clinic is an innovative approach that brings greater access for all patients in New Mexico.

Disclosure: **A. Bankhurst**, None; **S. Arora**, None; **S. Kalishman**, None; **J. F. Boyle**, None; **C. Olivas**, None; **R. Monette**, None; **D. Som**, None; **Y. Hubbard**, None.

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Uveitis Surveillance Through Lean-Six Sigma for Quality Assurance in Juvenile Idiopathic Arthritis. Anjali Patwardhan[1], Kelly Kelleher[1], Jeffery Hoffman[1], Karla B. Jones[2], Stacy P. Ardoin[3] and Charles H. Spencer[1]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]Nationwide Children's Hospital, Columbus, OH, [3]Ohio State University, Columbus, OH

Background/Purpose: Chronic asymptomatic iridocyclitis occurs in 10–20% of all patients with JIA leading to insidious but progressive morbidity and possible blindness. Patients with JIA-associated uveitis need to be seen by an ophthalmologist regularly. Lean thinking is based upon the following principles. 1) Identifying the customer value (value adding steps) and alleviating the redundant parts of the process hence minimize waste 2) developing an effective flow production 3) eliminate backflows 4) using "pull" techniques 5) striving to perfection.

Methods: Various tools of lean methodology were used throughout the development of a new process of uveitis surveillance for JIA patients visiting rheumatology clinics at Nationwide Children's Hospital. Problems were identified after paper chart review of 400 JIA patients. The key performance indicators used were 1) number of patients given eye examination request sheet 2) number of eye examination results received back from eye doctors & 3) number of eye examination results documented and available during the clinic visit. The hospital has switched to electronic medical records (EPIC) since 2006. It was found on baseline data that uveitis surveillance was inadequate and ineffective in paper charts. We identified the need to develop an electronic health record-based new surveillance process which can be more effective in improving communication between eye doctors, rheumatologists and patients/parents. We performed value stream mapping by stake holders to sketch the initial process and identify bottlenecks. Delphi survey was then used to reach consensus decisions, though out the project time. We charted current state, future state & ideal state and performed gap analysis. We then developed a pareto- matrix. The project methodology was based on the Deming's PDSA cycles. We developed a standard work based on our initial PDSA cycles. We evaluated the new process through KPIs.

Results: The uveitis surveillance process improved inter-team communication and quality of care. Inbuilt alerts in the process for presence of eye disease and missed eye appointments prompted rheumatologist to take appropriate timely action.

Conclusion: Implementation of lean tools and thinking can make provide smarter, quicker, easier, better and safer uveitis patient care delivery to the JIA patients by use of an effective uveitis surveillance process. We also emphasize the importance of seeing lean thinking as a part of the larger management shift towards planning for changes in mindsets and work places. This new surveillance process can be horizontally deployed for diabetic eye surveillance and drug toxicity monitoring in rheumatic patients on immunosuppressant.

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2040

Provisions of Quality Driven Care in Childhood-Onset Systemic Lupus Erythematosus. Matthew C. Hollander[1]. Jessica M. Sage[2], Alexandria J. Greenler[2], Tadej Avcin[3], Michael W. Beresford[4], Graciela Espada[5], Marisa S. Klein-Gitelman[6], Michael Henrickson[2], Tsz-Leung Lee[7], Joshua D. Pendl[2], Marilynn G. Punaro[8], Jennifer L. Huggins[2], Anne M. Stevens[9] and Hermine I. Brunner[2], [1]Seattle Children's Hospital, Seattle, WA, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]International Investigator Consortium for MAS Diagnostic Criteria, Ljubljana, Slovenia, [4]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [5]Childrens Hosp Ricardo Gutierrez, Buenos Aires, Argentina, [6]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [7]Queen Mary Hospital, Hong Kong, Hong Kong, [8]Texas Scottish Rite Hospital, Dallas, TX, [9]University of Washington, Seattle, WA

Background/Purpose: Quality Indicators (QI) are retrospectively measurable elements of practice performance for which there is evidence or consensus that can be used to assess the quality of care provided. Previous QI have been developed for adult systemic lupus erythematosus. This project was the second of two Delphi surveys used to identify QI in childhood-onset systemic lupus erythematosus (cSLE) that could serve as international benchmarks to assess quality of patient care.

Methods: Based on medical literature and a previous Delphi survey, a second survey was created and distributed via email to 348 individuals on the member lists of EULAR, PANLAR, PRINTO, PRES, ACR and CARRA. 265 individuals (76%) responded via online or paper survey, with 173 (65%) participants identifying themselves as pediatric rheumatologists. The survey design included a brief summary of relevant literature for each topic prior to the question. Participants had access to the referenced articles for each question through a hyperlink in the survey. Consensus was set at 80% agreement and blank responses were excluded from the analysis.

Results: Important process QI (IF/THEN statements) addressing the following treatment domains achieved consensus: bone health, education on cardiovascular risk factors, lupus nephritis and hypertension management, medication management, ophthalmological surveillance, transfer of care, use

of chronic steroids in cSLE management, and vaccinations (Table 1). A substantial amount of support was noted for clinical evaluation of disease activity every 3 months (71%), while the support for safety monitoring for medications was variable. The safety monitoring variables that reached consensus are displayed in Table 2.

Table 1. Quality indicators for patients with cSLE which yielded at least 80% consensus

Lupus Nephritis and Hypertension Management

1) IF a cSLE patient without known lupus nephritis has developed daily proteinuria of >500 mg or clinically relevant worsening of GFR/urinary sediment, THEN a kidney biopsy should be performed.

2) IF a patient has known lupus nephritis, THEN a clinical assessment for cSLE should occur at least every 3 months regardless of disease activity.

3) IF a cSLE patient has lupus nephritis plus evidence of ongoing proteinuria >500mg/day, THEN an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) should be prescribed, unless there are contraindications.

4) IF a patient has LN and/or hypertension, THEN disease co-management with a nephrologist should be considered.

Medication Management

5) IF a patient has cSLE, THEN antimalarial therapy should be prescribed, unless there are contraindications.

6) IF a cSLE patient is receiving a dose of steroids not acceptable for chronic use, then an attempt should be made to taper steroids.

7) IF a patient with cSLE is unable to decrease the dose of steroids acceptable for chronic use, THEN the addition of a steroid-sparing agent, or an increased dose of an existing steroid-sparing agent should be considered.

8) IF a cSLE patient is treated with medications, THEN laboratory surveillance for medication safety should be done at regular intervals (Table 2).

9) IF a patient has cSLE, THEN vaccination against influenza and encapsulated organisms should be prescribed, unless there are contraindications.

Bone Health with cSLE

10) IF a patient has received chronic systemic steroids, THEN the patient should have bone mineral density testing documented in the medical record.

11) IF baseline bone mineral density testing is outside of normal limits (Z-score ≤-2.0), THEN bone mineral density should be re-measured after one year.

12) IF a patient is on any steroid therapy, THEN calcium and vitamin supplementation should be recommended after 3 months.

Ophthalmological Surveillance

13) IF a cSLE patient is treated with corticosteroids, THEN an eye screening does not need to occur prior to treatment.

14) IF a cSLE patient is treated with corticosteroids, THEN eye screening should be done at least annually.

15) IF a cSLE patient is treated with antimalarial therapy, THEN eye screening should be done at least annually.

Transfer of Care with cSLE

16) IF an adolescent has cSLE, THEN a transition plan should be carefully designed to facilitate transfer of care to the appropriate adult health-care providers.

Education on Cardiovascular Risk Factors

17) IF a patient has cSLE, THEN education about cardiovascular risk factors should occur in regular intervals with the parent and the patient age 13 years or older.

Table 2. Medication Monitoring Table

IF a cSLE patient is treated with medications, THEN laboratory surveillance for medication safety should be done regularly as is documented below:

Interval	AZA	NSAIDS HCQ	1-monthly IV CTX	MMF/MPA 3-monthly CTX Cyclo-A	Prednisone	Rituximab	TNF-antagonists
Baseline	CBC Liver			CBC Liver		CBC	CBC
Every month			CBC Liver Renal				
Every 3 months	CBC Liver			CBC Liver Renal		CBC	CBC
Every 6 months	Renal	Liver Renal					Liver
Every 9 months		UA					
Every 12 months		CBC			CBC Renal Liver	Liver	Renal

AZA=azathioprine; HCQ= hydroxchloroquine; CTX=cyclophosphamide; MMF/MPA=mycophenolate mofetil/mycophenolic acid; Cyclo-A=cyclosporine-A; CBC=complete blood count and differential; Liver=liver function tests; Renal=renal function tests; UA=urinary protein excretion

Conclusion: Delphi questionnaires are efficient instruments for reaching international consensus for minimal standards of quality care for cSLE. Additional efforts will help refine items for which there is currently not consensus. The new QI identified through this project can be used to define and standardize best practices for children and adolescents with cSLE across the world.

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Improving Access and Patient Education in Rheumatology: the Gout Shared Medical Appointment; a Quality Improvement Initiative. Alicia J. Zbehlik[1] and Nicole M. Orzechowski[2]. [1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Dartmouth-Hitchcock Med Ctr, Lebanon, NH

Background/Purpose: Patients experience long waits for consultations in Rheumatology at Dartmouth-Hitchcock Medical Center (DHMC). The cause of this is multi-factorial, including provider referral patterns, patient preferences, constraints on clinic time in an academic medical practice, and system bottlenecks such as lack of available exam rooms. Regardless of the cause, the results are the same: potential for delayed treatment for rheumatologic diseases, pain and anxiety for patients, frustration for referring providers and poor practice performance. While matching capacity to demand improves access, increasing practice capacity without encroaching on physician teaching, research, and administrative time is challenging. To capitalize on this opportunity, the Rheumatology Access Team (RATE) adapted a shared medical appointment (SMA) to meet the needs of gout patients.

Methods: Following an SMA guide developed at DHMC, the team mapped an "ideal" pathway of patient care for the appointment; verified adequate patient volumes; secured access to meeting space and exam rooms; and produced written and electronic patient education materials. A physician, scribe, nurse, and SMA coordinator staff the SMA. The physician evaluates patients in brief, private exams and develops individual care plans while the scribe uses a template to record the history of present illness and exam findings. The nurse greets patients, takes vital signs, and facilitates discussion amongst the participants. The SMA coordinator schedules patients and enters lab orders (signed by the provider) to ensure labs are actionable at the time of the appointment. Feedback elicited from patients and staff informed iterative changes in the appointments using a continual improvement model. Billing is the equivalent of a regular gout follow up appointment.

Results: A gout SMA takes place every two months and includes education on diet and metabolic syndrome per patient requests. The current appointment has the capacity to serve up to 12 patients in a two-hour session for one provider. This increases potential new patient capacity in the clinic by a net of 4 visits per SMA. During the course of multiple interventions, access to Rheumatology improved steadily from April 2011 to April 2012 (107 to 56 days) but it has not reached our goal of 14 days. Patient satisfaction with the availability of an appointment in Rheumatology "when you wanted it" increased from 35% to 60% excellent during the intervention.

Conclusion: A gout SMA may improve access in Rheumatology, however a robust change in the wait times will require an increase in referrals to the SMA. The SMA is an excellent opportunity to practice principals of team-based iterative change. The SMA allows providers to operate at their level of training by eliminating order and data entry and allows them to focus on patients rather than computers during the visit. This model has potential to work within the framework of an accountable care organization. Further study of outcomes will be helpful in determining if these appointments provide value for patients and the institution beyond increasing access.

Disclosure: A. J. Zbehlik, None; N. M. Orzechowski, None.

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Enhancing Shared Decision-Making in Juvenile Idiopathic Arthritis. Jessica M. Sage, Ellen A. Lipstein, William B. Brinkman, Carole M. Lannon and Esi M. Morgan DeWitt. Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Juvenile idiopathic arthritis (JIA) is a chronic disease that requires long-term treatment. Patients and families face multiple treatment decisions over the course of illness that can often be complex. This project aims to improve the engagement of patients and families facing JIA treatment decisions, improve information exchange with care providers, and identify opportunities for a shared decision-making (SDM) intervention.

Methods: Sixteen pediatric rheumatology providers were recruited from four children's hospitals using purposive and snowball sampling to include a range of provider types (eg, nurse, physician, trainee) with unique approaches to working with families or a particular interest in education or decision-making. The providers participated in semi-structured interviews eliciting how they interact with patients and families in developing and adapting treatment plans. Interviews were audio-recorded and transcribed verbatim. The transcripts were coded by a multi-disciplinary team to determine major and minor themes. Based on the themes identified in the semi-structured interviews, multiple choice questions were presented at a conference of

pediatric rheumatology providers to enrich understanding of data from individual interviews. An audience response system captured the pattern of responses and helped the research team facilitate conversation about the reasons for variation among multi-site participants (n=24). Data was retained for analysis and detailed notes were taken.

Results: Treatment decisions were consistently initiated by the physician, with other providers focused on educating families and assessing barriers to treatment adherence. Physicians differed in their preferred treatment algorithm and options initially presented to families. Physicians' decisions focused on expected improvement with treatment, rather than treatment risks or family preferences. Providers described a range of approaches to inform families about treatment options and to tailor information according to providers' perceptions of a family's information needs, level of comprehension or mood (eg, anxiety). Participants described including families in the decision to initiate JIA treatment after limiting the options to fit the clinical situation and the physician's preferences. In contrast, providers described multiple methods for involving families in decisions related to the implementation of chosen treatments. Family preferences were also seen as particularly integral in the decision to stop treatment after symptom remission.

Conclusion: Decision-making on initial JIA treatment is largely driven by treatment guidelines and physician preferences. Such guidelines do not exist around treatment discontinuation and in that scenario family preferences are more likely to be considered. The uncertainty around standardized procedures for treatment discontinuation may make it the ideal time for a shared decision-making intervention (SDM) between the patient, family and provider. Next steps include engaging a stakeholder panel consisting of providers, educators and parents to discuss and evaluate possible interventions.

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2043

Documentation of Improvement Over 2 Months in Osteoarthritis, Systemic Lupus Erythematosus, Spondyloarthropathy and Gout Similarly to Rheumatoid Arthritis According to Function, Pain, Patient Global Estimate and RAPID3 On a Multidimensional Health Assessment Questionnaire (MDHAQ). Isabel Castrejón[1], Martin J. Bergman[2] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Taylor Hospital, Ridley Park, PA

Background/Purpose: The health assessment questionnaire (HAQ) and multidimensional HAQ (MDHAQ) were developed initially to assess patients with rheumatoid arthritis (RA). The most feasible method to ensure that each RA patient completes an MDHAQ at each visit is for the receptionist to present an MDHAQ to each patient with any diagnosis when registering for the visit, to complete in the waiting area. Data are then available for patients with all diagnoses, providing an opportunity to compare baseline scores and change over 2 months in patients with any rheumatic disease to patients with RA.

Methods: In the private practice of one rheumatologist, every patient with any diagnosis completes a 2-page MDHAQ at every visit before seeing the doctor. The MDHAQ includes 0–10 scores for physical function (MDHAQ-FN), pain and patient global estimate (PATGL), and a 0–30 score for routine assessment of patient index data (RAPID3), an index of the 3 patient self-report RA Core Data Set measures. Mean scores for individual measures and RAPID3 were compared at first visit and 2 months later for 141 new patients with 5 diagnoses: RA (n=39), osteoarthritis (OA) (n=41), systemic lupus erythematosus (SLE) (n=14), spondyloarthropathy (SpA) (n=23) and gout (n=24). Statistical significance was assessed by t test for change from baseline to 2 months later within each diagnostic group, and by analysis of variance (ANOVA) for change across diagnostic groups.

Results: Mean MDHAQ-FN scores at baseline ranged from 1.5 to 2.5, and from 1.1 to 1.9 two months later, documenting improvement of 9.4–26.8% in all diseases but OA ($p <0.05$ for all patients and RA). Mean pain scores at baseline ranged from 4.2 to 5.9, and from 3.0 to 4.7 two months later, documenting improvement of 20.2–35.3% in the 5 diagnoses ($p <0.05$ for all patients, RA, OA and gout). Mean PATGL at baseline ranged from 4.3 to 5.6, and from 3.3 to 5.0 two months later, documenting improvement of 11.2–30.4% ($p \leq 0.05$ for all patients, RA, OA and gout). RAPID3 scores at baseline ranged from 10.1 to 13.7, and from 7.4 to 11.3 two months later, documenting improvement of 16.8–27.5% ($p <0.05$ for all patients, RA, OA and gout). No differences for mean change from baseline to 2 months between diagnostic groups were statistically significant.

	Baseline Mean (SD)	2 months Mean (SD)	P*	Mean change**	% improvement
Physical function (MDHAQ-FN) (0–10)					
All patients (n = 141)	2.2 (1.7)	1.7 (1.7)	0.0028	0.34	15.5%
RA (n = 39)	2.5 (2.1)	1.9 (1.8)	0.02	0.65	26.0%
OA (n = 41)	1.8 (1.4)	1.8 (1.7)	0.95	0.01	0.6%
SLE (n = 14)	1.5 (1.3)	1.1 (1.7)	0.21	0.36	24.0%
SpA (n = 23)	2.2 (2.1)	1.6 (1.7)	0.06	0.59	26.8%
Gout (n = 24)	1.6 (1.3)	1.4 (1.8)	0.45	0.15	9.4%
Pain (0–10)					
All patients	5.2 (2.9)	3.8 (3.0)	<0.0001	1.40	26.9%
RA	5.2 (2.6)	3.9 (3.2)	0.014	1.32	25.4%
OA	5.3 (2.9)	3.9 (2.8)	0.0012	1.45	27.4%
SLE	4.2 (2.8)	3.0 (3.0)	0.10	1.18	28.1%
SpA	5.9 (3.1)	4.7 (3.0)	0.10	1.19	20.2%
Gout	4.9 (3.3)	3.2 (3.1)	0.02	1.73	35.3%
Patient global estimate (PATGL) (0–10)					
All patients	5.0 (2.7)	4.0 (3.1)	<0.0001	0.98	19.6%
RA	4.9 (2.8)	3.4 (3.0)	0.004	1.49	30.4%
OA	5.2 (2.5)	4.6 (3.0)	0.09	0.62	11.9%
SLE	4.5 (2.9)	3.3 (3.5)	0.14	1.18	26.2%
SpA	5.6 (2.6)	5.0 (2.9)	0.31	0.63	11.3%
Gout	4.3 (2.8)	3.3 (3.2)	0.05	1.00	23.3%
RAPID3 (0–30)					
All patients	12.1 (6.3)	9.5 (7.3)	<0.0001	2.71	22.2%
RA	12.6 (6.4)	9.2 (7.6)	0.0037	3.46	27.5%
OA	12.4 (6.0)	10.3 (6.9)	0.012	2.08	16.8%
SLE	10.1 (6.2)	7.4 (7.8)	0.089	2.71	26.8%
SpA	13.7 (6.7)	11.3 (7.1)	0.096	2.42	17.7%
Gout	10.9 (6.6)	8.0 (7.4)	0.024	2.88	26.4%

*P, repeated measures t test (change from baseline over 2 months for each disease)
**P not significant by ANOVA, comparison between RA and each diagnosis for mean change from baseline for all measures.

Conclusion: Disease severity and improvement over 2 months according to MDHAQ-FN, pain, PATGL and RAPID3 scores were similar to RA in OA, SLE, SpA and gout. Physicians appropriately view these 5 diagnoses as distinct, based on differences in their pathophysiology and treatments, emphasizing the need for a knowledgeable physician to establish distinct, accurate diagnoses in individual patients. However, from the patients' perspective, most rheumatic diseases are viewed more similarly than may be recognized by health professionals, documented by MDHAQ/RAPID3 scores.

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Trying to Improve Care: A Review of the Morbidity and Mortality Conference in the Division of Rheumotology. Michelle Batthish[1], Shirley Tse[1], Brian M. Feldman[1], G. Ross Baker[2] and Ronald M. Laxer[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]The University of Toronto, Toronto, ON

Background/Purpose: The morbidity and mortality conference (M&MC) is one of academic medicine's most visible fora for discussion of adverse events and errors; however it is unclear whether the M&MC is effective in its role to help reduce these events and thereby improve healthcare. In some contexts, the M&MC has been shown to be an effective forum for addressing patient safety and quality improvement competencies. However, there is marked variability in the process and standards for the M&MC. Little is known regarding the extent to which adverse events and errors are actually discussed in the M&MC. To describe the frequency of reported events as well as system improvement recommendations in the M&MC within the Division of Rheumatology at the Hospital for Sick Children (SickKids).

Methods: A five-year retrospective review of the M&MC minutes within the Division of Rheumatology at SickKids was completed. Descriptive data including the number of cases, attendance and types and location of reported events were collected. All events were categorized using an adaptation of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index. Recommendations were classified in the categories used by the Institute for Safe Medication Practices (ISMP) Canada.

Results: Between January 2007 and December 2011, a total of 30 regularly scheduled M&MCs were held. The mean attendance was 19 individuals per session. Eighty-one cases were reviewed (mean 2.7 cases/ session) with 2 reported deaths and 4 planned transfers to the intensive care unit. The most common type of events were related to "miscommunication" (35.8% of cases) followed by events related to a treatment/test/procedure

(23.5%). There were fewer events related to medications such as adverse drug reactions (12.3%), medication administration errors (8.7%). Most events occurred in the in-patient setting (40%) followed by the Medical Day Care Unit (26%). Category A events ("an event that has the capacity to cause error") were the most common (46.9%). The next most common events were Category C events ("an event occurred that reached the patient but did not cause harm") followed by Category E events ("an event occurred that may have contributed to or resulted in temporary harm and required intervention") with 24.7% and 19.8% of the cases, respectively. A total of 89 recommendations were made over the 5 year period. Just over half of these were classified as "information" according to ISMP Canada (58.4%). This was followed by 11 "rules and policies" recommendations (12.4%) and 8 "reminders, check lists and double check systems" recommendations (9%). There were 36 action items generated from these recommendations; 36% have been completed while 27.8% are ongoing.

Conclusion: The M&MC within the Division of Rheumatology reviews a varied number of adverse events. Increased reporting and study of adverse events and errors can lead to system improvements and safer health care. Further research is needed to develop innovative models of the M&MC, which focus on patient safety and systems improvement. This could lead to the creation of a standard review process which has greater potential to improve quality of care.

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Treatment Patterns and Monitoring of Serum Uric Acid Levels in a Large Cohort of Gout Patients in the United States: Is There Room for Improvement? Yong Chen[1], Kasem S. Akhras[2], Michael Grabner[1], Rima H. Tawk[3] and Ralph Quimbo[1]. [1]HealthCore, Inc., Wilmington, DE, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [3]University of Illinois at Chicago, Chicago, IL

Background/Purpose: Currently, there are no guidelines in the United States on monitoring serum uric acid (sUA) levels in gout and gout treatment patterns. However, there are guidelines from the European League Against Rheumatism gout task force and the British Society for Rheumatology/British Health Professionals in Rheumatology. Our aim was to assess treatment patterns for gout and laboratory sUA monitoring in a managed care population in the U.S., relative to international guidelines.

Methods: Data were extracted from the HealthCore Integrated Research Database (HIRD^{SM}), which contains integrated medical and pharmacy claims and laboratory result data from a large commercial U.S. health insurer. Eligible patients had either ≥2 medical claims for gout (ICD-9-CM code = 274) or ≥1 pharmacy claim for gout medications (allopurinol, colchicine, febuxostat, probenecid, sulphinpyrazone) between 01/01/2008 and 05/31/2011. The date of the earliest relevant claim was set as the index date. We included patients ≥18 years of age on index date, with ≥12 months of continuous eligibility pre-index date. Key guidelines selected in this study included initiating dose of allopurinol, mean time to dose escalation, maximum dosing levels, and sUA lab testing. We focused on a subgroup of patients initiating urate-lowering therapies (ULTs) after a new gout diagnosis (no pre-existing gout at baseline). Additionally, for a subset of patients with available electronic laboratory data, sUA levels were assessed within a year prior to and after initiation of ULTs. Treatment patterns were assessed until end of eligibility or end of the study period using descriptive statistics.

Results: We identified 93,546 eligible patients; 26% (n=24,555) were female and 35% (n=32,729) initiated ULTs. Mean ($\pm$ SD) age was 58$\pm$14.83 years and Charlson Comorbidity Index score was 1.35$\pm$ 2.02. Allopurinol accounted for 96% (n=31,388) of all first-line ULT fills, followed by probenecid (n=1,032) and febuxostat (n=309). No patients initiated sulphinpyrazone. Compared to guidelines, the mean starting dose of allopurinol was higher (213$\pm$114.48 mg/day vs. 100mg) and mean time to dose escalation was longer (24$\pm$28.6 weeks vs. 2–4 weeks); however, maximum daily dosing levels (244$\pm$117.12 mg/day) were within the recommended range. While 61% (n=19,843) of patients who initiated ULT had ≥1 sUA test prior to ULT initiation, only 34% (n=11,256) had ≥1 sUA test pre- and post-ULT initiation. Among 10,926 patients with sUA levels above target range (sUA >6 mg/dL) prior to ULT initiation, only 11% (n=1,190) achieved the goal of sUA ≤6mg/dL within a year of ULT initiation.

Conclusion: Comparing the results of this study to international guidelines shows room for improvement, specifically in laboratory monitoring of sUA levels relative to gout treatment. The results may be due in part to lack
of U.S. guidelines regarding the appropriate frequency of sUA testing relative to starting ULT, dose adjustment, and achievement of target sUA levels.

Disclosure: Y. Chen, None; **K. S. Akhras**, Takeda Pharmaceuticals International, Inc., 3; **M. Grabner**, None; **R. H. Tawk**, UIC/Takeda Fellow, 3; **R. Quimbo**, None.

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Matching of Patients' Actual and Desired Roles in Treatment Decision Making and Trust in Physicians. Akiko Aoki[1], Akiko Suda[2], Shouhei Nagaoka[3], Mitsuhiro Takeno[4], Yoshiaki Ishigatsubo[4], Tatsuto Ashizawa[5], Osamu Takahashi[6], Sachiko Ohde[7] and Sadayoshi Ohbu[8]. [1]Tokyo Medical University Hachioji Medical Center, Tokyo, Japan, [2]Yokohama Minami Kyousai Hospital, Yokohama, Japan, [3]Yokohama Minami Kyosai Hospital, Yokohama, Japan, [4]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [5]Tokyo Medical University Hachioji Medical Center, Chuo-ku,Tokyo, Japan, [6]St Luke's life science instutute, Chuo-ku, Tokyo, Japan, [7]St.Luke's Life of Science Institute, Tokyo, Japan, [8]Rikkyo University, Tokyo, Japan

Background/Purpose: Shared decision-making (SDM), in which the physician and patient work together through all phases of the decision-making process, has been of increasing significance. But the previous studies reported not all patients preferred SDM. This study explored rheumatoid arthritis (RA) patients' preferences and experiences for participation in treatment decision making at the Japanese rheumatology clinics. In addition, we examined how often their actual roles matched their desired roles, and whether the concordance between actual and desired roles was associated with trust in physicians.

Methods: A cross-sectional study was performed using a self-administered anonymous questionnaire between October and December 2010 on 406 RA outpatients who consecutively visited 3 hospitals in Japan. The following variables were investigated; (1) the patients' actual roles; their experiences when the current DMARDs were decided. (2) The patients' desired roles; their preferences for participation in treatment decision making. The patients were asked to choose one actual and one desired role of the following three options; #1 passive role; your doctor chooses the best drug for you. #2 collaborative role; you and your doctor decide the drug together. #3 active role; you choose the best drug and recommend it to your doctor. (3) Patient's trust in the physicians and adherence to the treatment. (4) Patients' evaluations of physician's attitudes of patient-centeredness. (5) The demographic data (e.g. age, gender, and educational status) and the RA-specific characteristics including the past and current use of disease modifying anti-rheumatic drugs (DMARDs). Multivariate analyses were used to assess the relationship between matching of patients' actual and desired roles and patients' trusts.

Results: The response rate was 58.6%. 82% were women, and the mean age was 65.1 $\pm$ 10.1 years. 26.8% of the patients perceived that the doctor chose the DMARDs for them. However, the majority (62%) of the patients preferred to collaborate with their doctors in making the treatment decision. The patients who want the passive roles in the decision making were more likely to have their preferences met than patients who wish to collaborate the doctors (98% vs. 42%, p<0.01). The overall concordance rate was 62%. In multivariate analyses, patients' attitudes of patient-centeredness and the concordance between patients' actual and desired roles were independent predictors of trust in physicians.

Conclusion: Physicians need to assess the decision making preferences on an individual basis to gain the patients' trust in physicians.

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2047

Impact of a Rheumatology Consultation Service in Hospitalized Patients. Shirley L. Chow[1], Dafna D. Gladman Gladman[2] and Heather McDonald-Blumer[3]. [1]University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Mt. Sinai Hospital, Toronto, ON

Background/Purpose: Rheumatologists provide hospital in-patient consultation for urgent and emergency referrals. In an increasingly cost-conscious, accountable, and integrated health-care system, the appropriate role of specialty care is under scrutiny. There is currently little information on the influence of inpatient rheumatology consultation on patient outcome.

Tuesday, November 13

The aims of our study were 1) To describe the nature of the hospital rheumatology consultations 10 years apart for educational merit 2) To determine whether a hospital rheumatology consultation service alters diagnostic accuracy, changes or expedites treatment, and whether treatment recommendations was adopted by the primary service. 3) To evaluate if needs are met by assessing the complexity of the rheumatology consult service referrals

Methods: Consecutive patients seen on the consultation service at an academic university hospital from July 1 2010 to December 31 2010 were recorded in a logbook. Using a standardized case form, the charts were reviewed and the patient's demographic information, admitting diagnosis, reason for consultation, referring service, final rheumatologic diagnosis, duration of hospital stay, treatment implemented and outcome were recorded. These were compared to a similar review in 1999.

Results: 268 patients were recorded in the log books over the 6 month period in 2010. These included 163 females and 105 males with a mean age of 55 years (range 19 to 92 years). This is more than the 238 consults seen over a 10 month period in 1999.

The most common diagnoses seen included: 62 connective tissue diseases (23%), 59 crystal induced arthritis (22%), 25 vasculitis (9%), 22 polyarthritis (8%); 15 osteoarthritis (6%); 14 regional syndromes (5%); 14 infections (5%); 10 spondyloarthritis (4%), and 8 others (3%). The remaining 38 had non-rheumatologic conditions (14%). This is similar in breadth as 1999.

The consults were requested from different services, but most commonly internal medicine at 104 (39%). There were 82 emergency referrals (31%), 158 urgent referrals (59%), and 28 non-urgent referrals (10%). The rheumatology team helped establish the diagnosis in 177 patients (66%) and confirmed the diagnosis in 57 consults (21%). 74 of 80 patients with swollen joints had their joints aspirated or injected (93%). 94 patients had steroids or disease modifying therapy initiated or adjusted. 126 patients had follow-up with a rheumatologist (47%).

Conclusion: The rheumatology hospital consultation service provides consultation from various specialties for a variety of rheumatic diseases, thus providing an excellent educational experience. Most referrals were for emergent or urgent rheumatic diseases. The service helped establish or confirm the diagnosis and helped initiate treatment. In general the suggestions were adopted by the team.

Disclosure: S. L. Chow, None; **D. D. G. Gladman**, None; **H. McDonald-Blumer**, None.

2048

Four Physician Global Assessments for Overall Status, Inflammation, Damage, and Unexplained Symptoms Are Useful in Usual Care of Patients with Osteoarthritis, Fibromyalgia, Systemic Lupus Erythematosus, and Spondyloarthropathy, As Well As Rheumatoid Arthritis. Isabel Castrejón[1], Martin J. Bergman[2] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Taylor Hospital, Ridley Park, PA

Background/Purpose: A physician global estimate (DOCGL) is important in clinical decisions concerning patients with rheumatoid arthritis (RA), and often is the most efficient of the 7 RA Core Data Set measures to distinguish active from control treatments in RA clinical trials. DOCGL is designed to assess inflammatory activity, but may be influenced by organ damage and "unexplained" chronic pain syndromes. Therefore, 3 subscale DOCGL visual analog scales (VAS) have been developed to estimate level of *a*) inflammation, *b*) damage, and *c*) "unexplained symptoms," in addition to overall status, reflecting the expertise of the rheumatologist concerning whether patient symptoms result primarily from one of these 3 bases. We analyzed the 4 DOCGL estimates for inflammation, damage, "unexplained" and overall status in consecutive patients with 5 rheumatic diagnoses: RA, osteoarthritis (OA), fibromyalgia (FM), systemic lupus erythematosus (SLE), and spondyloarthropathy (SpA).

Methods: The study was conducted in the private practice of one rheumatologist. All consecutive patients, regardless of diagnosis, complete a patient questionnaire, and are assigned four DOCGL estimates: overall status, inflammation, damage to any organ (e.g., joint, kidney) and "unexplained symptoms." Overall DOCGL was scored 0–10; the other 3 scales were scored 0–3 and recoded to 0–10, the current practice. Physician estimates at first visit of consecutive patients for the 4 DOCGL scales were analyzed in 5 diagnostic categories: RA (n=39), OA (n=41), FM (n=15), SLE (n=14) and SpA (n=23). Mean (standard deviation) and Spearman correlations were computed for overall physician global estimate with subscale estimates for inflammation, damage and "unexplained," as well as patient global estimate of status.

Results: DOCGL for overall status ranged from 2.6 to 5.0, highest for patients with FM (5.0), followed by RA (3.9), SpA (3.9), OA (3.6), and SLE (2.6). Physician subscale estimates were higher for inflammation than for damage or "unexplained" in RA, SLE, and SpA; higher for damage than for inflammation or "unexplained" in OA; and higher for "unexplained" than for inflammation or damage in FM (Table). Highest correlations of overall DOCGL were seen with physician subscale estimates for inflammation in RA, SLE, and SpA; with damage in OA; and with "unexplained" in FM.

Table. Mean (± SD) of 4 global estimates, and Spearman correlations between physician global for overall status and three physician subscale estimates as well as patient global estimate, according to diagnosis

	RA N = 39	OA N = 41	FM N = 15	SLE N = 14	SpA N = 23
Mean (± SD) for four 0–10 physician global estimates					
Overall Status (0–10 scale)	3.9 (±1.6)	3.6 (±1.9)	5.0 (±2.1)	2.6 (±1.9)	3.9 (±1.8)
Inflammation (0–10)	4.2 (±2.5)	1.3 (±2.0)	1.2 (±1.6)	2.4 (±2.6)	4.4 (±2.4)
Damage (0–10)	1.8 (±2.3)	3.2 (±2.7)	0.7 (±1.4)	1.2 (±2.2)	1.9 (±2.9)
Unexplained symptoms (0–10)	1.2 (±2.1)	0.9 (±2.5)	6.4 (±3.6)	1.5 (±3.1)	1.9 (±2.7)
Spearman correlations with overall physician global estimate					
Inflammation	0.79**	0.09	−0.52	0.61*	0.54*
Damage	0.23	0.51*	−0.22	−0.05	0.13
Unexplained Symptoms	0.01	0.17	0.67*	0.57	0.51*
Patient global estimate	0.41*	0.43*	0.07	0.50	0.29

*$p < 0.01$; **$p < 0.001$

Conclusion: Physician estimates for inflammation, damage and "unexplained symptoms" differ in patients with different rheumatic diagnoses. These 3 subscales reflect the expertise of the rheumatologist to estimate the basis for patient symptoms, and supplement the overall physician global estimate as a quantitative summary of the physical examination to assess and monitor patients with all rheumatic diseases in usual care.

Disclosure: I. Castrejón, None; **M. J. Bergman**, None; **T. Pincus**, None.

2049

Improving Pneumococcal Vaccination and Documentation for Immunosuppressed Patients At a University-Based Rheumatology Clinic. Christine Peoples, Rohit Aggarwal, Heena Sheth, Aarat Patel, Daniel Lupash, Christine McBurney, Ashima Malik, Swati Modi, Ximena D. Ruiz and Douglas W. Lienesch. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Centers for Disease Control and Prevention Guidelines recommend that all immunosuppressed patients receive the pneumococcal vaccine. The American College of Rheumatology Task Force Panel recommends vaccination for patients initiating therapy with disease-modifying anti-rheumatic drugs (DMARDs) or biologic therapies. Patients with chronic rheumatologic conditions have approximately double the incidence of infection compared to the normal population and those taking immunosuppressive agents show the highest risk, with the majority involving respiratory tract infections by common pathogens including *S. pneumoniae*. Prior studies show the rate of pneumococcal vaccination is low in this population. The aim of this study was to improve both administration and documentation rates of pneumococcal vaccine in immunosuppressed patients taking DMARDs and/or biologic agents at a university-based rheumatology clinic.

Methods: This study is a pre- and post-intervention comparison. Intervention phase data was collected from 1/23/2012–6/15/2012. Pre-intervention data included patients seen between 1/1/2009–12/31/2010 that were prescribed an immunosuppressive medication. Regularly seen patients were defined as having at least 2 visits, with either 1) at least 1 visit within the first 12 months of the measurement period and at least 1 visit within the second 12 months, or 2) 2 visits within only the second 12 month measurement period, with the first and last visits being separated by a minimum of 90 days. Patients eligible for pneumococcal vaccine and patients who were up-to-date with pneumococcal vaccination were determined. For the intervention phase, a report was generated of patients on immunosuppressant medications who had not received the pneumococcal vaccine who had upcoming visits. Clinic staff flagged these patients and a pneumococcal vaccine information sheet along with a brief form for the patient to complete were given to the patient. The medical assistant (MA) gathered information and documented in the electronic record. The MA communicated to RN who ordered and administered the vaccine. In select cases, physician approval and order were required prior to vaccination.

Results: Baseline data included 968 patients. Only 148 (15.3%) patients had received the pneumococcal vaccine. Post-intervention pneumococcal vaccination compliance revealed 361/1044 (34.6%) of patients had received the vaccine. This was a significant improvement from baseline (p<0.0001). An additional 114 (10.9%) patients were offered vaccination but had either already received the vaccine or deferred. A total of 45.5% had documentation, which was also significant improvement from baseline of 15.8% (p<0.0001).

Conclusion: Pneumonia vaccination administration rates in immunosuppressed patients with rheumatologic diseases are low and do not meet published guidelines. Implementation of an e-record and ancillary-staff-based intervention significantly improved vaccination and documentations rates without the need for considerable physician input. Ancillary staff review and physician communication were the key components in improving compliance with vaccination.

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2050

Are Patients Meeting the Updated Physical Activity Guidelines? Physical Activity Participation, Recommendation, and Preferences Among Adults with Rheumatic Diseases. Victoria L. Manning[1], Michael V. Hurley[2], David L. Scott[1] and Lindsay M. Bearne[1]. [1]King's College London, London, United Kingdom, [2]St George's University of London, London, United Kingdom

Background/Purpose: Physical activity (PA) reduces disability, comorbidity, and risk of premature mortality in people with rheumatic diseases, and clinical guidelines recommend that PA should be integral to rheumatic disease management (NICE 2008, 2009). Updated PA guidelines (published: US 2008, UK 2011) recommend that adults complete ≥150 minutes of moderate intensity PA or ≥75 minutes of vigorous intensity PA (or equivalent) in bouts of ≥10 minutes/week. Currently, the PA levels of adults with rheumatic diseases, assessed against these guidelines, are unknown. This study evaluates the PA levels of adults with rheumatic diseases against the updated guidelines. It assesses respondents' PA preferences and the proportion who report ever receiving PA advice from a healthcare professional (HCP).

Methods: 508 rheumatology outpatients (24% male, 76% female; 53% rheumatoid arthritis, 13% osteoarthritis, 7% psoriatic arthritis, 6% systemic lupus erythematosis, 5% fibromyalgia, 18% other; disease duration: 27% ≤1 year, 30% >1 to ≤5 years, 15% >5 to ≤10 years, 28% >10 years) were recruited from an inner city UK hospital (July-October 2010). Participants completed the short International PA Questionnaire, and 3 questions: "Has a doctor or other HCP ever suggested PA or exercise to help your arthritis or joint symptoms?" (Answers: yes, no, don't know), "Would you like help from your doctor or health service to become more physically active?" (Answers: yes, no, don't know), and "Which PAs do you enjoy?" (Answers: multiple options including free text response). Descriptive statistics were completed on all data, energy expenditure calculated (metabolic equivalent (MET) minutes/week = METs × weekly minutes × weekly days; walking = 3.3 METs, moderate = 4 METs, vigorous = 8 METs), and associations evaluated with Pearson's chi-square test. Respondents were categorized as: 1) Meeting guidelines (≥500 metabolic equivalent (MET) minutes/week; equivalent to ≥150 minutes of moderate intensity PA/week or ≥75 minutes of vigorous intensity PA/week), 2) Low (<500 MET minutes/week), or 3) Inactive (no PA ≥10 minutes (per activity bout)/week).

Results: 61% of respondents met the updated PA guidelines, and 39% did not meet the guidelines (12% low, 27% inactive). Physical inactivity increased with age (P<0.01). 43% of respondents reported that they had discussed PA with a HCP, and 50% that they would "like help" to become more physically active. Those diagnosed within the last year and those categorized as 'low' PA were least likely to report ever receiving PA advice (both P<0.05). Walking was the most preferred PA (65%), and accounted for 70% of respondents' total weekly energy expenditure.

Conclusion: Two thirds of urban UK adults with rheumatic diseases meet the updated public health guidelines for PA. However, despite the potential health benefits related to even low levels of PA, many are entirely inactive. PA advice may not be routinely included in the management of rheumatic diseases, despite patients reporting that they would like help to become more physically active. HCPs need to increase awareness of PA guidelines, and actively encourage regular PA. Walking may provide an easy and accessible form of exercise for people with rheumatic diseases.

Disclosure: **V. L. Manning**, None; **M. V. Hurley**, None; **D. L. Scott**, None; **L. M. Bearne**, None.

2051

Standardized Data Collection Supports Reliable Reporting of Rheumatoid Arthritis (RA) Measures for the Medicare Physicians' Quality Reporting System. J. Timothy Harrington[1], George Reed[2], Katherine C. Saunders[3], Lisa Lemire[3], Aimee Whitworth[3], Jeffrey D. Greenberg[4] and Joel M. Kremer[5]. [1]University of Wisconsin (retired), Madison, WI, [2]UMass Medical School, Worcester, MA, [3]CORRONA, Inc., Southborough, MA, [4]New York University School of Medicine, New York, NY, [5]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: The Medicare Physicians' Quality Reporting System (PQRS) program encourages physicians to measure and report clinical processes and disease outcomes that correlate with quality care, including an Rheumtoid Arthritis (RA) measures bundle. Physicians typically review patients' records for a single visit to determine how many measures are documented and met, or not. An alternative approach is to proactively collect standardized clinical data at each visit that includes that required for documenting each measure.

Methods: The Consortium of Rheumatology Researchers of North America (CORRONA) registry collects standardized clinical data from RA patients and their rheumatologists during routine office visits, including the data for each RA measure. As examples, patients complete a modified Health Assessment Questionnaire (mHAQ)(Measure 178) and investigators complete a 0 – 10 segmented Physician Global Assessment (Measure 177). All enrolled patients have completed informed consent for the CORRONA registry. In 2011, at least 1 visit report was submitted for 15,615 unique RA patients by 213 CORRONA investigators. Measures evaluated included Measure 108: Disease Modifying Anti-rheumatic Drug (DMARD) Therapy is or is not prescribed, and if not, why not?; Measure 176: For patients started on a first biologic, is a TB skin test or Quantiferon assay documented during the 6 months prior to starting the treatment, or not; Measure 177: Is RA disease activity documented as controlled,-low, moderate or high; Measure 178: Has functional status been assessed during the previous 12 months? Measure 179: Is RA prognosis assessed and documented as good, poor, or undetermined? Measure 180: Is the patient on =>/ 10 mg of prednisone for greater than 6 months or not, and if so, is a management plan documented to either increase other treatments and/or taper the prednisone dose. The most recent 2011 report for each patient was studied.

Results: The number (N) and percent (%) of visit reports meeting or not meeting each measure are shown, as are the number of reports meeting exclusion criteria for each measure, such as patients with controlled disease off DMARD treatment being excluded for Measure 108 (N = 521), and those who were not starting a first biologic being excluded from Measure 176.

Measure Number	Total Sample N	Performance Exclusion n (% of N)	Total Met+UnMet M	Performance Met n (% of M)	Performance Not Met n (% of M)
108	15615	521 (3.3)	15094	14,599 (96.7)	495 (3.3)
176	15615	15,407 (98.7)	208	39 (18.8)	169 (81.2)
177	15615	0 (0.0)	15615	15,588 (99.8)	27 (0.2)
178	15615	0 (0.0)	15615	13,652 (87.4)	1963 (12.6)
179	15615	0 (0.0)	15615	13,866 (88.8)	1,749 (11.2)
180	15615	47 (0.3)	15568	15,545 (99.85)	23 (0.15)

Conclusion: Collecting standardized data assures reliable measures reporting. The percents of Performance Met were high, except for Tb testing before DMARD initiation.

Disclosure: **J. T. Harrington**, Consortium of Rheumatology Researchers of North America CORRONA), 5, Abbott Laboratories, 5, Joiner Associates LLC, 4, Springer Publishers, 7, Abbott Laboratories, 8, US Treat to Target Committee, 8, American Orthopedic Association, 5; **G. Reed**, Corrona, 5, Corrona, 2; **K. C. Saunders**, Corrona, 3; **L. Lemire**, Corrona, 3; **A. Whitworth**, Corrona, 3; **J. D. Greenberg**, Corrona,Inc., 1, Astra Zeneca, Corrona, inc. Novartis, Pfizer, 5; **J. M. Kremer**, Amgen, 2, Amgen, 5, Amgen, 8.

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Effect of Community Characteristics On Quality of Care in Systemic Lupus Erythematosus. Edward Yelin[1], Laura Trupin[2], Chris Tonner[3] and Jinoos Yazdany[1]. [1]University of California San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA, [3]UCSF, San Francisco, CA

Background/Purpose: In prior studies we established that living in communities of concentrated poverty was associated with fewer physician visits and select SLE outcomes after taking characteristics of the individual into account (Trupin, JRheumatol 2008; Tonner, Arthritis Care Res 2010) and the presence and type of insurance was associated with the quality of SLE

care (Yazdany, J Gen Intern Med 2012). Here we examine whether community characteristics affect performance on quality measures for SLE after taking individual characteristics into account.

Methods: Data derive from 3 annual waves (2009–2011) of the UCSF Lupus Outcomes Study, a prospective cohort study of persons with SLE interviewed annually by telephone. Data on 13 SLE quality indicators covering diagnosis, monitoring, treatment, and preventive services were collected. Participant addresses were matched to information on characteristics of local communities, defined at various levels of aggregation. Community data include the American Community Survey for neighborhood poverty level, Dartmouth Health Care Atlas for nature of health care markets, and Rural Urban Codes to categorize health care markets as rural, small city, or major city. We used general estimating equations to assess the impact of characteristics of communities and individuals on the overall "pass rate" for quality measures in SLE (number received given eligibility) and on 2 important individual quality measures, drug toxicity monitoring (RXTOX) and cardiovascular risk factor evaluation (CVD). All models controlled for age, gender, race/ethnicity, disease duration, disease activity, education, # physician visits for SLE, and presence and type of insurance. Net of 28 subjects without physician visits during the year, data on 869 were analyzed.

Results: Among the 869 participants, 93% were female, 37% non-white, mean age was 50($\pm$13), disease duration was 17($\pm$9), and they were eligible for 5.1 quality measures/year. Overall pass rates averaged 67% (95% CI 66–68%) over the 3 years and did not differ significantly among years. Pass rates were slightly but significantly lower in areas with the highest quartile of rheumatologists/capita (64 vs. 67– 68% in the other quartiles). Pass rates were higher in small cities than in rural or major cities (70 vs. 65–66%) and differed among the 9 major Census regions (range 59 to 71%). Size of health referral region, number of primary care physicians per capita, and concentration of poverty were not associated with overall pass rates. Over the 3 years, 31% (95%CI 29–33%), of those eligible received RXTX and 70% (95% CI 67–73%) received CVD. Health referral areas in small cities were associated with higher rates of RXTX than in major cities (78 vs. 67%). No other community characteristic was associated with RXTX and none were associated with CVD. In all models, lack of health insurance was associated with lower pass rates, while public managed care plans were associated with better quality of care among the insured.

Conclusion: Lack of consistent community effects on quality of care suggests that quality improvement efforts in SLE not be targeted geographically and that the focus should continue to be on increased access to good health insurance coverage.

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Tele-Rheumatology: The Future Is Now. Daniel Albert[1], Krista Merrihew[2] and Sarah Pletcher[2]. [1]Dartmouth-Hitchcock Medical Center, Geisel School of Medicine, Lebanon, NH, [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

Background/Purpose: Access to rheumatologic consultation is limited by available expertise due to inadequate manpower and maldistribution of resources. Rural New England is particularly challenging because of sparse population, prolonged transportation times, and weather conditions that make travel difficult or impossible. Nearly every medical specialty and subspecialty is underrepresented (and often completely absent) in the northern 2/3 of New Hampshire, and this population's poorer health status and outcomes from disease and injury illustrate the 'rural penalty'. Dartmouth-Hitchcock Medical Center (DHMC), a Level 1 quaternary academic medical center located in the Upper Connecticut River Valley, is the only referral center for New Hampshire and parts of Vermont, Maine, and Eastern Upper New York State. Weeks Medical Center–Lancaster is a Rural Health Clinic associated with Weeks Medical Center, a 25 bed rural critical access hospital located in northern New Hampshire approximately 2 ½ hours by car north of DHMC. To provide rheumatologic access; we initiated a Tele-Rheumatology pilot clinic between a physician at DHMC and a trained nurse at Weeks Medical Center.

Methods: A two way live synchronous video conference was set up connecting a conference room at DHMC and an exam room at Weeks. Patients were scheduled at both institutions and referral notes and documentation were faxed to DHMC prior to the visit. Patients were seen at Weeks with a nurse who had shadowed the rheumatologist at DHMC and was instructed on joint examinations prior to the encounter. Vital signs, medications, and a problem list were communicated from the nurse at Weeks to the nurse at DHMC. Patients were interviewed and physical examination was achieved with assistance of the trained nurse at Weeks. The encounter was

documented at DHMC and electronically communicated to the referring physician. Management included medications electronically prescribed to patient's pharmacy, laboratory testing and ancillary services at Weeks. All patients are given the option to be seen at DHMC; however, since none of the patients needed to be seenat DHMC follow-up was arranged at the time of the encounter as a return telemedicine appointment. Issues that needed to be resolved before initiation included a contract between the hospitals, credentialing, billing procedures (both facilities billed, Weeks-facility charges and nurse visit, DHMC-professional fee), coding issues, and distribution of responsibilities. Most of these were facilitated by a face-to-face meeting.

Results: Patient, physician, and staff satisfaction was high. We have plans to extend this regionally to more than two dozen rural sites in the region.

Conclusion: As a substitute for outreach clinics telemedicine appears to be more cost effective and efficient limiting valuable specialist time that would otherwise be spent in travel, learning new computer systems and familiarizing themselves with procedures and protocols of different hospitals. It is possible to extend this service to homebound patients through portable units staffed by visiting nurses. Additionally, it would be possible to extend this to utilize instructional videos, web links to treatment information, or multiway conferencing.

2054

Safety of Joint and Soft Tissue Injections in Patients On Warfarin Anti-Coagulation. Richard Conway, Finbar (Barry) D. O'Shea, Gaye Cunnane and Michele Doran. St James's Hospital, Dublin, Ireland

Background/Purpose: Joint and soft tissue injections are commonly performed in clinical practice. An increasing number of patients are prescribed warfarin. Joint and soft tissue injections are frequently indicated in these patients. The limited available evidence suggests that joint and soft tissue injections are safe in therapeutically anti-coagulated patients receiving warfarin. Many authorities, including the New England Journal of Medicine, continue to recommend reversal of anti-coagulation in patients receiving warfarin who require these procedures. The aim of this study was to evaluate the safety of two approaches to the management of patients prescribed warfarin requiring joint or soft tissue injection

Methods: The protocol in our department prior to September 2011 was to hold warfarin and replace it with low molecular weight heparin for joint and soft tissue injections. A systematic literature review was performed which provided support to the performance of these procedures in patients on warfarin with an INR <3. A retrospective chart review was initiated at this point to assess the safety of the existing protocol. A new protocol was introduced whereby warfarin was continued with an INR check within 1 day of the procedure. The procedure was performed if the INR was <3. All patients receiving joint or soft tissue injections under the care of our service are provided with a helpline phone number to contact if symptoms worsen. In the event of persistent worsening symptoms >48 hours post-procedure arthrocentesis would be performed.

Results: In patients in whom warfarin was held, 32 procedures were performed in 18 patients. Of these 30 were joint injections (24 knee, 5 glenohumeral, 1 elbow) and there were 2 soft tissue injections (1 trochanteric bursa, 1 subacromial bursa). Conditions requiring injection were 13 rheumatoid arthritis, 11 osteoarthritis, 5 spondyloarthritis, and 1 each of adhesive capsulitis, rotator cuff tendinopathy and trochanteric bursitis. There were no clinical hemarthroses or complications. In patients who continued warfarin, 32 procedures were performed in 21 patients. Of these 27 were joint injections (24 knee, 1 glenohumeral, 1 elbow, 1 metatarsophalangeal) and there were 5 soft tissue injections (4 subacromial bursa, 1 carpal tunnel). Conditions requiring injection were 11 rheumatoid arthritis, 7 osteoarthritis, 6 crystal arthritis, 4 rotator cuff tendinopathy, 2 spondyloarthritis and 1 each of adhesive capsulitis and carpal tunnel syndrome. There were no clinical hemarthroses or complications. Full details of the study population are shown in Table 1.

Table 1. Comparison of Procedures Performed with Warfarin Held or Continued

	Warfarin held	Warfarin continued
Procedures, n	32	32
Patients, n	18	21
Joint injections, n (%)	30 (94%)	27 (84%)
Soft tissue injections, n (%)	2 (6%)	5 (16%)
Male, n (%)	14 (44)	14 (44)
Age, mean	77	74
INR, median (IQR)	1.2 (1.1–1.5)	2.4 (2.1–2.6)
Aspirin, n (%)	3 (9%)	1 (3%)
Clopidogrel, n (%)	0 (0%)	0 (0%)
Complications, n	0	0
Clinical haemarthroses, n	0	0

Conclusion: Joint and soft tissue injections appear to be safe in patients receiving warfarin anti-coagulation with an INR <3. Continuation of anti-coagulants reduces staff workload and patient inconvenience with no evidence of increased risk of complications.

2055

TEAM-Managed Care of Biological Patients At A Canadian Centre.
Melissa Deamude[1], Dawn Heap[2], Melanie Kanellos[2], Debbie Kislinsky[3], Kathy Kislinsky[3], Cynthia Mech[4], Helena Ross[3], Peggy Saldanha[3], Lauri Vanstone[3], Kathleen Brown[3] and William G. Bensen[5], [1] Dr. William G. Bensen Medicine Professional Corporation, Hamilton, ON, [2]Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [3]Dr. William Bensen Rheumatology Clinic, Hamilton, ON, [4]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [5]St. Joseph's Hospital and McMaster University, Hamilton, ON, Hamilton, ON

Background/Purpose: Managing complex arthritic patients with biologics is exacting and time consuming. As a result in January 2008 we established a separate biologic clinic with a clinic manager and team of experienced Registered Nurses linked to the general rheumatology clinic and early inflammatory arthritis clinic to assess, initiate, and follow patients with Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), and Psoriatic Arthritis (PsA) needing to transition to biologic treatment and requiring care and follow-up while on biologics. This team approach using experienced rheumatology nurses allows for triaging and timely access to care.

Methods: Approximately 770 patients, 60% RA, 20% PsA and 20% AS are being followed in the biologic program. All patients are initially assessed by an RN, examined to a standard protocol and then the treatment, assessment and plan of care is reviewed by the attending rheumatologist. The clinic is structured using a primary care nursing model which promotes continuity and a patient centered therapeutic approach to care. Nurses are responsible for assessing their patients providing disease and treatment related heath teaching and providing injection training. The nurses also perform the clinical outcome measurements including spondylarthropathy measures, joint evaluations and administration and scoring of patient reported outcome questionnaires. The team manages and reviews routine labs and diagnostics daily, provides follow-up calls to patients to discuss adverse events, flares, concerns and treatment related inquiries. Patients are seen a minimum of 3 times per year with most followed 6 times per year because of flares, co-morbidities, treatment adjustment or financial issues. The clinic operates as a primary point of contact for organizing management of co-morbidities, infusions and injections and ensures patients are being treated to target. The nurses are occasional speakers at national and regional rheumatology meetings to share best practices on the management of biological patients and how a team-based approach can improve efficiency and promote better patient outcomes.

Results: This rheumatology health team managing patients on biologic treatment has exponentially grown and has worked well over a four-year period. The team approach allows one rheumatologist to follow 5–7 times the number of patients seen by the average rheumatologist who does not have the team support. Currently in Canada we have approximately 1/3 of the rheumatologists we need for optimal care and a team based approach can help fill this gap, reducing the burden on the health care system with fewer visits to urgent care or Emergency departments. The team assesses 3–5 new patients a week for biologics and starts 2–3 patients per week on biologics.

Conclusion: The goal in the biologic clinic is treating to target for remission or lowest disease activity possible within the shortest period of time. This team approach to care has resulted in improved adherence to therapy, less risks and reported adverse events, improved safety monitoring and better patient satisfaction.

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Effectiveness of a Focused Educational Intervention in Improving the Supplementation of Vitamin D Deficiency and Insufficiency. Candice Low, Richard Conway, Gaye Cunnane, Michele Doran and Finbar (Barry) D. O'Shea, St James's Hospital, Dublin, Ireland

Background/Purpose: Vitamin D deficiency and insufficiency are important clinical states with the potential for adverse skeletal and non-skeletal consequences. In our experience the management of these states is frequently suboptimal. Focused educational initiatives are a proven means to improve patient care. The aim of this study was to evaluate the effectiveness of a focused educational intervention in improving the supplementation of patients with vitamin D deficiency and insufficiency.

Methods: A prospective study of 100 consecutive patients in the general rheumatology clinic with 25-hydroxyvitamin D deficiency or insufficiency (as defined as <30ng/ml) measured within the previous year was undertaken. A systematic literature review was performed and a consensus decision was made to supplement all patients with 25-hydroxyvitamin D <30ng/ml with 2000 units of vitamin D a day, with repeat testing at the next visit to ensure adequate but not excess supplementation. Following this a teaching session was held educating members of the multi-disciplinary team on the importance of vitamin D supplementation and reminders to supplement patients were placed in the clinic offices. Following the education intervention a further prospective study of 100 consecutive patients with 25-hydroxyvitamin D <30ng/ml measured within the previous year was performed.

Results: In the initial 100 patients screened, 25% were male, mean age was 56 years. Primary diagnosis was inflammatory arthritis (IA) in 62%, connective tissue disease (CTD) in 14%, osteoarthritis (OA) in 12% and other conditions in 12%. 18% had known osteoporosis and 13% had previous fractures. Mean 25-hydroxyvitamin D was 17.8 ng/ml. 20 patients had 25-hydroxyvitamin D <12ng/ml, 40 had 25-hydroxyvitamin D 12–20ng/ml, 40 had 25-hydroxyvitamin D 20–30ng/ml. Pre-education only 28 patients had additional vitamin D prescribed as a result. Following the educational intervention, in the population screened 25% were male, mean age was 55 years. Primary diagnosis was IA in 47%, OA in 16%, CTD in 11% and other conditions in 26%. 15% had known osteoporosis and 12% had previous fractures. Mean 25-hydroxyvitamin D was 16.4 ng/ml. 31 patients had 25-hydroxyvitamin D <12ng/ml, 39 had 25-hydroxyvitamin D 12–20ng/ml, 30 had 25-hydroxyvitamin D 20–30ng/ml. As a consequence of our educational intervention, 80 patients had additional vitamin D prescribed. The change in vitamin D prescriptions following the educational intervention is shown in figure 1.
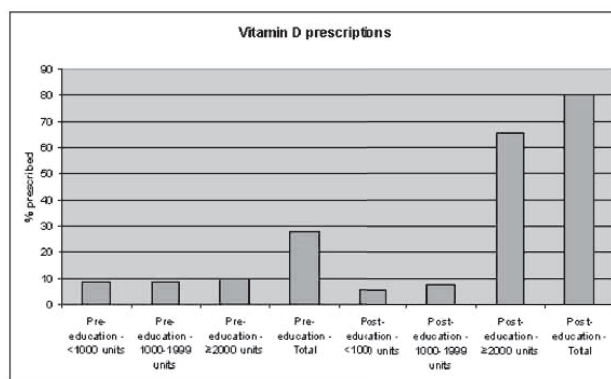
Figure 1. % of Patients prescribed, and dose prescribed of, vitamin D pre and post an educational initiative.

Conclusion: A focused educational intervention has the potential to improve vitamin D supplementation and patient care in the management of low vitamin D states. Failure to identify and adequately treat vitamin D deficiency has the potential for serious adverse consequences for our patients.

Analysis of the Adherence to the Monitoring of Glucocorticoid Eye Toxicity and of the Prevalence of Cataracts and Glaucoma Among Patients with Systemic Lupus Erythematosus. Linda Carli[1], Chiari Tani[1], Francesca Querci[1], Alessandra Della Rossa[1]. Sabrina Vagnani[1], Anna d'Ascanio[1], Rossella Neri[1], Antonio Tavoni[2], Stefano Bombardieri[1] and Marta Mosca[1], [1]Rheumatology Unit, Department of Internal Medicine, University of Pisa, PISA, Italy, [2]Immunoallergology Unit, Department of Internal Meicine, University of Pisa, PISA, Italy

Background/Purpose: Cataracts and glaucoma are among the main causes of impaired visual acuity and have a prevalence respectively of 9–17% and 1–2% among subjects older than 70 years. Chronic glucocorticoid (GC) therapy is associated with an increased risk of developing cataracts and glaucoma and recommendations have been developed for monitoring these side effects in patients with rheumatic diseases.

The aim of this study was to assess the adherence to the existing recommendations for monitoring eye toxicity of chronic GC therapy and the prevalence of cataracts and glaucoma among systemic lupus erythematosus (SLE) patients followed at our Unit.

Methods: Retrospective analysis of clinical charts to evaluate epidemiological data (disease duration, age at last assessment), cumulative and mean daily dose of GC and administration of GC pulses, number and frequency of eye assessment during follow up. Presence/absence of cataracts and glaucoma as reported in the last available eye assessment.

Results: One hundred and seventy charts were examined, 34 (20%) of these (mean follow up 83.6 ± 66.5; mean age 42.5 ± 14.8 years) never underwent an eye assessment. The remaining 136 (mean follow up 152.5 ± 99.8 months, age 45.4 ± 12.5 years), underwent an eye assessment on average with an interval of 75 ± 61.7 months. However, only 45 (33%) had received an evaluation during the previous 12 months. All these 170 patients were taking chronic CG therapy at a mean daily dose of 5.4 ± 2.4 mg prednisone (PDN), and a mean cumulative dose of 27.6 ± 20.5 gms. Out of the 136 patients with at least one eye assessment (mean PDN 5.5 ± 2.4 mg, mean cumulative dose 29.8 ± 21.5 gms), cataracts were observed in 39 patients (29%) and glaucoma in 4 patients (3%). Cataracts were diagnosed at a mean age of 46.5 ± 10 years; the development of cataracts was associated with age, disease duration and cumulative GC dose (cataracts vs not cataracts: mean cumulative PDN dose 32,8 vs 20,4 gms; p<0,0001). Glaucoma was diagnosed at a mean age of 40.5 ± 16 years; due to the small number of patients no correlations were made.

Conclusion: Although 80% of patients have at least one eye assessment, the adherence to recommendations is suboptimal as only 33% of patients underwent an eye assessment over the previous 12 months. As expected the prevalence of cataracts and glaucoma is higher than in the general population and these conditions occur early in the life of SLE patients. As not all patients have a recent eye evaluation our data could underestimate the real incidence of these two potentially severe conditions. An association between GC and cataracts is confirmed. These data reinforce the need to improve adherence to recommendations to eye monitoring among SLE patients under chronic therapy with GC.

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Differences in Psychological Characteristics Between Patients with Rheumatoid and Psoriatic Arthritis. Panagiota Tsitsi[1], Athina Theodoridou[1], Foteini Lada[1], Konstantinos Papanikolaou[2], Despina Dimopoulou[1], Georgios Garyfallos[3], Alexios Benos[4] and Alexandros Garyfallos[1]. [1]4th Department of Internal Medicine,Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2]Psychiatric Hospital of Petra Olympus, Katerini, Greece, Katerini, Greece, [3]2nd Department of Psychiatry, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, [4]Department of Hygiene, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background/Purpose: Both rheumatoid (RA) and psoriatic arthritis (PsA) seem to have a negative impact on patients' psychological status mostly due to the chronic character of the disease. Literature reports and clinical practice evidence support that patients suffering from PsA express their discomfort and complaints more often than those who suffer from RA, even when the physical disability is similar between them. The aim of the study is to compare aspects of the psychological profile of the two groups of patients and to examine the differences between their behavior

Methods: The study sample consisted of 59 outpatients of the 4th Medical Department of Internal Medicine of Aristotle University of Thessaloniki, suffering from RA and PsA. Disease activity was measured using DAS28 score. Psychological characteristics were evaluated with the use of SCL-90-R questionnaire while other information including quality of life (QoL), general health (GH) and disability were assessed with the use of SF-36, GHQ and HAQ-DI. Patients suffering from extended psoriatic skin lesions (BSA>5) as well as those who presented axial joint damage were excluded in order to ensure clinical similarity between the two groups of patients.

Results: A total of 32 patients suffering from RA and 27 from PsA were recruited. Mean age for RA group was 48.2 ($\pm$10.6) and PsA 49.3 ($\pm$7.6) years. No significant difference in DAS (p=0.843), disability (p=0.466), GH (p=0.801) and VAS score (p=0.855) was found between the two groups. As far as QoL is concerned, the two groups did not demonstrate difference in any of the subscales of SF-36. Patients with RA demonstrated lower scores in Interpersonal Sensitivity (Subscale III of SCL-90-R) (p=0.044) than those with PsA.

In the RA group, DAS was found to correlate with disability (r=0.804, p=0.000), GH (r=0.519 p=0.002), Somatization (I) (r=0.440 p=0.012) and Depression (IV) (r=0.426 p=0.015). Only the physical component (PCS) of the SF-36 correlates with the DAS28 score (r=-0.741 p=0.000). Both disability and GH correlate with I and IV (r= 0.604 p=0.000) (r=0.536 p=0.002) (r=0.416 p=0.018) (r=0.431 p=0.014) respectively.

In the PsA group DAS28 score does not correlate with GH (p=0.702) or IV (p=0.123) but it does correlate with HAQ score (r=0.491 p=0.009), I (r=0.312 p=0.033) and PCS (r=-0.606 p=0.001). HAQ score correlates with IV (r=0.559 p=0.002) as well as the PCS (r=0.812 p=0.000). GH correlates with most of the subscales of SCL-90-R except for the III (p=0.054) while there is no correlation with the PCS (p=0.275) contrary to the Mental Component (MCS) (r=-0.476 p=0.012). Finally the III subscale of SCL-90-R does not correlate with any of the measured clinical parameters.

Conclusion: In consistence with findings from everyday interaction during clinical evaluation, PsA patients rather than RA ones seem to meet with feelings of self- deprivation, uneasiness, discomfort during interpersonal interaction, personal inadequacy and inferiority in comparison with others. Moreover, the differences in psychological characteristics between patients with RA and PsA cannot be attributed to the degree of skin lesion, disease activity or disability.

Disclosure: **P. Tsitsi**, None; **A. Theodoridou**, None; **F. Lada**, None; **K. Papanikolaou**, None; **D. Dimopoulou**, None; **G. Garyfallos**, None; **A. Benos**, None; **A. Garyfallos**, None.

The Efficacy of Clinical Guidelines in Promoting Co-Prescription of Bone Protection with Glucocorticoids Among Hospital Doctors Treating Inpatients. Leonard C. Harty[1], James Clare[2], Dylan Finnerty[2], Susan Van Der Kamp[2], Fionnuala Kennedy[3], Malachi McKenna[4] and Oliver M. Fitz-Gerald[1]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]Department of Rheumatology, St. Vincent's University Hospital, Dublin, Ireland, [3]Pharmacy Department, St. Vincent's University Hospital, Dublin, Ireland, [4]Department of Endocrinology & Metabolic Bone Disease, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Therapeutic glucocorticoids (GC) rapidly decrease bone mineral density, inducing a remodelling imbalance by promoting osteoclast differentiation and activation and by inhibiting osctecoytes. Current guidelines direct that bisphosphonates (BP's) and elemental calcium (Ca^{++}) with Vitamin D (Vit. D) should be given at initiation of GC therapy, as it is known that bone remodelling imbalance occurs early with steroid usage. We circulated these guidelines within our hospital after auditing the existing practice of the hospitals doctors and 1yr later we sought to measure the efficacy of our intervention by completing an audit loop.

Methods: A cross sectional audit was performed of all adult medical and surgical inpatients in a tertiary referral centre teaching hospital. Prescribed GC and concurrent anti osteoporotic medication were noted. Subsequent to the initial audit, guidelines promoting the use of BP's, Ca^{++} and Vit. D when prescribing GC's were advertised on hospital notice boards, in hospital bulletins, hospital prescribing guidelines and on the hospital website. One year after promoting guidelines the audit loop was completed by performing a similar cross sectional audit.

Tuesday, November 13

Results: All inpatient medical records (n=417) were reviewed in Jan 2010. 52% of the inpatients were female and 58% were older than 65. 66/417 (16%) inpatients had been prescribed GC's. Ca^{++} with Vit. D was prescribed for 20% of patients on GC's with 2% also receiving BP therapy. 3% of patients were also receiving-post menopausal hormone replacement therapy.

In Nov 2011 one year after guideline publication, all 452 inpatient medical records (n=452) were reviewed. 63% of the patients were female and 60% were older than 65. 55/452 (12%) inpatients were prescribed GC's. Ca^{++} with Vit. D was prescribed for 55% of patients on systemic steroids with 20% also receiving BP therapy.

The resultant improvement in the co-prescription of Ca^{++} & Vit. D and BP's with GC's by the order of 2.35 and 10 respectively can be attributed in part to the circulation of hospital guidelines. However 45% of patients on systemic steroids continued to receive no bone protection and 80% received suboptimal bone protection from steroid induced osteoporosis.

Conclusion: Publication and advertisement of current bone protection guidelines when prescribing systemic steroids resulted in a substantial but suboptimal improvement by hospital doctors in our hospital in the co-prescription of bone protecting drugs to prevent steroid induced osteoporosis. In this audit it appears that the majority of prescribers do recognise the necessity to protect bone health when a patient requires steroids. However a substantial number of patients did not receive any bone protection. It is our perception that many physicians are not aware that short courses of steroids reduce bone mineral density and therefore greater efforts must be made to enhance doctor awareness of the necessity for bone protection to be prescribed at initiation of systemic steroids.

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Using the Electronic Medical Record to Increase Rates of Physician Assessment of Lipids in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis: A Quality Improvement Initiative. Astrud Lorraine Leyva, Laura L. Tarter, Elizabeth Blair Solow and David R. Karp. UT Southwestern Medical Center, Dallas, TX

Background/Purpose: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Guidelines for the management of both SLE and RA recommend evaluation of and intervention for known cardiovascular risk factors, including dyslipidemia. However, studies suggest that screening rates remain suboptimal. Quality improvement methodology offers a practical approach to bridge this gap in care. The fellowship training setting is an ideal environment in which to pilot such a project, as the American College of Graduate Medical Education requires that fellows demonstrate the ability to continuously improve patient care. Our aim was to improve the rate of recording lipid panel results in patients with SLE or RA to over 50% in a one month period.

Methods: In our busy outpatient rheumatology clinic in a county hospital setting, we examined patient, provider, and health system factors that could be barriers to providing routine cardiovascular risk assessment for our patients. For our first Plan-Do-Act-Check (PDCA) cycle, we examined the frequency with which physicians recorded lipid panel results in clinic notes during routine visits. We obtained baseline data for all RA or SLE patient visits for each of our six clinical fellows one month period. Our hospital district utilizes the EPIC electronic medical record (EMR); thus we devised a simple "dotphrase" to assist providers in ascertaining the date and results of a patient's most recent lipid panel with just a few keystrokes. We then organized an educational session for our providers to inform them about the initiative, the collective baseline data and applying the "dotphrase". Each clinical fellow also received an individual summary of their baseline screening rates.

Results: We reviewed 91 patient visits during the pre-intervention period (69% RA, 31% SLE). Patients were 46.7 years old (SD 14.7) and 83% female. Forty-two percent of patients had a lipid panel sent within the past year. Lipid panels were ordered by primary care physicians (63%), rheumatologists (15%), and other physicians (22%). Twenty percent of patients were on statin therapy. Our providers documented lipid panel results, however, in only 12% of the visits. Following the implementation of the EMR "dotphrase", we reviewed an additional 92 patient visits over a one month period. Baseline characteristics were similar to our pre-intervention group. Our providers augmented their lipid panel recording to a rate of 65% after the intervention.

Conclusion: In our hospital district setting with an integrated EMR, the use of a simple "dotphrase" was effective in improving provider documentation of lipid panel results in patients with RA and SLE. Future PDCA cycles will focus on increasing rates of obtaining screening lipid panels and intervening in patients with documented dyslipidemia.

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Physician Variation in Documentation of Rheumatoid Arthritis Quality Measures and Evaluation of Relationship with Radiographic Progression. Sonali Desai[1], Jinoos Yazdany[2], Nancy A. Shadick[3], Siri Lillegraven[4], Chih-Chin Liu[5], Michelle A. Frits[6], Tabatha Norton[7], Jonathan S. Coblyn[8], Michael Weinblatt[5] and Daniel H. Solomon[1]. [1]Boston, MA, [2]University of California San Francisco, San Francisco, CA, [3]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [6]Brigham and Women's Hospital, Boston, MA, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [8]Brigham & Womens Hosp, Boston, MA

Background/Purpose: Documentation of quality measures (QMs) in rheumatoid arthritis (RA) has been proposed as a way to demonstrate quality of care, but data linking appropriate documentation to improved clinical outcomes are lacking. We examined the variation in physician documentation of RA QMs on disease activity and functional status and the association with radiographic outcomes.

Methods: We studied a subset of 286 patients participating in a longitudinal RA cohort followed from 2003–2008 at an academic medical center with complete data on total sharp score (TSS) (2 hand x-rays approximately 2 years apart). All clinical notes from 18 different rheumatologists during a 24-month period preceding the date of the second hand x-ray were examined for the presence or absence of the RA QMs on disease activity and functional status. Disease activity QM documentation was defined as mention of disease activity assessment in the medical record, with details categorizing disease activity into low, medium or high. Functional status QM documentation was defined as mention of how RA impacted activities of daily living. Change in TSS was defined as an annualized progression rate and dichotomized as progression ($\geq$1U per year) or no progression ($<$1U per year). We examined: patient visits per MD per year; RA QM documentation as either disease activity, functional status or both; and mean % of visits with RA QM documentation. We compared the mean change in TSS across patients grouped by percentage of visits meeting a QM, i.e., none or some documentation of disease activity and functional status.

Results: The mean age of our patients was 57.0 ($\pm$14.0) years, 82.0% were female, mean disease duration was 10.4 ($\pm$10.9) years, baseline DAS28 score was 3.7 ($\pm$1.5) and 65.9% were either RF or CCP positive. 76.6% of patients were on a non-biologic and 31.5% were on a biologic DMARD. Radiographic progression of RA was reported in 27.0% of patients. There was at least one chart note with documentation of disease activity for 26.0% of patients and functional status for 75.0%, during the 24-month period. For the seven rheumatologists with at least 10 patients in the study, there was variation in the number of visits per patient per year and documentation of disease activity and functional status in chart notes (**Table**). In unadjusted analyses, there was no relationship between performance on either disease activity (p=0.6) or functional status (p=0.5) and change in TSS.

Table. Differences in RA visits and QM documentation by rheumatologist

MD	Study sample patients N (%)	Patient visits per year mean (min-max)	Disease activity at least once N (%)	Functional status at least once N (%)	Both QMs at least once N (%)	% of visit with QM (mean)	
N=7*	N=242	24-month follow-up	24-month follow-up	24-month follow-up	24-month follow-up	Disease activity	Functional status
A	50 (20.7)	8.6 (3–14)	4 (8)	27 (54)	1 (2)	1.6	22.0
B	20 (8.3)	9 (6–12)	0	12 (60)	0	0.0	11.0
C	28 (11.6)	8.9 (4–15)	9 (32.1)	18 (64.3)	3 (10.7)	8.8	19.2
D	10 (4.1)	6.9 (4–12)	3 (30)	4 (40)	1 (10)	11.3	11.2
E	10 (4.1)	9.4 (5–16)	3 (30)	7 (70)	1 (10)	5.0	18.3
F	21 (8.7)	8 (4–19)	3 (14.3)	21 (100)	1 (4.8)	2.5	46.8
G	103 (42.6)	7.8 (3–18)	42 (40.8)	90 (87.4)	22 (21.4)	8.5	53.7

The 7 rheumatologists represented in this table contributed at least 10 patients to the study sample

Conclusion: Among this cohort of RA patients with established disease, overall documentation of RA QMs on disease activity and functional status was inconsistent across rheumatologists. We did not find an association between the % of visits with an RA QM documented and radiographic outcome over a 24-month follow-up period.

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Increasing Pneumococcal Vaccination for Immunosuppressed Patients: A Cluster Quality Improvement Trial. Sonali Desai[1], Lara Szent-gyorgyi[1], Alexander Turchin[1]. Bing Lu[2], Anna A. Bogdanova[1], Michael Weinblatt[3], Jonathan S. Coblyn[4], Jeffrey O. Greenberg[1], Allen Kachalia[1] and Daniel H. Solomon[5], [1]Boston, MA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [4]Brigham & Womens Hosp, Boston, MA, [5]Division of Rheumatology, Brigham & Women's Hospital, Boston, MA

Background/Purpose: It is important for patients on immunosuppressive medications to receive pneumococcal vaccination. Prior studies suggest that most patients do not undergo vaccination. We evaluated the effects of a point-of-care paper reminder form on being up-to-date with pneumococcal vaccination in a rheumatology practice.

Methods: Selected rheumatologists at five ambulatory practice sites received a point-of-care paper reminder form for patients who were not up-to-date with pneumococcal vaccination. Interrupted time-series analyses were used to measure the effect of the paper reminder form upon the intervention rheumatologists compared to the control rheumatologists. Adjusted Cox proportional hazards models were examined to identify independent predictors of being up-to-date with pneumococcal vaccination.

Results: We evaluated a total of 3,717 patients on immunosuppressive medications. In this group 66.0% had rheumatoid arthritis:74.1% were female, and the mean age was 53.7 years. Rheumatologists who received the intervention had a significant increase in the rate of patients up-to-date with pneumococcal vaccination from 67.6% to 80.0% in the time period following the intervention (p=0.006), whereas rheumatologists in the control group had stable rate from 52.3% to 52.0% (p=0.90). In regression models, the intervention [hazard ratio, HR=3.58, (95% CI 2.46–5.20)], having a primary care physician affiliated with our hospital [HR=1.68, (95% CI 1.44–1.97)], and having a diagnosis of diabetes mellitus [HR =1.57, (95% CI 1.02–2.41)] were positive predictors of being up-to-date with vaccination.

Figure 1 shows the percentage of patients up-to-date with pneumococcal vaccination over time. The intervention was applied in two waves, with ten physicians receiving the intervention in June 2010 and four additional physicians receiving the intervention in October 2010. In order to synchronize these data, time 0 was defined as the time that the intervention was applied to the patients of the treating rheumatologist. The red line represents the 21 rheumatologists in the control group and the blue line represents the 14 rheumatologists in the intervention group.
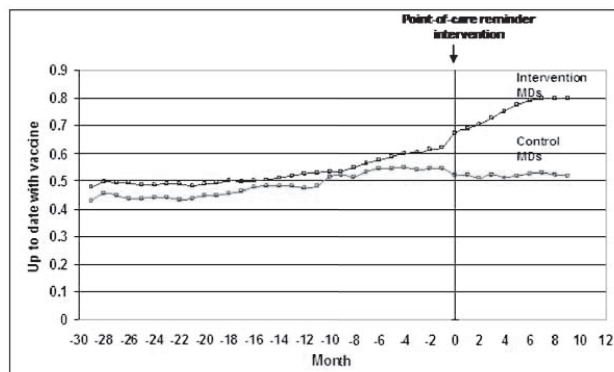
Figure 1. Pneumococcal vaccination over time, before and after point-of-care reminder intervention.

Conclusion: A simple point-of-care paper reminder for patients on immunosuppressive medications significantly increased the rate of being up-to-date with pneumococcal vaccination among intervention rheumatologists over a six-month period.

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Detection of Inflammatory Arthritis and Musculoskeletal Conditions in a First Nations Community: Results of an Onsite Screening Program. Cheryl Barnabe[1], Carrissa Low Horn[2], Margaret Kargard[2], Stephen Mintsioulis[2], Sharon Leclercq[1], Dianne P. Mosher[1], Hani S. El-Gabalawy[3], Tyler White[2] and Marvin J. Fritzler[1]. [1]University of Calgary, Calgary, AB, [2]Siksika Health Services, Siksika, AB, [3]University of Manitoba, Winnipeg, MB

Background/Purpose: RA and SLE are more severe and at least twice as prevalent in the First Nations population of Canada compared to the Caucasian population. Difficulties in accessing rheumatology care have been previously documented. A collaboration between a Blackfoot community (n= 3,700) and rheumatologists from a nearby urban centre was initiated to enable better consultative services for the Nation's members, and allow for established rheumatology patients to receive care in their home community. Parallel to this initiative, we established an arthritis screening program, with the primary goal being to identify new cases of inflammatory arthritis (IA) early in the disease course.

Methods: A weekly community-based screening program started in June 2011. Consenting participants undergo a musculoskeletal (MSK) history and examination by a rheumatologist and complete a Health Assessment Questionnaire (HAQ). Serologic testing (rheumatoid factor (RF), antinuclear antibody (ANA), extractable nuclear antigens (ENA), anti-cyclic citrullinated peptide (anti-CCP)) is offered and further investigations initiated as appropriate to confirm a diagnosis. Management is provided in conjunction with primary care providers. We provide here a descriptive summary of the program's outcomes after 1 year.

Results: 144 individuals have been reviewed (74% female, mean age 52.4 years). Half the cohort have a family history of RA (52%) or SLE (18%). All individuals have at least 1 MSK symptom, and 68% report fatigue. The most common sites of joint pain are the hands (81%), knees (75%), lumbar spine (64%), and shoulders (55%). A primary care provider had been consulted by 72% of the cohort prior to the screening program, with 15% having seen a rheumatologist and 15% an orthopedic surgeon in the past. The median HAQ score was 0.88, the median pain score (0–10 VAS) 5, and the median patient global score 5 (0–10 VAS). Seventeen new cases of rheumatic disease have been diagnosed (10 RA, 3 PsA, 1 JIA, 1 Sjogren Syndrome with arthralgias, 2 crystal arthropathies) and 4 individuals remain under observation. Fourteen patients with established rheumatic diseases (6 RA, 1 PsA, 1 spondyloarthritis, 5 SLE, 1 JIA) have re-engaged in active rheumatology care. OA and/or degenerative disk disease was present in 58% of the participants screened, 42% had soft tissue syndromes, 2% had fibromyalgia and 6% had a neurologic condition causing pain. RF and anti-CCP antibodies were rarely positive; anti-CCP was present in low or medium titres in 4 individuals with either soft tissue syndromes or OA. ANA was positive in 52% of the group, with 28% having titres >1:320. In those with positive ANA, only 5 had a history of SLE, IA or RA.

Conclusion: The screening program has been successful in detecting new cases of early IA and returning established rheumatology patients to active care in this First Nations community. There is a significant burden of OA in the community, and many residents are ANA positive in the absence of apparent connective tissue disorders. These findings highlight the need for a multidisciplinary team of primary care providers, allied health professionals, and specialists to maximize MSK care in the community. Limitations at this early phase include participation bias.

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Regular Measure of Disease Activity During the Routine Care of Rheumatoid Arthritis Patients Involves Some Extra Work but Positive Results. Lissiane K. N. Guedes, Ana Cristina Medeiros Ribeiro, Karina Rossi Bonfiglioli, Diogo Domiciano, Carolina Reither Vizioli, Gilmara Franco da Cunha, Andressa Silva Abreu, Filipi M. Mello, Ana Luiza de Aguiar Foelkel, Celio R. Gonçalves and Ieda Laurindo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: According to treat to target recommendations the use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions with the final objective of reaching remission or low disease activity in patients with RA.Objective: to study the outcome of adding a validated composite measure of disease activity (DAS28) to routine clinical visits.

Methods: Since 2007 all RA patients (ACR-1987 criteria) in regular follow-up at the Rheumatology Service of a tertiary center change to electronic files with a DAS28-ESR calculator and this measure became mandatory in the routine care visits. Inclusion criteria: patients in regular follow-up for at least 2 years before 2007and no use of biologic agents during the study period (January 2007-December 2011). All patients could receive, free of charge, traditional DMARDs (chloroquine, methotrexate, sulfasalazine, leflunomide and azathioprine), corticosteroids (including intra-articular injections), analgesic and antiinflamatory medications as needed and according to a pre-established protocol. The first DAS28 recorded in the electronic files was compared to the last one recorded in 2011, after 4 years of regular measure of disease activity guiding therapeutic decisions (RA-study group). ERA patients (less than one year of symptoms at the beginning of treatment) submitted to a therapeutic strategy of tight control and DAS28 based clinical decisions were also evaluated.

Results: a total of 304 patients was included, 217 consisting our study group(RA-SG) (86% female, mean age 63 ± 11yrs, mean disease duration 22 ± 10yrs) and 87 ERA patients (83% female, mean age 53 ± 12yrs, mean disease duration 6.7 ± 1.6yrs). ERA patients were significantly younger and with shorter disease duration. DAS28 values and different levels of disease activity are depicted below:

	RA-SG n=217		ERA n=87	
	2007	2011	2007	2011
DAS28 mean (SD)	3.9* (1.4)	3.3* (1.3)	3.7** (1.7)	2.9** (1.4)
% DAS28 <2.6	17*	34*	29**	45**
% low disease activity	18	16	12**	24**
% moderate disease activity	47	39	30**	9**
% high disease activity	18	11	24	16

*,** p<0.05

Conclusion: regularly applying validate composite indexes such as DAS 28 leads to better control of disease activity, mainly an increased percentage of patients in DAS28 remission.

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Uptake of the American College of Rheumatology's (ACR) Rheumatology Clinical Registry (RCR): Quality Measure Summary Data. Salahuddin Kazi[1], Itara Barnes[2], Jinoos Yazdany[3] and Rachel Myslinski[2]. [1]UT Southwestern Medical Center, Dallas, TX, [2]American College of Rheumatology, Atlanta, GA, [3]University of California San Francisco, San Francisco, CA

Background: The RCR was launched by the ACR to provide members with an infrastructure for quality reporting related to rheumatoid arthritis, gout, osteoarthritis, osteoporosis, and drug safety. The RCR is now in its third year of operation with data on over 26,000 patients. Here we report the uptake of the RCR by U.S. rheumatologists, and performance on measures regarding functional status, DMARD use, TB screening, prognosis, and disease activity assessment for RA patients in rheumatology practice.

Methods: Data derive from retrospective medical records abstractions performed by providers and designated practice staff for a sample of patients seen by the rheumatologist. Reporters submit data on quality measures via a secure, web-based registry system. Patients included in the denominator of all quality measures are >18 years of age with a diagnosis of RA who are receiving treatment by the reporting rheumatology provider. Additional details of each measure are listed in Table 1. We report the mean performance on each quality measure, defined as percentage of eligible patients receiving recommended care.

Table. Performance on RA Measures Assessed through the RCR (01/11–12/11)

	Total eligible patients (n)	Performance on Quality Measure (%)
Functional status assessment performed at least once within 12 months, and documented using a standardized descriptive or numeric scale, or notation of assessment of the impact on patient activities of daily living	8077	70.5%
Patient prescribed, dispensed, or administered at least one ambulatory prescription for a DMARD within 12 months	7808	97.9%
Documentation of TB screening performed and results interpreted within 6 months prior to receiving first course DMARD	1650	73.6%
Assessment and classification of disease prognosis at least once within 12 months	7771	49.5%
Disease activity assessed and classified at least once within 12 months, using a standardized descriptive or numeric scale or composite index	8075	43.3%

Results: 257 rheumatology providers in 143 practices submitted data on 8096 patients with RA from January 1, 2011 to December 31, 2011. Reporting providers practice in sites ranging from solo offices to large academic centers.

Conclusion:

- Rheumatologists across the country used the RCR in 2011 to report quality data establishing RCR as a mechanism for quality reporting (consistent with the ACR goal that RCR provide maximal benefit from data submission).
- Next steps planned for the ACR registry efforts include the continual enhancement of the quality of data collected, analytic reports promoting key performance indicators, and EHR-enabled reporting and quality improvement analysis through a federated registry network.
- RCR provides an opportunity for rheumatology providers to facilitate practice improvement, contribute to collaborative improvement projects, and contribute to national data, led by their professional society.

Disclosure: S. Kazi, None; **I. Barnes**, None; **J. Yazdany**, None; **R. Myslinski**, None.

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Improving Outpatient Follow-up for Osteoporosis Management After a Hip Fracture. Anika Alarakhia[1] and Robert Quinet[2], [1] Ochsner Medical Center, New Orleans, LA, [2]Ochsner Medical Center - New Orleans, New Orleans, LA

Background/Purpose: Patients hospitalized for hip fractures are routinely scheduled for a Rheumatology follow-up appointment to assess their risk of future fractures and need for treatment. Follow-up in our clinic after hospitalization for a hip fracture has been notoriously poor. The purpose of this study was to determine the rate of outpatient follow-up after a hip fracture and implement an intervention to increase the rate.

Methods: We conducted a chart review involving 50 hospitalized hip fracture patients prior to intervention, and 50 hospitalized hip fracture patients after intervention. The intervention included an informational handout which explained the risk of osteoporosis and risks that can lead to further fractures, the importance of receiving a bone density scan, and different treatments to help prevent further fractures that can be implemented as an outpatient. This informational handout was given to the patient and/or family prior to hospital discharge. The results were documented comparing clinic follow-up rates prior to intervention and follow-up rates after intervention.

Results: After reviewing 50 charts from July 2006 to March 2011 of hospitalized hip fracture patients, it was noted that only 3/50 (6%) of patients followed up in our clinic. After implementing our intervention, a chart review was then done from May 2011 to February 2012 and 20/50 (40%) of patients have followed up to our clinic following their hospitalization. This shows a significant increase in follow-up rates after the intervention was initiated.

Conclusion: Outpatient follow-up for a patient after being hospitalized for a hip fracture is extremely important to prevent further fractures which can increase a patient's morbidity and mortality. After receiving an informational handout while in the hospital, we found that the outpatient follow-up rate increased dramatically. It is concluded that once patients and their families fully understood the importance of seeing a physician to assist in preventing further fractures, they were more willing to make a follow-up appointment in the outpatient setting.

Disclosure: **A. Alarakhia**, None; **R. Quinet**, None.

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Access to Technology and Interest in Mobile "app" for Disease Management Among Patients with Systemic Lupus Erythematosus Seeking Care At a Large Referral Center. Wendy Marder[1], Holly Witteman[2], Margaret Hyzy[3], Martha Ganser[1], Emily C. Somers[1] and Lawrence An[3]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI, [3]Universitiy of Michigan, Ann Arbor, MI

Background/Purpose: Some of the challenges facing patients with chronic diseases such as systemic lupus erythematosus (SLE) include identifying triggers for disease "flares" and accurately recalling medication changes they make in response to flares, e.g, self-adjustments of daily prednisone doses. We sought to assess interest in and applicability of smartphone technology as a convenient tool for disease self-management, as well as assessing usage patterns among a heterogeneous group of lupus patients at an academic outpatient clinic. These data will inform the design of a mobile application ("app"), a feature of which will allow SLE patients to conveniently and accurately record disease activity trends and prednisone use over time between rheumatology clinic appointments.

Methods: Lupus patients from the University of Michigan rheumatology clinics who met ≥4 ACR criteria and age ≥18 years. Participants completed a survey containing questions on sociodemographics, healthcare information needs and satisfaction, and access to technology, including smartphone usage patterns. Multivariable logistic regression was used to examine the likelihood of mobile app use among three indicators of socioeconomic status, adjusting for age, sex and race.

Results: Among 100 SLE patient respondents, demographics were: 89% female, mean age 40 years (SD 13); race 66% white, 21% black, 13% other/unknown.; education 16% ≤high school, 34% some college or technical school, 16% college graduate, 33% graduate degree; insurance coverage 23% Medicaid/none, 12% Medicare; 65% private. Participants expressed high interest in a mobile app for lupus: 70% rate app usage would be "extremely helpful" (5 on a 1–5 scale) as a "simple way to get in touch with your healthcare team." The majority reported the following mobile app features would be "extremely helpful": automatic reminders (60%), ability to track flares & triggers of disease activity (59%), and sharing this information with healthcare providers (58%). Younger age was associated with increased mobile app usage: 95% among 20–29 yrs, 73% among 30–49 yrs, 22% among ≥50 yrs (OR for 10 yr interval 0.31, 95%CI 0.2–0.5). When adjusted for age, sex, and race, mobile app usage was similar according to education level (all p=NS). According to type of insurance coverage, those with Medicaid/none reported less mobile app use compared to privately insured (OR 0.16, 95% CI 0.03, 0.86), while those with Medicare were comparable to private (OR 0.77, 95% CI 0.14, 4.3).

Conclusion: These data reveal broad interest in a mobile app for lupus, including proposed features for disease management, across sociodemographic groups. The majority of respondents use smartphone/mobile app technology, with younger age being a significant predictor. However, across different indicators of socioeconomic status, various usage patterns emerge. These data can be used to help target efforts to increase accessibility to this technology.

Disclosure: **W. Marder**, None; **H. Witteman**, None; **M. Hyzy**, None; **M. Ganser**, None; **E. C. Somers**, None; **L. An**, None.

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Is There a Difference in Rheumatology Patient Reported Outcomes When Measured At Home Versus the Clinic Setting? C.J. Inman[1], Frederick Wolfe[2] and Kaleb Michaud[3]. [1]University of Utah, Salt Lake City, UT, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Registries have become a common tool for collecting patient-centered outcome measures. Clinical effectiveness research may be improved if data from multiple registries could be combined allowing for richer data sets in that patients in one registry could supplement data which has been collected in a separate registry. However, the question remains as to whether data that is collected in two separate registries are equivalent. While the registries may ask the same clinical question, if they collect it in unique formats, such as online at home versus in the clinical setting, it is not clear if the metrics are equal. We attempted to address this question of data equivalence through evaluating a patient entered registry versus a registry collected at the point of clinical care.

Methods: Patients were participants in a rheumatology clinic research database that collected patient data via paper questionnaires at clinic visits. They were also participants in a longitudinal, observational study that collected patient data at 6-month intervals from their home via paper, web, or telephone-interview questionnaires at patient's preference from 2007–2012. Four patient measures were congruent between the studies: HAQ-II and pain, patient global assessment, and fatigue visual analog scales. General estimating equations (GEE) assessed longitudinal effects between clinical and at-home data collection methods adjusting for sociodemographic status and number of clinic visits.

Results: A total of 1439 patients enrolled in both studies (40% rheumatoid arthritis, 22% osteoarthritis, and 38% other rheumatic diseases). Mean (SD) age at enrollment was 56.5 (14.0) years, 20.5% were male, 92.0% were Caucasian, and mean (SD) education was 14.0 (2.2) years. Primary rheumatic disease duration was 8.2 (9.3) years and rheumatic disease comorbidity index was 2.0 (1.6). Baseline measures were: HAQ-II 0.87 (0.65), pain 4.0 (2.8), global 3.8 (2.5), and fatigue 4.6 (3.1). Results of the GEE are shown in Table 1; clinic paper questionnaire as well as non-clinic formats of web and telephone were compared to non-clinic paper questionnaires.

Table 1. Relative effect of location and questionnaire media on outcomes through general estimating equations

Outcome Measure	Clinic Paper	Paper (ref)	Non-clinic (e.g., at home) Web	Telephone
HAQ-II (0–3)	0.07 (0.06, 0.08)	0.0	0.02 (0.00, 0.04)	0.18 (0.15, 0.21)
Pain (0–10)	0.98 (0.90, 1.06)	0.0	−0.12 (−0.24, 0.01)	0.71 (0.51, 0.91)
Global assessment (0–10)	0.55 (0.47, 0.62)	0.0	−0.02 (−0.14, 0.10)	0.00 (−0.19, 0.18)
Fatigue (0–10)	0.75 (0.67, 0.83)	0.0	−0.02 (−0.15, 0.10)	1.12 (1.01, 1.39)

Conclusion: On average patients report a higher level of disease severity during a clinic visit than when they report from home while those who respond from home via the web do not differ from paper respondents. As expected, patients that choose telephone interviews reported worse outcomes except for global assessment. Patients respond at home when they are willing and available which may delay responses during spans of poorer health. Patients seen in the clinic, notably those seen more often, could have more severe health care needs from increased disease severity. Further study is needed to determine if the accuracy of such assessments differ.

Disclosure: **C. J. Inman**, None; **F. Wolfe**, None; **K. Michaud**, None.

ACR/ARHP Poster Session C
Rheumatoid Arthritis: Animal Models
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Proteinase Activated Receptor-4 Stimulation Promotes Leukocyte Adhesion in the Rat Knee Joint. Jason J. McDougall. Dalhousie University, Halifax, NS

Background/Purpose: Proteinase activated receptors (PARs) are a family of G protein-coupled receptors that signal by enzymatic cleavage of the receptor in a specific extracellular domain. Since PAR-4 has been shown to cause pain and inflammation in synovial joints, the aim of this study was to examine the effect of PAR-4 activation on leukocyte kinetics in the synovial microvasculature.

Methods: Male c57/bl6 mice were deeply anaesthetised and the right knee joint was exposed. An intravenous injection of 0.05% rhodamine was administered to label circulating leukocytes. Intravital microscopy was used to measure leukocyte trafficking in the joint in response to local adminis-

tration of the PAR-4 agonist AYPGKF-NH2 (50mM). Comparisons were made in wild-type and P-selectin knockout mice. The effect of the PAR-4 antagonist pepducin p4Pal10 on leukocyte kinetics in an adjuvant mono-arthritic knee was also assessed.

Results: In wild-type animals, AYPGKF-NH2 caused a gradual increase in leukocyte rolling and adherence which was not present in P-selectin knockout mice (P<0.0001, n=8). Treatment of arthritic mice with pepducin p4Pal10 reduced leukocyte rolling and accumulation in the joint (P<0.0001).

Conclusion: Activation of PAR-4 in rat knee joints causes leukocyte rolling and adhesion that is P-selectin-dependent. In an arthritic joint, blockade of PAR-4 with pepducin p4Pal10 reversed these pro-inflammatory changes indicating that PAR-4 antagonism can have an anti-inflammatory outcome.

Disclosure: J. J. McDougall, None.

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Myeloid-Derived Suppressor Cells Accumulated in Spleens of Mice with Collagen-Induced Arthritis and Inhibited Immune Response of CD4^{+} T Cells.

Wataru Fujii[1], Eishi Ashihara[2], Hideyo Hirai[3], Hidetake Nagahara[1], Kazuki Fujioka[1], Ken Murakami[1], Kaoru Nakamura[1], Takahiro Seno[1], Aihiro Yamamoto[1], Hidetaka Ishino[1], Masataka Kohno[1], Taira Maekawa[3] and Yutaka Kawahito[1]. [1]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Kyoto Pharmaceutical University, Kyoto, Japan, [3]Kyoto University Hospital, Kyoto, Japan

Background/Purpose: Myeloid-derived suppressor cells (MDSCs), firstly reported in patients with cancer, have a myeloid origin and an ability to suppress T cell responses. MDSCs are characterized by the co-expression of the myeloid-cell lineage differentiation antigens Gr1 and CD11b. Many investigators have demonstrated that MDSCs promote tumor progression via T cell tolerance in patients with cancers and tumor-bearing mice. However, as for autoimmune diseases, the roles of MDSCs in autoimmune disease remain controversial. Here we investigate the roles of MDSCs in autoimmune arthritis using collagen-induced arthritis (CIA) models.

Methods: CIA was induced in 7–8week-old DBA/1 mice by intradermal injection of 200 μg of bovine type II collagen (CII) in Freund's complete adjuvant on day 0, followed by a booster injection of 200 μg of CII in Freund's incomplete adjuvant on day 21. The severity of arthritis in each paw was evaluated 3 times weekly. We first analyzed the number of Gr1^{+}/CD11b^{+} MDSCs in the spleens of mice with CIA by flow cytometry at the onset, the peak, and the convalescence of CIA. Next, MDSCs were isolated from spleens of mice with CIA by magnetic cell separation. Carboxyfluorescein diacetate succinimidyl ester (CFSE)-labeled CD4^{+} T cells were stimulated with anti-CD3/CD28 antibodies (Abs) and cultured in the presence of 30 U/ml interleukin (IL)-2 with or without MDSCs for 5 days. We investigated CD4^{+} T cell proliferation using flow cytometric measurement of CFSE dye dilution. Next, MDSCs were co-cultured with CD4^{+} T cells stimulated with anti-CD3/CD28 Abs for 3 days. We measured cytokines released into supernatant using specific enzyme-linked immunosorbent assay (ELISA).

Results: In a murine arthritis model, MDSCs significantly accumulated in the spleens of mice with CIA at the peak of its severity. MDSCs inhibited the proliferation of CD4^{+} T cells in response to anti-CD3/CD28 Abs *in vitro*. When we co-cultured CD4^{+} T cells and MDSCs interferon (IFN)-γ and IL-6 released into supernatant were significantly decreased, 97.6 ± 16.1 pg/ml to 79.8 ± 10.1 pg/ml ($p < 0.05$), 10.4 ± 2.1 pg/ml to 2.9 ± 1.0 pg/ml ($p < 0.01$), respectively.

Conclusion: MDSCs accumulated in the spleens of mice with CIA. These MDSCs inhibited CD4^{+} T cell proliferation and pro-inflammatory cytokine production *in vitro*. These findings may indicate the protective roles of MDSCs against autoimmune arthritis, which could be exploited for new cell-based therapies. We are now investigating the function of MDSCs *in vivo*.

Disclosure: W. Fujii, None; E. Ashihara, None; H. Hirai, None; H. Nagahara, None; K. Fujioka, None; K. Murakami, None; K. Nakamura, None; T. Seno, None; A. Yamamoto, None; H. Ishino, None; M. Kohno, None; T. Maekawa, None; Y. Kawahito, None.

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The Potent, Highly Selective and Orally Bioavailable Spleen Tyrosine Kinase Inhibitor GSK143 Demonstrates Efficacy in B Cell Receptor and Fc Receptor Signalling in Models of Inflammatory and Autoimmune Disease.

Marion C. Dickson, Nicholas Smithers, Huw Lewis, Cesar Ramirez-Molina, Scott McCleary, Mike Barker and John Liddle. GSK, Stevenage, United Kingdom

Background/Purpose: Spleen tyrosine kinase (Syk), a 72 KDa cytosolic non-receptor tyrosine kinase is a key mediator of B cell receptor (BCR) and Fc receptor (FcR) signalling in a variety of inflammatory cell types and has been implicated in the pathogenesis of a number of allergic and autoimmune diseases including Asthma, Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). Several Syk inhibitors are currently in clinical development and here we report an extended pharmacological and biological profile of GSK143 a novel, highly selective, orally bio-available Syk inhibitor.

Methods: GSK143 inhibitory activity (dose range 10uM to 1nM) on BCR signalling was evaluated in human and murine whole blood by assessing the cell surface expression of IgM stimulated CD69 using flow cytometry. IgM antibody titres in a 7 day murine T independent immunisation model, induced by a TNP-ficol challenge, were measured after once daily dosing (5, 10, 15 and 30mg/kg) to determine in-vivo activity. The effect of GSK143 (dose range 10uM to 10nM) on TNFa production was explored in human monocytic cells, from 8 donors, differentiated to a pro-inflammatory M1 macrophage phenotype with GM-CSF. Macrophages were stimulated with Ig-conjugated sepharose beads to mimic immune complex activation of the Fc gamma receptor (FcγR).

Results: GSK143 dose dependently inhibited the IgM stimulated CD69 expression in both human and murine whole blood with IC50s of 185nM (pIC50 6.734 +/− 0.06) and 364nM (pIC50 6.44 +/−0.28) respectively. In the murine model of T cell independent immunisation, GSK143 administered orally once daily (qd) from day 1 to day 6, produced a significant reduction in the concentration of IgM antibodies (ng/mL) in comparison to that of the corresponding vehicle control group (22843.11 ± 3377.88 ng/mL) vs (15484.62 ± 1984.15 ng/mL, P < 0.01)), (11135.83 ± 2129.6 ng/mL, P < 0.001), (5919.73 ± 1539.03 ng/mL, P < 0.001) and (2877.67 ± 722.79 ng/mL, P < 0.001) at the 5, 10, 15 and 30 mg/kg doses respectively. The systemic exposure observed on day 6 increased with the administered dose with AUC$_{0-24h}$ (ng.h/mL) values of 1435.3 ± 808.2 ng.h/mL, 2457.1 ± 640.1 ng.h/mL, 5533.6 ± 2772.4 ng.h/mL and 7901.7 ± 3058.7 ng.h/mL for the 5, 10, 15 and 30 mg/kg doses, respectively. In human GM-CSF differentiated macrophages stimulated with Ig conjugated beads, GSK143 inhibited FcγR mediated TNFa release in a concentration dependent manner (IC50 = 34nM, pIC50 of 7.47 +/− 0.31).

Conclusion: GSK143, a potent, highly selective and orally bio-available Syk inhibitor blocked FcγR and BCR signalling in pre-clinical human and rodent *in-vitro* and *in-vivo* models of inflammatory and autoimmune diseases.

Disclosure: M. C. Dickson, GSK, 3; N. Smithers, GSK, 3; H. Lewis, GSK, 3; C. Ramirez-Molina, GSK, 3; S. McCleary, GSK, 3; M. Barker, GSK, 3; J. Liddle, GSK, 3.

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Bone Formation and Resorption Are Both Increased in Autoimmune Arthritis.

Kresten K. Keller[1], Jesper Skovhus Thomsen[2], Kristian Stengaard-Pedersen[1], Frederik Dagnæs-Hansen[3], Jens R. Nyengaard[4] and Ellen-Margrethe Hauge[1]. [1]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [2]Institute of Anatomy, Aarhus University, [3]Institute of Medical Microbiology and Immunology, Aarhus University, Aarhus, Denmark, [4]Stereology and Electron Microscopy Laboratory, Centre for Stochastic Geometry and Advanced Bioimaging. Aarhus University hospital, Aarhus, Denmark

Background/Purpose: Bone destruction in the joints of patients with rheumatoid arthritis (RA) is the result of a combination of osteoclastic bone resorption and osteoblastic bone formation. This process is not completely understood, and especially the importance of local inflammation needs further investigation. We used 3D stereological estimators to evaluate how bone formation and bone resorption are altered in autoimmune arthritis.

Methods: Twenty one 9–12-weeks-old female SKG mice were randomised to either an arthritis group or a control group. Arthritis was scored twice weekly by an observer blinded for group distribution. The fluorescent label tetracycline was injected intraperitoneally 8 days before termination of

the study at the end of week 6. Right hind paws were fixed in alcohol and embedded undecalcified in methylmethacrylate. Seven-μm-thick sections were cut exhaustively according to the principles of vertical sectioning. Systematic sampling was used to obtain approximately10 levels each with 12 sections. Using newCAST stereological software, intercepts between a line grid and the tissue of interest were counted by an observer blinded for the group distribution. Osteoclast-covered bone surfaces (Oc.S) and eroded surfaces (ES) were estimated on sections stained for TRAP and mineralising surfaces (MS) were estimated on unstained sections using fluorescent microscopy. The absolute number of osteoclasts (N.Oc) was estimated using the physical fractionator. All parameters were assessed in the tarsus on the periosteal and endosteal surfaces, and the presence of adjacent inflammatory tissue was evaluated for each intersection and cell count. The relevant reference bone surface (BS) was estimated for all parameters. The results were expressed as relative values (MS/BS, ES/BS, Oc.S/BS, and N.Oc/BS).

Results: At the end of week 1 and until termination, the arthritis score was higher in arthritic animals ($p<0.01$). Likewise, MS/BS, ES/BS, Oc.S/BS, and N.Oc/BS were elevated in arthritic mice compared to normal mice both at the endosteal surface and the periosteal surface ($p<0.001$). On surfaces both adjacent to and not adjacent to inflammation in arthritic mice MS/BS were elevated on endosteal as well as periosteal surfaces compared to normal mice ($p<0.001$). In arthritic mice, ES/BS and Oc.S/BS were larger on endosteal as well as periosteal surfaces adjacent to inflammation compared to surfaces without inflammation ($p<0.01$). However, the difference between MS/BS at surfaces adjacent to and not adjacent to inflammation on either periosteal or endosteal surfaces did not reach the level of statistical significance.

Conclusion: Arthritis caused bone formation to occur on more bone surfaces, irrespectively of the adjacent tissue being inflamed. However, bone degradation was present almost exclusively on surfaces with adjacent inflammation. Therefore, arthritic bone loss is likely to be explained by an imbalance of erosion and formation of bone rather than a general down-regulation of bone formation. These findings may be important for the development of new bone targeting drugs in RA. The present study is the first to apply 3D stereological estimators to quantify bone formation and degradation in a model of RA.

Disclosure: **K. K. Keller**, None; **J. S. Thomsen**, None; **K. Stengaard-Pedersen**, None; **F. Dagnæs-Hansen**, None; **J. R. Nyengaard**, None; **E. M. Hauge**, None.

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Green Tea Epigallocatechin-3-Gallate Ameliorates Murine Arthritis by Inducing IDO Producing Dendritic Cells Via Nrf2 Antioxidant Pathway. Soyoun Min, Mei Yan, Kamala Vanarsa, Anna Bashmakov and Chandra Mohan. University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: To examine the immunomodulatory effects and mechanisms of Green Tea ($-$)-epigallocatechin-3-gallate (EGCG) on experimental arthritis in mice, we investigated whether EGCG can afford therapeutic benefit in collagen-induced arthritis (CIA) subjected mice.

Methods: EGCG (10 mg/kg body weight) was administered by oral feeding three times per week for three weeks after booster immunization, while the control mice were administered phosphate-buffered saline (PBS). The effects of EGCG were examined by assessment of joint swelling, histological changes, and immune cell populations, and the mice were sacrificed 7 weeks after the first immunization. The level of protein obtained from spleen cells and joint homogenates was examined by Western Blotting analysis. Serum levels of anti-type II collagen specific antibodies and cytokine production were measured by ELISA.

Results: EGCG treatment ameliorated clinical symptoms and reduced histological scores in arthritic mice (7.2 ± 1.2 vs 12.4 ± 2.3, P < 0.01). The serum concentrations of type-II collagen-specific IgG2a antibodies were significantly lower in EGCG-fed mice compared to PBS-treated mice (0.105 ± 0.01vs 0.283 ± 0.25 OD units, P < 0.05). EGCG significantly suppressed T cell activation by reducing [3H]-thymidine uptake and cell division as assessed by CFSE dilution. EGCG also reduced CD4 and CD8 T cells, B cells, marginal zone B cells, T1 and T2 transitional B-cells in the draining lymph node (dLN) and spleen, suggesting that down-regulation of several immune cell populations is one of the mechanisms of EGCG action. EGCG treatment increased the frequency of CD4$^+$ Foxp3$^+$ regulatory T cells ($6.4 \pm 1.25\%$ vs 1.94 ± 1.0, P < 0.05) and IDO expression within CD11b$^+$ dLN cells. The increased CD11b$^+$ DCs elicited by EGCG could induce CD4$^+$CD25$^+$ Tregs in an IDO dependent manner *in vitro*. Additionally, CD11b$^+$ DCs in spleen cells and the joint homogenates from EGCG-fed mice exhibited significantly increased NF-E2-related factor-2 (Nrf-2) and heme

oxygenase-1 (HO-1) compared with PBS-fed mice, alluding to the importance of anti-oxidants.

Conclusion: EGCG ameliorated experimental arthritis in mice eliciting IDO-producing DCs and the activation of the Nrf-2 anti-oxidant pathway. Our results also indicate that ECGC may be of potential therapeutic value for inhibiting cartilage destruction and increasing immunoregulatory cells in arthritic joints. It remains to be established whether EGCG is useful for the prevention and treatment of rheumatoid arthritis.

Disclosure: **S. Min**, None; **M. Yan**, None; **K. Vanarsa**, None; **A. Bashmakov**, None; **C. Mohan**, None.

2074

Combined Effects of a c-Fos/AP-1 Inhibitor T-5224 and Methotrexate On Collagen-Induced Arthritis in Mice. Tomomi Date[1], Yukihiko Aikawa[1], Tetsuya Yamamoto[1], Hirokazu Narita[1], Shuichi Hirono[2] and Shunichi Shiozawa[3]. [1]Research Laboratories, Toyama Chemical Co., Ltd, Toyama, Japan, [2]Department of Pharmaceutical Sciences, School of Pharmacy, Kitasato University, Tokyo, Japan, [3]Department of Medicine & Rheumatology, Kyushu University Beppu Hospital, Beppu, Japan

Background/Purpose: Activator protein-1 (AP-1) is an important transcription factor for cytokine production and joint destruction in rheumatoid arthritis (RA), and a potential target for the treatment of RA. We previously reported the preventive and therapeutic effects of T-5224, a small molecule inhibitor of c-Fos/AP-1, on type II collagen-induced arthritis (CIA) in mice. The purpose of this study was to investigate the effect of T-5224 in combination with or with add-on to methotrexate (MTX) on the development of arthritis and joint destruction in mice with CIA.

Methods: CIA was induced in DBA/1J mice by the immunization with bovine type II collagen twice on days 0 and 21. In a combination study, T-5224 (3 mg/kg/day) and/or MTX (0.5–5 mg/kg/day) were orally administered once daily from the day of the 2nd immunization (day 21) to day 34. In an add-on study, MTX (0.5 mg/kg/day) was administered from day 21 to day 49. The add-on treatment of T-5224 (3 mg/kg/day) to MTX (0.5 mg/kg/day) or MTX at a dose increased to 5 mg/kg/day started from day 27. In both studies, anti-rheumatic efficacy was determined by arthritis score, X-ray examination, and serum interleukin-1β (IL-1β) on days 35 and 50, respectively.

Results: In a combination study, MTX alone showed dose dependent reduction in arthritis scores by 15% to 58% at 0.5 to 5 mg/kg/day. T-5224 at 3 mg/kg/day in combination with MTX at 0.5 and 1.5 mg/kg/day decreased the arthritis scores by 57% and 62%, respectively, which was similar to that achieved by MTX alone at 5 mg/kg/day (58%). The joint destruction was suppressed by 78% and 90%, respectively, in combination of T-5224 and MTX at 0.5 and 1.5 mg/kg/day, which was more potentiated than MTX alone at 5 mg/kg/day. Elevated IL-1β level in the serum reduced by combined treatment of T-5224 and MTX, whereas MTX alone at 0.5 and 1.5 mg/kg was without effects.

Add-on treatment of T-5224 (3 mg/kg/day) with MTX (0.5 mg/kg/day) decreased the arthritis scores by 70%, which was more marked than MTX alone at a dose escalated from 0.5 to 5 mg/kg/day (29%), when started dosing from day 27 after the onset of arthritis. Add-on treatment of T-5224 with MTX reduced the joint destruction scores by 81%, while MTX alone did by 46%. Serum level of IL-1β decreased only in mice treated with T-5224 added-on to MTX.

Conclusion: These results indicate that either combined or add-on use of T-5224 and MTX with a different mode of anti-arthritic actions is expected to augment anti-rheumatic and anti-joint destructive effects in the therapy of RA.

Disclosure: **Y. Aikawa**, Toyama Chemical Co., Ltd., 3; **T. Yamamoto**, Toyama Chemical Co., Ltd., 3; **H. Narita**, Toyama Chemical Co., Ltd., 3; **S. Hirono**, None; **S. Shiozawa**, None.

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CCR6$^+$ Foxp3$^+$ Regulatory T Cells Regulate the Development of Collagen Induced Arthritis in T Cell Specific RORγt Transgenic Mice. Yuya Kondo, Masahiro Tahara, Mana Iizuka, Hiroto Tsuboi, Satoru Takahashi, Isao Matsumoto and Takayuki Sumida. University of Tsukuba, Tsukuba, Japan

Background/Purpose: Recent studies reported that IL-17 producing Th-17 cells appear to play an important role in the generation of several autoimmune arthritis models. We previously reported that T-bet expression regulates the development of collagen induced arthritis by suppression of

antigen reactive Th17 cells differentiation via the repression of RORγt expression (Kondo Y et al. *Arthritis Rheum* 64,162-72, 2012). This observation suggested that RORγt might be pivotal on the development of autoimmune arthritis. The aim of this study is to clarify the effect of RORγt expression on T cells in the development of autoimmune arthritis.

Methods: 1) Incidence and severity of collagen induced arthritis (CIA) were assessed in C57BL/6 (B6) and T cell specific RORγt transgenic (RORγt Tg) mice under the control of CD2 promoter. 2) Histological assessment of inflamed joints was performed with hematoxilin-eosin staining. 3) Collagen type II (CII) specific antibody in sera was measured with ELISA. 4) Draining lymph node cells were harvested from B6 and RORγt Tg mice at 10 days after the immunization of CII, and cultured in the medium containing CII. Cytokine level in supernatants were analyzed by ELISA. 5) Draining lymph node cells were cultured in vitro as described in 4), transcription factors expression on CD4$^+$T cells was analyzed by FACS and real-time PCR. 6) The correlation between the expression of transcription factors and chemokine receptor 6 (CCR6) was analyzed by FACS.

Results: 1) CIA was significantly suppressed in RORγt Tg mice compared with B6 mice. 2) Histological assessments revealed that inflammation and bone destruction were milder in RORγt Tg mice than B6 mice. 3) Anti-CII antibody was significantly lower in RORγt Tg mice than B6 mice ($P < 0.05$). 4) IL-17 level in supernatant was significantly increased in RORγt Tg mice compared with B6 mice ($P < 0.05$). 5) FACS analysis showed that RORγt expression on CD4$^+$ T cells was significantly higher in RORγt Tg mice than B6 mice. Although there was no significant difference of Foxp3 expression on CD4$^+$ T cells between B6 mice and RORγt Tg mice, most of Foxp3$^+$ CD4$^+$ T cells also expressed RORγt in RORγt Tg mice. Bcl-6 expression on CD4$^+$ T cells of RORγt Tg mice was comparable to that of B6 mice. 6) The expression of CCR6 on CD4$^+$ T cells was significantly higher in RORγt Tg mice compared with B6 mice ($P < 0.01$). In particular, CCR6 was remarkably upregulated in Foxp3$^+$ CD4$^+$ T cells of RORγt Tg mice compared with that of B6 mice ($P < 0.01$).

Conclusion: CIA was significantly suppressed in RORγt Tg mice, although IL-17 production from CII reactive T cells was increased. The inhibition of arthritis might be related with the increase in CCR6$^+$ Foxp3$^+$ CD4$^+$ T cells in RORγt Tg mice.

Disclosure: **Y. Kondo**, None; **M. Tahara**, None; **M. Iizuka**, None; **H. Tsuboi**, None; **S. Takahashi**, None; **I. Matsumoto**, None; **T. Sumida**, None.

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Efficacy of the Potent PI3K-δ,γ Inhibitor IPI-145 in Rat Adjuvant Arthritis. David L. Boyle, Katharyn Topoleweski and Gary S. Firestein. UCSD School of Medicine, La Jolla, CA

Background/Purpose: Phosphoinositide 3-kinase (PI3K) is a family of intracellular signaling transducers and could be targeted to treat inflammatory diseases like rheumatoid arthritis (RA). However, blockade of the a and b isoforms could cause significant toxicity due to their ubiquitous expression. On the other hand, g and d isoform expression is restricted mainly to leukocytes and, for the latter, synovial fibroblasts. These enzymes regulate a variety of innate and adaptive immune pathways, especially through activation of AKT. In this study, IPI-145, a novel potent PI3K-δ,γ inhibitor (K$_i$'s: PI3K-d: 16 pM, PI3K-g: 244 pM, PI3K-β: 1.6 nM and PI3K-a: 25.9 nM) was tested for its activity in the rat adjuvant induced arthritis model.

Methods: Rat adjuvant arthritis was induced by immunizing Lewis rats with CFA. Then, from either Day 8 or Day 14 through Day 21 one of three treatments (vehicle, 10 or 50mg/kg/d IPI-145) was administered daily by oral gavage. Paw swelling was assessed by plethysmometry, radiographs by a semi-quantitative scoring system, ankle gene expression by qPCR (relative expression units; REU), and pAKT and AKT by Western blot. Clinical endpoints were assessed every other day from Day 0 through Day 21.

Results: Treatment with 10 or 50 mg/kg/d of IPI-145 (n=16/group) beginning on day 8 prior to onset of ankle swelling inhibited arthritis progression in a dose dependent fashion. Disease progression was significantly reduced at 50 mg/kg from Day 12 through Day 21 (see Figure; p<0.05) when initiated on Day 8. Treatment of established disease with 50 mg/kg of IPI-145 starting on Day 13 resulted in 70% less swelling relative to vehicle treated animals (see Figure; p<0.05). Synovial IL-6 and MMP3 gene expression on Day 21 were similar between groups, however MMP13 expression was substantially inhibited in the 50 mg/kg group (Vehicle, 4.5±0.9; 50 mg/kg, 1.2±0.3 p<0.05). MMP13 was reduced by over 80% in the delayed IPI-145 treated groups (Vehicle, 4.5±0,9; IPI-145 0.6±0.1 p<0.05) PI3K-δ,γ blockade significantly decreased radiographic bone destruction in both regimens (vehicle 3.5±0.4, 50 mg/kg=1.5±0.4; day 13,

2.8±4 p<0.05). AKT phosphorylation in ankles was reduced on day 21 in both regimens (pAKT/AKT ratio: Vehicle 0.57±0.02; day 8 protocol, 0.23±0.06; day 13 protocol, 0.28±0.02 p<0.05).
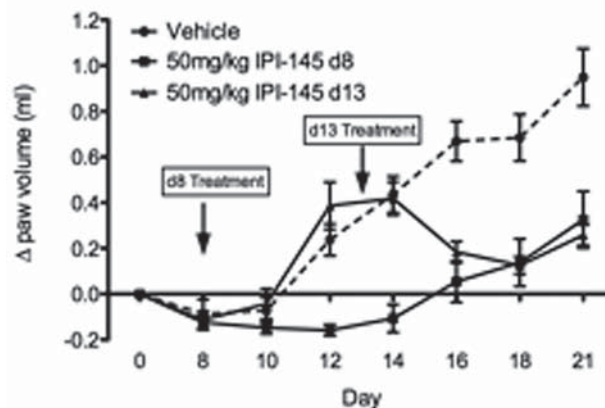
Conclusion: PI3K-δ,γ blockade demonstrated prominent disease-modifying effects in both pretreatment and established preclinical arthritis protocols with statistically significant reductions in ankle swelling, MMP13 gene expression, radiographic bone destruction, and AKT phosphorylation. Compared with broad spectrum or single isoform inhibitors, PI3K-δ,γ inhibitors could have a favorable therapeutic profile.

Disclosure: **D. L. Boyle**, None; **K. Topoleweski**, None; **G. S. Firestein**, Infinity Pharmaceuticals, 2.

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IL-6 Blockade Augments the Anti-Inflammatory Effect without Increasing the Side Effects of Steroids in Collagen-Induced Arthritis. Miho Suzuki[1], Hiroto Yoshida[1], Misato Hashizume[1], Masashi Shiina[1], Keisuke Tanaka[1] and Yoshihiro Matsumoto[2]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka, Japan, [2]Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

Background/Purpose: Steroids are the main therapy for chronic inflammatory diseases. They are very effective, but induce many side effects, such as osteoporosis, making it important that the dose steroids be reduced. However, some patients with chronic inflammatory disease may have difficulty tapering off steroids. It is thought that IL-6 might be involved in the steroid resistance because elevated levels of IL-6 are found in these patients. Here, we elucidated the role of IL-6 in several effects of steroids using a collagen-induced arthritis (CIA) mouse model to examine the possibility of combination therapy.

Methods: To prepare a CIA model, DBA/1J mice were immunized intradermally with bovine type II collagen, and 21 days later (Day 21) once again given a booster injection. Mice were treated with the steroid prednisolone (PSL) intraperitoneally from Day 21 at doses of 1, 3, and 6 mg/kg five times a week or were administered with 8 mg of rat anti-mouse IL-6R monoclonal antibody (MR16-1) intraperitoneally once on Day 21. Another group was given a combination of the two from Day 21. Clinical symptoms of arthritis were evaluated by observation and expressed as an arthritis score on a scale of 0–4 for each limb. To assess the side effects of PSL, BMD was measured with DXA, and neutrophils and lymphocytes were quantified in blood using a sysmex system. Furthermore, synovial cells from CIA mice were cultured in the presence of dexamethasone (DEX) for 3 h after IL-6 pretreatment, and then COXII mRNA was quantified by real-time PCR.

Results: PSL dose-dependently reduced the arthritis score in the CIA model on the peak (Day 33) of arthritis. At the same time, neutrophil count was increased and lymphocyte count was decreased in a dose-dependent manner. MR16-1 in combination with low doses of PSL (1, 3 mg/kg) improved clinical symptoms significantly more than the same dose of PSL alone on Day 33 even though administration of MR16-1 alone resulted in no improvement. Interestingly, neutrophil and lymphocyte counts did not change and BMD was not reduced. To explore how MR16-1 could improve the anti-inflammatory effect of PSL, we next examined the influence of IL-6 on DEX activity *in vitro*. COXII expression was clearly suppressed by DEX, but IL-6 pretreatment attenuated the inhibitory effect of DEX.

Conclusion: We demonstrated that IL-6 blockade augmented the anti-inflammatory effect of PSL without changing BMD or neutrophil and lymphocyte counts in CIA mice. IL-6 blockade might make steroid tapering possible.

Disclosure: **M. Suzuki**, None; **H. Yoshida**, None; **M. Hashizume**, None; **M. Shiina**, None; **K. Tanaka**, None; **Y. Matsumoto**, None.

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Low-Density Lipoprotein Receptor Deficiency Ameliorates the Development of Inflammatory Arthritis. Shawn Rose and Harris R. Perlman. Northwestern University, Chicago, IL

Background/Purpose: Patients with rheumatoid arthritis (RA) carry a higher risk of cardiovascular disease compared to the general population. The low-density lipoprotein receptor (LDLR) and Apolipoprotein E (ApoE) have been shown to modulate atherosclerosis in mice, yet murine models of RA-like disease have yielded conflicting data regarding the development of joint disease in mice lacking ApoE. Here, we examined the effect of deleting ApoE or the LDLR on the development of the effector phase of RA-like disease and on the formation of atherosclerotic lesions in arthritic mice.

Methods: The K/BxN serum transfer-induced arthritis (STIA) model was utilized in control, LDLR$^{-/-}$, and ApoE$^{-/-}$ mice. Inflammatory arthritis severity was assessed using clinical indices and by immunohistochemical staining of ankle joint specimens. Serum cholesterol levels were determined via enzymatic assays. Serum cytokine and chemokine levels were measured utilizing luminex-based assays. Aortic atherosclerotic plaque burden was quantitated using Sudan IV staining.

Results: LDLR-deficiency resulted in a reduction in arthritis severity as compared to controls. In contrast, ApoE deficiency had no effect on arthritis intensity. LDLR$^{-/-}$ and ApoE$^{-/-}$ mice exhibited comparable serum levels of total, low-density lipoprotein, and high-density lipoprotein cholesterol. However, LDLR$^{-/-}$ STIA mice expressed lower levels of circulating IL-6 compared to ApoE$^{-/-}$ STIA mice, which correlated with diminished arthritis severity. Arthritic LDLR$^{-/-}$ and ApoE$^{-/-}$ mice displayed a similar degree of aortic atherosclerosis.

Conclusion: STIA was reduced in LDLR$^{-/-}$ mice but not ApoE$^{-/-}$ mice despite similar serum cholesterol profiles in these animals. These data suggest that factors other than altered cholesterol levels are responsible for the decreased arthritis severity observed in LDLR$^{-/-}$ mice. In contrast, atherosclerotic burden was unaffected by the presence of arthritis in either ApoE$^{-/-}$ or LDLR$^{-/-}$ mice. Thus, targeting the LDLR may be a viable strategy to reduce arthritis disease activity in RA.

Disclosure: **S. Rose**, None; **H. R. Perlman**, None.

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Anti-Interleukin-6 Receptor Antibody Improves Systemic Osteoporosis in a Mice Model of Glucose-6-Phosphate Isomerase-Induced Arthritis. Hiroto Yoshida[1], Miho Suzuki[1], Misato Hashizume[1], Keisuke Tanaka[1], Masashi Shiina[1], Isao Matsumoto[2], Takayuki Sumida[2] and Yoshihiro Matsumoto[1]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka, Japan, [2]University of Tsukuba, Tsukuba City, Japan

Background/Purpose: Patients with rheumatoid arthritis (RA) have a high risk of osteoporosis and osteoporotic fracture. In addition to the primary risk factors for osteoporosis, osteoporosis in RA is characterized by a complexity of other risk factors, including inflammation, immobilization, and use of corticosteroids. Anti-human interleukin-6 (IL-6) receptor antibody and various TNF inhibitors have an excellent therapeutic effect on RA symptoms, such as inflammation, pain, and swelling of joints. However, it is not fully understood whether inhibition of IL-6 and TNF-α can improve osteoporosis in patients with RA. Here, we investigated the interaction between proinflammatory cytokines and bone loss, using glucose-6-phosphate isomerase (GPI)-induced arthritis.

Methods: GPI-induced arthritis in DBA/1J mice was triggered by intradermal injection of recombinant GPI. Mice were injected once with anti-mouse IL-6 receptor antibody (MR16-1) intraperitoneally 5 days after immunization. On the other hand, TNF receptor-Fc (TNFR-Fc) was given intraperitoneally 3 times per week from the 5th day of immunization. The femurs of mice were harvested at various time points and the lumbar spine was excised at day 35. The trabecular bone volume (BV/TV) of the femurs and the lumbar spine was analyzed by using micro-computed tomography (μCT).

Results: First, we examined the severity of bone loss in GPI-induced arthritis. In immunized mice, BV/TV of femurs had significantly declined by 32.5% on day 7 (beginning of swelling) and by 61.5% on day 14 (peak of swelling) compared with non-immunized mice. Thereafter, as the swelling decreased, BV/TV of femurs in immunized mice was gradually recovered to 61.0% of non-immunized mice by day 35. Because arthritis significantly decreased the bone volume of femurs in mice, we next examined the involvement of IL-6 and TNF-α in bone loss in GPI-induced arthritis. Both MR16-1 and TNFR-Fc significantly suppressed the development of arthritis compared with untreated immunized mice. In MR16-1-treated mice, BV/TV of femurs and lumbar spine on day 35 was significantly increased to 1.3-fold and 1.2-fold that in untreated arthritic mice. On the other hand, TNFR-Fc increased the bone volume of femurs to 1.2-fold, but it did not affect that of the lumbar spine.

Conclusion: We demonstrated that IL-6 and TNF-α play a crucial role in bone loss of femurs caused by inflammatory arthritis in mice. However, in the lumbar spine, IL-6 is involved in bone loss but TNF-α is not. This suggests that blockade of IL-6 would have a beneficial effect on systemic osteoporosis in RA patients.

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IL-20 Is Not Involved in Mouse Collagen Induced Arthritis. Christina Andersson[1], Kyle Serikawa[2], Hermann Pelzer[1], Peter Thygesen[1], Patricia Smith[2], Kim Kruse[2], Shameek Biswas[2], Brian Fox[2], Anders Milner[1], Peter Kvist[1], Josephine Hebsgaard[1], Jesper Pass[1] and John Rømer[1]. [1]Biopharmaceutical Research Unit, Novo Nordisk A/S, Måløv, Denmark, [2]Biopharmaceutical Research Unit, Novo Nordisk A/S, Seattle, WA

Background/Purpose: Interleukin-20 (IL-20) is a pro-inflammatory cytokine involved in the pathogenesis of rheumatoid arthritis (RA). Clinical phase 2a testing has shown that treatment with an anti-IL-20 monoclonal antibody (NNC0109-0012) reduces disease activity in patients with RA. In order to further explore the role of IL-20 in arthritis pathogenesis we have investigated the effects of a neutralizing anti-IL-20 antibody in the collagen induced arthritis (CIA) model.

Methods: Two separate experiments in the mouse CIA model were conducted to test the effect of an anti-IL-20 antibody (5B7, human IgG4), which cross reacts with mouse IL-20. Two doses of 5B7 (1 and 10 mg/kg, 3xweek for 6 weeks) were tested in a prophylactic setting with dosing from day 0 after immunization. Three doses of 5B7 (1, 10, and 40 mg/kg, 3xweek for 3 weeks) were tested in a late prophylactic setting with dosing from day 21. Serum samples were collected for exposure analysis and to test for anti-drug antibodies and anti-collagen type II (CII) antibody levels. Paws were collected for histopathological evaluation. Overall mRNA expression profiles were assessed with RNA sequencing in paws from non-treated CIA mice with different degrees of disease.

Results: Prophylactic administration of anti-IL-20 5B7 starting from either day 0 or day 21 after immunization did not affect the clinical disease activity scores, whereas administration of a TNFα inhibitor decreased disease activity. Histopathological evaluation revealed no effects of anti-IL-20 treatment on i) the degree of synovitis based on scoring of HE stained paw tissues and ii) the number of TRAP+ osteoclasts as an indicator of bone destruction. Analysis of blood samples from CIA mice dosed from day 0 showed that anti-IL-20 treatment did not affect the levels of the pathogenic anti-CII antibodies. The pharmacokinetic profile revealed that the mice have been adequately exposed to anti-IL-20 throughout the experiments and no formation of anti-drug antibodies was detectable. IL-20 mRNA expression data from the paws and lymph nodes of non-treated CIA mouse with varying degrees of arthritis (mild, moderate, severe) showed a very low level of IL-20 mRNA expression in all analysed paws. Importantly, there was no correlation to disease activity in the individual paws. The level of mRNAs for IL-20R1 and IL-20R2 were also low and indicated a negative correlation with paw disease scores.

Conclusion: Very low expression of IL-20 locally in the diseased paws and lack of correlation with disease severity may explain the lack of efficacy of anti-IL-20 treatment in the mouse CIA model. In contrast to previous data showing that anti-IL-20 treatment decrease disease activity in the rat CIA model, our findings indicate that IL-20 does not play a pathogenic role in the mouse CIA arthritis model.

Disclosure: **C. Andersson**, Novo Nordisk, 1, Novo Nordisk, 3; **K. Serikawa**, Novo Nordisk, 1, Novo Nordisk, 3; **H. Pelzer**, Novo Nordisk, 1, Novo Nordisk, 3; **P. Thygesen**, Novo Nordisk, 1, Novo Nordisk, 3; **P. Smith**, Novo Nordisk, 1, Novo Nordisk, 3; **K. Kruse**, Novo Nordisk, 1, Novo Nordisk, 3; **S. Biswas**, Novo Nordisk, 1, Novo Nordisk, 3; **B. Fox**, Novo Nordisk, 1, Novo Nordisk, 3; **A. Milner**, Novo Nordisk, 1, Novo Nordisk, 3; **P. Kvist**, Novo Nordisk, 1, Novo Nordisk, 3; **J. Hebsgaard**, Novo Nordisk, 1, Novo Nordisk, 3; **J. Pass**, Novo Nordisk, 1, Novo Nordisk, 3; **J. Rømer**, Novo Nordisk, 1, Novo Nordisk, 3.

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Aνβ3 Integrin Inhibition with Cilengitide Both Prevents and Treats Collagen Induced Arthritis. Despoina Sykoutri[1], Nisha Geetha[1], Silvia Hayer[1], Peter Mandl[1], Josef S. Smolen[2], Gerald Prager[1] and Kurt Redlich[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation and osteoclast (OC) mediated bone erosions. AlphaVbeta3 ($\alpha v \beta 3$) integrin is highly expressed in osteoclasts and its inhibition disturbs their function. Aνβ3 blocking antibodies can reduce bone resorption and mice lacking $\beta 3$ are osteopetrotic. However, the role of $\alpha v \beta 3$ in the development of collagen induced arthritis (CIA), a well established model for human RA, has not been examined extensively. We aimed to study the role of the $\alpha v \beta 3$ inhibitor cilengitide, a synthetic Arginine-Glycine-Asparagine amino acid peptide (RGD peptide), on osteoclastogenesis and its efficacy in preventing and treating CIA.

Methods: For *in vitro* analysis mouse bone marrow-derived cells (BMCs) were differentiated into tartrate resistant acid phosphatase positive (TRAP+) mononuclear OC precursor cells (pre-OCs) and TRAP+ multinucleated mature OCs in the presence of macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappaB ligand (RANKL). Cilengitide, was added in increasing concentrations (2nM to 20μM) to the culture. Moreover, we performed these osteoclastogenesis assays on plates coated with RGD containing matrix molecules such as osteopontin, fibronectin and fibrinogen but also on Poly-D-lysine coatings to asses for $\alpha v \beta 3$ independent adhesion.

For *in vivo* analysis CIA was induced in 6–8 week old male DBA/1 mice by immunisation with bovine type II collagen at day 1, followed by boosting at day 21. For the CIA prevention study mice were injected 1,5mg/kg cilengitide (n=15) or placebo (n=15) subcutaneously (s.c.), 5 days per week, starting 1 day prior to CIA induction until day 53. In the CIA treatment study mice with established arthritis were randomized and treated s.c. with 1,5 mg/kg (low dose, n=19) or 75 mg/kg (high dose, n=7) cilengitide or placebo (n=21) 5 days per week until day 59. The preventive and treatment effects were evaluated by investigating the clinical course of arthritis assessed by paw thickness and grip strength.

Results: *In vitro* increasing concentrations of cilengitide (IC50: 250nM) dose-dependently reduced pre-OC numbers on all plate coatings, indicating an inhibiting effect at the early stage of pre-OC proliferation. OCs were significantly reduced between 20nM and 200nM, followed by complete blockade of OC formation above 2μM. At 200nM an intriguing morphological difference was observed with reduction in OC size, suggesting that cilengitide may disrupt spreading and the fusion capacity at the early pre-OC stage. In the *in vivo* preventive experiment, cilengitide significantly reduced incidence (92,8% vs. 40%) and severity of CIA as evidenced by the reduction of the clinical disease activity scores of paw swelling and grip strength. In the *in vivo* treatment experiment, both low dose and high dose cilengitide effectively inhibited the progression of established arthritis.

Conclusion: Osteoclastogenesis requires intact $\alpha v \beta 3$ integrin function. Systemic $\alpha v \beta 3$ integrin inhibition with cilengitide potently prevents and treats experimental CIA arthritis. Therefore, cilengitide may be a novel therapeutic target in RA.

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Peripheral and Local Effects of Anti-C5aR Treatment in the Collagen Induced Arthritis Model. Christina Andersson. Carola Wenander, Pernille Usher, Josephine Hebsgaard and Lars Hornum, Biopharmaceutical Research Unit, Novo Nordisk A/S, Måløv, Denmark

Background/Purpose: The activated C5a-fragment of complement factor C5 is a potent pro-inflammatory effector molecule that chemo-attracts and activates myeloid cells such as neutrophils, monocytes, and macrophages. C5a levels are elevated in rheumatoid arthritis (RA) synovial fluids, and C5a receptor (C5aR)–expressing cells infiltrate RA synovial tissues. Currently, a Novo Nordisk clinical trial is investigating the potential of an anti-C5aR antibody as a treatment for RA. Because C5a and C5aR-expressing cells are found also in affected joints of collagen-induced arthritis (CIA) mice, we investigated whether a blocking anti-mC5aR antibody is efficacious in inhibiting disease progression in already established arthritis in the CIA model. Furthermore, an analysis of the mechanism of action in the therapeutic

CIA model qualified a number of peripheral and locally produced biomarkers with translational potential for future verification of anti-C5aR treatments effects in human trials.

Methods: DBA/1 mice were immunized s.c. with collagen type II in complete Freund's adjuvant at day 0 and received a boost immunization at day 21. Therapeutic s.c. treatment with an anti-mC5aR mAb was initiated in mice with already established arthritis. Mice were sacrificed after two weeks of treatment (0.5 mg/mouse three times a week) or 48 hours after one single treatment. TNFα inhibition was used as reference treatment. Blood samples were analysed by flow cytometry for cell type and activation state. Cytokine and chemokine profiles were obtained on blood samples and paw homogenates.

Results: Anti-mC5aR treatment was able to halt disease development. Histopathology and serum MMP-3 levels confirmed the clinical treatment effect. In comparison to treatment with a TNFa inhibitor or control antibody, peripheral blood neutrophils from anti-mC5aR treated mice exhibited significantly reduced CD11b expression after two weeks of treatment, indicating reduced activation. The numbers of circulating neutrophils were reduced in both the anti-TNFα and anti-mC5aR treated groups. The CD11b expression was reduced 48 hours after one single anti-mC5aR treatment. Cytokine and chemokine profiles showed significant impact on local inflammatory mediators in the paw, such as IL-6, KC, MCP-1, and MIP-2 already 48 hours after a single anti-mC5aR treatment but not after a single treatment with a TNFα inhibitor. Anti-mC5aR had no impact on the level of anti-collagen type II antibodies.

Conclusion: The data suggest that C5aR blockade has a rapid effect on joint inflammation by down-regulation of pro-inflammatory mediators. This may be due to a direct effect on infiltrating myeloid cells, as C5a induces cytokine and chemokine release by macrophages and other cells. The effect on the circulating neutrophil number and activation stage indicate also a peripheral effect on target cells, suggesting that leukocyte activation and recruitment may also be targeted by C5aR blockade. The effects on peripheral cells may be used as biomarkers in human clinical trials. In conclusion, mechanistic data from the CIA model suggest that C5aR blockade is a potential novel treatment for arthritis that may elicit rapid clinical effects on both infiltrating and peripheral leukocytes.

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New Treatment Approach of Rheumatoid Arthritis Based On Inhibition of Cyclin Dependent Kinase-9. Annelie Hellvard[1], Lutz Zeitlmann[2], Ulrich Heiser[3], André Niestroj[3], Hans-Ulrich Demuth[3], Jan Potempa[4] and Piotr Mydel[1]. [1]Broegelmann Research Laboratory, The Gade Institute, University of Bergen, Bergen, Norway, [2]Ingenium Pharmaceuticals GmbH, Martinsried, Germany, [3]Probiodrug AG, Halle/Saale, Germany, [4]Jagiellonian University, Krakow, Poland

Background/Purpose: Cyclin dependent kinase-9 (cdk-9) is transcription regulator of the carboxyterminal domain of RNA polymerase II. The usage of pan-cdk inhibitors such as flavopiridol has proven to be efficient in the treatment of cancer, targeting both cell cycle- and transcription-regulating cyclin dependent kinases. In this study we sought to investigate the effect of specific small molecular inhibitor of cell cycle independent cdk-9 development and progression of collagen induced arthritis.

Methods: DBA/1 mice were immunized with 100ug bovine collagen type II at day 0 and day 21. During experiment mice were treated orally with highly specific cdk-9 inhibitors (compound 1 and compound 2), either 10mg/kg daily or 10mg/kg and 30mg/kg twice a week, respectively. Clinical scoring was performed every second day during experiment and was followed by histological evaluation at end of experiment. Protein expression of Mcl-1 and survivin in spleens was determined by western immunoblotting. Flow cytometric analysis of regulatory T cells in spleens from arthritic mice following daily treatment as well as 7day treatment of healthy NMRI mice was performed.

Peripheral blood mononuclear cells were incubated with compound 1 and induction of apoptosis, as well as protein and RNA expression of Mcl-1 was investigated. Caspase-3 activity, LDH activity and Mcl-1 protein expression was assessed in human monocyte derived macrophages following incubation with compound 1.

Results: Mice treated with compound compound 1 or compound 2 showed striking delay in onset as well as significant reduction in severity of arthritis. This effect was shown, not only in daily treatment but also in bi-weekly regime. Western blot of spleens showed decreased level of Mcl-1 in a dose dependent manner, whereas survivin levels were significantly increased. Flow cytometric analysis of splenocytes in arthritic- and healthy mice treated with inhibitors showed an increase in frequency of regulatory T cells.

Cdk-9 inhibition in peripheral blood mononuclear cells resulted in loss of Mcl-1 expression both on protein and RNA level with a subsequent increase in apoptosis. Down-regulation of Mcl-1 was also observed in monocyte derived macrophages with an activation of caspase-3.

Conclusion: This study provides clear results that inhibition of cdk-9 is working in an immunomodulatory manner, independent of high survivin expression and may in the future serve as an alternative treatment, not only of cancer, but also of autoimmune- and inflammatory diseases.

Disclosure: **A. Hellvard**, None; **L. Zeitlmann**, Ingenium Pharmaceuticals GmbH, 3; **U. Heiser**, Probiodrug AG, 3; **A. Niestroj**, Probiodrug AG, 3; **H. U. Demuth**, Probiodrug AG, 3; **J. Potempa**, None; **P. Mydel**, None.

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ASP015K: A Novel JAK Inhibitor Demonstrated Potent Efficacy in Adjuvant-Induced Arthritis Model in Rats. Shunji Yamazaki, Masamichi Inami, Misato Ito, Yasutomo Fujii, Kaori Hanaoka, Kaoru Yamagami, Kenji Okuma, Yoshiaki Morita, Shohei Shirakami, Takayuki Inoue, Susumu Miyata and Yasuyuki Higashi. Astellas Pharma Inc., Tsukuba, Japan

Background/Purpose: The Janus kinase (JAK) family of enzymes plays a key role in cytokine signaling, which is involved in the pathogenic events of immune-mediated disorders such as rheumatoid arthritis (RA). The objectives of this study were to identify *in vitro* and *in vivo* pharmacological profiles of a novel synthesized compound, ASP015K, and to evaluate its therapeutic potential in the treatment of RA patients using an experimental animal model.

Methods: *In vitro* enzyme inhibition assays were conducted against JAKs and tyrosine kinase 2 (TYK2) enzymes. Cell-based assays were also conducted to assess the selectivity of ASP015K for signaling via JAK1/JAK3 over JAK2/JAK2. JAK1/3 activation was evaluated by interleukin (IL)-2-stimulated T cell proliferation; JAK2/2 action was evaluated by erythropoietin (EPO)-stimulated erythroleukemia cell proliferation. In order to evaluate the potential efficacy of ASP015K to reduce clinical signs and symptoms of RA as well as disease progression, the reduction of paw swelling and ankle bone destruction in adjuvant-induced arthritic (AIA) rats were assessed after both prophylactic and therapeutic dosing regimens of ASP015K. Dunnett's and Steel's multiple comparison tests were used to compare ASP015K-treated groups with the control group of the paw volume and ankle bone destruction score, respectively.

Results: ASP015K inhibited JAK1, JAK2, JAK3 and TYK2 enzyme activities with IC_{50} values of 3.9, 5.0, 0.71 and 4.8 nM, respectively. ASP015K inhibited the IL-2-induced proliferation of human T cells with an IC_{50} value of 18 nM. Moreover, ASP015K was 14-fold more potent against JAK1/3 than JAK2/2 on the basis of EPO-induced proliferation of human leukemia cells. This selectivity suggests that ASP015K has the potential to demonstrate JAK1/3-mediated immunomodulatory effects without the occurrence of JAK2-mediated hematopoietic effects. In rat AIA model, the hind paw volume gradually increased starting 10 days after adjuvant injection and ankle bone destruction was established by day 25, the end of the experiment. After once-daily oral administration of ASP015K 1 to 30 mg/kg in prophylactic dosing regimen, the increase in paw volume was significantly ($p<0.05$) decreased in a dose-dependent manner and was completely suppressed at the highest dose compared to control. Similar findings of dose-dependent reduction in ankle bone destruction score were observed. In therapeutic dosing regimens initiated after paw swelling was established, paw swelling and ankle bone destruction score was also suppressed in a dose-dependent manner.

Conclusion: Data from the current study demonstrates that ASP015K potently inhibits human JAK enzymes with moderate selectivity against JAK1/3 over JAK2/2, which may translate to less hematological side effects observed in the clinic such as anemia. In rat AIA model, ASP015K demonstrated a dose-dependent reduction in paw swelling and suppression of ankle bone destruction scores after both prophylactic and therapeutic dosing regimens. The data suggests that ASP015K has the potential to reduce clinical signs and symptoms as well as prevent disease progression in RA patients warranting further clinical investigation.

Disclosure: **S. Yamazaki**, Astellas Pharma Inc., 3; **M. Inami**, Astellas Pharma Inc., 3; **M. Ito**, Astellas Pharma Inc., 3; **Y. Fujii**, Astellas Pharma Inc., 3; **K. Hanaoka**, Astellas Pharma Inc., 3; **K. Yamagami**, Astellas Pharma Inc., 3; **K. Okuma**, Astellas Pharma Inc., 3; **Y. Morita**, Astellas Pharma Inc., 3; **S. Shirakami**, Astellas Pharma Inc., 3; **T. Inoue**, Astellas Pharma Inc., 3; **S. Miyata**, Astellas Pharma Inc., 3; **Y. Higashi**, Astellas Pharma Inc., 3.

2085

T Cell-Mediated Murine Antigen-Induced Arthritis Is Resistant to Transgenic Disruption of Glucocorticoid Signaling in Osteoblasts and Osteocytes in Vivo. Cornelia M. Spies[1], Edgar Wiebe[1], Jinwen W. Tu[2], Aiqing Li[2], Timo Gaber[1], Dörte Huscher[1], Markus J. Seibel[2], Hong Zhou[2] and Frank Buttgereit[1]. [1]Charité University Medicine, Berlin, Germany, [2]ANZAC Research Institute, The University of Sydney, Concord, Australia

Background/Purpose: The role of endogenous glucocorticoids (GC) in, and their contribution to the susceptibility and severity of rheumatoid arthritis remains inconclusive. We previously demonstrated that disruption of GC signaling in osteoblasts results in attenuation of arthritis in the antibody-mediated mouse model of K/BxN serum-induced arthritis (Buttgereit *et al.*, Arthritis Rheum 2009). The aim of this study was to test whether GC-dependent osteoblast effects have a similar impact on the T cell-mediated model of antigen-induced arthritis (AIA).

Methods: GC signaling in osteoblasts was disrupted by transgenic overexpression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) under the control of a type I collagen promoter. Arthritis was induced by intra-articular injection of mBSA into one knee joint of pre-immunised 11-week old male transgenic mice (tg) and their wild-type (WT) littermates. Controls received PBS. Knee joint swelling was assessed continuously for 14 days until the mice were sacrificed. The mice were examined by histology, histomorphometry, and micro-CT. In a part of the animals, arthritis was prolonged through three weekly repeated intravenous injections of mBSA until day 28. Statistical analysis was performed by repeated measures analysis.

Results: Acute and significant arthritis developed in both 11β-HSD2-tg and WT mice with maximum knee joint swelling on day 1 and abatement thereafter, with no significant difference in knee joint swelling between tg (n=14) and WT mice (n=17). Histological indices of inflammation, cartilage damage and bone erosion of WT and tg mice, respectively, accordingly showed no differences. Bone turnover and bone volume measured at the contralateral knee remained unchanged. In the prolonged AIA model with repeated intravenous antigen boosts, a significant arthritis with flares on days 7, 14 and 21 was achieved, but also without significant differences between tg mice (n=7) and their WT littermates (n=8) and corroborating histological findings.

Conclusion: In contrast to K/BxN serum-induced arthritis, murine antigen-induced arthritis is resistant to disruption of GC signaling in osteoblasts. This suggests that osteoblasts do not modulate the T cell-mediated inflammatory response but the antibody-mediated inflammatory response (complement, Fc receptors, neutrophils, monocytes/macrophages) via a GC-dependent pathway.

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2086

PI3-Kinase Controls Inflammatory Bone Destruction by Regulating the Osteoclastogenic Potential of Myeloid Cells. Stephan Blueml[1], Gernot Schabbauer[2], Antonia Puchner[2], Emine Sahin[2], Victoria Saferding[1], Birgit Niederreiter[1], Josef S. Smolen[3] and Kurt Redlich[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University Vienna, Vienna, Austria, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Local bone destruction in rheumatoid arthritis, psoriasisarthritis or ankylosing spondylitis is a serious health burden and the major cause of disability and severely reduced quality of life in these diseases. This damage to the bony structures is exclusively mediated by a special cell type, the osteoclast (OC). Therefore, it is important to understand factors and pathways regulating the generation of OCs under inflammatory conditions. As PTEN is a lipid phosphatase and one of the main antagonists of the PI3-kinase, we analyzed the impact of the PI3-Kinase/PTEN axis on OC generation and bone biology in an animal model of inflammatory bone loss.

Methods: We induced osteoclastogenesis in wt and PTEN deficient bone marrow cells and measured the generation of OCs, their resorptive capacity and induction of OC differentiation markers *in vitro*. Moreover, we analyzed mice with a monocyte/macrophage-specific deletion of PTEN (myeloid specific PTEN$^{-/-}$) by bone histomorphometry and crossed these mice into hTNFtg animals.

Results: We show that myeloid specific PTEN$^{-/-}$ mice have increased osteoclastogenesis *in vitro* and *in vivo* when compared to wild-type animals. However, under non-inflammatory conditions, enhanced osteoclastogenesis did not result in systemic bone loss *in vivo*. However, when we crossed myeloid specific PTEN$^{-/-}$ into hTNFtg mice we found significantly decreased grip strength scores in myeloid specific PTEN$^{-/-}$/hTNFtg mice compared to wt hTNFtg mice. Joint swelling scores, however, were not different between both groups. In line, myeloid specific PTEN$^{-/-}$/hTNFtg mice displayed enhanced local bone destruction as well as OC formation in the inflamed joints, whereas the extent of synovial inflammation was not different between the groups. Analysis of the synovial membranes of wt and myeloid specific PTEN$^{-/-}$ animals revealed similar relative compositions of the cellular infiltrate including macrophages, which serve as OC precursors. This suggests that increased capacity for osteoclastogenic differentiation rather than enhanced recruitment of precursor cells is responsible for the enhanced local generation of OCs.

Conclusion: Taken together, these data demonstrate that sustained PI3-Kinase activity in myeloid cells specifically elevated the osteoclastogenic potential of these cells, leading to enhanced inflammatory local bone destruction. Therefore, targeting the PI3-Kinase pathway therapeutically may be especially useful for the prevention of structural joint damage.

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2087

Regulatory Effect of the Combination of Methotrexate and 1,25-Dihydroxyvitamin D3 On the Balance of Treg and Th17 in Collagen-Induced Arthritis. Jing Luo. the Second Hospital of Shanxi Medical University, Taiyuan, China

Background/Purpose: 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) is the physiologically active metabolite of vitamin D, and it may modulate inflammatory response, cell maturation and cell differentiation. More recently, animal and human studies have suggested that vitamin D is a potential modifier of autoimmune diseases such as rheumatoid arthritis (RA), but the mechanism is not yet clear.In this study, we aimed to determine the effect of methotrexate (MTX) and 1,25-(OH)2D3, used alone or in combination, in the balance of CD4(+) CD25(+) Tregs and Th17, in a rat model of collagen induced arthritis (CIA).

Methods: Arthritis was induced in 50 female Sprague-Dawley rats. After the clinical onset of CIA, rats were assigned to treatment with MTX (1 mg/kg/week), 1,25-(OH)2D3 (5 mg/kg twice weekly), both treatments at the same regimens, or vehicle. Arthritis score and paw thickness were recorded twice weekly.At termination of the experiment (day 56), bone mineral density (BMD) was analyzed by densitometry, and hind paws were removed for radiographic, histological and immunohistochemical analysis. mRNA expression of transcription factor and proinflammatory mediators was determined by reverse transcriptase–polymerase chain reaction (RT-PCR), and purified T cell proliferation was assessed using [3H]-thymidine incorporated assay, and T-cell phenotypes and activation were assessed by fluorescence-activated cell sorting analysis and T helper (Th) 17/Th1/Th2/Tregs type cytokine production from supernatants from spleen, lymph node and paw cultures was examined by ELISA.

Results: The combination of 1,25-(OH)2D3 with MTX was more effective than MTX alone for reducing the incidence and severity of CIA, and inhibited the production of interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6, IL-2, interferon (IFN)-γ, and matrix metalloproteinases (MMP)-3 and up-regulated anti-inflammatory cytokines IL-4, IL-10. Cytokine analysis indicated that the combination of 1,25-(OH)2D3 with MTX not only modulated the T-helper cell balance from Th1 to Th2 effector function but also associated with the upregulation of CD4(+) CD25(+) Tregs, downregulation of Th17 differentiation. Correspondingly, the mRNA expression of IL-17A and RORrt (a specific transcription factor for Th17) was also reduced.

Conclusion: A combination of MTX and 1,25-(OH)2D3 had beneficial effects on CIA by regulating the balance of CD4(+) CD25(+) Tregs and Th17. These two different mechanisms of action provide support for the use of a combination of these two drugs to improve the prevention of structural joint damage in RA.

Disclosure: J. Luo, None;

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Annexin A1 Receptor Agonist Suppresses Development of Inflammatory Arthritis. Yuan Hang Yang[1], Yuan Jia[2], Wenping Kao[1], Wuqi Song[3], Zhan-guo Li[2] and Eric F. Morand[1]. [1]Monash University, Melbourne, Australia, [2]Peking University People's Hospital, Beijing, China, [3]Harbin Medical University, Harbin, China

Background/Purpose: Annexin A1 (AnxA1) is recognized as an endogenous anti-inflammatory molecule. An AnxA1 receptor, formyl-peptide receptor 2 (FPR2), has been identified in human and mice. The contribution of FPR2 to rheumatoid arthritis (RA) is not well understood. We investigated the contribution of AnxA1 and FPR2 to the regulation of inflammatory arthritis.

Methods: Arthritis was induced by injection of K/B×N serum (38μl/mouse, ip) in wild-type or AnxA1−/− mice at day 0 and 2. Wild-type mice were treated with Compound 43, an agonist of FPR1/2, at 6–30μg/g on days 0–4. RA synovial like fibroblasts (FLS) were treated with FPR2 ligand or antagonist compounds, and AnxA1 was silenced using siRNA.

Results: Deficiency of AnxA1 significantly increased arthritis clinical and histopathological severity. Treatment of wild-type mice with Compound 43 dose-dependently and significantly suppressed clinical scores (Fig 1A), paw thickness (Fig 1B) and histopathologic severity. AnxA1 silencing increased RAFLS proliferation, ERK and NFKB activation. RAFLS expressed FPR2, and an FPR ligand inhibited proliferation while, blocking FPR2 significantly increased proliferation, ERK and NF-κB activation, and IL-6 release.
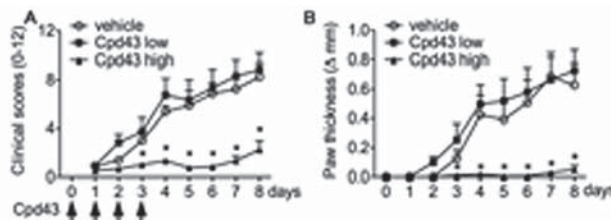
Figure 1. Mice were injected with KB×N serum on day 0 and 2 and Compound 43 from day 0 to 4. *P<0.05. A. Clinical scores B. Paw thickness.

Conclusion: Compound 43 was potently therapeutic in K/BxN arthritis and FPR2 regulates RAFLS activation. These data suggest that FPR2 ligands may have important beneficial actions on RA.

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2089

High Local Cathepsin Activity in a Murine Rheumatoid Arthritis Model, but Not in an Osteoarthritis Model, Explains the Difference in Cartilage Vdipen Neoepitope Formation. Eline A. Vermeij, Marije I. Koenders, Onno J. Arntz, Miranda B. Bennink. Arjen B. Blom, Peter L.E.M. van Lent, Wim B. van den Berg and Fons A.J. van de Loo, Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation and connective tissue destruction. On the other hand, osteoarthritis (OA) is regarded as a joint disease with cartilage destruction, but the role of inflammation in OA is still debatable. During joint inflammation and destruction, a variety of proteases are upregulated, including different cathepsins and matrix-metalloproteinases (MMPs). MMPs are a large group of enzymes known to degrade the extracellular matrix during both RA and OA, causing cartilage proteoglycan depletion and breakdown of the collagen network, leading to erosion. Cathepsins are lysosomal proteases which are abundantly found in the synovial fluid and the lining tissue of arthritic joints. In this study we investigated cathepsin and

MMP activity in the process of cartilage destruction, in both a RA and an OA model.

Methods: Collagen-induced arthritis (CIA) was induced in DBA1/J mice, mimicking a RA model. Destabilization of the medial meniscus (DMM) was induced in C57Bl6/N mice causing instability of the joint and subsequently osteoarthritic features. For the CIA model at day 30 and for the DMM model at day 56, fluorescent imaging was performed using Sense 680 probes (PerkinElmer, Massachusetts, USA) and enzyme activity was detected using the IVIS Lumina (Caliper Life Sciences). The ProSense 680 probe becomes activated upon enzymatic cleavage by cathepsins, whereas the MMPSense 680 can be activated by different MMPs. After imaging, mice were sacrificed and knee and ankle joints were dissected and processed for histology. Sections were also immunostained for VDIPEN, a neoepitope of aggrecan cleaved by MMPs.

Results: The ProSense as well as the MMPSense showed a 3 times higher fluorescent signal intensity during CIA, indicating both cathepsin and MMP activity in this model. Interestingly, on the other hand, only MMP activity (1,5 times higher), but no cathepsins activity, could be measured in the DMM model. On histological level, although different in severity, the CIA model and the DMM model both showed features of cartilage damage. In the CIA model, more VDIPEN staining was seen with increasing severity of the disease; on the other hand, in the DMM model no VDIPEN staining was seen above baseline levels.

Conclusion: In the CIA model, inflammation and destruction are correlated, while the DMM model showed MMP activity without inflammation. Mort *et al.* (1998) showed that cathepsin-B can also cleave aggrecan, and can thereby form the VDIPEN neoepitope. Because no cathepsin activity could be measured in the DMM model, this can explain the absence of the VDIPEN neoepitope. This argues for a role of cathepsins in cartilage destruction but their role in CIA remains to be determined. Combining the imaging of local enzyme activity using activatable fluorescent probes together with cartilage neoepitope immunolocalization may unravel the processes involved in joint destruction.

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2090

Orchestrating the Orchestrators: Blockade of Flt3L Signaling-Dependent Dendritic Cells Protects Against Collagen Induced Arthritis.
Maria I. Martins Ramos[1], Karpus O.N. Karpus[1], Pleun Broekstra[1], Saïda Aarrass[1], Paul P. Tak[2] and Maria C. Lebre[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center, University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: Autoimmune diseases often result from inappropriate or unregulated activation of autoreactive T cells. The induction and maintenance of T cell tolerance to tissue antigens is essential to prevent autoimmunity. A key requirement for tolerance is the presentation of antigens in a correct context. Dendritic cells (DCs) are the central antigen-presenting cells (APCs) for the initiation of T cell responses. In this context, stimulation of the Flt3 via Flt3L is known to drive expansion and differentiation of DCs. Traditional approaches to treatment of autoimmune diseases through immunosuppression have focused on direct inhibition of T cells. In the present study, we examined the targeted inhibition of APCs as a mean to downregulate/prevent autoimmune disease in a mouse model for rheumatoid arthritis.

Methods: Collagen-induced arthritis (CIA) was induced in mice lacking Flt3L (Flt3L$^{-/-}$) and WT littermates (C57/BL6 background, 9–10 weeks old). The arthritis severity was assessed using an established semiquantitative scoring system (0–4). After 60 days (chronic phase) phenotypical and functional analysis of spleen and lymph nodes was performed: T and B cell markers, FoxP3 expression, activation markers, co-stimulatory markers and cytokine production. Collagen type II specific antibodies and a panel of inflammatory cytokines were measured in the serum. Histological markers for cellular infiltration, cartilage destruction and peptidoglican loss were performed, as well as immunohistochemistry stainings for cellular markers.

Results: In CIA abrogation of Flt3 signaling led to decreased disease incidence (area under the curve p<0.0005) and severity (p<0.005). CIA Flt3L−/− mice showed reduced spleen and lymph node cellularity (p< 0.0001) and reduced percentage of activated CD4$^+$CD25$^+$ T cells compared with WT (p=0.03). Flt3L−/− CD4$^+$ T cells also produce significantly less IL-17 (p=0.016) and TNF-a (p=0.010), and CD8$^+$ T cells less IFN-γ (p=0.029) compared to WT. We also observed less infiltration of inflammatory cells and less peptidoglican loss.

Conclusion: Mice lacking Flt3L are protected from CIA. We observed that Flt3L deletion influences the magnitude (cell numbers) and quality (CD25 expression and cytokine expression) of T cell responses. Stimulation of lymphocytes by different types of DC, DC at different stages of maturity and producing and responding to different growth factors might contribute for this change in T cell numbers and/or effector functions in Flt3L−/− mice. Targeting this signaling pathway might be considered as a good therapeutic strategy in RA.

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2091

The Effect of Pretreatment with Capsaicin On Measurement of Arthritis Pain by Dynamic Weight Bearing and Evoked Pain Responses in an Acute Murine Arthritis Model.
Hollis E. Krug[1], Christopher W. Dorman[2], Sandra Frizelle[2] and Maren L. Mahowald[3]. [1]VA Health Care System, Minneapolis, MN, [2]Minneapolis VA Health Care System, Minneapolis, MN, [3]University of Minnesota Medical School and Minneapolis VA Health Care System, Minneapolis, MN

Background/Purpose: Murine models are important to study arthritis pain and new analgesics, however measuring pain in mice is challenging. The Dynamic Weight Bearing (DWB) device measures individual limb forces during spontaneous activity and time spent bearing weight on each limb. Evoked pain behaviors in mice are sensitive to change due to arthritis pain and analgesia. We hypothesized that mice with acute arthritis would have measurable changes in DWB due to joint pain and that this could be prevented by pre-treating with intra-articular (IA) capsaicin.

Objectives: We measured DWB and Evoked Pain Scores (EPS) in acute arthritis to determine if DWB correlates with EPS and whether it is a reliable measure of spontaneous pain behavior in animals with arthritis. To test the reliability of DWB in differentiating arthritic from nonarthritic animals, some mice were pretreated with capsaicin to prevent development of arthritis.

Methods: C57Bl6 mice were used for all experiments. Acute inflammatory arthritis was produced by IA injection of $10\mu l$ 2.5% carrageenan into the left knee 2–4 hours prior to pain behavior testing. Analgesic controls were injected with 2.5% carrageenan diluted in morphine (MOR) solution (morphine dose of $0.15\mu g$/knee). Some mice were injected IA with capsaicin (0.305 mmol) 7 days before induction of arthritis. DWB was measured with a Dynamic Weight Bearing apparatus (Bioseb, Vitrolles, France). Evoked pain behavior was measured by tallying fights + vocalizations/1 min with repeated firm palpation of the knee.

Results: Arthritis pain was clearly and reproducibly indicated by increased Evoked Pain Scores (EPS) in arthritic mice. DWB was significantly reduced by acute arthritis in the affected limb measured by both % weight bearing and time on the affected limb. IA MOR improved EPS but did not improve DWB significantly. Pretreatment with capsaicin abolished the increased EPS from carrageenan arthritis and normalized DWB by all measures. IA capsaicin injection alone had no effect on DWB or EPS by day 7.

Mean (SEM)	Naive	Sham Injected	Acute Arthritis	MOR Rx Acute Arthritis	MOR Alone	Capsaicin Pre-treatment	Capsaicin Alone
EPS	1.25 (0.49)	1.67 (0.88)	*12.75 (3.41)*	*5.38 (1.34)*	1.88 (0.85)	0.33 (0.33)	*1.67 (1.67)*
DWB L/R Ratio % Weight	0.975 (0.065)	1.189 (0.134)	*0.581 (0.105)*	*0.515 (0.128)*	1.303 (0.136)	1.002 (0.134)	0.838 (0.131)
DWB L/R Ratio % Time on Limb	0.961 (0.023)	0.992 (0.027)	*0.757 (0.085)*	*0.830 (0.084)*	0.988 (0.023)	1.030 (0.017)	0.967 (0.047)

Conclusion: Pain can be quantitated in murine arthritis models using measures of DWB and EPS. EPS increased and DWB of the affected limb decreased significantly with acute inflammatory arthritis. Animals pretreated with capsaicin did not develop pain as measured by EPS or DWB. IA MOR was not effective in normalizing DWB in this small experiment, but was effective in reducing EPS in arthritic mice. DWB appears to have significant utility for measuring arthritis pain in animal models. It is sensitive to change, has good reproducibility between mice and is highly correlated with other measure of arthritis pain in mice.

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2092

No Significant Effect of Hepatitis B Virus Infection On Disease Activity, Synovitis or Joint Destruction in Rheumatoid Arthritis. Chan Juan Zou, Yan Hua Li, Ying Qian Mo, Lang Jing Zhu, Dong Hui Zheng, Jian Da Ma, Xia Ouyang and Lie Dai. Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background/Purpose: The prevalence of chronic hepatitis B virus (HBV) infection is high in China. 4% patients with HBV infection can present with polyarthritis and positive rheumatic factor similar to RA, which implied similar pathogenic mechanism.We aimed to investigate the association between HBV infection and serological, radiological or histological disease status in RA.

Methods: 223 continuous hospitalized Chinese patients with RA were enrolled retrospectively. Clinical and laboratory data including HBV detection, and hand X ray were collected. Among 133 active RA patients, synovium was obtained by closed-needle biopsy from inflamed knee joint. Serial tissue sections were stained immunohistochemically for HBV surface antigen (HBsAg), CD79a, CD20, CD38, CD68, CD3, and CD34. Densities of positive-staining cells and synovitis score were determined.

Results: According to HBV infection status, 25/223 had chronic HBV infection (including 4 chronic hepatitis B and 21 HBV carriers), 72/223 had past HBV infection and 126/223 had no HBV infection. The prevalence of HBsAg positivity and chronic hepatitis B in RA was 11.2% and 1.7%, not significantly different with age-matched general Chinese population (8.7% from 2006 Chinese national epidemiological survey and 1.0% from 2005 local survey, respectively, P>0.05). Clinical parameters, DAS28 or Sharp scores showed no significant difference among chronic HBV infection, past HBV infection and no HBV infection groups in 206 active RA or 140 active RA patients without any corticosteroid or DMARDs treatment (all P>0.05). Synovial immunohistochemical staining showed negative HBsAg in 10 HBV carriers and 10 past HBV infection patients. Except for higher sublining CD3+ cell density in past HBV infection group, Krenn's synovitis score, mean densities of sublining positive-staining cells (CD20, CD38, CD79a and CD68) and CD34+ microvessel counts showed no significant difference among RA patients with HBV carrier, past HBV infection or no HBV infection (all P>0.05).

Conclusion: The prevalence of HBV infection in RA patients was consistent with general Chinese population. Chronic HBV infection have no significant effect on disease activity, synovitis or joint destruction in RA, implying that chronic HBV infection may play neither promotive nor protective role in RA.

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Rates of Opportunistic Infections Among Rheumatoid Arthritis Patients Switching Biologic Therapy. John Baddley[1], Shuo Yang[1], Klye Brizendine[2], Scott DuVall[3], Kevin L. Winthrop[4], Mary J. Burton[5], Nivedita M. Patkar[6], Elizabeth S. Delzell[1], Monika M. Safford[1], Jasvinder A. Singh[1], Iris E. Navarro[1], Grant W. Cannon[7], Ted R. Mikuls[8], Lang Chen[1], Kenneth G. Saag[6], Kimberly Alexander[9], Pavel Napalkov[9], Aaron Kamauu[10] and Jeffrey R. Curtis[6]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Birmingham, AL, [3]VA Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [4]Oregon Health & Science University, Portland, OR, [5]VA Hospital, Jackson, [6]Univ of Alabama-Birmingham, Birmingham, AL, [7]George E. Wahlen VA Medical Center, Salt Lake City, UT, [8]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [9]Genentech, Inc., South San Francisco, CA, [10]Anolinx, Bountiful, UT

Background/Purpose: The incidence of opportunistic infections (OIs) in patients on biologics is low, but may approach several cases per 100 person-years (PY). Data on risks for OIs associated with newer biologics and in those switching biologics among rheumatoid arthritis (RA) patients are limited.

Methods: Using data from 1998–2011 from the U.S. Veteran's Health Administration we identified a cohort of rheumatologist-diagnosed RA patients

(n=36,433). Patients eligible for this analysis started anti-TNF therapy (adalimumab, infliximab, etanercept) after previous anti-TNF exposure, or rituximab (RTX) or abatacept (ABA). To minimize confounding from channeling of patients to certain biologics, those patients with a history of hematologic malignancy in the past year were excluded. Potential OIs were identified using ICD-9 codes and/or available laboratory results (cultures, serology). With the exception of zoster, where ICD-9 code alone identified a case, all other OIs were confirmed by chart review using standardized case definitions. Patients were censored at first OI event. Baseline co-morbidities were defined in the 1-year period prior to treatment initiation. Exposure was "as treated" on the basis of days supply or usual dosing intervals. Exposure was extended 60 days after the end of the day's supply; RTX exposure was assumed to be 12 months after infusion. Frequencies of OIs were calculated and crude OI incidence rates were estimated using a Poisson distribution.

Results: A total of 2917 unique RA patients contributed 3774 treatment episodes (ABA 338; RTX 511, TNFs 2925). Two-thirds of TNF use was adalimumab. Mean age of the cohort was 60.8 ± 10.7 years; 87% were male. Hypertension (55.5%), diabetes (25.6%) and COPD (14.2%) were common. Overall, 84 OIs (2.9%) in 2917 patients were identified, yielding an overall rate of 1.5 (95% CI 1.2, 1.9) OIs per 100 PY(Table). The most common OIs were zoster, rate 1.17 (0.9, 1.5) per 100 PY and tuberculosis, rate 0.05 (0.02, 1.6) per 100 PY. Crude rates of OIs per 100 PY among TNFs, ABA and RTX users were 1.5 (1.2, 1.9); 1.1 (0.4, 2.6), and 1.8 (1.0, 3.2), respectively. Among TNFs, rates per 100 PY were infliximab 0.8 (0.3, 2.1), adalimumab 1.6 (1.2, 2.2) and etanercept 1.6 (1.0. 2.5). For the 19 confirmed OIs other than zoster, 7 (37%) were identified by screening lab data and were not identified by ICD-9 codes.

Table. Frequency of Physician-Confirmed Opportunistic Infections (OIs) by Biologic Exposure

Opportunistic Infection	Abatacept N=338 PY=486	Adalimumab N=1826 PY=2727	Etanercept N=741 PY=1181	Infliximab N=358 PY=511	Rituximab N=511 PY=651	TOTAL N=3774 PY=5538
Zoster	5	38	16	2	4	65
Tuberculosis	0	0	2	0	1	3
Pneumocystosis	0	0	0	0	3	3
Legionellosis	0	3	0	0	0	3
Coccidioidomycosis	0	0	1	0	2	3
Histoplasmosis	0	1	0	1	0	2
Non-tuberculous mycobacteria	0	1	0	0	1	2
Salmonellosis	0	1	0	0	1	2
Nocardiosis	0	0	0	1	0	1
Total OIs	5	44	19	4	12	84
IR (95% CI) per 100 p-years	1.1(0.4, 2.6)	1.6 (1.2, 2.2)	1.6 (1.0, 2.5)	0.8 (0.3, 2.1)	1.8 (1.0, 3.2)	1.5 (1.2, 1.9)

OI=opportunistic infection; IR=incidence rate

Conclusion: In US veterans with RA, overall crude OI rates were low and similar among biologics. The most common OI was zoster. The availability of serologic and culture data for OI screening yielded a meaningfully higher proportion of OI cases compared to administrative data alone.

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Reactivation of Hepatitis B Virus in Autoimmune Disease Patients Receiving Immunosuppressive Agents. Daisuke Kobayashi[1], Satoshi Ito[1], Megumi Unno[1], Ichiei Narita[2] and Akira Murasawa[1]. [1]Niigata Rheumatic Center, Niigata, Japan, [2]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Background/Purpose: Reactivation of resolved hepatitis B in patients undergoing immunosuppressive therapy is now considered to be a complication of major clinical importance. Because this is still an emerging concept, the majority of our patients with autoimmune disease have been tested only for hepatitis B surface antigen (HBsAg), and not for hepatitis B surface antibody (anti-HBs) or hepatitis B core antibody (anti-HBc) in our country.

We evaluated the prevalence of previous infection of hepatitis B virus (HBV) in patients with autoimmune disease and the incidence of its reactivation.

Methods: We enrolled 318 patients (63 males, 255 females) with autoimmune disease, who were receiving, or were scheduled to receive, immunosuppressants at our hospital. The immunosuppressants included methotrexate (MTX), tacrolimus (TAC), mizoribine (MZR), prednisolone (PSL) at over 30 mg/day, azathioprine (AZ), cyclosporine (CyA), cyclophosphamide (CPA), etanercept (ETN), infliximab (IFX), tocilizumab (TCZ), adalimumab (ADA), and abatacept (ABA). Patients underwent HBV serological examination including HBsAg, anti-HBs, and anti-HBc. When HBsAg, anti-HBs and/or anti-HBc were positive, HBV-DNA was measured once a month using a real-time polymerase chain reaction assay. Clinical data were examined by reviewing the medical records.

Results: Among the 318 patients, 4 were HBsAg positive and the rest were HBsAg negative; 61 patients were anti-HBs positive and 70 were anti-HBc positive. Eighty patients (rheumatoid arthritis (RA) 72, systemic lupus erythematosus (SLE) 4, adult-onset Still's disease 1, polymyositis 1, polymyalgia rheumatica 1, juvenile rheumatoid arthritis 1) showed HBsAg negative and anti-HBs and/or anti-HBc positive serology, indicating previous HBV infection. Among these patients, 72 had already been treated with immunosuppressive agents as monotherapy or in combination (MTX 42, TAC 25, MZR 11, high-dose PSL 5, AZ 3, CyA 1, CPA 1, ETN 9, IFX 7, TCZ 4, ADA 1, ABA 1) for 43.9 ± 44.4 months (range 4–248 months, median 32 months) before evaluation of anti-HBs and anti-HBc without developing acute hepatitis. Another 8 patients were scheduled to begin immunosuppressive therapy. Among patients with past HBV infection, 5 were positive for viral replication (>2.1 log copies/ml). The first of these patients had SLE, and the other four had RA. Among them, a patient was treated with high-dose PSL and CPA. She was HBsAg negative at the start of immunosuppressant therapy, but 3 months later HBV-PCR increased to 7.9 log copies/ml, and HBsAg became weakly positive with elevation of the transaminase level. The second patient was treated with 3 mg/day TAC, 150 mg/day MZR and 5 mg/day PSL, and the third with 3 mg/day TAC and 5 mg/day PSL. Two patients who were treated only with sulfasalazine and bucillamine, showed reactivation of HBV in the absence of immunosuppressants.

Conclusion: Reactivation of HBV sometimes occurs without MTX or biological agents. Patients in whom hepatitis B infection has serologically been resolved, need to be monitored carefully even when receiving immunosuppressants other than MTX, or biological agents.

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2095

Identifying Arthralgia Patients At Risk for Rheumatoid Arthritis in the Rotterdam Early Arthritis Cohort. M. van der Veer[1], D. van Zeben[2], A.E.A.M. Weel[3], P.J. Barendregt[3], A.H. Gerards[4], Johanna M.W. Hazes[5] and Jolanda J. Luime[6]. [1]ErasmusMC, Rotterdam, Netherlands, [2]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]Vlietland Hospital, Schiedam, Netherlands, [5]Erasmus Medical Center, Rotterdam, Netherlands, [6]Erasmus MC - University Medical Center, Rotterdam, Netherlands

Background/Purpose: Patients with rheumatoid arthritis (RA) frequently have a high disease burden and erosions at first presentation because of the insidious nature of the disease. Previous studies showed that early recognition and initiation of therapy lowers the risk for developing erosive disease and leads to a better quality of life. Our aim is to identify predictive features in patients at risk for rheumatoid arthritis when inflammatory joint complaints are present but before synovitis is observed.

Methods: We used data from the Rotterdam Early Arthritis Cohort (REACH). Patients with two or more joints with pain or loss of movement with two or more of the following criteria: morning stiffness for more than 1 hour; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings or shoes; a family history of RA; unexplained fatigue for less than 1 year were eligible. All patients did not have synovitis at baseline. Data were analyzed using simple descriptive analysis and univariate logistic regression in STATA12.

Results: 458 patients fulfilled the REACH criteria without synovitis at baseline. After 12 months 40 patients developed arthritis (8.7%), 34 out of those 40 developed arthritis within the first six months (85%). Rheumatoid arthritis was diagnosed 16 times in the arthritis group (40%). A predictor for developing arthritis was positive ACPA (OR 10.5, 95% CI 4.5–24.5). In the 28 ACPA positive patients at baseline, 12 patients developed arthritis (43%),

after 12 months 16 patients were still free from arthritis. Increasing ESR was the second predictive feature (OR 1.06 per point ESR, 95% CI 1.03–1.09). RF was a less strong predictor (OR 2.86, 95% CI 1.08–7.52). No difference was observed for age, gender, tender joint count, symmetry of joint complaints, distribution of joints in a rheumatoid arthritis pattern, smoking, education level, VAS and CRP.

Conclusion: In patients with inflammatory joint complaints, raised ESR and positive ACPA both predicted the development of arthritis within 12 months. Therefore, we advise to monitor patients with inflammatory joint complaints with positive ACPA or/and raised ESR carefully.

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A Prediction Rule for the Progression to Rheumatoid Arthritis Applied in a Mexican Mestizo Cohort with Undifferentiated Arthritis. Ana Arana Guajardo, Lorena Pérez Barbosa, David Vega Morales, Janett Riega Torres, Roberto Negrete López, Jacqueline Rodríguez Amado, Jorge Esquivel Valerio, Cassandra Skinner Taylor. Diana Flores Alvarado, Dionicio Galarza Delgado, Miguel Villarreal Alarcon and Mario Garza Elizondo, Hospital Universitario, UANL, Monterrey, Mexico

Background/Purpose: A high proportion of patients who present with recent-onset arthritis have undifferentiated arthritis (UA), as these patients do not fulfill the classification criteria for a specific diagnosis. Several cohort studies in UA have used predictive score models to screen patients at risk to develop rheumatoid arthritis (RA). Our objective is to validate the Leiden Prediction Rule (LPR) in an inception cohort of patients with UA.

Methods: We included patients with UA diagnosed from 2008 to 2011, mostly from a community based epidemiological study (COPCORD), who met the following characteristics: >18 years old, at least 1 swollen joint, with a symptom duration of >1 week to 1 year. We excluded patients with pregnancy or with well-defined inflammatory disease. During one year the patients were followed every 2 months. We applied the LPR at the first visit, which includes sex, age, morning stiffness, disease distribution, painful and swollen joints, C-reactive protein (CRP), rheumatoid factor assay (RF) anti-cyclic citrullinated peptide (anti-CCP) antibodies; in each visit they were evaluated for clinical signs of inflammation including the metacarpophalangeal (MCP)/metatarsophalangeal (MTP) squeeze test (ST). Subsequently we reclassified patients a year after their diagnosis of UA. The diagnosis of RA was made according to 1987 ACR classification criteria. Statistic Analysis. The results were expressed as means and standard deviations. The groups were compared with Mann Whitney U test. Chi-Square test was applied for categorical variables. The association between MCP/MTP ST and LPR was established by relative risk (RR) with a confidence interval (CI) of 95%.

Results: We included 47 patients with UA with a mean age of 51.6 years + 9.5 SD, 98% were females. One year after diagnosis, the patients were reclassified as follows: RA 20(43%), and non-RA which included: persistent UA 12(25%), other inflammatory arthritis 9(19%) and spontaneous remission 6(13%). There were no statistical differences between the groups on the number of swollen or painful joints (p=0.576 and p =0.564, respectively) or titers of CRP, RF and anti-CCP antibodies (p=0.754, p=0.97, p=0.29, respectively). In patients who progressed to RA, LPR was ≥ 8 points in only 15% (3 patients), while 85% (17 patients) had <8 points in LPR. When we compared the score obtained from LPR between groups, we did not find any significant difference (p=0.940). We found an association between the MCP/MTP squeeze test (ST) and patients who progressed to RA, RR 1.74; 95% CI [0.92 – 3.28] on MCP ST and RR 2.99; 95% CI [1.12 – 4.70] on MTP ST.

Conclusion: A proportion of 43% of our patients with UA had progression to RA after 1 year of follow-up; 100% patients who scored >8 points in the LPR progressed to RA. These proportions are similar to the data published previously from other UA cohorts. Notably, an important difference is the 56% of patients who progressed to RA with a score <6 points on LPR compared to the Leiden cohort were it was less than 10%. We did find that the presence of pain during the MCP/MTP squeeze test is associated with the progression of RA.

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Adiponectin Is Associated with Pro-Inflammatory Cytokines in Autoantibody Positive First-Degree Relatives (FDRs) of Patients with Rheumatoid Arthritis. Jan M. Hughes-Austin[1], Kevin D. Deane[2], Lezlie A. Derber[3], Gary O. Zerbe[1], Dana M. Dabelea[1], Jeremy Sokolove[4], William H. Robinson[5], V. Michael Holers[2] and Jill M. Norris[6]. [1]Colorado School of Public Health / University of Colorado Anschutz Medical Campus, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]University of Colorado Anschutz Medical Campus, Aurora, CO, [4]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [5]Stanford University, Palo Alto, CA, [6]Colorado School of Public Health, Aurora, CO

Background/Purpose: While adiponectin is generally considered an anti-inflammatory adipokine, it has also been shown to participate in active RA in inflammatory, matrix-destructive and fibrotic processes leading to joint destruction. Because adiponectin's role as a pro- or anti-inflammatory adipokine has been controversial in situations of autoimmunity and chronic inflammation, we sought to determine the relationship of adiponectin to rheumatoid arthritis (RA)-related autoantibodies and markers of inflammation in a population without RA, but at increased risk for future development of the disease.

Methods: We selected all visits of 113 FDRs who were positive for rheumatoid factor (RF), RF isotypes IgM, IgG, IgA, or anti-cyclic citrullinated peptide (anti-CCP2) at least once, and 100 FDRs who were never autoantibody positive. In blood obtained from these 391 visits, we measured cytokines/chemokines, high-sensitivity C-reactive protein (hsCRP), and adiponectin. As a comprehensive measure of inflammation, we calculated a Cytokine Score by summing all cytokine/chemokine levels, weighted by their regression coefficients for RA-autoantibody association. We first compared the effect of adiponectin on two autoantibody phenotypes: positivity for RF, and positivity for the high-risk autoantibody profile (HRP) (positive for anti-CCP2 and/or $\geq$ 2 RF isotypes) that we have shown in previous work to be highly specific ($>96\%$) for future RA; and then tested the interaction between autoantibodies and adiponectin on markers of inflammation using mixed models to account for multiple samples per FDR. All analyses were adjusted for age, sex, ethnicity, body mass index, pack-years of smoking, a delay in sample processing, and current use of statins.

Results: Adiponectin was not associated with either RF (p=0.44) or HRP (p=0.60) positivity. Adiponectin was inversely associated with hsCRP (β=-0.31 $\pm$ 0.10; p=0.002) and IL-5 (β=-0.21 $\pm$ 0.10; p=0.044). The relationship between adiponectin and TNF-α, GM-CSF, and the Cytokine Score differed by HRP status, where a 10% increase in adiponectin resulted in a 5% increase in TNFa and 4% increase in GM-CSF among HRP+ FDRs; whereas no association was observed among HRP- FDRs (Interaction p=0.016, p=0.028 for TNF-α and GM-CSF, respectively). Similarly, a 10% increase in adiponectin was associated with a 2% increase in Cytokine Score among HRP+ FDRs, but not in HRP- FDRs (Interaction p=0.038).

Conclusion: In a population without RA, elevations of adiponectin were associated with elevations of several pro-inflammatory cytokines as well as a marker of overall inflammation, Cytokine Score, in the setting of autoantibody positivity; and were inversely associated with elevations of another marker of inflammation, hsCRP. These findings indicate that adiponectin may have a complex role in early RA-related autoimmunity and inflammation, and that adiponectin may respond differentially according to inflammatory triggers and functions. Further study is needed to determine the role of adiponectin in early RA pathogenesis.

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Patient Report Outcomes Variance Between Centers Is Much Lower Than Physician and Laboratory Assessed Measures of Rheumatoid Arthritis Activity: Results From a Multinational Study. Nasim A. Khan[1], Horace Spencer[2], Tuulikki Sokka[3] and QUEST-RA[4]. [1]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [2]University of Arkansas for Medical Sciences, Little Rock, AR, [3]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [4]Jyväskylä

Background/Purpose: Clinical trials and epidemiological rheumatoid arthritis (RA) studies often recruit patients from multiple centers. We studied the proportion of variance in the American College of Rheumatology (ACR) core set measure, Disease Activity Score 28 (DAS28, representative physician and laboratory measure derived composite index), and Routine Assessment of Patient Index Data 3 (RAPID3, representative PRO derived composite index) explained by between-center differences in a multinational study.

Methods: 7568 patients receiving usual care from rheumatologists in 83 centers located in 30 countries were recruited using standard protocol in the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) study. Mixed-effects analyses of covariance (ANCOVA) models were used to model each ACR core set measure as functions of demographic, medical characteristics and remaining ACR core set measures. Demographic variables included age, race (white, other races), gender, and education > 12 years (yes, no); while medical characteristics included RA duration, rheumatoid factor status, patient's fatigue score (0–10), Psychological Health Assessment Questionaire score (Psych HAQ, 0–3), morning stiffness (0, 1–60, and >60 minutes), comorbidity burden, body mass index, fibromyalgia (yes, no), osteoarthritis (yes, no), and chronic back pain (yes, no). DAS28 model included patient's pain score (0–10 cm) and HAQ, while the RAPID3 model included tender joint count (TJC), swollen joint count (SJC) and erythrocyte sedimentation rate (ESR) in addition to demographic and medical characteristics. The patient recruiting center was included as a random effect to estimate the amount of the residual variance explained by it. MIXED procedure in SAS was used.

Results: Patient reported outcomes had lower proportion (3.25–6.87%) of residual variance that was explained by between recruiting center differences compared to clinician and laboratory derived measures (10.36–14.86%) of RA activity (Table). Similarly, DAS28 had a much larger proportion of variance explained by between recruiting center difference than RAPID3.

Table. Variance of RA disease activity measures accounted for by between recruiting center differences

Variable	Clinic	Residual Variance Unexplained	Total	% Residual Variance Explained by Clinic
PTGL	0.0942	2.8039	2.8981	3.25
Pain	0.0629	2.527	2.5899	2.43
HAQ	0.0169	0.2291	0.246	6.87
MDGL	0.3463	1.9836	2.3299	14.86
SJC	1.7836	14.4741	16.2577	10.97
TJC	4.5332	27.762	32.2952	14.04
ESR	48.329	418.33	466.659	10.36
DAS28	0.3979	1.3654	1.7633	22.57
RAPID3	0.9806	17.4026	18.3832	5.33

PTGL, patient's global assessment of RA activity; HAQ, health assessment questionnaire, MDGL, clinician's global assessment of RA activity.

Conclusion: Patient reported outcomes variance accounted for by between different centers is considerably lower than clinician and laboratory derived measures after adjusting for potential demographic, medical and RA related characteristics. This is despite patient recruitment in QUEST-RA study from several countries with widely different cultural and socio-economic differences. These results highlight the need for implementation of procedures to standardize RA activity assessment by clinicians involved in multi-center studies.

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Patient Self-Assessments and Selected Patient Reported Outcomes May Reliably Identify Rheumatoid Disease Flare in Early Rheumatoid Arthritis Patients. Vivian P. Bykerk[1], CO Bingham III[2], Ernest Choy[3], Juan Xiong[4], Gilles Boire[5], Carol A. Hitchon[6], Janet E. Pope[7], J. Carter Thorne[8], Boulos Haraoui[9], Edward Keystone[10] and Susan J. Bartlett[11]. [1]Hospital for Special Surgery, New York, NY, [2]Johns Hopkins University, Baltimore, MD, [3]Cardiff University School of Medicine, Cardiff, United Kingdom, [4]Mount Sinai Hospital, Toronto, ON, [5]CHUS - Sherbrooke University, Sherbrooke, QC, [6]University of Manitoba, Winnipeg, MB, [7]Western University of Canada, St. Joseph's Health Care, London, ON, [8]Southlake Regional Health Centre, Newmarket, ON, [9]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [10]University of Toronto, Toronto, ON, [11]McGill University, Montreal, QC

Background/Purpose: Significant RA worsening or flare may predict poorer outcomes and signal a need for treatment reassessment. However, there is little agreement about how to reliably identify a flare. Candidate domains essential for assessing RA flare were identified by OMERACT patients (pts)and health care providers including pain, function, stiffness, participation, coping, patient global assessment, fatigue and self-management[1]. We aimed to determine the extent of agreement between pts

and treating rheumatologists (MD) in identifying a flare, and concordance of clinical and patient-reported outcomes (PROs) with flare status.

Methods: Pts in the Canadian early ArThritis CoHort (CATCH) completed the OMERACT preliminary flare questionnaire (PFQ). In the PFQ pts were asked if they were in a flare and to rate severity, pain, function, stiffness, participation, coping, patient global assessment and fatigue (0–10 NRS). Pts also identified tender and swollen joints (TJC and SJC)(42 joint homunculus). MDs rated if their patient (pt) was in a flare and performed a joint count. Pt-MD agreement on flare status was assessed using Cohen's kappa. Wilcoxon rank sum test was used to compare MD and pt reported joint counts. Clinical indices and PROs between flare and non-flare pts were compared using paired t-tests.

Results: 512 pts (75% female) answered PFQ: 13% at baseline, 39% at 3–12 months and 49% at 12 months+ after study entry. Pts had a mean age of 53 ± 14 yrs; 18% were smokers, 63% RF+, 51% CCP+ and 18% had erosions. 149 (29%) reported a flare at study visits. Pts and MDs agreed about flare status 72% of the time (Kappa=0.34). Changes in DAS28 and CDAI from previous visits were higher in flare vs. non flare pts(0.44 vs. −0.14) (1.67 vs.−3.20) (both p<.0001). PROs were significantly different between flare and non-flare pts and were highest when pts and MDs both agreed the pt was in a flare (p<.0001) (see Table). Pts in a flare reported higher TJC/SJCs than MDs. The differences between pt and MD TJC & SJC were 3.74 (p<.0001) and 2.31 (p<.0004). Agreement was modest (Kappa=.32) when pts/MDs agreed on flare status but poor then they didn't (Kappa=.20)

Table 1. Ratings of flare severity and PROs by Patient/MD concordance

Domain	Pt Flare/ MD Flare (n=86)	Pt Flare/ MD Non-Flare (n=63)	Pt Non Flare/ MD Flare (n=83)	Pt Non Flare/ MD Non Flare (n=280)	p-values
Flare severity	6.2 (2.4)	5.2 (2.6)	0.3 (1.5)	0.2 (0.8)	<.001
Pain	6.3 (2.4)	5.1 (2.7)	3.7 (2.6)	1.7 (1.9)	<.001
Function	6.2 (2.6)	4.1 (3.2)	3.7 (2.8)	1.3 (1.8)	<.001
Stiffness	5.8 (2.8)	4.3 (2.9)	3.7 (2.5)	1.7 (1.9)	<.001
Participation	5.6 (2.8)	3.8 (3.0)	3.4 (2.8)	1.2 (1.9)	<.001
Fatigue	5.6 (2.8)	4.7 (3.1)	4.1 (3.0)	2.0 (2.5)	<.001
Coping	4.8 (2.6)	3.2 (2.7)	3.1 (2.6)	1.1 (1.8)	<.001

Values are mean (SD)
* Domains scored 0–10 on a numerical rating score, ascending by severity.

Conclusion: Pts reporting a flare have clinical indices reflecting worsening disease activity. PROs (pain, function, stiffness, coping, participation, and fatigue) significantly discriminated between pts reporting flare vs. no flare. There is modest agreement between pts and MDs regarding flare status. Flare pts identify more swollen and tender joints than MDs. PROs and pt-joint counts may reliably identify pts in disease flares but some ratings are higher in pts than MDs. More research is needed to identify predictors of concordance and discrepancy between pts and providers in flare assessment.

1. Bartlett SJ, et al. ArthRheum 2011;63(suppl):128.

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Relative, Reliability-Adjusted Diagnostic Test Accuracy of Erosion Detection Between Magnetic Resonance Imaging and Radiography in Rheumatoid Arthritis. Ruben Tavares[1], Naveen Parasu[2], Karen Finlay[2], Erik Jurriaans[2], Hao Wu[1], Karen A. Beattie[1], Maggie Larche[1], Lawrence E. Hart[3], William G. Bensen[4], Raja S. Bobba[1], Alfred A. Cividino[1], Colin E. Webber[5], Jean-Eric Tarride[6] and Jonathan D. Adachi[7]. [1]McMaster University, Hamilton, ON, [2]Hamilton Health Sciences, Hamilton, [3]St. Joseph's Health Care, Hamilton, ON, [4]St. Joseph's Hospital and McMaster University, Hamilton, ON, Hamilton, ON, [5]Hamilton Health Sciences, Hamilton, ON, [6]Programs for Assessment of Technology in Health (PATH) Research Institute, Hamilton, ON, [7]Charlton Medical Centre, Hamilton, ON

Background/Purpose: In rheumatoid arthritis (RA), erosion detection on radiography (X-ray) compared to magnetic resonance imaging (MRI) is characterized by low sensitivity and high specificity. This supports the hypothesis that MRI has a lower limit of detection for erosion than X-ray. To date, however, no studies have directly assessed measurement reliability. The objective of this study was to determine the relative diagnostic test accuracy of MRI and X-ray for erosion detection while accounting for inter-rater reliability.

Methods: A paired, cross-sectional study of 65 RA patients with a range of symptom duration was conducted. For each participant, MRI scans of the bilateral metacarpophalangeal joints (MCP) 2–5 and X-ray of both hands, wrists and feet were taken. Comparisons were limited to the MCP 2–5 joints. The Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis magnetic resonance imaging score (RAMRIS) and the van der Heijde-modified Sharp (vdHSS) scores were used to evaluate the MRI and X-ray images, respectively. Data were paired at the smallest level of analysis common to both measures: the joint. A total of 488 paired joints were compared. Odds ratio (OR), sensitivity (Se), specificity (Sp), and accuracy were calculated and the smallest detectable difference (SDD)-adjusted and unadjusted evaluations were compared.

Results: The association between erosion detection on MRI and X-ray of MCP 2–5 had an OR of 1.8 (1.2–2.9), Se of 0.31±0.03, Sp of 0.80±0.03, and accuracy of 0.47. Adjusting for measurement reliability increased the OR, Sp, and accuracy to 3.2 (1.5–6.1), 0.93±0.01, and 0.79, respectively, while decreased the Se to 0.19±0.04. Reliability-adjustment decreased the number of erosions detected per joint from 67.8% to 18.6% on MRI and 27.5% to 9.8% on X-ray. Per MCP joint, 2.6- to 8.0-fold the erosions detected on X-ray were detected on MRI. Compared by affected MCP 2–5 joint set, adjustment resulted in MRI detection of 2.1-fold the erosive disease detected on X-ray. At the patient level of analysis, bilateral MRI of the MCP 2–5 joints resulted in the detection of erosive disease in 1.1-fold the number detected on X-ray of hands, wrists and feet (McNemar's test, $p = 0.83$, Cohen's k=0.17±0.13, $p=0.16$). The correlation between SDD-adjusted vdHSS erosion score and symptom duration was 0.37 ($p<0.0001$). Correlation between MRI and symptom duration was non-significant (0.10, $p=0.26$).

Conclusion: Following reliability-adjustment of evaluations at the unit of measurement, a greater proportion of erosive disease is detected on MRI compared to X-ray per joint imaged. At the patient level of analysis, the relative performance of the two imaging modalities is highly dependent on the anatomy imaged. Despite detecting similar proportions with erosive disease when bilateral MRI of MCP 2–5 and X-ray of the hands, and feet are compared, the non-significant low level of agreement indicates that the proportions detected by each modality are unique. The interaction with symptom duration suggests that MRI may detect a greater proportion of patients with erosions at earlier stages of disease progression.

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How Much Can Patient Reported Outcomes Improve Among Rheumatoid Arthritis Patients Who Have a Clinical Response to Biologic Therapy but Have Not Attained Low Disease Activity? Jeffrey Curtis[1], Ying Shan, Jie Zhang[1], Jeffrey D. Greenberg[3] and George W. Reed[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]New York University School of Medicine, New York, NY, [3]University of Massachusetts Medical School, Worcester, MA

Background/Purpose: Current treat-to-target (T2T) recommendations suggest that rheumatoid arthritis (RA) patients should strive for remission or low disease activity (LDA) as a goal. Treatment changes as often as every 3 months are recommended if necessary. However, it is unclear whether patients that have had a good clinical response to anti-TNF therapy by 3 months but who are not yet in LDA or remission might experience further meaningful improvement in patient reported outcomes (PROs) if they subsequently achieve these T2T disease state targets.

Methods: We used data from the Consortium of Rheumatology Researchers of North America (CORRONA) to study participants with RA (n = 31701 total) who initiating anti-TNF therapy with a subsequent follow-up visit approximately 3 months later. The analysis cohort was restricted to patients who had clinical improvement (CDAI improvement by >= 10 units) at three months. Subsequent clinical response for patients who remained on the same anti-TNF therapy was examined approximately 6 months later to assess whether PROs (global, pain, disability by mHAQ) improved more among those who improved their CDAI category (from LDA to remission, or moderate/high disease activity to low disease activity) compared to those who stayed in the same CDAI category.

Results: A total of 293 patients who initiated anti-TNF therapy and who had an improvement in CDAI of >= 10 units three months later were identified. After excluding 61 patients in CDAI remission (CDAI <=2.8) at 3 months, there were 120 individuals in LDA (CDAI 2.8 – 10) and 112 in

moderate/high CDAI (CDAI > 10) eligible for analysis. Among patients who achieved LDA at 3 months, 45 (38%) subsequently went on to achieve CDAI remission, 26 (22%) stayed in LDA; 49 (41%) worsened to moderate/high disease activity and were excluded. Among the 112 patients still in moderate/high disease activity patients at 3 months, 40 (36%) went on to achieve LDA (CDAI <= 10) and the remainder stayed in moderate/high disease activity. The mean change in PROs was compared. Patients who improved their CDAI disease activity category were significantly better for patient global and pain and no different for mHAQ versus those who stayed in the same disease CDAI activity category.

Patient Reported Outcome	Adjusted* Mean Change (95% CI) for Patients Who Improved to a Better CDAI Disease Activity Category Compared to Those Who Stayed the Same	Adjusted* p value
Patient Global (0–100 scale)	−14.7 (−20.4, −8.9)	<0.001
Patient Pain (0–100 scale)	−11.5 (−17.5, −5.6)	<0.001
Disability (mHAQ)	−0.02 (−0.10, 0.07)	0.74

* adjusted for age, gender, duration of RA, CDAI at 3 months, and baseline PRO

Conclusion: Among patients with a clinical response to anti-TNF therapy at 3 months but who have not yet attained LDA or remission, the magnitude of further change in patient reported outcomes for those who achieve these disease states 6 months later was relatively small compared to those who stayed the same. Some improvement was observed for patient global and pain but not for disability. These results suggest that patients may not experience much additional benefit in their PROs from subsequently attaining the LDA or remission targets recommended in T2T guidelines as long as they have had a good clinical response.

2102

Patient Versus Physician Global Assessments in Ethnic Patients Wtih Rheumatoid Arthritis. Gail S. Kerr[1], Yusuf Yazici[2], Christopher J. Swearingen[3], Luis R. Espinoza[4], Edward L. Treadwell[5], Yvonne R. S. Sherrer[6], Angelia D. Mosley-Williams[7], Akgun Ince[8], Raj G. Nair[9], Theresa Lawrence Ford[10], Jeffrey Huang[11] and Carl A. Nunziato[11]. [1]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [2]New York University, New York, NY, [3]University of Arkansas, Little Rock, AR, [4]Louisiana State University, New Orleans, LA, [5]East Carolina University, Greenville, NC, [6]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [7]John Dingell VAMC, Detroit, MI, [8]Saint Louis University, St. Louis, MO, [9]Washington Hospital Center, Washington DC, DC, [10]North Georgia Rheumatology, Lawrenceville, GA, [11]Howard University Hospital, Washington, DC

Background/Purpose: Patient reported outcomes in rheumatoid arthritis (RA) are validated tools that assess disease status, are easily administered and used as components of RA composite disease activity scores. Further, patient global score is a criterion for RA remission and recent data suggest a 5mm difference in patient (PT) and physician (MD) global scores significant. Ethnic Minority RA Consortium (EMRAC) is a clinical registry of disease characteristics collected in a "real-world" setting. We evaluated ethnic RA subsets for differences in and associations of PT and MD global scores.

Methods: IRB consented patients enrolled in EMRAC were evaluated. In addition to PT and MD global scores, differences in PT/MD scores (PT-MD >5mm, >10 mm), socio-demographic data, pain scores, parameters of RA disease status (MDHAQ, TJC, SJC) and composite RA disease measures (RAPID3, CDAI, DAS28) were collected. Comparisons of baseline data amongst ethnic groups were analyzed, and correlations of PT, MD global scores and differences in PT/MD scores with years of education, pain, MD-HAQ, TJC/SJC, treatments (DMRAD, biologic) and composite scores in each ethnic group were evaluated.

Results: Analyses of 625 EMRAC patients were performed [Table]. Mostly female, the mean age was 55.5 (16.2) yrs and African Americans (AA) were the majority. RAPID3 composite scores were significantly higher in Hispanics vs all ethnic groups. AA and Hispanics had significantly higher MD- HAQ, pain and PT global scores than Caucasians. Mean difference in PT-MD global scores was 1.5(2.8), but significantly greater in Hispanics and Others compared to AA and Caucasians [2.7(2.5), 2.1(2.6), vs 1.2(2.8), 1.4 (3.0), p=0.005, respectively]. Similarly, PT-MD global score differentials of >5mm and >10mm were more frequent in Hispanics (80,76%) and Others (70,60%), compared to 50% in both AA and Caucasians, (p=0.004, p=0.01,

respectively). In comparison to Caucasians, correlation of PT global scores with disease duration, pain and RAPID3 scores was significantly lower in AA. Age showed less correlation with PT global scores in AA than Hispanics, (p=0.002). Hispanics had the greatest correlation of MD global scores with TJC compared to AA (p=0.001) and Caucasians (p<0.001). While MD global scores correlated less with CDAI in Caucasians than in Hispanics, the RAPID3 showed less correlation in Caucasians vs Other, (p=0.004, p=0.006 respectively). The ESR correlated with MD global in Hispanics vs AA (p=0.004) and Other (p<0.001).

	Total	African-American	Caucasian	Hispanic	Other†	P-value
N	625	228	207	120	70	–
Age (years)	55.5 (16.2)	59.0 (13.9)	54.5 (18.5)	53.5 (15.0)	50.7 (15.7)	<0.001
Duration (years)	10.1 (10.0)	10.5 (10.0)	10.3 (10.8)	8.8 (8.9)	10.1 (9.6)	0.464
Education (years)	14.2 (3.5)	13.6 (3.1)	15.7 (2.9)	12.5 (3.9)	15.0 (3.6)	<0.001
Female [N (%)]	533 (85%)	206 (90%)	171 (83%)	96 (80%)	60 (86%)	0.036*
Patient Global [0-10]	4.5 (2.9)	4.6 (2.8)	3.9 (2.8)	5.3 (2.9)	4.3 (3.3)	0.002
MD Global [0-10]	3.0 (2.3)	3.4 (2.5)	2.7 (2.0)	2.7 (2.0)	2.8 (2.0)	0.176
Patient-MD Global [mm]						
Difference	1.5 (2.8)	1.2 (2.8)	1.4 (3.0)	2.7 (2.5)	2.1 (2.6)	0.005
>5	232 (59%)	109 (56%)	57 (51%)	36 (80%)	30 (70%)	0.004*
>10	213 (54%)	100 (52%)	53 (48%)	34 (76%)	26 (60%)	0.010*
RAPID3 [0-30]	11.8 (7.2)	12.5 (7.0)	10.3 (6.9)	13.7 (7.1)	11.1 (8.0)	0.001
CDAI [0-72]	13.9 (12.3)	13.7 (12.5)	14.6 (11.2)	10.8 (9.5)	15.4 (14.2)	0.216
DAS28 [0-10]	3.9 (1.5)	3.9 (1.5)	3.8 (1.6)	3.0 (1.9)	4.2 (1.5)	0.597
Treatment						
Prednisone [N (%)]	241 (39%)	107 (47%)	66 (32%)	44 (37%)	24 (34%)	0.010*
DMARDs [N (%)]	448 (72%)	183 (80%)	131 (63%)	83 (69%)	51 (73%)	0.001*
Biologics [N (%)]	206 (33%)	50 (22%)	81 (39%)	50 (42%)	25 (36%)	<0.001*

† Asian and Pacific Islanders
*N (%) and Chi-square reported. Otherwise, Mean (SD) and Kruskal-Wallis reported.

Conclusion: In a diverse ethnic RA cohort, significant differences in patient and physician global scores were found. Multiple contributors and confounders may account for these findings, and may vary amongst ethnic subsets. Patient input from multiple ethnic groups is imperative to identify relevant parameters of disease function and standardize patient reported outcomes in the definition of remission.

2103

Reliability of DAS28 in Rheumatoid Arthritis When Based On Patient Self-Assessment of Tender and Swollen Joints. Ole Rintek Madsen and Cecilie Heegaard. Copenhagen University Hospital Gentofte, Hellerup, Denmark

Background/Purpose: Clinical assessment of disease activity is a routine procedure when evaluating individual rheumatoid arthritis (RA) patients in daily practice. Swollen joint count (SJC) and tender joint count (TJC) are traditionally performed by the physician (Ph) or the nurse. Patient (Pa) assessed joint count may be an advantage in the busy clinic. The reliability of DAS28 based on patient self-assessment of tender and swollen joints has not previously been reported. The objective of this study was to examine the agreement between patient and physician evaluation of SJC and TJC, to examine the agreement between physician and patient derived DAS28 and to evaluate the reproducibility of these measures when assessed by the physician and the patient, respectively.

Methods: 30 out-clinic RA patients (mean age 60±15 years) with a disease duration of at least 5 years, who were familiar with physician joint counting and who were considered to have a stable and controlled disease activity were included. 28 TJC and SJC were assessed by patient self-evaluation and by an experienced specialist in rheumatology (the same specialist for all patients) on two different days (median interval 7 days, range 4–10 days) under standardised conditions. Patient global assessment (PaGA) (range 0–100) and CRP (mg/l) were also determined on both occasions. DAS28-CRP with four variables (4V) and three variables (3V) were calculated (1). The association between the duplicate measures was expressed by Pearson's coefficient of correlation (r). Lower and upper limits of agreement (LOA) were calculated as the mean difference between scores of duplicate measurements (the bias) ± 1.96 × SD of these differences (2).

Results: The mean values for SJC, TJC, DAS(4V) and DAS(3V) based on Ph joint count versus Pa self-evaluation at the first visit was 3.7±2.4 vs.

3.6±3.2 (NS), 4.1±5.2 vs. 4.1±4.7 (NS), 3.5± 1.0 vs. 3.6±1.1 (NS) and 3.4±0.9 vs. 3.5±0.9 (NS). Mean values for CRP and PaGA were 7.9±6.5 and 33±28, respectively. Ph-DAS(4V) and Pa-DAS (4V) were highly correlated (r = 0.90, p < 0.0001), and so were corresponding DAS scores based on 3V (r = 0.85, p < 0.0001). The bias for Ph-DAS(4V) vs. Pa-DAS(4V) and associated lower and upper LOA were −0.1 (NS), −0.9 and +0.8, respectively. For DAS(3V) the corresponding results were −0.1 (NS), −1.1 and +0.9. The bias for the duplicate Pa-DAS(4V) assessments was −0.1 (NS) with lower and upper LOA of −0.9 and +0.8; and for Pa-DAS(3V) 0.0 (NS), −0.9 and +0.9. For duplicate Ph-DAS(4V) assessments the bias was 0.0 (NS), and LOA were −1.1 and +1.1. For Ph-DAS(3V) the corresponding figures were: 0.0 (NS), −1.2 and +1.2.

Conclusion: On group level, patient and physician derived DAS scores were in practical identical. Differences between patient and physician derived DAS on the individual level corresponded to the intra-rater agreement for both patients and physicians with LOA approximating ±1. Thus, patient-derived DAS seems to have suitable reliability and may therefore substitute traditional assessment by the physician, at least when the disease activity is stable.

Ref.
1. http://www.das-score.nl/www.das-score.nl/. Accessed 17 June 2011. 2. Altman DG, Bland JM. Lancet 1986; 1: 307-10.

Disclosure: O. Rintek Madsen, None; **C. Heegaard**, None.

2104

Quantitation in Patients with Rheumatoid Arthritis of Inflammation, Joint Damage and "Unexplained Symptoms" (e.g., Fibromyalgia) in Addition to Overall Status, According to 4 Physician Global Estimates Scored 0–10. Isabel Castrejón[1], Martin J. Bergman[2] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Taylor Hospital, Ridley Park, PA

Background/Purpose: A physician global estimate (DOCGL) of patient clinical status in rheumatoid arthritis (RA) is scored by many rheumatologists entirely based on inflammation, but others may incorporate joint damage and chronic pain, which may affect many RA patients. To address this matter, three 0–10 physician global visual analog subscales (VAS) have been developed to estimate levels of *a)* inflammation, *b)* damage, and *c)* "unexplained symptoms" (e.g., fibromyalgia), in addition to *d)* overall status.

Methods: A random visit was analyzed of all 103 patients with RA seen between Dec 2007 and March 2011 in the private practice of one rheumatologist. All patients complete a multidimensional health assessment questionnaire (MDHAQ) at each visit, which includes 10 physical function items (MDHAQ-FN) and a query, "Are you able to deal with feelings of depression or feeling blue?" with 4 response options in the patient-friendly HAQ format: without any difficulty (=0), with some difficulty (=1), with much difficulty (=2), and unable to do (=3). A formal 28 tender and swollen joint count is performed in all patients with RA. Duration of disease, and 4 DOCGL 0–10 VAS estimates for inflammation, damage, "unexplained'" and overall status are assigned by the rheumatologist. Regression models were computed to explain variation in each of the 4 DOCGL estimates according to variables that were correlated significantly with at least one DOCGL estimate, including swollen joint count (SJC28), duration of disease, depression score and MDHAQ-FN scores.

Results: Mean age of the patients was 61.3 years, disease duration 10.3 years, MDHAQ-FN score (0–10) 1.7, RAPID3 (0–30) 8.5, SJC28 4.2, depression score (0–3) 0.37. The 4 DOCGLs were recorded in about 5 seconds. MDHAQ-FN scores were independently statistically significant to explain variation in all 4 DOCGLs (Table: 1st Models); therefore, a second set of regressions not including MDHAQ-FN was computed (Table: 2nd Models). Variation in DOCGL-Inflammation was explained significantly by SJC28, but not by disease duration or depression score, in both models. Variation in DOCGL-Joint Damage was explained significantly by disease duration, but not by SJC28 or depression score, in both models. Variation in DOCGL-"Unexplained Symptoms" was explained significantly only by MDHAQ-FN in the first model, and by depression score, but not SJC28 or disease duration, in the second model. DOCGL-

Overall Status variation was explained significantly by SJC28 (and MDHAQ-FN) in the first model, and SJC28 and depression score in the second model, but not by disease duration.

Table. Multivariate regression models to recognize significant explanatory variables for 4 physician global estimates (DOCGL) for inflammation, damage, "unexplained symptoms" and overall status in 103 patients with RA

	DOCGL: Inflammation		DOCGL: Damage		DOCGL: "Unexplained"		DOCGL: Overall status	
	Coeff	P	Coeff	P	Coeff	P	Coeff	P
First Models								
SJC28	0.09	<0.001	0.01	NS	0.01	NS	0.25	<0.001
Disease Duration	−0.006	NS	0.04	<0.001	0.01	NS		NS
Depression	−0.13	NS	−0.08	NS	0.15	NS	−0.006	NS
MDHAQ Function	0.32	<0.001	0.47	<0.001	0.30	<0.001	1.01	<0.001
Second Models								
SJC28	0.10	<0.001	0.02	NS	0.01	NS	0.26	<0.001
Disease Duration	−0.004	NS	0.04	<0.001	0.002	NS	−0.02	NS
Depression	0.01	NS	0.10	NS	0.28	<0.001	0.57	0.003

Coeff = regression coefficient; MDHAQ = multidimensional health assessment questionnaire; NS = not statistically significant; SJC28 = 28 swollen joint count.

Conclusion: Variation in DOCGLs for inflammation, damage and "unexplained symptoms" are explained significantly by MDHAQ-FN and/or only 1 of 3 other measures: SJC28, disease duration, and patient self-report depression score, respectively. The 4 DOCGLs have face validity, and are recorded in about 5 seconds.

Disclosure: I. Castrejón, None; **M. J. Bergman**, None; **T. Pincus**, None.

2105

Significant Correlation Between ACR/EULAR Remission Criteria and a Simplified Measure Using RAPID3 and Careful Joint Examination without a Formal Joint Count. Martin J. Bergman[1], Isabel Castrejón[2] and Theodore Pincus[2]. [1]Taylor Hospital, Ridley Park, PA, [2]NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Definitions for the classification of "remission" have been proposed by ACR/EULAR: Boolean and SDAI<3.3. These criteria require a formal tender and swollen joint count, a patient global assessment, a C-reactive protein (CRP) and (for SDAI definition) a physician global assessment. Rheumatologists usually perform a careful joint examination, but do not perform formal joint counts at most visits, and CRP often is missing at the time of the visit. RAPID3, a patient reported disease activity measure, is correlated significantly with DAS28, CDAI, and other RA indices and can be calculated in less than 5 seconds, compared to 90 seconds to perform a formal joint count. Simply counting >1 swollen joint can be performed without interfering with usual patient interactions, unlike a full formal joint count. We sought to analyze the capacity of a novel description of remission in RA using RAPID3 and the presence or absence of greater than 1 swollen joint, and compared results to ACR/EULAR remission.

Methods: All patients (with any diagnosis) in a solo Rheumatology practice are given an MDHAQ to be completed by the patient in the waiting area and RAPID3 is calculated before the patient is seen. Patients are instructed to obtain standard laboratory tests approximately 1 week prior to the visit, including a CRP, so that CRP values will be available at the time of the visit. A formal joint count (28 tender/28 swollen) is performed in all RA patients, and, a physician global score is assigned. A random patient visit was selected which included all measures. Patients were identified as in remission or not, according to ACR/EULAR Criteria or "RAPID3RJ" defined as a RAPID3 score <=3.0 AND ≤1 swollen joint. Comparisons of the two descriptions were analyzed using Spearman correlations and kappa statistics.

Results: 191 patients with RA were identified. Complete data were available in 122 patients. ACR/EULAR remission criteria were met in 27 of 122 patients; RAPIDRJ1 in 23 patients (Table 1). 22 patients were in agreement using both measures; 5 in ACR/EULAR were not in RAPIDRJ, 1 in RAPIDRJ were not in ACR/EULAR. Spearman rho was 0.86 (p<0.0001); Kappa=0.85 (substantial agreement).

Table 1.

RAPID3≤3 + SWOLLEN JOINT COUNT ≤1 (RAPIDRJ1)	ACR/EULAR REMISSION CRITERIA		
	NO	YES	TOTAL
NO	94	5	99
YES	1	22	23
TOTAL	95	27	122

Kappa=0.85 p<10⁻⁴ Spearman rho=0.86

Kappa=0.85 $p<10^{-4}$ Spearman rho=0.86

Conclusion: The classification of remission can be made using a simple patient questionnaire and requiring only the identification of ≤1 swollen joint. Future studies are planned to determine if this new definition of remission will also predict X-ray progression, one of the criteria for the development of the ACR/EULAR criteria.

Disclosure: **M. J. Bergman**, None; **I. Castrejón**, None; **T. Pincus**, None.

2106

Patient Characteristics Associated with Discrepancies in Evaluator-Reported and Patient-Reported Outcomes in U.S. Veterans with Rheumatoid Arthritis. Archana Jain[1], Rebecca Belsom[1], Jeffrey Curtis[2], Shuo Yang[2], Ted R. Mikuls[3], Lang Chen[2] and Angelo L. Gaffo[4]. [1]University of Alabama, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [4]Birmingham VA Medical Center and University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Validated tools that incorporate evaluator and patient reported outcomes (PROs) are used for guiding therapy in patients with rheumatoid arthritis (RA). PROs used in RA evaluation may be influenced by co-morbidities (i.e. diabetes, coronary artery disease, congestive heart failure). We hypothesized that these co-morbidities lead to discrepancies between the tender and swollen joint counts and between patient- and evaluator-reported global assessments of RA activity.

Methods: We performed a cross-sectional analysis at baseline visit for all patients enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry with linkage to the VA Decision Support System (DSS). Patient global assessments (PGA) and evaluator global assessments (EGA) of disease activity distribution were divided into tertiles. PGA and EGA values in the same tertiles were defined as concordant, whereas the values in different tertiles were defined as discordant. Swollen joint count (SJC) to tender joint count (TJC) ratio of ≥ 0.8 was defined as concordant, whereas ratio < 0.4 was defined as discordant. Demographic characteristics and frequencies of DSS-derived co-morbidities in patients with concordant and discordant PGA and EGA; and TJC and SJC respectively were compared. Additionally, a longitudinal analysis of the subset of patients with at least 2 visits was performed to determine which ratio of SJC/TJC was associated with a decision to switch to a new biologic agent in patients with at least moderate disease activity (DAS28ESR > 3.2).

Results: 1305 unique patients with linkage to DSS were identified. The mean age was 68.2 years and 90.5% were males. PGA and EGA data was available for 529 patients. There were 95 (18%) patients with a discordant PGA worse than EGA, 123 (23.3%) with a discordant EGA worse than PGA, and 311 (58.8%) patients with concordant PGA and EGA. There was no significant difference in socio-demographics and prevalence of co-morbidities in patients with discordant worse PGA subgroup as compared to patients with concordant PGA and EGA. SJC and TJC data was available for all 1305 patients. There were 825 (63.2%) patients with SJC/TJC < 0.4, 326 (25%) patients with SJC/TJC ≥0.8, and 154 (11.8%) patients in-between these categories. Patients with SJC/TJC ratio < 0.4 were older than those with ratio ≥0.8 (68.8 yrs vs 67.2 yrs, p 0.02). There were no other significant differences in socio-demographic variables or prevalence of co-morbidities. Among all VARA patients treated with biologics who were in moderate or high disease activity (DAS28ESR > 3.2) at a VARA visit (n=1365 visits), approximately 7% were switched at that visit to another biologic. The likelihood of switching for patients with a SJC/TJC > 0.4 was 2.5 (1.5–4.4) fold greater compared to those with a SJC/TJC ratio ≤ 0.4.

Conclusion: There was no association of co-morbidities with discordantly high PGA or low TJC/SJC ratio. A SJC/TJC ratio < 0.4 appears useful to identify patients whose patient reported outcome data is unduly affected by factors other than RA and might be used to screen for patients not appropriate for traditional treat-to-target strategy cutpoints.

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2107

Assessing Subclinical Synovitis in Rheumatoid Arthritis: Arthrosonographic Findings in Patients with Good Response to Therapy. Matthias Witt, Felix Mueller, Axel Nigg, Christiane Reindl, Hendrik Schulze-Koops and Mathias Grunke. Division of Rheumatology and Clinical Immunology, Medizinische Klinik und Poliklinik IV, University of Munich, Munich, Germany

Background/Purpose: Treat-to-target is a key principle in rheumatoid arthritis. Composite scores such as the DAS-28 help to monitor disease activity and response to therapy. However, in patients without clinical activity, ultrasound examination may reveal subclinical synovitis. While some findings have prognostic relevance, little is known about the relevance of borderline (grade 1) ultrasound findings in asymptomatic joints of patients with good response to therapy. This study was undertaken to give a sonographic analysis of subclinical synovitis in this subset of RA patients.

Methods: Patients with newly diagnosed RA were included. At baseline, patients were assessed by clinical examination and ultrasound. Ultrasound was performed with grey scale (GSUS) and power Doppler (PDUS) in the metacarpophalangeal, proximal interphalangeal, metatarsophalangeal and wrist joints, using the dorsal approach in each joint. Synovitic findings in GSUS and PDUS were graded semiquantitatively from 0 to 3 as specified before. After the initial assessment, patients were treated with anti-rheumatic drugs according to national guidelines and were seen on a regular outpatient basis. Clinical and sonographic reevaluation together with assessment of EULAR responses was performed at month 6.

Results: Sofar, 40 patients were included into this ongoing study. Patients' characteristics are consistent with a typical RA cohort. By month 6, good, moderate and no EULAR responses were reached by 65.7%, 25.7% and 8.6% of the patients, respectively. In the group with good EULAR response, 7.2% of the joints had clinical synovitis, while 92.8% of the joints were asymptomatic. In the asymptomatic group, ultrasound detected subclinical synovitis in 11.1% in GSUS and in 3.8% in PDUS with significant differences for both modalities in comparison to the clinically apparent group. The sonographic findings in the subclinical group could be classified as grade 1, grade 2 and grade 3 in 78.9%, 19.7% and 1.3% in GSUS, and in 76.9%, 23.0% and 0% in PDUS. Grade 1 GSUS and PDUS findings were found significantly more often in the subclinical group, while non-grade 1, i.e. grade 2 and grade 3 GSUS and PDUS findings were significantly more prevalent in the clinically apparent group.

Conclusion: More than 90% of the joints were asymptomatic in the group with good response. Ultrasound of these joints revealed subclinical synovitis in 11.1% in GSUS and in 3.8% in PDUS. Concerning the pattern of ultrasound findings, grade 1 findings were most prevalent in both modalities and were found significantly more often than in the clinically apparent group. Of note, grade 1 GSUS findings are also found in healthy individuals and hence, the clinical relevance seems to be questionable. While persistent PDUS activity in general has been linked to clinical relapses in asymptomatic patients, the specific relevance of grade 1 PDUS findings needs to be further clarified. Taken together, these data indicate that the relevance of subclinical synovitis may be overestimated in asymptomatic joints of patients with a good clinical treatment response. In this situation ultrasound seems to add little to the clinical overall impression. Further analysis is underway to clarify the role of grade 1 PDUS findings.

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2108

Identification of Four Parameters That Drive the Discordance Between the Patient and Physician Global Assessment in Rheumatoid Arthritis. William Bensen[1], Denis Choquette[2], Milton F. Baker[3], Susan M. Otawa[4] and Hayssam Khalil[4]. [1]St. Joseph's Hospital and McMaster University, Hamilton, ON, [2]University of Montreal, Notre-dame Hospital, Montreal, QC, [3]University of Victoria, Victoria, BC, [4]Janssen Canada Inc, Toronto, ON

Background/Purpose: Patient (PtGA) and physician (MDGA) global assessment of disease activity are standard outcome measures used to ascertain physician and patient subjective perception of disease activity in rheumatoid arthritis (RA). Given that the PtGA and MDGA measure the same construct from two different perspectives, assessing their discordance may provide valuable insight on patient and physician differences with respect to the relative importance placed on specific disease parameters.

Methods: BioTRAC is an ongoing Canadian registry of patients initiating treatment with infliximab or golimumab as first biologics. PtGA and MDGA were measured at baseline using a 10cm VAS. Using tertiles of the baseline MDGA-PtGA distribution every patient was classified as having higher assess-

ment than the physician (range: −10.0 to −0.5), agreement (range: −0.4 to 1.1) or lower assessment than the physician (range: 1.2 to 8.0).

Results: 841 patients with baseline data for both PtGA and MDGA were included. Among these 623 (74.1%) were female, mean age was 57.0 yrs and mean disease duration was 9.8 yrs. Mean (SD) PtGA and MDGA were 6.1 (2.4) and 6.5 (2.1), respectively, and the mean (SD) PtGA – MDGA was 0.4 (2.4) with a median of 0.3; for 6.4% of the patients the PtGA-MDGA was nil.

Significant differences between patients with lower, equal or higher assessment relative to the physician assessment were identified. When compared to patients with higher PtGA relative to MDGA, patients with lower assessment of their disease activity had lower morning (AM) stiffness, pain, and HAQ-DI but higher SJC (Table 1). AM stiffness, SJC, TJC, and HAQ-DI were highest in patients with PtGA-MDGA agreement. Age, gender, and SJC/TJC ratio were not different for the three groups. Linear regression using backwards selection identified pain (P<0.001), SJC (P<0.001), and HAQ-DI (P=0.056) as independent predictors of PtGA-MDGA.

Table. Patient Baseline Characteristics by Degree of Difference Between MDGA and PtGA

Mean (SD)	Lower PtGA vs. MDGA[1]	Higher PtGA vs. MDGA[2]	P-Value[3]
Age: Years	56.9 (13.8)	57.2 (13.2)	0.815
Disease Duration: Years	9.0 (8.3)	10.0 (10.5)	0.478
AM Stiffness: min	62.0 (44.5)	70.7 (43.2)	*0.019*
Pain: VAS mm	42.0 (22.4)	67.4 (21.2)	*<0.001*
SJC-28	11.1 (7.0)	9.1 (6.4)	*<0.001*
TJC-28	12.0 (8.1)	11.4 (7.3)	0.326
SJC/TJC	1.1 (1.1)	1.1 (1.6)	0.805
HAQ-DI	1.42 (0.73)	1.69 (0.65)	*<0.001*

[1] MDGA-PtGA range: 1.2 to 8.0
[2] MDGA-PtGA range: −10.0 to −0.5
[3] P-Value was assessed with a t-test for independent samples

Conclusion: The relative importance of morning stiffness, pain, HAQ, and SJC in assessing disease activity may be different between patients and physicians. These results have implications for development of assessment tools that better represent both patient and physician perspectives of disease activity.

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2109

Discrepancy Between Patient and Physician Global Assessments Over Time in Early Rheumatoid Arthritis. Pooneh Akhavan[1], Vivian P. Bykerk[2], Juan Xiong[3], Janet Pope[4], Boulos Haraoui[5], J. Carter Thorne[6], Gilles Boire[7], Carol A. Hitchon[8], Diane Tin[6], E. Keystone[3] and CATCH[9]. [1]University of Toronto, Toronto, ON, [2]Hospital for Special Surgery, New York, NY, [3]Mount Sinai Hospital, Toronto, ON, [4]Schulich School of Medicine and Dentistry, Western University, London, ON, [5]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [6]Southlake Regional Health Centre, Newmarket, ON, [7]CHUS - Sherbrooke University, Sherbrooke, QC, [8]University of Manitoba, Winnipeg, MB, [9]Toronto

Background/Purpose: Discrepancy between patient (PGA) and physician (MDGA) global assessments in RA can adversely affect therapeutic decisions in many cases. The purpose of this study is to assess whether baseline PGA-MDGA discrepancy predictors change after one year in patients with early RA.

Methods: Patients with RA were recruited from the Canadian Early Arthritis Cohort (CATCH) a prospective cohort where data is collected according to a standardized protocol. CATCH patients were considered for this analysis if they initiated DMARDs at baseline, were biologic naïve and had ≥12 months follow up. PGA and MDGA were scored out of 100. PGA-MDGA discrepancy was calculated by subtracting MDGA from PGA at baseline. A clinically meaningful discrepancy was considered a difference of ≥30 (PGA-MDGA > 30: Positive (Pos) and PGA-MDGA < −30: Negative (Neg)). Linear regression analysis was used to evaluate factors associated with the PGA-MDGA discrepancy, MDGA and PGA when adjusted for potential confounders at baseline and at 1 year separately. To address the variability of the rheumatologists' influence on the discrepancy we included CATCH recruiting "site" as one of the predictors. Sites with more than 25 patients were considered for analysis.

Results: Baseline characteristics of the 480 RA patients who met inclusion criteria for this study included: 74% female, mean (SD) age 54(14.5), disease duration 0.5(0.24) years, TJC 8.6 (6.8), SJC 8.7 (6.3) (of 28), DAS28 5.2 (1.4), ESR 28.6 (22.6), CRP 15.0 (19.6) mg/L, PGA 58.7 (29.4) and MDGA 51.6 (24.8). Discrepancy rates are shown in Table 1. At baseline significant predictors of PGA-MDGA were Pain (p<.0001), SJC (p<.0001), TJC (p=0.008), ESR (p=0.02) and "site" (p=0.0006). At 12 months significant predictors of PGA-

MDGA were Pain (<.0001), SJC (p<.0001), TJC (p=0.02), age (0.04) and "site" (p=0.0002). At baseline PGA was significantly associated with pain, HAQ, SJC, age and "site" and at 12 months with pain and "site" only. Baseline factors associated with MDGA were SJC, TJC, pain, ESR, HAQ and "site" and at 12 months ESR and HAQ were no longer significant.

Table 1. Discrepancy rates at baseline and 12 months

	No discrepancy	Positive discrepancy	Negative discrepancy
Baseline	65%*	25%	10%
12 months	73%*	23%	4%

(*P<0.05)

Conclusion: PGA-MDGA discrepancy rate decreases over time but the pattern remains the same in early RA. Pain and SJC significantly influence PGA-MDGA discrepancy at baseline and this persists after one year when the disease is better controlled. Although previous studies have emphasized the pain score as a major factor affecting the PGA-MDGA discrepancy; we have also demonstrated a significant influence of the SJC.

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Prospective Assessement of Bone Texture Parameters At the Hand in Rheumatoid Arthritis. Laetitia Sparsa[1], Sami Kolta[1], Karine Briot[1], Simon Paternotte[1], Rashra Masri[2], Damien Loeuille[2], Piet P. Geusens[3] and Christian Roux[1]. [1]Paris Descartes University, Cochin hospital, Paris, France, [2]CHU Brabois, Vandoeuvre les Nancy, France, [3]Maastricht University, Maastricht, Netherlands

Background/Purpose: Bone and cartilage loss and destruction is associated with rheumatoid arthritis (RA) and inflammation. There is a need for tools for prediction of potential severe patients with poor outcome. The BMA device (D3ATM Medical Systems, Orleans, France) is a high resolution X-ray technique, used to image bone and joints, and to measure bone texture parameters including the fractal dimension (Hmean). The aims of this study were to evaluate, by BMA analysis, the metacarpal bone texture in a cohort of 165 RA patients after 1 year of follow up, and to assess the relationship between these parameters and RA disease parameters at baseline and over 1 year.

Methods: Patients with RA according to ACR criteria were included. They were assessed every 6 months over 1 year, in the context of a prospective study conducted in Maastricht. For this substudy, activity of the disease was assessed by erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and Disease Activity Score (DAS 28) performed at each visit. Radiographic bone damage is assessed using hand and feet conventional posterior-anterior radiographs at baseline and on a 1-year basis The bone texture parameters were evaluated on the second and third metacarpal heads of the left hand (MCP2 and MCP3) using BMA device, with standard acquisition at baseline, 6 and 12 months. A single investigator performed all the analyses, with standardized position of regions of interest in the bones. The calculated parameter was Hmean as an approach to bone roughness.

Results: 165 patients were included 57 men and 108 women, mean age 63.63 years [33–89]. The mean disease duration was 9.67 years [2–36]. Among the 138 cases where rheumatoid factor results were available, 75 were positive and among the 11 cases where anti CCP antibodies were available only 6 were positive. 53 patients were followed using BMA device and a total of 632 joints were studied. 24/53 (45.3%) patients had RA damage (erosions, joint space narrowing). The mean DAS28 score was 3.34 [0.63–7.35]. Twenty four patients were receiving bisphosphonate during the study. Hmean was similar in MCP2 and MCP3 at baseline: 0.411 ± 0.038 and 0.412 ± 0.043 respectively; H mean MCP2 was correlated with disease duration (-0.17, p=0.03). There was an increase in H mean MCP2 (+ 1.0 % p=0.0004) over 1 year. ESR and CRP were correlated with H mean MCP3 at baseline (-0,15, p=0.055; −0.15 p=0.06) and 6 months (-0.22 p=0.006, −0.25 p=0.002 respectively). DAS was correlated with H mean MCP3 at 6 months (-0.14, p=0.07) and H mean MCP2 at 12 months (-0.16 p=0.04).

Conclusion: This new high resolution digital X-ray device provides bone texture parameters of metacarpal heads in RA patients. This preliminary analysis suggests that these parameters measured at the metacarpal heads are influenced by disease duration and activity.

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Diagnostic Performance of the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis: Systematic Literature Review and Meta-Analysis. Garifallia Sakellariou[1], Carlo Alberto Scirè[2], Roberto Caporali[1] and Carlomaurizio Montecucco[3]. [1]Division of Rheumatology, University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy, [2]Epidemiology Unit, Italian Society for Rheumatology (SIR), Milano, Italy, [3]University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Background/Purpose: in 2010 ACR and EULAR proposed new classification criteria for rheumatoid arthritis (RA). This new set of criteria has been tested in several external populations. The aim of the present study was to summarize the available evidence performing a systematic literature review and meta-analysis of their diagnostic accuracy.

Methods: We searched PubMed, EMBASE, Cochrane and screened the abstracts of the ACR and EULAR congresses from 2010 to 2012. The inclusion criteria were: 1) population of patients with recent onset arthritis, at least one swollen joint, no alternative diagnosis; 2) The ACR/EULAR 2010 criteria (cut-off of 6) as index test; 3) The use of methotrexate (MTX) or disease modifying antirheumatic drugs (DMARDs) as reference standard; 4) Diagnostic accuracy, case control, prospective or retrospective cohort studies; 5) Sufficient data to build a 2×2 table of diagnostic accuracy. Sensitivity (Se) and specificity (Sp) were calculated for each study, data were pooled using a hierarchical summary receiving operator characteristic curve (HSROC) with confidence and prediction intervals. Three separate meta-analysis were performed, considering MTX, DMARDs or their combination as reference standard. To test the robustness of the results, diagnostic odds ratio (DOR) was calculated and an exploratory meta-regression was performed for the analysis of MTX+DMARDs, considering as confounders symptom duration, rheumatoid factor, anti cyclic citrullinated petide antibodies and the timing of assessment of the reference standard. The risk of bias of the included studies was evaluated using the modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) proposed by the Cochrane collaboration.

Results: A total of 1,257 references were retrieved, after screening title and abstract 4 full papers were included, together with 6 abstracts from the ACR and EULAR congresses. Using MTX as reference standard, the first meta-analysis showed: Se (95% confidence interval, CI) was 0.73 (0.64,0.80), Sp was 0.74 (0.68,0.79), positive likelihood ratio (LR+) (95% CI) was 2.85 (2.53,3.22), negative LR (LR-) 0.35 (0.27,0.45), DOR 8.03 (6.4,10.09). Using DMARDs as reference standard, Se 0.80 (0.74,0.85), Sp was 0.61 (0.56,0.67), LR+ 2.11 (1.92,2.32), LR− 0.31 (0.25,0.38), DOR 6.74 (5.49,8.28). Using the combination of MTX and DMARDs as reference standard, Se was 0.76 (0.71,0.81), Sp was 0.69 (0.61,0.75), LR+ 2.48 (2.08,2.95), LR− 0.33 (0.29,0.38), OR 7.38 (6.33, 8.62). Meta-regression demonstrated no influence of the possible confounders on the results. The risk of bias was low or unclear for most of the studies.

Conclusion: the new classification criteria have a good sensitivity, while specificity is lower. The development of an optimal diagnostic tool for RA is limited by the absence of a real reference standard. In fact, also the decision to start MTX or DMARDs depends on the rheumatologist and the setting. However, these results confirm the mainly classificative and not diagnostic role of the criteria.

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Combination of Magnetic Resonance Imaging (MRI)-Proven Osteitis with 2010 RA Classification Criteria Improves the Diagnostic Probability of Rheumatoid Arthritis (RA). Mami Tamai[1], Yoshikazu Nakashima[1], Takahisa Suzuki[2], Yoshiro Horai[2], Akitomo Okada[2], Junko Kita[2], Shin-ya Kawashiri[2], Naoki Iwamoto[1], Kunihiro Ichinose[2], Kazuhiko Arima[1], Hideki Nakamura[1], Tomoki Origuchi[2], Masataka Uetani[2], Kiyoshi Aoyagi[2], Katsumi Eguchi[3] and Atsushi Kawakami[2]. [1]Nagasaki University, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Sasebo City General Hospital, Sasebo, Nagasaki, Japan

Background/Purpose: In the articles of 2010 rheumatoid arthritis (RA) classification criteria, it is stated that additional evidence of joint injury from other imaging techniques such as magnetic resonance imaging (MRI) may be used for confirmation of the clinical findings. Considering the impact of MRI on the clinical assessment of inflammatory arthritides, it would be desirable to address the algorithm toward earlier classification of RA by the MRI findings combining to 2010 RA classification criteria. We have tried to investigate whether MRI-proven joint injury assist the diagnostic performance of 2010 RA classification criteria toward early arthritis patients.

Methods: Two hundred patients with early arthritis patients, whose median duration of symptoms at entry is 3 months, were consecutively enrolled into this study. Patients, whose diagnoses were compatible as other rheumatic diseases than RA or obvious to plain radiographic erosion at entry, were excluded in the present study. All of the patients were examined by Japan College of Rheumatology (JCR)-certified rheumatologists and considered as RA potentially at entry. Patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. All of the subjects had been examined by physical examination, blood tests, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI and plain radiograph of both wrist and finger joints at the same day. Gold standard RA in the present study was defined as the patients received disease-modifying antirheumatic drugs (DMARDs) therapy during the first year. Patients were evaluated by the 2010 RA classification criteria at the initial visit. Diagnostic performance of 2010 RA criteria combined with or without the finding of MRI-proven joint injury were investigated. One hundred fifteen were diagnosed as gold standard RA whereas 85 were not.

Results: 2010 RA classification criteria classified RA at sensitivity 59.8%, specificity 80.7%, positive predictive value (PPV) 81.4%, respectively. Osteitis was the most specific MRI finding toward gold standard RA (sensitivity 45.3%, specificity 90.4%, PPV 86.9%) as compared with symmetrical synovitis and bone erosion. We have proposed the decision tree algorithm of 2010 RA classification criteria combined with MRI-proven osteitis which demonstrate initially applied 2010 RA classification criteria, and if the patients do not fulfill 2010 RA classification criteria, MRI-proven osteitis rule is introduced. The tree algorithm has shown to differentiate the patients more efficiently compared with 2010 RA classification criteria alone as sensitivity 74.4%, specificity 94.0%, PPV 94.6%, respectively.

Conclusion: The present data indicate that combination of MRI-proven osteitis with 2010 RA classification criteria improves the diagnostic probability of RA at earlier stage.

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Performance of the New ACR/EULAR Classification Criteria for Rheumatoid Arthritis - A Systematic Literature Review. Helga Radner[1], Josef Smolen[2] and Daniel Aletaha[3]. [1]Medical University Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [3]Medical University of Vienna, Vienna, Austria

Background/Purpose: Since introduction of the new ACR/EULAR classification criteria of rheumatoid arthritis (RA) several studies were published validating the new criteria in different cohorts using different approaches and goldstandards. Performing a systematic literature review we want to summerize published studies and assess the sensitivity and specificity of the new ACR/EULAR classification criteria in comparison to the 1987 ACR criteria using different cohorts and goldstandards.

Methods: A systematic literature review was performed in the three main databases (Medline, EMBASE and Cochrane Central). Information of all included studies were extracted and raw data of patients fulfilling different criteria and goldstandards were extracted in order to calculate sensitivity and specificity, positive and negative predictive values as well as standard deviations. Taking into consideration heterogeneity meta-analyses were performed if possible.

Results: In total 1080 articles were retrieved by the search strategy, of which 14 studies (total 6200 patients) could be included. 9 studies included early arthritis patients, 3 established RA, 1 undifferentiated arthritis (UA) and 1 patients with joint symptoms. 5 studies used initiation of MTX (range sensitivity (sens) 0.68 to 0.88 and specificity (spec) 0.3 to 0.72;pooled (95%CI): sens 0.86 (0.84–0.88); spec 0.49 (0.46–0.52)), 3 studies initiation of DMARD (range sens 0.62 to 0.85 and spec 0.38 to 0.78; pooled (95%CI): sens 0.80 (0.78–0.82); spec 0.61 (0.57–0.64)), and 6 studies used expert opinion as goldstandard, out of them 3 in early arthritis patients (range sens 0.62 to 0.91; spec 0.35 to 0.78; pooled (95%CI): sens 0.87 (0.85–0.89) spec 0.45 (0.41–0.49)); 2 in established RA (sens 0.66 to 0.78); 1 in UA (sens 0.47, spec 0.71). Two studies used expert opinion and DMARD as goldstandard (sens 0.58 to 0.74, spec 0.8 to 0.86). Considering different joint counts (JC) no differences of sens and spec could be observed (28JC 3 studies (sens 0.83 to 0.86; spec 0.37 to 0.6); 40JC 3 studies (sens 0.64 to 0.88; spec 0.53 to 0.76); 66/68JC 7 studies (sens 0.48 to 0.88; spec 0.54 to 0.83) no pooling due to different goldstandards/cohorts).

Seven studies directly compared 2010 with 1987 criteria using different goldstandards showing an slightly lower overall specificity (mean delta Sensitivity 2010 Π Sensitivity 1987 criteria = −0,05) but higher overall sensitivity (mean delta Sensitivity 2010–Sensitivity 1987 criteria =+0,13) of the new 2010 criteria compared to the 1987 criteria (**figure 1**).

STUDY	Cohort	N	Goldstandard	1987 criteria		2010 criteria	
				sens	spec	sens	spec
Van de...	early arthritis	330	DMARD use + Expert opinion	0,84	0,8	0,58	0,80
Kaarela...	juba synovcom	424	...	0,87	0,03	0,73	0,71
...	early arthritis	145	MTX use + ...	0,42	0,8	0,58	0,72
...	early arthritis	428	MTX use + ...	0,70	0,53	0,85	0,5
Naum...	early arthritis	434	MTX use + ...	0,80	0,3	0,88	0,37
Cram...	early arthritis	344	Expert opinion after 3.0 ...	0,57	0,75	0,6	0,80
... Leiden	early arthritis	338	MTX use + MTX after 1 year	0,80	0,74	0,84	0,8

◇ Difference sens of dg by 2010 – de-criteria's sens
◆ Difference of spec of dg by 2010 – Specificity's spec

Favours 1987 criteria | Favours 2010 criteria

-02   -01   0   01   02

Conclusion: The new ACR/EULAR classification criteria seems valid independent of goldstandard and cohort used. Compared to the 1987 criteria they show higher sensitivity and almost equal specificity.

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Joint Damage Progression in Rheumatoid Arthritis: Role of the HLA-DRB1 Shared Epitope and Anti-CCP. Jose Felix Restrepo[1], Inmaculada del Rincon[1], Roy W. Haas[1], Daniel F. Battafarano[2] and Agustin Escalante[1]. [1]University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]Brooke Army Medical Ctr, San Antonio, TX

Background/Purpose: The HLA-DRB1 shared epitope (SE) and antibodies to cyclic citrullinated peptides (anti-CCP) are important to the susceptibility to rheumatoid arthritis (RA), and are thought to be involved in pathogenesis. Clinically, their presence identifies patients with more severe disease. Few studies have examined their combined effect on RA outcome. We studied a large cohort of RA patients focusing on the association of radiographic joint damage with the presence of the SE and anti-CCP.

Methods: A radiograph of both hands and wrists was used to measure erosions and joint-space narrowing in patients with RA, using the technique developed by Sharp et al. The SE was genotyped using sequence-specific primer amplification, and anti-CCP was measured using ELISA. An anti-CCP concentration of 20 IU or higher was considered-positive. Patients were followed over time with repeated hand radiographs. We used generalized estimating equations (GEE) with the Sharp score as a dependent variable to examine association between the SE and anti-CCP.

Results: We studied 1,328 RA patients. Of these, 1,264 (95%) had hand radiographs, as well as SE and anti-CCP results. There were 3,824 radiographs, or 3.0 films per patient, over 8,700 patient-years of observation (6.9 years per patient). The Sharp score at baseline was 47 (SD 61, range 0 to 294). The Sharp score progressed at a rate of 4.09 units per year (95% CI 3.96, 4.22) in the cohort considered as a whole. Among the 157 patients who were negative for both the SE and anti-CCP, the Sharp score progressed at a rate of 2.76 units per year (2.44, 3.08). Among 449 patients who were positive for either the SE or the anti-CCP, the Sharp progression rate was 4.02 (3.82, 4.22, P < 0.001). Among 658 patients who were positive for both the SE and anti-CCP, Sharp progression rate was 4.50 (4.34, 4.67, P < 0.001). We also examined at what point in time the mean Sharp score diverged significantly between the groups defined by SE and anti-CCP. Compared to patients who had negative SE and negative anti-CCP, patients who had positive SE and/or positive anti-CCP did not develop significantly higher Sharp score until 17 years of disease duration had passed.

Conclusion: Joint damage progressed more rapidly among RA patients who had positive SE and/or anti-CCP. However, it was not until well into the second decade of disease that the amount of damage in the patients with positive SE and/or positive anti-CCP became significantly different from those in whom these markers were negative.

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Altered Serum Levels of Bone Metabolism Markers in Rheumatoid Arthritis. Lang Jing Zhu, Xia Ouyang, Lie Dai, Dong Hui Zheng, Ying Qian Mo, Xiu Ning Wei, Chan Juan Zou and Bai Yu Zhang. Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease leading to joint destruction and disability. Previous studies showed abnormal activation of osteoclasts as well as altered skeletal bone metabolism and co-morbid conditions in RA. Tumor necrosis factor receptor-associated factor (TRAF) 6 is one of the critical modulator in differentiation and resorption activity of osteoclasts. New biochemical markers of bone formation showed contradictory results in different studies, although markers of bone resorption have shown significant increase in patients with RA. This study aimed to evaluate serum levels of bone metabolism markers and their correlation with synovial TRAF6 expression, as well as clinical and biological parameters that reflect the activity and severity of RA.

Methods: Serum C-terminal telopeptide of type I collagen (CTX-I), N-terminal propeptide of type I collagen (PINP) and N-terminal midfragment of Osteocalcin (N-MID.OC) was tested by chemiluminescence in 30 patients with active RA, as well as 60 age and gender matched healthy controls. Synovial tissue samples were obtained by needle biopsy from

RA patients, and semiquantitative analysis was performed to evaluate the intensity of TRAF6+ cells. Serological and clinical parameters that reflect the activity and severity of RA, as well as radiographic joint destruction (Sharp score) were collected simultaneously.

Results: Serum CTX-I level was significantly higher in RA patients compared with healthy controls (0.56 ± 0.37 vs. 0.34 ± 0.21, p=0.004). No significant difference was found in serum PINP or N-MID.OC level. Spearman's correlation test showed serum PINP and N-MID.OC level of RA patients correlated negatively with morning stiffness (r=−0.450 and −0.267, p=0.016 and 0.046, respectively) and pain VAS (r=−0.247 and −0.354, p=0.049 and 0.045, respectively), but correlated positively with gripping power (r=0.676 and 0.621, p=0.005 and 0.006, respectively). Significant correlation was found between synovial TRAF6 expression and serum PINP level (r=0.381, p=0.038), as well as serum N-MID.OC level (r=0.345, p=0.042). Subanalysis of lining and sublining TRAF6 expression showed that PINP correlated significantly with sublining TRAF6 expression (r=0.353, p=0.046), N-MID.OC correlated significantly with lining TRAF6 expression (r=0.407, p=0.025).

Conclusion: Increased bone resorption and altered skeletal bone metabolism was found in RA. PINP and N-MID.OC may be a helpful biomarker for disease activity in RA. Synovial TRAF6 expression in RA correlated significantly with serum PINP and N-MID.OC level and maybe involved in the pathogenesis of bone metabolism disbalance in RA.

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The Associations of HLA-DR Shared Epitope Alleles and Serum Cytokines Among Postmenopausal Women with Rheumatoid Factor and Anti-Citrullinated Protein Antibody-Positive Rheumatoid Arthritis.
Mehret Birru Talabi[1], Rachel Mackey[2], Larry W. Moreland[2], Jan Dorman[3], Kevin D. Deane[4], Jeremy Sokolove[5], V. Michael Holers[4], William H. Robinson[6], Brian Wallitt[7] and Lewis Kuller[2]. [1]University of Pittsburgh Medical Center, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Nursing, Pittsburgh, PA, [4]University of Colorado School of Medicine, Aurora, CO, [5]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [6]Stanford University, Palo Alto, CA, [7]Washington Hospital Center, Baltimore, MD

Background/Purpose: This study evaluates associations between HLA-DRβ1 associated shared epitope (SE) alleles and cytokines among postmenopausal women with rheumatoid arthritis (RA). Presence of 1 or 2 versus absence of SE alleles is associated with more erosive RA in a number of studies. Fewer studies have examined if the number of SE alleles is associated with markers of inflammation.

Methods: Participants (n=2877) were enrolled in a substudy of the Women's Health Initiative, and reported RA on questionnaires. Rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), HLA- DRβ1 genotyping, and cytokines (IL-1B, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-12, IL-17, TNFα, MCP-1, MIF-1, IFN-Y, GCSF) were measured. SEs included QKRAA, KRRAA, RRRAA. Kruskal-Wallis tests were used to evaluate median cytokine concentrations by SE allele frequencies.

Results: Women included in this analysis (n=591) were RF and ACPA-positive. N=208 had 0 SE alleles, n=288 had 1 SE, and n=95 had 2 SEs. Several cytokines showed a dose-response increase from 0 to 1 to 2 SEs (underlined in table), with IL-2 and IL-6 showing the most marked differences (p<0.05 for differences between SE categories).

Table 1. Median (Interquartile Range) Cytokine Levels by Number of Shared Epitopes in ACPA/RF+ Women

Cytokines	Shared Epitopes			p-value
	0 (n=208)	1 (n=288)	2 (n=95)	
IL-2	11.3 (4.3–35.1)	12.7 (5.6–41.6)	19.0 (6.4–60.6)	0.047
IL-6	11.8 (6.4–32.6)	15.3 (8.5–35.3)	20.3 (10.1–56.5)	0.003
IFN-Y	68.8 (39.1–171.2)	77.4 (43.8–196.8)	87.7 (48.6–214.6)	0.22
MCP1	20.2 (13.4–33.1)	21.5 (15.1–36.7)	23.6 (13.5–42.6)	0.24
IL-1b	2.2 (1.4–5.0)	2.4 (1.6–6.4)	2.6 (1.7–7.1)	0.18
IL-10	3.0 (2.0–5.3)	3.2 (2.3–5.0)	3.5 (2.4–5.7)	0.32
IL-4	2.3 (1.3–3.7)	2.32 (1.5–3.6)	2.2 (1.5–3.2)	0.80
IL-5	4.0 (2.8–5.9)	4.2 (3.0–6.6)	4.0 (2.9–6.0)	0.46
IL-7	8.4 (6.0–11.5)	8.6 (6.5–12.8)	8.4 (6.1–11.6)	0.47
IL-8	9.6 (7.4–12.8)	10.1 (7.4–13.2)	9.6 (7.3–12.7)	0.50
IL-12	22.2 (12.2–65.5)	23.3 (14.0–53.4)	21.7 (13.5–69.6)	0.82
IL-13	4.0 (2.3–10.5)	4.4 (2.7–10.2)	4.2 (2.6–11.3)	0.46
GCSF	165.8 (112.7–224.2)	175.2 (120.0–235.8)	167.4 (124.8)	0.62
MIP1b	44.2 (33.0–61.5)	47.5 (34.4–65.8)	45.9 (36.1–64.6)	0.40
TNF-α	35.3 (20.1–79.6)	38.8 (23.6–88.5)	38.5 (24.7–125.0)	0.22
IL-17	4.6 (0–11.6)	4.6 (0–13.3)	3.1 (0–8.7)	0.23

Conclusion: ACPA/RF+ women with 2 SE alleles had higher IL-2 and IL-6 levels than did women with fewer SE alleles. Studies indicate that Il-6 induces IL-2 proliferation, which in turn induces cytotoxic T cell differentiation. A pro-inflammatory milieu may explain why higher numbers of SE alleles are associated with more destructive arthropathy. IL-6 may be a particularly important therapeutic target among these women. Future work should examine whether these associations differ with use of disease-modifying anti-rheumatic drugs.

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Algorithm Using Genome-Wide SNP Analysis for Prediction of Radiographic Progression Per Year in RA Patients From Multiple Medical Cohorts.
Tsukasa Matsubara[1], Satoru Koyano[2], Yoshitada Sakai[3], Keiko Funahashi[2], James E. Middleton[2], Takako Miura[1], Kosuke Okuda[1], Takeshi Nakamura[1], Akira Sagawa[4], Takeo Sakurai[5], Hiroaki Matsuno[6], Tomomaro Izumihara[7] and Eisuke Shono[8]. [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Kobe University Hospital, Kobe, Japan, [4]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [5]Inoue Hospital, Takasaki, Japan, [6]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [7]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [8]Shono Rheumatology Clinic, Fukuoka, Japan

Background/Purpose: Although not yet fully possible, ideally, since patients with rapidly progressing joint destruction need tight initial control, predicting the progression of joint destruction would be pivotal in establishing a treatment strategy for individual RA patients. We developed a SNP algorithm with the aim of enabling the prediction of yearly radiographic progression by means of genome-wide SNP analysis using multiple medical cohorts.

Methods: One-hundred twenty-four RA patients whose disease duration was 5 years or less were enrolled in this study from 6 hospitals in different regions of Japan. All patients were treated with biologics after the failure of DMARDs therapy. Radiographic progression of joint destruction was estimated by Sharp score per year of disease duration. We defined three groups, rapid, intermediate, and slow radiographic progression, according to Sharp score per year of disease duration. Twenty-three patients had a yearly Sharp score of >50 (rapid radiographic progression), 76 had a yearly score of 50-10 (intermediate radiographic progression) and 25 had a yearly score of <10 (slow radiographic progression). Case-control analyses between 278,347 SNPs and radiographic progression (rapid vs. intermediate+slow or rapid+intermediate vs. slow) were examined by Fisher's exact test. We selected 10 SNPs closely associated with radiographic progression (p < 0.0001). We then scored a relationship between each SNP and radiographic progression, the estimated total score of the 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in rapid radiographic progression group: +1 point, hetero allele: 0 point, and homo allele in the majority of intermediate+slow radiographic progression group: −1 point), and examined relationships between the rapid and intermediate+slow group, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)) and sensitivity (true positive/(true positive+false negative)) of the algorithm for distinguishing the rapid progression group from the intermediate+slow progression group ranged from 93–96%. Accuracy, specificity and sensitivity of the algorithm for distinguishing the rapid+intermediate progression group from the slow progression group ranged from 88–90%. It is therefore suggested that this SNP algorithm may enable the prediction of rapidly progressing severe joint destruction.

Conclusion: This highly accurate algorithm using SNP analysis may be useful in initially diagnosing rapid radiographic progression, and, in this way, may contribute to establishing a strategy of treatment for individual RA patients.

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Validation of Prognostic Biomarkers for RA: Testing of 14-3-3 Eta According to the Omeract Soluble Biomarker Criteria. Walter P. Maksymowych[1], Désirée van der Heijde[2], R. Landewe[3], George A. Wells[4], Joan M. Bathon[5], CO Bingham III[6], Vivian P. Bykerk[7], Mikkel Ostergaard[8], Hilde B. Hammer[9], Maarten Boers[10], Paul Peter Tak[11], Oliver M. FitzGerald[12], Christopher T. Ritchlin[13], Dafna Gladman[14], Philip Mease[15], Dirkjan van Schaardenburg[16], Marina Backhaus[17], Bernard Combe[18], Gianfranco Ferraccioli[19] and Anthony Marotta[20]. [1]University of Alberta, Edmonton, AB, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Univ of Ottawa Faculty of Med, Ottawa, ON, [5]Columbia University Medical Center, New York, NY, [6]Johns Hopkins University, Baltimore, MD, [7]Hospital for Special Surgery, New York, NY, [8]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [9]Diakonhjemmet Hospital, Oslo, Norway, [10]VU University Medical Center, Amsterdam, Netherlands, [11]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [12]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [13]University of Rochester Medical Center, Rochester, NY, [14]Toronto Western Hospital and University of Toronto, Toronto, ON, [15]Swedish Rheumatology Research Group, Seattle, WA, [16]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [17]Charite University Hospital, Berlin, Germany, [18]Hopital Lapeyronie, Montpellier, France, [19]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [20]Augurex Life Sciences Corp, North Vancouver, BC

Background/Purpose: The OMERACT soluble biomarker subcommittee has published validation criteria related to truth, discrimination and feasibility for biomarkers reflecting structural damage[1]. The large majority of biomarker assays assessed in RA have not undergone such validation, particularly the key performance criteria considered essential prior to clinical validation studies[2]. Extracellular 14-3-3 eta is 1) a synovial-derived novel mediator of inflammation/damage with serum levels being differentially expressed in early and established RA compared with controls, 2) modifiable with TNF therapy and 3) independently associated with joint damage in RA and PsA. With 14-3-3 eta fulfilling several OMERACT criteria, this study aimed to focus on aspects of feasibility and discrimination by testing assay reproducibility, reliability, biomarker stability, and sources of variability.

Methods: The 14-3-3 eta ELISA was evaluated for intra- and inter-assay reproducibility by running 20 duplicate measurements on 3 samples within a single assay and over 4 days by 4 operators. Possible interferents [hemoglobin, lipids, bilirubin, albumin, RF, erythrocytes, Aspirin, MTX, and anti-TNFs] were spiked into serum and 14-3-3 eta % recovery was determined. Biomarker stability was examined in 1) 3 samples over 3 freeze-thaw cycles and 2) 6 samples up to 2 years of storage at $-80°C$. Age and gender effects were assessed on 100 healthy controls, 50 males and 50 females [median age 55.0 and 57.5 years]. The effect of menopause was evaluated in the 50 females, 20 under and 30 over the age of 51. Correlations were used to evaluate the relationship of age and 14-3-3 eta concentration. 2-tailed t-tests and Mann-Whitney U-tests were performed to examine mean and median differences between genders and menopausal status.

Results: The intra- and inter assay coefficients of variation (CV%) were less than 10% [range (R)=6.0–9.2%]. Interference testing delivered a 106% median 14-3-3 eta recovery [R=100–115%] across the analytes tested demonstrating 14-3-3 eta quantification is not confounded by common RA patient serum substances. Results from sample stability testing indicate that serum 14-3-3 eta is stable over 3 freeze-thaw cycles with the median CV% being 109% [R=92–129%]. Long-term storage studies show that samples negative for 14-3-3 eta remain negative while those with levels above the upper limit of quantification of >20ng/ml have substantially equivalent levels. Stability of 14-3-3 eta was further confirmed using samples with levels in the linear range of the assay; median CV% was 104% of the original values [R=89–128%]. There was no correlation between age and 14-3-3 eta. Median 14-3-3 eta serum concentrations in healthy males and females did not differ significantly nor were there any significant differences in females aged over and under 51 years.

Conclusion: This 14-3-3 eta ELISA fulfills several key performance criteria considered essential by OMERACT. Quantification of 14-3-3 eta using this assay is reproducible and the biomarker is highly stable with no confounding of age, gender or menopause.

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Interleukin-6 As a Biomarker for the Clinical and Radiological Effectiveness of Methotrexate in Rheumatoid Arthritis. Naoshi Nishina, Hideto Kameda, Yuko Kaneko, Masataka Kuwana and Tsutomu Takeuchi. Keio University School of Medicine, Tokyo, Japan

Background/Purpose: Methotrexate (MTX) is now an anchor drug in the treatment strategy of rheumatoid arthritis (RA) and its effectiveness has been established. However it is still unclear how MTX should work in the pathologically complicated cytokine network in RA including tumor necrosis factor (TNF)-α and interleukin (IL)-6. The aims of this study were to reveal the kinetics of TNF-α and IL-6 during the treatment of MTX and to assess the relationship between these cytokines and clinical and radiological states.

Methods: Sixty two RA patients were enrolled in this study whose estimated disease duration before the diagnosis of RA was less than 36 months and who received MTX treatment without biologic agents for at least 3 months. Plasma IL-6 and TNF-α level were measured by CLEIA before the start of the treatment and several months after, and the clinical characteristics were gathered at the same time. Radiography assessment was performed by means of van der Heijde modified Sharp Score (mTSS). The comparison of two continuous variables was performed by Wilcoxon signed-ranks test and the correlations with two variables were analyzed by logistic and multiple regression model.

Results: Of 62 patients, 49 (79%) were female. Mean age was 57 ± 15 years and median estimated disease duration was 3 months. The time when the cytokines were measured after the start of the treatment was at a median of 11 months (5–18). Forty six patients (74%) were positive for RF and 47 patients (76%) for anti-CCP antibody. Mean MTX dosage was 8.7 ± 2.3 mg/week. With concomitant use of MTX, steroid and synthetic DMARDs were prescribed in 20 patients (prednisolone in 6 patients, bucillamine 6, salazosulfapyridine 6, bucillamine and salazosulfapyridine 1, tacrolimus 1). Compared with the values of median DAS 28, serum CRP and plasma IL-6 before the start of the treatment, those after the use of MTX were decreased significantly from 4.42 to 2.58, 0.55 to 0.06 mg/dl and 4.72 to 1.04 pg/ml, respectively ($p<0.01$ for all), while plasma TNF-α level didn't change from 0.87 to 0.83 pg/ml (Table 1). Of those parameters, the estimated yearly progression of mTSS (ΔmTSS) was not correlated with CRP but significantly correlated with plasma IL-6 level after the use of MTX (Figure 1, R^2=0.05, 0.45, respectively). In multivariate analysis, rapid radiographic progression (ΔmTSS$\geq$5) was associated only with high plasma IL-6 level after the treatment [OR 1.15, 95%CI 1.02–1.32].

Table 1. Changes of the clinical parameters before and after the MTX treatment

	before	after	p value
DAS 28	4.42 [3.60, 5.62]	2.58 [1.93, 3.16]	<0.01
CRP (mg/dl)	0.55 [0.10, 1.43]	0.06 [0.02, 0.18]	<0.01
IL-6 (pg/ml)	4.72 [2, 11.55]	1.04 [0.58, 5.41]	<0.01
TNFα (pg/ml)	0.87 [<0.55, 1.58]	0.83 [<0.55, 1.18]	0.14

Results are expressed as median [IQR]. IL, interleukin; TNF, tumor necrosis factor
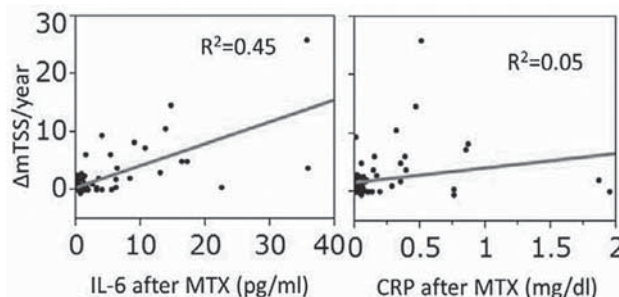
Figure 1. The correlation of ΔmTSS with plasma IL-6 level nad CRP after MTX treatment.

Conclusion: In the treatment of RA, MTX had a great effect on decreasing plasma IL-6 and the level of IL-6 after the use of MTX was the greatest impact on the radiological progression.

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Predictive Value of Anti-CCP Positivity On Disease Course and Response to Therapy in Early Rheumatoid Arthritis. Results From the Swedish EIRA Study. Saedis Saevarsdottir[1], Marie Holmqvist[2], Johan Askling[2], Lars Alfredsson[3] and Lars Klareskog[2]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden, [3]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Does anti-CCP-positivity predict disease course and response to therapy in early rheumatoid arthritis (RA)?

Methods: We retrieved clinical follow-up data for patients entering the EIRA cohort 1996–2009 from the Swedish Rheumatology Quality Register (1996–2010). Overall, 1,640 of the 2,567 registered RA patients were followed from diagnosis. Then, 99 received no DMARD treatment, 41 received only prednisolone, 670 only methotrexate, 476 methotrexate and prednisolone, 224 sulfasalazine, whereas 130 patients received other DMARDs or combinations. The association between anti-CCP-positivity and EULAR good response was evaluated by logistic regression and expressed as univariate p-values and multivariate odds ratios (OR) with 95% confidence intervals (CI), adjusted for gender, age, inclusion year, symptom duration, HAQ score and cigarette smoking habits.

Results: The proportion starting DMARD/methotrexate at diagnosis increased during the inclusion period (p<0.0001/<0.0001). In the subgroup receiving no DMARD, anti-CCP-positive patients were, compared to anti-CCP-negative patients, less likely to fulfil the criteria for 'good response' after 3 months (15% vs. 48%, p=0.002; adjusted odds ratio=0.24; 95%CI 0.07–0.82). A smaller, but significant difference was observed between anti-CCP-positive and anti-CCP-negative patients receiving methotrexate only (31% vs. 41%, p=0.02; adjusted odds ratio=0.65; 95%CI 0.44–0.94), whereas no difference was observed between anti-CCP-positive and anti-CCP-negative patients receiving both methotrexate and prednisolone (52% vs. 49%, p=0.5; adjusted odds ratio=1.23; 95%CI 0.78–1.92). No significant differences were observed in patients receiving sulfasalazine or in the entire cohort during 2 years follow-up.

Conclusion: Anti-CCP positivity predicts persistent disease activity in early RA patients not receiving DMARD treatment, while its predictive value for response is limited in patients treated with MTX, SSZ and prednisolone, and in the entire group of RA patients reflecting all treatment options over time. Our findings also indicate that the less chance of a favorable clinical disease course in anti-CCP positive patients may be compensated for with treatment, namely that today′s standard care with methotrexate and low dose prednisolone may have its main effects in ACPA-positive patients. This highlights the importance of performing a careful subgrouping of the RA syndrome in all controlled as well as observational studies on drug treatment.

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A Multi-Biomarker Disease Activity (VECTRA™ DA Algorithm) Score Reflects Clinical Disease Activity and Structural Changes in Rheumatoid Arthritis Patients Treated with Tocilizumab. Yoshiya Tanaka[1], Kentaro Hanami[1], Hisashi Tasaka[1], Shunsuke Fukuyo[1], Douglas J. Haney[2], Nadine Defranoux[2], Rebecca Bolce[2], Guy Cavet[2], David Chernoff[2], Kunihiro Yamaoka[1], Kazuyoshi Saito[1] and Shintaro Hirata[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Crescendo Bioscience Inc., South San Francisco, CA

Background/Purpose: The multi-biomarker disease activity (MBDA) score assessed with 0.2 mL serum has been reported as a novel composite disease activity index for patients with rheumatoid arthritis (RA). We reported the correlation of MBDA score with conventional composite measures such as DAS28 in patients with RA. However, the estimation of the MBDA score in RA patients treated with anti-IL-6 receptor antibody tocilizumab (TCZ) has not been investigated. Purpose of this study is to clarify if the MBDA score could reflect disease activity and track therapeutic effect including clinical and radiographic outcomes in RA patients treated with TCZ.

Methods: Fifty two RA patients who treated with TCZ were enrolled. The MBDA algorithm combines 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) into a single score from 1–100 according the Vectra™ DA algorithm. MBDA disease activity categories were defined as high (HDA>44), moderate (MDA>29≤44), low (LDA<25≤29) and remission (REM≤25). Radiographic changes were assessed by the modified total Sharp score (mTSS). For statistic analysis, Spearman's rank correlation coefficients and Pearson's chi-square test were used. All p-values are two sided and <0.05 were considered significant.

Results: At baseline (BL), patients had median age of 57 ± 18, disease duration of 12.4 ± 11.2 years, DAS28 of 5.6 ± 1.3, CDAI of 22.1 ± 12.2, HAQ-DI of 1.4 ± 0.9 and mTSS of 106 ± 112. MTX was used in 86.5% and positivity of RF was 78.8%. MBDA score at BL was 57.7 ± 19.2 and were correlated well with DAS28 and CDAI (ρ=0.63 and 0.57, respectively, p<0.0001). TCZ improved MBDA score from 57.7 to 43.7 and 42.5 at W24 and W52, respectively, DAS28 from 5.6 to 2.5 and 2.9, CDAI from 22.2 to 6.4 and 5.6, at BL, W24 and W52, respectively. Changes of MBDA from BL to 52W by TCZ were significantly correlated with those of DAS28 (r=0.471, p<0.001) and CDAI (r=0.373, p<0.01). MBDA-REM ratio at W52 was significantly correlated with DAS28-REM ratio (AUROC=0.643) and CDAI-REM ratio (0.768). Yearly progression of mTSS (ΔmTSS) was improved from 12.3 ± 14.9 to 0.5 ± 2.5 by TCZ and 77% achieved ΔmTSS<0. Interestingly, all patients who achieved MBDA-LDA (8), MBDA-REM (3) or Boolean-REM (5) at W24 showed ΔmTSS<0.5, whereas some of DAS28-REM and CDAI-REM did ΔmTSS>0.5. Patients who achieved MBDA-REM or Boolean-REM at W24 revealed higher likelihood ratio for achieving both radiographic and functional REM at W52 than those who DAS28-REM and CDAI-REM.

Conclusion: This is the first report of the MBDA estimated in RA patients treated with TCZ. TCZ efficiently improved MBDA score and BL and changes of MBDA were correlated with those of conventional composite measures. Although additional data are needed to assess the relationship between MBDA and radiographic and functional remission, The MBDA score reflects disease activity and tracks therapeutic effects and MBDA-REM might be preferable to DAS28-REM for predicting good outcome in both radiographic damage and physical function in RA patients treated with TCZ.

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Plasma chemerin as a Useful Marker for Disease Activity in Patients with Rheumatoid Arthritis. Sang Tae Choi[1], You-Jung HA[2], Eun-Jin Kang[3], Kwang-Hoon Lee[4] and Jung-Soo Song[1]. [1]Chung-Ang University College of Medicine, Seoul, South Korea, [2]Kwanding University College of Medicine, Myongji Hospital, Goyang, South Korea, [3]Busan Medical Center, Busan, South Korea, [4]Dongguk University Ilsan Hospital, Goyang, South Korea

Background/Purpose: Chemerin is an adipokine that is linked to adipogenesis and chemotaxis of the innate immune system. It is expressed on macrophage, dendritic cells, and synovial lining and sublining cells. It has been reported that chemerin has both pro-inflammatory and anti-inflammatory roles, and higher level of chemerin was detected in various chronic inflammatory diseases. Recent studies have showed that its expression is increased in the synovium of patients with rheumatoid arthritis (RA), and the chemerin may play an important role in the pathogenesis of RA. However, the association between plasma chemerin level and disease activity in RA patients remains unclear. This study aims to determine whether plasma

chemerin level is elevated in patient with RA and its correlation with disease activity and other parameters.

Methods: This study includes 71 RA patients and 42 age- and sex-matched healthy controls. Plasma samples were obtained from healthy controls and patients with RA during active and inactive disease status. We assessed the clinical characteristics and laboratory parameters including body mass index (BMI), erythrocyte sedimentation rate, C-reactive protein, and disease activity score 28 (DAS28). The plasma level of chemerin and tumor necrosis factor (TNF)-α were determined using enzyme-linked immunosorbent assay (ELISA).

Results: Plasma chemerin level was significantly elevated in patients with RA than healthy control (9.074 ± 13.513 pg/mL vs 0.370 ± 0.219 pg/mL, p<0.001). In RA patients, the adjusted plasma chemerin level according to BMI was correlated with DAS28 (γ=0.340, p=0.004), but not plasma TNF-α level. The adjusted plasma chemerin level of active disease group patients (DAS28 ≥ 2.6) was significantly higher than that of remission group patients (DAS28 < 2.6) (0.591 ± 0.879 pg/mL vs 0.220 ± 0.154 pg/mL, $p = 0.015$).

Conclusion: Patients with RA showed higher plasma chemerin than that of healthy controls. The adjusted plasma chemerin level according to BMI was well correlated with RA disease activity. These findings suggest that plasma chemerin could play a role in the inflammatory process of RA, and that it may be a useful disease activity marker in RA.

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Circulating Mir-223 Is Associated with Disease Activity and May Predict the Response to Therapy in Treatment naïve Patients with Early Rheumatoid Arthritis. Maria Filkova[1], Caroline Ospelt[1], Serena Vettori[1], Ladislav SĚnolt[2], Herman F. Mann[2], Beat A. Michel[3], Jiri Vencovsky[2], Karel Pavelka[2], Renate E. Gay[1], Steffen Gay[1] and Astrid Jüngel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, Zurich, Switzerland, [2]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Parameters/ predictors of treatment response in patients with early rheumatoid arthritis (ERA) are needed to optimize treatment management based on the expected disease course. miRNAs are stable in cell-free form in body fluids and have therefore a potential to serve as biomarkers for diagnosis and treatment response. Our aim was to analyze the association between the expression of miRNAs in sera of patients with ERA with disease activity and outcome.

Methods: The study included 34 patients with ERA (64.52% RF+, 51.61% ACPA+) who fulfilled 2010 ACR/EULAR classification criteria for RA with symptom duration <8 months. Total RNA was isolated using phenol-chloroform extraction from whole sera obtained at baseline and after 3 months of therapy with DMARDs. The expression of miR-146a, 155, 223, 203, 132, 124a, 16 and let-7a was analyzed using specific primers by TaqMan Real-Time PCR. Peripheral blood mononuclear cells (PBMC) were treated with methotrexate (MTX, 25ug/ml) *in vitro.*

Results: In treatment naïve ERA patients, the expression of miR-223 positively correlated with baseline DAS28 (p=0.031), with change of DAS28 (DDAS28) calculated as the difference between DAS28 at 3 months follow up and baseline (p=0.014), CRP (p=0.008) and peripheral leukocyte count (p=0.007). After treatment, the correlation of miR-223 with the leukocyte count remained significant (p=0.004). Levels of miR-223 were lower in patients with positivity of both RF and ACPA in comparison with patients that were RF+/ACPA−, RF−/ACPA+ or RF−/ACPA− (p=0.02). None of the other miRNAs analysed in our study were associated with clinical activity of ERA.

Expression of miR-223 was significantly decreased after 3 months of treatment with DMARDs in comparison with baseline (p=0.007). Further analysis revealed 2 groups of patients with opposing change in the expression of miR-223. One group ("miR-223/-", n=24; 52.4% RF+, 30.1% ACPA+) developed decreased levels of miR-223 (p<0.0001) while another group ("miR-223/+", n=10; 90% RF+, 80% ACPA+) showed an increase in miR-223 expression after treatment (p=0.002). In the miR-223/− group, the baseline levels of miR-223

correlated with DDAS28 (p=0.039) and the change in miR-223 was associated with DDAS28 (p=0.007). In contrast, no correlations between miR-223 and parameters of disease activity were found in the miR-223/+ group.

The change in expression of miR-223 in sera may be attributable to the change in number of leukocytes between 3 months and baseline concluded from the positive correlations between these variables (p=0.025). In addition, the expression of miR-223 in PBMC is downregulated by 15% (p=0.001) after treatment with MTX.

Conclusion: Our data support the potential of miR-223, known to be upregulated in T cells in RA (Sebastini GD et al. 2011), to serve as a marker of disease activity in patients with treatment naïve ERA and its association with disease outcome in a short time follow up. We hypothesize that differential expression of miR-223 in RF+/ACPA+ patients may characterize ERA patients who are at risk of more severe disease progression.

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Serum Concentrations of Soluble Interferon Receptor in Patients with Rheumatoid Arthritis. Masao Sato, Masao Takemura, Ryuki Shinohe, Tsuneo Watanabe and Katsuji Shimizu. Gifu University, Gifu, Japan

Background/Purpose: Interferon (IFN) exerts antiviral and antineoplastic activities, and is involved in immunoregulatory activities. IFN probably plays an important role in the pathogenesis of rheumatoid arthritis (RA), which is a chronic and progressive inflammatory disease. IFN is eliminated from the bloodstream, with a half-life of 2 h, it is difficult to detect IFN concentrations in the sera. IFN, similar to other cytokines, exerts its biological activities by binding to cell-surface receptors. In this study, we evaluated the serum concentrations of soluble IFN α/β receptor (sIFNR) in patients with RA.

Methods: The study involved 57 patients (11 men and 46 women) with RA who met the American College of Rheumatology 1987 RA classification criteria. The patients were aged 31 – 85 y (mean age, 61.2 y). The control group consisted of 16 patients with osteoarthritis (OA) of the knee and 216 healthy subjects, (mean age, 57.1 y and 52.3 y, respectively); the sIFNR concentrations of these subjects were determined. All the subjects recruited in this study were negative for hepatitis B surface antigens and hepatitis C antibodies. Blood samples were obtained from the subjects, and serum fractions separated from the blood samples were stored at −80 degree, until the assay was performed.

Results: The serum concentrations of sIFNR in RA patients that varied from 0.7 to 5.8 ng/ml (mean, +/− SD: 2.1 +/− 1.2 ng/ml) and were significantly higher than those in the OA patients (mean, +/− SD: 1.4 +/− 0.7 ng/ml: p < 0.03) and the healthy subjects (mean, +/− SD: 1.0 +/− 0.5 ng/ml: p < 0.001). The serum levels of sIFNR in the RA patients with radiographic stage scores of II, III, and IV were 1.0 +/− 0.2 ng/ml, 1.3 +/− 0.3 ng/ml, and 2.5 +/− 1.2 ng/ml, respectively. The serum levels of sIFNR in the RA patients with activities of daily living (ADL) scores of 2, 3, and 4 were 1.2 +/− 0.2 ng/ml, 2.5 +/− 1.0 ng/ml, and 3.8 +/− 1.5 ng/ml, respectively. The serum levels of sIFNR in the RA patients were positively correlated with the disease durations (r = 0.55: p < 0.0001).

Conclusion: In this study, we observed that the serum levels of sIFNR in the RA patients were significantly higher than those in the OA patients and the healthy subjects. A significant correlation was observed between the serum levels of sIFNR in the RA patients and the RA stage scores, ADL scores, and disease durations. Therefore, serum levels of sIFNR might be a useful predictor for the prognosis of chronic conditions and RA.

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Response to Methotrexate Plus Prednisone in Camera II Using a Multi-Biomarker Disease Activity (Vectra™ DA) Test and DAS28-ESR. J.W.J. Bijlsma[1], M. Verhoef-Jurgens[1], M.F. Bakker[1], J.W.G. Jacobs[1], F.P.J.G. Lafeber[1], P.M.J. Welsing[1], G. Cavet[2], D. Chernoff[2] and D.J. Haney[2]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Crescendo Bioscience, Inc., South San Francisco, CA

Background/Purpose: The CAMERA II study (Computer Assisted Management in Early RA) demonstrated that the addition of prednisone to a MTX-based tight control strategy increased effectiveness of therapy, including reductions in disease activity, disability, and joint erosion, increased likelihood of achieving sustained remission, and less frequent need for biological treatment. The purpose of this study was to evaluate changes in biomarker levels over time with MTX and MTX + prednisone treatment.

Methods: Clinical and biomarker assessments were performed for 104 patients at multiple visits between Baseline (BL) and 1 year. The average number of visits per patient was 4. Clinical assessments were used to calculate the DAS28-ESR, and 12 serum biomarker concentrations were combined to produce a score between 1 and 100 using the MBDA algorithm, which is a validated biomarker-based measure of disease activity. Association between DAS28-ESR response and Multi-Biomarker Disease Activity (MBDA) response was assessed using Spearman's correlation. Changes from BL were analyzed using the paired t-test.

Results: There was a significant association between change in DAS28-ESR from BL to 1 year and change in MBDA from BL to 1 year in both the MTX-only arm ($r = 0.57$, $p < 0.001$, $n = 31$) and in the MTX + prednisone arm ($r = 0.57$, $p = 0.002$, $n = 28$). Improvements in DAS28-ESR ($p < 0.001$) and MBDA ($p = 0.01$) were observed as early as 1 month post-BL in the MTX + prednisone arm. Significant reduction in disease activity in the MTX-only arm was first observed at 2 months for DAS28-ESR ($p = 0.02$) and at 4 months for MBDA ($p = 0.03$).

| | | DAS28-ESR | | | | | MBDA | | |
| | | MTX | | MTX + pred. | | | MTX | | MTX + pred. |
Timepoint	n	Mean Chg.	n	Mean Chg.		n	Mean Chg.	n	Mean Chg.
1 Month	16	−0.3 (p = 0.24)	11	−1.9 (p < 0.001)	18	−3 (p = 0.27)	14	−12 (p = 0.01)
2 Months	15	−0.7 (p = 0.02)	11	−2.4 (p < 0.001)	17	−3 (p = 0.25)	14	−11 (p = 0.02)
3 Months	22	−1.3 (p < 0.001)	13	−3.0 (p < 0.001)	25	−5 (p = 0.09)	17	−15 (p = 0.002)
4 Months	13	−1.8 (p < 0.001)	10	−3.9 (p < 0.001)	17	−9 (p = 0.03)	14	−19 (p = 0.003)
5 Months	15	−2.2 (p < 0.001)	10	−4.2 (p < 0.001)	18	−13 (p = 0.006)	12	−21 (p = 0.003)
6 Months	18	−2.8 (p < 0.001)	12	−3.0 (p = 0.001)	29	−20 (p < 0.001)	19	−16 (p < 0.001)
9 Months	17	−2.7 (p < 0.001)	12	−3.2 (p = 0.001)	24	−24 (p < 0.001)	17	−20 (p < 0.001)
12 Months	31	−2.8 (p < 0.001)	28	−3.1 (p < 0.001)	44	−20 (p < 0.001)	37	−16 (p < 0.001)

Conclusion: The biomarker-based MBDA test and DAS28-ESR responded quickly to combination therapy with MTX and prednisone and were correlated with one another. MBDA may be useful in combination with clinical assessment to evaluate early response to therapy with MTX or MTX + prednisone.

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Changes of Serological Markers in the Course of Traditional and Biological Disease Modifying Therapy of Rheumatoid Arthritis. Christoph Böhler[1], Helga Radner[1], Josef S. Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) are established markers in the diagnostic approach to rheumatoid arthritis (RA). Both auto-antibodies (AAB) also have a prognostic value, since they are associated with more aggressive, destructive disease [1]. Therefore decreases in AAB levels may be highly relevant to improve the long-term outcome of RA. We aimed to investigate the changeability of ACPA and RF levels under anti-rheumatic therapy, with special focus on the influence of treatment response.

Methods: We obtained data of outpatients from a long-term observational database with prospective data entry. We retrieved clinical and serological data of patients treated with traditional disease modifying anti-rheumatic drugs (DMARDs) and/or biological response modifiers from the treatment start and after 6 months of therapy. We used non-parametric tests to analyse changes of ACPA and RF levels between the two visits, as well as differences

between treatment responders and non-responders. SDAI50 criteria were used to define treatment response [2]. Furthermore, we investigated the trend of ACPA, RF and SDAI over a period of 18 months.

Results: 143 ACPA and RF positive patients were included. As depicted in Figure 1, the median (25th /75th percentile) relative changes after six months were −35.6% (−63.3; −8.3) for RF, and −15.2% (-40.0; 10.0) for ACPA (p<0.001 for both). The changes of RF levels were significantly greater than those seen for ACPA (p<0.001). SDAI50 response was achieved in 60 (42%) patients. As can be seen in Figure 2, the decrease of ACPA and RF was significantly higher in patients with treatment response than in those without (p=0.034 and p=0.01, respectively). After 3 months the decline of ACPA, RF, and SDAI amounted to 4.6%, 13.2%, and 23.5%, respectively; after 12 months it was 16.9%, 31.4% and 40.5, and after 18 months 23.8%, 35.2%, and 44.3%, respectively.
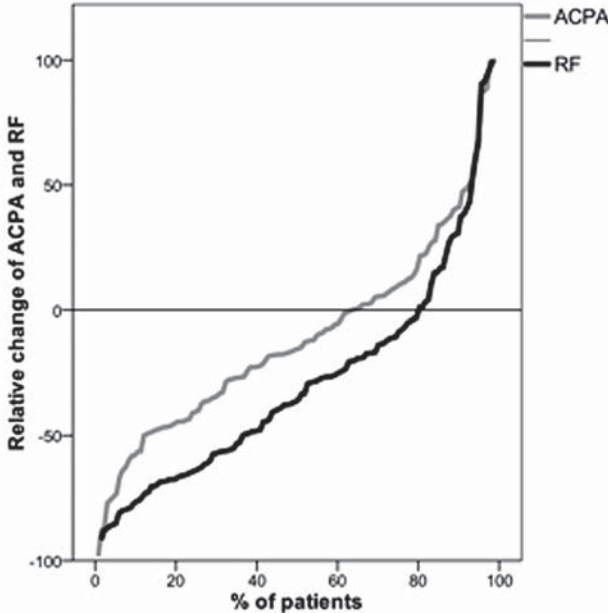
Figure 1. Fractional rank depiction of relative ACPA and RF changes.
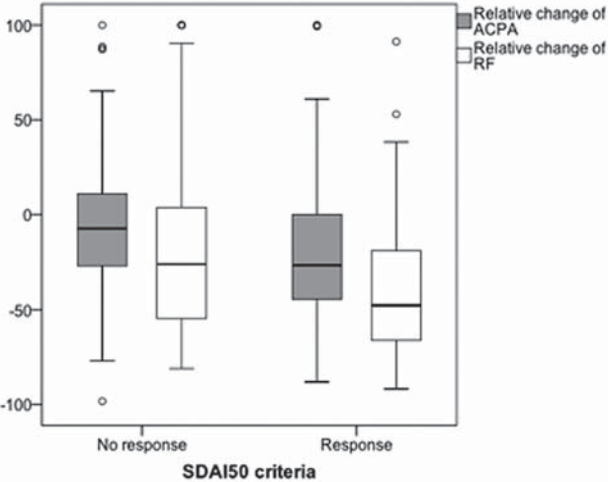
Figure 2. Differences of ACPA and RF changes between responders and non responders due to SDAI 50 criteria.

Conclusion: ACPA and RF levels decreased significantly after 6 months of therapy. Reduction of both AAB were closely linked to a reduction of disease activity. RF declined faster, to a larger extent and in greater numbers of patients than ACPA. Further research is needed to investigate whether reductions of ACPA and RF levels are associated with a better radiographic outcome.

1. De Rycke L et al. *Ann Rheum Dis* 2004;63(12):1587-93.
2. Aletaha D et al. *Ann Rheum Dis* 2012;71(7):1190-6.

Rheumatoid Arthritis (RA) Patients Discordant for Rheumatoid Factor and Anti-CCP Positivity Have Different Clinical and Laboratory Features Than RA Patients Seropositive or Seronegative for Both Markers. Swati Modi[1], Yona Cloonan[1], Danielle Goudeau[1], Donald M. Jones[2], Christine L. Amity[3], Lynne M. Frydrych[2], Kelly A. Reckley[4], Heather Eng[3], Stephen R. Wisniewski[5], Larry W. Moreland[1] and Marc C. Levesque[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Univ of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh School of Medicine, Pittsburgh, PA, [5]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA

Background/Purpose: Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) positive rheumatoid arthritis (RA) patients develop more extra-articular disease manifestations and erosions, and have a worse prognosis than seronegative RA patients. Levels of RA and CCP may be regulated independently. Therefore, our aim was to identify demographic and clinical differences between RA patients grouped according to RF and CCP status.

Methods: Cross-sectional analysis of RA subjects from the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry was performed. The analysis included data from the first visit at which both RF and CCP levels were available (n=884). Patients were categorized based on clinical cut-offs: RF+CCP+, RF+CCP-, RF-CCP+, RF-CCP-. The following demographic and clinical data were compared across RF/CCP groups: age, race, gender, disease duration, CRP, RF, CCP, disease activity (DAS28, CDAI),rheumatoid nodules, morning stiffness, physician/patient global health assessment, and medication use (ever used DMARD, biologic, corticosteroid). Categorical and continuous variables were analyzed using chi-square and Kruskal-Wallis tests, respectively

Results: 60% of subjects were RF+CCP+, 12% RF+CCP-, 10% RF-CCP+ and 18% RF-CCP-. Disease duration, RF, CCP, CRP, DAS28 score, presence of rheumatoid nodules, morning stiffness, and use of biologic therapy were statistically significantly different across groups (p<0.05). RF+CCP+ patients had longer disease duration than other patients (median 143 vs 88–93 months), and higher median RF (122 vs 20–28) and CCP (118 vs 2–47). Mean CRP ranged from 2.8 (RF+CCP+) to 8.1 (RF-CCP-). Morning stiffness was most common in the RF-CCP- group (54% vs 26–40%), while rheumatoid nodules were more common in the CCP+ groups (12–15% CCP+ vs 5–6% CCP-). The proportion of patients ever having used biologic therapy ranged from 28% (RF+CCP+) to 56% (RF-CCP+). There were no statistically significant differences for the remaining demographic and clinical characteristics.

Conclusion: There were statistically significant demographic, clinical and laboratory differences between RA subjects grouped on the basis of RF and CCP positivity. RF+/CCP+ subjects had longer disease duration but were similar in age to the other groups, suggesting that earlier age of RA onset may be associated with the development of high levels of both RF and anti-CCP. The associations of disease activity measures with RF levels (and not with CCP), suggests that RF levels vary with the degree of inflammation and disease activity (as does CRP) and are likely regulated by different factors than those that govern CCP levels. The greater use of biologic therapies by CCP+ subjects suggests that these RA patients may experience greater disease severity. An understanding of the differences between RA subjects grouped on the basis of RF and CCP status may allow for individualized treatment and will form the basis for future studies of the mechanisms differentially regulating RF and CCP levels.

Matrix Metalloproteinase 3: A Biomarker of Disease Activity in Rheumatoid Arthritis. Sandra Reuter[1], Torsten Matthias[2] and Bruno Larida[3], [1]AIRA e.V., AESKU.KIPP Institute, Wendelsheim, Germany, [2]AESKU. Diagnostics GmbH & Co. KG, Wendelsheim, Germany, [3]AESKU. DIAGNOSTICS INC, Oakland, CA

Background/Purpose: New biomarkers for monitoring Rheumatoid Arthritis (RA) disease activity and prognosis of progression are urgently needed to individually optimize drug therapy and prevent joint destruction. Serum Matrix Metalloproteinase 3 (MMP-3) has been proposed to be such a marker. Thus we set out to correlate MMP-3 serum levels in Rheumatoid Arthritis patients with their individual disease activity.

Methods: 64 sera from adult patients (44 female, 20 male) with established RA and 97 control sera from adult healthy donors (48 female, 49 male) were analyzed using the AESKULISA DF MMP-3 kit. The 64 RA patients were classified as "Active" or "Inactive" according to their individual disease activity based on clinical data. Both RA groups were correlated to their individual MMP-3 serum concentrations (termed as "elevated" and "non-elevated" MMP-3 levels). The normal range of MMP-3 concentration in serum was determined by calculating the 95th percentile of the measured MMP-3 concentrations for each gender.

Results: Of the 64 RA patients, 35 were classified as "Active" and 29 as "Inactive" based on their individual disease activity. Normal MMP-3 serum concentrations were determined as: up to 60 ng/ml and up to 120 ng/ml for females and males, respectively. 89% (31/35) of "Active" patients had elevated and only 11% (4/35) had normal or borderline MMP-3 levels. 90% (26/29) of "Inactive" patients had normal and only 10% (3/29) had elevated MMP-3 levels.

Conclusion: Serum concentration of MMP-3 exhibits a high correlation with RA disease activity.

Dickkopf-1 Is Increased in Rheumatoid Arthritis of Recent Onset and Might Be a New Biomarker of Structural Progression. Data From the Espoir Cohort. Raphaèle Seror[1], Stephan Pavy[2], Thierry Schaeverbeke[3], Alain Saraux[4], Xavier Mariette[5] and Corinne Miceli-Richard[1]. [1]Université Paris Sud, Le Kremlin Bicêtre, France, [2]Hopital Bicetre, Paris, France, [3]Groupe Hospitalier Pellegrin, Bordeaux, France, [4]CHU de la Cavale Blanche, Brest Cedex, France, [5]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Dickkopf-1 (DKK-1) is an inhibitory protein of the Wnt signalling pathway that could be involved in subchondral bone erosions occurring in rheumatoid arthritis (RA). Few studies have investigated the role of DKK1 in RA. We aimed to investigate DKK-1 serum levels in patients with recent inflammatory arthritis fulfilling ACR/EULAR criteria for RA and to investigate the parameters associated with DKK-1 increase and the relationship between DKK-1 levels and radiographic changes in RA.

Methods: The ESPOIR cohort is a prospective, multicenter French cohort of patients with early arthritis, including 813 patients between 2002 and 2008. DKK-1 serum levels were assessed at baseline on the whole cohort by sandwich ELISA (Biomedica, Vienna). DDK-1 serum levels were further analyzed at inclusion in the subgroup of patients fulfilling ACR/EULAR criteria for RA after 2 years of follow-up (N=694; 85.3%) and compared with serum levels from 70 age and sex-matched controls (without autoimmune or chronic inflammatory disease). Uni and multivariate analyses were conducted to look for parameters associated or correlated with DKK-1 serum levels. DKK-1 serum levels were also compared between patients with and without radiographic change at baseline and after 2 years of follow-up.

Results: Among the 813 patients with early arthritis, 694 of them (85%) fulfilled ACR/EULAR criteria for RA (mean age 48.5±12.3, 78.2% female, with mean baseline DAS28=5.3±1.2, 54.6% anti-CCP positive). Serum DKK-1 level was significantly increased in RA patients compared to healthy controls (28.0±13.2 vs 10.8±9.3; p<0.0001). In univariate analysis, the level of DDK-1 was significantly correlated with the level of CRP (r=0.16; p<0.0001), ESR (r=0.11; p=0.005), patient global assessment (PGA) (r=0.08; p=0.046) and DAS28 (r=0.09; p=0.02). In addition, we found that DKK-1 level was significantly higher in patients with typical erosion related to RA at baseline, compared to those without (32.4±14.0 vs 27.2±12.9; p=0.0001). In the multivariate analysis adjusted for DAS28, PGA, and smoking status, only CRP levels and the presence of typical erosions related to RA remained associated with DKK-1 levels. Last, the most interesting result was that baseline DKK-1 levels was predictive of radiological progression (defined by increase of modified Sharp score >1) (29.3±13.0 in patients with progression vs 16.7±12.1 in patients without progression; p=0.025). Nevertheless, DKK-1 was no more associated with radiological progression in a model including other main predictors of severity (erosion at baseline, and anti-CCP positivity) in the multivariate analysis.

Conclusion: This study conducted in a large cohort of patients presenting with early onset RA clearly showed an increase in DKK-1 serum levels, associated with disease activity, biological inflammation and bone erosions at baseline. More interestingly, increase in DKK-1 serum levels were predictive of structural progression at 2 years and, then might be an interesting new structural biomarker in early RA.

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Studies of Disease and Therapy-Response Biomarkers in Early Rheumatoid Arthritis Treated with Methotrexate. Aase Haj Hensvold[1], Saedis Saevarsdottir*[1], Wanyiang Li*[2], Vivianne Malmström[1], Guy Cavet[3], Lars Klareskog[4] and Anca Irinel Catrina[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Crescendo Bioscience Inc. 341 Oyster Point Blvd South San Francisco, CA 94080, San Francisco, CA, [3]Crescendo Bioscience Inc., South San Francisco, CA, [4]Karolinska Institute, Stockholm, Sweden *equally contributed

Background/Purpose: To identify disease and therapy response serum biomarkers in early untreated RA patients started on methotrexate as the only DMARD.

Methods: 186 patients with early treatment naïve RA (symptom disease duration less than 1 year), started on methotrexate (MTX) monotherapy at diagnosis were included in the current study. All patients are part of a larger cohort of early RA named EIRA (epidemiology investigation of rheumatoid arthritis) and had available blood samples at baseline and a median of 3 months after treatment initiation. Concentrations of 12 serum biomarkers were measured at baseline and a median of 3 months after treatment start to calculate multi-biomarker disease activity (MBDA) scores [1]. Additionally ELISA for CCP-2 was performed at baseline. Associations between different biomarkers were calculated using Spearman's rank correlation. The ability of MBDA score in tracking and differentiating clinical response was estimated by correlation between the change of MBDA score and the change of DAS28ESR from baseline to 3-months visit, and also by calculating area under the ROC curves (AUROCs) for classifying good/moderate EULAR responders versus non-responders at 3-months visit.

Results: No differences in the baseline characteristics were observed between patients included in the current study and MTX treated patients in the original large EIRA cohort (n=873) with a median (IQR) age of 52 (42–59), % female of 72%, % anti-CCP positive of 67% and median (IQR) DAS28ESR of 5.7 (5.0–6.2). At 3 months, 29% of the patients were good EULAR responders, 37% were moderate responders and 34% were non-responders. The change of MBDA score from baseline to 3-months visit was significantly correlated with the change of DAS28ESR and able to differentiate EULAR responders and non-responders (AUROC = 0.79, p-value<0.001). The median decrease in the MBDA score was significantly greater in the anti-CCP negative group than in the positive group but correlated with DAS28ESR changes in both groups.

Conclusion: We confirm the value of MBDA as a surrogate marker for measuring clinical disease activity and differentiate clinical response in early RA patients treated with MTX whether they were anti citrullinated-protein antibodies (ACPA) negative or positive.

[1] J. R. Curtis, Validation of a Novel Multi-Biomarker Test to Assess Rheumatoid Arthritis Disease Activity, Arthritis Care & Research, accepted, to be online

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An Evaluation of Prognostic Factors for Orthopaedic Joint Surgery in Rheumatoid Arthritis. Results From Two Multicentre UK Inception Cohorts (1986–2011). Elena Nikiphorou[1], Lewis Carpenter[2], Sam Norton[3], David James[4], Patrick D. Kiely[5], David Walsh[6], Richard Williams[7] and Adam Young[8]. [1]ERAS, St Albans City Hospital & University College London (UCL), London, United Kingdom, [2]University of Hertfordshire, Hatfield, United Kingdom, [3]ERAS, St Albans City Hospital, St Albans, United Kingdom, [4]Diana Princess of Wales Hospital, Grimsby, United Kingdom, [5]St. Georges Hospital, London, United Kingdom, [6]City Hospital, Nottingham, United Kingdom, [7]County Hospital, Hereford, United Kingdom, [8]St Albans City Hospital, St Albans, United Kingdom

Background/Purpose: The need for orthopaedic surgery in Rheumatoid Arthritis (RA) is the result of failed medical treatment and a surrogate marker for joint destruction. Reliable prognostic markers are currently limited but have a potential role in guiding clinicians in early management decisions.

Methods: Standardised clinical, laboratory and X-ray measures were performed at baseline, prior to DMARD therapy and then yearly in both the Early RA Study (ERAS, n=1465, 1986–1998) and Early RA Network (ERAN, n=1236, 2002–2011), median follow up 18 and 6 years respectively, maximum 25 years. Treatment of patients included disease modifying, steroid and biologic therapies according to standard UK practices for management of hospital based RA patients. Source data of all orthopaedic interventions included clinical datasets (patient reports and medical records from 1986) and national data: Hospital Episode Statistics and the National Joint Registry. Length of follow up was based on the National Death Registry. For analysis, interventions were grouped into major (total large joint replacements), intermediate (mainly synovectomies, arthroplasties and fusion procedures of wrist, hand, hind/forefoot), and minor (mainly soft tissue and tendon surgery).

Results: 1602 procedures were performed in 770 out of 2701 patients (29%). 576 were large joint replacements (mainly of hips and knees) in 354 (out of 2701) patients (13%), 392 intermediate in 221 (8%), 552 minor in 361 (13%), 55 internal fixations for hip fracture in 53 (2%), 9 cervical spine fusions and the remainder were miscellaneous/not classified procedures. 232 (8.6%) patients had more than one major and/or intermediate procedure. 1255 had minimum 10 year follow up (46%) of whom 531 (42%) had orthopaedic surgery. In univariate analysis, baseline and 1 year Health Assessment Questionnaire (HAQ), Erythrocyte Sedimentation Rate (ESR), high Disease Activity Scores (DAS), erosions and low haemoglobin(HB) all predicted major and intermediate surgery with odds ratios (ORs) all significant around 1.5–2, but these variables were not predictive of minor surgery. Strongest predictors for major surgery were low HB (OR 2.6, 95% CI 2–3.3), high Body Mass Index (BMI) only for total knee replacements (OR 1.7, 95% CI 1.2–2.4), for intermediate surgery were women (OR 3.2, 95% CI 2.21–4.7), DAS (OR 3.8, 95% CI 2.1–7.0) and RA related shared epitope (SE, OR 1.6, 95% CI 1.0–2.4). For multiple surgery, strongest predictors were erosions (OR 2.7, 95% CI 1.6–4.3), HAQ (OR 2.6, 95% CI 1.6–4.2), HB (OR 3.4, 95% CI 2.3–4.9), ESR (OR 3.1, 95% CI 1.9–4.7), SE (OR 1.9, 95% CI 1.2–3.4), ESR (OR 3.3, 95% CI 2.3–4.8). In Cox regression, sex, onset age and erosions predicted intermediate surgery, and sex, onset age and HB predicted major surgery.

Conclusion: Orthopaedic surgery is an important and common outcome in RA, not often reported and difficult to predict. HB does not normally perform well as a predictor of outcome in RA, but did for orthopaedic intervention, especially major and multiple surgery.

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Disease Activity and Anti-CCP Status, but Not Sociodemographic Factors or Patient Comorbidities, Affect Time to Diagnosis in Early Rheumatoid Arthritis. Cheryl Barnabe[1], Juan Xiong[2], Gilles Boire[3], Carol A. Hitchon[4], Boulos Haraoui[5], Janet E. Pope[6], J. Carter Thorne[7], Edward Keystone[8], Diane Tin[7], Vivian P. Bykerk[9] and Canadian ArThritis CoHort[10]. [1]University of Calgary, Calgary, AB, [2]University of Toronto, Toronto, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]University of Manitoba, Winnipeg, MB, [5]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [6]St. Joseph's Health Care London, London, ON, [7]Southlake Regional Health Centre, Newmarket, ON, [8]University of Toronto, Toronto, ON, [9]Hospital for Special Surgery, New York, NY, [10]Toronto

Background/Purpose: Delays in patient presentation to primary care providers, subsequent referral for rheumatology assessment, and recognition of rheumatoid arthritis (RA) by the rheumatologist increase time to diagnosis. This time period is a modifiable determinant of joint damage and affects the odds of entering remission, and factors impacting this time must be elicited. Our aim was to evaluate whether time to diagnosis is influenced by measures of disease severity or a family history of RA, sociodemographic factors affecting access to care (age, sex, socioeconomic status [SES], education level, ethnicity), or comorbidities that may influence the physical examination, such as obesity, mental health conditions, or other musculoskeletal pain conditions.

Methods: A prospective national cohort of patients with confirmed or possible RA by 2010 ACR criteria (n=1,151) was evaluated for predictors of the duration of time to diagnosis. Variables examined in univariate analysis are summarized in Table 1. Simple linear regression was applied to each variable, and significant predictors carried forward to multivariate linear regression.

Table 1. Variables Assessed in Univariate Analysis for Time to Diagnosis

Female	74%
Age, mean (SD)	54 (14.7) years
Caucasian ethnicity	83%
BMI, mean (SD)	28.6 (10.5)
DAS28, mean (SD)	5.02 (1.44)
Swollen joint count, mean (SD)	28 Joints: 7.7 (6.0); 66 Joints: 9.8 (7.9)
Tender joint count, mean (SD)	28 Joints: 8.3 (6.5); 66 Joints: 12.7 (9.4)
HAQ, mean (SD)	1.02 (0.70)
Patient Global (VAS 0-10), mean (SD)	5.7 (2.9)
Acute Phase Reactants, mean (SD)	ESR: 28.1 (22.6) mm/hr; CRP: 14.4 (17.8) mg/L
Serology	Rheumatoid factor positive 67%; Anti-CCP positive 58%
Education	Only elementary or high school 46%; College or post-secondary 51%
Annual Income	<$20,000: 12%; $20,000-$50,000: 24%; $50,000-$100,000: 18%; >$100,000: 8%
Mental Health Condition	Depression: 11%; Other: 1%
Fibromyalgia	2%
Osteoarthritis	11%
Family History of RA	22%

The mean symptom duration at the baseline rheumatology visit was 6.0 months (range 0.1–19.6). In univariate analysis, age, joint counts, DAS28, patient global, HAQ, ESR, CRP, education level and anti-CCP status were all significant predictors (p<0.05) for time to diagnosis, whereas BMI, sex, ethnicity, income, RF status, family history of RA, and history of depression, fibromyalgia or osteoarthritis had no effect. In multivariate analysis, higher swollen joint counts, higher ESR, worse patient global scores, and negative anti-CCP antibody status were significant predictors of shorter time to diagnosis (Table 2).

Results:

Table. 2. Multivariate Analysis for Predictors of Time to Diagnosis

Parameter	Estimate	95% CI	P-value
Intercept	7.789	7.257; 8.322	<.0001
Swollen Joints	−0.051	−0.089; −0.013	0.0085
ESR	−0.016	−0.026; −0.006	0.0017
Patient Global Score	−0.085	−0.161; −0.009	0.0280
Damaged joint count	−0.090	−0.204; 0.023	0.1192
Anti-CCP Positive	0.814	0.383; 1.245	0.0002

Conclusion: Recognition of RA is not affected by a family history, sociodemographic factors, body habitus, mental health conditions, or other musculoskeletal pain syndromes. Worse patient global, more swollen joints, higher ESR and anti-CCP status influence time to diagnosis. The impact of fewer swollen joints and normal laboratory parameters on delay to diagnosis merits further consideration.

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Relationship Between Clinical Response and Radiographic Outcomes in Patients with Moderate Rheumatoid Arthritis. Josef S. Smolen[1], Ronald F. van Vollenhoven[2], Andrew S. Koenig[3], Ronald Pedersen[3], Annette Szumski[3] and Eustratios Bananis[3]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]The Karolinska Institute, Stockholm, Sweden, [3]Pfizer Inc., Collegeville, PA

Background/Purpose: Clinical evidence has established the importance of early, intensive treatment of rheumatoid arthritis (RA) to decrease disease activity and prevent joint damage.[1] The objective of this analysis is to examine the relationships between disease activity and inhibition of radiographic progression after 36 weeks of etanercept (ETN) + methotrexate (MTX) therapy in patients with moderate RA.

Methods: In the PRESERVE trial, patients with moderately active RA (DAS28 3.2–5.1) despite stable MTX for ≥3 months received open-label ETN 50 mg once weekly + MTX for 36 weeks. Week 36 (final time point) mTSS, defined as the sum of baseline mTSS and mTSS progression rate (units/year), was analyzed in relationship to disease activity by CDAI and DAS28.

Results: 704 patients who received ≥1 dose of ETN 50 mg + MTX and had available X-rays were included in this analysis. The percentage of patients achieving CDAI and DAS28 remission was 28% and 69%, respectively, and LDA including remission was seen in 87% and 88%. Both week 36 CDAI and week 36 DAS28 remitters had lower week 36 mTSS progression rate (units/year) compared with non-remitters (P<0.05). Week 36 CDAI remitters

also had lower baseline mTSS and lower week 36 mTSS (P<0.05; Table). CDAI and DAS28 week 36 disease activity categories (remission, LDA excluding remission, and NR) had similar proportions of patients (80–87%) who achieved radiographic non-progression (mTSS Δ ≤0.5). A significant relationship (P<0.001) was observed between baseline mTSS quartiles and week 36 mTSS progression rate categories (≤0.5, >0.5≤3, >3); the lowest baseline mTSS quartile (≤5) had the highest proportion of non-progressors (≤0.5; 28%) and the highest quartile (>51) yielded the highest percentage (54%) of patients with large radiographic progression (>3). A similar, significant (P<0.01) relationship was seen between baseline mTSS quartiles and week 36 CDAI response categories, with the lowest quartile having the highest proportion of CDAI remitters (33%) and highest quartile having the largest proportion of CDAI NR (31%).

Table. Descriptive Statistics for mTSS by Week 36 Clinical Disease Response Category

		ETN + MTX mTSS		
Week 36 Response	**n**	**Baseline, Units Mean (Median)**	**Final Time Point,† Units Mean (Median)**	**Progression Rate, Units/Yr Mean (95% CI)**
CDAI Remission (≤2.8)	195	36.5 (14.5)*	36.6 (14.5)*	0.1 (−0.1, 0.4)*
CDAI LDA (>2.8≤10)	415	39.3 (17.5)	39.7 (19.5)	0.4 (0.2, 0.6)
CDAI NR (>10)	94	44.4 (22.3)	45.0 (22.3)	0.6 (−0.3, 1.4)
DAS28 Remission (≤2.6)	487	37.9 (16.5)	38.2 (18.0)	0.3 (0.2, 0.5)*
DAS28 LDA (>2.6≤3.2)	135	41.9 (19.4)	42.1 (19.5)	0.2 (−0.1, 0.6)
DAS28 NR (>3.2)	82	42.6 (16.0)	43.3 (17.0)	0.7 (−0.2, 1.6)

*P < 0.05, Kruskal Walis test for differences in distributions. †Final time point defined as the sum of baseline and progression rate. DAS28 = 28-joint Disease Activity Score; CDAI = Clinical Disease Activity Index; LDA = low disease activity; NR = no response.

Conclusion: A large proportion of patients treated with ETN+ MTX achieved remission as measured by CDAI and DAS28 which inhibited radiographic progression regardless of week 36 disease activity. Overall, patients had less radiographic progression if they also achieved remission compared to LDA or NR. These results indicate that achievement of clinical goals in moderate RA has implications for structural benefits.

Reference
1. Combe B. *Best Pract Res Clin Rheumatol*. 2007;21:27–42.

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The Changed Prognosis of Patients with Early Rheumatoid Arthritis. Karin Britsemmer[1] and D. van Schaardenburg[2]. [1]Jan van Breemen Research Institute / Reade, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands

Background/Purpose: The treatment of rheumatoid arthritis (RA) has changed greatly during the past fifteen to twenty years. Major steps in this development were the introduction of methotrexate in the early nineties, the use of combination therapies including high-dose corticosteroids in the late nineties and the introduction of biologic therapies in the past decade. These improvements resulted in a better outcome and clinical remission became an attainable goal for many patients. This study documents trends in patient outcome over the last decades.

Methods: Five-year follow-up data was used from consecutive early RA patients (according to the 2010 ACR/EULAR criteria), included in the periods 1995–1999, 2000–2004 and 2005–2009. Disease activity (DAS-28), functional status (HAQ) and employment status (hours paid work per week) were used as outcome measures.

Results: 322, 369 and 389 patients were included in the three time periods, respectively. Median follow-up was 2 years. Patients included in 1995–1999 were older compared to the patients from the other periods, while the percentage of ACPA positive patients was higher in the last period. General practitioners referred patients increasingly sooner during the last 15 years. In the periods 1995–1999, 2000–2004 and 2005–2009 new patients with RA were treated in the first year with combination therapy in 13, 45 and 59% and/or biologics in 0, 9 and 19%, respectively. The baseline values of DAS-28, but not HAQ and hours paid work, showed a slight decrease over the three periods. However, after 5 years follow-up these differences were no longer significant. The trends in HAQ did not show differences between the three groups. The hours paid work of patients included in 2005–2009 remained stable during follow-up while the other groups showed a decrease over time. Data on radiographic progression are currently being analyzed.

Table. Baseline differences between patients of the three time periods

	1995–1999	2000–2004	p-value*	2005–2009	p-value*	p-value$
Age, yr	57 (15)	53 (14)	<0.001	53 (13)	<0.001	ns
Female, %	69	72	ns	72	ns	ns
ACPA, %	59	61	ns	75	<0.001	<0.001
RF, %	57	59	ns	58	ns	ns
Disease duration, mos.	5.0 (3.4–8.0)	4.3 (2.6–7.2)	0.015	2.8 (1.6–5.9)	<0.001	<0.001
GP-delay, wk	13 (8–29)	9 (4–21)	<0.001	4 (1–13)	<0.001	<0.001
DAS-28	5.2 (1.2)	5.1 (1.3)	ns	4.9 (1.3)	0.021	*0.052*
HAQ	1.13 (0.5–1.75)	1.13 (0.75–1.75)	ns	1.13 (0.63–1.63)	ns	ns
Work, h/wk	32.9 (15.9)	30.0 (11.0)	ns	32.6 (12.8)	ns	ns

Values are expressed as mean (SD) or median (IQR) * p-value compared to period 1995-1999
$ p-value compares period 2000-2004 vs 2005–2009
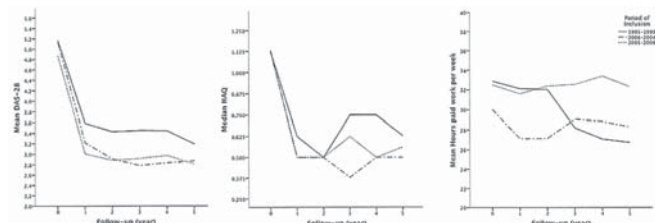
Conclusion: The results document an increasingly better prognosis of early RA patients over the last 15 years. Early recognition and referral by general practitioners has led to a lower disease activity at baseline. Next, more intensive treatment resulted in improved outcomes. However, despite a favorable trend in work participation, there still remains ample opportunity for a further reduction of disease activity and improvement of function.

Disclosure: **K. Britsemmer**, None; **D. van Schaardenburg**, None.

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Trabecular Bone Texture parameters are Correlated with Magnetic Resonance Imaging (MRI) bone Edema At Hand and Wrist in Active Rheumatoid Arthritis (RA). Thao Pham[1], Sophie Trijau[1], Roland Chapurlat[2], Damien Loeuille[3], Thierry Schaeverbeke[4], Christian Roux[5], Claude-Laurent Benhamou[6], Olivier Vittecoq[7], Jean Sibilia[8], Frederic Mistretta[9] and Cécile Hacquard-Bouder[10]. [1]Sainte Marguerite Hospital, Marseille, France, [2]Hôpital Edouard Herriot, Lyon, France, [3]CHU Brabois, Vandoeuvre les Nancy, France, [4]Groupe Hospitalier Pellegrin, Bordeaux, France, [5]Paris Descartes University, Paris, France, [6]EA 4708 University Orleans, Orleans, France, [7]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France, [8]CHU Hautepierre, Strasbourg, France, [9]Lyon, France, [10]Abbott France, Rungis, France

Background/Purpose: In RA, bone marrow edema (BME) is predictive of erosive progression. Bone erosions are assumed to appear through activation of local bone resorption mechanisms, reflected by periarticular osteopenia. Measurement of periarticular bone mineral density by DXA requires specific hand software limiting its application in large population, and does not assess bone texture. A new high resolution direct digital X-ray device has been recently developed to provide bone texture analysis reflecting changes in trabecular bone architecture, with a very low radiation exposure.

Objectives: To assess the correlation between MRI bone edema and trabecular bone texture parameters in active RA.

Methods: *Study design:* cross-sectional multicenter study. Comparative MRI and high resolution X-rays of the dominant hand and wrist were obtained from 55 patients with active RA according to ACR/EULAR criteria (DAS 28 ≥ 3.2). Clinical examination and radiographs of the hands and wrist were also performed. *High resolution direct digital X-ray* (BMA™, D3A Medical Systems): The fractal trabecular bone texture parameter (Hmean) was evaluated on the 2nd and 3rd metacarpal head, capitatum and lunatum. *MRI:* BME was scored according to the RA MRI score (RAMRIS) by two independent and experienced radiologists (central reading). BME was also specifically assessed on the 4 bones where Hmean was evaluated (BME4 score). *Radiographs:* plain radiographs were scored using the modified Sharp-van der Heijde method. *Analysis:* Inter-reader reliability: ICC. Correlation between BME and Hmean: Spearman test.

Results: Data from 53 patients were analyzable. The main patients characteristics were (mean ± SD): age 57 ± 14 years, 75% women, disease duration 8.6 ± 9.2 years, DAS28 5.4 ± 1.3, anti-CCP 76%, Sharp-DvdH 23.8 ± 31.3, currently treated with DMARDs 74%, biologics 47%, corticosteroids 60% (mean daily dosage 9.1 ± 6.6 mg). The mean ± SD [median] RAMRIS BME, BME4 and Hmean scores were 12.7 ± 14.6 [5.0], 2.7 ± 2.8 [1.0] and 0.60 ± 0.06 [0.61], respectively. RAMRIS BME inter-reader reliability: ICC=0.96. Correlations between Hmean and both RAMRIS BME and BME4 scores were r=-0.31 (p=0.022) and r=-0.32 (p=0.018), respectively. When evaluated only on the 2nd and 3rd metacarpal head, Hmean was significantly correlated with the total BME score r=-0.28 (p=0.038) whereas it was not when evaluated on lunatum and capitatum (r=-0.22 – p=0.120).

Conclusion: This study demonstrated trabecular bone texture parameters are correlated to MRI bone edema scores. It would be interesting to assess if bone texture impairment, measured with a high resolution digital Xray device, could predict RA radiographic progression in a wider range prospective study.

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Alcohol Use and Radiographic Disease Progression in African Americans with Recent Onset Rheumatoid Arthritis. Marshall Davis[1], Kaleb Michaud[1], Harlan Sayles[1], Doyt L. Conn[2], Larry W. Moreland[3], S. Louis Bridges Jr.[4] and Ted R. Mikuls[1], [1]University of Nebraska Medical Center, Omaha, NE, [2]Emory Univ School of Medicine, Atlanta, GA, [3]University of Pittsburgh, Pittsburgh, PA, [4]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Previous studies have shown that alcoholic beverage consumption can modify levels of circulating inflammatory cytokines and alter expression of innate immune system receptors. Recognizing these changes, investigators have sought to identify the association of alcohol consumption with rheumatoid arthritis (RA) risk and progression. To date, studies have primarily been limited to patients of European ancestry and have yielded conflicting results. To address this gap of knowledge we sought to investigate alcohol consumption and RA disease progression in African Americans; a historically understudied cohort. Specifically, the aim of our study was to determine if alcohol consumption, stratified by dose, is associated with radiographic disease progression in African Americans during the early stages of RA.

Methods: RA patients included in the study were participants in the Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR) registry with < 2 years disease duration from symptom onset. Patients reported the average number of alcoholic beverages consumed per month and a modified Sharp/van der Heijde score was computed to assess disease progression using joint space narrowing and erosion totals in radiographs of the wrists, hands, and

feet. Upon visual inspection, a clear natural break with an inflection in the slope was identified at 15 beverages per month. Patients were subsequently categorized into two groups: those consuming < 15 beverages per month versus those consuming ≥ 15 per month. Associations of radiographic disease progression over a one to three year period of observation with alcohol consumption was evaluated using generalized estimating equations adjusting for patient demographics, current RA therapy, anti-CCP, RF-IgM, c-reactive protein, and smoking status.

Results: There were 166 patients included in the study; 139 reported that they consumed, on average, < 15 alcoholic beverages per month and 27 reported consuming ≥ 15 per month. A "checkmark-shaped" relationship of alcohol consumption and radiographic disease progression was identified and is shown in Figure 1. In patients consuming ≥ 15 alcoholic beverages per month, alcohol intake was associated with an increased risk of radiographic disease progression ($p = 0.017$) after multivariate adjustment. There was no evidence of a relationship in those consuming < 15 beverages per month ($p = 0.802$).
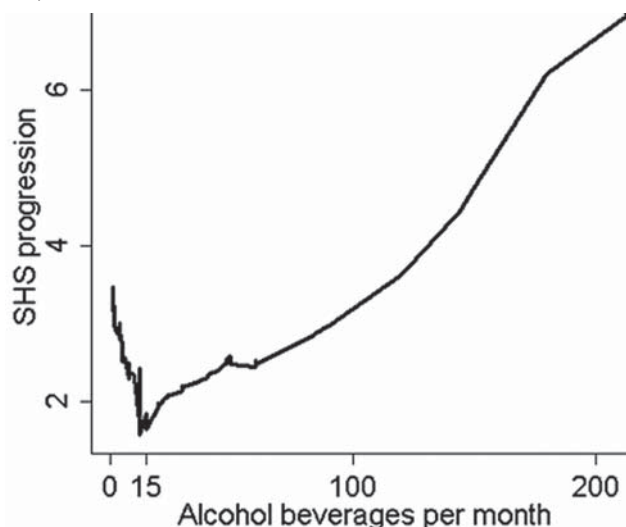
Figure 1. Radiographic disease progression summarized based on the average number of alcoholic beverages consumed per month.

Conclusion: There appears to be a dose-dependent relationship between alcohol use and radiographic disease progression in African Americans with RA. Individuals who consume 15 or more alcoholic beverages per month may have accelerated rates of radiographic joint damage compared to those with lower levels of consumption.

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Contribution of Disease Activity, Joint Damage and Comorbidity to Impairment (SOFI) and Disability (HAQ) in Rheumatoid Arthritis Patients Over 20 Years.
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Background/Purpose: To study the contribution of disease activity, joint damage and co-morbidity on development of impairment measured by signals of functional impairment (SOFI) and disability measured by health assessment questionnaire (HAQ) in rheumatoid arthritis (RA) patients prospectively followed over 20 years after diagnosis.

Methods: 183 RA patients diagnosed between 1985 and 1989 were prospectively monitored over 20 years. There were 116 (63 %) women, mean (SD) age was 52 (12) years and symptom duration before inclusion was 11 (7) months. Disease activity was measured by 44-joint DAS, joint damage by Larsen score of radiographs of hands and feet, comorbidity by Charlson Comorbidity Index (17 diagnoses each weighted by mortality risk), impairment by SOFI (3-parts performance based index measuring hand, arm and leg function) and disability by HAQ. Two separate multiple regression models with SOFI and HAQ as outcome variables at 0, 5, 10, 15 and 20 year follow up were created.

Results: Altogether, disease activity, radiographic joint damage and co-morbidity explained 22–38% of SOFI and 14–38 % of HAQ (figure). For SOFI, DAS contributed with 2–27% with a peak at 5 years. Radiographic damage contributed increasingly (6–35%). For HAQ, DAS contributed significantly at all follow up times (7–28%), with a peak at 5 years whereas radiographic damage had minor contribution (0–10%). Comorbidity showed minor contribution both to SOFI and HAQ.
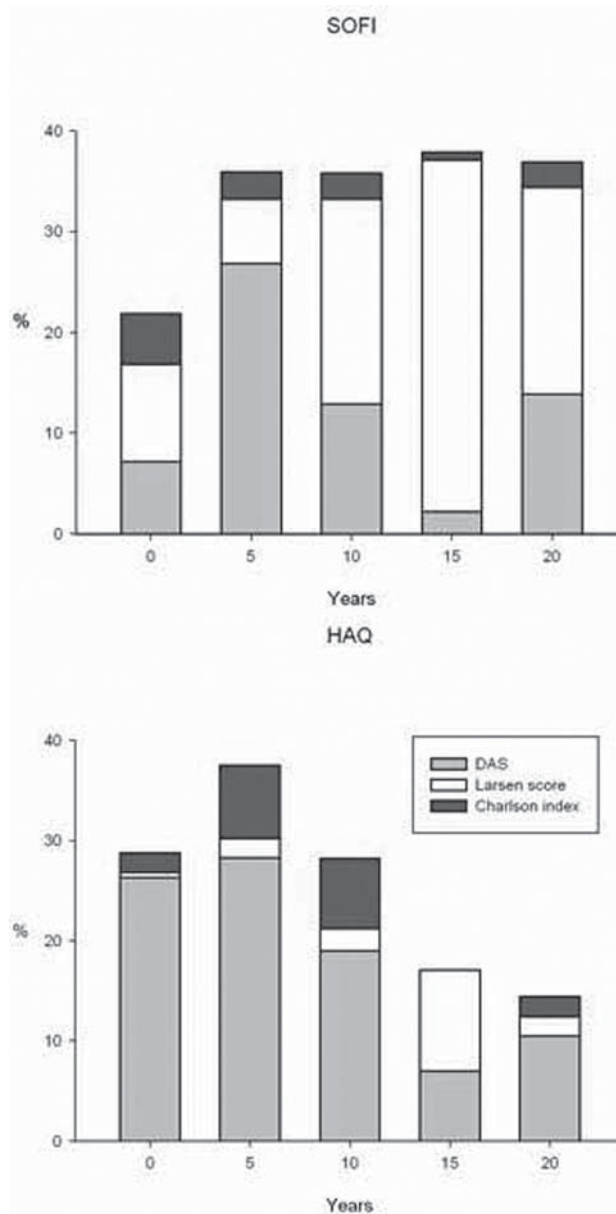
Figure. Contribution of disease activity (DAS), joint damage (Larsen score) and comorbidity (Charlson comorbidity index) to impairment (SOFI) and disability (HAQ) in rheumatoid arthritis patients over 20 years

Conclusion: In the long-term perspective impairment is increasingly explained by radiographic damage, whereas disability is less well explained by RA related factors over time. Comorbidity contributed only to small extend to both impairment and disability.

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Racial and Ethnic Disparities in Rheumatoid Arthritis Outcomes in Community-Based U.S. Rheumatology Practices: Results From the Consortium of Rheumatology Researchers of North America Registry.

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Background/Purpose: Disparities in medication use and clinical outcomes have been reported in patients with rheumatoid arthritis (RA) and other chronic diseases. However, there is little information regarding whether disparities exist in RA clinical outcomes in black and Hispanic patients treated in community-based rheumatology practices in the U.S..

Methods: We examined data from RA patients (pts) participating in the Consortium of Rheumatology Researchers of North America (CORRONA) registry, an independent registry collecting patient and physician-derived data from both academic-affiliated and community-based practice sites. Among the 30,869 RA pts enrolled in the registry across 146 academic and community-based sites, we examined data from 26,640 RA pts under the care of 109 community-based rheumatology practices. We performed a cross-sectional study using data collected from the most recent registry visit as of 05/05/2012. We compared medication use and RA outcomes across race/ ethnic groups, comparing non-Hispanic white RA pts versus black and Hispanic RA pts based on self-reported race/ethnicity categories. Specifically, we compared measures of RA disease activity (DAS28 and CDAI), as well as patient-reported outcomes (pain VAS and HAQ score). Pairwise statistical comparisons were performed versus the white RA cohort.

Results: The study cohorts included 23,396 non-Hispanic whites,1,890 black and 1,354 Hispanic pts. The mean duration of RA was greater for whites (11.6 yrs) vs blacks (9.4 yrs, p<0.001) and Hispanics (10.8 yrs, p<0.001). Similar proportions of Hispanics (58.3%) and white pts (59.7%) were treated with methotrexate (MTX), and more blacks (62.4%) were treated with MTX versus whites. Prescribed MTX dosages were comparable across groups, although blacks and Hispanics reported taking significantly lower dosages. Estimated MTX adherence calculated as patient-reported dosage divided by the prescribed dosage varied from 89% in whites to 78.5% in blacks and 82.6% in Hispanics. Slightly higher rates of biologic use were observed for whites (44.9%) vs. blacks (42.8), although not significantly different (p=0.07). In comparison to whites, Hispanics actually had higher rates of biologic use (48.7%, p<0.01). Higher levels of disease activity using both the CDAI and DAS28 were observed for blacks and Hispanics vs. whites (p<0.001, see Table). Higher patient pain scores (p<0.001) and worse functional status (p<0.001) were also reported by both black and Hispanic RA pts vs. whites.

Table. Medication Use and Outcomes by Racial and Ethnic Group

	White (N=23,396)	Black (N=1,890)	Hispanic (N=1,354)
Clinical Outcomes			
Disease Activity Score (DAS28), mean	3.3	3.6***	3.6***
Clinical Disease Activity Index (CDAI)	11.2	12.5***	13.4***
MD global VAS, mean	18.3	23.0***	21.9***
Patient global VAS, mean	29.8	34.8***	33.3***
Tender joint count, mean	3.2	3.4	4.4***
Swollen joint count, mean	3.1	3.2	3.6***
Patient Pain Score (VAS), mean	32.1	37.3***	35.7***
Functional Status (HAQ Score), mean	0.69	0.82***	0.77**
RA Treatment			
Biologic prescribed currently (%)	44.9	42.8	48.7**
MTX prescribed currently (%)	59.7	62.4*	58.3
MTX dose prescribed, mean (mg/wk)	15.9	16.1	15.5
MTX dose self-reported, mean (mg/wk)	14.2	12.7*	12.8*

Note: ***p<0.001, **p<0.01, *p<0.05

Conclusion: Although some differences in RA medication prescribing were observed, both black and Hispanic pts treated in community-based practices demonstrated higher RA disease activity, higher pain scores and worse functional outcomes than white RA pts.

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Smoking Is Associated with Worsening Functional Status Over Time in a Diverse Cohort of Patients with Rheumatoid Arthritis.

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Background/Purpose: Although the effects of tobacco use on disease onset, severity, and response to therapy have been well studied in rheumatoid arthritis (RA), there is little data addressing the effect of smoking on the functional status of patients with RA. This study assesses the relationship between tobacco use and change in functional status over time in patients with RA.

Methods: Retrospective analysis of 121 subjects with confirmed RA in an ethnically diverse outpatient rheumatology clinic at a public hospital. Primary outcome was the difference between baseline HAQ score and repeated assessment of HAQ 2–5 years later. Primary predictor variable was current smoking at baseline. Covariates included time between HAQ assessments, age, gender, rheumatoid factor positivity, baseline HAQ and DAS28-ESR scores, synthetic DMARD use, biologic use, and disease duration. Student's t-test was used to compare the mean change in HAQ over time between smokers and non-smokers. Association between smoking and change in HAQ over time, controlling for all covariates, was assessed with multivariate linear regression. Multivariate logistic regression was then used to assess the odds of achieving the accepted clinically meaningful improvement in HAQ score of −0.22[1] during this time period.

Results: Of the 121 subjects, 14 (12%) were current smokers at baseline assessment, 108 (89%) were female, and 114 (94%) were non-Caucasian. Mean age was 53 (+13). Mean baseline HAQ score was 1.32, mean time between HAQ assessments was 3.5 years, and mean change in HAQ over time was 0.088. Individual change in HAQ score ranged from −1.88 to 2.0. Mean change in HAQ was 0.411 among smokers and 0.046 among non-smokers (p = 0.043). One of 14 smokers (7%), and 33 of 107 non-smokers (31%), achieved a clinically meaningful improvement in HAQ during this time period. Multivariate linear regression demonstrated that smoking is independently associated with a worsening HAQ over time (coefficient= 0.33, p= 0.047). Multivariate logistic regression demonstrated that smoking decreased the odds of achieving a clinically meaningful improvement in HAQ (OR 0.07, 95% CI 0.01–0.83).

Conclusion: Cigarette smoking was associated with worsening functional status among patients in this cohort over a mean time of 3.5 years. In addition, the odds of achieving a clinically meaningful improvement in functional status during this follow-up period were significantly lower in smokers as compared to non-smokers.

[1]Wolfe. J Rheumatol 2005; 32:583.

2140

A Longitudinal Study of Prognostic Factors in Patients with Early RA Providing Direction for Future Clinical Treatment- Predict Study.

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Background/Purpose: Despite the conspicuous increase in available treatment for rheumatoid arthritis [RA], and the shift to early, more aggressive management, there is a paucity of reliable prognostic markers to assist in the stratification of therapy in individual patients. As a result, individualized risk-adapted therapy for patients with RA remains a desirable, but elusive goal. The primary objective of this study was to assess the association between baseline clinical prognostic factors and subsequent DAS remission in early RA patients.

Methods: The study utilised point of care clinical software to collect data from *20* participating rheumatology treatment centres. Newly diagnosed RA patients over the age of 18 years treated at a participating clinic were eligible. Patients were required to have attended the clinic on at least two occasions in 6 months and have at least two available DAS assessments. Clinical predictors of outcome were identified and the list was refined by consensus. Data captured included baseline demographics, mode of disease onset, pattern of joint involvement at onset, smoking status, DAS, RF and CCP titre, time from onset of symptoms to presentation and disease activity at baseline. Statistical analysis utilized a univariate and multivariate logistic regression of DAS28ESR remission 12 months after the first assessment.

Results: 1,121 patients were included in the analysis (71% female, 29% male). 434 patients were RF positive, 265 CCP positive. Mean age 61.3 years (SD 13.4).

The strongest baseline predictors of DAS28ESR remission at 12 months were younger age, male and low disease activity at baseline. There was no statistically significant association between joint onset patterns, mode of onset, RF or CCP status and smoking status.

The association between DAS28ESR remission at 12 months and age was borderline significant. Odds ratio for age was 0.985 (95% CI = (0.969, 1.01)). For each additional decade of age, the odds of being in remission at 12 months decreased by 15% (p = 0.057)

For female patients the odds of being in remission at 12 months was 0.887;for male patients the odds of being in remission at 12 months was 2.00; therefore the odds of a male patient being in remission at 12 months was 2.256 times greater than those for female patients (OR 2.256, 95% CI = (1.384, 3.675), P<0.001.)).

For patients who were in remission at baseline the odds of being in remission at 12 months was 2.44; for patients who were not in remission at baseline the odds of being in remission at 12 months was 0.57; therefore the odds of a patient in remission at baseline being in remission at 12 months were 4.28 time greater than those patients not in remission at baseline (OR 4.28, 95% CI = (2.56, 7.17), P < 0.001.)).

Conclusion: The strongest baseline predictors of DAS remission at 12 months were younger age, low baseline disease activity and male gender. Traditional prognostic factors associated with outcome such as smoking and CCP status were not strong predictors of outcome at 12 months. The study identifies potential high-risk groups that may benefit from more frequent clinical assessment and therapy adjustment. The cohort will be followed over the next five years to provide data on long term outcome.

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Effects of Cigarette Smoking On EARLY Arthritis (CONAART). Maria Haye Salinas[1], Ana C. Alvarez[1], Rafael Chaparro del Moral[2], Mariana Benegas[2], Christian A. Waimann[3], Rodolfo Perez Alamino[3], Rodrigo Garcia Salinas[4], Ana Lucía Barbaglia[5], Veronica Bellomio[5], Josefina Marcos[6], Adrian Salas[6], Cristian Quiroz[7], Federico Ceccato[8], Sergio Paira[8], Dora Lia Vazquez[9], Gabriela Salvatierra[10], M. Crespo[11], Edson Javier Velozo[12], Oscar L. Rillo[13], Enrique Soriano[14], Antonio Catalan Pellet[4], Alberto Berman Sr.[5], Juan Carlos Marcos[6], Gustavo Citera[15] and Francisco Caeiro[16]. [1]Hospital Privado, Córdoba, Argentina, [2]Hospital Tornu, Buenos Aires, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Hospital Rivadavia, Buenos Aires, Argentina, [5]Hospital Padilla, Tucuman, Argentina, [6]Hospital San Martin, La Plata, Argentina, [7]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [8]Hospital Jose Maria Cullen, Santa Fe, Argentina, [9]Centro Integral de Reumatologia, Santiago del Estero, Argentina, [10]Centro de enfermedades Reumaticas, Santiago Del Estero, Argentina, [11]Hospital Señor del Milagro, Salta, Argentina, [12]Sanatorio Adventista del Plata, Entre Rios, Argentina, [13]Hospital Tornú, Buenos Aires, Argentina, [14]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [15]Instituto de Rehabilitación Psicofísica., Buenos Aires, Argentina, [16]Hospital privado de Cordoba, Cordoba, Argentina

Background/Purpose: According to recent reports the cigarette smoking persons have 2–4 times greater risk of developing rheumatoid arthritis (RA). The cigarette smoking is associated with an early onset, a greater seropositivity, erosions and severity in patients with early arthritis. The purposes of our study was to analyze the effects of cigarette smoking on the disease activity, serology, presence of extra-articular manifestations (ExM) and radiographic damage in patients with early arthritis.

Methods: This cross-sectional study involving 1.305 patients (729 diagnosed with rheumatoid arthritis (American College of Rheumatology '87 criteria) and 576 undifferentiated arthritis) belonging to CONAART (Argentine Consortium for Early Arthritis) that includes patients older than 16 yrs with arthritis in at least 1 joint and less than two years of disease. The patients have been divided in never smokers, former smokers and current smokers and these last two were classified according the amount of pack years smoked. The following variables were assessed: ExM, joint count, Health Assessment Questionnaire (HAQ), Disease Activity Score of 28 joint (DAS28), Rheumatoid Arthritis Disease Activity Index (RADAI), The Rheumatoid Arthritis Quality of Life (RAQoL), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Rheumatoid Factor (RF) and Simple Erosion Narrowing Score (SENS) of radiographs.

Categorical variables were compared with chi square and continuous with ANOVA or Kruskal Wallis. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals.

Results: Mean age was 48 ± 14 years and 82% were female. Were current smokers 23.1%, former smokers 9.5% and never smokers 67.4%. Univariate analysis is showed on table one. Variables independently associated with cigarette smoking were RADAI (OR=1.18, 95% CI 1.04–1.33; $p=$ 0.007) and SENS (OR=1.04, 95% CI 1.02–1.71; $p=$ 0.003). No relationship was found between disease activity and severity and number of pack years.

Table 1. The features of arthritis according to smoking status.

	Current smokers n 302	Former smokers n 124	Never smokers n 879	p
Painful joints, M (R_Q)	10 (5–17)	7.5 (3–15.7)	8 (3–17)	**0.02**
Swollen joints, M (R_Q)	7 (3–13)	4.5 (3–10)	5 (2–10)	**0.003**
ExM, n (%)	7 (2.3)	2 (1.6)	16 (1.8)	0.83
DAS28, m ± DS	5.21 ± 1.45	5.05 ± 1.35	4.87 ± 1.41	**0.02***
HAQ, M (R_Q)	1.2 (0.5–1.8)	1.2 (0.5–1.7)	1.0 (0.5–1.6)	**0.01**
RADAI, m ± DS	5.04 ± 2.11	4.92 ± 2.21	4.39 ± 2.14	**<0.001*/0.03#**
RAQUOL, M (R_Q)	15 (9–22)	15 (9–20)	13 (6–20)	**0.008**
RF title, M (R_Q)	128 (32–282)	89.8 (19.2–226.5)	78.5 (17–180)	**0.010**
RF positive, n (%)	178 (67.7)	77 (67.5)	468 (58.8)	**0.014**
ESR, M (RQ)	25 (13–42)	25 (12.2–40)	25 (13–44.7)	0.59
CRP, M (R_Q)	2.55 (0.38–12)	1.88 (0.21–6.95)	2.47 (0.3–9.89)	0.54
SENS, M (R_Q)	11 (4–20)	13 (4.5–19)	9.5 (3–16)	**0.02**

*Current smokers compared with current smokers. # Former smokers compared with never smokers.

Conclusion: In this study, smokers exhibited higher frequency of seropositivity for RF, higher levels of disease activity, worse functional capacity and more severe radiographic damage. There was no increased frequency of ExM. In multivariable analysis the smoking was independently associated with RADAI and SENS. There was no relationship between the variables of disease activity and the magnitude of smoking. Our study reinforces the importance to quit smoking in patients with early arthritis.

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Magnetic Resonance Imaging-Proven Osteitis At Baseline Predicts the Early Rheumatoid Arthritis Patients Who Will Develop Rapid Radiographic Progression: MRI Is Beneficial to Find the Window of Opportunity in Early RA. Mami Tamai[1], Yoshikazu Nakashima[2], Takahisa Suzuki[2], Yoshiro Horai[2], Akitomo Okada[2], Junko Kita[2], Shin-ya Kawashiri[2], Naoki Iwamoto[1], Kunihiro Ichinose[2], Kazuhiko Arima[1], Hideki Nakamura[1], Tomoki Origuchi[2], Masataka Uetani[2], Kiyoshi Aoyagi[2], Katsumi Eguchi[3] and Atsushi Kawakami[2]. [1]Nagasaki University, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Sasebo City General Hospital, Sasebo, Nagasaki, Japan

Background/Purpose: Window of opportunity exists in the earlier phase of rheumatoid arthritis (RA), thus, early recognition of the RA patients who will develop rapid radiographic progression (RRP) is crucial. We have reported an importance of magnetic resonance imaging (MRI)-proven symmetrical synovitis, osteitis and bone erosion of wrist and finger joints toward

the early classification of RA from the prospective early arthritis cohort at Nagasaki University, Nagasaki, Japan. To investigate whether MRI assessment of joint injury at baseline predict the development of RRP at 2 years in patients with early RA by our cohort.

Methods: One hundred-eleven RA patients, who fulfilled 2010 RA classification criteria and introduced disease-modifying anti-rheumatic drugs (DMARDs) including biologics within the first 1 year, were consecutively enrolled in this study. These patients were referred to the RA patients in the present study. Patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. All of the subjects had been examined by gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI and plain radiograph of both wrist and finger joints at the same day every 6 months during 2 years. MRI-proven synovitis, osteitis and bone erosion were evaluated by RAMRI scoring (RAMRIS) technique. RRP was defined as yearly progression of Genant-modified Sharp score >3.0 during 2 years. We have examined what variables at entry, including MRI features, and the therapies during 2 years predict the development of RRP at 2 years by logistic regression analysis.

Results: The mean disease duration, age, % female, prevalence or titer of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), disease activity score (DAS) 28-CRP at entry were 4.0 months, 56.2 y.o., 66.7%, 60.4% or 95.5 ± 186.7 IU/ml, 58.6% or 160.3 ± 345.4 U/ml and 4.38, respectively. The frequency of MRI-proven symmetrical synovitis, osteitis and bone erosion at baseline was 80.7, 54.5, 37.2%. Biologics were administrated in 17.1% of the patients during 2 years. Twenty patients (18.0%) were classified as RRP at 2 years. Logistic regression analysis has shown that MRI osteitis at baseline, history of biologics use during 2 years, Genant-modified Sharp score at baseline are independent variables to predict the development of RRP at 2 years (Odds ratio = 3.88, 7.95 and 12.4, respectively. 95% confidence interval = 1.05–14.42, 2.29–27.56 and 1.03–1.50, respectively, p-value = 0.043, 0.0011 and 0.027, respectively. Akaike's information criterion = 91.50).

Conclusion: Our present data indicate that MRI-proven osteitis at baseline is a predictor toward the development of RRP in patients with early RA. MRI is beneficial to find the window of opportunity in these patients.

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Analysis of Factors Associated with the Health Assessment Questionnaire Score Change in Five Years. Shinji Yoshida[1], Katsunori Ikari[2], Kensuke Ochi[1], Yoshiaki Toyama[3], Atsuo Taniguchi[1], Hisashi Yamanaka[1] and Shigeki Momohara[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Shinjuku-ku, Japan, [3]Keio University, Shinjuku, Japan

Background/Purpose: The Health Assessment Questionnaire (HAQ) score is thought to be a disease specific tool for the assessment of inflammatory joint disorders including rheumatoid arthritis (RA). It is considered as the main and good functional outcome measure in RA. The purpose of this study was to find the factors associated with the magnitude of HAQ score change in five years from the baseline.

Methods: We enrolled 4408 RA patients, who participated in the IORRA (Institute of Rheumatology RA cohort) from 2000 to 2004, and from whom the HAQ score was obtained at the baseline and five years later. From the IORRA database, we collected demographic, clinical and therapeutic data: rheumatoid factor (RF) positivity, age and body mass index (BMI) at the baseline; gender; year of onset; average disease activity score with 28-joint counts (DAS28) score in five years from the baseline. The HAQ score change is calculated as the Year 5 value minus the baseline. Factors associated with the HAQ score change were analyzed by multiple linear regression analysis adjusted for baseline HAQ score.

Results: The multiple linear regression analysis adjusted for baseline HAQ score revealed that the lower levels of average DAS28 score was most significantly associated with the better HAQ change in five years (Table 1). Recent onset of the disease, older age of onset and male sex are also associated with the better HAQ change, while RF positivity and BMI at the baseline are not associated with HAQ change.

Table.

Factor	Standardized regression coefficient	P value
RF	0.01	0.42
Average DAS28	0.26	<2e-16
Gender (female)	0.03	0.002
BMI	0.008	0.40
Year of onset	−0.12	<2e-16
Age	−0.07	5.0e-12

Conclusion: The lower levels of average DAS28 score, recent onset of the disease, older age of onset and male sex are associated with the better HAQ change. The results of this study may help patients without these factors to get early and aggressive intervention.

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Early RA Patients Fulfilling the New 2010 ACR/EULAR Criteria, Display Better Clinical Responses to DMARD Therapy but Have Higher Radiographic Damage Progression Than Patients with Early RA Not Fulfilling the 2010 ACR/EULAR Criteria. Ruediger Mueller[1], Toni Kaegi[1], Axel Finckh[2] and Johannes von Kempis[1]. [1]MD, St. Gallen, Switzerland, [2]Geneva University Hospitals, Geneva 14, Switzerland

Background/Purpose: New ACR/EULAR criteria for the classification of rheumatoid arthritis (RA) were recently proposed. The aim of this analysis was to examine the impact of fulfilling the 2010 ACR/EULAR criteria at the initial visit on long-term progression of disease and radiographic progression.

Methods: For this observational cohort study within the Swiss RA registry SCQM, we included patients suffering from early RA or undifferentiated arthritis (UA, disease duration ≤1 year), as defined by the treating rheumatologist, who had not received any previous DMARDs. Baseline diagnosis of RA/UA was reassessed according to the 2010 ACR/EULAR criteria at baseline. Patients were separated into 2 groups depending on whether or not they fulfilled the 2010 ACR/EULAR criteria at baseline (≥ 6 points versus < 6 points). The primary outcome measures were the DAS 28 and erosions as measured by the Ratingen score over time.

Results: A total number 592 patients was analysed. 352 of them fulfilled the 2010 ACR/EULAR at baseline, 240 were not classifiable as RA according to the new criteria at baseline. The score calculated by the new ACR/EULAR criteria correlated with disease activity at disease onset. Treatment was initiated with DMARDs, mostly MTX, in all patients. There were no significant differences in the therapeutic strategies between patients fulfilling the classification criteria or not. The patients fulfilling ACR/EULAR criteria at baseline developed a 39.1%reduction of DAS 28 scores, as compared to a 33.6%reduction in ACR/EULAR-negative patients after 6 months, independent of their respective treatments. After 1 year of follow-up no differences were found comparing the mean DAS28 scores in the 2 groups. Average radiographic progression was higher among ACR/EULAR-positive patients (progression of Ratingen score/year 0.50 vs. 0.32, resp., p=0.03) after 3 years of follow up.

Conclusion: The 2010 ACR/EULAR criteria appeared to select a subset of patients among early RA/UA patients with a favourable clinical response to conventional anti-rheumatic therapy. Despite this therapy, radiographic progression was higher in 2010 ACR/EULAR positive patients.

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Age At Onset Determines Severity and choice of Treatment in Early Rheumatoid Arthritis. Lena Innala[1], Bozena Möller[2], Lotta Ljung[1], Torgny Smedby[3], Anna Södergren[1], Staffan Magnusson[4], Ewa H. Berglin[1], Solbritt M. Rantapää-Dahlqvist[1] and Solveig Wållberg-Jonsson[1]. [1]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umeå, Sweden, [2]Department of Rheumatology, Sunderby Hospital, Luleå, Sweden, [3]Department of Rheumatology, Östersund hospital, Östersund, Sweden, [4]Department of Internal Medicine, Sundsvall Hospital, Sundsvall, Sweden

Background/Purpose: Mortality is increased in rheumatoid arthritis (RA). Contributing factors are disease activity/severity and comorbidity. A relationship between age at onset and pharmacological treatment has been implicated. We evaluated the impact of age at onset on prognostic risk factors and given treatment during five years from disease onset.

Methods: All patients from the 4 most northern counties of Sweden diagnosed with RA (<12 months symptoms) are consecutively included in a large survey on the progress of the disease and its co-morbidities. Up till now 950 (649f, 301m) patients have been included. Median age at disease onset was 58 years (range 18–89). All patients have been followed on a regular basis; a survey of co-morbidities was made at inclusion and after 5 years, measures of disease activity (ESR, CRP, tender joints, swollen joints, VAS pain and VAS global, DAS28, HAQ) and X-ray of hands (erosions, Larsen score) were assessed regularly. Disease severity (extraarticular disease, rheumatoid nodules), co-morbidities and pharmacological treatment (DMARDs, corticosteroids, biologics, NSAIDs, COX2-inhibitors) were registered. Autoantibodies (RF, ANA, ACPAs) and genetic markers (HLA-shared epitope, PTPN22 T-variant) were analysed. Young (YORA)/late (LORA) onset of RA was defined as below/above median age (58 years) at disease onset. Data analyses were based on stratification of the patients in YORA and LORA.

Results: Patients with LORA had higher ESR (34.3 vs. 26.0 mm/h, p<0.001), VAS global (47.8 vs. 42.9, p=0.085) and HAQ (1.0 vs 0.8, p=0.075) at baseline and significantly higher accumulated disease activity (AUC for DAS28) at 6 (p=10.0), 12 (p<0.01) and 24 months (p<0.05) compared to YORA. Patients with YORA had more often ACPAs (72.4% vs 65%; p<0.01) and PTPN22 T-variant (37,8 vs 29.5, p=0.056). Presence of extraarticular disease was similar however nodules tended to be more common at young onset (p=0.069) and YORA had significantly higher Larsen score (p<0.001 at 0 and 24 mo). Patients with LORA were significantly more often treated with corticosteroids (77.5 vs. 68.8%; p<0.01), significantly less with methotrexate (81.9 vs. 90.2%; p<0.01) and with biologics (7.6 vs. 24.9%, <0.001). Patients with YORA were treated with DMARDs earlier (within 3 months from inclusion; 94.0% vs. 85.8%; p<0.01) and overall (98.9 vs. 96.7, p=0.05). NSAID was more common in the early onset group (90 vs. 75.9%, p<0.001) with no difference for COX2 inhibitors.

Conclusion: Patients with young onset of RA presented with more risk factors for poor prognosis but those with late onset had higher disease activity. YORA were treated with more DMARDs in early disease whilst those with LORA were treated more often with corticosteroids. This may have implications for development of co-morbidities.

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Impact of Severity Index for Rheumatoid Arthritis On Healthcare Costs and Utilizations in Patients with Rheumatoid Arthritis. Onur Baser[1], Li Wang[2], Juan Du[3], Hai Wang[3] and Lin Xie[3]. [1]STATinMED Research/The University of Michigan, Ann Arbor, MI, [2]STATinMED Research, Dallas, TX, [3]STATinMED Research, Ann Arbor, MI

Background/Purpose: Examine the impact of a claims-based severity index for rheumatoid arthritis (RA) on healthcare costs and utilizations of RA patients using large U.S. claims data.

Methods: Adult patients with at least two RA diagnoses and 12 months of continuous health plan enrollment before and after the index date (first RA diagnosis date) were identified from a large U.S. claims database (10/1/2008 to 09/30/2009). A severity index for rheumatoid arthritis (SIFRA) was developed by calculating a weighted sum of 34 RA-related indicators including laboratory, clinical and functional status, extra-articular manifestations, surgical history, and medications as assessed by an expert Delphi panel of six rheumatologists. The relationship between SIFRA terciles and healthcare utilizations and costs was also examined using histograms. A regression model was used to examine the improvement of the model fitting by adding SIFRA.

Results: A total of 23,951 RA patients (mean SIFRA: 9.14) with laboratory information were identified. Descriptive analysis showed that patients in the upper tercile of SIFRA incurred $9,123 more all-cause healthcare costs and $1,326 more RA-related healthcare costs than patients in the lower tercile of SIFRA. The most dramatic difference between highest and lowest SIFRA terciles occurred with pharmacy costs ($6,860 vs. $1,919, p<0.001). Healthcare visits followed a similar to healthcare costs for SIFRA terciles. Patients in the highest SIFRA tercile had higher total office visits (110.14 vs. 77.16, p<0.001) and higher RA-related visits (6.72 vs. 3.93, p<0.001) compared to patients in the lowest tercile. Regression results showed that the model was more than 6-times (611%) superior in explaining the variation in outcomes after adding SIFRA into the model.

Conclusion: SIFRA demonstrated evidence of being a significant determinant of healthcare costs and utilizations for RA patients. This study suggests that SIFRA could be an important methodological tool to control for severity in RA-related outcomes research.

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Risks to Visit Emergency Room in Patients with Rheumatoid Arthritis: A Two-Year Retrospective Study. Yoshiki Nagai, Naoto Yokogawa, Kota Shimada and Shoji Sugii. Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

Background/Purpose: Patients with rheumatoid arthritis (RA) suffer from both physical disabilities and medical comorbidities and tend to use emergency room for many reasons. However, the detail has not been well investigated from the perspective of emergency medicine. The aim of this study is to identify the risks to visit emergency room in RA patients.

Methods: We retrospectively reviewed all emergency room visits in RA patients followed at Tokyo Metropolitan Tama Medical Center from April 2007 to March 2009 using an electric health record system. We compared the characteristics of RA patients who visited emergency room ("ER user group") to those who did not visit emergency room ("Control"). We compared the background characteristics between the two groups. A logistic regression analysis was performed to evaluate the risks of emergency room visits.

Results: "ER user group" and "Control" included 294 and 298 patients. The background characteristics of both groups were summarized in Table 1. By a logistic regression analysis, cardiovascular diseases, prednisolone>5mg/d, anti-TNF agents, age over 65, and pulmonary diseases predicted emergency room visits with odds ratio of 4.2, 3.5, 3.3, 1.7, and 1.6 respectively (Table 2).

Table 1

Background characteristics of "ER user" and "Control"

	ER user (294 pts) N (%)	Control (298 pts) N (%)	p
Age, year±SD	68.0±11.1	63.1±12.3	<0.001
Disease duration, year±SD	15.3±12.6	12.8±11.7	0.017
Female	235 (80%)	241 (81%)	NS
Diabetes mellitus	49 (17%)	27 (9%)	0.005
Pulmonary diseases[*1]	82 (28%)	49 (16%)	0.001
Cardiovascular diseases[*2]	40 (14%)	8 (3%)	<0.001
Glucocorticoids	214 (73%)	149(50%)	<0.001
Prednisolone equivalent (mg/day)	4.2±4.0	2.2±2.6	<0.001
Methotrexate	146 (50%)	143 (48%)	NS
Anti-TNF agents	28 (10%)	12 (4%)	0.007
Salazosulfapyridine	54 (18%)	55 (18%)	NS
Bucillamine	43 (15%)	32 (11%)	NS

[*1] Pulmonar diseases: interstitial lung disease, old tuberculosis, asthma, bronchiectasis, nontuberculous mycobacteriosis, chronic obstructive pulmonary disease

[*2] Cardiovascular diseases: heart failure, old myocardial infarction, angina pectoris

NS: not statistically significant

Table 2. Multivariate logistic analysis to predict emergency room visits

Variable	Odds ratio	P
Cardiovascular disease	4.2	<0.001
Prednisolone equivalent >5mg/d	3.5	<0.001
Anti-TNF agents	3.3	0.001
Age over 65	1.7	0.003
Diabetes mellitus	1.7	NS (0.051)
Pulmonary disease	1.6	0.030

[*1] Pulmonar diseases: interstitial lung disease, old tuberculosis, asthma, bronchiectasis, nontuberculous mycobacteriosis, chronic obstructive pulmonary disease
[*2] Cardiovascular diseases: heart failure, old myocardial infarction, angina pectoris
NS: not statistically significant

Conclusion: Preexisting cardiovascular disease, prednisolone>5mg/d, and anti-TNF agents were considered higher risks for emergency room visits in patients with RA.

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Peer to Peer Mentoring for Individuals with Early Inflammatory Arthritis: Feasibility Pilot.
Mary J. Bell[1], Paula Veinot[2], Gayathri Embuldeniya[2], Joyce Nyhof-Young[3], Joanna Sale[4], Joan Sargeant[5], Peter Tugwell[6], Sydney Brooks[7], Susan Ross[7], Ruth Tonon[7], Sharron Sandhu[8], Dawn Richards[8], Jennifer Boyle[7], Kerry Knickle[9], Nicky Britten[10], Emma Bell[2], Fiona Webster[9] and Mary Cox-Dublanski[11], [1]Sunnybrook Health Sciences Centre and University of Toronto, Toronto, ON, [2]Sunnybrook Health Sciences Centre, Toronto, ON, [3]University Health Network, University of Toronto, Toronto, ON, [4]University of Toronto, St. Michael's Hospital, Toronto, ON, [5]Dalhousie University, Halifax, NS, [6]University of Ottawa, Ottawa General Hospital, Ottawa, ON, [7]The Arthritis Society, Ontario Division, Toronto, ON, [8]Canadian Arthritis Network Consumer Advisory Council, Toronto, ON, [9]University of Toronto, Toronto, ON, [10]University of Exeter, Exeter, United Kingdom, [11]St. Mary's General Hospital, Kitchener, ON

Background/Purpose: The goal of this research is to examine the potential benefit of early peer support to improve the health and quality of life of individuals with early inflammatory arthritis (EIA). This poster presents preliminary findings of a pilot study, as part of a complex healthcare intervention, to assess acceptability and feasibility of a peer support intervention for individuals with EIA.

Methods: Qualitative and quantitative methods were used to evaluate a feasibility pilot of a peer mentoring intervention for individuals with EIA. Individuals with IA (diagnosed at least 2 years and managing well) were recruited through a rheumatology clinic, The Arthritis Society, and research team to be trained as peer mentors A peer mentor training model was developed consisting of 18 hours of didactic and interactive sessions over 4 non-consecutive days. Individuals with EIA (mentees; disease duration 6–52 weeks) were recruited through 2 rheumatology clinics. Trained peer mentors were paired with an individual with EIA to provide one-on-one support (face-to-face or telephone) up to once a week over a 12 week period. Peer mentor *self-efficacy* was assessed at baseline, immediate post-training, immediate post-peer mentoring program and 3-months follow-up. Mentees were assessed at baseline, immediate post-program and 3-months follow-up re: *disease modifying anti-rheumatic drugs (DMARDs)/biologic treatment use, self-efficacy, self-management, health-related quality of life, anxiety, coping-efficacy, social support* and *disease activity*. Results were examined using descriptive statistics, and effect sizes were calculated to determine clinically important changes (changes >0.3 considered important). One-on-one interviews with participants were also conducted to examine acceptability and feasibility of study procedures and outcome measures and to gain perspectives on the value of peer support. Key themes were identified through constant comparison.

Results: Nine pairs participated. The training was well-received by peer mentors. Peer mentors' self-efficacy increased significantly after training completion. Mentees experienced improvement in overall arthritis impact on life, coping, and social support (effect size>0.3). Mentees perceived emotional, informational, appraisal, and instrumental support, while mentors themselves reported benefits (e.g., new self-management techniques, lifestyle changes), and learned from mentees' fortitude and self-management skills. Participants' experience of peer support was informed by the unique relationship they forged with their peer partner. All participants were unequivocal about the need for peer support for the newly diagnosed.

Conclusion: Early peer support is proposed as a way to augment current care in rheumatology. The intervention was well-received. The training process, peer support program, and outcome measurements were demon-strated to be feasible with modifications. This intervention has been expanded to a small pilot RCT study to demonstrate effectiveness of peer support in EIA management.

Disclosure: M. J. Bell, None; **P. Veinot**, Consultant, 5; **G. Embuldeniya**, Sunnybrook Health Sciences Centre, 3; **J. Nyhof-Young**, None; **J. Sale**, None; **J. Sargeant**, None; **P. Tugwell**, UCB, Chelsea, 5, BMS, 5, Actellion, Alderbio, Amgen, Ardea Biosciences, Astra Zeneca, Bristol Myers Squibb, 6, Jazz Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pfizer,Regeneron, Savient, Takeda, 6, EliLilly/Boehringer-Ingelheim, Genentech, Genzyme, Celgene, Centocor, Cypress/Forest, 6, Abbott, Roche, Schering Plough/Merck, UCB, BMS, 5; **S. Brooks**, The Arthritis Society, 3; **S. Ross**, None; **R. Tonon**, None; **S. Sandhu**, None; **D. Richards**, None; **J. Boyle**, None; **K. Knickle**, None; **N. Britten**, None; **E. Bell**, Consultant, 5; **F. Webster**, None; **M. Cox-Dublanski**, None.

ACR/ARHP Poster Session C
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

2149

Atsttrin-â, an Engineered Protein Derived From Progranulin Growth Factor, Binds to TNF Receptors and Exhibits Potent Anti-Inflammatory Activity in Mice.
Yunpeng Zhao[1], Qingyun Tian[1], Haicheng Song[1], Fanhua Wei[1] and Chuanju Liu[2]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]New York University, New York, NY

Background/Purpose: Progranulin (PGRN) is a multifunctional growth factor. Recently, we reported that PGRN and its derived protein Atsttrin-α (referred to as "Atsttrin" in our previous publication) directly bound to TNF receptors (TNFR), blocked the binding of TNF to TNFR and inhibited TNF activity (Tang, W., et al, *Science*, 2011 Apr 22;332 (6028):478–484). It is well established that TNF family ligands bind to receptors in a heterohexameric 3:3 complex. Atsttrin-α was comprised of the three functional fragments of PGRN, thus we hypothesized that the three fragments of Atsttrin-α act independently for interacting with TNFR. If so, change of order of the three fragments would not affect binding activity to TNFRs. In this study, we created a novel engineered protein, Atsttrin-β which comprised the same fragments as Atsttrin-α but in a different order. The purpose of this project is to determine whether the novel protein Atsttrin-β is able to block the binding of TNF-α to TNFR, and has therapeutic effect in inflammatory arthritis, as does Atsttrin-α.

Methods: Yeast-two hybrid assay was used to compare the binding to TNFR between Atsttrin-α and Atsttrin-β; Solid-phase binding was performed to determine the Atsttrin-β inhibition of TNF-α binding to TNFRs; Collagen-induced arthritis(CIA) in DBA-IJ mice and TNF-α transgenic (hTNF-tg) mice that spontaneous inflammatory arthritis. Mice were divided into various groups and injected intraperitoneally with PBS, etanercept, Atsttrin-α and Atsttrin-β. Clinical assessment for arthritis scores, micro CT for bone erosion and histological analysis of joint sections were performed.

Results: Yeast-two hybrid assay showed that Atsttrin-β bound to TNFR1 and TNFR2, as did Atsttrin-α; Solid-phase binding assay revealed that Atsttrin-β inhibited TNF-α from binding to TNFRs in a dose-dependent manner. Clinical scores, Micro CT and histological analysis of joints from CIA model and hTNF-tg mice demonstrated that Atsttrin-β attenuated synovial proliferation, infiltration of inflammatory cells, cartilage destruction and bone erosion compared with vehicle-treated mice, and these effects were shown in dose-dependent manners.

Conclusion: These findings suggest the three functional fragments of Atsttrin-α worked independently in binding to TNFRs and blocking TNF-α activity, and the novel engineered protein Atsttrin-β has anti-inflammatory effect and may represent a promising alternative in treatment of rheumatoid arthritis.

Disclosure: Y. Zhao, None; **Q. Tian**, None; **H. Song**, None; **F. Wei**, None; **C. Liu**, None.

2150

Action of Tofacitinib Via Human Dendritic Cells.
Satoshi Kubo, Kunihiro Yamaoka, Shigeru Iwata and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background/Purpose: Tofacitinib, an oral Janus Kinase (JAK) inhibitor, has gathered attention in treatment of Rheumatoid arthritis (RA). Although JAKs are well known for its importance in lymphocyte development and

expressed in monocyte lineage cells, the effect of tofacitinib on the maturation and function of human dendritic cells (DCs) remains unknown.

Methods: Human monocyte-derived DCs were generated with granulocyte macrophage colony-stimulating factor and IL-4. DCs were matured with lipo-polysaccharide (LPS) in the presence of tofacitinib in vitro for 48 hours and cytokine production, cell survival and surface markers were assessed by flow cytometry. After washout of tofacitinib, DCs were co-cultured with CD4+CD45RA+ naive T cells purified from healthy donor, and allogeneic-mixed lymphocyte reaction (aMLR) performed to evaluate T-cell stimulatory capacity.

Results: When DCs were stimulated with LPS, expression of CD80, CD86 and HLA-DR were strongly induced. However, the addition of tofacitinib to DCs reduced expression of CD80 and CD86, but not HLA-DR, indicating that maturation was disturbed. Tofacitinib also inhibited the production of TNF-α (6217ng/ml to 4964ng/ml), IL-6 (43640ng/ml to 33027ng/ml) and IL-1β (22ng/ml to 13ng/ml) at 300nM, and the inhibitory effect was in a dose dependent manner. On the contrary, the production of TGF-β from DCs was not affected. Notably, tofacitinib increased the levels of indoleamine 2, 3-dioxygenase (IDO), an immunomodulatory enzyme in DCs. Co-culture of tofacitinib-treated DCs with allogeneic naive T cells resulted in reduction of T-cell proliferation and IFN-γ production. However, CD4+CD25+ FoxP3+ regulatory T cell population was not affected.

Conclusion: In addition to the previously known effect of tofacitinib on acquired immunity, our results indicate that tofacitinib could affect the innate immunity. Importantly, tofacitinib attenuated the LPS-induced upregulation of costimulatory molecules during DC maturation. This resulted in a decreased allo-reactive T cell response. Moreover, tofacitinib suppressed inflammatory cytokine production and induced IDO expression. Taken together, these data provide novel potential mechanisms of action of tofacitinib, the restoration of immunoregulation as well as anti-inflammation, in patients with rheumatoid arthritis.

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Inhibitory Effect of Type I Interferon On Interleukin-17 Response in Rheumatoid Arthritis Fibroblast-Like Synoviocytes.
Eva Ruzicska[1], Hannelie F. Semmelink[2], Gyula Poor[3], P. P. Tak[4] and L.G.M. van Baarsen[5]. [1]Budapest, Hungary, [2]Amsterdam, Netherlands, [3]National Inst of Rheumatology, Budapest, Hungary, [4]Academic Medical Center/University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands, [5]: Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Type I interferon (IFN) response genes are upregulated in several inflammatory diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS). Whereas in SLE this type I IFN signature is associated with disease severity, IFN-beta (IFNβ) is a beneficial treatment in two-third of the patients with MS. In RA the functional role of the type I IFN signature in disease pathogenesis is unclear. The effects of type I IFN may be dependent on the specific type of interferon, the disease and the tissue. Recent studies have shown that administration of type I IFN can confine the inflammatory response by inhibiting Th17 development. The recently discovered interleukin (IL)-17 producing Th17 cells appear to play a pro-inflammatory role in the pathogenesis of RA. IL-17 has been shown to act on several cell types in order to protect against microbial infection but can also promote and maintain inflammatory processes. Accordingly, tight regulation of the IL-17 response is required to prevent inflammation and autoimmunity.

Giving the above mentioned function of type I IFN in limiting the Th17 response, we investigated whether type IFN can modulate the pro-inflammatory effect of IL-17 on fibroblast-like synoviocytes (FLS).

Methods: Synovial tissues were obtained by arthroscopy of eight rheumatoid arthritis patients (RA), two osteoarthritis patients (OA) and four non-disease control individuals (HD). Subsequently, FLS were isolated and cultured in the presence of TNF (1 ng/ml), IFNβ (100 U/ml), IL-17A (50

ng/ml), or combinations thereof. Supernatants were collected 24 or 48 hours after treatment and levels of IL-6 and IL-8 were measured by ELISA.

Results: We examined the modulatory effect of type I IFN on IL-17A induced IL-6 and IL-8 production by FLS in the presence and absence of TNF (Table 1). A large variation in IL-17 response between different donors was observed with respect to production of IL-6 and IL-8. As expected, TNF had a synergistic effect on the IL-17 induced cytokine response. On group level, IFNβ had no inhibitory effect on the IL-17 induced IL-6 cytokine production, but there was a large variation in IFNβ sensitivity between donors. While in some donors IFNβ had no effect on the IL-17 induced cytokine response, in other donors IFNβ had a clear inhibitory effect. Interestingly the IL-17 induced IL-8 production could be inhibited by IFNβ, after both 24 and 48 hours. No differences were observed between the different diagnoses.

Table 1.

Change in IL-6 production in the presence of IFNβ (median (IQR))	RA		HD		OA	
	24h	48h	24h	48h	24h	48h
Modulation of IL-17A response (%)	144.5 (104.4–150)	124.1 (75.74–161)	123.5 (99.42–169.6)	88.72 (73.21–118)	221.4 (123.3–319.6)	98.98 (41.52–185)
Modulation of TNF response (%)	104.3 (94.39–112.8)	91.6 (71.85–108.5)	109.9 (65.76–154.9)	89.12 (76.89–137.9)	117.3 (94.84–139.8)	110 (60.37–159.1)
Modulation of IL-17A+TNF response (%)	114.4 (85.74–160.3)	79.08 (45.11–140.9)	77.99 (66.02–100.5)	102.9 (77.01–124.7)	85.32 (78.43–92.22)	110 (103.8–116.2)
Change in IL-6 production in the presence of IFNβ (median (IQR))	RA		HD		OA	
	24h	48h	24h	48h	24h	48h
Modulation of IL-17A response (%)	31.09 (0–92.26)	48.18 (28.48–561.7)	47.87 (0–65.98)	81.43 (50.72–112.1)	67.92 (35.85–100)	50 (0–100)
Modulation of TNF response (%)	28.38 (0–37.3)	47.74 (29.41–63.61)	44.03 (32.88–47.35)	34.68 (27.46–41.91)	30.05 (23.2–36.91)	14.13 (2.223–26.04)
Modulation of IL-17A+TNF response (%)	54.59 (37.41–61.82)	79.82 (45.32–102)	57.88 (42.73–66.62)	86.74 (69.15–104.3)	59.97 (49.52–70.42)	48.91 (44.72–53.1)

Conclusion: These findings suggest that in a pro- inflammatory environment IFNβ can modulate the IL-17 response by inhibiting IL-8 production in FLS, whereas the effect on IL-6 production is donor dependent. These data provide further insight into the anti-inflammatory role of IFNβ in inflammatory diseases with possible implications for treatment.

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Inhibition of Fucose Incorporation Abrogates the Development of Arthritis by Suppressing the Inflammatory Macrophage Development and TNF-α Production.
Jun Li[1], Hui-Chen Hsu[2], PingAr Yang[1], Qi Wu[1], David M. Spalding[1], W. Winn Chatham[1], Robert P. Kimberly[1], S. Louis Bridges Jr.[1] and John D. Mountz[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham and Birmingham VA Medical center, Birmingham, AL

Background/Purpose: Fucosylation, catalyzed by fucosyltransferases (Futs), is an important glycosylation process involved in inflammation, cell death, and differentiation. We have observed an extremely high positive correlation between *Tnfα* and *Fucosyltransferases 1 and 3* (*Fut1* and *Fut3*, p=0.0001) in rheumatoid arthritis (RA) synovial tissues. However, the role of fucosylation in RA has not been extensively studied. The purpose of this study is to determine: *(i)* expression of *Futs* in different cell population isolated from human RA synovial fluid; *(ii)* the effect of a fucosylation inhibitor on RA effector cell differentiation; and *(iii)* the ability of a fucosylation inhibitor to suppress the development of collagen II-induced arthritis (CIA) in mice.

Methods: Twenty RA subjects were recruited in this study. Real-time PCR was used to determine the expression of *Fut1* and *Fut3* in FACS sorted cell subsets from fresh RA synovial fluids. Purified human synovial macrophages (MΦs) were cultured with GM-CSF and CD4 T cells were polarized towards Th1 and Th17 cells with and without the presence of 15 mM 6-Deoxy-L-galactose (fucose) or its analog, 2-Deoxy-D-galactose (2-D-gal) which can inhibit the fucosylation process. Cytokines in the supernatant were measured by ELISA. CIA was induced in DBA/1J mice. Fucose or 2-D-Gal

(200 mg/kg BW, every 2–3 days) was administered via I.P. initiated on Day 1. FACS, ELISA and histopathology analysis were performed on Day 40.

Results: In FACS sorted cells from fresh human RA synovial fluid, the expression of *Fut1* and *Fut3* was five-fold higher in M1 inflammatory MΦ (CD68⁺CD80⁺) compared to M2 MΦ (CD68⁺CD80⁻), with lower expression in Th1, Th17, total memory and naïve CD4 T cells. *In vitro* 2-D-gal treatment for 3 days lead to dramatic cell death of purified human MΦ and reduced levels of TNF-α (3800 pg/ml vs 450 pg/ml, p<0.001) in the supernatant. There was, however, no inhibitory effect of 2-D-gal on human Th1 or Th17 differentiation *in vitro*. *In vivo* treatment of 2-D-gal in DBA/1J mice immunized with bovine CII abrogates the development of arthritis whereas the same dose of fucose exacerbated it (arthritis scores: control, 9.5±1.7; 2-D-gal, 0.5± 0.3; Fucose, 15.3± 2.2, p<0.01). FACS analysis revealed that the percentages of inflammatory MΦ (CD11b⁺TNF-α⁺) in the draining LN were reduced by 2-D-gal but were increased by Fucose (control 1.1±0.23; 2-D-gal, 0.6±0.10; Fucose, 1.5± 0.32, p<0.05). 2-D-gal treatment also resulted in significantly decreased levels of TNF-α (130.1 vs 39.4pg/ml, p<0.05) and anti-CII total IgM and IgG in the serum. Joint histopathology showed a significantly decreased macrophage infiltration, synovial hyperplasia, cartilage damage, and bone erosion in 2-D-gal treated mice. No significant liver and renal toxicity and dysfunction was observed.

Conclusion: Our results show that *Futs* are highly expressed in inflammatory MΦ and fucosylation is a critical process regulating MΦ differentiation and TNF-α production. Inhibition of fucose incorporation by 2-D-gal significantly impairs inflammatory macrophage development and function, completely blocking development of arthritis without systematic toxicity. Our results suggest that MΦ fucosylation may be a new therapeutic target for RA.

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Target-Directed Development of a Proposed Biosimilar Rituximab (GP2013): Comparability of Antibody-Dependent Cellular Cytotoxicity Activity and Pre-Clinical Pharmacokinetics and Pharmacodynamics with Originator Rituximab. Antonio da Silva, Ulrich Kronthaler, Ines Meyer, Anastassia Papandrikopoulou, Thomas Stangler and Jan Marinus Visser, Sandoz Biopharmaceuticals / HEXAL AG, Holzkirchen, Germany

Background/Purpose: Biosimilars are biologics approved by highly-regulated markets as similar to existing agents, with the aim of offering more affordable treatment and thereby increasing patient access. Development of a biosimilar involves extensive characterization of the originator product over several years and a target-directed iterative development process to ensure a product that is highly comparable to the originator with similar clinical efficacy, safety and quality. Using antibody-dependent cellular cytotoxicity (ADCC), a main mode of action of rituximab, we illustrate how functional/structural relationship can be engineered into a biosimilar to ensure comparability at the *in vitro* level. Here we present pre-clinical data confirming *in vivo* comparability for the proposed biosimilar rituximab GP2013, in terms of pharmacokinetics (PK), pharmacodynamics (PD) and efficacy.

Methods: By employing a highly sensitive glycan quantitation method, relevant post-translational glycosylation patterns were assessed for their impact on *in vitro* ADCC relative potency data using the Raji and NK3.3 cell lines as target and effector cells, respectively. Subsequently, bioactivity of GP2013 and originator rituximab were evaluated in a dose-response manner across a wide concentration range against SU-DHL-4 (diffuse large B-cell lymphoma) and Daudi (Burkitt's lymphoma) cell lines using freshly purified human NK cells. *In vivo* anti-tumor activity was assessed in two xenograft SCID mouse models of non-Hodgkin's lymphoma (SU-DHL-4 and Jeko-1 cell lines). Comparative PK and PD were assessed in single (5 mg/kg, n=14) and multiple (20 or 100 mg/kg, n=8) dose studies in cynomolgus monkeys, the pharmacologically most relevant species.

Results: GP2013 and originator rituximab showed similar ADCC potency against both SU-DHL-4 and Daudi cells, with ADCC being reflective of engineered glycosylation patterns and structure-function relationships. In both xenograft mouse models, GP2013 and originator rituximab inhibited tumor growth to a similar extent, including at the more sensitive sub-optimal dose levels that are most likely to identify any potential differences. In primates, PK analysis confirmed bioequivalence between GP2013 and originator rituximab with nearly identical AUC values and 90% CIs entirely within the standard acceptance range of 0.8–1.25. Bioequivalence of PD response (B-cell depletion) was also shown, with 95% CIs of areas under the effect-time curves (AUEC) ratios for relative change from baseline in B-cell populations within the 0.8–1.25 acceptance range. The use of different doses indicated that comparable exposure and PD response can be expected for GP2013 and originator rituximab using indication-specific dosing regimens.

Conclusion: This pre-clinical comparability exercise confirms that GP2013 and originator rituximab are pharmacologically similar with regard to ADCC potency, anti-tumor activity, PK exposure (AUC) and B-cell depletion. As such, GP2013 is anticipated to show similar efficacy and safety as the originator product in ongoing clinical trials across different clinical indications.

Disclosure: **A. da Silva**, Sandoz Biopharmaceuticals / HEXAL AG, 3; **U. Kronthaler**, Sandoz Biopharmaceuticals / HEXAL AG, 3; **I. Meyer**, Sandoz Biopharmaceuticals / HEXAL AG, 3; **A. Papandrikopoulou**, Sandoz Biopharmaceuticals / HEXAL AG, 3; **T. Stangler**, Sandoz Biopharmaceuticals / HEXAL AG, 3; **J. M. Visser**, Sandoz Biopharmaceuticals / HEXAL AG, 3.

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Regulation of Folate Pathway Related Genes in Methotrexate naïve and Methotrexate Treated Patients with Rheumatoid Arthritis. Marjolein Blits[1], Gerrit Jansen[1], Saskia Vosslamber[1], Yehuda G. Assaraf[2] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Haifa, Israel

Background/Purpose: Rheumatoid arthritis (RA) is one of the most prevalent systemic autoimmune disorders. The folate antagonist methotrexate (MTX) is an anchor drug in the treatment of RA. Here, we aim to provide insight into the pharmacological effects of MTX by gene expression analysis

Methods: Subanalysis of microarray data was performed for a set of 18 genes involved in the methotrexate/folate pathway using peripheral blood gene expression data of 10 MTX naïve RA patients (MTX-), 25 RA patients treated with MTX (MTX+), and 15 healthy controls which were age and sex-matched (test cohort). Multiplex realtime PCR of these methotrexate/folate pathway related genes was performed on second cohort consisting of 28 MTX naïve RA patients (MTX-), 180 RA patients treated with MTX (MTX+) and 24 healthy controls (validation cohort). Statistical analysis was performed using Student's t test or Mann-Whitney U test. P-values of ≤0.05 were considered to be statistically significant.

Results: Several folate/MTX-related genes were markedly and significantly altered between the three study groups in the test cohort. Metabolizing enzymes FPGS (p=0.0035) and GGH (p<0.0001) were significantly up-regulated in the MTX⁻ RA group compared to the healthy control group (HC group). For the folate dependent enzymes we found that GART (p=0.0004) expression was decreased in the MTX⁻ group compared to HC. In the efflux transporters, MRP3 (p=0.0335) was significantly higher expressed in the MTX⁻ group compared to HC. The other genes displayed no significant change in the test cohort. In the validation cohort we were able to validate most of the genes except FPGS, GART for MTX⁻ compared to HC. In both test and validation cohort the differentially altered genes in the MTX⁻ group returned to a normal range as observed in the HC.

Conclusion: Overall, these results indicate that, under inflammatory conditions basal folate metabolism is altered in blood cells of RA patients compared to HC. Treatment with MTX restores expression of these genes to the levels within the range of the HC group.

Disclosure: **M. Blits**, None; **G. Jansen**, None; **S. Vosslamber**, None; **Y. G. Assaraf**, None; **C. L. Verweij**, None.

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The Annualized Progression of Radiologic Damage in Placebo Arms of Rheumatoid Arthritis Trials Is Much Lower Than the Mean Annual Progression Since Disease Onset. Jean-Marie Berthelot and Celine Cozic. Nantes University Hospital, Nantes, France

Background/Purpose: A previous meta-analysis by Graudal and Jürgens (*Arthritis Rheum.* 2010;62:2852–63) challenged the belief that biologics better protect rheumatoid arthritis (RA) from joint destruction than DMARDs or glucocorticoids. Destruction rates had been expressed as percentages of the maximal scores and annualized. We aimed to re-analyse this work and: 1-seek for differences in baseline radiologic scores, and mean progression of destruction rates since the onset of RA, according to the subset of drug tested

(DMARD, combination of DMARDS, glucocorticoids, biologics); 2-compare destruction rates since RA onset and during the period of the trial, both in the *verum* arms and placebo arms.

Methods: All studies from groups II to V of this meta-analysis were retrieved and re-analysed by two independent readers. Destruction rates could be calculated both since RA onset and per-trials in 41/55 studies (41 *verum* arms, and 43 control arms).

Results: Baseline scores were higher in patients from biologic trials, but duration of RA was also longer. Consequently, destruction rates before baseline were even lower in biologic trials. In absolute values, difference between *verum* and controls were not superior in trials of biologics, but when expressed as % of reduction as compared to per-trial destruction rates in the control arms, biologics seemed more efficient (71% +/ 19, median: 78%), than DMARDs (52% +/− 41, median: 64%) and glucocorticoids (52% +/− 22, median: 48%). The per-trial mean destruction rates were (much) lower than the mean destruction rates since RA onset in the four groups, even in the placebo arms, especially in biologic trials. Only placebo arms appear in the figure below. Boxplots represent median, lower and upper quartile, and 95th percentiles.

II = single DMARDs; III = combination DMARDs
IV = glucocorticoids; V = biologics
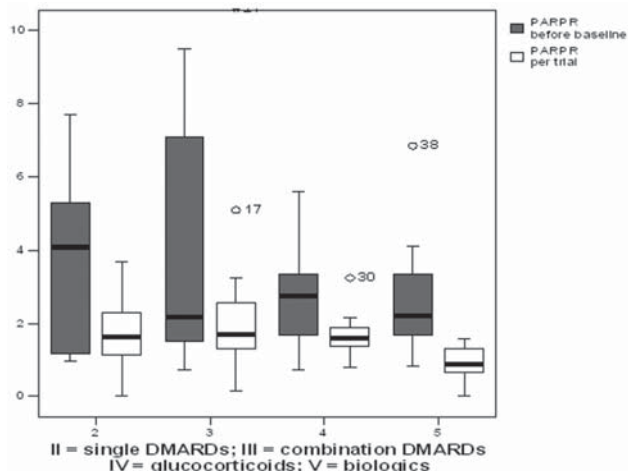
Conclusion: 1-The difference of per-trial radiographic progression might have biased the results of the previous meta-analysis. When expressed as ratio of destruction rates between *verum* and control arms, biologics performed better, although DMARDS and glucocorticoids were also clearly effective; 2-'expected worsening' as a substitute for placebo arms is inappropriate, and should be banned.

Disclosure: J. M. Berthelot, None; C. Cozic, None.

2156

Anti-Cyclic Citrullinated Protein Antibodies As a Predictor of Response to Tocilizumab in Patients with Rheumatoid arthritis A Prospective Study. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1], Kuniki Amano[2], Kazuhiko Hatta[3], Hiroyuki Ohta[4] and Noriko Kuwaba[5]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Sky Clinic, Hiroshima, Japan, [3]Hatta Clinic, Kure, Japan, [4]Hiroshima, Japan, [5]Sanki Clinical Link, Hiroshima, Japan

Background/Purpose: Tocilizumab, interleukin-6 receptor antibody is very effective in patients with rheumatoid arthritis (RA). Anti-cyclic citrullinated protein antibodies (ACPA) are highly specific and sensitive for RA. There are several reports that the correlation between the efficacy of anti-tumor necrosis factor and the titer of ACPA. There is no evidence that the correlation between the efficacy of Tocilizumab and ACPA.To investigate the Tocilizumab on ACPA, and its association with treatment response.

Methods: RA patients were eligible if they had active disease despite treatment with methotrexate (MTX). Fifty four consecutive IgM-rheumatoid factor positive patients with RA were treated with infusion of 8mg/kg tocilizumab every 4 weeks. Disease activity was assessed by DAS28 score. ACPA titer was measured by a commercial ELISA at Week 0 and Week 24.The primary outcome was correlation between clinical response to therapy and ACPA titer. Secondary outcome was the change of ACPA titer from baseline to week 24.

Results: Primary outcome: There was a significant correlation between clinical response to therapy and ACPA titer(r=0.54, p<0.02). Secondary outcome: There was no change of ACPA titer from baseline to week 24(p=0.76). No patient at baseline turned negative at week 24 for ACPA (negative cut off<4.5U/ml).

Conclusion: ACPA titer might be predictor of the efficacy of Tocilizumab in patients with RA. Tocilizumab treatment didn't affect the change of ACPA titer.

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Resveratrol Counters Pro-Atherogenic Effects of Systemic Lupus Erythematosus and Rheumatoid Arthritis Plasma On Cholesterol Efflux in Human Macrophages. Allison B. Reiss, Iryna Voloshyna, Ofek Hai, Michael J. Littlefield, Elise Belilos, Kristina B. Belostocki, Lois A. Bonetti, Gary C. Rosenblum and Steven E. Carsons. Winthrop University Hospital, Mineola, NY

Background/Purpose: Our group has demonstrated that resveratrol, a plant polyphenol, possesses atheroprotective properties, enhancing expression of reverse cholesterol transport (RCT) proteins. We have reported that Systemic Lupus Erythematosus (SLE) and rheumatoid arthritis (RA) patients manifest a pattern of disturbance in expression of RCT genes that is atheroma-promoting. The cholesterol efflux proteins 27-hydroxylase, ATP binding cassette transporter (ABC) A1 and ABCG1 are suppressed by plasma from persons with these autoimmune rheumatic diseases. These proteins are crucial for efficient cholesterol efflux from macrophages, a process that prevents foam cell formation (FCF) and protects against atherosclerosis. This study examines whether resveratrol can protect macrophages from pro-atherogenic effects of SLE and RA plasma on cholesterol metabolism.

Methods: ABCA1, ABCG1 and 27-hydroxylase expression were evaluated in THP-1 human macrophages, a pertinent model of atherosclerosis. Cells were incubated for 18h in 10% pooled SLE, RA or normal human plasma (NHP) $\pm$ resveratrol (25μM). mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative PCR with specific primers for each gene. Cell extracts were prepared for immunoblotting after 24h. FCF was quantified as % oil red O stained cells. Studies were done in triplicate.

Results: 10% SLE plasma suppressed ABCA1 and ABCG1 expression by $58.3 \pm 15.5\%$ (n=3, P<0.001) and $48.3 \pm 18.7\%$ (n=3, P<0.01) below NHP, respectively (NHP set as 100%). 10% RA plasma induced similar levels of ABC transporter downregulation. 27-hydroxylase message level fell by $36.2 \pm 12.8\%$ and $49.1 \pm 14.7\%$ (n=3, P<0.01) below NHP, respectively for SLE and RA plasma. When THP-1 macrophages were incubated with SLE or RA plasma + resveratrol, the resveratrol significantly negated downregulation of efflux proteins, restoring levels to that observed with NHP (Fig 1). FCF by THP-1 macrophages was significantly reduced by addition of resveratrol compared to SLE or RA plasma alone (by $22.2 \pm 5.1\%$ and $35 \pm 7.5\%$, respectively [n=3, P<0.01]).
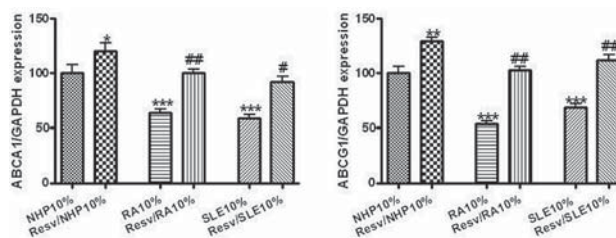
Fig 1. *-P<0.05; ** P<0.01; *** P<0.001 vs. NHP; # P<0.05, ## P<0.01 vs. corresponding plasma without resveratrol.

Conclusion: Resveratrol is able to counteract pro-atherogenic factors in SLE and RA plasma. Resveratrol acts as an anti-atherogenic agent by preventing lipid overload via effects on cholesterol transport. Since resveratrol has a strong safety profile and is well-tolerated, low cost, and can be used in combination with multiple other therapies without contraindication, these findings provide the rationale for a novel therapeutic approach to decrease the cardiovascular consequences of RA and SLE. Administration of resveratrol in these groups of patients might restore a critical defense mechanism against atherosclerosis and cardiovascular disease progression. Further in vivo studies are indicated for this promising treatment option.

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Baseline Folate Related Biomarkers in Serum and erythrocytes Are Not Associated with Methotrexate Response and Adverse Events in Rheumatoid Arthritis. Maurits C.F.J. De Rotte[1], Saskia M.F. Pluijm[2], Maja Bulatovic[3], Johanna M.W. Hazes[1] and Robert De Jonge[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus Medical center, Rotterdam, Netherlands, [3]University Medical Centre Utrecht, Netherlands

Background/Purpose: Methotrexate (MTX) is the most commonly used drug in rheumatoid arthritis (RA). 30% of patients fail to respond to the drug or suffer from adverse events. Therefore, there is a need to identify determinants of MTX response and adverse events in RA. MTX is an antagonist for folate and interferes with folate homeostasis. We investigated whether folate-related biomarkers, including homocysteine (HCy), vitamin B6, B12 and folate, measured at baseline were associated with MTX response and adverse events over nine months of treatment.

Methods: The study included patients from two longitudinal cohorts who were diagnosed with RA according to the 2010 ACR criteria and were treated with MTX therapy: 285 patients from the treatment in Rotterdam Early Arthritis Cohort (tREACH) (1) and 99 from the Methotrexate in Rotterdam (MTX-R) study. Serum concentrations of HCy, B6, B12 and folate, and folate in erythrocytes were determined at baseline (t0). MTX response was assessed with the disease activity score (DAS)-28 at 0,3,6 and 9 months after MTX start and EULAR response criteria at 3,6 and 9 months. Adverse events were defined as gastro-intestinal intolerance and overall complaints at 3,6 and 9 months. Using DAS 28 as outcome measure, analysis of covariance (ANCOVA), adjusted for age, gender, DAS28 at baseline, MTX dose, MTX route of administration, other DMARDs, NSAIDs, steroids and study cohort, was used. EULAR and adverse events were analyzed with logistic regression. Biomarkers were analyzed as continuous variables, quintiles and tertiles.

Results: Concentrations at baseline (mean/SD) were: homocysteine: 12.9 μmol/l (5.9), B6: 93 nmol/l (97), B12: 322 pmol/l (131), folate in serum: 23 nmol/l (35) and folate in erythrocytes: 1007 nmol/l (450). DAS28 was 4.76 (1.26) at baseline and 3.08 (1.20), 2.91 (1.22), 2.68 (1.16) at 3,6 and 9 months. 52%,26% and 24% had gastro-intestinal complaints at 3, 6 and 9 months, respectively. 46%, 49% and 47% of the patients reported one or more adverse events at 3 6 and 9 months of follow-up.

None of the biomarkers (defined as continuous measure) were associated with DAS28 at all 3 time-points (table). For HCy we only found a positive association at 6 months (standardized-β = 0.18, p = 0.001), whereas folate in erythrocytes was only associated negatively with DAS28 at 3 months (st-β = −0.14, p = 0.017). Analyses with biomarkers divided into quintiles or tertiles showed similar results. In addition, no associations were found between any of the baseline biomarkers and EULAR response criteria or adverse events.

Table. Analysis of covariance for the association between folate related biomarkers and DAS28

Biomarkers	3 months Standardized-β (p)	6 months Standardized-β (p)	9 months Standardized-β (p)
Homocysteine	−0.06 (0.278)	0.18 (0.001)*	−0.03 (0.650)
Vitamin B6	−0.01 (0.912)	−0.03 (0.633)	−0.08 (0.197)
Vitamin B12	0.01 (0.792)	−0.08 (0.141)	0.00 (0.949)
Folate in serum	−0.04 (0.396)	−0.05 (0.415)	−0.01 (0.928)
Folate in RBC	−0.14 (0.017)*	−0.07 (0.296)	0.06 (0.394)

* = significant. All analyses are adjusted for age, gender, DAS28 at baseline, MTX dose, MTX route of administration, other DMARDs, NSAIDs, steroids and study cohort.

Conclusion: In this first longitudinal study, folate-related biomarkers were unrelated to MTX treatment outcome in RA.

Reference
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Correlation of a Multi-Biomarker Disease Activity Response Assessment to Disease Activity Score 28 (C-Reactive Protein) Response Assessment and Omeract Ramris Scores in a Placebo-Controlled Rheumatoid Arthritis Clinical Trial with Abatacept (ASSET). DJ Haney[1], G. Cavet[2], P. Durez[3], R. Alten[4], G. R. Burmester[5], P. P. Tak[6], Anka. I. Catrina[7], C. Gaillez[8], M. Le Bars[8], S. Connolly[9] and R. Townsend[9]. [1]Crescendo Bioscience Inc., South San Francisco, CA, [2]Crescendo Bioscience, Inc., South San Francisco, CA, [3]Université Catholique de Louvain, Brussels, Belgium, [4]Schlosspark-Klinik, University Medicine, Berlin, Germany, [5]Charité-Universitätsmedizin, Berlin, Germany, [6]Academic Medical Center/University of Amsterdam, Amsterdam, the Netherlands; GlaxoSmithKline, Stevenage, United Kingdom, [7]Karolinska Institute, Stockholm, Sweden, [8]Bristol-Myers Squibb, Rueil Malmaison, France, [9]Bristol-Myers Squibb, Princeton, NJ

Background/Purpose: A novel multi-biomarker disease activity (MBDA) score has been validated and is a tool for monitoring disease activity in RA.[1] Here, we evaluate the relationship between MBDA scores and both clinical and MRI assessments in patients (pts) from the ASSET trial (NCT00420199) who received abatacept (ABA) or placebo (pbo).

Methods: Fifty pts with active RA, baseline (BL) DAS28-CRP >3.2 or Tender Joint Count and Swollen Joint Count >6 and CRP >upper limit of normal and inadequate response to MTX were randomly assigned 1:1 to receive ABA or pbo plus MTX, administered intravenously at BL; Days 15, 29; and every 28 days up to and including Day 113.[2] Concentrations of 12 serum biomarkers including inflammatory cytokines and receptors (IL-6, TNF-RI), growth factors (EGF, VEGF-A), matrix metalloproteinases (MMP-1, MMP-3), skeletal-related protein (YKL-40), hormones (leptin, resistin), acute phase proteins, and markers of systemic inflammation (CRP and SAA1) were measured in pt serum at BL, 2 and 4 wks to calculate MBDA scores between 1 and 100. Disease activity measures (DAS28-CRP) were evaluated at BL, Wks 2 and 4, and every 4 wks until Wk 16, EULAR response was assessed at Week 16, and OMERACT RAMRIS scores (components: erosion, osteitis, and synovitis scores) were evaluated at BL and Mth 4. Associations between MBDA scores and DAS28-CRP, and between MBDA scores and OMERACT RAMRIS scores, were evaluated *post hoc* using Spearman's rank correlation. The relationships of early changes in DAS28-CRP and MBDA score with subsequent EULAR response were evaluated by two-sample *t*-test. Comparisons of changes in disease activity scores between treatment arms were evaluated by two-sample *t*-tests.

Results: Statistically significant correlations were observed between DAS28-CRP and MBDA score (r=0.47, p<0.001, n=146; all time points combined), and between change in DAS28-CRP and change in MBDA score from BL to Wk 4 (r=0.58, p<0.001, n=48). Pts in the ABA + MTX arm experienced significantly greater improvements in MBDA score and DAS28-CRP versus pbo + MTX arm at Wk 4 (p=0.003 in each case). A significant association between change in DAS28-CRP from BL to Wk 4 and EULAR good response at Wk 16 (p=0.02) was observed, as well as a marginally significant association between change in MBDA at Wk 4 and good EULAR response at Wk 16 (p=0.05). There was a significant correlation between MBDA score and OMERACT RAMRIS synovitis and osteitis scores at BL (Table).

Disease activity measure	Synovitis Correlation	P value	n	Osteitis Correlation	P value	n	Erosion Correlation	P value	n
MBDA score	0.34	0.02	47	0.36	0.01	47	0.27	0.06	47
DAS28-CRP	0.08	0.60	47	0.10	0.52	47	0.10	0.49	47

Conclusion: In the ASSET trial, pts receiving abatacept had a better improvement in both clinical disease activity and disease activity biomarkers than pts in the pbo group. The MBDA score was correlated with disease activity and the OMERACT RAMRIS synovitis and osteitis scores. Monitoring of changes in MBDA score may be useful in RA pts in combination with clinical assessment.

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2160

Fcγ Receptor IIIb Polymorphism Is Associated with Injection Reaction to Adalimumab in Patients with Rheumatoid Arthritis. Masako Tsukamoto[1], Yosuke Hashimoto[1], Tatsuhiro Ohshige[1], Keiko Yoshimoto[1], Yuko Kaneko[2], Hideto Kameda[1] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Keio Univ School of Medicine, Shinjuku-ku, Japan

Background/Purpose: Biological agents targeting a specific molecule provide an effective means for therapeutic management of rheumatoid arthritis (RA), but infusion/injection reaction is a major adverse event in patients with RA treated with biological agents. We previously reported that a high affinity Fcγ receptor (FcγR) IIIB polymorphism (NA1/NA1) is an independent risk factor for the development of infusion reaction to infliximab in RA patients (*Ann Rheum Dis 70:299,2011*). In this study, we investigated whether FcγR IIIB polymorphisms are related with injection reaction to adalimumab (ADA), a fully human anti-TNFα monoclonal antibody in patients with RA.

Methods: Consecutive patients with RA who fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) for the classification of RA or the 2010 ACR/EULAR RA Classification Criteria were invited to participate in the study after informed consent. Peripheral blood samples and clinical records were obtained from 65 RA patients (56 females and 9 males) treated with ADA between July 2008 and May 2012. The genomic DNA was extracted from peripheral blood mononuclear cells. Genetic polymorphisms for FcγR IIIB were genotyped in *FCGR3B* NA1/2 alleles by real allelic discrimination assay. Clinical records in 65 patients were collected retrospectively. Genetic polymorphisms were subjected to logistic regression analysis to evaluate the association with clinical parameters.

Results: Injection reaction to ADA was observed in 8 patients, 2 patients of those discontinued ADA due to those injection reactions. There was no significant difference in clinical background between patients with injection reaction and those without. The *FCGR3B* NA1/NA1 genotype was found in 75.0% (6/8) of the patients with injection reaction whereas in only 28.1% (16/57) of those without injection reaction, indicating that this genotype is associated with the development of infusion reactions. In contrast, the genotypes NA1/NA2 and NA2/NA2 were only observed in 12.5% and 12.5% of the patients with injection reaction while in 42.1% and 29.8% of those without injection reaction. Analyses confirmed that the distribution of the *FCGR3B* genotypes between patients with and without injection reactions was significantly different (p=0.022). On the other hand, any clinical parameters tested in this study were not associated with injection reaction.

Conclusion: The *FCGR3B* NA1/NA1 genotype may be the potential predictive marker for the development of injection reaction to ADA as well as infusion reaction to infliximab in Japanese RA patients.

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Methotrexate Polyglutamate Concentrations in Erythrocytes Are a Potential Tool for Therapeutic Drug Monitoring of Methotrexate Response in Rheumatoid Arthritis. Maurits C.F.J. De Rotte[1], Ethan den Boer[2], Maja Bulatovic[3], Saskia M.F. Pluijm[4], Johanna M.W. Hazes[1] and Robert De Jonge[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus University Hospital, Rotterdam, Netherlands, [3]University Medical Centre Utrecht, Netherlands, [4]Erasmus Medical center, Rotterdam, Netherlands

Background/Purpose: Methotrexate (MTX) is the most commonly used drug in rheumatoid arthritis (RA). 30% of patients fail to respond to the drug or suffer from adverse events. Therefore, there is a need for therapeutic drug monitoring (TDM). MTX plasma concentrations decrease in a few hours, whereas MTX polyglutamates (MTX-PG) are accumulated intracellular over months inside cells, and therefore may be a tool for TDM.

Methods: The study included patients from two longitudinal cohorts who were diagnosed with RA according to the 2010 ACR criteria and were treated with MTX therapy: 285 patients from the treatment in Rotterdam Early Arthritis Cohort (tREACH) (1) and 99 from the Methotrexate in Rotterdam

(MTX-R) study. We measured MTX with a tail of 1,2,3,4 and 5 glutamates in erythrocytes at 3 months after MTX start with an LC-MS/MS assay. As outcome measure for MTX response we defined disease activity score (DAS) 28 at 0,3,6 and 9 months after MTX start and EULAR response criteria at 3,6 and 9 months. Adverse events were measured as gastro intestinal intolerance and overall complaints at 3,6 and 9 months. DAS28 was analyzed with analysis of covariance (ANCOVA). EULAR response and adverse events were analyzed with logistic regression. All MTX-PGs were analyzed as continuous variables, quintiles and tertiles. All analysis were adjusted for age, gender, DAS28 at baseline, MTX dose, MTX route of administration, other DMARDs, NSAIDs, steroids and study cohort.

Results: Concentrations at 3 months (mean/SD) were: MTX-PG1: 17.99 nmol/l (18.28), MTX-PG2: 9.25 nmol/l (4.61), MTX-PG3: 18.26 nmol/l (7.66), MTX-PG4: 7.78 nmol/l (5.95), MTX-PG5: 2.41 nmol/l (3.02) and total MTX-PG: 58.07 nmol/l (27.47). DAS28 was 4.76 (1.26) at baseline and 3.08 (1.20), 2.91 (1.22), 2.68 (1.16) at 3,6 and 9 months, respectively. At 3 months 52% had gastrointestinal complaints, at 6 months 26% and at 9 months 24%. 46%, 49% and 47% of the patients reported to have one or more adverse events at 3, 6 and 9 months. Lower DAS28 scores at 3,6 and 9 months were associated with higher MTX PG1, MTX-PG2 and total MTX-PG concentrations (table). Analysis in quintiles revealed that MTX-PG1,2 and total MTX-PG concentrations were non-linearly associated with EULAR response. As compared with patients in the lowest quintiles, patients in the highest quintiles had a higher chance to respond. No associations were found between any of the MTX-PG concentrations and adverse events.

Table. Analysis of covariance for the association between MTX-PG concentrations and DAS28

MTX-PG at 3 months	3 months Standardized-β (p)	6 months Standardized-β (p)	9 months Standardized-β (p)
MTX-PG1	−0.12 (0.022)*	−0.15 (0.015)*	−0.17 (0.012)*
MTX-PG2	−0.15 (0.003)*	−0.19 (0.001)*	−0.19 (0.003)*
MTX-PG3	−0.075 (0.196)	−0.05 (0.390)	−0.04 (0.558)
MTX-PG4	−0.04 (0.498)	−0.07 (0.281)	0.13 (0.074)
MTX-PG5	−0.03 (0.584)	0.10 (0.138)	0.20 (0.004)
MTX total PG	−0.15 (0.012)*	−0.13 (0.053)*	−0.16 (0.028)*

* = significant. All analyses are adjusted for age, gender, DAS28 at baseline, MTX dose, MTX route of administration, other DMARDs, NSAIDs, steroids and study cohort.

Conclusion: In this first longitudinal study, higher MTX-PG1,2 and total MTX-PG concentrations in erythrocytes were associated with MTX response over the first 9 months treatment and are therefore a potential tool for TDM of MTX in RA.

Funds: RDJ: Dutch Arthritis Association (nr. 06-02-402, 09-1-402).

Reference
1. De Jong PH, et al. Ann Rheum Dis. 2012 Jun 7.

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Correlation of A Multi-Biomarker Disease Activity (VECTRA™ DA) Score with Clinical Disease Activity and Its Components with Radiographic Progression in Rheumatoid Arthritis Patients Treated with Tofacitinib. Kunihiro Yamaoka[1], Satoshi Kubo[1], Koshiro Sonomoto[1], Shintaro Hirata[1], Guy Cavet[2], Rebecca Bolce[2], Michael W. Rowe[2], David Chernoff[2], Nadine Defranoux[2], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Crescendo Bioscience Inc., South San Francisco, CA

Background/Purpose: A multi-biomarker disease activity (MBDA) score has been developed for evaluation of disease activity of rheumatoid arthritis (RA) to complement clinical assessment and to provide information about underlying disease processes. We have reported the usefulness of MBDA as clinical measures of disease activity. However, relation of MBDA score with clinical features in RA patients treated with a JAK-inhibitor tofacitinib is unknown.

Methods: DAS28(ESR), SDAI, MBDA and modified total sharp score (mTSS) were evaluated at baseline and 1 year in 37 patients (31 women, mean age: 54.6 years, mean disease duration: 78.9 months) enrolled in phase II and III clinical trials of tofacitinib. Patients were randomized to different doses of tofacitinib or placebo for the first 3 to 6 months (8 patients with dosed tofacitinib as monotherapy and 29 patients with concomitant MTX). All patients were treated with tofacitinib 5 mg or 10 mg BID after 6 months. MBDA combines 12

serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) in a pre-specified algorithm resulting in a score between 1 and 100.

Results: (1) Disease activity significantly improved: MBDA, 60.8 to 28.5 as well as SDAI 37.7 to 6.2, DAS28-ESR 6.4 to 3.0, HAQ-DI 1.4 to 0.8,. HAQ-DI $\leq$0.5 was achieved in 19 patients (51%). Yearly progression of mTSS (ΔmTSS) significantly decreased from 14.7 to 0.9 and 21 patients (56%) achieved structural remission.

(2) Significant correlation was observed between yearly ΔMBDA score and ΔDAS28(ESR), ΔSDAI or ΔCDAI (p<0.01).

(3) When clinical remission was determined as MBDA $\leq$25, remission rate was similar among measurements. (SDAI 37.8%, DAS28-ESR 35.1%, MBDA 40.5%)

(4) No correlation was observed between ΔmTSS and ΔMBDA, ΔDAS28(ESR), ΔSDAI or ΔCDAI.

(5) The proportion of radiographic progressors in remission was similar among different measurements. (38.5% (5/13) of DAS28-ESR remission, 35.7% (5/14) of SDAI remission and 33.3% (5/15) of MBDA remission)

(6) IL-6 decreased from 163.0pg/ml to 25.1pg/ml and MMP-3 decreased from 159.1ng/ml to 39.5ng/ml. The measures of IL-6 and MMP-3 at 52 weeks significantly correlated with change of mTSS (69.1 to 70.0).

(7) When patients were separated into 2 groups with median value of serum IL-6 (9.0ng/ml) at 52 weeks, 78% achieved structural remission in low concentration group, whereas 38% was achievable in high concentration group.

Conclusion: MBDA significantly correlated with cpnventional composite measures of disease activity and equally contributed to remission rate in patients with RA. Although ΔMBDA did not correlate with ΔmTSS in this study size, concentration of IL-6 and MMP-3 at 52 weeks correlated with change of mTSS. These results indicate that tofacitinib acts through the inhibition of IL-6 and is able to prevent bone destruction. Our results further support the usefulness of MBDA as an additional composite measure for RA disease activity.

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Abatacept Monotherapy Effectively Reduces the Frequency of Osteoclast Precursor Cells in the Peripheral Blood of Patients with Rheumatoid Arthritis and Inhibits Their Differentiation Into Osteoclasts. Sandra Mueller-Schmucker[1]. Roland Axmann[1], Sonja Herman[2], Mario Zaiss[1], Manuela Le Bars[3], Thomas Harrer[1] and Georg A. Schett[4], [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Medical University of Vienna, Vienna, Austria, [3]Bristol-Myers Squibb, Rueil Malmaison, France, [4]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Bone resorbing osteoclasts origin from monocytes. We have recently shown that binding of abatacept (CTLA4-Ig) to CD80 and CD86 on the surface of monocytes blocks their differentiation into osteoclasts in vitro (Axmann et al, Ann Rheum Dis. 2008;67:1603-9). We thus speculated whether abatacept therapy impairs the potential of osteoclast differentiation in rheumatoid arthritis patients in vivo.

Methods: We compared the frequency of CD11b+CD115+ osteoclast precursor cells in the peripheral blood of 60 patients with rheumatoid arthritis (RA), either untreated (N= 15) or treated with methrotrexate (N=15), adalimumab (N= 15) or abatacept as monotherapies (N=25) using FACS analysis. We also performed osteoclast differentiation assays from the peripheral blood mononuclear cells from these patients to quantify osteoclast differentiation and to test for osteoclast gene expression profiles.

Results: The frequency of osteoclast precursors in the peripheral blood was significantly (p< 0.01) lower in abatacept treated patients (82,4 $\pm$ 1,8%) than in untreated controls (97,4 $\pm$ 0,6%), whereas no significant differences between controls and adalimumab and methotrexate treated patients, respectively, were found. In addition, osteoclast differentiation from peripheral blood was impaired in abatacept-treated patients (mean osteoclast number per well= 32,5) as compared to untreated controls (mean osteoclast number per well= 145,6). In addition, sequential analysis of patients before and after abatcept exposure showed reduced potential of osteoclast precursors to differentiate into osteoclasts

after the exposure to abatacept. Moreover, we found significant down regulation of essential osteoclast differentiation factors c-Fos and NFAT1c after in vitro exposure of monocytes to abatacept.

Conclusion: Abatacept treatment decreases osteoclast precursor cell frequency in RA patients as well as osteoclast differentiation potential of peripheral blood mononuclear cells. Moreover, abatcept leads to a down regulation of key osteoclast genes such as c-Fos and NFATc1. These data explain the mechanism by which abatcept may achieve bone protection during the treatment of RA patients.

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Evidence for NF-Kb Intracellular Signaling Involvement Following CTLA4-Ig (Abatacept) Treatment of Human Macrophages. Renata Brizzolara[1], Paola Montagna[1], Stefano Soldano[1], Alberto Sulli[1], Bruno Seriolo[1], Barbara Villaggio[2], Pierfranco Triolo[3], Lamberto Felli[4] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [2]Research Laboratory of Nephrology, Department of Internal Medicine, University of Genova, Genova, Italy, [3]Rheumatoid Arthritis Unit, Orthopedic Surgery Department, CTO Hospital, Turin, taly, Turin, Italy, [4]Orthopedic Department, University of Genova, Genova, Italy

Background/Purpose: The transcription factor NF-kB is an intracellular signaling essential for the expression of a variety of immune-response genes, including those related to pro-inflammatory cytokines [1]. Previous studies showed that a significant downregulation of TNFα, IL-1β and IL-6 was evident for cultured human macrophages treated with CTLA4-Ig [2,3]. Therefore, we investigated the involvement of the NF-kB pathway as possible intracellular signaling target during the CTLA4-Ig modulation of cytokine production in cultured human macrophages.

Methods: Human THP1 cell line cells, differentiated by phorbol myristate acetate in macrophages, were cultured with CTLA4-Ig (100 and 500 μg/ml; 3,12, 24 hours) or without CTLA4-Ig (cnt). CTLA4-Ig/CD86 binding was evaluated by fluorescence activated cell sorter (FACS) analysis. Quantitative RT-PCR analysis (qRT-PCR) of mRNA for NF-kB, its inhibitor IKBα and for TNFα, IL-1β, IL-6 was performed after 3 and 12 hours from CTLA4-Ig treatment. Western blot (WB) analysis for NF-kB and IKBα proteins was performed after 24 hours of CTLA4-Ig treatment.

Results: FACS analysis showed a reduction of B7.2 positivity on macrophages CTLA4-Ig-treated vs. cnt, due to CTLA4-Ig/B7.2 binding. The qRT-PCR analysis of NF-kB, at 3 and 12 hours from CTLA4-Ig [100, 500 μg/ml] treatment, showed a significant downregulation (both p<0.001) vs. cnt. On the contrary, IKBα showed, at 12 hours from CTLA4-Ig [500 μg/ml] treatment a significant increase (p<0.01), while after 3 hours from [100 and 500 μg/ml] CTLA4-Ig treatment vs. cnt, resulted unchanged. The qRT-PCR analysis of inflammatory cytokines, after 3 hours from treatment, showed for CTLA4-Ig [100 μg/ml] a significant decrease of TNFα and IL-6 (p<0.05), vs. cnt. CTLA4-Ig [500 μg/ml] reduced TNFα vs. cnt in a larger extent (p<0.001). After 12 hours from CTLA4-Ig [100, 500 μg/ml] treatment, it was still evident at qRT-PCR a significant downregulation (p<0.001) for all cytokine gene expression, vs. cnt. Finally, WB analysis showed that CTLA4-Ig treatment at higher concentration [500 μg/ml] was able to reduce NF-kB protein expression and to increase IKBα expression, vs. cnt.

Conclusion: CTLA4-Ig, while it reduces the inflammatory cytokine gene expression in human macrophages, seems to promote a downregulation of the intracellular signaling linked to the NF-kB pathway, including an increased expression of its cytoplasmatic inhibitor IKBα both at gene and protein level.

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Utility of Vectra-DA™ On Assessment of Rheumatoid Arthritis Disease Activity and Golimumab Response: Results of a Pilot Study From a Phase 3 Trial in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy. Sarah Lamberth, Yauheniya Cherkas, Carrie Brodmerkel and Mark Curran. Janssen Research and Development, LLC, Spring House, PA

Background/Purpose: Currently, disease activity in Rheumatoid Arthritis (RA) is measured using scoring systems that rely primarily on a collection of subjective measures from patients and clinicians. To improve care and treatment for RA patients, objective measurements of disease activity and response to treatment are desirable. Using a small cohort derived from an ongoing study of intravenously administered golimumab (GO-FURTHER), we evaluated the performance of Vectra-DA™ (Crescendo Biosciences), a multi-biomarker serum-based test designed to measure RA disease activity through correlation with DAS28-CRP and sensitive to anti-TNF therapy.[1] This analysis examines if Vectra-DA™ correlates with disease activity and golimumab response in a clinical trial setting.

Methods: 137 serum samples collected in a Phase III study of intravenously administered golimumab in patients with active RA despite methotrexate (MTX) therapy was analyzed using Vectra-DA™ (Crescendo Bioscience©; San Francisco, CA, USA). Samples were collected at weeks 0, 2, 4, and 14 from patients treated with IV placebo + MTX (PBO; n= 42) or IV golimumab 2mg/kg + MTX (GLM; n=95) who received study medications at Weeks 0, 4, and every 8 weeks thereafter. Healthy control serum samples (n=21) were obtained from Bioreclamation (Hicksville, NY).

Results: A subset of subjects was chosen for analysis with Vectra-DA™ from the GO-FURTHER study. The subset had an ACR50 response to golimumab of 35.8% (PBO 7.1%) at week 14 and 48.4% (PBO 16.7%) at week 24. Correlation of Vectra-DA™ and DAS28-CRP scores was r=0.51 (95% CI=0.45–0.57) using all four timepoints tested. Study subjects had statistically higher mean Vectra-DA™ scores (64.2 at wk 0; 45.5 at wk 2; 50.2 at wk4; 44.9 at wk14) compared to healthy controls (35.2). At baseline, there were no significant differences in GLM and PBO-treated subjects by Vectra-DA™ or DAS28-CRP scores. As early as week 2, GLM-treated subjects had a significant drop in Vectra-DA™ score of D= −18.7 (p=<2.2×10−16). The decrease in Vectra-DA™ score was maintained through week 14, whereas PBO-treated subjects did not have a significant change in Vectra-DA™ scores from baseline to weeks 2, 4 and 14. Vectra-DA™ scores were statistically different between GLM-treated subjects who achieved an ACR50 response at week 14 versus non-responders at weeks 0 (p=0.024), 4 (p=0.013), and 14 (p=0.009). Vectra-DA™ scores were not statistically different between GLM-treated subjects who achieved an ACR50 response at week 24 versus non-responders at all timepoints tested, though a trend was seen at week 14 (p= 0.054).

Conclusion: Vectra-DA™ offers a molecular measurement of RA disease activity that can discriminate between normal and RA subjects, and also PBO and GLM-treated subjects as early as week 2 post-treatment. GLM treated week 14 responders had significantly lower Vectra-DA™ scores compared with non-responders. The Vectra-DA™ score reflects a patient's disease activity before and after the treatment with intravenous golimumab.

[1] Weinblatt ME, Shadick NA, Manning W, et al. Use of a Multi-Biomarker Score for Rheumatoid Arthritis Disease Activity (Vectra™ DA) to Assess Response to Therapy. (Poster Session I: May 26, 2011, 11:45 BST). EULAR Congress 2011.

Disclosure: S. Lamberth, Janssen Research and Development, LLC, 3; **Y. Cherkas**, Janssen Research and Development, LLC, 3; **C. Brodmerkel**, Janssen Research and Development, LLC, 3; **M. Curran**, Janssen Research and Development, LLC, 3.

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Identification of Serological Biomarker Profiles Associated with Response to IL-6 Intervention in Rheumatoid Arthritis. Morten Asser Karsdal[1], Anne C. Bay-Jensen[1], Inger Byrjalsen[2], Andrew Kenwright[3], Adam Platt[3], Thierry Sornasse[4] and Claus Christiansen[5]. [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Nordic Bioscience, Herlev, Denmark, [3]Roche, Welwyn Garden City, United Kingdom, [4]Genentech, Inc., South San Francisco, USA, San Fransisco, CA, [5]CCBR, Ballerup, Denmark

Background/Purpose: RA is characterized by poly-articular synovial inflammation, cartilage loss and erosion of subchondral bone. It is critical to diagnose and effectively treat the disease early to suppress inflammation and halt destruction of the joint. Thus, identification of the patients most likely to respond to a given intervention should be pursued for optimal benefits for both patients and payers. The objectives were i) to investigate the early changes in biomarkers of bone, cartilage, synovium and inflammation as an effect of 8mg/kg tocilizumab (TCZ) treatment, and ii) to identify profiles associated with responders and non-responders biomarker profiles.

Methods: The prospective biomarker substudy of the LITHE trial included 626 patients. The LITHE trial (Roche WA17823) was a 2-year phase III, 3-arm randomized, double-blind, placebo-controlled, parallel group, including patients with moderate/severe active RA, and with inadequate response to DMARDs. The patients were randomized: TCZ8mg/kg (TCZ8), TCZ4mg/kg or placebo. Patients received an infusion of TCZ 8mg/kg, 4mg/kg or placebo every 4 weeks. Escape patients were defined as those who experienced <20% improvement in both swollen (SJC) and tender joint counts (TJC) at week 16 (non-responders). Current analysis only considered the TCZ8 group where serum was analyzed at baseline and 4 weeks. Following biomarkers were measured: C2M (cartilage degradation), C3M (synovial inflammation), MMP3, total CRP, CRPM (MMP-degraded CRP), VICM (Citrullinated and MMP-degraded Vimentin), ICTP (MMP destroyed type I collagen), osteocalcin (bone formation) and CTX-I (Bone resorption). This analysis consisted of 102 responders and 33 escape-therapies. Data is shown as geometric mean percentage change from baseline (Mann-Whitney test) and the odds ratio (OR) for response was calculated.

Results: The general inflammatory marker serum CRP was completely blocked (<10% of baseline) by TCZ8 in both the responder and non-responder group, with no significant ability to separate these groups (OR 1.6, *ns*). The level of serum CRPM was decreased to 72% in the responder group and only to 83% in the non-responder group (OR 4.0, *0.0014*). Cartilage degradation - C2M - was reduced to 89% of baseline levels upon treatment with TCZ8 in the responder group, whereas the level of serum C2M remained unaltered or increased to 102% of baseline level in the non-responder (OR 5.8, *0.0003*). The synovial turnover measure, serum C3M, was decreased to 73% of baseline in the responder group, compared to 88% in the non-responder group (OR 9.6, *0.0004*). There were only minimal differences in the bone resorption and formation markers, as well as in serum MMP-3, ICTP and VICM.

Conclusion: Biomarkers of cartilage and synovial turnover were able to discriminate between responders and non-responders to anti-IL-6R intervention at an early time point, in contrast to traditional CRP and the standard bone markers. These responder and non-responder profiles may enable identification of the optimal treatment for the individual patients, so-called Il-6 super-responders. Whether these response profiles are specific for IL-6 interventions or other biological treatments or other novel interventions remain to be investigated.

Disclosure: M. A. Karsdal, Nordic Bioscience Diagnostic, 4; **A. C. Bay-Jensen**, None; **I. Byrjalsen**, None; **A. Kenwright**, Roche Pharmaceuticals, 3; **A. Platt**, None; **T. Sornasse**, None; **C. Christiansen**, Nordic, Bioscience A/S, CCBR/Synarc,, Roche, Eli Lilly, Novartis, Novo Nordisk, Proctor and Gamble, Groupe Fournier, Besins Esco-Vesco, Merck Sharp and Dohme, Chiesi, Boehringer Mannheim, Pfizer, GlaxoSmith-Kline, Amgen., 5.

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Serum Based Biomarkers of Joint Destruction Can Identify Responders and Non-Responder to Tocilizumab. Anne C. Bay-Jensen[1], Inger Byrjalsen[2], Claus Christiansen[3] and Morten Asser Karsdal[1]. [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Nordic Bioscience, Herlev, Denmark, [3]CCBR, Ballerup, Denmark

Background/Purpose: RA is characterized by synovial inflammation, cartilage loss and erosion of subchondral bone. It is critical to diagnose and effectively treat the disease early to suppress inflammation and stop destruction of the joints. Inflammation results in the release of tissue fragments that reflects disease activity which are measurable in serum. Identification of the patients that would most likely respond and not respond to treatment would bring optimal benefits for patients. The objective of the study was to investigate whether early changes (within 4 weeks) in serum biomarkers were predictive of ACR50 response at week 52 to 4 and 8 mg/kg tocilizumab (TCZ) treatment of RA patients.

Methods: The prospective biomarker substudy of the LITHE trial included 693 patients. The LITHE trial (Roche WA17823) was a 2-year phase

III, 3-arm randomized, double-blind, placebo-controlled, parallel group, including patients with moderate/severe active RA, and with IR to DMARDs. The patients were randomized: TCZ8mg/kg (n=244), TCZ4mg/kg (n=207) or placebo (PBO, n=242) on a background of MTX. Biomarkers were measured in serum from baseline and 4 weeks: C2M (cartilage degradation), C3M (synovial inflammation), MMP3, total CRP, CRPM (MMP-degraded CRP), VICM (Citrullinated and MMP-degraded Vimentin), and ICTP (MMP destroyed type I collagen), osteocalcin (bone formation) and CTX-I (Bone resorption). Cut-off values for dichotomized analysis of the markers and the ACR50 response was determined by ROCs by best likelihood ratio for i) the individual markers at baseline, ii) changes from 4 weeks, and iii) ratio between markers. Decision trees (CART) were constructed using the cut-offs values and the predictive values for ACR50 response were calculated by 2×2 diagnostic tests.

Results: The proportion of ACR50 responders at week 52 for TCZ4 and PBO were 29% and 8.2%, corresponding to a number need-to-treat ratio (NNT) of 3.5 and 12, respectively. CART#1 (baseline C2M/CRP and C3M/CRPM ratios): A positive test resulted in identification of 68 TCZ4 cases which led to a PPV of 40% and a NPV of 76%. PBO; 1 out 19 cases with a positive test were responder. CART#2 (baseline MMP3 and C3M/CRPM ratio); A positive test resulted in identification of 86 TCZ4 cases, which led to a PPV of 43% and a NPV of 80%. PBO; 2 out 27 cases with a positive test were responder (NNT 2.3). CART#3 (CART#2 + 4-week change in osteocalcin and CTXI/C2M ratio); A positive test resulted in identification of 30 TCZ4 cases, which led to a PPV of 63% and a NPV of 79% (NNT 1.6). No PBO cases were selected. Similar data was obtained independently for TCZ 8mg/kg.

Conclusion: We identified more than 76% of the patients that did not respond to TCZ4 treatment. This increased the response rate from 29% up to 63%. We found that measurement of baseline biomarkers the need-to-treat ratio could be reduced from 3.5 to 2.3. If early changes in biomarkers were included then this need-to-treat ratio could be further reduced to 1.6. Whether this is an IL6 pathway-specific serological profile need to be investigated in additional clinical settings.

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Tolerance and Efficacy of Rituximab in Elderly Patients with Rheumatoid Arthritis Enrolled in the French Society of Rheumatology Air Registry.
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Background/Purpose: This study aimed to compare the efficacy and the safety of Rituximab (RTX)in elderly (aged ≥ 65years) and younger patients (aged 18–64 years) with active rheumatoid arthritis (RA).

Methods: We included all the RA patients in the Auto-immunity and RTX 7-years prospective registry with 2 years follow-up and divided them in 2 main groups on the basis of their age (aged ≥ 65 and aged <65). A minor group with the very old patients (75years old or more) was studied too. The primary efficacy outcome was EULAR response (good, moderate and no response), the secondary

efficacy outcome were low disease activity and remission. The primary tolerance outcome was drug discontinuation rates due to side effects.

Results: Among the 1709 patients having at least 2 years of follow up, 608 were ≥ 65years of whom 191 were ≥ 75years old, and 1101 were <65years. At baseline, the elderly patients showed a longer disease duration, a higher rate of CRP and ESR (medians respectively 21 vs 14mg/L, p<0.001, and 35 vs 32 mm, p<0.001), lower rate of previous aTNF therapy (71% vs 79.6%, p<0.001) and lower number of aTNF previously used (medians 1 vs 2, p<0.001). Disease activity, previous DMARDs rates, rheumatoid or aCCP rates and corticotherapy (yes/no) were not statistically different between the 2 groups. At 24 months, no significant difference was showed between groups for RTX discontinuation rates for side effects: 5.8% if < 65years, 4.9% if ≥ 65 years and 4.2% if ≥ 75years old. However, death rates increased with age: 2.5% if < 65years, 7.7% if ≥ 65 years and 16.2% if ≥ 75years old, p<0.001.The EULAR response criteria were not statistically different after 2 years (n=506) in the younger (<65 years, n=354)and older groups (≥ 65years, n=152) with respectively 64.1% and 68.4% of responders including 39.5% and 48% moderate responders, and 24.6% and 20.4% good responders respectively. However, there were significant differences concerning very old patients (≥75ans). Before adjustment younger patients and patients between 65 and 75years had more chances to be good responders at one year follow-up (n=642) than patients ≥ 75years old, with respectively OR= 3.54 (95% IC= [1.2–10.47]) and OR= 4.53 (95 IC= [1.12–12.33]). After adjustment, this difference was only significant between the old (≥ 65years) and very old patients (≥ 75years): OR= 3.71, 95% IC= [1.12;12.33] (n= 475). At 24 months, these differences were no longer significant with or without adjustment. Concerning remission, there was no significant difference between the young and the elderly, either at 1 year or at 2 years, respectively 12.05% vs 13% (adjusted p=0.372), and 15.6% vs 11.04% (adjusted p= 0.410).

Conclusion: This study is the first to date to compare tolerance and effectiveness of RTX between elderly and younger patients with RA. No significant difference in efficacy or discontinuation rate after 2 years of follow-up. Increase of mortality in the oldest patients is probably due to the decrease of life expectancy with age.

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Short to Medium Term Safety of Glucocorticoid Therapy in Rheumatoid Arthritis: A Systematic Review and Dose-Response Analysis of Randomized Controlled Trials.
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Background/Purpose: Concerns regarding Adverse Effects (AEs) often dominate decisions on applying Glucocorticoid (GC) therapy. Evidence of AEs is mainly based on observational data without proper control groups. Thus, an examination of Randomized Controlled Trials (RCTs) for short to medium term AEs from GC would be useful. Our aim was to assess the risk of selected AEs, ranked as most worrisome among patients and rheumatologists (1), in relation to dose.

Methods: A systematic search in MEDLINE, EMBASE, and CENTRAL was performed. Inclusion criteria were RCTs in patients with Rheumatoid Arthritis (RA) with any Prednisone Equivalent Dose Differences (PEDD) between trial arms, independent of type of administration, type of GC, or study duration. RCTs of GCs without a prednisone equivalent conversion factor were excluded. One reviewer extracted the data from the included trials and a second reviewer checked the extracted data. Analyses were based on differences in dose between trial arms (more vs. less) and therefore an assumption for linearity in response, e.g. 10 mg/d PEDD in trials of 10 vs. 0 mg was equal to 70 vs. 60 mg. For the meta-analyses, a random-effects (REML) model was used to estimate the pooled Risk Ratios (RR) with 95% Confidence Intervals (CI). The average daily and accumulated PEDD in mg between trial arms were estimated and categorized in following dose-groups:

low (≤7.5 mg), medium (>7.5, ≤30 mg), and high (>30 mg) for each RCT. Meta-regression and stratified analyses were conducted to explore dose-response, using daily and accumulated PEDD as covariates and dose-groups as strata for each outcome.

Results: Of 2821 references identified, 524 were reviewed in detail, and 59 RCTs (66 Randomized Comparisons with a total of 4831 patients) were eligible for inclusion. Overall, the risks of the selected AEs over 24 to 104 weeks were not increased when comparing more vs. less GC (Table). Although none of the analyses showed statistical significance, some of the meta-regression and stratified analyses suggested a trend for a dose-response for GC given up to doses of maximum 75 mg/d PEDD. There was a trend towards an increasing risk of osteoporosis (from RR 1.07 to 3.41 when applied in medium dose), cardiovascular diseases (from RR 1.19 to 2.75 when applied in high dose). Interestingly, with data for the high dose relatively limited, the dose-response pattern for both non-viral infections and diabetes showed a tendency to decreasing risk with increasing GC dose.

Outcome	No of Studies (RC)	No of Pt.	Pt. years	Overall RR 95%(CI)	Duration Median (weeks)	Daily PEDD Median (mg)	Accum. PEDD Median (mg)	Dose-Response RR (95%CI) Low dose Stratum	Medium dose stratum	High dose stratum	P-value for interaction
Diabetes	18	1880	2196	1.18 (0.56,2.49)	78	8.8	4612	1.72 (0.29,10.18)	1.03 (0.13,8.36)	1.03 (0.29,3.67)	0.84
Osteoporosis	12	1464	2166	1.31 (0.74,2.32)	104	5.0	3650	1.07 (0.51,2.25)	3.41 (0.68,7.13)	NA	0.17
Cardiovascular diseases	20	2180	2865	0.88 (0.59,1.32)	38	5	2730	1.19 (0.44,3.26)	2.41 (0.61,9.50)	2.75 (0.18,42.76)	0.27
Hypertension	21	2178	3047	1.24 (0,83,1,86)	104	5	3600	1.41 (0.85,2.35)	0.77 (0.40,1.50)	1.67 (0.35,7.84)	0.28
Infections (non-viral)	19	2107	2402	0.90 (0.78,1,04)	24	7.5	1425	0.95 (0.78,1.16)	0.82 (0.63,1.07)	0.36 (0.01,11.01)	0.53
Renal Dysfunction	15	2044	2724	1.41 (0.97,2.05)	78	5	1890	1.25 (0.64,2.43)	1.99 (0.11,35.44)	NA	0.72
Weight gain	18	1967	2626	1.19 (0.98,1.46)	78	7.3	3625	1.23 (0.83,1.83)	1.25 (0.92,1.71)	0.91 (0.49,1.70)	0.60

#PEDD: Prednisone Equivalent Dose Differences; RC: Randomized Comparisons; RR Risk Ratio; CI: Confidence Intervals; pt: patients.

Conclusion: This study presents empirical evidence, based on RCTs, that: 1) there is no statistical evidence to support concerns of an overall increased risk of the selected side effects of GCs, when the GC is used over a period of 24 to 104 weeks; 2) a tendency to a dose-dependent increased risk was noted for osteoporosis and cardiovascular side effects, while there may be decreasing risk for diabetes and non-viral infections.

References
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Methotrexate and Interstitial Lung Disease in Rheumatoid Arthritis – A Systematic Literature Review and Meta-Analysis. Richard Conway[1], Candice Low[2]. Robert J. Coughlan[3], Martin O'Donnell[3] and John J. Carey[3], [1]St James's Hospital, Dublin, Ireland, [2]St. James Hospital, Dublin, Ireland, [3]Galway University Hospitals, Galway, Ireland

Background/Purpose: Methotrexate is commonly prescribed for a variety of diseases including rheumatoid arthritis. Methotrexate has frequently been implicated as a causative agent in interstitial lung disease. Patients with rheumatoid arthritis can develop pulmonary disease for a variety of reasons including infection and rheumatoid interstitial lung disease. Distinguishing methotrexate lung toxicity from other aetiologies is vital in the clinical setting as methotrexate is an effective treatment for rheumatoid arthritis. The aim of this study was to evaluate if methotrexate is associated with an increased risk of lung disease in rheumatoid arthritis.

Methods: We performed a systematic literature search from 1st January 1990 to 31st March 2011 using Pubmed and Cochrane databases. The inclusion criteria for study selection were (1) randomised controlled trials; (2) human patients with rheumatoid arthritis; (3) studies in English; (4) studies consisting of a minimum of two arms, at least one receiving methotrexate and at least one not receiving methotrexate; (5) studies including only adults(>18 years); (6) trials of ≥6 months duration; (7) studies of ≥100 patients; (8) studies reporting respiratory side effects for methotrexate and comparator groups individually. Random effects meta-analysis using the Mantel-Haenszel method was used to assess total respiratory events, infectious respiratory events and non-infectious respi-

ratory events. Results were expressed as relative risks (RR) with 95% confidence intervals.

Results: 21 studies with a total of 8276 participants met our study's inclusion criteria and were included in the meta-analysis. Methotrexate was not associated with an increased risk of total adverse respiratory events, RR 1.1 (95% CI 1.0–1.2, $I^2=8\%$), Figure 1. No difference was identified in the risk of adverse events when analysed separately for infectious and non-infectious outcomes, RR 1.09 (95% CI 1.0–1.19, $I^2=0\%$) and 1.11 (95% CI 0.68–1.81, $I^2=48\%$) respectively. There was no difference in the risk of pulmonary death between the 2 groups, RR 1.41 (95% CI 0.43–4.63, $I^2=0\%$). A subgroup analysis of studies specifically reporting pneumonitis revealed an increased risk in the methotrexate group, RR 6.99 (95% CI 1.57–31.05, $I^2=0\%$); however none of the publications since 2001 in our study reported any cases of pneumonitis.

Study or Subgroup	Methotrexate Events	Total	Comparator Events	Total	Weight	Risk Ratio M-H, Random, 95%CI
Bathone et al, 2000	153	217	244	415	32.2%	1.20 [1.07, 1.35]
Boers et al, 1997	1	76	0	79	0.1%	3.12 [0.13, 76.36]
Breedveld et al, 2006	7	525	1	27	0.2%	3.65 [0.46, 29.54]
Cohen et al, 2001	142	190	129	190	29.4%	1.10 [0.97, 1.25]
Edwards et al, 2004	12	80	19	81	1.9%	0.64 [0.33, 1.23]
Emery et al, 2000	48	498	39	501	4.9%	1.24 [0.83, 1.85]
Emery et al, 2009	64	478	17	159	3.2%	1.25 [0.76, 2.07]
Haagsma et al, 1997	19	71	8	34	1.6%	1.14 [0.55, 2.39]
Hue et al, 2009	7	118	8	120	0.9%	0.89 [0.33, 2.38]
Jones et al, 2010	52	284	70	288	7.5%	0.75 [0.55, 1.04]
Keystone et al, 2009	1	311	1	133	0.1%	0.43 [0.03, 6.79]
Lue et al, 2009	1	163	1	326	0.1%	2.00 [0.13, 31.77]
Nishimoto et al, 2007	50	145	61	157	8.4%	0.89 [0.66, 1.20]
Nishimoto et al, 2009	12	64	15	61	1.8%	0.76 [0.39, 1.49]
O'Dell et al, 1996	2	67	1	35	0.2%	1.04 [0.10, 11.13]
Rau et al, 1997	4	87	3	87	0.4%	1.33 [0.31, 5.78]
van der Heijde et al, 2006	58	459	19	223	3.4%	1.48 [0.91, 2.43]
Wkie et al, 2009	0	158	0	296		Not estimable
Weinblatt et al, 1990	32	138	24	142	3.6%	1.37 [0.85, 2.21]
Williams et al, 1992	4	220	0	115	0.1%	4.72 [0.26, 86.99]
Zhang et al, 2008	0	106	0	105		Not estimable
Total (95%CI)		4455		3321	100.0%	1.10 [1.00, 1.20]

Total events: 689, 680
Heterogeneity: Tau² = 0.00; Chi² = 19.66, df = 18 (P = 0.35); I² = 8%
Test for overall effect: Z = 1.93 (P = 0.05)

Favours methotrexate / Favours comparator

Figure 1. Total Respiratory Events.

Conclusion: Our study did not find a significant increase in the risk of lung disease in RA patients treated with methotrexate. One subgroup analysis showed a significant increased risk of pneumonitis; however publications after 2001 have not reported this association.

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Comparative Efficacy of Biologics As Monotherapy and in Combination with Methotrexate in Rheumatoid Arthritis Patients with an Inadequate Response to Conventional Dmards: A Network Meta-Analysis. Felicity Buckley[1], Axel Finckh[2], Tom W. J. Huizinga[3], Fred Dejonckheere[4] and Jeroen P. Jansen[1]. [1]MAPI Consultancy, Boston, MA, [2]University Hospital of Geneva, Geneva, Switzerland, [3]Leiden University Medical Center, Leiden, Netherlands, [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background/Purpose: A number of meta-analyses compare the efficacy of biologics for rheumatoid arthritis (RA). However, systematic reviews comparing the efficacy of biologics as monotherapy versus combination with DMARDs are rare,[1] and none include all currently approved biologics. Our objective was to compare ACR response at 24 weeks in RA patients with an inadequate response to conventional DMARDs (DMARD-IR) receiving approved biologics as monotherapy or in combination with methotrexate (MTX).

Methods: A systematic literature review was undertaken to identify RCTs that assessed approved biologic therapies as monotherapy or in combination with MTX in DMARD-IR RA patients. 22 RCTs were identified that evaluated tocilizumab (TCZ), adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, or anakinra. ACR responses at 24 weeks were extracted and combined by means of Bayesian network meta-analyses to obtain treatment effect estimates between all interventions included in the analysis, whether directly or indirectly compared. As shown elsewhere,[1,2] an assumption was made that the effects of anti-TNF-α agents (aTNFs) are

exchangeable. Given this, and the limited data identified for these therapies in monotherapy, aTNF data were pooled.

Results: Using random effects models, TCZ + MTX was shown to be comparable to other biologics + MTX across the ACR outcomes. A higher expected treatment effect was seen with TCZ + MTX for ACR70, in line with earlier analyses.[3] When comparing biologic monotherapies with biologics + MTX, TCZ showed a comparable likelihood of ACR20, ACR50, and ACR70 response versus TCZ + MTX ([RR 0.98 (95% credible interval [CrI]: 0.70, 1.71)], [RR 0.92 [95% CrI: 0.62, 1.56)], and [RR 1.04 (95% CrI: 0.58, 2.08)], respectively). aTNF as monotherapy was likely to be less efficacious compared to aTNFs + MTX in terms of ACR20 and ACR50 response (probability better=13% [RR 0.71 (95% CrI: 0.48, 1.64)] and probability better=5% [RR 0.52 (95% CrI: 0.31, 1.25)], respectively). Between monotherapies, the chance of ACR20, ACR50, and ACR70 response for TCZ was found likely to be greater compared to responses for aTNFs (probability better=88%, 97%, and 96%, respectively), in line with recently reported outcomes of a trial[4] comparing TCZ and adalimumab.
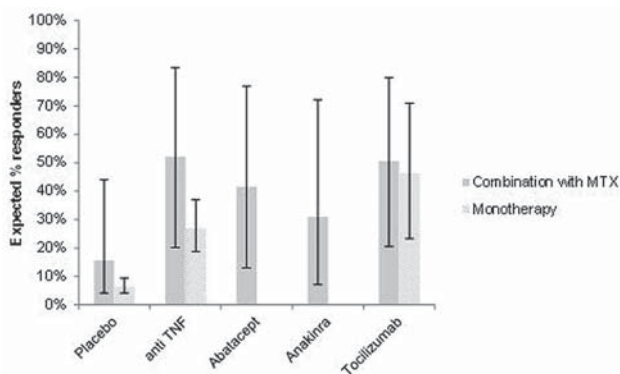
Figure 1. Expected ACR50 responcse at 24 weeks with combination therapy and monotherapy (random effects network meta-analysis)

Conclusion: Our network meta-analysis, involving indirect comparison of trial findings, suggests that in DMARD-IR patients, TCZ + MTX shows comparable efficacy to other biologics + MTX. In monotherapy, TCZ is likely to have a greater efficacy than aTNFs and shows comparable efficacy compared to TCZ + MTX, whereas aTNFs are likely to show lower efficacy compared to aTNFs + MTX.

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2172

An Update of Management of Coccidioidomycosis in Patients On Biologic Response Modifiers and Disease-Modifying Antirheumatic Drugs.
Susan Knowles[1], Dominick Sudano[1], Sara Taroumian[2], Neil M. Ampel[1], John Galgiani[3], Jeffrey R. Lisse[1] and Susan E. Hoover[1]. [1]University of Arizona, Tucson, AZ, [2]University of California, Los Angeles, Los Angeles, CA, [3]Valley Fever Center for Excellence, Tucson, AZ

Background/Purpose: Coccidioidomycosis (valley fever) is an endemic fungal infection in the Southwestern United States which typically causes a self-limited pulmonary illness. Patients with rheumatic disease on immunosuppressive medication, including methotrexate and tumor necrosis factor (TNF) antagonists, are at higher risk of more severe infection or dissemination. Currently, there are no guidelines for management of coccidioidomycosis in patients on disease-modifying antirheumatic drug (DMARD) or biologic response modifier (BRM) therapy.

Methods: A retrospective chart review identified patients at two centers in Tucson, Arizona, who developed coccidioidomycosis while on DMARD or BRM therapy. Review emphasized disease manifestations, antifungal therapy and duration, as well as management of BRM/DMARD therapy.

Results: Sixty-six patients who developed coccidioidomycosis while on DMARD and/or BRM therapy were identified. Forty-four of these have been previously reported, and their charts were re-reviewed for an additional 12 months of follow-up. Twenty-two new patients were identified. Rheumatologic treatment included BRM alone (18), DMARD alone (15), or combination therapy (33). Eighteen patients were on oral prednisone at the time of diagnosis, with doses ranging from 3 to 40 mg daily (median 10 mg). Manifestations of coccidioidomycosis were asymptomatic positive serologies (15), pulmonary illness (41), and dissemination (10). At the time of coccidioidomycosis diagnosis, 35 patients held all BRM and DMARD therapy, 9 patients held BRM but continued DMARD therapy, and 22 patients had no change in immunosuppressive therapy. Most patients (54) received antifungal therapy, usually for 3 months or longer.

Follow-up data were available for 56 patients. BRM and/or DMARD therapy was continued or resumed in 45 patients, of whom 17 continued concurrent antifungal therapy. Three patients with disseminated disease restarted BRM therapy. The most common reasons for continuing antifungal therapy were persistent positive serology or disseminated disease. The most common reason for stopping antifungal therapy was a negative serology. Follow-up for patients who stopped antifungal therapy or were never treated is 2 to 119 months (median 18 mos). One patient on DMARD and corticosteroid therapy died soon after diagnosis of severe disseminated coccidioidomycosis despite antifungal therapy. Another patient with coccidioidal meningitis had relapse of disease, possibly related to non-adherence to antifungal therapy. Otherwise, there have been no cases of subsequent dissemination or complications to date.

Conclusion: Continuing or restarting DMARD and/or BRM therapy after coccidioidomycosis appears to be safe in some patients with appropriate monitoring. If coccidioidomycosis is asymptomatic and rheumatic disease is active, continuation of DMARD and/or BRM can be considered. Patients with symptomatic infection should stop immunosuppressive therapy and continue antifungal therapy until the coccidioidomycosis is under control.

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Pharmacoeconomic Evaluation of Tocilizumab Monotherapy Vs. Adalimumab Monotherapy in Reducing Disease Activity in Patients with Rheumatoid Arthritis.
Navarro Sarabia F[1], Francisco J. Blanco[2], Alvaro Gracia JM[3], JA García Meijide[4] and Jl Poveda[5]. [1]Hospital. Virgen Macarena, Sevilla, Spain, [2]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [3]H. Universitario La Princesa, Madrid, Spain, [4]Hospital Ntra. Sra. La Esperanza, Santiago de Compostela, Spain, [5]Hospital Universitario La Fe, Valencia, Spain

Background/Purpose: ADACTA trial (Gabay C et al EULAR June 2012) showed that tocilizumab (TCZ) monotherapy was superior to adalimumab (ADA) monotherapy in reducing signs and symptoms of adult rheumatoid arthritis (RA) patients who were either intolerant to methotrexate (MTX) or for whom continued MTX treatment was inappropriate. The aim of the current study was to develop a cost-effectiveness analysis of TCZ vs. ADA in MTX-intolerant/contraindicated patients.

Methods: An economic evaluation based on the ADACTA study was conducted to estimate the incremental cost-effectiveness ratio (ICER) of TCZ vs. ADA. Time horizon was 24 weeks. In ADACTA study, patients were randomly assigned (1:1) to TCZ 8 mg/kg IV every 4 weeks or ADA 40 mg subcutaneously every 2 weeks. Baseline characteristics were similar between the TCZ and ADA. Mean weight considered in the analysis was 68 kgs (C. Rubio-Terrés et al. Farm Hosp 2007; 31: 78–92). To estimate treatment cost for each drug it was considered 6 doses for TCZ and 12 doses for ADA treatment. Patient's response in the model was measured through ACR responses (ACR20/ACR50/ACR70) and DAS28 remission. **Results** were presented as incremental cost of TCZ vs. ADA per response. The analysis was conducted from the perspective of the Spanish National Healthcare System, considering drug costs. Unitary costs (€, 2012) were obtained from a Spanish database. Simple univariate sensitivity analyses were performed, for this analysis it was considered weight and infusion cost.

Results: ACR20 response rates were achieved in 65% and 49.4% in the TCZ and ADA groups respectively (p<0.010). ACR50 response rates were achieved in 47.2% and 27.8% in TCZ and ADA groups (p<0.010) and ACR70 response rates in 32.5% and 17.9% in TCZ and ADA groups

(p<0.010) respectively. DAS28 remission was achieved in 39.9% and 10.5% in TCZ and ADA group (p<0.001). Treatment with TCZ provided better results in cost per response than ADA over 24 weeks in terms of ACR response (ACR20 €8,105 and €11,553; ACR50 €11,162 and €20,382; ACR70 €15,965 and €31,705) and DAS 28 remission €13,509 and €54,352 respectively. TCZ was dominant over ADA in ACR response and DAS28 remission. Sensitivity analysis confirmed the stability of the results.

Conclusion: The results of this analysis suggest that TCZ monotherapy represents an efficient and cost-effective strategy vs. ADA in Spain, for treating RA patients who are MTX intolerant/contraindicated.

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ACR/ARHP Poster Session C
Sjögren's Syndrome - Clinical
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Natural History of Sjögren's Syndrome Phenotypic Features in the Sjögren's International Collaborative Clinical Alliance Registry. Caroline Shiboski[1], Alan N. Baer[2], Mi Y. Lam[1], Stephen Challacombe[3], Hector Lanfranchi[4], Morten Schiødt[5], Hisanori Umehara[6], Frederick B. Vivino[7], Yan Zhao[8], Yi Dong[8], Bruce W. Kirkham[9], Kenneth E. Sack[10], Susumu Sugai[6], Cristina F. Vollenweider[11], Wen Zhang[8], John S. Greenspan[1], Troy Daniels[1], Lindsey A. Criswell[1] and Sjögren's International Collaborative Clinical Alliance[12]. [1]University of California San Francisco, San Francisco, CA, [2]Johns Hopkins University, Baltimore, MD, [3]Kings College London, London, United Kingdom, [4]University of Buenos Aires, Buenos Aires, Argentina, [5]Rigshospitalet, Copenhagen, Denmark, [6]Kanazawa Medical University, Ishikawa, Japan, [7]Penn Presbyt Med Ctr, Philadelphia, PA, [8]PUMCH, Bejing, China, [9]Guys Hospital, London, United Kingdom, [10]Univ of Calif-San Francisco, San Francisco, CA, [11]German Hospital, Buenos Aires, Argentina, [12]University of California San Francisco, CA

Background/Purpose: Sjögren's syndrome (SS) is known to be a relatively stable or slowly progressing disease, however, few studies have actually followed patients over time while taking into account all its components. We explore changes in the phenotypic features (serologic/ rheumatologic, oral, and ocular) of SS, and in SS status, using the new American College of Rheumatology (ACR) classification criteria for SS, among participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry over a 2-year time interval.

Methods: SICCA is an international registry enrolling participants with signs and/or symptoms suggestive of SS in 9 centers across 7 countries. It was created to develop new classification criteria, establish a patient data and biospecimen repository and make these available to the scientific community to explore the genotype, phenotype, pathogenesis and epidemiology of this chronic autoimmune disease. All participants found to have any objective measures of salivary hypofunction, ocular dryness, focal lymphocytic sialadenitis in a lip salivary gland (LSG) biopsy, or anti-SSA and/or B antibodies, are recalled 2 years after their baseline examinations to repeat all examinations and specimen collections. We explored change in phenotypic features and in SS status.

Results: As of September 30, 2011, 2510 participants had enrolled in SICCA, and 703, or nearly one third, presented for a 2-year follow-up visit. We found remarkable stability over time of both individual phenotypic features of SS and of SS status. For most phenotypic variables the percent unchanged exceeded 80%, ranging from 77% (for Schirmer's test) to 96% (for anti-SSA/B). The ocular staining score (OSS that may range from 0 to 12) increased from baseline (median=5) to follow-up (median=6) (p<0.0001; signed-rank test). Among 168 participants found to have SS using the 2012 ACR classification criteria, 90% again met these criteria after 2 years. Among those who did not meet the ACR classification criteria at baseline, 11% had progressed and met them at the follow-up visit. One case of mucosa-associated lymphoid tissue lymphoma was detected in a follow-up LSG biopsy. Three other cases of non-Hodgkin's lymphoma were diagnosed during the follow-up period by a study-independent physician.

Conclusion: There was remarkable stability over a 2-year time period of both individual phenotypic features of SS and of SS status. This suggests that to fully characterize longitudinal outcomes and progression,

a longer follow-up interval may be needed. Funded by NIH/NIDCR/NEI N01-DE32636.

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Interstitial Lung Disease in Sjogren Syndrome: A Population-Based Study. Carlotta Nannini[1], Adlene Jebakumar[2], Jay H. Ryu[2], Cynthia S. Crowson[2] and Eric Matteson[2]. [1]Prato Hospital, Prato, Italy, [2]Mayo Clinic, Rochester, MN

Background/Purpose: The reported frequency of pulmonary involvement in primary Sjögren's Syndrome (pSS) varies widely ranging from 8 to 75% depending on the detection method employed and consists of various forms of airways disease. There is little information regarding interstitial lung disease (ILD) patterns other than lymphocytic interstitial pneumonia occurring in pSS in terms of frequency and risk factors. We aimed to assess incidence, and mortality of ILD in a well-characterized, population-based cohort of patients with pSS.

Methods: We examined a population-based incidence cohort of patients diagnosed with pSS in 1976–2005. All subjects were followed longitudinally through their complete community medical records, until death, migration or August 2011. ILD was defined using strict, validated composite criteria developed by an expert panel including pulmonologists and rheumatologists. These criteria included physician diagnosis, radiologic data, pulmonary function parameters, lung biopsy and autopsy findings. Cumulative incidence adjusted for the competing risk of death was estimated. A Cox model with a time-dependent covariate for development of ILD was used to examine the impact of ILD on survival in patients with pSS.

Results: 105 patients with pSS were identified (mean age 58.1 years; range 23–95; 91% female). Lung disease was present prior to diagnosis of pSS in 12 patients and developed after diagnosis of pSS in 35 patients with a median follow-up time of 9.2 years (1205 total person-years). Among pSS patients without prior ILD, the cumulative incidence of ILD in patients with pSS was 10% (± 3%) at 1 year after diagnosis of pSS and increased to 20% (± 4%) by 5 years after pSS. The development of lung disease in pSS was associated with poor survival with an hazard ratio of 2.16 (95%CI: 0.99, 4.74) adjusted for age, sex, and calendar year. ILD was identified as the most frequent type of lung disease detected at or after pSS diagnosis (53%) followed by emphysema (13%).

Conclusion: Our findings emphasize the high incidence of ILD and the adverse effect on survival in patients with pSS. Patients with pSS should be carefully assessed for diagnosis and treatment of ILD in order to improve the detrimental survival experience.

Disclosure: **C. Nannini**, None; **A. Jebakumar**, None; **J. H. Ryu**, None; **C. S. Crowson**, None; **E. Matteson**, None.

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Pulmonary Manifestations and Treatment of Primary Sjogren's Syndrome-Associated Lung Involvement Patients: A Prospective Study. Hui Gao, Xuewu Zhang, Jing He, Min Feng, Wei Zhao, Yan Ding and Zhan-guo Li, Peking University People's Hospital, Beijing, China

Background/Purpose: Pulmonary involvement is common in primary Sjögren's syndrome (pSS). Clinicopathologic pulmonary manifestations associated with pSS have yet to be reviewed in a large series. However, the pulmonary functional and radiological characteristics of pSS-associated lung disease which are more practical in clinic were less studied. Besides, the treatment of those patients has hardly been explored before. Most studies were specifically designed to evaluate sicca features. We aimed to describe the clinical, radiologic, and pulmonary Functional characteristics in a large Chinese pSS patient with lung involvement, and to analyze efficacy and safety of corticosteroid therapy combined with hydroxychloroquine (HCQ) or intravenous cyclophosphamide (CTX) in pSS-associated lung disease.

Methods: A total of 112 hospitalized patients with pSS-associated lung disease were retrospectively analyzed. The high-resolution computed tomography (HRCT) was re-evaluated by two experienced chest radiologists. Autoantibodies, inflammation markers, arterial blood gas (ABG) and PFT results were obtained.

A total of 15 patients were recruited in the prospective study. Prednisone was prescribed initially at a dosage of 30–40mg/day, and was tapered to 7.5mg/d within 4 months. HCQ was administered at a dosage of 200mg, twice a day. CTX was administered intravenously at an initial dosage of 400mg, every 2 weeks for 6 months, and then tapered to 400mg every 4 weeks.

Results: Among the 112 pSS patients with lung involvement, 102 (91.10%) were female. The mean age was 61.74 ± 10.24 years old. The disease duration was 60 months (12.00 to 147.00 months). Elevated IgG was prominent in those patients. There were more frequent and severer of the lower lung lobes involvement. The most frequent HRCT findings were linear opacities (94.2%), ground-glass attenuation (87.0%), reticular pattern (65.2%) and pleural involvement (65.2%). Impaired diffusing capacity was the most significant (74.3%). Among the 36 patients who took ABG, 20 patients had hypoxia and 7 had Type 1 respiratory failure.

Seven patients took oral prednisone combined with HCQ and 8 patients received oral prednisone combined with intravenous CTX. One patient from CTX group withdrew from the study for stopping DMARDs to have surgery. The rest were followed up for 11.57 ± 4.91 months. There was evidence of improvement in HRCT for most of the patients, and no obvious deterioration of PFT was observed. One patient in HCQ group presented hypoleukemia, which was ameliorated after reducing to 100mg, twice a day. Two patients had pneumonia and one had herpes zoster virus (HZV) infection in CTX group.

Conclusion: The distribution of the abnormalities and severe parenchymal involvement are most pronounced in the lower lobes of pSS patients. Impaired diffusing capacity is the most significant PFT abnormalities. Hypoxia is not rare for pSS-association lung involvement patients. Corticosteroid therapy combined with hydroxychloroquine or intravenous cyclophosphamide is administered with a favorable response seen in the majority of patients. This should be further confirmed in a large cohort.

Disclosure: **H. Gao**, None; **X. Zhang**, None; **J. He**, None; **M. Feng**, None; **W. Zhao**, None; **Y. Ding**, None; **Z. G. Li**, None.

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The Forced Oscillation Technique Is a Sensitive Method for Detection of Obstructive Airway Disease in Patients with Primary Sjögren's Syndrome.
Anna M. Nilsson[1], Elke Theander[2], Roger Hesselstrand[3], Per Wollmer[2] and Thomas Mandl[2]. [1]Skane University Hospital Malmo, Lund University, Malmo, Sweden, [2]Skane University Hospital Malmo, Lund University, Malmö, Sweden, [3]Skane University Hospital Lund, Lund University, Lund, Sweden

Background/Purpose: To study signs of obstructive airway disease in patients with primary Sjögren's syndrome (pSS) by the forced oscillation technique (FOT), a method that may aid in distinguishing between peripheral and central airway obstruction.

Methods: 37 female pSS patients (median age 64, range 38–77 years) without known chronic obstructive pulmonary disease (COPD), participating in a longitudinal follow-up study of pulmonary function, and 74 female population-based controls (median age 64, range 47–77 years), also without known COPD, and matched with regard to gender, age, height, weight and tobacco consumption were included in the study. The pSS patients and controls were after inhalation of beta agonist studied by the FOT, evaluating airway resistance and reactance, at different oscillation frequencies, as well as the resonance frequency. pSS patients were also assessed by spirometry according to which 14 were diagnosed with obstructive airway disease (OAD) (12 with COPD and 2 with abnormal reversibility test).

Results: pSS patients had significantly increased resistances at 5–25Hz (p<0.001), decreased reactances at 10–35Hz (p<0.001) and an increased resonance frequency (p=0.002) whilst the resistance slope between 5 and 20Hz was not significantly different (p=NS) in comparison with controls. Airway resistance was negatively correlated and airway reactance positively correlated to the vital capacity, the forced expiratory volume in 1 second and the diffusion capacity for carbon monoxide. Both pSS patients with and without OAD had significantly increased resistances at 5–25Hz (p<0.001) and decreased reactances at 10–35Hz (p<0.001) in comparison with controls respectively, whilst only the former had a significantly increased resonance frequency (p<0.001).

Conclusion: pSS patients showed FOT signs of airway obstruction, possibly due to airway sicca, impaired mucus clearance and bronchial inflammation. OAD also affect central airways in pSS. Also pSS patients without spirometric signs of OAD show clear FOT signs of airway obstruction. FOT thus seems to be a sensitive method in detecting airway obstruction in pSS patients.

Disclosure: **A. M. Nilsson**, None; **E. Theander**, None; **R. Hesselstrand**, None; **P. Wollmer**, None; **T. Mandl**, None.

2178

18-Fludeoxyglucose Positron Emission Tomography Is a Valuable Marker of Activity of Interstitial Lung Disease in Primary Sjogren's Syndrome.
Camille Cohen[1], Arsene Mekinian[1], Michael Soussan[2], Yurdagul Uzunhan[2], Veronique Eder[2], Robin Dhote[3], Dominique Valeyre[4] and Olivier Fain[5]. [1]Jean Verdier Hospital, Bondy, France, [2]Bobigny, France, [3]Avicenne Hospital, Bobigny, France, [4]Avicenne Hospital (AP-HP), Bobigny, France, [5]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France

Background/Purpose: To assess the value of 18-Fludeoxyglucose Positron Emission Tomography (PET) in patients with primary Sjogren's Syndrome (pSS).

Methods: All patients with confirmed pSS (AECG) from 3 French university centers who underwent PET were retrospectively analysed. PET was realized to assess activity in SS-related interstitial lung disease (ILD) (n=24), lymphoma suspicion (n=10) or systematically (n=5). Positive PET was defined as FDG uptake >2.5 SUVmax. A control group was constituted of patients with PET for isolated pulmonary nodule (n=17).

Results: Thirty-nine patients with pSS were included (table 1). FDG uptake was noted in 30 cases (83%): salivary gland (n=20 (57%); median SUVmax 3.1 [2,8-4]); lymph nodes (n=24 (67%); median SUVmax 5 [4–8]); pulmonary uptake (n=13 (33%); median SUVmax 3,3 [3–6]) and thyroiditis (n=3). Salivary gland uptake was more frequent and SUVmax was higher in pSS than in the control group (median 3 [2,8-4] versus 2 [1,5-2,5]; p<0,001).

	All patients N=39	PET to exclude lymphoma N= 15	PET to assess activity in patients with ILD N= 24
Clinical data			
Age (years)	54 [47–67]	54 [46–67]	54 [49–64]
Sex (males)	8 (22%)	4 (26,6%)	4 (16%)
Asthenia	38 (98%)	14 (93%)	24 (100%)
Subjective Xerophtalmia	35 (90%)	14 (93%)	21 (88%)
Subjective Xerostomia	36 (92%)	15 (100%)	21 (88)
Glandular hypertrophy	8 (21%)	5 (33,%)	3 (13%)
Objective xerophtalmia	14 (56%)	8 (54%)	7 (29%)
Objective xerostomia	18 (70%)	7 (47%)	11 (46)
ESSDAI score	21 [10–24]	10 [7–13]	24 [21–28]*
Organ involvement (n; %)			
Skin	16 (41%)	4 (27%)	12 (50%)
Neurological	8 (21%)	5 (33%)	3 (13%)
Joint	18 (46%)	5 (33%)	13 (54%)
Pulmonary	24 (62%)	–	-
Lymphoma	7 (18%)	2 (13%)	5 (21%)
Laboratory data (median IQR25-75)			
ESR	24 [12–49]	13 [10–23]	54 [33–80]*
C-reactive protein (g/l)	9 [4–22]	4 [3–5]	17 [7–33]**
Gammaglobulins (g/l)	12 [8–27]	11 [8–15]	16 [10–29]
Hg (g/dl)	12,5 [11–13]	12,75 [11,75–13,75]	12,2 [11–13,1]
Platelets (G/L)	250 [183–293]	246 [189–250]	250 [178–320]
Lymphocytes (n/mm3)	1550 [1160–1992]	1300 [900–1500]	1830 [1350–2000]
Cryoglobulinemia	4 (10%)	1 (0,06%)	3 (13%)
Treatments			
Corticosteroids	16 (41%)	4 (26%)	12 (50%)
Corticosteroids dose (mg/day)	10 [10–15]	10 [10–10]	10 [10–15]
Hydroxychloroquine	17 (44%)	5 (33%)	12 (50%)
PET results			
Pulmonary uptake	13 (33,3%)	0	13 (57%)*
Lung SUVmax	3,3 [3–6]	0	3,3 [3–6]
Lymph node fixation	24 (67%)	7 (50%)	18 (75%)
Lymph node SUVmax	5 [4–8]	3,8 [3–4]	5,4 [4–8]
Salivary gland fixation	20 (57%)	10 (71%)	11 (48%)
Salivary gland SUVmax	3,1 [2,8–4]	2,7 [2,7 –3]	3 [2,7–4]

* p<0,005
** p =0,006

In 24 patients with ILD, 13 (57%) had FDG pulmonary uptake (median SUVmax 3 [3–6]). Whereas there were no clinical, biological or functional respiratory test difference between ILD patients with/without FDG uptake, patients with pulmonary FDG uptake had also more lymph node uptake, and PET allowed the diagnosis of active ILD in these patients, with 100% specificity.

In 10 patients with PET for suspected lymphoma, PET confirmed diagnosis in 6 cases, and confirmed the remission in 1 case.

Lymph node FDG uptake was present in 24 (67%) cases and was significantly associated with pulmonary uptake in ILD patients. With a follow up of 2 years [0,8-4], no patient with lymph node FDG uptake developed lymphoma.

Conclusion: Whereas salivary uptake is frequent in pSS, in patients with ILD, PET could constitute an interesting tool to assess activity, and necessitate to be confirmed in prospective study.

Disclosure: **C. Cohen**, None; **A. Mekinian**, None; **M. Soussan**, None; **Y. Uzunhan**, None; **V. Eder**, None; **R. Dhote**, None; **D. Valeyre**, None; **O. Fain**, None.

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High Resolution CT Findings and Concomitant Nontuberculosis Mycobacterial Infection (NTM) in Patients with the Diagnosis of Primary Sjogren's Syndrome Evaluated At a Respiratory Referral Center. Mehrnaz Maleki-Fischbach[1] and Gloria M. Russell[2]. [1]National Jewish Health, Denver, CO, [2]Pontificia Universidad Católica Madre y Maestra, Santiago, Dominican Republic

Background/Purpose: Although lung disease can occur with primary Sjogren's syndrome (pSS), far too little is known about the clinical phenotype or natural history of its lung involvement. The objective of this retrospective observational study was to characterize a cohort of subjects with pSS-associated lung disease. It also seems that there is an association between pSS and nontuberculousis mycobacterial (NTM) infection.

Methods: We identified all subjects evaluated at our center between Jan. 2008–May 2012 that fulfilled the American-European classification criteria for the diagnosis of pSS and that had respiratory symptoms along with thoracic high resolution CT (HRCT) available to review. All clinical data were extracted from the medical record by comprehensive review. We excluded patients with secondary Sjogren's syndrome.

Results: A total of 38 subjects were identified. Mean age was 63.7 years (range 50–78) and all but one of the subjects were women. A history of past smoking was reported in 14 (37%) and only one subject was an active smoker. All reported xerostomia and keratoconjunctivitis sicca Other pSS associated manifestations included the presence of Reynaud's in 5 (13%), arthritis in 8 (21.0%), arthralgias in 31 (82%), and esophageal reflux in 27 (71%). All of the subjects had positive SS-A and/or SS-B antibodies. 37 were SS-A positive, 26 were SS-B positive and 25 had both positive. (Mean SS-A & SS-B were 106.5 and 78.1 units respectively) Also all of the patients had positive ANA (titer range 1:160-1:2560) by direct immunofluorescence. ANA patterns identified; 26 (68.4%) speckled, 1 (2.6%) homogeneous, 1 (2.6%) centromere, 6 (15.7%) speckled and nucleolar, and 4 (10.5%) speckled and homogeneous. 22 were rheumatoid factor positive. All of the subjects had respiratory symptoms as manifested either by isolated cough (n=33, 87%), dyspnea (n=36, 95%) or both. 12 (31.6%) patients had proven infection with Nontuberculousis Mycobacteriosis (NTM).

High resolution CT (HRCT) of the chest showed 24 (63.1%) patients with airway disease including 1 (2.6%) with large airway disease, 3 (7.9%) with bronchiolitis, 3 (7.9%) with bronchiolitis plus bronchiectasis and 17 (44.7) with bronchiectasis out of which 11 (28.9%) had proven NTM infection as well. 4 (10.5%) patients were found to have interstitial lung disease (ILD); 3 (7.9%) patients with lymphoid interstitial pneumonia (LIP) and 1 (2.6%) patient with nonspecific interstitial pneumonia (NSIP). 10 (26.3) patients had combined ILD and airway disease including 1 (2.6%) with LIP, bronchiectasis and bronchioloitis; 4 (10.5%) with LIP and bronchiectasis; 3 (7.9%) with NSIP and bronchiolitis and 2 (5.3%) with NSIP and bronchiectasis. One (2.6%) of the patients with LIP and bronchiectasis also had concomitant NTM infection.

Conclusion: There is a myriad of pulmonary manifestations associated with pSS. In this cohort, the most common lung manifestation was airway disease. It also seems that pSS may predispose patients to NTM infection and NTM having a causative effect on worsening their lung condition. Further studies are needed to better define the natural history of pSS-associated lung disease and possible relationship with NTM infection especially among middle age and elderly women.

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Coronary Flow Reserve and Asymmetric Dimethylarginine Levels: New Measurements for Identifying Subclinical Atherosclerosis in Patients with Primary Sjögren's Syndrome. F. Atzeni[1], L. Boccassini[1], M.C. Signorello[2], MA Carrideo[2], L. Gianturco[2], V. De Gennaro Colonna[3], L. Drago[4], M. Turiel[2] and P. Sarzi-Puttini[1]. [1]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, [2]IRCCS Galeazzi Orthopedic Institute, University of Milan, Department of Health Technologies, Cardiology Unit,, Milan, Italy, [3]Pharmacology Department, University of Milan, Milan, Italy, [4]Laboratory Unit, IRCCS Galeazzi Orthopedic Institute, Department of Health Technologies, University of Milan, Milan, Italy

Background/Purpose: Clinical and biochemical data suggest that autoimmune diseases are associated with endothelial dysfunction and increased atherosclerosis. We have previously shown that asymmetric dimethylarginine (ADMA) levels and coronary flow reserve (CFR) are impaired in patients with early rheumatoid arthritis, but it is not known whether the same is true of patients with primary Sjögren's syndrome (SS). We therefore investigated sub-clinical cardiovascular involvement in primary SS patients by means of ADMA and coronary flow reserve (CFR) assessments.

Methods: The study involved 15 patients who fulfilled the ACR criteria for primary SS without any documentable cardiovascular disease and 20 age- and gender-matched control subjects. Dipyridamole transthoracic stress echocardiography was used to evaluate wall motion and CFR in the distal segment of the left anterior descending coronary artery before and after dipyridamole infusion (0.86 mg/kg over six minutes). A CFR value of <2.5 was considered a sign of impaired coronary functionPlasma ADMA levels were determined using high-performance liquid chromatography. Linearity was assessed in the range of ADMA 0.1–20 μM. The mean correlation coefficient was >0.99. The ADMA limit of quantitation (LOQ) was 0.01 μM.The continuous variables were expressed as mean values and standard deviations, and the non-continuous variables as median values and interquartile ranges (IQR). The data were analysed using SAS statistical software 9.2. All tests were two-tailed, and probability (p) values of less than 0.05 were considered statistically significant.

Results: All of the patients were affected by primary SS, the majority of patients were being treated with hydroxychloroquine (HCQ) at dose of 400 mg/day, two were taking methotrexate (MTX) and four azathioprine (AZA) at a mean dose of 150 mg/day (range 50–200 mg). Only 3 patients used corticosteroids—one at a dosage of 2.5 mg and two at 5 mg/daily. All of the patients were ANA and/or RF and anti-SSB and/or anti-SSA positive. The patients' mean age and ejection fraction were respectively 62 ± 8 years and 65% ± 6% (not significant). Although within the normal range, their CFR was lower than that of the controls (median 3.0, IQR 2.5–3.5 *vs* median 3.4, IQR 3.2–3.82, P=0.02), whereas their ADMA levels were significantly higher (median 0.80 mM, IQR 0.78–0.82mM *vs* median 0.55mM, IQR 0.49–0.59mM respectively; P <0.0001) and their E/A ratios significantly lower (median 0.8, IQR 0.7–1.1 *vs* median 1.3, IQR 1.3, 1.2–1.4; P <0.0001).

Conclusion: Higher ADMA levels suggest the presence of endothelial dysfunction and sub-clinical atherosclerosis in primary SS patients, even in the case of normal CFR. Our preliminary data indicate that ADMA may be a useful marker for identifying early endothelial dysfunction in primary SS patients.

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Concomitant Atheosclerosis and Impaired Bone Health in Patients with Primary Sjogren's Syndrome. Clio P. Mavragani[1], Fotini Gravani[2], Andrianos Nezos[1], Eleni Antypa[3], Kiki Maselou[3], Dimitrios Ioakeimidis[4], Michael Koutsilieris[1] and Haralampos M. Moutsopoulos[5]. [1]School of Medicine, University of Athens, Athens, Greece, Athens, Greece, [2]School of Medicine, University of Athens, Athens, Greece, M Asias st, Athens, Greece, Athens, Greece, [3]General Hospital of Athens, Greece, [4]General Hospital of Athens "G. Gennimatas", Greece, Greece, [5]School of Medicine, University of Athens, Athens, Greece

Background/Purpose: To determine the prevalence of subclinical atherosclerosis and impaired bone health in primary Sjogren's syndrome (pSS) patients and to explore whether they associate with clinical and

serological disease features, traditional risk factors for cardiovascular disease (CVD) and osteoporosis as well as with activation of the Receptor activator of nuclear factor kappa-B ligand (RANKL)-RANK system, previously implicated in the pathophysiology of both CVD and osteoporosis.

Methods: 64 consecutive pSS patients according to the American-European Classification Criteria (mean age $\pm$SD 57.19$\pm$12.4) and 39 healthy controls °f similar age and sex distribution (mean age $\pm$SD 53.6$\pm$7.04) were enrolled. Demographic data, clinical, laboratory and histopathological features were recorded and classical risk factors for atherosclerosis and osteoporosis were evaluated. Patients and controls underwent intimal-medial thickness score (IMT) and bone mineral density (BMD) levels measurements. The presence of carotid/femoral plaque and fractures was also determined by ultrasound and lateral spine radiographs respectively. Serum RANKL and osteoprotegerin levels were determined by ELISA. RANKL and osteoprotegerin mRNA levels were determined in cDNA derived from minor salivary gland (MSG) tissues from 19 pSS patients, 9 pSS patients complicated by lymphoma and 11 sicca controls by real time PCR. Determinants of IMT/BMD levels and the presence of plaque were assessed by univariate and multivariate models. Comparisons between groups were performed by Fisher's exact two tailed test and Mann Whitney test.

Results: Increased prevalence of subclinical atherosclerosis (defined as IMT >0.90mm) and osteoporosis/osteopenia was detected in pSS patients compared to controls [58.7% vs 27.5%, p=0.0071 and 61.2% vs 20.5%, p=0.0001) with fracture rates not significantly differing between the two groups. Multivariate analysis in the pSS group revealed age, BMI and periepithelial disease (defined as peribronchial, interstitial nephritis, primary biliary cirrhosis) as independent predictors of IMT, age and lymphopenia as independent determinants of carotid and/or femoral artery plaque and increased urine PH, periepithelial disease and total steroid dose as independent predictors of osteoporosis and/or osteopenia. The latter was independently associated with the presence of plaque, when independent predictors for both variables were included in the multivariate model [(OR:4.75 (1.05–21.47, p=0.043)]. Compared to the control group, pSS patients displayed increased serum RANKL levels (p=0.0003) while at MSG tissue, mRNA RANKL/osteoprotegerin ratio was significantly increased in pSS patients complicated by lymphoma compared to sicca controls.

Conclusion: pSS patients are characterized by higher levels of concomitantly occurring subclinical atherosclerosis and impaired bone health compared to their healthy counterparts, with traditional risk factors, disease related features and activation of RANKL system being potential contributors. The significance of RANKL activation in pathogenesis of SS related complications remains to be further explored.

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Prevalence of Fibromyalgia Is Increased in Primary Sjögren's Syndrome Compared with SLE and Associated with Depression and Severe Vitamin D Deficiency. Byoong Yong Choi, Hye Jin Oh, Jun Won Park, Bon Seung Ku, Sung Hae Chang, Eun Young Lee, Eun Bong Lee and Yeong Wook Song. Seoul National University Hospital, Seoul, South Korea

Background/Purpose: Although clinical features of primary Sjögren's syndrome (pSS) overlap with those of fibromyalgia (FM), the relationship between FM and pSS has remained unclear. Furthermore, ACR preliminary diagnostic criteria for FM developed in 2010 do not require a tender point exam and focus on the presence of widespread pain or somatic symptoms. This cross-sectional study was conducted to investigate the prevalence and risk factors of FM in pSS.

Methods: Sixty-nine with pSS and 97 with systemic lupus erythematosus (SLE) were assessed to identify the presence of FM based on the 2010 ACR criteria. Clinical and laboratory data for pSS or SLE were collected from all patients. Additional assessments included number of tender points (TPs), visual analogue scale (VAS) of pain, fatigue, and Fibromyalgia Impact Questionnaire, Hamilton depression rating scale 17-items (HAM-D). Serum 25-hydroxy vitamin D (25-OH-D) levels were determined in patients with pSS. Disease activities in pSS were measured using EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

Results: The prevalence of FM was 28% [95%CI: 17.0–38.0] in pSS and 3.0% [95% CI: 0–7.0] in SLE. Primary SS patients had more frequent somatic symptoms such as myalgia (p=0.016), insomnia (p=0.048), headache (p=0.018) and cognitive dysfunction (p<0.001) compared to SLE patients. The widespread pain index (WPI) and score of somatic symptom scale (SS scale) in pSS patients were also significantly higher than those of SLE. Multiple linear stepwise regression analysis showed that HAM-D, ESSDAI and serum 25-OH-D levels were the significant determinants of WPI; HAM-D and serum 25-OH-D levels were also the significant determinants of score of SS scale in pSS patients. Depression and severe 25-OH-D deficiency (<10 ng/mL) in pSS was associated with presence of FM (OR: 34.00 [95% CI: 6.72–171.9], OR: 4.15 [95% CI: 1.09–15.83], respectively).

Conclusion: The prevalence of FM was higher in patients with pSS compared to SLE. Depressive mood and severe vitamin D deficiency in pSS patients was associated with the presence of FM.

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Common Features in Lymphoproliferative Complications in the Course of Primary Sjögren's Syndrome: Results From a Multi-center Cohort of 1170 Patients. Luca Quartuccio[1], Chiara Baldini[2], Roberta Priori[3], Elena Bartoloni Bocci[4], Francesco Carubbi[5], Miriam Isola[6], Marta Maset[1], Sara Salvin[1], Nicoletta Luciano[2], Giovanna Picarelli[3], Alessia Alunno[4], Roberto Giacomelli[7], Roberto Gerli[8], Guido Valesini[9], Stefano Bombardieri[2] and Salvatore De Vita[10]. [1]Rheumatology Clinic, DSMB, University of Udine, Italy, Udine, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy, [3]Rheumatology Unit, Sapienza University of Rome, Rome, Italy, [4]Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Perugia, Perugia, Italy, [5]Rheumatology Clinic, University of L'Aquila, L'Aquila, Italy, [6]Institute of Statistics, University of Udine, Udine, Italy, [7]Rheumatology Unit, University of Aquila, L'Aquila, Italy, [8]Rheumatology Unit, University of Perugia, Perugia, Italy, [9]Sapienza, Universita di Roma, Rome, Italy, [10]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy

Background/Purpose: To describe the prevalence of lymphoproliferative complications (defined as B-cell lymphoma or definite conditions predisposing to lymphoma, i.e, cryoglobulinemic vasculitis (CV) and major salivary gland swelling) in the course of primary Sjögren's syndrome (pSS) in a large cohort of patients followed in five Rheumatologic Centres.

Methods: Demographic, clinical, laboratory and histopathologic data in 1170 pSS were retrospectively collected according to a standard protocol. Univariate and multivariate analyses were performed.

Results: Prevalence of lymphoma in this SS cohort was 4.4% (51/1170), prevalence of CV was 3.9% (33/850), and prevalence of salivary gland swelling and/or myoepithelial syaladenitis was 30.9% (362/1170). Salivary gland swelling and/or MESA, CV and lymphoma shared many laboratory features, i.e., positive rheumatoid factor, hypocomplementemia and leucopenia, as well as a the presence of purpura as clinical hallmark of the circulating immune complexes (table 1). Interestingly, polyclonal hypergammaglobulinemia was strictly associated with salivary gland swelling, but it was not associated with CV or lymphoma; on the other hand, serum monoclonal component was significantly associated with CV or lymphoma, but not with salivary gland swelling and/or MESA (table 1). Younger age was associated with salvary gland swelling and/or MESA, while male sex with an increased risk of lymphoma (OR 5.4 95% CI 2.4–11.7) (table 1). By multivariate analyses, glandular swelling (OR 8.9 95%CI 4.0–19.9, p<0.0001), low C4 (OR 6.2 95%CI 3.0–12.8, p<0.0001), anti-La (OR 3.8 95%CI 1.8–7.9, p<0.0001), leukopenia (OR 2.8 95%CI 1.4–5.7) and monoclonal component (OR 3.2 95%CI 1.3–7.9, p=0.01) were strictly related to lymphoma, while peripheral nervous system involvement (OR 6.8 95%CI 2.1–21.6, p=0.001), low C4 (OR 7.3 95%CI 2.7–19.8, p<0.0001) and leukopenia (OR 6.5 95%CI 2.3–17.9) with CV, and, finally, younger age (OR 0.97 95%CI 0.96–0.98, p<0.0001), lymphoma (OR 7.9 95%CI 3.9–16.1, p<0.0001) and hypergammaglobulinemia (OR 1.5 95%CI 1.1–2.0, p=0.007) with salivary gland swelling and/or MESA.

Feature	SS with salivary gland swelling and/or MESA (362/1170: 30.9%) P value	SS with cryoglobulinemic vasculitis (33/850: 3.9%) P value	SS with lymphoma (5I/1170: 4.4%) P value
Age (yrs)	<0.0001 (for youngers)	ns	ns
Sex	ns	ns	<0.0001 (for males)
Salivary gland swelling and/or MESA	NA	ns	<0.0001
Cryoglobulinemic vasculitis	0.009	NA	0.001
Lymphoma	<0.0001	<0.0001	NA
Purpura	0.03	<0.0001	0.02
Peripheral nervous system	ns	<0.0001	0.04
Renal involvement	ns	0.007	ns
Fibromyalgia	ns	0.007	ns
ANA positivity	0.001	ns	ns
Anti-SSA positivity	<0.0001	ns	0.005
Anti-SSB positivity	<0.0001	ns	<0.0001
Rheumatoid factor positivity	<0.0001	<0.0001	<0.0001
Presence of serum cryoglobulins	ns	<0.0001	<0.0001
Low C3	0.003	<0.0001	0.02
Low C4	<0.0001	<0.0001	<0.0001
Leukopenia (<3000/mmc)	0.004	<0.0001	<0.0001
Hypergammaglobulinemia (>1.7 g/l)	<0.0001	ns	ns
Presence of serum M-component	ns	<0.0001	<0.0001

Conclusion: Salivary gland swelling, CV and B-cell lymphoma are consequent to B-cell deregulation in SS. B-cell clonal proliferation from polyclonal to monoclonal likely occurs in the pathologic target tissue of SS (i.e., salivary gland MALT tissue), predisposing to CV and/or to B-cell lymphoma.

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Pregnancy and Fetal Outcome in Patients with an Established Diagnosis of Primary Sjögren's Syndrome.. Roberta Priori[1], Angelica Gattamelata[1], Mariagrazia Modesti[1], Serena Colafrancesco[1], Marta Maset[2], Luca Quartuccio[2], Salvatore De Vita[2], Elena Bartoloni Bocci[3], Alessia Alunno[3], Roberto Gerli[3], Francesca Strigini[4], Chiara Baldini[4], Chiari Tani[4], Marta Mosca[4], Stefano Bombardieri[4] and Guido Valesini[1]. [1]Rheumatology Unit, Sapienza University of Rome, Rome, Italy, [2]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [3]Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Perugia, Perugia, Italy, [4]Rheumatology Unit, University of Pisa, Pisa, Italy

Background/Purpose: To investigate pregnancy and fetal outcome in patients with an established diagnosis of primary Sjögren's syndrome (pSS).

Methods: The clinical charts of 1075 women with pSS, from four Italian referral rheumatology centres were retrospectively evaluated. When a pregnancy has occurred after pSS diagnosis, the patient was personally interviewed to obtain more detailed information regarding obstetric history; obstetric clinical charts were reviewed as well. In a subgroup analysis from a single center, each delivery in patients with an established diagnosis of pSS was compared with the first 8 consecutive deliveries occurred during the same month in the referral universitary hospital. Chi square and Mann-Whitney test, SPSS release 15.00, were used for statistical analysis.

Results: Patients' mean age was 59 yr (17–89), mean age at diagnosis 51,4 yr; 139/1075 (12,8%) were diagnosed before 35 yr. Thirty-six women (31 with anti-SSA/Ro and/or anti-SSA/La antibodies) with an established diagnosis of pSS had 45 pregnancies which ended with the delivery of 40 newborns. Two miscarriages, 2 fetal death and one induced abortion were recorded. Mean age at the first pregnancy was 33,9 yr (range 27–44), mean number of pregnancy 1,25 (1–3); 18/40 (45%) cesarean sections were performed, mean pregnancy length was 38,5 week (range 32–43) with 6 preterm delivery. The mean Apgar score at 5 minute was 8,9 (range 5–10), mean birth weight was 2920 mg (range 826–4060). Congenital heart block (CHB) occurred in 2/36 newborns (5,5%) of 31

mothers with anti-SSA and/or SSB antibodies with fatal outcome. The reported rate of breastfeeding for at least one month was 60,5% (range 1–21 months), 44,7% for 3 months, During pregnancy one patient presented thrombocytopenia and another palpable purpura. In 4/40 pregnancies (10%) a flare of disease activity was observed within a year from delivery. In the case-control subgroup analysis no significant differences were found regarding age at delivery, pregnancy duration, way of delivery, baby sex. The neonates of primary SS mothers tended to have a lower weight and a lower Apgar score but the difference was not significant.

Conclusion: Even if pSS generally starts after menopause, it can appear during the childbearing age. pSS can have successful pregnancies, which might be followed by a mild relapse. CHB, a fearful complication for women with anti-SSA/Ro and or anti-SSB/La antibodies, is the only cause of death for offspring of pSS mothers.

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Prevalence of Severe Extra-Glandular Manifestations in a Large Cohort of Patients with Primary Sjögren's Syndrome. Chiara Baldini[1], Pasquale Pepe[1], Luca Quartuccio[2], Roberta Priori[3], Elena Bartoloni Bocci[4], Alessia Alunno[4], Serena Colafrancesco[3], Angelica Gattamelata[3], Marta Maset[2], Mariagrazia Modesti[3], Antonio Tavoni[1], Salvatore De Vita[2], Roberto Gerli[4], Guido Valesini[3] and Stefano Bombardieri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Rheumatology Clinic, DSMB, University of Udine, Italy, Udine, Italy, [3]Rheumatology Unit, Sapienza University of Rome, Rome, Italy, [4]Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Perugia, Perugia, Italy

Background/Purpose: i) to describe the clinico- serological features of a cohort of 1115 patients with primary Sjögren's syndrome (pSS); ii) to assess the prevalence of systemic extra-glandular manifestations in the cohort; iii) to estimate the impact of the serological and immunological patients' features on disease different phenotypes and on the utilization of immunosuppressive drugs

Methods: The case records of 1115 patients with a diagnosis of pSS attending four Italian reference centers were reviewed. Clinical and laboratory data of the patients enrolled were retrieved according to a standard form. Independent risk factors for glandular and extra-glandular disease manifestations were identified by logistic regression.

Results: The cohort consisted of 1115 pSS patients (1067 F: 48 M; mean age at the diagnosis of 51.6 ± 13.8 yrs; mean follow-up 5.8 ± 6.5 yrs). All the patients included fulfilled the European classification criteria for pSS, while the AECG criteria were fulfilled in 926/1115 (83%) cases. Xerostomia (93%), xerophtalmia (95%) and articular involvement (62%) were the most commonly detected clinical manifestations followed by hematological involvement (32%) and salivary gland enlargement (31%). A systemic extra-glandular involvement was diagnosed in 475/1115 (42%) patients. Severe extraglandular manifestations included: active synovitis (11%), axonal sensory-motor neuropathy (2%), diffuse purpura or ulcers (6%) renal involvement (0.7%), myositis (0.5%), cerebral vasculitis (0.5%) and transverse myelitis (0.2%). Finally, 50 cases of non-Hodgkin lymphoma were documented. Patients with a systemic disease had a lower mean age at diagnosis (p=0.002), a longer follow up (p<0.0001) and a higher frequency of serologic markers (ANA, RF, anti-Ro/SS-A antibodies, anti-LA/SS-B antibodies, cryoglobulins, hypergammaglobulinemia, low C3/C4 levels) in the univariate analysis. The adjusted multivariate analysis identified as independent serological risk factors for severe extraglandular involvement: low C3 (OR 2.6, 95% CI 1.6–4.1), low C4 (OR1.9, 95% CI 1.1–3.3), hypergammaglobulinemia (OR 2.1, 95% CI 1.5–2.9), cryoglobulins (OR 7.6, 95% CI 2.6–22.3), Rheumatoid factor (OR 2.5, 95% CI 1.5–22.9). No correlation was found among pSS extraglandular involvement and fulfillment of the AECG criteria or positive minor salivary gland biopsy at the diagnosis.

Conclusion: Although the hallmark features of pSS are represented by glandular manifestations, this study support the evidence that severe systemic manifestations may occur in about the 20% of the patients.

Patients presenting an active serological profile should be more closely monitored and may deserve more aggressive immunosuppressive drugs.

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Ultrasonography of Major Salivary Glands in Primary Sjögren's syndrome. Malin V. Jonsson[1], Daniel Hammenfors[2], Johan G. Brun[2] and Roland Jonsson[1]. [1]University of Bergen, Bergen, Norway, [2]Haukeland University Hospital, Bergen, Norway

Background/Purpose: Minor salivary gland biopsy is part of the diagnostic process for primary Sjögren's syndrome (pSS), but is not suitable for repeated follow-up. Ultrasound (US) represents a non-invasive imaging method of the major salivary glands that may serve as a supplement to minor salivary gland biopsy. The aim of this study was to investigate parotid and submandibular gland ultrasound in relation to sicca symptoms, glandular function and minor salivary gland inflammation.

Methods: Patients with primary Sjögren's syndrome were recruited from Haukeland University Hospital (n=41). The parotid and submandibular glands were examined by US using a GE LogiqE9 with a linear transducer with 6–16MHz. Glandular homogeneity and presence of hypoechogenic areas was evaluated and scored (0–3) according to Hocevar et al 2005. Scores 0–1 were considered normal and scores 2–3 pathological. Sicca symptoms of the mouth and eyes were recorded. Salivary gland functional capacity was evaluated by unstimulated and stimulated sialometry. Tear secretion was evaluated by the Schirmer I-test. Minor salivary gland inflammation was evaluated by focus score.

Results: Ultrasound was performed in 40 patients, with scores ranging 0–1 (n=22) and 2–3 (n=18). Mean age of patients with normal US findings was 63 years compared to 52 years in patients with pathological US findings ($p<0.05$), and correlated with ultrasound score ($p<0.05$, r=-0.388, n=40). Oral sicca symptoms correlated with sicca symptoms of the eyes ($p<0.001$, r=592, n=41), ultrasound score ($p<0.05$, r=0.402, n=40), and saliva levels ($p<0.05$, r=-0.392, n=41) and ($p<0.05$, r=-0.363, n=41), unstimulated and stimulated saliva respectively. In patients with normal and pathological US, mean unstimulated saliva was 2.2 ml/15 min and 0.5 ml/15 min ($p<0.01$), and the stimulated saliva levels were 6.1 ml/5 min and 2.5 ml/5 min ($p<0.001$). Levels of unstimulated and stimulated saliva correlated ($p=0.001$, r=0.509, n=41). Ultrasound scores correlated with unstimulated ($p<0.001$, r=-0.531, n=40) and stimulated saliva ($p<0.01$, r=-0.454, n=40). 17/27 patients with unstimulated saliva ≤ 1.5ml/15 min had pathological ultrasound changes compared to 1/13 with normal unstimulated saliva ($p<0.01$). 13/17 patients with stimulated saliva ≤ 3.5ml/5 min had pathological ultrasound compared to 5/23 with normal stimulated saliva ($p<0.01$). Tear secretion by the Schirmer I-test correlated in the right and left eye ($p<0.001$, r=0.749, n=39). Unstimulated saliva secretion correlated with tear secretion ($p<0.001$, r=0.537, n=39) and ($p<0.05$, r=0.343, n=39), right and left eye, respectively. Focus score was available in 31/41 patients, and correlated with ultrasound score ($p<0.05$, r=0.373, n=30). Mean focus score was 2.6 in patients with ultrasound pathology and 1.3 in patients with normal ultrasound ($p=0.051$).

Conclusion: In this cohort of patients with pSS findings from non-invasive imaging method ultrasound correlate with oral sicca symptoms, glandular function and minor salivary gland inflammation. Ultrasound of major salivary glands seems to be a useful tool for diagnostics and follow-up of patients with pSS.

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Safety of Minor Labial Salivary Gland Biopsy. Žiga Rotar, Alojzija Hočevar, Nataš A. Gašeršč, Branka Hostnik, Anita Antolić and Matija Tomšič. University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia

Background/Purpose: Histopathological analysis of minor salivary glands is a part of the latest classification criteria for SS proposed by the American-European Consensus Group (AECG), and the ACR.[1, 2] Recently it has been proposed that the presence of germinal center like structures in diagnostic minor salivary gland biopsies may be a highly predictive marker for NHL development in primary SS.[3] Our aim was to prospectively evaluate adverse events of minor salivary gland biopsy performed by rheumatologists in patients suspect of having Sjögren's syndrome.

Methods: At our rheumatology department we run a weekly diagnostic outpatient clinic where we see patients presenting with symptoms suggestive of Sjögren's syndrome referred to us by their rheumatologists. We evaluate them using the AECG criteria. In consenting patients who cannot be classified on the basis of history, clinical tests, and serological tests we perform the minor salivary gland biopsy.

Under aseptic conditions an assistant exposes mucosa of the lower lip. We clean it with 0.2% chlorhexidine digluconate solution, and infiltrate the lateral third of the lip with approx. 0.5–1 cm^3 of 2% lidocaine near one of the many orifices of the minor salivary gland excretory ducts identified by observation of nascent droplets of saliva. The rheumatologist makes an approx. 5 mm linear incision of the mucosa, removes all the exposed glands using a forceps, and places a single suture to close the wound using 4-0 absorbable braided polyglycolic acid. Removed glands are transported to pathology laboratory in 10% formalin.

Before the biopsy we informed each patient orally and in writing about possible adverse events and appropriate responses. Ten days to two weeks following the biopsy, a nurse phoned each patient to inquire about the pain (0–10 scale, VAS) during biopsy, and in the week following it; the survival of sutures, and whether the patient's GP or dentist had to remove them; and any other adverse events experienced by the patient.

Results: From 02/01/2007 to 12/15/2010 350 patients were referred for biopsy (89.7% females, average age 56.9±12.5 years). Incision length was measured and was on average 5.0±0.8 mm. The average volume of the obtained tissue sample was 26.5±72.8 mm^3. 322 patients responded to the follow up call by the nurse. During the biopsy 89.8%, 5.3%, and 1.5% reported pain on VAS of 0, 1–3, and 4–5, respectively, while 3.4% provided no answer. In the week following the biopsy 78.9%, 12.4%, 2.8%, 1.9%, 0.9% scored their pain on VAS 0, 1–3, 4, 5, and 6–8, respectively, while 3.1% provided no answer. 80.1% of patients report no adverse events, the rest complained about paresthesia, wound suppuration, hematoma, irritating mucosal scar, and lower lip swelling in 5.6%, 5%, 3.4%, 3.4%, and 2.5%, respectively. All the adverse events were transient and have resolved within the first three days after biopsy in 95.5% of patients.

The average suture survival was 3.7±2.1 days. In 15.5% of patients sutures were removed by their GP or dentist after on average 4.8±2.3 days.

Conclusion: Minor salivary gland biopsy is a safe outpatient procedure in the hands of rheumatologists.

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How to Better Define Inclusion Criteria in a Large Controlled Trial in Primary Sjogren Syndrome? Valerie Devauchelle-Pensec[1], Xavier Mariette[2], Jacques-Eric Gottenberg[3], Raphaèle Seror[4], Anne-Laure Fauchais[5], Olivier Vittecoq[6], Véronique Le Guern[7], Jacques Morel[8], JJ Dubost[9], Philippe Dieude[10], Eric Hachulla[11], Pierre yves Hatron[12], C. Larroche[13], Aleth Perdriger[14], Xavier Puechal[15], Damien Sene Sr.[16], Stephanie Rist[17] and Alain Saraux[18]. [1]Brest Occidentale university, Brest, France, [2]Université Paris-Sud, Le Kremlin Bicetre, France, [3]Strasbourg University Hospital, Strasbourg, France, [4]Bicetre university hospital, LE Kremlin-Bicetre, France, [5]Hospital, Limoges, France, [6]Rouen University Hospital & Inserm905, University of Rouen, Rouen Cedex, France, [7]Cochin Hospital, Paris, France, [8]Hopital Lapeyronie, Montpellier, France, [9]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [10]APHP, Hopital Bichat, Paris, France, [11]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [12]Hôpital Claude Huriez, Université Lille II, Lille, France, Paris, France, [13]Hospital University Bobigny, France, [14]Hôpital Sud, Rennes, France, [15]Hôpital Cochin, Paris, France, [16]Groupe Hospitalier Pitié-Salpétrière, Université Pierre et Marie Curie, Paris, France, [17]Orleans Hospital, Orleans, France, [18]Université Brest Occidentale, Brest, France

Background/Purpose: The subsets of primary Sjögren's syndrome (pSS) patients justifying biological therapy (BT) remain a matter of debate. Our goal was [1] to describe which inclusion criteria have been used in all previous studies using BT in pSS and [2] to evaluate the proportion of patients who may be included in further trials evaluating a biologic according to the chosen criteria.

Methods: We performed a literature review using pubmed and clinicaltrial.gov of all studies evaluating BT in pSS to identify their inclusion criteria. Then, we evaluated in the ASSESS cohort (a French national multi-center prospective cohort set up in 2006 to identify valuable predictive factors lymphoma during a 5-year prospective follow-up in which 15 tertiary centers

included 410 patients with pSS) the proportion of pSS patients who could be included in a trial according to the chosen criteria.

Results: Our literature review identified 16 studies evaluating biologics in pSS: Two open label studies and two double blind studies have been conducted to evaluate anti TNF. Only one open label study evaluated epratuzumab, in patients with B-cell activity. Five open-label studies and 4 randomized studies evaluated or are evaluating prospectively rituximab. Two studies are ongoing with belimumab. The main frequently used inclusion criteria were AECG criteria, disease duration (less than 4, 5 or 10 years), presence of systemic involvement (ESSDAI>1), visual analogic score (VAS) for dryness, pain, and fatigue higher to 5/10 and biological markers of activity (hypergammaglobulinemia and/or cryoglobulinemia and/or β2 microglobulinemia and/or low level of C4). In the ASSESS cohort, 263 patients had all data available. **Table 1** shows a tree representing the number of patients of the ASSESS cohort which fulfil each of these criteria. Their combinations show that if we limit inclusion to patients with systemic and recent pSS (less than 4 years), with 2/3 VAS>5/10 and biological activity, only 52/263 (20%) of the patients could be included. If we consider systemic or recent pSS, 2/3 VAS>5/10 and biological activity, 166/263 (63%) could be included.

Tuesday, November 13
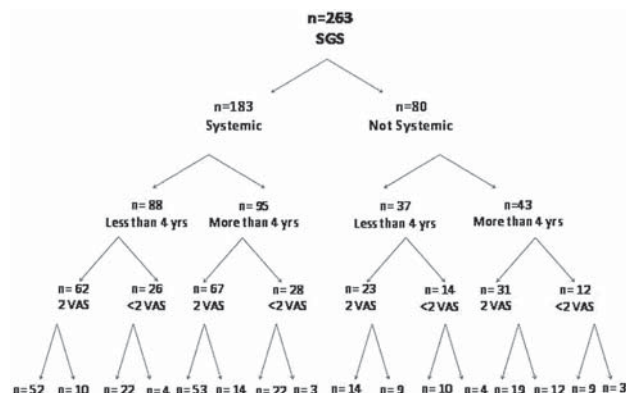
Figure 1. Number of patients in the ASSESS cohort fulfilling each criteria First step: AECG criteria, second step: systematic disease or not , third step: Disease of less than 4years, fourth step: visual analogic scale; fifth step: biological activity.

Conclusion: The number of patients that could be include in a trial evaluating pSS, depends highly on the inclusion criteria. Even with a slightly selective criterion of systemic involvement (ESSDAI >1), a small number of patients with very recent disease could be included. Most patients reported 2 VAS higher to 50/100 and have biological markers of activity.

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Efficacy of Belimumab On Non-Malignant Parotid Swelling and Systemic Manifestations of Sjögren's Syndrome: Results of the Beliss Study. Salvatore De Vita[1], Raphaèle Seror[2], Luca Quartuccio[3], Frederic Desmoulins[4], Sara Salvin[3], Gabriel Baron[5], Martina Fabris[6], Philippe Ravaud[5], Miriam Isola[7] and Xavier Mariette[8]. [1]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [2]Université Paris-Sud, Le Kremlin Bicêtre, LE Kremlin-Bicetre, France, [3]Rheumatology Clinic, DSMB, University of Udine,, Udine, Italy, [4]Université Paris-Sud, Le Kremlin Bicêtre, Le Kremlin Bicetre, France, [5]Université Paris-Descartes, Paris,, Paris, France, [6]Institute of Clinical Pathology, Udine, Italy, [7]Institute of Statistics, University of Udine, Udine, Italy, [8]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: to report the effects of anti-BAFF/BLyS antibody belimumab (BEL) on the different ogan manifestations of primary Sjögren's syndrome (pSS), by evaluating the ESSDAI score and the single ESSDAI domains.

Methods: Thirty patients (15+15) with pSS (positive classification criteria and positive anti-SSA/SSB antibodies) were investigated in two European Centres to assess the efficacy and safety of BEL in pSS. They were all females (49.5±16.5 years). At least one of the following items was needed for enrolment: a) parotid swelling and/or systemic involvement; b) objective

sicca with at least one laboratory sign of B-cell hyperactivation in serum (increased IgG, increased free Ig light chains, increased beta2-microglobulin, decreased C4, monoclonal gammopathy or cryoglobulinemia); c) recent onset of sicca symptoms (<5 years). Belimumab 10 mg/kg was administered intravenously on days 0, 14, 28 and then every 28 days through 48 wks, with a final evaluation at wk52, and after drug suspension. Concomitant therapies were left unchanged.

Results: 29/30 patients completed the 28 wk infusions, and 1 case with lymphoma and cryoglobulinemic vasculitis was withdrawn at w12 for worsening. Wk52 data are available in one Centre.

At wk 28, the ESSDAI score decreased from a median of 7 (1–33) to 4 (0–23) (p= 0.0001, Wilcoxon) with a decrease of $\geq$ 3 points in 14/29 (48.3%) and of $\geq$ 2 points in 18/29 (62.1%). The following domains mainly contributed to the ESSDAI score at baseline: glandular, biological, lymphadenopathy, articular, haematological and pulmonary. Activity (low-moderate-high) was present (baseline vs. wk28) in these domains as follows: glandular 15/30 vs. 7/29; biologic 27/30 vs. 20/29; lymphadenopathy 9/30 vs. 3/29; articular 9/30 vs. 3/29; haematological 5/30 vs. 3/29; pulmonary 4/30 vs. 5/29. At wk 28 the glandular domain improved in 10/13 (76.9%) patients with non-malignant parotid swelling (confirmed by biopsy, whenever possible), while no improvement occurred in 2/2 patients with parotid low-grade lymphoma (stage IE). Data available at wk52 showed persistent disappearance of swelling in 4/5 patients and further amelioration in 1/5. After BEL suspension parotid swelling relapsed in 2/5 of these responders (4 and 14 months later).

Overall, 13/15 patients completed the trial at w52 in one Centre. The median ESSDAI at wk52 was 2 (0–12) [vs. 3 (1–16) at w28 vs. 8 (2–33) at baseline; p=0.003, wk52 vs. baseline, Wilcoxon)], with activity in the ESSDAI domains (baseline vs. wk28 vs. wk52) as follows: glandular 7/15 vs. 2/14 vs. 2/13; biologic 13/15 vs. 11/14 vs. 10/13; lymphadenopathy 8/15 vs. 3/14 vs. 0/13; articular 4/15 vs. 0/14 vs. 0/13; 1/15 vs. 1/14 vs. 0/13; pulmonary 2/15 vs. 2/14 vs. 2/13. At wk52 we no additional side effects, if compared to wk28, were observed in the available cases.

Conclusion: Belimumab proved to be beneficial for non malignant glandular swelling in pSS. Recently, BAFF serum level were significantly increased in this subset of patients (Quartuccio L. et al., Rheumatology 2012, in press), supporting the rationale and the results observed. Other systemic features of pSS might also improve with BEL therapy. A controlled randomized trial is advisable.

Disclosure: S. De Vita, Human Genome Sciences, Inc., 2; **R. Seror**, Human Genome Sciences, Inc., 2, GlaxoSmithKline, 5; **L. Quartuccio**, None; **F. Desmoulins**, None; **S. Salvin**, None; **G. Baron**, None; **M. Fabris**, None; **P. Ravaud**, None; **M. Isola**, None; **X. Mariette**, Human Genome Sciences, Inc., 2, GlaxoSmithKline, 5.

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Antimalarials for Sjogren's Syndrome Treatment in Adults, Meta-Analysis. Vibian A. Coy[1], Carlos E. Granados[2], Diana Gil[1], Alejandro Junca[1], Daniel Jaramillo[1], Antonio A. Iglesias-Gamarra[3], Jose Felix Restrepo[4] and Federico Rondon-Herrera[4]. [1]Fellow of Rheumatology Universidad Nacional de Colombia, Bogotá, Colombia, [2]Professor - Universidad Nacional de Colombia, Bogotá, Colombia, [3]Professor-Universidad Nacional de Colombia, Bogota, Colombia, [4]Professor-Universidad Nacional de Colombia, Bogota, Colombia

Background/Purpose: Sjögren's syndrome (SS) is a chronic *inflammatory autoimmune disease* that is presented with lymphocytic infiltration of exocrine glands. Its secondary secretory dysfunction may involved extraglandular or extracraneal tissues. Antimalarials have been used for treatment of sicca symptoms and inflammation. However its effectiveness remains controversial. The objective of this systematic review is to evaluate the effectiveness and toxicity of antimalarials to treat adults with SS.

Methods: Between September 2010 and May 2012 we conducted an electronic search in the following databases: MEDLINE, Embase, LILACS, ISI WEB OF KNOWLEDGE, Cochrane Central Register of Controlled Trials and International Clinical Trials Registry of the World Health Organization (WHO ICTRP). *We included experimental, quasi-experimental and uncontrolled before and after studies.* Evaluated outcomes were: improvement in xerophtalmia, xerostomia and Schirmer's test; change in inflammatory markers and adverse events. Quality assessment of the trials was done by two authors independently. I2 and Chi-square tests were performed to estimate heterogeneity. The Mantel-Haenszel random-effects method with odds ratio (OR) as association measure were used for dichotomous outcomes, and mean difference for continuous data. All Statistical analysis was performed using RevMan 5.0

Results: 22 trials were found and 6 were included in the analysis. A total of 140 patients were included, all women. There were no statistically significant differences with respect to improvement in xerophtalmia (OR 2.27; 95% CI, 0.38 to 13.34), xerostomia (OR 1.0; 95% CI, 0.02 to 5) and Schirmer′s test (MD −1.03; 95% CI, −2.38 to 0.32). We observed a tendency in favor of antimalarials for decreasing erythrocyte sedimentation rate (MD −6.98; 95% CI, −20.73 to 6.76). One trial evaluated adverse effects (ocular, hepatic, hospitalization or dead) without significant differences. It was not possible to explore publication bias.

Conclusion: Up to the moment the available evidence has poor quality. The best evidence did not identify a clear benefit of antimalarials in the reviewed outcomes. The analyzed data reported low incidence of adverse events. More and good quality research (RCT′s) are needed to answer this question.

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Secretagogue Use in Patients with Primary Sjogren's Syndrome.
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Background/Purpose: Secretagogues are commonly used to treat xerostomia in primary Sjogren's syndrome (pSS). Side effects and/or lack of efficacy sometimes result in cessation of therapy. Our aim was to determine clinical and laboratory predictors associated with therapeutic failures.

Methods: We retrospectively reviewed use of the secretagogues, pilocarpine (PC) and cevimeline (CV), in patients with pSS who fulfilled the 2002 American European Consensus Group criteria; followed from January 2002 to June 2012. Individuals with inadequate follow up (less than two visits) were excluded. Baseline variables included age, sex, duration of xerostomia, anti Ro (SSA) and anti La (SSB) antibodies, rheumatoid factor, antinuclear antibodies (ANA), complement levels, beta 2 microglobulin, serum protein electrophoresis, smoking history, unstimulated salivary flow rate, scintigraphy scores, focus score on lip biopsy, and previous use of hydroxychloroquine. Failure of therapy was defined as the clinician or patient's decision to stop treatment either due to lack of efficacy or side effects.

Results: Among 118 patients with pSS (92.4% female, mean age 61.4 years), PC was used in 72 (59 first users, 13 second users) and CV in 91 (59 first users, 32 second users). Cevimeline was associated with lower failure rates among all users (29/91, 31.9%) than PC (44/72, 61.1%) (p<0.001). Among first-time users, CV was also associated with lower failure rates (16/59, 27.1%) versus PC (28/59, 47.5%). (p=0.02). Severe sweating was the most frequent side effect leading to cessation of therapy and occurred more frequently among patients using PC (18/72, 25%) than CV (10/91, 11%) (p=0.02). Patients who previously failed one secretagogue were less likely to discontinue treatment with the other agent: i.e. 61/118 (51.7%) of first-time users compared to 12/45 (26.7%) of second-time users (p= 0.004). Among all users, the proportion of subjects stopping medication for any documented side effect tended to be higher in the PC group (31/72, 43.1%) than CV group (23/91, 25.3%) (p=0.09). Among the various clinical and laboratory parameters studied; only ANA positivity was associated with therapeutic failure: 45/76 (59%) of ANA-positive patients vs. 15/40 (38%) of ANA-negative patients discontinued for any reason. (p=0.03)

Conclusion: Our data suggests that patients with pSS who take secretagogues for xerostomia are more likely to continue cevimeline than pilocarpine long-term. This is primarily due to a lower incidence of severe sweating (the most common side effect of therapy). However, therapeutic failure of one secretagogue did not predict similar results with the other. Second time users may be more likely to continue long-term treatment due to the lack of effective therapeutic alternatives. Among various clinical and laboratory features of pSS, only ANA positivity was associated with a higher likelihood of treatment failure. Further studies are needed to confirm these observations.

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Phenotypic Features of Sjögren's Syndrome Among Patients with Low-Titer SSA/B Antibodies.
Mara McAdams DeMarco[1], Mi Y. Lam[2], Steve Shiboski[2], Lindsey A. Criswell[3], Caroline Shiboski[2] and Alan N. Baer[4]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]University of California, San Francisco, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA, [4]Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, MD

Background/Purpose: The significance of a low titer of SSA and/or SSB antibodies (SSA/B-Ab) in individuals with clinical or other laboratory findings suggestive of Sjögren's syndrome (SS) is unclear. Low titers may represent false positive immunoassay results, seropositivity in the absence of clinical disease, or true markers of a connective tissue disease, such as SS. It is unclear whether low titers represent a distinct phenotype or one more similar to those with negative titers. We sought to explore the association between SSA/B titer levels and phenotypic features of SS, including histopathological characteristics.

Methods: The Sjögren's International Collaborative Clinical Alliance (SICCA) is an NIH-funded registry of individuals with suspected or established SS. Each participant undergoes a uniform and protocol-driven evaluation for SS, including rheumatologic, oral, and ophthalmologic examinations, serologic testing, labial salivary gland biopsy, and ocular staining. SSA/B-Ab testing was performed by Quest Laboratories, using an automated multiplex flow immunoassay. Positive results were expressed in "antibody index" (AI) units and provided as continuous variables measure up to a level of 8 AI. Levels more than >8 AI were not quantified. We compared the mean and prevalence of phenotypic features of SS by category of SSA/B-Ab (High: both SSA-Ab and/or SSB-Ab>8; Low: SSA-Ab and/or SSB-Ab≥1 but both ≤8; Negative: both SSA-Ab and SSB-Ab<1).

Results: Among the SICCA participants, low titers of SSA/B-Ab were present in 277 (14.1%), high titer SSA/B-Ab in 434 (22.1%) and negative SSA/B-Ab in 1256 (63.8%). The associations between these three strata of SSA/B-Ab titers and phenotypic features of SS are shown in the Table. Mean age decreased while focus score increased as SSA/B-Ab titers increased. The percentage of participants with each phenotypic feature was greater for those with high SSA/B-Ab compared with those with low titers and greater for those with low titers compared with negative titers.

Table. Phenotypic Features of Sjögren's Syndrome by SSA/B Antibody Titer

	High		Low		Negative		
	N	Mean or %	N	Mean or %	N	Mean or %	p
Age (years)	454	50.79	287	51.33	1270	54.48	<.0001
Focus score (foci/ 4 mm^2)	367	3.32	204	2.79	527	1.50	<.0001
ANA≥1:320	455	69.5%	287	44.3%	1276	16.1%	<.0001
Rheumatoid factor ≥ 30 IU/ml	454	49.8%	287	34.2%	1275	10.0%	<.0001
IgG>1445 mg/dl	455	62.0%	285	49.5%	1273	12.1%	<.0001
C4<16 mg/dl	455	22.6%	285	17.2%	1273	10.6%	<.0001
WBC ≤ 4000/mm^3	448	27.5%	283	19.4%	1266	7.4%	<.0001
FLS or F/SLS focus score ≥ 1*	434	74.0%	277	57.4%	1256	19.1%	<.0001
Germinal centers in lip biopsy	454	23.8%	285	7.4%	1273	4.2%	<.0001
Schirmer's ≤5 mm either eye	454	46.0%	286	37.8%	1276	24.3%	<.0001
Ocular surface staining ≥ 3	454	94.1%	286	83.2%	1275	67.2%	<.0001
Unstimulated saliva ≤0.5 ml/5 min	455	64.4%	286	61.2%	1274	48.0%	<.0001

*FLS=focal lymphocytic sialadenitis; F/SLS=focal /sclerosing lymphocytic sialadenitis.

Conclusion: There is a higher prevalence of all phenotypic features of SS among those with higher SSA/B-Ab titer. Low antibody titers occur in approximately 14% of patients suspected of having SS and may represent an intermediary phenotype distinct from those with high or negative titers.

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Validity of Low Titers of SSA/B Antibodies in Predicting A Key Feature of Sjögren's Syndrome. Mara McAdams DeMarco[1], Mi Y. Lam[2], Steve Shiboski[2], Lindsey A. Criswell[3], Caroline Shiboski[2] and Alan N. Baer[4]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]University of California, San Francisco, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA, [4]Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, MD

Background/Purpose: The validity of low titers of SSA and/or SSB (SSA/B) antibodies (Ab) in the diagnosis of Sjögren's syndrome (SS) has not been defined. We explored the validity of using varying SSA/B-ab titers to predict a "positive lip biopsy", a known objective test used in the ACR classification of SS (Arth Care Res 2012;64:375).

Methods: SICCA is an NIH-funded registry in which patients with suspected or established SS undergo a uniform evaluation, including minor salivary gland (lip) biopsy. SSA/B-Ab testing was performed by Quest Laboratories, using a multiplex flow immunoassay. Positive results were expressed in "antibody index" (AI) units and as continuous measure variables up to a level of 8 AI, beyond which the units were not quantified. We defined "low titer" SSA/B-Ab as those between 1 and 8 AI. A "positive lip biopsy" was defined as focal or focal/sclerosing lymphocytic sialadenitis with a focus score $\geq$ 1. The validity of SSA/B-Ab testing was defined by the degree to which patients were correctly classified as having or not having a positive lip biopsy, used in lieu of a gold standard. This was quantified by sensitivity and specificity across the range of AI units for 1) SSA-Ab alone, 2) SSB-Ab alone, and 3) combinations of SSA/B-Ab.

Results: Of the 1,861 SICCA patients, the mean age was 53, 91% were female and 629 (34%) had a positive lip biopsy. For SSA-Ab, 431 (23%) >8 AI and 139 (7%) had low titers. For SSB-Ab, 184 (9%) >8 AI and 168 (9%) had low titers. SSA- and SSB-Ab > 8 AI had unacceptably low sensitivity (see Table). With increasing SSA-Ab cutoff levels, the likelihood of misclassifying a patient with a negative lip biopsy decreased (specificity 84 $\rightarrow$ 91%) while the likelihood of not identifying a patient with a positive lip biopsy increased (sensitivity 60 $\rightarrow$ 51%). Use of the SSB-Ab test alone was associated with high specificity but low sensitivity. In the combined analysis, the sensitivity and specificity respectively, were, 1) SSA-Ab$\geq$1 & SSB-Ab<1: 0.35 & 0.89; 2) SSA-Ab$\geq$1 & SSB-Ab$\geq$1: 0.51 & 0.94; 3) SSA-Ab<1 & SSB-Ab$\geq$1: 0.05 & 0.98 and; 4) SSA-Ab>1 or SSB-Ab>1: 0.62 & 0.82. Results were similar when the study was restricted to those patients with an objective parameter indicative of dry eye syndrome.

Table. Sensitivity, Specificity and 95% Confidence Intervals by SSA/B Threshold

SSA/SSB Threshold	SSA test alone		SSB test alone	
	Sensitivity	Specificity	Sensitivity	Specificity
>1	0.60 (0.56, 0.64)	0.84 (0.82, 0.86)	0.41 (0.38, 0.45)	0.93 (0.91, 0.94)
>2	0.59 (0.55, 0.63)	0.86 (0.84, 0.88)	0.35 (0.31, 0.39)	0.94 (0.93, 0.96)
>3	0.58 (0.54, 0.62)	0.87 (0.85, 0.88)	0.32 (0.28, 0.36)	0.95 (0.94, 0.96)
>4	0.57 (0.53, 0.61)	0.88 (0.86, 0.89)	0.29 (0.26, 0.33)	0.96 (0.94, 0.97)
>5	0.56 (0.52, 0.60)	0.89 (0.87, 0.90)	0.28 (0.24, 0.31)	0.96 (0.95, 0.97)
>6	0.52 (0.49, 0.56)	0.90 (0.88, 0.91)	0.26 (0.23, 0.30)	0.97 (0.95, 0.98)
>7	0.52 (0.48, 0.56)	0.90 (0.89, 0.92)	0.25 (0.22, 0.29)	0.97 (0.96, 0.98)
>8	0.51 (0.47, 0.55)	0.91 (0.89, 0.93)	0.24 (0.21, 0.27)	0.97 (0.96, 0.98)

Conclusion: SSA- and SSB-Ab > 8AI had low sensitivity and the inclusion of low titers resulted in a minimal improvement in the test's moderate sensitivity and minimal decrease in specificity. This confirms the need to perform additional objective tests, such as a lip biopsy, in the diagnosis of SS.

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Cathepsin S Activity in Tears As a Marker of Sjögren's Syndrome. S.E. Whitt[1], K. Renduchintala[1], S. Janga[2], M. Shah[2], J. Zhu[3], K. Silka[3], S. Bricel[3], D. Bach[3], M. Heur[4], S. Christianakis[3], J. Irvine[4], D. Arkfeld[3], W.J. Mack[3], William Stohl[3] and S.F. Hamm-Alvarez[2]. [1]University of Southern California Keck School of Medicine - These authors contributed equally to this work, Los Angeles, CA, [2]University of Southern California School of Pharmacy, Los Angeles, CA, [3]University of Southern California Keck School of Medicine, Los Angeles, CA, [4]Doheny Eye Institute, Los Angeles, CA

Background/Purpose: Currently used biomarkers for Sjögren's Syndrome (SS), such as anti-SSA/Ro or anti-SSB/La, lack sensitivity and specificity. The goal of the work presented here is to evaluate the association of elevated Cathepsin S (CATS) with SS and contrast this to CATS associations with other autoimmune or dry eye disorders.

Methods: Patients were recruited from outpatient Rheumatology and Ophthalmology clinics. Schirmer's tests were administered to patients with primary or secondary SS (n=47), rheumatoid arthritis (RA) without SS (n=41), systemic lupus erythematosus (SLE) without SS (n=18), other autoimmune diseases without SS (n=10), non-autoimmune dry eyes (n=13), and blepharitis (n=8). The Schirmer's strips were immediately placed on ice after tear collection, and tear proteins were eluted and analyzed within 4 hours for CATS activity using commercial assay kits. CATS activity was normalized to protein concentration. Serum positivity for anti-SSA and anti-SSB in autoimmune disease patients was determined by a clinical laboratory.

Results: CATS data were log-transformed prior to analysis to deemphasize outlier values. To compare log CATS activity among patient groups accounting for correlated data (correlation among eyes), generalized estimating equations were used. Median CATS activity in SS patients (median 5140) was compared to non-SS patient groups: SS vs. RA (median 1476, p=<.00001), SS vs. SLE (median 2226, p=.0008), SS vs. Blepharitis (median 1770, p=.022), SS vs. Dry Eye (median 2768, p=.003), and SS vs. Other (median 1770, p=.013). CATS activity did not significantly differ (p=0.31) between primary SS (n=11; median 5514) and secondary SS (n=36; median 4970). Anti-SSA-positive SS patients (n=30; median 3288) and anti-SSA-negative SS patients (n=8; median 1732) also did not significantly differ on CATS activity (p=0.29). The data did not demonstrate a significant difference (p=0.25) in median CATS activity between SSB-positive (n=13; median 5321) and SSB-negative (n=25; median 4456) groups.

Conclusion: Normalized CATS activity is significantly greater in the tears of SS patients than in the tears of patients with non-SS autoimmune or non-autoimmune diseases. Determination of CATS activity in tears may be clinically useful by shortening the lag time in diagnosing patients with SS, thereby promoting earlier initiation of appropriate therapy. The simplicity of the test may permit its automation and use in real-world clinical settings.

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Long-Term Changes in Autoantibody Profile After Pandemic Unadjuvanted Influenza A/H1N1 Vaccine in Sjögren's Syndrome. Sandra G. Pasoto[1], Ana C. Ribeiro[1], Vilma S.T. Viana[1], Elaine P. Leon[2], Cleonice Bueno[1], Mauricio Levy Neto[1], Alexander R. Precioso[3], Maria do Carmo S. Timenetsky[4] and Eloisa Bonfa[1]. [1]Division of Rheumatology - Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Fundação Butantan - Instituto Butantan, São Paulo, Brazil, [4]Instituto Adolfo Lutz - Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: Despite WHO recommendations about the A/California/7/2009/H1N1-like virus vaccination, there are no studies evaluating its possible influence on clinical manifestations and autoantibody profile in (primary) Sjögren's syndrome (SS). Objectives: To evaluate short/long-term effect of influenza A/California/7/2009/H1N1-like virus vaccination on clinical manifestations and autoantibody profile in SS.

Methods: Thirty-six SS patients (The American-European Consensus Group Criteria, 2002) and 36 gender-, age-, matched-healthy controls were evaluated before and 21-days after vaccination with unadjuvanted influenza A/H1N1-like virus regarding seroprotection/seroconversion, factor increase in geometric mean titre (FI-GMT) and side effects. New onset of parotiditis, arthritis, vasculitis, pneumonitis or neurological disorders and autoantibody profile [antinuclear antibodies (ANA), rheumatoid factor (RF), anti-dsDNA, anti-Ro(SS-A)/La(SS-B), anti-alpha-fodrin, anti-RNP, anti-Sm and anticardiolipin] were assessed before, 21-days and 1-year after vaccination.

Results: Patients and controls had similar rates of seroconversion (78 vs. 69%, p= 0.42), seroprotection (83 vs. 72%, p= 0.26) and FI-GMT (p= 0.85). Pre-vaccination evaluation revealed that disease duration, glucocorticoid (mean dose 10.1 +− 5.1 mg/day), methotrexate (up to 17.5 mg/week) or azathioprine (up to 100 mg/day) did not affect seroconversion (p> 0.05). Regarding short-term analysis, no change in the frequency or levels of autoantibodies was observed (p> 0.05) and only mild side effects were

observed in comparable rates to controls (p> 0.05). At 1-year follow-up, the rate of new disease flares was similar to the previous year (11 vs. 19%, p= 0.51) and four seroconverted patients developed positivity to one of the following specificities: anti-Ro/SS-A, anti-La/SS-B, anti-alpha-fodrin, or IgM anticardiolipin. None developed other specific lupus autoantibodies. Of note, a significant increase in the mean levels of anti-Ro/SS-A (p< 0.0001) and anti-La/SS-B (p< 0.002) was detected after 1-year with no change in the other autoantibodies.

Conclusion: This is the first study to indicate that influenza A/H1N1 vaccine induces long-term changes in autoantibody profile restricted to SS spectrum without a deleterious effect in disease course. FAPESP grant: 2010/10749-0.

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Decreased Expression of TSLP in Labial Salivary Glands of Patients with pSS Is Associated with Local and Systemic Disease Parameters.
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Background/Purpose: Thymic Stromal Lymphopoietin (TSLP) is a potent immunomodulatory cytokine involved in Th2-mediated immune responses and homeostatic T-cell expansion. Reduced TSLP expression by intestinal epithelial cells was recently shown to lead to reduced Th2 responses and development of Th1-mediated experimental colitis. In addition, TSLP is described as a proinflammatory factor in rheumatoid arthritis, which is driven by Th1/Th17 responses. A Th1/Th17 polarized environment is also present in the salivary glands of patients with Primary Sjögren's syndrome (pSS).The aim of this research was to investigate TSLP expression in salivary glands of pSS patients as compared to non-SS Sicca (nSS) patients and to study the relationship to local and systemic disease parameters.

Methods: Tissue sections of minor salivary glands from 38 pSS and 18 nSS patients were stained with a monoclonal antibody (mAb) against human TSLP or an isotype control. In addition, sections were stained with a mAb against the epithelial cell marker Cytokeratin High Molecular Weight (CK HMW) or stained with alcian blue to detect mucus production. The number of cells that stained positive for TSLP was assessed. In addition, TSLP was quantified at sites where only intact (CK HMW positive), functional (alcian blue positive) structures were present. TSLP expression was correlated to local (lymphocyte focus score, LFS; %IgA positive plasma cells) and systemic (erythrocyte sedimentation rate, ESR; serum IgG levels) disease parameters.

Results: TSLP was almost exclusively expressed by acinar cells in both pSS and nSS patients. The number of TSLP-expressing cells per mm^2 was significantly decreased in pSS patients as compared to nSS patients (462 ± 42 vs. 773 ± 84, p<0.01) and correlated negatively to LFS (r= −0.48, p<0.001) ESR (r= −0.41, p<0.01), serum IgG levels (r= −0.41, p<0.01) and positively to the percentage of local IgA producing plasma cells (r= 0.35, p<0.05). At sites with intact, functional epithelium TSLP expression tended to be reduced in pSS patients as compared to nSS patients (840 ± 75 vs. 1064 ± 72, p=0.079). Furthermore, pSS patients with a LFS equal to or higher than 3 had significantly lower numbers of TSLP-producing cells per mm^2 at these sites compared to nSS patients (677 ± 105 vs. 1064 ± 72, p<0.01). Also, in intact and functional epithelium, the number of TSLP-producing cells correlated negatively to LFS (r= −0.40, p<0.01), ESR (r= −0.32, p<0.05) and serum IgG levels (r= −0.27, p<0.05)

Conclusion: TSLP expression is reduced in pSS patients, associated with local and systemic inflammatory markers including increased lymphocytic infiltration. Considering the described role of TSLP in promoting Th2 responses at mucosal sites, we hypothesize that TSLP is constitutively expressed in salivary glands and promotes a protective Th2 milieu, whereas loss of TSLP expression may contribute to Th1/Th17 associated immunopathology in pSS.

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Diagnostic Value of Blood B-Cell Subset Profiling and Autoimmunity Markers in Anti-SSA-Negative Sjögren's Syndrome Patients.
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Background/Purpose: Recently published ACR classification criteria for primary Sjögren's syndrome (pSS) suggest considering antinuclear antibodies (ANA) titer and rheumatoid factor (RF) positivity in patients negative for anti-Ro/SSA antibodies. The diagnostic value of these tests for pSS has to be confirmed in independant cohorts. Besides, we have shown in a previous case-control study that blood B-cell subset profiling through (Bm2+Bm2′)/(eBm5+Bm5) ratio computation is abnormal in pSS patients. Gammaglobulins and IgG titers are often increased in these patients. The aim of this study was to evaluate the diagnostic value of these B-cell markers for pSS, and to assess if they could improve American-European Consensus Group (AECG) criteria.

Methods: This cross-sectional study was conducted in a monocentric cohort of patients with suspected pSS, prospectively included between November 2006 and September 2011. Clinical examination, basic biology, immunological tests and minor labial salivary gland biopsy (SGB) were performed systematically. For blood B-cell subset profiling, the (Bm2+Bm2′)/(eBm5+Bm5) ratio (referred to as B-cell ratio) was determined using flow cytometry. The gold standard for the analysis was a clinical diagnosis of pSS performed by a group of experts, blinded to the results of B-cell profiling. The diagnostic values and the independance of the different tests were compared using logistic regression analysis.

Results: 181 patients have been included in the study (mean age 56±13 years, symptoms duration 6.0±6.9 years, 92.2% females). 77 patients had pSS diagnosed by the experts. No differences were found between the 2 groups concerning age, disease duration, and sex ratio. The sensitivity (Se) and specificity (Sp) of the different tests were respectively: 60.6% and 99.0% for anti-SSA/SSB; 81.7% and 61.1% for ANA≥1:320; 70.4% and 83.2% for ANA≥1:640; 45.5% and 79.8% for IgM-RF; 42.3% and 97.9% for IgA-RF; 46.5% and 92.6% for gammaglobulins ≥14 g/l; and 49.6% and 91.6% for IgG ≥14 g/l. The mean B-cell ratio was significantly higher in the pSS group than in the non-pSS group (7.4±6.9 vs 3.2±2.3, $P<0.001$), and a ratio ≥5 had 52.1% Se and 83.2% Sp. Logistic regression analysis selected only ANA≥1:640 and B-cell ratio ≥5, with a similar weight. The combination of these two tests (ANA and ratio) displayed 37.7% Se and 96.2% Sp in the whole population, but only 12.9% Se in anti-SSA-negative patients. The association of the two tests (ANA or ratio) displayed 85.7% Se and 67.3% Sp in the whole group, and 71.0% Se in anti-SSA-negative patients. The modification of AECG criteria including the two tests in association (ANA or ratio) increased the Se from 83.1% to 90.9%, but decreased the Sp from 97.1% to 85.6%, whereas using the tests in combination (ANA and ratio) did not modify significantly their diagnostic value.

Conclusion: Blood B-cell subset profiling using flow cytometry is a simple test which has good diagnostic properties for pSS. However, the inclusion of this test, associated or not with ANA positivity, does not improve current classification criteria. Anti-SSA/SSB antibodies remain the best serologic item for the diagnosis of pSS.

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Interstitial Lung Disease in Primary Sjogren's Syndrome: Any Association with IgG4 Related Sclerosing Disease?
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Background/Purpose: Various forms of interstitial lung disease (ILD) are associated with primary Sjögren's syndrome. IgG4-related sclerosing disease (ISD) is a recently described systemic fibroinflammatory disease associated with dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells. Sicca symptoms and ILD are two of the known manifestations of ISD, and are also characteristic of Sjögren's syndrome. We aimed to describe the lung histopathology in a series of patients with Sjögren's syndrome who underwent open lung biopsy for evaluation of ILD, and to evaluate the occurrence of IgG4 in the lung parenchyma from a subset of these patients.

Methods: The archived pathology specimens of 15 patients with primary Sjögren's syndrome related ILD who underwent lung biopsies between 1998 and 2010 were reviewed, and evaluated for the presence of IG4 by immunohistochemical staining. Diagnosis was based on 2002 American European Consensus Group criteria for primary Sjogren's syndrome. Patient demographic data and findings from high resolution computed tomography (HRCT) findings of the lungs of these patients were recorded.

Results: Among the 15 identified patients, 11 (73%) were female; mean age was 58 years. All of these patients had dry eyes and dry mouth symptoms. Anti-nuclear antibodies were present in 11 (85%) of 13 tested patients. Of 12 patients tested, 12 (100%) had anti- SSA antibodies and 9 (75%) had anti-SSB antibodies. Six (55%) of 11 tested patients were rheumatoid factor positive, and hypergammaglobulinemia was noted in 9 (75%) of 12 tested patients. Six (40%) patients had positive smoking history. Lung histopathology revealed usual interstitial pneumonia (UIP) in 6 patients; 3 patients had non-specific interstitial pneumonia (NSIP). The other patients had bronchiolitis (n=1), cryptogenic organizing pneumonia (n=1), desquamative interstitial pneumonia (n=1), follicular bronchiolitis with amyloid (n=1), obstructive pneumonitis (n=1), and lymphocytic interstitial pneumonia (n=1). Immunohistochemical staining of these lung biopsy specimens for IgG4 were negative for 7 (100%) of 7 patients. HRCT was performed in 12 of 15 patients. Linear or reticular opacities were noted in 9 patients, ground glass or non-solid opacities in 8 patients, and bronchiectasis in 8 patients. Other common HRCT findings were lymphadenopathy (n=3) honey-combing (n=3), multifocal cysts (n=3) and solid nodules (n=3).

Conclusion: The most common form of ILD in these patients with Sjögren's syndrome undergoing lung biopsy is UIP, and the majority had linear and/or ground opacities on HRCT. While there are reports that dacroadenitis and sialoadenitis is associated with IgG4 deposition, we found no evidence of IgG4 in the lung tissue of patients with primary Sjögren's syndrome suffering from ILD.

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Elevated IgG4 Serum Levels Among Primary Sjogren's Syndrome Patients: Do They Unmask Underlying IgG4-Related Disease? Clio P. Mavragani[1], George Fragoulis[2], Dimitra Rontogianni[3], Maria Kanariou[4] and Haralampos M. Moutsopoulos[2]. [1]School of Medicine, University of Athens, Athens, Greece, Athens, Greece, [2]School of Medicine, University of Athens, Athens, Greece, [3]Evangelismos General Hospital, Athens, Greece, [4]"Aghia Sophia" Children's Hospital, Athens, Greece

Background/Purpose: To determine IgG4 serum levels in a cohort of patients fulfilling the classification criteria for primary Sjogren's syndrome (pSS) and to explore whether they associate with distinct clinical, serological and histopathological parameters.

Methods: IgG4 levels were measured by nephelometry in sera from 140 consecutive pSS patients and 45 healthy controls of similar age and sex distribution. Immunohistochemical IgG4 analysis was performed on paraffin-embedded salivary gland tissues from patients with high and low IgG4 serum levels.

Results: Raised IgG4 serum levels defined as higher than 135mg/dl were detected in 8 out of 81 pSS patients analyzed (9.9%) ("High-IgG4" group) and in none of controls (p=0.05). Compared to their counterparts with normal IgG4 serum levels, the "High-IgG4" subset is characterized by significantly increased prevalence of IgG4-related features such as autoimmune pancreatitis, cholangitis and interstitial nephritis (p=0.006), lower rates of ANA (p=0.05) and anti-Ro/SSA (p=0.05) positivity. Although not statistically significant, sicca features and anti-La/SSB positivity occurred less frequently in the "High-IgG4" group. Multivariate logistic regression analysis revealed interstitial nephritis (p=0.048), autoimmune cholangitis (p=0.012) or pancreatitis (p=0.027) and absence of ANA (p=0.005) as independent predictors of IgG4 serum levels. Positive staining for IgG4+ plasma cells was detected in one out of four available MSG biopsies in the "High-IgG4" group but in none of the control patients with normal IgG4 serum levels. Analysis of the whole group is in process.

Conclusion: Raised IgG4 levels occur approximately in 10% of patients with pSS and characterize a subgroup with high prevalence of IgG4-related clinical and serological features. Whether these patients represent a distinct pSS subset or a misclassified IgG4-Related (IgG4-RD) disease group remains to be defined.

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2200

IgE Autoantibodies Against SSA and SSB in Patients with Sjögren's Syndrome and Healthy Controls. Stamatina Danielides[1], Barbara Dema[2], Juan Rivera[2] and Gabor G. Illei[3]. [1]NIH, Bethesda, MD, [2]Laboratory of Molecular Immunogenetics, NIAMS, NIH, Bethesda, MD, [3]NIDCR/ NIH, Bethesda, MD

Background/Purpose: Sjögren's syndrome (SS) is a chronic autoimmune disorder, presenting as an autoimmune exocrinopathy. Although the pathogenesis of this disease is largely unknown, evidence indicates that B cells, and hence the T helper 2 environment, may play an important role in its development. Recent evidence supports that IgE double stranded DNA (dsDNA) autoantibodies may be involved in the amplification loop of T helper 2 cells in lupus. In addition, there is a correlation between the presence of IgE autoantibodies and disease activity, measured by low complement levels. We sought to determine whether autoreactive IgE autoantibodies can be found in patients with Sjögren's syndrome.

Methods: We included 180 patients with the diagnosis of Sjögren's syndrome based on the American European consensus group criteria and 53 blood bank donors. We performed ELISA to determine the levels of IgG and IgE antibodies against SSA, SSB, dsDNA and Sm-RNP. Subjects with autoantibody levels over the mean +2SD of the controls were considered autoantibody positive. Statistical analysis was done with the Wilcoxon test.

Results: IgE autoantibodies against SSA and SSB were found in higher titers and higher frequencies in SS patients compared to blood bank donors (SSA 33.8% vs 6.81%, SSB 41.67% vs 1.85% in patients vs controls respectively, p<0.0001 for both), IgE autoantibodies to Sm-RNP and albeit less frequently anti-dsDNA were also seen more commonly in SS patients than controls (Sm RNP 25% vs 1.85%, p<0.0001 and dsDNA 15.70 vs 5.55%, p=0.0156).

The presence of IgE autoantibodies was not exclusive to the group of patients with positive IgG autoantibodies, as 29.2% of patients were discordant for SSA and 26.25% for SSB IgG and IgE antibodies.

The difference between IgG and IgE antibodies was striking for antiSm-RNP, as 7.25% of SS patients had IgG Sm-RNP and 25% had IgE Sm-RNP positivity.

No correlation was seen between IgE antibody titers and serum IgE levels or the respective IgG antibodies.

Among IgG antibodies only SSA IgG was associated with low complement levels, however several IgE autoantibodies were associated with low complements (low C3 and SSB IgE, p=0.0107; low C4 and SSB IgE p=0.0023; low C4 and SSA IgE, p=0.0316, low C4 and dsDNA IgE, p=0.0078).

There was no association between SSA or SSB IgE and focus scores.

Conclusion: IgE autoantibodies are present in a high proportion of SS patients compared to controls, and they appear independent from their respective IgG autoantibodies. Preliminary data suggest that IgE autoantibodies may be associated with hypocomplementemia, but further studies are needed to clarify their role in the cascade of events leading to disease pathogenesis.

Disclosure: **S. Danielides**, None; **B. Dema**, None; **J. Rivera**, None; **G. G. Illei**, None.

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Involvement of Interleukin-33 in the Pathogenesis of Sjögren's Syndrome. Ahmad Awada, Valérie Gangji and Muhammad S. Soyfoo. Hôpital Erasme,Université Libre de Bruxelles, Brussels, Belgium

Background/Purpose: To investigate the role of IL-33/ST2 in the pathophysiology of primary Sjögren's syndrome (pSS)

Methods: Serum levels of IL-33 and sST2 was determined by ELISA. The expression of IL-33 and ST2 was examined in the salivary glands of patients by immunohistochemistry and western blot. PBMC were isolated and stimulated with IL-33, IL-12 and IL-23 and the cytokine profile response was examined by flow cytometry. Intracellular cytokine detection of IFN-gamma and IL-17 was performed by flow cytometry. RT-PCR was performed to detect IL-33, sST2 and ST2L transcripts after PBMC stimulation by TNF-a and IL-1b with and without LPS.

Results: IL-33 and sST2 was increased in pSS patients compared to controls. Expression of IL-33 was upregulated in the salivary glands of pSS patients with Chisholm scores of 2 and 3 but comparable to controls for patients with Chisholm score of 4. sST2 expression was downregulated in pSS patients. IL-33 in a dose related fashion increased the secretion of TNF, IL-1,IL-6 and IL-10. Moreover, IL-33 acts synergistically with IL-12 and

IL-23 promoting IFN production. NK and NKT cells were identified as main producers of IFN. TNF and IL-1 increased the ST2L transcripts levels while no IL-33 expression was detected

Conclusion: IL-33 is released in pSS, favouring the secretion of pro-inflammatory cytokines.Our study reveals IL-33/ST2 axis in the pathophysiology of pSS.

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2202

Classification Criteria for Sjögren's Syndrome: Comparison of the Performance of the 2002 American-European Consensus Group Criteria (AECG) and the 2012 ACR Criteria. Elke Theander[1], Peter Olsson[2] and Thomas Mandl[3]. [1]Skane University Hospital, Lund University, Malmö, Sweden, [2]Department of Rheumatology, Skåne University Hospital, Lund University, Malmö, Sweden, [3]Skane University Hospital Malmo, Lund University, Malmö, Sweden

Background/Purpose: To assess level of agreement between 2002 AECC and 2012 ACR criteria for primary Sjögren's Syndrome syndrome (pSS) within the Malmö Sjögren's Syndrome Registry

Methods: The Malmö Sjögren's Syndrome Registry was established 1984. Patients not fulfilling the AECG criteria were after 2002 designated as having Sicca-Syndrome in contrast to pSS. To date 368 pSS according to AECG and 264 Sicca patients are registered. Here the ACR-criteria ocular staining score (OSS) ≥ 3 was substituted by van Bijsterveld score ≥ 3. An inter-criteria reliability analysis with Kappa statistic was performed to determine classification consistency.

Results: Of 264 Sicca patients not fulfilling AECG, 81% had sufficient data available to make a decision about fulfilling the ACR criteria. Seven patients (2.7%) fulfilled the ACR critiera but not AECG. All of these fulfilled the ACR criteria due to high titres of ANA and positive RF. None was positive for anti-Ro or La or had a positive salivary gland biopsy. Nor did they have signs of lymphoma risk or had developed lymphoma. Thus, in 97% of the evaluable sicca patients the two criteria sets agreed. Of 368 fulfilling AECG, 268 (73%) had information on all ACR items available, 309 (84%) had sufficient information to evaluate fulfillment of the ACR criteria set. Forty-eight (15%) of AECG positive patients were negative when applying the ACR criteria. 261 of 309 evaluable AECG positive patients were positive according to the ACR criteria, resulting in a consensus in 85%. A calculated kappa-value of 0.781 signals a substantial agreement between the two criteria sets.Amongst the patients not identified by the ACR-criteria there were several with known risk factors for development of lymphoma (table 1). One lymphoma patients (pos biopsy, low C3, high titre ANA but no SSA/SSB or RF, low OSS) was negative in the ACR criteria. Seventeen of the 46 patients not identified by the ACR criteria were previously included in an analysis of germinal center (GC) formation in salivary gland biopsies. Two of these (12%) were positive for GC. These patients with low complement levels, polyneuropathy, low salivary flow were missed applying the ACR criteria due to lack of severe eye disease and SSA/SSB.

Characteristics of 46 patients fulfilling AECG- but not ACR-criteria (n/% of available)

Pos autoimmune sialadenitis	32 (70%)
Pos SSA/SSB	13 (29%)
Low C3 (<0.8 g/l)	4 (11,4%)
Low C4 (<0.20 g/l)	8 (23%)
High IgG (>16 g/l)	7 (17%)
Parotid swelling	9 (21%)
Purpura Waldenstršm	2 (4%)
Cryoglobulinemia	2 (4%)
Low CD4/CD8 ratio	1 (2%)
Lymphoma	1 (2%)

Conclusion: The 2002 AECG and 2012 ACR criteria for SS identify mainly the same patient population (Kappa: 0.781), when applied to the Malmö SS registry containing 386 pSS and 264 sicca syndrome patients. A subgroup of patients lacking SSA/SSB antibodies can be catched only by the ACR criteria. The patients classified as Sjögren's syndrome by the ACR-criteria in our sicca-cohort had mild disease. On the other hand, several patients with high risk disease manifestations such as hypocomplementemia, GC formation or parotid swelling were missed using the ACR criteria because they lacked severe keratoconjunctivitis sicca. Sensitivity and specificity of the ACR criteria were 85% and 97% respectively.

Disclosure: **E. Theander**, None; **P. Olsson**, None; **T. Mandl**, None.

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Effects of Reclassification Using the American College of Rheumatology Criteria On a Large cohort Sjögren's Syndrome Patients. Astrid Rasmussen[1], John A. Ice[1], He Li[2], Kiely Grundahl[3], Jennifer A. Kelly[1], Lida Radfar[4], Kimberly S. Hefner[5], Donald U. Stone[4], Juan-Manuel Anaya[6], Michael Rohrer[7], Glen D. Houston[4], David M. Lewis[4], James Chodosh[8], John B. Harley[9], Pamela Hughes[7], Jacen S. Maier-Moore[4], Courtney G. Montgomery[1], Nelson L. Rhodus[7], A. Darise Farris[10], Barbara M. Segal[11], Christopher J. Lessard[12], R. Hal Scofield[10] and Kathy Moser Sivils[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [3]Oklahoma Medical Research Foundation, oklahoma CIty, OK, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Hefner Eye Care and Optical Center, Oklahoma City, OK, [6]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [7]University of Minnesota, Minneapolis, MN, [8]Harvard Clinical and Translational Science Center, Boston, MA, [9]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [10]Oklahoma Medical Research Foun, Oklahoma City, OK, [11]Hennepin County Medical Center, Minneapolis, MN, [12]Oklahoma Medical Research Foundation; University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background/Purpose: There is no single clinical diagnostic test for primary Sjögren's syndrome (pSS). For research purposes, multiple classification criteria have been proposed over the past decades. These include the 2002 American-European Consensus Group (AECG) criteria as well as the newly proposed (2012) American College of Rheumatology (ACR) criteria. We compared the performance of these two sets of criteria in a large carefully characterized sicca cohort.

Methods: In a multidisciplinary (eye, mouth, and medicine) clinic for the evaluation of sicca, we determined the classification of subjects under the AECG and new ACR criteria(n=584) and the mRNA expression profile in whole blood of a subset of 201 participants (pSS by both criteria sets n=127, ACR+/AECG-: n =7, ACR-/AECG +: n=29 and controls n=38). The data points recorded for each patient for classification purposes were: the answers to subjective eye and mouth symptoms (according to the AECG questionnaire), Schirmer's I test, ocular dye score (lissamine green + fluorescein staining of conjunctiva and cornea quantified either by the van Bijsterveld score or the OSS score), salivary whole unstimulated flow, histopathology of minor salivary gland biopsy, serology (antiRo, antiLa, ANA and rheumatoid factor antibodies).

Results: The initial cohort of participants evaluated at either the Sjögren's Clinic at Oklahoma Medical Research Foundation and/or the Sjögren's Clinic at the University of Minnesota consisted of 748 individuals. Of these, a complete data set was available for 584 subjects and these constitute the study cohort. The two cohorts are comparable in terms of age, sex, race and ethnicity. Among the 584 subjects with complete data, 259 were classified as pSS under AECG, and 249 were so classified under ACR criteria while 222 met both sets of criteria and they represent 78% of all pSS cases. The two sets of criteria were not significantly different (p=0.26, McNemar's test; concordance = 0.77, Kappa statistic, 95% CI=72.5–82.9); the ACR criteria had a sensitivity of 0.86 (95% CI=0.81–0.90) and a specificity of 0.92 (95% CI=0.88–0.94). Thirty seven subjects were classified as pSS by AECG only (ACR-/AECG+), of whom 29 (78%) had a minor salivary gland biopsy focal score >1, while 8 (22%) had positive anti-Ro/La. On the other hand, there were 27 ACR+/AECG- and they met ACR criteria mainly due to differences in the scoring of the corneal staining (OSS ≥ 3 for ACR; van Bijsterveld ≥ 4 for AECG). Interestingly, when attempting to correlate the subgroups generated by the classification criteria with their global gene expression profiles, we were unable to identify distinct clustering.

Conclusion: When considering any subject who would meet classification for pSS by either set of criteria, only 75% would be so classified by both. Twenty five percent would be classified by only one set, leading to heterogeneity by either. This suggests that further refinement of the criteria using molecular data is warranted.

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Overall Agreement Between Sjögrens's Minor Salivary Gland Biopsy and 2002 and 2012 Classification Criteria. Laura Aline Martinez[1], Candido Flores[2], Alberto Arana Fraustro[2] and Luis H. Silveira[3]. [1]Instituto Nacional de Cardiologia Ignacion Chavez, Mexico City, Mexico, [2]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico, [3]Instituto Nacional Cardiología Ignacio Chávez, Mexico City, Mexico

Background/Purpose: Sjögren's syndrome (SS) is an inflammatory autoimmune disease characterized by lymphoid infiltration of exocrine glands, although extraglandular involvement is frequently observed. Prevalence is around 0.5% to 1%. There have always been difficulties for the classification and diagnosis of patients. Several criteria have been proposed. The classification criteria used in recent years where those established by the American-European Consensus Group in 2002. Recently, new classification criteria have been published by the International Collaborative Clinical Alliance Cohort; these criteria have been approved by the American College of Rheumatology. Although minor salivary gland biopsy has been used throughout the years, its findings are not highly specific.

Objectives: *Primary.* To determine the agreement between a positive minor salivary gland biopsy and having al least 4 of the 6, 2002 criteria, as well as having 2 of the 3, 2012 criteria. *Secondary:* To determine the agreement between 2002 and 2012 SS classification criteria.

Methods: This is a retrospective study consisting of clinical chart review from patients with primary SS (PSS) and secondary SS (SSS), having minor salivary gland biopsy report. Clinical chart review included patients attending the Rheumatology Clinic at the National Institute of Cardiology in Mexico City, between January 1, 2000, and May 31, 2011. Clinical manifestations, serology, and the biopsy report were obtained in all patients. Biopsies were considered positive when a focal lymphocytic sialadenitis with a focus score $\geq$ 1 focus ($>$ 50 cells)/4 mm^2 was observed. Biopsies were assessed by the same expert pathologist. The 2002 and 2012 criteria were applied according to their requirements. Descriptive statistic was used and kappa index was calculated as an agreement measure. A p value $<$ 0.05 was considered significant. SPSS version 15.0 was used for the statistical analysis.

Results: A total of 75 clinical charts with a biopsy report were reviewed; 8 patients were excluded because information was incomplete. 67 patients were included in the analysis, 62 women and 5 men. 55.2% had PSS and 44.8% had SSS. The agreement between a positive biopsy and having 4 of the 6, 2002 criteria, was weak (kappa = 0.27; p = 0.01); the agreement of a positive biopsy with having 2 of the 3, 2012 criteria, was moderate (kappa = 0.5; p $<$ 0.0001). The agreement between the 2002 criteria and the 2012 criteria was good (kappa = 0.70; p $<$ 0.0001), when all the patients were considered. In the SSS patients, the agreement decreased (kappa = 0.44; p = 0.003).

Conclusion: The agreement between a positive biopsy and having 4 of the 2002 criteria was low, and moderate when having 2 of the 20012 criteria. The agreement between the 2002 and the 2012 criteria was very good when PSS patients were included, however, it decreased when only the SSS patients were included.

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Longitudinal Evaluation of the Performance of Different Classification Criteria in Patients with Primary Sjögren's Syndrome. Martina Plešivčnik Novljan[1], Žiga Rotar[1], Aleš Ambrozič[1], Gaj Vidmar[2] and Matija Tomšič[1]. [1]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [2]University Rehabilitation Institute, 1000 Ljubljana, Slovenia

Background/Purpose: Over the past 3 decades, 10 different classification criteria for Sjögren's syndrome (SS) had been proposed. In 2001 and 2002 222 consecutive patients suspected of having primary SS (pSS) were each evaluated for pSS using the Copenhagen (COP), Californian (CA), European (EU) and American-European consensus group (AECG) criteria. 90 patients could be classified as pSS by at least one of the criteria.(1) The purpose of our current study was to prospectively compare the longitudinal performance of different classification criteria by reassessing the diagnosis in 2009 in the group of patients classified as pSS in 2001 and 2002.

Methods: Eligible patients were invited for reassessment. In each patient we repeated diagnostic tests as required by any of the respective classification criteria. Additionally, we used the new ACR criteria (ocular stain score $\geq$3 was replaced by Rose Bengal score $\geq$ 3 following the Bijsterveld's method) to classify the patients on the data from the initial cohort and at reassessment (2).

Results: In 2009 63/90 (70%) of patients from the initial cohort consented to participate. The flow of the patients is summarized in Figure 1.

During the 7.5-year follow up period we observed a transition from pSS to secondary SS (sSS) in 9/63 (14%) patients on average after 4.0±0.9 years. While cases of transition from pSS to sSS were observed for all criteria used to make the initial diagnosis of pSS, it was significantly more common if the diagnosis of pSS was initially made using AECG (17%, p=0.008), or ACR (17%, p= 0.016) criteria.

In the 34 patients who underwent a full diagnostic reassessment the diagnosis retention rate was statistically significant for the CA, AECG, COP and ACR criteria, but not for the EU criteria (Table 1). At reassessment 3/32 (9%), and 2/26 (8%) of patients initially diagnosed as pSS using the EU, and COP criteria, respectively could not be classified as pSS by any of the criteria.

Although the difference between classification using the AECG, and new ACR criteria almost reached statistical significance for the initial 90 patients (p=0.063), the difference was lost at reassessment (p=1.000).
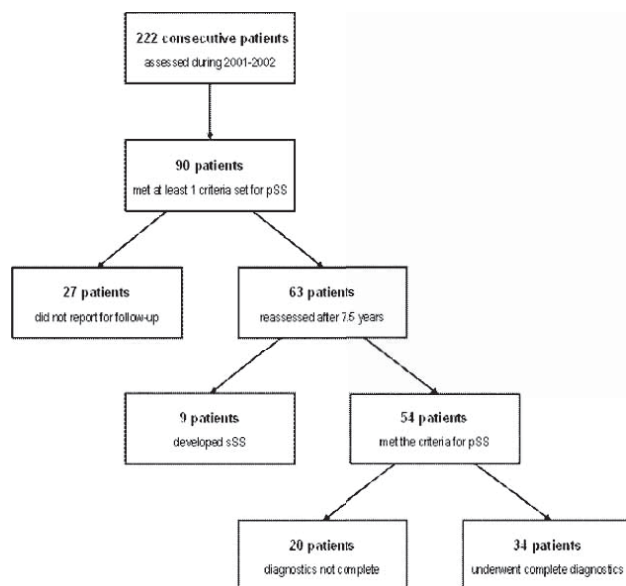
Figure 1.

Table 1.

Patients (100%)	Meeting the criteria for pSS				
	Copenhagen	Californian	European	AECG 2002	ACR 2012
All the 34 pts. before 7.5 years	26/34(76%)	12/34(35%)	32/34(94%)	24/34(71%)	22/34 (65%)
pSS not confirmed after 7.5 years	2/26 (8%)	0/12 (0%)	3/32 (9%)	0/24 (0%)	0/22 (0%)
pSS confirmed anew after 7.5 years	2/26 (8%)	1/12 (8%)	2/32 (6%)	1/24 (4%)	2/22 (9%)
All the 34 pts. at follow-up	26/34 (76%)	13/34 (38%)	31/34 (91%)	25/34 (74%)	24/34 (71%)
	Agreement between initial assessment and reassessment				
Cohen's Kappa (95% confidence interval; significance)	κ=0.673 (0.377, 0.969; p=0.001)	κ=0.937 (0.815, 1.000; p<0.001)	κ=−0.076 (−0.148, −0.004; p=1.000)	κ=0.927 (0.787, 1.000; p<0.001)	κ=0.866 (0.688, 1.000; p<0.001)

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Conclusion: The longitudinal diagnosis retention rate is highest for the Californian and AECG criteria and lowest for the European criteria. Regardless of the classification criteria we observed that with time some patients develop sSS. When using classification criteria without mandatory positivity in immunoserology or histology there is a caveat of misclassification of patients as pSS.

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Patients Fulfilling the Imaging-Arm and Patients Fulfilling the HLA-B27+ Arm of the Assessment of Spondyloarthritis International Society Axial Spondyloarthritis Classification Criteria: Are They Similar? Rosaline van den Berg, Manouk de Hooge, Floris van Gaalen, Monique Reijnierse, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: It is possible to classify patients as having spondyloarthritis (SpA) according to the ASAS axial SpA (axSpA) criteria HLA-B27+ arm without any signs of sacroiliitis on MRI or X-ray. The question arises whether patients fulfilling the HLA-B27+ arm reflect a group of patients similar to those fulfilling the imaging-arm of the ASAS axSpA criteria[1]. Therefore, we compared demographics, number of SpA-features and level of disease activity in patients fulfilling the imaging-arm to patients fulfilling the HLA-B27+ arm of the ASAS axSpA criteria.

Methods: The SPondyloArthritis Caught Early (SPACE)-cohort is set-up in the Leiden University Medical Center (LUMC) aiming to diagnose and treat patients with axSpA at an earlier stage. Patients with back pain (≥3 months, but ≤2 years, onset <45 years) visiting the rheumatology outpatient clinic were included. All patients of the SPACE-cohort (n=157) fulfilling the ASAS axSpA criteria were included in this analysis (n=60). Patients were compared on demographics, presence of SpA-features and level of disease activity.

Results: Of those 60 patients, 30 fulfilled the imaging-arm (11 patients fulfilling the modified New York (mNY) criteria; 19 patients had sacroiliitis on MRI only); 30 fulfilled the HLA-B27+ arm. Patients fulfilling the HLA-B27+ arm have significantly more often a positive family history for SpA (p=0.001), are more frequently female (p=0.04) and have a significantly shorter symptom duration (p=0.02). Moreover, there was a trend toward more uveitis (p=0.07). Patients in both arms are very similar with respect to all other SpA-features and level of disease activity (BASDAI and ASDAS). Within the imaging-arm, patients with sacroiliitis on X-ray did not differ significantly from patients with sacroiliitis on MRI in any of the tested variables including symptom duration and disease activity.

Imaging-arm, n=30

	mNY+, n=11	mNY-, n=19	Total, n=30	HLA-B27+ arm, n=30
Age (years) at inclusion, mean ± SD	28.6 ± 9.6	32.9 ± 8.7	31.2 ± 9.0	28.2 ± 8.4
Male, n (%)	8 (72.7)	11 (57.9)	19 (63.3)#	10 (33.3)#
Duration of back pain (months), mean ± SD	15.6 ± 8.5	16.0 ± 6.9	15.5 ± 7.6#	11.4 ± 7.3#
HLA-B27 positive, n (%)	6 (54.5)	11 (61.1)	17 (58.6)#	30 (100)#
Pos. fam. history SpA, n (%)	4 (36.4)	5 (26.3)	9 (30.0)#	22 (73.3)#
IBP, n (%)	9 (81.8)	14 (73.7)	23 (76.7)	27 (90.0)
Psoriasis, n (%)	2 (18.2)	2 (10.5)	4 (13.3)	4 (13.3)
Dactylitis, n (%)	0 (0.0)	2 (10.5)	2 (6.7)	1 (3.3)
Enthesitis, n (%)	2 (18.2)	2 (10.5)	4 (13.3)	4 (13.3)
Uveitis, n (%)	1 (9.1)	1 (5.3)	2 (6.7)	7 (23.3)
IBD, n(%)	2 (18.2)	1 (5.3)	3 (10.0)	0 (0.0)
Preceding infection, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
CRP (mg/l), mean ± SD	6.9 ± 7.2	7.6 ± 8.6	7.3 ± 8.0	15.6 ± 18.9
ESR (mm/h), mean ± SD	11.4 ± 13.9	14.2 ± 14.8	13.2 ± 14.3	9.4 ± 14.9
Alternating buttock pain, n (%)	6 (54.5)	5 (26.3)	11 (36.7)	5 (16.7)
Good response to NSAIDs, n (%)	6 (54.5)	10 (52.6)	16 (53.3)	13 (43.3)
Elevated CRP/ESR, n (%)	4 (36.4)	5 (26.3)	9 (30.0)	7 (23.3)
Asymmetric lower limb arthritis, n (%)	0 (0.0)	4 (21.1)	4 (13.3)	4 (13.3)
Sacroiliitis X-ray, n (%)	11 (100)	0 (0.0)	11 (36.7)#	0 (0.0)#
Sacroiliitis MRI, n (%)	6 (60.0)	19 (100)	25 (86.2)#	0 (0.0)#
BASDAI	3.71 ± 1.8	4.01 ±2.5	3.90 ± 2.3	3.92 ± 1.9
ASDAS	2.37 ± 0.7	2.46 ± 0.9	2.43 ± 0.8	4.44 ± 0.9

IBP, Inflammatory Back Pain; IBD, Inflammatory Bowel Disease; age, age at baseline; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, Human Leukocyte Antigen; preceding infection can be balinitis, urethritis, cervicitis and/or acute diarrhea; mNY, modified New York criteria. # represent a statistical significant difference between patients fulfilling the imaging-arm and patients fulfilling the HLA-B27+ arm (p-value <0.05).

Conclusion: Patients with sacroiliitis on X-ray have the same level of disease activity and symptom duration as patients with sacroiliitis on MRI only. Patients fulfilling the HLA-B27+ arm are remarkably similar to patients fulfilling the imaging-arm of the ASAS axSpA criteria, with respect to the presence of most SpA-features and level of disease activity.

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How Useful Is Imaging of the Sacroiliac Joints (MRI and/or X-ray) in Patients with Possible Spondyloarthritis in the Diagnostic Work-up? Rosaline van den Berg, Manouk de Hooge, Victoria Navarro-Compán, Floris van Gaalen, Monique Reijnierse, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: In daily practice, the diagnostic work-up of patients with possible axial spondyloarthritis (axSpA) starts with clinical and laboratory data. In many patients MRI and/or X-rays of the sacroiliac joints (MRI-SIJ and X-SIJ) is performed to be able to diagnose patients with confidence. We investigated the contribution of imaging (MRI-SIJ and X-SIJ) in making a final diagnosis with confidence.

Methods: All patients with chronic back pain (≥3 months, but ≤2 years, onset ≤45 years) in the SPondyloArthritis Caught Early (SPACE)-cohort in our clinic underwent a diagnostic work-up according a fixed protocol. First, medical history, physical examination and laboratory assessments, including HLA-B27 typing, were performed. Based on this information, an experienced rheumatologist diagnosed all patients as either SpA or no-SpA with a level of confidence (scale 0 (not confident at all) to 10 (very confident)). Second, imaging (MRI-SIJ and X-SIJ) was performed and a diagnosis was recorded by the same rheumatologist with a new level of confidence. For the analyses, cut-off values of ≤5 (not confident) and ≥6 (confident) were used.

Results: The results are presented in the table. In 52/157 of the patients (33%), the rheumatologist was confident about the diagnosis, either SpA (n=31) or no-SpA (n=21), based on clinical and laboratory data only. Imaging was positive in 32/157 patients (20.4%). In 3/157 patients (1.9%) the rheumatologist was confident about the diagnosis no-SpA, but revised the diagnosis into confident SpA after imaging. In 9/157 patients (5.7%) the rheumatologist reduced the level of confidence about the diagnosis SpA after imaging was performed, since imaging was negative. In 105/157 of the patients (67%), the rheumatologist was not confident about the diagnosis. After performing imaging, the rheumatologist was confident about the diagnosis in 73/105 patients: SpA in 21/105 (20%) patients and no-SpA in 52/105 (50%) patients. In the remaining 32/105 patients (30%) imaging did not change confidence, nor diagnosis.

	Before imaging	After imaging	MRI pos, n	X-ray pos, n	MRI & X-ray pos, n
Confident n=52	SpA n=31	Conf SpA n=22	5	0	1
		Conf no-SpA n=0	-	-	-
		Not conf SpA n=9	0	0	0
		Not conf no-SpA n=0	-	-	-
	No-SpA n=21	Conf SpA n=3	2	0	1
		Conf no-SpA n=18	0	0	0
		Not conf SpA n=0	-	-	-
		Not conf no-SpA n=0	-	-	-
Not Confident n=105	SpA n=17	Conf SpA n=5	3	0	2
		Conf no-SpA n=1	0	0	0
		Not conf SpA n=11	0	0	0
		Not conf no-SpA n=0	-	-	-
	No-SpA n=88	Conf SpA n=16	9	4	3
		Conf no-SpA n=51	0	0	0
		Not conf SpA n=2	1	0	0
		Not conf no-SpA n=19	0	1	0

Conclusion: Imaging (MRI-SIJ and/or X-SIJ) is useful for the rheumatologist in the large majority of patients with possible axSpA, except for the patients in which the rheumatologist is confident about the diagnosis of SpA before imaging.

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Referral Patterns and Diagnosis of Patients with Axial Spondyloarthritis: Results of an International Survey. Désirée van der Heijde[1], Joachim Sieper[2], Dirk Elewaut[3], Aileen L. Pangan[4] and Dianne Nguyen[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Charité Universitätesmedizin Berlin, Berlin, Germany, [3]Ghent University Hospital, Ghent, Belgium, [4]Abbott Laboratories, Abbott Park, IL, [5]Abbott Laboratories, Singapore, Singapore

Background/Purpose: This analysis compares referral patterns and diagnostic tools for axial spondyloarthritis (axSpA) used by rheumatologists working in academic centers and in community clinical practice settings.

Methods: The MAXIMA (**M**anagement of **Axi**al SpA **I**nternational and **M**ulticentric **A**pproaches) survey asked respondents questions pertaining to referral, diagnosis, and management of patients with axSpA. The survey was completed anonymously online by participants from 42 countries in Europe, Latin America, and North America. The MAXIMA survey was funded by Abbott Laboratories and conducted by a third-party vendor with guidance and approval of the questionnaire by a steering committee of SpA experts. None of the participants were compensated for completing the survey.

Results: 500 surveys were completed by 141 rheumatologists in academic practice settings (28%) and 359 rheumatologists in community practice settings (72%). Only 58% of academic rheumatologists compared to 72% of clinical rheumatologists agreed that the concept of axial SpA is clear to the rheumatology community. However, responses to various questions about referral and diagnostic work-up for patients with axSpA were generally similar in both practice settings (table). The majority of respondents (87%) reported that primary care providers referred patients with chronic back pain for 3 months and onset <45 yrs old; 47% of respondents received referrals from other specialists such as dermatologists, gastroenterologists, and ophthalmologists. Other than chronic and inflammatory back pain, referrals from non-rheumatology specialists were triggered by the occurrence of uveitis (82%), inflammatory bowel disease (48%) and skin lesions (46%). At the time of referral to the rheumatologist, 48% of patients have symptoms for ≥3 yrs. The ASAS criteria (85%) were cited as the most common classification criteria that guide respondents in the diagnosis of axSpA in clinical practice, compared to the modified New York criteria for AS (23%), ESSG (8%), and Amor (6%). In terms of diagnostic work-up, approximately half systematically request HLA-B27 typing. MRI of the sacroiliac joints is the most commonly used imaging test, closely followed by pelvic x-rays.

Table. Response rates in MAXIMA survey regarding SpA referral patterns and diagnosis

	Rheumatology Practice Setting		
Question	Academic Center N=141	Community Clinical Practice N=359	Overall N=500
Patients with back pain ≥3 mo, <45 yrs old			
Source of referrals[a]			
Primary care provider	82	89	87
Physiotherapist	18	30	27
Private office rheumatologist	22	18	19
Other specialist[b]	50	46	47
Duration of symptoms			
<1 yr	9	10	10
1–2 yrs	36	45	42
3–4 yrs	41	30	33
>5 yrs	14	15	15
Triggers of past referrals from other specialists			
Uveitis	81	82	82
Chronic back pain	69	64	65
IBP	38	44	42
Skin lesions	47	45	46
Nail lesions	23	30	28
Inflammatory bowel disease	45	49	48
Diagnosis in daily practice			
Classification guides used for diagnosis of axSpA in practice			
ASAS	92	83	85
Modified New York criteria for AS	21	24	23
ESSG	4	10	8
HLA-B27 typing performed routinely	49	50	49
Imaging tests used			
MRI sacroiliac joint	92	93	93
Pelvic x-ray	88	85	86
Spinal x-ray	71	78	76
MRI spine	56	58	57

[a]Respondents may have indicated >1 source of referrals. [b]Other specialist = dermatologist, gastroenterologist, ophthalmologist. AS, ankylosing spondylitis; ASAS, Assessments in Spondyloarthritis International Society; axSpA, axial spondyloarthritis;; BASDAI, Bath AS Disease Activity Index; ESSG, European Spondylarthropathy Study Group; IBP, inflammatory back pain; mo, months; MRI, magnetic resonance imaging; SpA, spondyloarthritis; yr, year.

Conclusion: Results of the MAXIMA survey show general agreement in referral patterns and use of diagnostic tools by rheumatologists in academic and clinical practice settings when evaluating patients for axSpA. Half of the patients are still being seen by rheumatologists several years after onset of symptoms, which indicates the need for appropriate early referral.

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Assessing Active Inflammation in Sacroiliac Joints in Spondyloarthritis Patients: No Added Value of Gadolinium Compared to Short Tau Inversion Recovery Sequence. Manouk de Hooge, Rosaline van den Berg, Victoria Navarro-Compán, Floris van Gaalen, Désirée van der Heijde, Tom Huizinga and Monique Reijnierse. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: MRI is used as a diagnostic tool to detect active disease of the sacroiliac joint. T1 weighted and STIR images are generally used and ASAS definition is based on bone marrow edema (BME). However, imaging after intravenous administration of gadolinium (Gd) may improve the detection of BME, synovitis, capsulitis and/or enthesitis compared to STIR sequence[1].

The purpose of this study is to investigate the additional value of T1 fatsat after Gd (T1/Gd), compared to T1 and STIR sequence in the detection of active lesions of the SIJ typical for spondyloarthritis (SpA) and to assess its influence on final MRI diagnosis based on the ASAS definition of active sacroiliitis.

Methods: All patients included in the SpondyloArthritis Caught Early (SPACE)-project received MRI of the SIJ (MRI-SIJ). Inclusion criterion for this study was chronic back pain of short duration ≥3 months, ≤2 years, onset ≤45 years). Imaging was performed on 1.5T (Philips, Best, Netherlands). Acquired sequences were coronal oblique T1, STIR and T1/Gd. The parameters evaluated were BME, synovitis and capsulitis/enthesitis. Parameters were scored on STIR as well as T1/Gd sequence and compared in conjunction with unenhanced T1 images. A positive MRI was defined as the presence of BME on the STIR images according to the ASAS definition. Scoring was done by three blinded trained readers. If 2 out 3 readers stated positive, the MRI was considered as such.

Results: In 127 patients that were included a baseline, MRI was obtained and in 67 patients also a follow-up MRI after 3 months was obtained. 22/127 patients (17.3%) were diagnosed with active sacroiliitis according to the ASAS definition based on the STIR sequence. No additional BME was found on the T1/Gd. At baseline, in 7 patients (5.5%) in addition to present BME, synovitis and/or capsulitis/enthesitis were found. All patients with capsulitis also showed synovitis. In 1 patient (0.8%) synovitis was an isolated finding. This patient did not fulfill the ASAS, ESSG, Amor or modified New York classification criteria. These findings did not change at follow up. The patients with a positive MRI, capsulitis or synovitis at follow-up were the same patients who show this signs at baseline (table 1).

	Baseline (n=127)		Follow-up (n=67)	
	STIR	T1/Gd	STIR	T1/Gd
Positive MRI (according to ASAS)	22	22	11	11
Enthesitis/Capsulitis	0	2	0	1
Synovitis	*		*	4

* not estimated with STIR

Conclusion: STIR sequence by itself is sufficient to detect active sacroiliitis according to the ASAS definition. The additional presence of synovitis, capulitis/enthesitis observed with gadolinium, is seen in the presence of BME, except in one patient without clinical SpA. In line with the recommendations by ASAS, our data show that Gd is not needed in the MRI assessment of patients with SpA.

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The Canada-Denmark Fat Spondyloarthritis Spine Score: Validation of a New Scoring Method for the Evaluation of Fat Lesions in the Spine of Patients with Axial Spondyloarthritis. Susanne Juhl Pedersen[1], Zheng Zhao[2], Robert GW Lambert[3], Mikkel Østergaard[1], Ulrich Weber[4] and Walter P. Maksymowych[3]. [1]Glostrup Hospital, Copenhagen, Denmark, [2]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China, [3]University of Alberta, Edmonton, AB, [4]Balgrist University Hospital, Zurich, Switzerland

Background/Purpose: Fat metaplasia has been shown to follow resolution of inflammation in axial SpA and this may be evident within one year (1). Fat metaplasia at vertebral corners has also been shown to predict the development of new syndesmophytes (2). Consequently, the scoring of fat lesions in the spine may constitute both an important measure of treatment efficacy as well as a responsive surrogate for new bone formation. Because of this, we developed and validated a new scoring system for fat lesions in the spine, the CanDen Fat SpA Spine Score (FASSS), which addresses the localization and phenotypic diversity of fat lesions in SpA.

Methods: In 2007, the Canada-Denmark MRI working group developed anatomy-based definitions of fat lesions on T1 weighted sagittal MRI scans of the spine (3). In 2011, further definitions, a reference image module, and an online spinal unit schematic for data entry were developed, which formed the basis for a scoring method. The method comprises six different types of fat lesions defined according to their anatomical location, which are recorded dichotomously (present/absent) at each vertebral endplate from C2 lower to S1 upper (scoring range per disco-vertebral unit in C spine: 0–8, and in T and L spine: 0–18). Two rheumatologists assessed spine MRI scans obtained at two time points (mean 1.5 years (SD 0.5)) in chronological order of 66 patients with axial SpA (exercise 1). Scoring methodology and reference image set were revised based on discrepant cases in exercise 1. Then the two readers re-read 30 randomly selected pairs of MRI scans from the first exercise together with 40 new pairs of MRI scans (exercise 2) (mean 1.7 years (SD: 0.8)) (exercise 2). Inter-observer reliability were assessed by intra-class correlation coefficients (ICCs), and responsiveness as mean change per year by standardized response mean (SRM).

Results: In exercise 2, the change in fat scores ranged from −34 to 52 for reader A and from −38 to 61 for reader B. Inter-observer ICC scores were high to very high for the FASSS baseline scores, and improved substantially in change scores from exercise 1 to 2 (Table). This was particularly notable for the 30 patients evaluated in both exercises. Inter-observer ICCs for baseline scores were high for all spinal segments, and change scores improved from small to moderate (C spine), and from moderate to high (L spine) and very high (T spine). For total FASSS score the mean change/year and SRM were 2.4 and 0.34 for reader A and 3.7 and 0.26 for reader B.

Table. Interobserver ICCs for spinal segments scored according to the CanDen Fat SpA Spine Score (FASSS)

| | Inter-observer ICCs (CI95%) | | | | | |
| | Exercise 1 (n=65) | | Exercise 2 (n=70) | | Exercise 1 (n=30)* | Exercise 2 (n=30)* |
	Baseline ICC (95% CI)	Change ICC (95% CI)	Baseline ICC (95% CI)	Change ICC (95% CI)	Change ICC (95% CI)	Change ICC (95% CI)
C spine	0.76 (0.62;0.85)	0.38 (0.16;0.57)	0.82 (0.72;0.88)	0.49 (0.29;0.65)	0.27 (−0.05;0.56)	0.54 (0.23;0.75)
T spine	0.89 (0.78;0.94)	0.55 (0.32;0.71)	0.88 (0.64;0.95)	0.94 (0.87;0.97)	0.42 (0.08;0.67)	0.70 (0.46;0.85)
L spine	0.77 (0.60;0.87)	0.45 (0.22;0.63)	0.92 (0.88;0.94)	0.74 (0.64;0.82)	0.48 (0.15;0.71)	0.75 (0.48;0.88)
FASSS	0.89 (0.78;0.93)	0.53 (0.21;0.71)	0.95 (0.91;0.97)	0.84 (0.75;0.90)	0.41 (0.02;0.68)	0.64 (0.37;0.81)

*The 30 patients, that were scored two times, were a subgroup of patients in exercise 1 and 2.

Conclusion: The FASSS meets essential validation criteria for further assessment in axial SpA, and may thus be useful for follow-up of SpA in clinical trials and practice.

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Is It Useful to Repeat an MRI of the Sacroiliac Joints in the Diagnostic Work-up for Spondyloarthritis? Rosaline van den Berg, Manouk de Hooge, Victoria Navarro-Compán, Floris van Gaalen, Monique Reijnierse, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: In the diagnostic work-up of spondyloarthritis (SpA), imaging of the sacroiliac joints by MRI (MRI-SIJ) is an important step. One study showed that in HLA-B27+ patients and male patients it might be useful to repeat an MRI-SIJ after one or two years[1]. It is not known if repeating an MRI-SIJ after a shorter period than 1 year is useful. Therefore, we investigated whether it is useful to repeat an MRI-SIJ after 3 months in the diagnostic process for SpA.

Methods: Patients with chronic back pain (n=157) (≥3 months, but ≤2 years, onset <45 years) included in the SPondyloArthritis Caught Early (SPACE)-cohort in the Leiden University Medical Center (LUMC) underwent an MRI-SIJ during baseline visit. All patients with SpA and possible SpA are included for follow-up (n=90) and received a second MRI-SIJ during a follow-up visit after 3 months. All MRI-SIJs of both time points were scored by 3 independent readers 'positive' or 'negative' according to the ASAS definition[2], blinded for the time-sequence. If 2/3 reads were positive, the MRI-SIJ was marked as positive.

Univariate and multivariate regression analyses were performed to investigate which variables (IBP, elevated CRP, MRI-SIJ status at baseline, gender, HLA-B27 status and age at onset) could predict a positive MRI-SIJ at 3 months.

Results: Only patients with complete MRI-SIJ data are included in this analysis (n=90). In the univariate analysis, MRI-SIJ positivity at baseline was the strongest predictor of a positive MRI-SIJ over time (OR 51.0, 95% CI 12.2–212.8, p<0.001). Regardless MRI-SIJ status, gender and HLA-B27-status (OR 7.7, 95% CI 2.6–23.1, p<0.001 and OR 2.6, 95% CI 0.9–7.0, p=0.07, respectively) are strong predictors of a positive MRI-SIJ over time. The latter 2 variables were used in a multivariate model. Groups were made based on this model (table). In the majority of the patients (90%), MRI-SIJ status, either positive (n=15) or negative (n=66), did not change over time. Of the patients with a negative MRI-SIJ at baseline (n=71), 5 (7%) developed a positive MRI-SIJ after 3 months, and in 4/19 (21.1%) lesions on MRI-SIJ disappeared over time. Two out of 5 patients in whom MRI-SIJ was positive for the first time at follow-up fulfilled the ASAS axial SpA criteria only at follow-up.

	Only baseline MRI-SIJ pos, n (%)	Only 3-months MRI-SIJ pos, n (%)	Both baseline and 3-months MRI-SIJ pos, n (%)
HLA-B27- female, n=38	1 (2.6)	1 (2.6)	2 (5.3)
HLA-B27+ female, n=21	0 (0.0)	1 (4.8)	2 (9.5)
HLA-B27- male, n=14	2 (14.3)	1 (7.1)	4 (28.6)
HLA-B27+ male, n=17	1 (5.9)	2 (11.8)	7 (41.2)

Conclusion: We confirmed that a positive MRI-SIJ at baseline is a very strong predictor for a positive MRI-SIJ after 3 months. In patients with a negative MRI-SIJ at baseline, male gender and HLA-B27+ are predictive for a later positive MRI-SIJ.

In this group of patients with short symptom duration, variation in MRI-SIJ positivity occurred in 10% of the patients over a very short period of only 3 months. A positive change of MRI-SIJ has led to a different classification in 2 patients (2.2%). More data are needed to decide if it is necessary to repeat MRI-SIJ, and if so, with what time interval.

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2212

How Much Does the Spondyloarthritis Research Consortium of Canada Score of the Sacroiliac Joints Change Over a 3-Month Period in Patients On Non-Biological Treatment? Rosaline van den Berg, Manouk de Hooge, Victoria Navarro-Compán, Floris van Gaalen, Monique Reijnierse, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The SpondyloArthritis Research Consortium of Canada (SPARCC) score of the sacroiliac joints (SIJ) is often used in clinical trials to detect changes over time. It is important to know if the SPARCC score spontaneously change over time in patients on non-biological treatment. We investigated how much change in the SPARCC score of the SIJ can be detected over a 3-month period in patients on non-biological treatment.

Methods: Ninety patients with chronic back pain (≥3 months, but ≤2 years, onset <45 years) in the SPondyloArthritis Caught Early (SPACE)-cohort underwent a baseline and 3-month follow-up MRI of the SIJ (MRI-SIJ). All MRI-SIJs were scored according to the SPARCC score by 2 independent readers, blinded for time sequence. The mean SPARCC scores (2 readers) were used in this analysis. Delta scores in SPARCC between both time points were calculated. Patients were treated by their rheumatologist, who was unaware of the MRI scores; treatment was recorded.

Results: In 45 (50%) patients (41 patient with a SPARCC score of 0; 2 with a SPARCC score of 1; 2 with a SPARCC score ≥2), the SPARCC score did not change over the period of 3 months. In 18 (20%) patients, the SPARCC score changed 1 point (increased in 10 and decreased in 8 patients). In 27 (30%) patients the SPARCC score changed ≥2 points (13 patients showed an increase and 14 patients a decrease). In the patients that showed a change, the mean (SD) change in score was −0.7 (6.0), the median (range; IQR) change was −1 (−17 to 16; −3 to 1.3).

In the 45 patients without SPARCC score changes, 10 (11%) patients did not use any medication, 16 (18%) patients were on stable non-biological treatment, and 19 (21%) changed treatment (9 patients switched NSAIDs, 5 started NSAID treatment, 4 stopped treatment with NSAIDs, 1 patient started NSAIDs and stopped after 2 months during the follow-up period).

Of all patients (n=45) with SPARCC score changes, 10 (11%) patients did not use any medication, 22 (24%) patients were on stable non-biological treatment, and 13 (14%) patients changed treatment during the 3-month period. Eight of them switched to another NSAID (SPARCC score decreased 1 point in 3 patients, 4 points in 1 patient and 6 points in another patient, and increased 1 and 2 points in the remaining patients). Four patients started treatment with NSAIDs, and SPARCC score decreased in all of them (17 points, 3 points, 2 points and 1 point). One patient stopped NSAID treatment and SPARCC score increased 1 point.

Treatment over the 3-month period (baseline–follow-up)	No SPARCC score change, n=45	SPARCC score change, n=45	
		Decrease, n=22	Increase, n=23
No medication, n=20	10	3*	7*
Stable non-biological treatment, n=38	16	9*	13*
Switch NSAIDs, n=17	9	6*	2*
Start NSAID, n=9	5	4*	–
Stop NSAID, n=5	4	–	1†
Start and stop NSAID, n=1	1	–	–

*Range 1–17 points, †1 point

Conclusion: Over a short period of 3 months, the SPARCC score changed without the start of a TNF-blocker in 45 patients (50%) on non-biological treatment, with a range from −17 to 16 points. The observed changes in SPARCC score do not seem to be influenced by non-biologic treatment. While analyzing results of clinical trials, it is important to keep in mind that a change in SPARCC score in patients on non-biological treatment is possible. This is important information for the power calculation of a trial.

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Ankylosing Spondylitis Is Strongly Related to Clinical Spine Fractures Independently of Drugs Use: A Register-Based Case-Control Study.
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Background/Purpose: Ankylosing Spondylitis (AS) is associated not only with systemic low bone mass, but also with locally increased fragility due to biomechanical changes in the spine. However, data on the impact of AS on clinical spine fracture risk is scarce. We used a large population-based registry from Denmark to investigate the association between AS and fractures, with a particular focus on the spine.

Methods: We carried out a case control study. From the Danish National Health Service Registers, we identified 124,655 fracture cases and 373,962 age- and gender-matched controls. Prevalence of AS in cases and controls

was estimated. Crude odds ratios (OR) and 95% confidence intervals (CI) according to AS status were calculated using conditional logistic regression. We further adjusted the analyses for: 1. use of oral corticosteroids; and 2.use of oral corticosteroids, NSAIDs and strong analgesics. Similar analyses were repeated separately for the spine, hip and forearm fracture cases and corresponding matched controls.

Results: Among 124,655 cases, 139 (0.11%) had a diagnosis of AS, while 271 (0.07%) out of 373,962 controls had AS (crude OR 1.54 [95%CI 1.26–1.89]). Similarly, 18 (0.54%) out of 3,364 spine fracture cases compared to 10 (0.10%) matched controls had AS (crude OR 5.42 [2.50–11.70]). Among 10,530 hip fracture cases 7 (0.07%) AS patients were identified, and 27 (0.09%) of 31,356 controls suffered AS (crude OR 0.78 [0.34–1.78]). Finally, 20,035 forearm fracture cases were screened for AS, and a prevalence of 0.08% (n=16) was found, compared to 0.04% (23) in the controls: unadjusted OR 2.09 [1.10–3.95]. The observed associations remained significant after adjustment for use of oral corticosteroids [see Table]. Conversely, all of them were attenuated when adjusted for use of NSAIDs and strong analgesics but the association between AS and clinical spine fracture (adjusted OR 4.41 [1.90–10.20]).

Table. Results for the association between fracture and AS status (conditional logistic regression).

Skeletal Site	Unadjusted OR (95%CI)	Adjusted for use of oral corticosteroids	Adjusted for use of oral corticosteroids, NSAIDs and strong analgesics
All clinical fractures	1.54 (1.26–1.89)	1.49 (1.22–1.83)	1.12 (0.91–1.38)
Clinical spine	5.42 (2.50–11.7)	5.19 (2.39–11.3)	4.41 (1.90–10.2)
Hip	0.78 (0.34–1.78)	0.76 (0.33–1.76)	0.60 (0.25–1.36)
Forearm	2.09 (1.10–3.95)	2.05 (1.08–3.89)	1.70 (0.89–3.22)

OR = Odds Ratio; 95%CI = 95% Confidence Interval

Conclusion: AS-affected patients are at increased risk for fractures independently of oral corticosteroid use. Clinical spine fractures are the most strongly related to AS, with a multivariate adjusted OR of almost 4.5, independent of use of drugs commonly used for the treatment of AS including oral corticosteroids and NSAIDs. Patients with AS should be fully assessed for fracture risk as part of their clinical management.

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Similar Levels of Disease Activity in Patients with Oligoarticular Vs. Polyarticular Peripheral Spondyloarthritis.
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Background/Purpose: The ASAS criteria for peripheral spondyloarthritis (SpA) allow for classification of patients with SpA who present with peripheral arthritis, enthesitis and/or dactylitis.[1] ABILITY-2, a placebo-controlled trial of adalimumab (ADA) for the treatment of peripheral SpA in patients not previously diagnosed with psoriasis or psoriatic arthritis (PsA), is the first pivotal study to use the ASAS criteria to classify patients for study entry. This analysis characterizes ABILITY-2 patients based on gender and the pattern of joint involvement – oligoarticular vs. polyarticular.

Methods: ABILITY-2 is an ongoing, randomized, controlled multicenter phase 3 study. Eligible patients were age ≥18 yrs, fulfilled ASAS peripheral SpA criteria, did not have a diagnosis of psoriasis, PsA, or ankylosing spondylitis, and had inadequate response or intolerance to NSAIDs. Required baseline disease activity at study entry included patient global assessment of disease activity (PGA) and of pain (PGA-pain) ≥40mm (0–100 mm VAS), ≥2 SJC and TJC, ≥2 digits with dactylitis or enthesitis accompanied by at least 1 joint with active arthritis, or ≥2 sites with enthesitis judged to be severe by the investigator. Subgroup analyses of baseline demographics and disease activity were conducted by gender and by pattern of joint involvement (oligoarticular 2–4 vs. polyarticular >4 joints which are either tender and/or swollen).

Results: Of the 165 patients randomized, 90 (54.5%) were female and 125 (75.8%) had polyarticular disease. Females were slightly older and had a

lower proportion with HLA-B27 positivity, but overall, had similar disease activity parameters as males (table). Predominantly lower limb involvement was observed at baseline in 57% of males, 50% of females, 59% of patients with oligoarticular disease, and 51% of patients with polyarticular disease. More patients with polyarthritis were HLA-B27+ compared to those with oligoarthritis (table). Although fewer polyarticular patients had an abnormal hs-CRP at baseline, the mean hs-CRP and the proportion of patients with accompanying enthesitis and dactylitis were greater in those with polyarticular disease. Otherwise, both patient and physician global assessments, BASDAI, HAQ-S and the physical component score of the SF-36v2 were similar between these 2 subgroups.

Table. Baseline demographics and disease characteristics in subgroups of peripheral SpA patients based on gender and pattern of joint involvement

| | Gender | | Pattern of Joint Involvement | |
Randomized Patients N=165	Male n = 75	Female n = 90	Oligoarticular n = 34	Polyarticular n = 125
Demographics				
Age, years	38.5	42.3	39.6	41.2
Female, %	–	–	55.9	55.2
SpA symptom duration[a], years	6.62	7.67	6.65	7.45
HLA-B27+, %	65.3	58.4	52.9	62.1
Disease Activity				
hs-CRP, mg/L	11.2	9.4	8.3	11.0
hs-CRP abnormal, %	46.7	41.1	52.9	42.4
TJC, 0–78	10.77	15.38	3.00	16.69
SJC, 0–76	6.21	7.11	2.12	8.24
MASES, 0–13	2.51	4.07	1.44	3.89
MASES >0, %	73.3	75.6	52.9	80.0
Leeds enthesitis index, 0–6	1.29	1.59	0.56	1.73
Leeds >0, %	65.3	60.0	44.1	68.0
SPARCC enthesitis index, 0–16	3.53	4.28	1.91	4.54
SPARCC >0, %	81.3	75.6	64.7	81.6
Dactylitis count	0.41	0.57	0.12	0.63
Dactylitis >0, %	20.0	24.7	8.8	27.4
PGA, 0–100 mm	63.71	67.59	63.97	66.50
PGA-pain, 0–100 mm	62.45	67.01	62.47	65.70
PhGA, 0–100 mm	59.29	58.18	56.12	59.72
BASDAI, 0–10	5.21	5.97	5.37	5.72
SF–36v2 PCS	35.65	33.58	36.77	33.88
HAQ-S	0.83	1.11	0.88	1.02

Values are the mean unless otherwise indicated. [a]N=73, 88, 34, 121, respectively. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HAQ-S, Health Assessment Questionnaire modified for Spondyloarthropathies; hs-CRP, high-sensitivity C-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PGA, Patient's Global Assessment of disease activity; PGA-pain, Patient's Global Assessment of pain; PhGA, Physician's Global Assessment; SF-36v2 PCS, Short Form-36 Health Status Survey version 2 physical component summary; SJC, swollen joint count; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC, tender joint count

Conclusion: In non-PsA peripheral SpA patients with inadequate response or intolerance to NSAIDs, similar levels of disease activity as measured by patient and physician global assessments were observed regardless of extent of joint involvement. Likewise, functional impairment was also comparable between patients with oligo- and polyarticular joint disease.

Reference

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Assessment of Vascular Age in Psoriatic Arthritis Patients. Jl Rosales-Alexander. César Magro Checa, Juan Salvatierra, Jesús Cantero Hinojosa and Enrique Raya Álvarez, University Hospital San Cecilio, Granada, Spain

Background/Purpose: The European League Against Rheumatism (EULAR) recommends cardiovascular risk (CV) assessment using the systematic coronary risk evaluation (SCORE) chart in inflammatory arthritis patients. However, the absolute 10 years CV risk is a statistical and epidemiological concept that could be difficult to understand by our patients, resulting in a lack of adherence to treatment. The Framinghan heart study (FHS) incorporated the concept of vascular age, as the age of the arteries, a concept more easily understood by all patients. Recently, a calibrated vascular age chart (VAC) according to the SCORE scales was published for european people.

Objective: To assess vascular age (VA) in psoriatic arthritis (APs) patients without CV risk factors/ previous ischemic events using the VAC comparing it with healthy controls. To assess the correlation of several clinical and serological variables with VA in APs patients.

Methods: We included 80 consecutive APs patients, according to the CASPAR criteria without CV risk factors neither previous ischemic events and matched to 80 healthy controls according to sex, age and gender. We recorded demographic data, clinical and laboratory parameters of disease activity like ESR, CRP, tender and swollen joint counts, DAS28, patient global assessment by visual analogue scale, lipid profile and APs characteristics. We assessed VA using the VAC. Data was analyzed with the statistical software SPSS 15. Descriptive data were shown as percentages and mean±SD. To analyze data, we use simple lineal regression test with correlation and the multiple lineal regression analysis. The limit of statistical significance was located in the α error of 0,05.

Results: In APs patients, the median chronologic age (CA) was 47,8±12,4 years, VA was 52,48±12,82, disease duration was 11,09±7,8 and absolute CV risk was 1,99±3,5. Of these patients, 50% were female, 64% had axial and peripheral involvement and 37,5% was HLA-B27 positive. In controls, CA was 47,4±12,2, VA was 49,67±12,67 and absolute CV risk was 1,01±1,7. After applying lineal regression test, VA was correlated with CA (beta 0.973, p=0.000); and there were differences in VA between both groups (beta −2,46, p=0,000). Of interest, after adjusting for confounding factors, VA in APs seem to be correlated with time of disease (p=0,003) and with highest values on the score chart (p=0,000).

Conclusion: In our study, we found that APs patients without CV risk factors had higher VA than healthy controls. Also, we found a good correlation between VA and CA. Time of disease and highest values on the SCORE CV risk chart seem to predict higher VA in APs patients.

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Cardiovascular Risk Assessment in Spondyloarthritis Using the Score Chart and Reclassification by Presence of Plaques On Ultrasonography. Jl Rosales-Alexander, Juan Salvatierra, César Magro Checa, Jesús Cantero Hinojosa and Enrique Raya Álvarez. University Hospital San Cecilio, Granada, Spain

Background/Purpose: Increased cardiovascular (CV) risk have been described in patients with rheumatic diseases including spondyloarthritis (SpA). Besides traditional CV risk factors, disease specific factors have been suggested as possible etiologic factors for atherosclerosis. Increased carotid Intima-media thickness (IMT) has been found to be increased in rheumatic diseases. In RA and other inflammatory arthritis, EULAR recommends annual CV risk assessment according to national guidelines, but there is not a calibrated SCORE chart for SpA patients.

Objectives: To asses CV risk in SpA patients using the SCORE chart calibrated for Spain (SCOREm) and to determine the percentage of patients reclassified according to the presence of plaques by the use of common carotid artery (CCA) ultrasonography (US). To analyse the factors that predict a higher global CV risk.

Methods: All patients with SpA, fulfilling the "Assessment of SpondyloArthritis international Society" (ASAS) classification criteria, without previous ischemic events were prospectively included in a database, containing demographic and clinical information. For the study, 90 living Spanish patients were selected. Classic CV risk factors, acute phase reactants (APR), disease activity indexes and lipid profile were obtained. CV risk was calculated using the SCOREm and the presence of plaques – measure of the CCA IMT was evaluated by B-doppler US. Chi-square or McNemar's tests were used to assess differences between qualitative variables, and ANOVA with Bonferroni adjustment for comparing means. Factors predicting higher global CV risk were evaluated by multivariate lineal regression analysis.

Results: Most patients (54%) were men, 77% were HLA-B27 positive. Mean age was 46,32±14,4 years and mean disease duration was 8,8±6,8 years. Mean SCOREm was 1,3±2,7. Low CV risk was found in 64(71%) patients, intermediate, high and very high risk in 23(25,7%), 2 (2,2%) and 1(1,1%) patients respectively. After CCA US was performed, plaques were found in 10/90(11,1 %) patients. Of these, reclassification to high risk was done in 3 and 5 patients with low and intermediate risk respectively (p<0,001). Mean IMT was 0,61±0,11 mm. Higher global CV risk was predicted by hypertension (β 3,66; p=0,00), dyslipidemia (β −1,77; p=0,016), time of disease (β 0,075; p=0,040) and HLA-B7 positivity (β −1,82; p=0,002).

Conclusion: In our study most SpA patients have low and intermediate CV risk using the SCOREm chart, but after performing CCA US 8(8,9%) patients were reclassified into high risk by the presence of plaques. Besides classic CV risk factors, some disease characteristics might contribute to the expression of higher global CV risk in these patients.

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Even After Pretreatment with up to Three Biologics, Anti-TNFs Shows Effectiveness in Active Psoriatic Arthritis Patients. Frank Behrens[1], Michaela Koehm[1], Diamant Thaci[2], Brigitte Krummel-Lorenz[3], Gerd Greger[4], Bianca Wittig[4] and Harald Burkhardt[5]. [1]CIRI/Div. Rheumatologie, J.W. Goethe-University, Frankfurt/Main, Germany, [2]Klinik für Dermatologie, Venerologie und Allergologie, J.W. Goethe University, Frankfurt/Main, Germany, [3]CIRI/Endokrinologikum, Frankfurt/Main, Germany, [4]Abbott GmbH & Co KG, Wiesbaden, Germany, [5]CIRI/Div. Rheumatology, J.W. Goethe University, Frankfurt/Main, Germany

Background/Purpose: For the treatment of patients with psoriatic arthritis (PsA) only antiTNF biologics are licensed. Therefore, failures to anti-TNF are often switched to a different antiTNF treatment, despite the fact that only little evidence of effectiveness is available for anti TNF switch.

Methods: A multicentre, prospective observational study included patients (n=3320) with moderate to severe PsA treated with Adalimumab (ADA). Treatment response of ADA therapy when used as first-, second- or third/fourth line antiTNF-therapy regimen in patients with active psoriatic arthritis in clinical routine care in Germany was measured. Besides documentation of demographic data, disease activity assessments such as number of swollen (SJC) and tender joints (TJC), disease activity score 28 (DAS28), enthesitis, dactylitis as well as target lesion score (TLS) and body surface area (BSA) for skin involvement were calculated at baseline, month 3, 6, 12 and 24.

Results: Treatment with ADA is effective in patients with active PsA. The reduction of disease activity is clinical meaningful independently from the number of previous used antiTNF agents (0, 1, ≥ 2). The swollen joint count (SJC) was reduced from 8.7 at baseline to 1.4 after 24 months (TNFnaive). A comparable reduction was seen in patients pretreated with one (7.7 to 2.8) or two and more (8.5 to 1.9) antiTNF agents.

A higher reduction in DAS28 was seen in the group of biologic naive patients (−2.22) than in those with pretreatment of at least one TNF (−1.79). This leads to a mean DAS after two years of treatment with ADA near to remission (DAS28 2.62) while those switching to ADA from another TNF achieved a mean DAS of 2.89 (failed one antiTNF) and 3.12 (failed two or more antiTNF) respectively. Comparable reduction of percentages of patients with dactylitis was seen in all groups while enthesitis responses better in TNF naïve versus those who faile one or more antiTNF. Additionally, skin response in all groups was comparable measured by reduction in TLS.

Conclusion: ADA treatment is effective in patients with active PsA on all facets of the disease (arthritis, enthesitis, dactylitis and skin involvement). A switch from another antiTNF results in a meaningful reduction of disease activity. In contrast to rheumatoid arthritis in which previous antiTNF use leads to a significant decrease of response, in PsA the reduction in SJC is independent from a pretreatment with antiTNF agents. Nevertheless, the mean DAS after two years of treatment was significant lower in antiTNF naive patients than in those with up to 3 previous biologics.

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5 Year Safety, Efficacy, and Radiographic Data in Patients with Active Psoriatic Arthritis Treated with Golimumab: Results From the Long-Term Extension of a Randomized, Placebo-Controlled Study. Arthur Kavanaugh[1], Desiree van der Heijde[2], Iain B. McInnes[3], Philip Mease[4], Gerald G. Krueger[5], Dafna Gladman[6], Yiying Zhou[7], J. D. Lu[7], Zhenhua Xu[7], Lenore Noonan[7] and Anna Beutler[7]. [1]UCSD School of Medicine, La Jolla, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University of Glasgow, Glasgow, United Kingdom, [4]Swedish Medical Center, Seattle, WA, [5]University of Utah, Salt Lake City, UT, [6]Toronto Western Hospital and University of Toronto, Toronto, ON, [7]Janssen Research & Development, LLC, Spring House, PA

Background/Purpose: GO-REVEAL is the first study evaluating outcomes of anti-TNF tx in active PsA through 5 years. Safety and efficacy, including radiographic progression in golimumab (GLM) tx'd patients (pts) from the long-term extension of GO-REVEAL is presented.

Methods: 405 adult PsA pts (≥3 swollen, ≥3 tender joints) were randomized to SC injections of placebo (PBO, Grp1, n=113), GLM50mg (Grp2, n=146), or GLM100mg (Grp3, n=146) q4wks through wk20. Concomitant MTX at baseline was allowed but not required. Starting at wk16, PBO pts with <10% improvement in swollen and tender joints received GLM50mg, remaining PBO pts received GLM50mg starting at wk24; all pts received GLM from wk24 forward. After wk52, pts could change the dose from GLM50 mg to 100mg based on investigator judgment. The last GLM injection was at wk 252. Efficacy was assessed at wk 256 based on randomized grp and completer analyses using ACR response criteria, DAS28-CRP, PASI, HAQ, enthesitis, dactylitis, NAPSI scores, and the PsA-modified Sharp/van der Heijde Score (SHS). Safety evaluations included all pts who received at least one GLM dose through 5 years.

Results: Of 405 randomized,335 continued in the study at wk104, and 279 pts (69%) continued GLM tx through wk252. 29% of Grp2 pts dose escalated to GLM100mg; 25% of Grp3 pts decreased the dose from 100mg to 50mg. Baseline characteristics of pts who continued in the study at Wk 104 are provided in Table 1. Efficacy results are presented in Table 2. ACR and PASI responses were similar in pts tx'd with or without MTX; changes from baseline in SHS scores were minimal and numerically less in pts tx'd with GLM and MTX compared with GLM alone. Overall, 88%, and 21% GLM tx'd pts experienced AE and SAE, resp. 12% of pts discontinued GLM tx due to AE, and 5% and 4% pts experienced malignancy (including NMSC), and serious infection, resp. Antibodies to golimumab were detected in 6% of pts.

Table 1. Mean (SD) baseline characteristics

	Group 1[a]	Group 2[b]	Group 3[c]
No. of pts continued in the study at wk104	88	118	129
DAS28 score	5.0 (0.1)	4.9 (1.1)	4.8 (1.0)
PASI (in pts with ≥3%BSA)	7.7 (5.7)	9.4 (7.6)	11.2 (9.6)
HAQ-DI score (0–3)	1.1 (0.5)	1.0 (0.6)	1.1 (0.6)
Enthesitis score (0–15)	5.1 (4.0)	5.6 (3.8)	5.8 (4.1)
Dactylitis score (0–60)	2.9 (2.0)	6.8 (6.5)	5.5 (6.9)
Total SHS (0–528)	19.4 (30.2)	26.2 (36.9)	23.3 (36.7)

Table 2. Clinical and radiographic efficacy at wk 256

	Group 1[a]	Group 2[b]	Group 3[c]
No. of pts continued in the study at wk256	77	95	109
Clinical efficacy			
ACR20 (% of pts)	77.9%	76.8%	78.0%
ACR50 (% of pts)	49.4%	58.9%	56.9%
ACR70 (% of pts)	36.4%	41.1%	39.4%
DAS28-CR response (% of pts)	91.9%	94.5%	91.3%
Mean (SD) improvement in HAQ-DI	0.5 (0.6)	0.5 (0.5)	0.5 (0.6)
PASI75 (in pts with ≥3%BSA) (% of pts)	72.7%	68.6%	78.5%
Mean % improvement in enthesitis score	68.3%	73.7%	72.4%
Mean % improvement in dactylitis score	74.7%	85.8%	72.0%
Mean % improvement in NAPSI score	79.2%	75.9%	76.5%
Radiographic progression			
Estimated annual rate of progression at baseline (mean total SHS/mean PsA disease duration)	2.1	3.1	2.5
Mean annual rate of progression (change from baseline in total SHS/5yrs)	0.06	0.06	0.01
Mean (SD) change from baseline in total SHS	0.3 (3.8)	0.3 (4.1)	0.1 (2.7)

[a]Includes pts randomized to PBO who switched to GLM at wk16 or 24; after wk 52 pts could receive GLM50mg or 100mg.
[b] Includes pts randomized to GLM50 mg; after wk 52 pts could receive GLM50 mg or 100mg.
[c] Includes pts randomized to GLM100 mg; after wk 52 pts could receive GLM100mg or 50mg.

Conclusion: Pt attrition through 5yrs of GLM tx was low. GLM tx resulted in long-term maintenance of clinically meaningful responses in the arthritic and skin components of PsA, improved physical function, and arrest of radiographic progression. No apparent differences between long-term safety and efficacy of 2 GLM doses administered q4wks were observed, however the interpretation of the data is limited due the tx changes allowed across randomized grps.

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Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis Show Similar Response Rates After One Year of Treatment with Etanercept - results of the Esther Trial.

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Background/Purpose: In patients with early axial spondyloarthritis (SpA) with a disease duration < 5 years we assessed whether there is a difference to etanercept (ETA) treatment in patients with ankylosing spondylitis (AS) compared to non-radiographic axial SpA (nr-axSpA).

Methods: AS (n= 34) and nr-axSpA (n= 32) patients who were treated with ETA for one year were compared for differences in baseline data and treatment effect [1, 2]. Clinical, laboratory and magnetic resonance imaging of sacroiliac joints (SI-joints) and spine were analysed.

Results: At baseline there were no significant differences between the 34 AS and the 32 nr-axSpA patients regarding age (34.4 ($\pm$ 7.7) vs. 33.5 ($\pm$ 9.2) years), disease duration (4.0 ($\pm$ 2.2) vs. 3.1 ($\pm$ 1.8), male gender (55.9% vs. 56.3%), clinical disease activity in terms of BASDAI (5.0 ($\pm$2.0) vs. 5.4 ($\pm$ 1.5), CRP (7.7 ($\pm$ 8.7) vs. 11.2 ($\pm$ 13.7)), HLA-B27 (91.2% vs. 75.0%) and MRI SI-joint (6.7 ($\pm$ 6.2) vs. 5.1 ($\pm$ 5.4)) and spine scores (2.5 ($\pm$ 3.6) vs. 1.1 ($\pm$ 2.1)) in the AS compared to the nr-ax SpA group. After one year of treatment with ETA the treatment effect was similarly good in AS and nr-ax SpA (reduction of BASDAI by 2.1 (95% CI 1.5– 2.7) vs. 2.4 (95% CI 1.8– 2.9) and reduction of ASDAS by 1.3 (95% CI 1.0– 1.5) vs. 1.2 (95% CI 0.9– 1.5), respectively).

Table 1. Comparison of Efficacy Parameters between patients with AS and nr-ax SpA after one year of treatment with etanercept

Parameter	ETA, AS, (n= 34)	ETA, nr-ax SpA (n= 32)
BASDAI50, % (95% CI)	59.4 (42.0–76.3)	74.2 (56.9–87.4)
ASAS40, % (95% CI)	68.8 (50.0–83.9)	67.7 (50.0–83.3)
ASAS partial remission, % (95% CI)	28.7% (19.4–42.5%)	37.9% (27.7–51.8%)
ASAS major improvement, % (95% CI)	24.1 (10.3–42.3)	25.0 (10.7–44.1)
ASDAS inactive disease (< 1.3), % (95% CI)	27.6% (18.7–40.5%)	27.3% (18.9%–39.4%)
Change in BASDAI (95% CI)	2.1 (1.5–2.7)	2.4 (1.8–2.9)
Change in ASDAS (95% CI)	1.3 (1.0–1.5)	1.2 (0.9–1.5)
Change CRP (95% CI)	5.0 (2.3–7.6)	4.6 (1.9–7.3)
Change MRI SI-joint score (95% CI)	3.7 (3.0–4.4)	4.3 (3.6–5.0)
Change MRI spine score (95% CI)	1.1 (0.6–1.7)	0.9 (0.3–1.5)

Conclusion: The response rate to TNF-blockers does not differ between AS and nr-ax SpA if the baseline data regarding symptom duration and disease activity are similar for the two groups.

[1] Song I.-H. et al. Ann Rheum Dis. 2011;70(7):1257–63.
[2] Song I.-H. et al. Ann Rheum Dis. 2012 Jul;71(7):1212–5.

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Development of the Pulsar (Program to Understand the Longterm Outcomes in Spondyloarthritis) Registry.

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Background/Purpose: The spondyloarthritides are a group of conditions characterized by inflammation in the axial skeleton or peripheral joints. The arthritis may present as the primary manifestation (e.g. ankylosing spondylitis, reactive arthritis), or a related condition may predominate (inflammatory bowel disease (IBD), uveitis, or cutaneous psoriasis). To better characterize the clinical and pathophysiologic aspects of these diseases, a registry for veterans with spondyloarthritis and related conditions was initiated in 2007.

Methods: A set of electronic medical record templates was developed for standardizing collection of clinical information at outpatient visits for spondyloarthritis patients. Internal Review Board (IRB) approval for the PULSAR registry was obtained at 7 VA sites (Albany, NY, Dallas, TX, Denver, CO, Jackson, MS, Phoenix, AZ, Salt Lake City, UT, Washington, DC). Data collected includes demographics (age, gender, race/ethnicity, education, smoking status, comorbidities) and disease-specific features (disease classification, disease activity measures (BASDAI, BASFI, pain and global assessments, psoriasis area and global assessments), medications, laboratory and imaging results, and HLA-B27 status). Each patient's DNA, RNA, serum, and plasma are stored in a biorepository.

Results: The PULSAR registry has enrolled 513 patients, whose diagnoses are psoriatic arthritis (29.2%), ankylosing spondylitis (20.7%), reactive arthritis (6.2%), anterior uveitis (5.5%), and IBD-related arthritis (3.7%). Patients without arthritis but with IBD or cutaneous psoriasis make up the rest of the registry and are available as controls. To date, 3677 clinic visits have been recorded, representing 2246 patient years of observation. Patients are 92% male, with mean age of 58.5 years and 13 or more years of schooling in 61.7% of the cohort. Current tobacco use is present in 24% while 62% are former smokers. Of 275 patients tested to date, 58.5% are HLA-B27 positive. The most common comorbidities are hypertension, hyperlipidemia, osteoarthritis, diabetes, and obesity. Forty percent are currently on biologic medication, 39% take an analgesic or NSAID, 36% are on a traditional DMARD, and 29% take an osteoporosis medication. The five most commonly used medications are adalimumab, methotrexate, etanercept, hydrocodone, and ibuprofen (Table).

Medication Use

Current		Ever	
Adalimumab	17%	Methotrexate	28%
Methotrexate	16%	Etanercept	25%
Etanercept	15%	Adalimumab	23%
Hydrocodone	15%	Etodolac	21%
Ibuprofen	11%	Hydrocodone	20%
Tramadol	11%	Acetaminophen	18%
Etodolac	10%	Ibuprofen	17%
Acetaminophen	10%	Sulfasalazine	16%
Sulfasalazine	9%	Tramadol	15%
Infliximab	8%	Infliximab	14%

Conclusion: The PULSAR registry is a growing resource for study of spondyloarthritis and related conditions. Anti-TNFa medications are the most commonly prescribed drugs in the registry. Standardized multi-site data collection allows for improved disease characterization and assessment of

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disease activity. As most participants receive all their medical care in the VA system, a particular strength of PULSAR is the comprehensive acquisition of pharmacy and comorbidity data.

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Major Adverse Cardiovascular Events Are More Common in Rheumatoid Arthritis Than in Psoriatic Arthritis and Are Associated with Different Risk Factors. Allen P. Anandarajah[1], Katherine C. Saunders[2], George W. Reed[3], Alina U. Onofrei[4], Jeffrey D. Greenberg[5] and Christopher T. Ritchlin[6]. [1]Univ of Rochester Medical Ctr, Rochester, NY, [2]CORRONA, Inc., Southborough, MA, [3]University of Massachusetts Medical School, Worcester, MA, [4]UMass Medical School, Worcester, MA, [5]NYU Hospital for Joint Diseases, New York, NY, [6]University of Rochester Medical Center, Rochester, NY

Background/Purpose: Rheumatoid Arthritis (RA) is associated with increased cardiovascular mortality and morbidity rates. Similarly several studies have reported an increased risk for cardiovascular events in patients with psoriasis. There, however, are few studies that have reported on the risk factors for major adverse cardiovascular events (MACE) in patients with psoriatic arthritis (PsA). Furthermore, no studies have compared the risk for MACE in PsA patients with RA patients.

Objective: To determine if the prevalence and risk factors for MACE in PsA patients and compare with prevalence and risk factors for MACE in RA patients.

Methods: All patients with RA and PsA with at least one follow up visit were identified from the Consortium of Rheumatology Researchers of North America (CORRONA) database. The incident rates (IR) for MACE per 100 person years of follow up were estimated. MACE was defined as myocardial infarction, stroke/transient ischemic attacks and death secondary to cardiovascular events. Follow up time was counted from enrollment in CORRONA to the first reported event or the last follow up. Cox regression models estimated the association of the following covariates with MACE rates: age, gender, body mass index (BMI), physician global assessment of disease activity (PGDA), disease duration, bone erosion status, disease modifying anti-rheumatic drugs, steroids, aspirin, smoking, diabetes, and hypertension.

Results: A total of 25,700 RA patients (81,104 person years of follow-up) and 3,909 PsA patients (11,828 person years of follow-up) were identified. Patients with RA were older, had a lower BMI, higher MD global assessment scores, longer disease duration, were less likely to have diabetes and less likely to be on biologic therapies but more likely to be on DMARDs or steroids than PsA patients. The percentage of previous and current smokers was similar between RA and PsA patients. The unadjusted IR for MACE events in RA and PsA patients were 0.65 (95% CI: 0.60–0.71) and 0.35 (CI: 0.25–0.47) respectively. The unadjusted IR for MACE events was higher in RA patients with erosions (0.71, 0.61–0.81) compared with those without erosions (0.53, 0.45–0.63) but in PsA patients the IR was slightly higher in those without erosions (0.33, 0.19–0.55) than in those with erosions (0.25, 0.10–0.51). Age, gender, history of hypertension, disease duration, steroids, diabetes and PGDA were identified as significant risk factors for MACE in the RA population. In contrast, in PsA patients, age, hypertension, gender and PGDA were the only risk factors.

Table 1. Hazard Ratios (HR) from Multivariate Cox Regression Models in RA and PsA patients

	HR for risk of MACE events	
	RA patients	**PsA patients**
Female	0.55 [0.46, 0.67]	0.41 [0.21, 0.80]
Age	1	1
<50	2.16 [1.46, 3.19]	3.32 [1.05, 10.51]
50–60	3.52 [2.41, 5.15]	8.61 [2.76, 26.91]
60–70	7.07 [4.85, 10.30]	8.75 [2.46, 31.05]
≥70		
Smoking status	1	1
Never	1.19 [0.95, 1.48]	1.74 [0.85, 3.56]
Previous	2.28 [1.81, 2.86]	2.55 [1.06, 6.11]
Current		
History of Hypertension	1.39 [1.16, 1.67]	2.08 [1.07, 4.03]
MD global assessment (risk per unit change)	1.006 [1.002, 1.010]	1.018 [1.003, 1.033]
History of diabetes	1.59 [1.22, 2.07]	1.08 [0.46, 2.51]
Duration of disease (risk per yr)	1.016 [1.008, 1.024]	
Steroid use	1.55 [1.30, 1.86]	

Conclusion: Unadjusted MACE events are more common in RA than in PsA. Only age, gender, hypertension, and PGDA were common risk factors

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Spinal Mobility Measures in Normal Individuals – the Mobility Study. Sofia Ramiro[1], Carmen Stolwijk[2], A.M. Van Tubergen[2], Désirée van der Heijde[3] and Robert Landewé[4]. [1]Academic Medical Center, University of Amsterdam, The Netherlands and Hospital Garcia de Orta, Almada, Portugal, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Academic Medical Center, University of Amsterdam and Atrium Medical Center, Heerlen, Netherlands

Background/Purpose: Spinal mobility is one of the core outcomes recommended by the Assessment of Spondyloarthritis international Society (ASAS) for following patients with axial SpA. It is currently unknown how these spinal mobility measures perform in healthy subjects and to what extent they are influenced by age, gender and height. We aimed to assess the effect of age, gender and height on spinal mobility measures among healthy individuals.

Methods: A cross-sectional study ("MOBILITY-study") was conducted in healthy volunteers aged 20–69 years old. Recruitment was stratified by gender, age (10-year categories) and height (10cm categories). Participants were Caucasians volunteering to be measured in the Netherlands and Portugal. Exclusion criteria were factors potentially influencing spinal mobility (such as previous back surgery, known spinal osteoarthritis or low back pain). The following measures were assessed: tragus-to-wall distance (TTW, cm), occiput-to-wall distance (OTW, cm), lateral spinal flexion (LSF, cm), cervical rotation (CR, degrees), intermalleolar distance (IMD, cm), chest expansion (CE, cm) and Schober's test. The Bath Ankylosing Spondylitis Mobility Index (BASMI) was computed. The effects of age, gender, height and weight were investigated using linear regression analyses (univariable followed by multivariable, forward selection procedure), adjusting for potential confounders and taking relevant interactions into account.

Results: 393 volunteers were included. A significant decrease in all spinal mobility measures was found by increasing age, and age was included in all multivariable models (some of the models are presented in the table). E.g. an increase of 10 years was associated with a decrease of 1.5cm in LSF or a decrease of 3.4cm in IMD. Height was associated with the following spinal mobility measures: TTW, LSF, CE, IMD and BASMI, with a higher height being associated with better mobility. E.g. every increase in height of 10cm resulted in an increase of 4.2cm in IMD, an increase of 0.3cm in LSF and an increase of 1.1cm in CE. Gender was associated with CE and CR, with women having a worse mobility. Weight was positively associated with TTW, OTW and Schober's test: An increase of 10kg resulted in an increase of 0.3cm in TTW, 0.2cm in OTW and 0.2cm in Schober's test. There was a significant interaction between the effects of age and gender on BASMI: in women, age was the only factor with a significant effect on BASMI (β 0.03, 95%CI 0.03; 0.04). In men, age (β 0.03, 95%CI 0.02; 0.04), and weight (β −0.01, 95%CI −0.01; −0.00) significantly contributed to BASMI.

Table. Effect of age, gender, height and weight on spinal mobility measures

Measure	Univariable linear regression β (95% CI)	Multivariable linear regression β (95% CI)
Lateral spinal flexion (cm)		
Age (years)	−0.15 (−0.17; −0.13)	−0.15 (−0.17; −0.13)
Gender (female vs male)	−0.50 (−1.23; 0.23)	
Height (cm)	0.03 (0.00; 0.06)	0.03 (0.00; 0.07)
Weight (kg)	−0.01 (−0.04; 0.01)	−0.01 (−0.04; 0.02)
Intermalleolar distance (cm)		
Age (years)	−0.46 (−0.42; −0.27)	−0.44 (−0.53; −0.36)
Gender (female vs male)	−1.05 (−3.92; 1.83)	
Height (cm)	0.44 (0.33; 0.55)	0.42 (0.33; 0.52)
Weight (kg)	0.14 (0.05; 0.23)	
Cervical rotation (degrees)		
Age (years)	−0.35 (−0.42; −0.27)	−0.34 (−0.42; −0.27)
Gender (female vs male)	−4.13 (−6.43; −1.82)	−3.83 (−5.89; −1.77)
Height (cm)	0.12 (0.03; 0.21)	
Weight (kg)	−0.03 (−0.10; 0.04)	
BASMI (0−10)		
Age (years)	0.03 (0.03; 0.04)	Significant interaction age X gender (see text)
Gender (female vs male)	0.21 (0.05; 0.38)	
Height (cm)	−0.01 (−0.02; −0.00)	
Weight (kg)	−0.00 (−0.01; 0.00)	

Conclusion: All spinal mobility measures decrease with increasing age. Height significantly influences some spinal mobility measures, especially IMD and LSF. These factors have to be taken into account when assessing patients' spinal mobility, and should be included in reference values for these measurements.

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Dysregulation of Chromatin Modification Enzymes in Psoriatic Arthritis. Remy Pollock, Fawnda Pellett, Vinod Chandran and Dafna Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Chromatin modification enzymes regulate gene expression by altering the accessibility of promoters to transcription factors. Several of these enzymes are dysregulated in rheumatoid arthritis, suggesting a role for epigenetic factors in inflammatory arthritis. We sought to determine whether they are dysregulated in psoriatic arthritis (PsA), a seronegative inflammatory arthritis that develops in 30% of patients with cutaneous psoriasis (PsC).

Methods: Total RNA was isolated from peripheral blood of psoriatic disease (PsD) patients (PsA & PsC) and controls. Quantitative RT-PCR arrays were used to profile mRNA expression of 84 genes encoding DNA and histone modification enzymes. Significant fold changes were calculated using the ΔΔCt method and Student's t-test. Univariate regressions were performed to examine correlations between gene expression (ΔCt) and clinical data.

Results: Gene expression profiling was performed on 20 PsA patients satisfying CASPAR criteria (mean age 48 years, males 45%, age at psoriasis 25 years, age at PsA 32 years, PASI 5.0, active joint count 11, axial disease 35%, treated with methotrexate 35% and prednisone 25%), 18 PsC patients (mean age 45 years, males 50%, age at psoriasis 25 years, PASI 5.2), and 19 controls (mean age 43 years, males 53%). Significantly dysregulated genes (fold change >1.5 or <0.68, p<0.05) are summarized in Table 1. Two genes were significantly dysregulated in PsD vs. controls. In PsC vs. controls, no genes were significantly dysregulated >1.5 or <0.68-fold, but 6 genes were dysregulated >1.2 or <0.84-fold. Eleven genes were significantly dysregulated in PsA vs. controls: HAT1, RPS6KA3, AURKC, HDAC11 (upregulated), and ASH1L, KDM6B, EHMT2, SETD1A, MLL, HDAC9, MLL3 (downregulated). In PsA vs. PsC, 3 genes were significantly dysregulated: HAT1, PRMT8, and HDAC11. In PsA patients, SETD1A expression was positively correlated with methotrexate therapy (p=0.008, r=0.58) but negatively correlated with prednisone therapy (p=0.038, r=−0.47), active joint count (p=0.017, r=−0.53), and axial disease (p=0.014, r=−0.54).

Table 1. Significantly dysregulated genes (p<0.05, fold change >1.5 or <0.68).

Comparison	Gene	Description	Fold Change	95% CI	P-value
PsD vs. Controls	HAT1	Histone acetyltransferase 1	1.54	(1.03, 2.04)	0.017
	RPS6KA3	Ribosomal protein S6 kinase, 90kDa, polypeptide 3	1.50	(1.15, 1.81)	0.002
PsC vs. Controls†	AURKC	Aurora kinase C	1.39	(0.81, 1.97)	0.049
	HDAC11	Histone deacetylase 11	1.30	(0.78, 1.82)	0.022
	UBE2A	Ubiquitin-conjugating enzyme E2A	1.24	(1.01, 1.47)	0.041
	ASH1L	Ash1 (absent, small, or homeotic)-like	0.84	(0.67, 1.01)	0.022
	SETD1A	SET domain containing 1A	0.83	(0.66, 0.99)	0.035
	MLL3	Myeloid/lymphoid or mixed-lineage leukemia 3	0.82	(0.64, 0.99)	0.034
PsA vs. Controls	HAT1	Histone acetyltransferase 1	2.13	(1.38, 2.89)	1.0E-04
	RPS6KA3	Ribosomal protein S6 kinase, 90kDa, polypeptide 3	1.65	(1.24, 2.07)	3.0E-04
	ESCO1	Establishment of cohesion 1 homolog 1	1.56	(1.17, 1.94)	0.001
	USP16	Ubiquitin specific peptidase 16	1.54	(1.20, 1.89)	2.0E-04
	ASH1L	Ash1 (absent, small, or homeotic)-like	0.68	(0.52, 0.85)	0.001
	KDM6B	Lysine (K)-specific demethylase 6B	0.68	(0.49, 0.86)	0.011
	EHMT2	Euchromatic histone-lysine N-methyltransferase 2	0.68	(0.54, 0.82)	0.001
	SETD1A	SET domain containing 1A	0.63	(0.51, 0.76)	4.2E-05
	MLL	Myeloid/lymphoid or mixed-lineage leukemia	0.62	(0.46, 0.79)	0.001
	HDAC9	Histone deacetylase 9	0.61	(0.31, 0.91)	0.018
	MLL3	Myeloid/lymphoid or mixed-lineage leukemia 3	0.61	(0.47, 0.74)	6.8E-05
PsA vs. PsC	HAT1	Histone acetyltransferase 1	2.00	(1.39, 2.61)	1.0E-04
	PRMT8	Protein arginine methyltransferase 8	1.57	(1.21, 1.93)	3.0E-4
	HDAC11	Histone deacetylase 11	0.62	(0.31, 0.94)	0.017

† Fold change > 1.2 or < 0.83.

Conclusion: We identified several dysregulated chromatin modification enzymes in psoriatic disease, including histone methyltransferase complex component SETD1A which was downregulated in PsA and correlated with disease expression and therapy. SETD1A is located in a PsA susceptibility region on 16p11.2 that harbors genes involved in IL-23/IL-17/NF-κB signaling. HDAC11, a histone deacetylase involved in inflammation by influencing immune activation versus tolerance was downregulated in PsA compared with PsC. Future studies will seek to validate these results, examine the role of these enzymes in the epigenetic basis of PsA, and determine whether they can serve as biomarkers of PsA susceptibility and disease expression.

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Oral Contraceptive Pill Use in Women with Ankylosing Spondylitis Is Associated with a Younger Age At Diagnosis. Dharini Mahendira[1], Arane Thavaneswaran[2], Adele Carty[3], Nigil Haroon[4], Ammepa Anton[3], Laura A. Passalent[3], Khalid A. Alnaqbi[3], Laurie M. Savage[5], Elin Aslanyan[6] and Robert D. Inman[7]. [1]St Michael's Hospital, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Toronto Western Hospital, Toronto, ON, [4]University Health Network, Toronto Western Research Institute, University of Toronto, Toronto, ON, [5]Spondylitis Association of America, Van Nuys, CA, [6]Spondylitis Association of America, Van Nuys, [7]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: While AS is traditionally recognized as a predominantly male disease, the impact of gender differences on AS pathogenesis has not been clearly established. Specifically, the potential role of sex hormones in mediating gender impact on both AS susceptibility and disease severity remains unanswered. Both exogenous and endogenous estrogens may play a key role in AS disease expression in women. Our objective is to elucidate the potential impact of exogenous estrogen on AS initiation and severity. We hypothesized that exogenous estrogen, in the form of oral contraceptive pills (OCP), may alter AS disease activity and severity in premenopausal women.

Methods: The study population consists of premenopausal women with AS seen in our longitudinal clinic, as well as members of the Spondylitis Association of America (SAA). Measures of disease severity included: use of biological agents, hip replacement surgery, and BASFI scores as a surrogate marker of disability. A patient questionnaire was created and used to obtain information on patient demographics, past and present OCP use, menstrual history, pregnancy history, AS duration, medication use, and hip replacement.

Results: A total of 655 women participated in this study. This was comprised of 516 OCP users and 139 non-OCP users. The mean age of OCP users was 42.2 (+/− 11.5) and 47.9 (+/− 12.2) years in non-OCP users. While no difference was noted with respect to initial onset of back pain, OCP users were significantly younger at the age of diagnosis of AS (35.7 years vs. 38.6 years, p=0.01). (Table) There was no significant difference in anti-TNF or opioid use, pregnancy complications, nor rates of hip surgery between OCP and non-OCP users. A trend towards higher rate of pregnancy complications was noted in all OCP users, although this was not statistically significant (45.4% vs. 36.5%, p=0.13). There was no significant difference in reported BASFI scores between the groups.

Table. Women with AS – Clinical Features in OCP Users vs Non-users

	OCP Users (n=516)	Non-OCP Users (n=139)	P-value
Age at diagnosis of AS	35.7 (11.2)	38.6 (12.2)	0.01
Age at onset of back pain	24.1 (10.2)	24.7 (10.5)	0.52
Race (% Caucasian)	457 (90.7%)	112 (83.0%)	0.02
Use of Anti-TNF agents	330 (64%)	80 (58.4%)	0.23
Use of Opioids	186 (41.5%)	56 (45.5%)	0.47
Past hip surgery	20 (4.4%)	8 (6.5%)	0.34
Past pregnancy complications	152 (45.4%)	35 (36.5%)	0.13

Conclusion: The use of exogenous estrogens in the form of oral contraceptive pills is associated with a significantly earlier diagnosis of AS in women. To date, this is the largest study investigating the potential impact of exogenous estrogens in women with AS. While exogenous estrogens are not associated with surrogate indicators of disease severity, the earlier age of diagnosis of AS amongst women taking OCP suggests hormone modulation of disease expression in the early stages of disease.

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Improvement in Signs and Symptoms of Active Ankylosing Spondylitis Following Treatment with Anti-Interleukin (IL)-17A Monoclonal Antibody Secukinumab Are Paralleled by Reductions in Acute Phase Markers and Inflammatory Markers S100A8 and A9 (Calgranulin A and B).
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Background/Purpose: Secukinumab has shown to be well tolerated and effective in active ankylosing spondylitis (AS) patients in a proof-of-concept trial[1]. Briefly, at Week (Wk) 6, 61% (14/23) patients on secukinumab achieved Assessment of SpondyloArthritis International Society (ASAS) 20 response vs 17% (1/6) patients on placebo and the primary endpoint was met. Here we explored the modulation of markers of inflammation following secukinumab treatment, including CRP, ESR and S100 proteins A8 and A9 (calgranulin A and B), recently postulated to play a role as markers of inflammation in inflammatory arthritis[2].

Methods: 30 patients were randomized 4:1 to either secukinumab 2×10 mg/kg or placebo (i.v. infusion, 3 wks apart). Primary endpoint was the proportion of patients achieving ASAS 20 response at Wk 6. Key secondary endpoints included safety and tolerability and ASAS responses up to Wk 24. S100 calgranulins were analyzed pre- and post-treatment using an in-house validated multiplex assay and high sensitivity (hs) CRP assay. In accordance with the protocol, descriptive statistics were applied for exploratory analyses, due to the small sample size in the placebo arm. No group comparisons were conducted between secukinumab and placebo.

Results: Measurements from pre-treatment (Wk 0) and post-treatment (Wk 6) were available from 21 (CRP) and 14 secukinumab patients (S100A8/9), respectively. Baseline mean (SD) CRP values were 13.84 mg/L (17.40) for CRP; 1819 (717) for S100A8; and 2013 (835) ng/mL for S100A9, respectively. Baseline elevations of CRP (> normal upper limit of 10 mg/L) were observed for only a minority of patients on secukinumab (N=8). Comparing Wk 0 with Wk 6, significant changes were seen for CRP (−19%, p=0.027, n=21), S100A8 (−25%, p=0.012, n=14) and S100A9 (−21%, p=0.008, n=14) (Figure 1). Baseline levels of CRP neither correlated with Wk 6 ASAS20 nor ASAS40 responses (R=0.03 for both). Likewise, DCRP

(Wk 0–6) neither correlated with Wk 6 ASAS20 (R=0.13) nor ASAS40 (R=0.15). In contrast, correlations were seen for S100A8 and A9 baseline concentrations with ASAS20 (R=0.55 and 0.39, respectively), and ASAS40 (R=0.40 and 0.59, respectively). Moreover, DS100A8 (Wk 0–6) was correlated with Wk 6 ASAS20 (R=0.43) and ASAS40 (R=0.52); and DS100A9 (Wk 0–6) with Wk 6 ASAS20 (R=0.28) and ASAS40 (R=0.64).
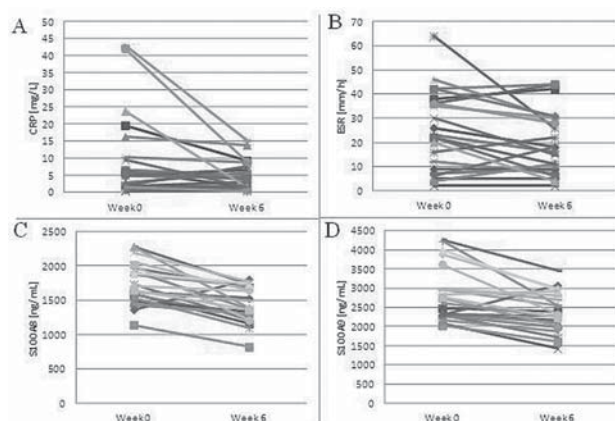
Figure 1. Markers of inflammation A) CRP B) ESR C) S100 A8 D) S100 A9 at baseline (Week 0) and Week 6, following secukinumab 2×10mg/kg i.v. at Week 0 and 3.

Conclusion: In this trial of secukinumab in AS, exploratory analyses of selected inflammatory markers suggest that secukinumab reduces CRP, S100A8 and S100A9, but only S100A8/9 reductions appear to correlate with clinical responses at Wk 6. Lack of correlation of CRP reductions with Wk 6 ASAS response may be attributable to the low number of patients with baseline CRP elevations. Further studies of S100 proteins in AS and their relationship with IL-17A blockade are warranted.

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Application of Classification Criteria for Psoriatic Arthritis to Patients of the Rotterdam Early Arthritis Cohort.
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Background/Purpose: Psoriatic arthritis (PsA) poses a diagnostic challenge due to lack of a clear case definition. This has led to varying reports on prevalence, which is held to be 20 to 100 per 100000 [1–3], while in the past some have even questioned whether PsA should be treated as an individual entity at all[4]. Currently, the distinction between rheumatoid arthritis (RA) and PsA is still defined on clinical grounds. We compared the number of patients clinically diagnosed with PsA with the number meeting currently used classification criteria for PsA in the REACH-population.

Methods: 1216 patients from the Rotterdam Early Arthritis Cohort were used for this analysis. Patients were eligible for REACH with confirmed arthritis in at least 1 joint or 2 painful joints and at least 2 of the following criteria: morning stiffness for more than 1 hour; inability to clench a fist in the morning; pain when shaking someone's hand; pins and

needles in the fingers; difficulties wearing rings or shoes; a family history of RA; unexplained fatigue for less than 1 year. The criteria sets considered were the Classification of Psoriatic Arthritis (CASPAR) criteria [5], the Moll & Wright (M&W) criteria[6], and the European Spondyloarthropathy Study Group (ESSG) criteria for PsA [7]. These sets were applied at baseline using descriptive statistics in STATA12. Inflammatory spinal pain was not measured in REACH and the non-specific presence of low back pain was felt to be inappropriate due to high prevalence in the REACH cohort (50%).

Results: In this cohort 45 (3.7%) patients were clinically diagnosed with PsA, similar to numbers previously reported[8]. In the remaining group, 60 (4.9%) met the CASPAR criteria, 33 (2.7%) met the M&W criteria and 2 (0.2%)met the modified ESSG criteria. Patients satisfying the CASPAR criteria and M&W criteria mainly had a negative Rheumatoid Factor and presence of current psoriasis. Among patients fulfilling the CASPAR criteria (n=60) the most frequent clinical diagnoses were oligo- or polyartritis e.c.i, (n=19), artralgia or myalgia (n=12), osteoarthritis (n=8), monoathritis e.c.i (n=6) and rheumatoid arthritis (n=5). For fulfilling the M&W criteria inflammatory arthritis is mandatory, so compared to the CASPAR criteria, patients with artralgia or myalgia did not fulfill these. The ESSG criteria for PsA were met in 2 patients with M.Bechterew and positive family history for PsA. The total number of patients meeting classification criteria was thus 62, not including patients clinically diagnosed with PsA (n=45).

Conclusion: The number of patients meeting the different classification criteria sets exceeded the total number clinically diagnosed with PsA, emphasizing the diagnostic challenge in this disease. Out of the used criteria sets, the CASPAR criteria were met in most patients.

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Low dosage with Escalating Dosage of Infliximab in Psoriatic Arthritis Gives the Same Treatment Results as Standard Dosage of Adalimumab or Etanercept: Results From the Nationwide Registry ICEBIO. Bjorn Gudbjornsson[1] and Niels Steen Krogh[2]. [1]Center for Rheumatology Research, Reykjavik, Iceland, [2]ZiteLab ApS, Copenhagen, Denmark

Background/Purpose: To explore differences in response to low dosage (2.3mg/kg) regimen of infliximab with possible escalating dosage in comparison to standard dosage of etanercept and adalimumab over time in patients with psoriatic arthritis (PsA).

Methods: Patients with PsA who were all biologic naïve and initiating anti-TNF-α therapy were selected from the ICEBIO registry which is based on the DANBIO IT platform. Demographics and clinical differences at baseline, including DAS-28CRP, were compared in four treatment groups: 1) Those who responded to low dosage of infliximab ($<$ 4 mg/kg) 2) those who needed to increase the dosage of infliximab above 4 mg/kg, and those who received a standard dosage of 3) etanercept or 4) adalimumab. Follow-up data at 26 $\pm$ 6 and 52 $\pm$ 6 weeks and on the last visit (at least 13 weeks after the initiation of the treatment) were also compared. The Kruskal-Wallis rank sum test was used for comparison of the groups and the Wilcoxon test was used to compare the two infliximab dosage regimens.

Results: 185 patients, 113 women and 72 men, were identified; 84 patients received infliximab, 66 etanercept and 35 adalinmumab. Only 19% of the patients (16/84) treated with infliximab needed to escalate their dosage to exceed 4 mg/kg; thus those still on a low dosage regimen had a mean dosage of infliximab 2.9 mg/kg, but those who had escalated their dosage had a mean dosage of 4.5 mg/kg, i.e. still under the recommended 5 mg/kg. At baseline those who continued low dosage infliximab had a shorter disease duration (8 vs. 10 years), while those who needed to increase their dosage of infliximab had a higher CRP (10.4 vs 17.2 g/L), but neither value reached significant differences. No significant differences were observed at baseline in respect to numbers of swollen or tender joints, HAQ, VAS pain, VAS fatigue or in DAS28-CRP values. A similar treatment response was observed in all four treatment groups on follow-up.

Conclusion: In respect to treatment effects a low dosage of infliximab, with starting dosage of 2.3mg/kg with possible escalating dosage, is acceptable for the majority of psoriatic arthritis patients who are in need of biological treatment. This "low dosage treatment regimen" with infliximab significantly reduces the burden of drug cost for the society.

*ICEBIO: Erlendsson K, Geirsson AJ, Grondal G, Jonsson H, Jonsdottir T, Ludviksson BR, Steinsson K, Tomasson G, Valtysdottir S, Vikingsson A.

Disclosure: **B. Gudbjornsson**, None; **N. S. Krogh**, None.

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The Caspar Classification Criteria and Response to TNF Blockade in Rheumatologists Practice: A Large Observational Cohort Study. Burkhard Moller[1], Almut Scherer[2], J. Dudler[3], Bettina Weiss[4], Nikhil Yawalkar[5] and Peter M. Villiger[6]. [1]Inselspital University Hospital, Bern, Switzerland, [2]SCQM Foundation, Zurich, Switzerland, [3]Cantonal Hospital Fribourg, Fribourg, Switzerland, [4]Balgrist University Hospital, Zurich, Switzerland, [5]MD, Bern, Switzerland, [6]Inselspital-University Hospital of Bern, Bern, Switzerland

Background/Purpose: Background/Purpose: Definition of the CASPAR classification criteria and TNF blocker therapy were milestones in the area of psoriatic arthritis (PsA). We aimed to identify the 'CASPAR-positive' patients in a large patient population, and to compare the results of TNF blockade in 'CASPAR-positive' and in 'CASPAR-negative' patients with background psoriasis.

Methods: Patients in the SCQM database had a primary diagnosis of PsA on an individual decision by the treating board certified rheumatologist. Classification relevant data were in addition requested at baseline and at annual intervals. Disease activity was displayed by the physician global (PhG), patient global (PG) and pain assessment, the 66 swollen (SJC) and 68 tender joint counts (TJC), the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) serum concentrations, and numeric rating scales for skin and nail involvement.

Results: 543 female and 601 male patients were included with PsA diagnosis. Only 183 (16%) of them came from academic centers, but 231 (20%) from other hospitals and 690 (60.3%) from practice based rheumatologists. A current or a history of arthritis (81%), enthesitis (46%) or dactylitis (49.5%) was reported either alone or in combination. Axial involvement (38%) without further specification and inflammatory back pain (12%) were less frequent. Current skin psoriasis (71%) at inclusion was mild or moderate in 52% and/or obtained from the patient history in 70%. Nail involvement was registered in 9%, a positive patient's family history in 22%, positive rheumatoid factor testing in 1.8%, and PsA-typical juxta-articular osteoproliferation in 13.5% of the patients. The proportion of CASPAR-positive SCQM-PsA patients (n=625 or 54.6%) was equally distributed among the university centers and practices.

361 CASPAR-positive and 239 CASPAR-negative PsA patients were started on a TNF blocker: 223 on adalimumab (104 with background MTX), 180 on etanercept (79 plus MTX), 73 on infliximab (45 plus MTX) and 24 patients on golimumab (8 plus MTX). 302 CASPAR-positive and 188 CASPAR-negative PsA patients had at least one follow-up visit one year later, when the following parameters had improved: SJC from mean 4.5 (SD: 6.1) to 2.0 (SD: 4.6), TJC from 8.1 (SD: 11.5) to 4.4 (SD: 8.5), CRP from 11.4 (SD: 16.4) to 6.3 mg per liter (SD: 6.4), PhG from 4.2 (SD: 2.4) to 2.0 (SD: 1.9), PG from 5.1 (SD: 2.9) to 3.4 (SD: 2.7) and pain from 5.0 (SD: 2.8) to 3.5 (SD: 2.8). There were no differences in these disease activity measures between patients satisfying the CASPAR criteria and the 'CASPAR-negative' patients, neither at baseline nor at 1-year post TNF blocker initiation.

Conclusion: This study confirms that the CASPAR classification criteria could be useful in practice for affirming PsA diagnosis, but they should not stringently be used as an exclusive selection criterion for anti-TNF therapy in patients with background psoriasis.

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Analysis of Clinical, CRP- and MRI- Responses to TNF-Blockade in Axial Spondyloarthritis Patients with Short Vs Long Symptom Duration. Anja Weiss[1], In-Ho Song[2], Hildrun Haibel[2], Joachim Listing[3] and Joachim Sieper male[4]. [1]German Rheumatism Research Centre, Berlin, Germany, [2]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [3]German Rheumatism Research Center, Berlin, Germany, [4]Charité Universitätesmedizin Berlin, Berlin, Germany

Background/Purpose: To investigate the impact of disease duration on treatment response in patients with axial spondylarthritis (SPA) treated with etanercept (ETA) or adalimumab (ADA).

Methods: Data of 112 patients with axial SpA originally enrolled in two randomized controlled trials were pooled and analyzed. The following outcome parameters assessed after one year of treatment with ETA n=66 (1) or ADA n= 46 (2) were investigated: Bath AS disease activity index (BASDAI), functional index (BASFI), AS disease activity score (ASDAS), CRP, and active inflammation on MRI in the sacroiliac joints (SIJ) and spine. Comparisons were made between patients with a short (< 4 years) versus those with a longer (>=4 years) duration of symptoms. A mixed model approach was applied to compare the changes in the outcome parameters between baseline and end of year one between the symptom duration groups after adjustment for baseline status and gender. Partial Spearman correlation coefficients were calculated to analyse the relationship between change scores after taking their dependence from the baseline scores into account.

Results: Clinical parameters such as BASDAI, BASFI and ASDAS showed significantly better improvement in short vs longer diseased patients (Table 1). No significant differences were observed for MRI scores and for CRP. Furthermore, in short diseased patients the change in BASDAI correlated significantly with the change in SIJ score (rho=0.33, p=0.03) and the change in CRP (rho=0.40, p=0.003). In contrast, in patients with a long disease duration this correlations was poor (change in BASDAI vs change in SIJ score rho=−0.01, p=0.95, change in BASDAI vs change in CRP rho=0.22, p=0.13). We further stratified the patients into CRP positive and CRP negative patients according to their status at baseline and observed larger differences between short and longer diseased patients in the CRP negative subgroup (improvement: BASDAI: 3 [2.3, 3.7] vs. 1.31 [0.7, 1.9], BASFI: 2.42 [1.8, 3.1] vs. 0.93 [0.4, 1.5]) than in the CRP positive subgroup (improvement BASDAI: 3.34 [2.7, 4] vs. 2.41 [1.5, 3.3]), BASFI: 2.44 [1.8, 3] vs. 1.79 [0.9, 2.7]).

Table 1. Mean changes in clinical outcome parameters adjusted for the status at baseline and gender

Parameter	Baseline value (mean)	Adjusted mean changes (95% CI)		p-value
		<4 years n=58	>=4 years n=54	
BASDAI	5.4	3.2 (2.7, 3.7)	1.7 (1.1, 2.2)	<.0001
BASFI	4.4	2.4 (2, 2.9)	1.2 (0.7, 1.6)	0.0003
BASMI	1.8	0.3 (0, 0.6)	−0.1 (−0.4, 0.2)	0.09
ASDAS	3.1	1.5 (1.3, 1.8)	1.1 (0.8, 1.4)	0.04
CRP	8.0	3.8 (1.7, 5.9)	1.2 (−0.9, 3.3)	0.09
MRI spine score	1.8	0.8 (0.4, 1.3)	1.5 (0.8, 2.1)	0.10
MRI SIJ score	6.0	3.9 (3.3, 4.6)	3.7 (2.8, 4.6)	0.71

Conclusion: 1. Axial SpA patients with short symptom duration respond clearly better to TNF-blocker therapy. 2. A good correlation between improvement of patients' reported outcome parameters and objective parameters of inflammation was found in short but not in longer diseased patients. 3. CRP-negative axial SpA patients respond well in case of short symptom duration. These data indicate that patients with longer symptom duration, even in absence of significant structural damage and despite good suppression of inflammation, respond less well to TNF-blockade for reasons which have still to be defined.

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The Early Clinical Response of TNF-Alpha Blockers Is a Predictor of Metrology Outcome in Ankylosing Spondylitis. Eon Jeong Nam, Jung Soo Eun, Na Ri Kim, Jong Wan Kang, Churl Hyun Im and Young Mo Kang. Kyungpook National University School of Medicine, Daegu, South Korea

Background/Purpose: TNF-α blocker is the only treatment that shows a significant effect on spinal inflammation and life quality of patients with ankylosing spondylitis (AS). However, the predicting factors for the metrology outcome in AS patients treated with TNF-α blockers have not been reported. In this study, we investigated whether the early clinical efficacy of TNF-α blockers determines the metrology outcome in AS patients.

Methods: A retrospective study was conducted in a total of 119 cases who were treated with TNF-α blockers for 21 months (85 patients with one TNF-α blocker and 17 patients with two). Patients were evaluated at baseline, after three months of TNF-α blockers, and then every six months. Clinical efficacy was evaluated using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), ASAS20, ASAS40, ASAS5/6, BASDAI50, and acute phase reactants (ESR and CRP). Metrology outcome was assessed by BASMI and chest expansion. Primary resistance was defined as a failure of improvement of at least 20% or of absolute improvement at least two units in BASDAI scores at month 3. Kaplan-Meier (KM) survival curves were plotted to determine the rates of continuation of TNF-α blockers (drug survival).

Results: Etanercept was used in 57 cases (47.9%), adalimumab in 49 (41.2%), and infliximab in 13 (10.3%). TNF-α blockers showed a similar drug survival rate and clinical efficacy. Primary resistance developed in 5 patients (4.2%). ASAS20 response rate was 90.2%, 91.7%, 92.4%, and 90% at months 3, 9, 15, and 21, respectively. TNF-α blockers showed a clinical response rate ranging 77.2 to 83.5% by ASAS40, 74.6 to 84.5% by ASAS5/6, and 74.3 to 92.1% by BASDAI50. TNF-α blockers were associated with significantly improved metrology indices including BASMI, BASMI components, and chest expansion at months 3, 9, 15, and 21. The changes in the BASMI significantly correlated with the changes in the BASDAI (r=0.260, $P < 0.001$), BASFI (r=0.726, $P < 0.001$), patient's global assessment score (r=0.479, $P < 0.001$), physician's global assessment score (r=0.517, $P < 0.001$), pain score (r=0.394, $P < 0.001$), and acute phase reactants (ESR, r=0.184, $P < 0.001$; CRP, r=0.118, $P < 0.001$). ASAS20 responders at month 3 had a significant reduction in BASMI and chest expansion, compared to those of baseline (p<0.001), while ASAS20 non-responders did not show a significant change. Reduction of metrology indices was maintained until month 21.
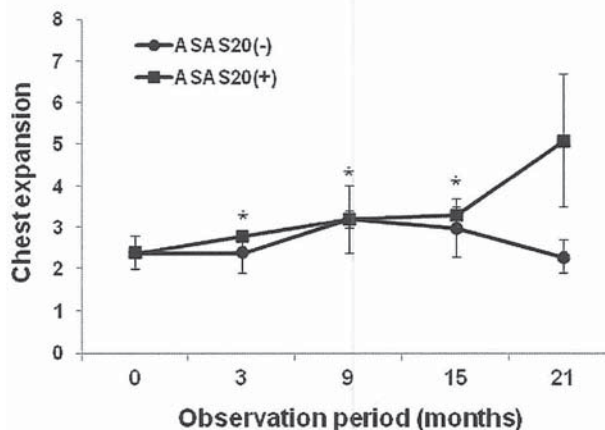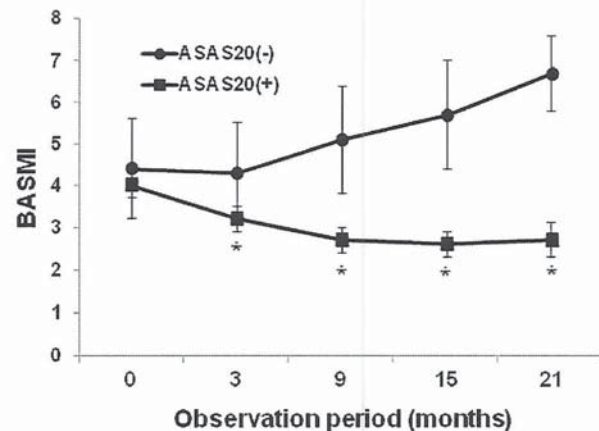
Conclusion: ASAS20 response at month 3 may be a valuable predictor for metrology outcome. Further studies are required to determine whether ASAS20 at month 3 is a good predictor of radiologic results along with metrology outcome in assessment of axial involvement.

Disclosure: E. J. Nam, None; **J. S. Eun**, None; **N. R. Kim**, None; **J. W. Kang**, None; **C. H. Im**, None; **Y. M. Kang**, None.

2231

Treatment of Psoriatic Arthritis with Tumour Necrosis Factor α Antagonists Successfully Maintains Work Capacity: 2 Year Results of a Prospective Cohort Study.

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Background/Purpose: Treatment resistant psoriatic arthritis (PsA) may render a patient unwell, disabled and incapable of work with previous reports suggesting that unemployment levels among PsA patients range from 30–50%, higher than the current national unemployment level of 14.7%. It is argued that the clinical, functional and quality of life benefits of tumour necrosis factor α inhibitor drugs (TNFi) may not be sufficient to justify their significant economic cost (national cost, $>€100$ million/year in 2010). We sought to evaluate longitudinal employment levels among PsA patients treated with TNFi therapy.

Methods: A prospective cohort study of TNFi treated PsA patients between the ages of 18–65 fulfilling the ClASsification of Psoriatic ARthritis (CASPAR) criteria with active disease despite DMARD therapy was undertaken. Economic status and disease activity were recorded at baseline and following commencement of TNFi therapy. DDAS >1.2 was considered a good clinical response. Descriptive variables are presented as means (Standard Deviation) or percentages.

Results: Employment status of 114 PsA patients was reviewed at a mean of 26 months (22) after starting TNFi therapy. 51% were female, mean age 48 (11) and mean duration of disease of 13 years (8). 50% patients were treated with etanercept, 38% adalimumab, 6% golimumab and 6% infliximab with 46% also receiving DMARD therapy. 2% and 15% continued to take low dose oral steroids and PRN NSAIDs respectively. 79% of patients were judged good clinical responders. 92 patients were in full time employment at baseline. 83/92 (90%) continued in employment with 6 retiring and 3 becoming redundant. Those who retired or became redundant had a higher DAS 28 score at follow up than those who remained in employment (2.4 v 3.2 (ns)). 22 patients were unemployed upon commencing TNFi with 5 of them returning to the workforce. Of those who did not, 14 were on disability benefit prior to starting TNFi, 2 were unemployed and 1 had retired. Only 4% of all patients required home help.

Conclusion: 90% of TNFi treated PsA patients maintain their employed status with 23% of previously unemployed TNFi treated PsA patients returning to the workforce. Cumulatively, 22.8% of our TNFi treated PsA patients are unemployed, an improvement on previous published levels indicating a potential economic benefit of TNFi that may become more apparent in the future. Maintenance of an individual's work capacity likely results in societal savings that help to offset the substantial cost of TNFi treatment.

Disclosure: L. C. Harty, None; **A. Franciosi**, None; **N. Pettysan**, None; **P. Rushe**, None; **O. M. FitzGerald**, Abbott Laboratories Ireland, Bristol-Myers Squibb, 2, Abbott Laboratories Ireland, UCB, 5, Abbott Laboratories Ireland, 8.

2232

Performance of Berlin Criteria in Patients with EARLY Spondyloarthritis.

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Background/Purpose: Berlin criteria are a diagnostic algorithm based on calculation of the likelihood ratio (LR) product of currently available diagnostic test for spondyloarthritis (SpA). However, these probabilities were calculated on a longstanding population, with different features from those of an early SpA cohort. ESPeranza (ESP) is a national health care multicentre program for the early diagnosis and treatment of SpA. ESP patient characteristics were collected from baseline to onset, so it permits to explore Bayesian probabilities of each feature and reproduce Berlin algorithm. OBJECTIVEs: 1. To evaluate, in an early SpA, the LR of different symptoms and signs included in Berlin criteria. 2. To evaluate the validity of Berlin algorithm for SpA diagnosis.

Methods: Patients were referred from general practitioners according with this criteria: 1) age <45years old; 2) symptom duration 3–24 months; 3) at least one of the following: inflammatory back pain (IBP), asymmetrical arthritis, SpA features associated to back pain or arthralgias (psoriasis, inflammatory bowel disease, anterior uveitis, radiographic sacroiliitis, HLA B27 positive or a family history of SpA). Patients with axial symptoms were selected (those with only arthritis were excluded) and categorized according to experts clinical diagnosis (SpA or not SpA). Data from ESP included: demographics (gender, age), clinical features (IBP characteristics, sacroiliac syndrome, enthesitis, arthritis, dactilitis, psoriasis, inflammatory bowel disease, diarrhea, urethritis, cervicitis, prostatitis, positive family history for SpA or good response to NSAIDs), HLA B27 or imaging data (sacroiliitis in x-ray or MRI, according to Omeract). Descriptive analysis was performed. Sensitivity and specificity, and LR positive were calculated. Classification according to Berlin LR product method was performed. In case of an LR product '200, a classification of axial SpA is made.

Results: From the 1179 patients referred in ESP program, only 422 fulfilled inclusion criteria with axial symptoms. 316 were diagnosed as SpA. Insidious onset and > 3months onset were the most frequent symptoms (73% and 84%, respectively). The most useful feature among IBP was the improvement with exercise (LR+ 2.2), more frequent than alternating buttock pain. Arthritis was the most useful symptom for the diagnosis (LR+ 7), apart from MRI, following by enthesitis, but heel pain (LR 5.7). Dactiyitis and uveitis and other features were less helpful, (see table). Finally, MRI was the most beneficial feature (LR+ 16), although it was not always available. Berlin criteria applied to this early SpA population showed a lower sensitivity (65%) and higher specificity (98%) than Berlin group.

	Frequent (n)	Percentage (%)	SENS %	SPE %	PPV	PNV	LR+	LR-
Inflammatory back pain	247	58.5	63.9	57.5	81.8	34.9	1.5	0.6
>3 month onset	356	84.4	83.2	12.3	73.9	19.7	0.9	1.4
Morning stiffness ^{3}30min	241	57.1	59.2	49.1	77.6	28.7	1.2	0.8
Improvement with exercise	230	54.5	63.0	70.8	86.5	39.1	2.2	0.5
No improvement with rest	262	62.1	67.7	54.7	81.7	36.3	1.5	0.6
Pain at night	195	46.2	50.9	67.9	82.6	31.7	1.6	0.7
Alternating buttock pain	126	29.9	33.9	82.1	84.9	29.4	1.9	0.8
Insidious onset	309	73.2	74.4	30.2	76.1	28.3	1.1	0.8
Arthritis	87	20.6	26.3	96.2	95.4	30.4	7.0	0.8
Heel pain	75	17.8	21.2	92.5	89.3	28.2	2.8	0.9
Enthesitis, but heel pain	18	4.3	5.4	99.1	94.4	26.0	5.7	1.0
Iritis	17	4.1	4.4	97.2	82.4	25.4	1.6	1.0
Dactylitis	18	4.3	5.7	100.0	100.0	26.2	.	0.9
Inflammatory bowel disease	16	3.8	4.4	98.1	87.5	25.6	2.4	1.0
Psoriasis	35	8.3	9.2	94.3	82.9	25.8	1.6	1.0
Uretritis/cervicitis/diarrhea	7	1.7	2.2	100.0	100.0	25.5	.	1.0
Raised CRP	97	24.6	29.8	92.4	92.8	28.6	3.9	0.8
HLA B27 positive	208	49.3	59.2	80.2	89.9	39.7	3.0	0.5
Family history	99	23.5	27.5	88.7	87.9	29.1	2.4	0.8
Sacroiliitis X-ray	203	48.1	36.8	100.0	100.0	30.0	.	0.6
Sacroiliitis RMI	99	23.5	63.0	96.2	98.0	46.6	16.7	0.4
Good response to NSAID	252	59.7	63.6	51.9	79.8	32.4	1.3	0.7
Berlin Criteria	210	49.7	65.2	96.2	98.1	48.1	17.3	0.4

Conclusion: Our data shows that MRI is a key symptom in early SpA, while HLA B27 was less useful than results from Berlin group. Berlin diagnostic algorithm should be revisited according to these data, at least in early SpA patients.

Disclosure: B. E. Joven, None; **M. Gobbo**, None; **M. A. Descalzo**, None; **E. De Miguel**, None.

2233

Assessing the Clinical and Economic Burden of U.S. Veteran Ankylosing Spondylitis Patients. Lin Xie[1], Onur Baser[2], Ahong Huang[3], Lu Li[3], Elyse K. Fritschel[3] and Li Wang[3]. [1]STATinMED Research, Ann Arbor, MI, [2]STATinMED Research/The University of Michigan, Ann Arbor, MI, [3]STATinMED Research, Dallas, TX

Background/Purpose: To examine the economic burden, demographic and clinical characteristics of ankylosing spondylitis (AS) in the U.S. veteran population.

Methods: A retrospective database analysis was performed using the Veterans Health Administration (VHA) Medical SAS Datasets from October 1, 2007 to September 30, 2011. Patients with AS were identified using International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) diagnosis code 720.0x. Survival was determined with the PROC LIFETEST procedure, and descriptive statistics were calculated as means ± standard deviation (SD) and percentages to measure demographics, costs and utilization distribution in the sample.

Results: In patients identified with AS (n=2,455), total survival rates in the 12-month follow-up period were 98.1% for patients age ≤39, 97.0% for those age 40–64, and 89.6% for those age ≥65. The most common comorbidities in AS patients were hypertension (62.77%), any tumor or malignancy (25.50%), and diabetes (24.11%). The percentage of patients who had follow-up inpatient visits was 14.34%, which translated into $6,240 in inpatient costs per patient. The percentage of patients who had follow-up outpatient visits was 99.88%, which translated into $6,838 outpatient costs per patient. The average number of inpatient (0.25, SD=0.79), emergency room (ER) (0.10, SD=0.58), physician office (15.99, SD=16.63) and outpatient visits (17.54, SD=17.88) were also calculated for AS patients.

Conclusion: Comorbidities may play an important role in the costs of AS treatment, since more than 20% of the study population was also diagnosed with any combination of hypertension, diabetes, and tumor or malignancy.

Disclosure: L. Xie, None; **O. Baser**, None; **A. Huang**, None; **L. Li**, None; **E. K. Fritschel**, None; **L. Wang**, None.

2234

US Treatment Patterns of Psoriatic Arthritis Patients Newly Initiated On Etanercept or Adalimumab. Frank Zhang[1], Stan Li[1] and Jeffrey R. Curtis[2]. [1]Celgene Corporation, Warren, NJ, [2]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Etanercept (ETN) and Adalimumab (ADA) are commonly used biologic disease-modifying antirheumatic drugs (DMARDs) for psoriatic arthritis (PsA) patients (pts). However, little is known about subsequent treatment changes after the initiation of these two biologics. The objective of this study was to describe treatment patterns following the initiation of ETN and ADA in PsA patients in US in a real-world setting.

Methods: Adult PsA pts were selected from MarketScan Commercial Claims database (2005–2009). First ETN/ADA prescription date was defined as the index date. Pts were required to have continuous enrollment 6-month prior to (baseline period) and 12-month post index date (study period), no use of the index biologic treatment during baseline, have received ≥2 PsA diagnoses from physician office visits at any time over the 18-month period, with at least one PsA diagnosis during baseline period, and no diagnosis of ankylosing spondylitis. ETN/ADA combo therapy was defined as having at least 28 days of concomitant use of a non-biologic DMARD following the index date; otherwise ETN/ADA monotherapy was defined. Treatment patterns were captured over the 12-month study period and were defined as the following: complete treatment discontinuation—a treatment interruption of ≥60 consecutive days past the end of the days' supply (discontinuation date) and no other DMARD therapy between the discontinuation date and the end of the study period; a switch in therapy—the initiation of a new non-biologic/ biologic DMARD (not used during baseline) within 60 days of the discontinuation date; intermittent use of the index biologic -- ≥60 days of treatment gap of the index biologic; step-down -- discontinuation of one of the DMARD therapies among patients previously on combo therapy; step-up— adding another DMARD (not used during baseline) concomitantly with the index biologic for ≥28 consecutive days. Therapy modification was defined as any switch, intermittent use, step-down or step-up.

Results: A total of 2,037 and 2,217 PsA pts were newly initiated on ETN and ADA respectively, most on monotherapy (ETN: 69.2%, ADA: 67.5%). Over the 12-month study period, the majority of the pts had ≥ 1 therapy change (ETN: 65.3%, ADA: 69.1%), with median time to change 113 days and 112 days respectively. Among pts initiated on mono ETN/ADA, 40.7% ETN and 33.5% ADA pts remained on the index mono therapy. 12.1% ETN and 11.6% ADA pts discontinued the treatment, 18.2% ETN and 14.7% ADA pts had intermittent treatment, 7.0% ETN and 11.4% ADA pts switched to another mono therapy, and 21.9% ETN and 29.1% ADA pts step-up to combo therapy. Among pts initiated on ETN/ADA in combination with an oral DMARD, a proportion of pts remained on the original combo therapy (ETN: 21.4%, ADA: 26.8%). The majority of the patients 'stepped down' to monotherapy (ETN: 77.5%, ADA: 72.7%). Very few pts discontinued both drugs in the combo therapy (ETN: 0.5%, ADA: 0.1%) or adopting intermittent biologic therapy (ETN: 0.6%, ADA: 0.3%).

Conclusion: This study suggests that most of the PsA patients newly initiated on ETN or ADA have a therapy change over the first year. Both 'step-up' and 'step down' strategy are observed frequently.

Disclosure: F. Zhang, Celgene Corporation, 3; **S. Li**, Celgene, 5; **J. R. Curtis**, Celgene, 5.

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How Important Is the Assessment of ASDAS in the Long-Term Evaluation of Disease Activity in Ankylosing Spondylitis? A Comparison with Currently Used Clinical Parameters. Xenofon Baraliakos[1], Claudia Fritz[2], Joachim Listing[3], Hildrun Haibel[4], Joachim Sieper male[5] and Jürgen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]German Rheumatism Research Center, Berlin, Germany, [4]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [5]Charité Universitätsmedizin Berlin, Berlin, Germany

Background/Purpose: Measures for disease activity (BASDAI) or response to therapy (ASAS partial remission (PR)) are widely used in the assessment of patients with ankylosing spondylitis (AS). The recently developed ASDAS is a composite score, which includes clinical measures and CRP and has a high discriminatory capacity for assessing disease activity. However, only little is known about the course of ASDAS as compared to all other clinical assessments in the long-term outcome of patients with AS. In this study we compare the performance of ASDAS-CRP vs. the BASDAI and ASAS outcomes in assessing and predicting clinical response in AS patients under longterm TNF-blocker therapy.

Methods: Initially, 69 patients were included in this first study of anti-TNF treatment with infliximab in AS, of whom 43 (63.2%) finished the 3rd, 42/69 (60.9%) the 5th and 29 (42.2%) the 10th study year (y). Low disease activity status was measured by the BASDAI (<3 units) and was compared to the ASDAS definition of low disease activity (<2.1 units), while for clinical response, the ASAS-PR was compared to ASDAS inactive disease status (ASDAS <1.3) at different time points over the 10y of follow-up.

Results: There was significant decrease in both ASDAS (BL: 4.3±0.8, 3y: 1.5±0.9, 5y: 1.6±1.0, 10y: 1.7±1.0) and BASDAI (BL: 6.4±1.4, 3y: 2.4±1.9, 5y: 2.4±2.0, 10: 2.7±2.0). Overall, a BASDAI <3 was achieved by 19/29 (65.5%), 18/29 patients (62.1%), and 17/29 patients (58.6%), while ASDAS <2.1 was achieved by 23/29 (79.3%), 20/29 (69%) and 19/29 (65.5%) patients at 3y, 5y and 10y, respectively. In comparison, ASAS-PR was found in 10/29 (34.5%) at 3y and 5y and in 5/29 (17.2%) patients at 10y while ASDAS<1.3 was found in 13/29 (44.8%) at 3y and in 12/29 (41.4%) at 5y and 10y. Clinical outcome after 12 weeks of treatment was a significant predictor for achieving ASAS-PR over the 10 years of the study: for each unit of decreasing in BASDAI status at week 12, achievement of ASAS-PR at 10y increased with an OR [95% CI] of 3.64 [1.17–11.20] (p=0.025), while the OR for each unit of decreasing in ASDAS status at week 12 in order to reach ASAS-PR at 10y was 4.76 [1.20–18.90] (p=0.027). Similar results were found for ASDAS inactive disease at the end of year 10: for each unit of decreasing in ASDAS status at week 12, achievement of ASDAS inactive disease at 10y increased with an OR [95% CI] of 2.20 [1.00–4.86] (p=0.05), while the OR for each unit of decreasing in BASDAI status at week 12 in order to reach ASDAS inactive disease at 10y was 1.64 [1.05–2.58] (p=0.029).

Conclusion: The long-term course of BASDAI and ASDAS showed similar magnitude of improvement. Interestingly the clinical outcome after 12 weeks of treatment was a significant predictor of the outcome at the end of year 10. The significant decrease of ASAS-PR rates after 10 years can be explained by the inclusion of functional assessments (BASFI) in this measure, which are not

included in the ASDAS. The higher discriminative value of ASDAS in comparison to other widely used measurements needs to be considered in clinical trials but also daily practice for assessment of long-term outcomes in patient with AS.

Disclosure: X. Baraliakos, None; C. Fritz, None; J. Listing, None; H. Haibel, None; J. Sieper male, None; J. Braun, None.

ACR/ARHP Poster Session C
Systemic Lupus Erythematosus: Clinical Aspects
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

2236

Cross Cultural Validation of English and French Versions of a Disease Specific Patient Reported Outcome Measure for Lupus in Canada. Josiane Bourré-Tessier[1], Ann E. Clarke[2], Rachel A. Mikolaitis[3], Mark Kosinski[4], Sasha Bernatsky[5], Joel A. Block[3] and Meenakshi Jolly[3]. [1]McGill University, Montréal, QC, [2]McGill University, Montreal, QC, [3]Rush University Medical Center, Chicago, IL, [4]QualityMetric Inc, Lincoln, RI, [5]McGill, Montreal, QC

Background/Purpose: The LupusPRO, a disease targeted Patient Reported Outcome measure, was developed and validated in US patients with Systemic Lupus Erythematosus (SLE). We aimed to validate English and French versions of the LupusPRO among SLE patients in Canada.

Methods: The English version of the LupusPRO was administered to English-speaking SLE patients in Canada and the French version to French-speaking patients. Patients also completed the MOS SF-36. Physicians assessed disease activity (SELENA-SLEDAI and visual analogue scale) and damage (SLICC-ACR SDI and visual analogue scale). A mail back LupusPRO was completed within 2–3 days of the index visit. Internal consistency reliability (ICR), test-retest reliability (TRT), concurrent validity (corresponding domains of the SF-36) and criterion validity (against disease activity and damage) were tested. Confirmatory factor analysis results were available thus far only for the English version. All reported p values are two tailed.

Results: A total of 222 Canadian SLE patients participated—123 English speaking and 99 French speaking (table 1). Among the English-speaking patients, the ICR of the LupusPRO domains ranged from 0.60–0.93, while TRT ranged from 0.62–0.95. Concurrent validity with corresponding domains of the SF-36 was present and the LupusPRO domains performed well against disease activity and/or damage measures establishing its criterion validity. Confirmatory factor analysis showed a good fit.

Among the French-speaking patients, the ICR of the LupusPRO domains ranged from 0.81–0.93, except for Lupus Symptoms (0.58), Procreation (0.79) and Coping (0.44) domains. By deleting the item on religiosity/spirituality from the Coping domain, the ICR of this domain improved to 0.64. TRT ranged from 0.72–0.95. Concurrent validity with corresponding domains of the SF-36 was present. Lupus Symptoms domain correlated with disease activity as assessed by the total SLEDAI (r −0.26, p 0.01) and physician completed visual analog scale (r −0.49, p 0.001). Other domains also performed well against disease activity and/or damage.

Table 1. Description of the study cohort

	English-speaking patients N= 123	French-speaking patients N = 99
Age (Mean, SD) years	47.7 (14.8)	45.2 (14.5)
Female (%)	94	97
Ethnicity (%)	–	–
Caucasian	60.0	73.7
Asian	23.0	6.1
African-Caribbean	9.0	11.1
Other	8.0	9.1
SELENA SLEDAI (Median, IQR)	4.0 (6.0)	3.0 (6.0)
MD-Activity VAS (Median, IQR)	0.2 (0.95)	0.2 (1.00)
SDI (Median, IQR)	1.0 (3.0)	1.0 (2.0)
MD-Damage VAS (Median, IQR)	0.3 (2.8)	0.2 (3.4)

Conclusion: The English and French versions of the LupusPRO have fair psychometric properties among Canadian patients with SLE, and are now available to be included in clinical trials and in longitudinal studies for testing of responsiveness to change.

Disclosure: J. Bourré-Tessier, GlaxoSmithKline, 5; A. E. Clarke, Human Genome Sciences, Inc., 5, Glaxo Smith Kline, 8, Bristol-Myers Squibb, 5, MedImmune, 5; R. A. Mikolaitis, None; M. Kosinski, None; S. Bernatsky, None; J. A. Block, None; M. Jolly, GlaxoSmithKline, 5, MedImmune, 7, The Binding Site, 2, Lupus Foundation of America, 2.

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Application and Feasibility of Proposed Systemic Lupus Erythematosus Reproductive Health Care Quality Indicators At a Public Urban Rheumatology Clinic. Itziar Quinzanos[1], Angela Keniston[1], Joann Zell[2], Jinoos Yazdany[3], Alyssa Nash[1], Rebecca Fransen[1], Jennifer Stichman[1] and Joel M. Hirsh[1]. [1]Denver Health Med Ctr, Denver, CO, [2]National Jewish Health, Denver, CO, [3]University of California San Francisco, San Francisco, CA

Background/Purpose: Reproductive health quality indicators (QIs) for systemic lupus erythematosus (SLE) have recently been developed: anti-ssA, anti-ssB, and phospholipid antibody (aPL) screening prior to pregnancy; appropriate treatment of pregnancy associated anti-phospholipid antibody syndrome (PAPS); and counseling regarding risk and contraception in women taking potentially teratogenic medications (methotrexate, azathioprine, leflunomide, mycophenolate mofetil, cyclosporine, cyclophosphamide, or thalidomide). We examined performance on these QIs, their feasibility for use in a safety net rheumatology clinic, as well as sociodemographic predictors of higher performance.

Methods: Using data from the Denver Health (DH) electronic health record (EHR), we identified rheumatology clinic patients seen between July 2006 and August 2011 who had SLE, were female, and were between the ages of 18–50 years. We queried sociodemographic and other data from the EHR including age, race/ethnicity, primary language, use of interpreter services, and primary payer. Manual EHR review was conducted to determine adherence to the QIs. As a measure of feasibility, we tracked the time spent extracting the QIs. We calculated performance on each measure. For the QI regarding teratogenicity counseling, which had the largest number of eligible patients, we used either chi-square or Student's t-tests to identify the relationship between demographic characteristics and performance.

Results: 137 female SLE patients aged 18–50 years were identified. Of these, 15 were postmenopausal or status post tubal ligation or hysterectomy. Twelve pregnancies were documented during this 5-year period. Performance on the QI regarding anti-ssA, anti-ssB or aPL testing was 100%. We were unable to assess QI#2 as no pregnant patient met criteria for PAPS. 65 patients (53%) received potentially teratogenic medications. Only 30 of these patients (46%) had documented discussions about these medications' potential risk to a developing fetus upon their initiation. Age was the only sociodemographic or other variable and that predicted performance on QI#3. Patients who received teratogenicity counseling were younger on average than those who did not (29 + 8 and 35 + 10 respectively, p-value = 0.0073). The chart review time was 46 hours.

Conclusion: The new SLE reproductive health QIs allowed us to detect an important gap in counseling regarding the teratogenic risk of medications in our public health academic clinic. Greater attention to this issue is needed as only about half the patients of childbearing age received appropriate counseling, with older reproductive age women having the largest gap in care. Although extraction of the QIs was technically feasible, the time for manual EHR review was long. Electronic specification of these measures may be one way to reduce their collection burden in the future.

Disclosure: I. Quinzanos, None; A. Keniston, None; J. Zell, None; J. Yazdany, None; A. Nash, None; R. Fransen, None; J. Stichman, None; J. M. Hirsh, None.

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Alpha-Chlorofatty Acid Does Not Correlate with Baseline Subclinical Cardiovascular Disease in Systemic Lupus Erythematosus. Mary A. Mahieu[1], Camelia Guild[2], Carolyn J. Albert[2], George Kondos[3], James Carr[1], Daniel Edmundowicz[4], David A. Ford[2] and Rosalind Ramsey-Goldman[1]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Saint Louis University, Saint Louis, MO, [3]University of Illinois at Chicago, Chicago, IL, [4]Temple University School of Medicine, Philadelphia

Background/Purpose: Serum alpha-chlorofatty acid (α-ClFA) directly reflects in vivo myeloperoxidase activity, an important regulator of atherogenesis. The objective of our study was to investigate whether α-ClFA may be a biomarker for detection of subclinical cardiovascular disease (CVD) in patients with systemic lupus erythematosus (SLE).

Methods: One hundred eighty-five women with SLE and 186 controls participated in this ancillary study of the Study of Lupus Vascular and Bone Long-term Endpoints (SOLVABLE). Information on demographics, CVD risk factors, SLE risk factors, and baseline laboratory assessments were obtained at the first study visit. Using stored serum, α-ClFA was measured by liquid chromatography-electrospray ionization mass spectrometry with selected reaction monitoring detections. Each sample was run in triplicate. Coronary artery calcium (CAC) and aorta calcium (AC) were measured by either electron beam computed

tomography (EBCT) or multi-detector computed tomography (MDCT), and calcium scores were calculated with a densitometric program using the Agatston method. Outcome measures were the presence of higher risk CAC or AC scores (CAC >10 or AC >100) versus lower risk scores (CAC ≤10 or AC ≤100). Descriptive characteristics and univariate analyses were used to identify significant associations. Multivariate analyses controlled for established traditional CVD risk factors and variables found to be significant in the univariate analysis by p<0.05 between cases and controls.

Results: SLE patients had higher baseline levels of α-ClFA than controls (42.2 fmol/μl ± 19.2 vs 34.5 fmol/μl ± 10.9, p=0.014). Cases with lower risk CAC and AC scores had statistically higher levels of α-ClFA compared to controls (42.0 fmol/μl ± 17.6 vs 33.7 fmol/μl ± 10.5, p=0.010 for CAC; 40.4 fmol/μl ± 12.3 vs 33.9 fmol/μl ± 10.5, p=0.023 for AC). In contrast, cases and controls with higher risk CAC and AC scores had similar α-ClFA levels (43.3 fmol/μl ± 21.5 vs 44.0 fmol/μl ± 14.8, p=0.951 for CAC; 39.3 fmol/μl ± 7.8 vs 37.6 fmol/μl ± 13.1, p=0.743 for AC). In multivariate analyses, SLE had the strongest independent association with higher risk CAC scores (odds ratio (OR) 5.81; 95% confidence interval (CI) 2.28 to 14.83), followed by dyslipidemia (OR 5.67; 95% CI 1.50 to 21.36), and older age (OR 1.11; 95% CI 1.05 to 1.17). Dyslipidemia was defined as fasting total cholesterol >200, low-density lipoprotein >100, high-density lipoprotein <40, triglyceride >150, or use of lipid-lowering medication. SLE also had the strongest independent association with higher risk AC scores (OR 3.73; 95% CI 1.59 to 8.78), followed by history of tobacco use (OR 2.31; 95% CI 1.13 to 4.74), older age (OR 1.17; 95% CI 1.10 to 1.25), and c-reactive protein level (OR 1.05; 95% CI 1.01 to 1.11). α-ClFA was not independently associated with higher risk CAC scores (OR 1.00; 95% CI 0.99 to 1.01) or higher risk AC scores (OR 1.01; 95% CI 0.99 to 1.02).

Conclusion: SLE had the strongest association with the presence of higher risk subclinical CVD as measured by CAC and AC scores. Baseline serum α-ClFA levels were not independently associated with higher risk CAC or AC scores.

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Characterization of Pure Membranous Lupus Nephritis: A Cohort of 150 Patients. Lucía Silva[1], Teresa Oton[1], Anca Askanase[2], Patricia Carreira[3], Francisco Javier López-Longo[4], Anne Riveros[5], Iñigo Rúa-Figueroa[6], Javier Narvaez[7], Esther Ruiz-Lucea[8], Mariano Andres[9], Enrique Calvo[10], Francisco Toyos[11], Juan J. Alegre[12], Eva Tomero[13], Carlos Montilla[14], Antonio Zea[15], Esther Uriarte-Isacelaya[16], Jaime Calvo-Alen[17], Carlos Marras[18], Víctor M. Martínez-Taboada[19], María Ángeles Belmonte[20], Jose Rosas[21], Enrique Raya[22], Gema Bonilla[23] and Mercedes Freire[24]. [1]Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda (Madrid), Spain, [2]NYU School of Medicine, New York, NY, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [5]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [6]Hospital Universitario Dr Negrín, Las Palmas de Gran Canaria, Spain, [7]Hospital Universitario de Bellvitge, Barcelona, Spain, [8]Hospital de Basurto, Bilbao, Spain, [9]Hospital General Universitario de Alicante, Alicante, Spain, [10]Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain, [11]Hospital Universitario Virgen Macarena, Sevilla, Spain, [12]Hospital Universitario Dr Peset, Valencia, Spain, [13]Hospital Universitario La Princesa, Madrid, Spain, [14]Hospital Universitario de Salamanca, Salamanca, Spain, [15]Hospital Universitario Ramon y Cajal, Madrid, Spain, [16]Hospital Universitario de Donostia, Donosti, Spain, [17]Hospital Sierrallana, Torrelavega, Spain, [18]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [19]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [20]Hospital Universitario Carlos Haya, Málaga, Spain, [21]Hospital Marina Baixa, Villajoyosa, Spain, [22]University Hospital San Cecilio, Granada, Spain, [23]Hospital La Paz-IdiPaz, Madrid, Spain, [24]Hospital Universitario Juan Canalejo, La Coruña, Spain

Background/Purpose: Over 50% of patients with SLE develop renal involvement but only 20% of these are found to have pure membranous lupus nephritis (MLN) on biopsy. Few studies have addressed its pathogenesis and there is no big series describing its characteristics. Our aim is to establish the clinical characteristics, treatment and prognosis of MLN and to make international and intersocial comparisons.

Methods: Twenty-four Spanish centres and 1 in the US participated in the study. All SLE patients with biopsy proven MLN were included. Data on clinical and laboratory features, prescribed drugs, renal outcomes and survival were collected. Descriptive statistics were used to describe the main features of the series. Chi-squared distribution and Fisher test were used to analyse categorical variables and the U Mann-Whitney test for quantitative variable. A p value <.05 was considered significant. Multivariate models were built using variables that were significant in the previous univariate analysis.

Results: A total of 150 patients were included. Patients' characteristics are shown in the table. Spaniards (.032), patients with Public Health Coverage (.031), with a lower basal serum creatinine (BSC) (0.86 Vs 1,23 mg/dl;.014), a lower basal serum albumin (2.89 Vs 3.55 g/dl;.05), without previous venous thrombosis (.036) and those who had received chloroquine (.004) or azathioprine (AZA) (.022) for MLN were more prone to achieving a final proteinuria <.05 g. Female sex (.017), a low BSC (0.85 Vs 1.39 mg/dl;.001), low CRP (4.51 Vs 22.88 mg/l;.017), not having nephrotic syndrome at diagnosis (.028) and previous treatment with AZA (.03) were predictors of final proteinuria <1 g. Patients with final doubled creatinine had a greater initial BSC (1.92 Vs 0.86 mg/dl;.005) and a lower creatinine clearance (59.23 Vs 102.2 ml/min;.016). Moreover, male sex (.001), basal high blood pressure (<.001), chronic cardiopathy (.018) and peripheral artheriopathy (.039) were risk factors for doubling BSC. Renal failure was predicted by male sex (.001), HBP (.001), active sediment (.027), nephrotic syndrome (.008), higher BSC (1.97 Vs 0.81 mg/dl;.001), higher ESR (.043) and CRP (.013) and not having received angiotensin converting enzyme inhibitors (.036). Lastly, cardiac failure (.013), ischemic cardiopathy (.001), peripheral (.013) and cerebral (.012) artheriopathy, hemodialysis (.003) and not having received hydroxychloroquine (.03) or mophetil mycophenolate (.039) for MLN predicted death. Multivariate analysis for the different outcomes showed the type of health coverage and cardiovascular disease as the main predictors of poor outcome.

Table. Patients baseline characteristics

	All (150)	Spain (102)	NYC (48)	p
MLN Diagnosis				
Age at diagnosis, years	34.22 ± 12.49	33.46 ± 12.34	35.85 ± 12.78	0.275
Sex, % women	78.7	78.4	79.2	0.550
Race (Cauc/Hisp/Af-Am/As)	98/22/12/8	93/7/1/0	5/15/11/8	<0.001
Health Insurance (Pub/Priv/No)	104/22/24	102/0/0	2/22/24	<0.001
SLE duration, months	46.47 ± 64.78	37.98 ± 61.23	68.15 ± 69.21	0.012
Serum Creatinine, mg/dl	0.98 ± 0.78	0.89 ± 0.48	1.18 ± 1.20	0.047
Proteinuria 24 h, g	4.64 ± 3.55	4.72 ± 3.74	4.47 ± 3.11	0.695
Serum Albumin, g/dl	3.87 ± 5.47	4.30 ± 6.66	3.03 ± 0.82	0.222
Nephrotic Syndrome, n patients (%)	93 (67.9)	56 (56.6)	37 (97.4)	<0.001
Tobaco, no smokers	50 (46.3)	44 (48.4)	6 (35.3)	0.269
Basal HBP, n patients (%)	7 (52.1)	46 (46)	27 (67.5)	0.017
Diabetes mellitus, n patients (%)	9 (6.8)	5 (5.3)	4 (10.5)	0.232
Dyslipidemia, n patients (%)	53 (40.5)	42 (44.2)	11 (30.6)	0.110
White blood cells/mmc	6,628 ± 3,310	6,369 ± 3,314	7,254 ± 3,254	0.151
Lymphocytes, cells/mmc	1,692 ± 1,185	1,680 ± 1,126	1,723 ± 1,339	0.858
Platelets/mmc	257,209 ± 84,186	251,602 ± 90,771	269,243 ± 67,416	0.269
C3	75.65 ± 36.82	75.41 ± 37.27	76.23 ± 36.20	0.906
C4	16.29 ± 13.21	14.75 ± 11.56	19.92 ± 16.06	0.038
Positive ANA, n patients (%)	143 (95.3)	101 (99)	42 (87.5)	0.005
Positive Anti-dsDNA, n patients (%)	110 (73.3)	74 (72.5)	36 (75)	0.457
aPL positivity, n patients (%)	32 (24.6)	26 (26.3)	6 (19.4)	0.300
ESR, mm	54.19 ± 35.95	51.08 ± 30.76	63.74 ± 48.08	0.119
CRP, mg/l	9.70 ± 26.52	6.73 ± 12.72	18.48 ± 47.85	0.095
MLN Treatment				
Hydroxychloroquine, n patients (%)	47 (31.3)	37 (36.3)	10 (20.8)	0.041
Chloroquine, n patients (%)	18 (12)	18 (17.6)	0 (0)	0.001
IV Metilprednisolone, n patients (%)	13 (8.7)	11 (10.8)	2 (4.2)	0.150
Prednisone, n patients (%)	133 (88.7)	101 (99)	32 (66.7)	<0.001
Azathioprine, n patients (%)	47 (31.3)	40 (39.2)	7 (14.6)	0.002
MMF, n patients (%)	66 (44)	43 (42.2)	23 (47.9)	0.313
Cyclophosphamide, n patients (%)	38 (25.3)	29 (28.4)	9 (18.8)	0.142
Cyclosporine, n patients (%)	20 (13.3)	19 (18.6)	1 (2.1)	0.003
Tacrolimus, n patients (%)	5 (3.3)	4 (3.9)	1 (2.1)	0.486
Plasmapheresis, n patients (%)	2 (1.3)	2 (2)	0 (0)	0.461
IV Immunoglobulins, n patients (%)	2 (1.3)	2 (2)	0 (0)	0.461
Rituximab, n patients (%)	5 (3.3)	2 (2)	3 (6.3)	0.187
ACEI, n patients (%)	69 (46)	47 (46.1)	22 (45.8)	0.559
ARB, n patients (%)	30 (20)	25 (24.5)	5 (10.4)	0.033
Diuretics, n patients (%)	37 (24.7)	36 (35.3)	1 (2.1)	<0.001
Statins, n patients (%)	44 (29.3)	42 (41.2)	2 (4.2)	<0.001
Antiagregants, n patients (%)	22 (14.7)	19 (18.6)	3 (6.3)	0.035
Anticoagulants, n patients (%)	11 (7.3)	9 (8.8)	2 (4.2)	0.254
Hemodialysis, n patients (%)	6 (4)	5 (4.9)	1 (2.1)	0.374
Peritoneal dialysis, n patients (%)	1 (0.7)	0 (0)	1 (2.1)	0.320
Kidney Transplant, n patients (%)	5 (3.3)	5 (4.9)	0 (0)	0.141
Follow-up				
Mean follow-up, months	91.18 ± 89.42	117.73 ± 95.03	34.77 ± 34.16	<0.0001
Proteinuria 24 h < 0.5 g, n patients (%)	82 (64.6)	65 (69.9)	17 (50)	0.032
Proteinuria 24 h < 1 g, n patients (%)	91 (72.8)	67 (75.2)	24 (70.6)	0.525
Doubling creatinine, n patients (%)	11 (8.4)	8 (8.2)	3 (9.1)	0.557
Renal failure (Creat ≥1.2), n patients (%)	21 (15.5)	12 (34.4)	9 (9.2)	0.01
ESRD, n patients (%)	8 (5.3)	6 (5.9)	2 (4.2)	0.499
Final HBP, n patients (%)	51 (40.2)	29 (29.6)	22 (75.9)	<0.001
Death, n patients (%)	9 (6)	8 (7.8)	1 (2.1)	0.155

Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; aPL, Antiphospholipidic; ARB, Angiotensin receptor blockers; CRP, C reactive protein; ESR, Erytrosedimentation rate; ESRD, End-Stage Renal Disease; HBP, High Blood Pressure; MMF, Mophetil Mycophenolate; SLE, Systemic Lupus Erythematosus.

Conclusion: MLN usually begins with nephrotic syndrome, high proteinuria and normal serum creatinine. Its prognosis is favourable in maintaining renal function although proteinuria usually persists over time. Cardiovascular disease and some socio-sanitary factors are related with poor prognosis.

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Systematic Review of Skin Nontuberculous Mycobacteria Infection in Systemic Lupus Erythematosus: An Unusual Skin Infection Mimicking Lupus Vasculitis. Zahi Touma[1], Amir Haddad[1], Dafna D. Gladman[2], Elizabeth Uleryk[3] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [3]The Hospital for Sick Children, Toronto, ON

Background/Purpose: Nontuberculous mycobacteria (NTM) have become pathogens frequently associated with skin infection in patients on immunosuppression. NTM is not unusual in lupus patients and the unawareness of this complication delays diagnosis and treatment. Studies on infections in lupus identified the common typical bacterial pathogens and little has been published on atypical pathogens in particular NTM.

We aimed to systematically review the medical literature addressing skin NTM in lupus.

Methods: We searched Ovid Medline (1946 to March 12, 2012), Embase (1980 to March 12, 2012) for relevant publications. A study was included in the review if: 1) it included lupus patients with NTM of mucocutaneous system or soft tissue 2) it was published up to March 12, 2012 and 3) it had well-documented clinical summaries and relevant information to the objective of this study. We scanned the titles and abstracts for initial selection. Selected articles were retrieved in full and two reviewers assessed them for eligibility and extracted the data. Descriptive statistics were used to report the results of the analysis.

Results: Of the 1356 retrieved abstracts, 17 publications were identified and 25 cases of skin NTM were extracted. In this review we included only patients with skin NTM and in all but 5 patients the infection was limited to the skin. The majority of the cases occurred in females (92%). The mean age at the time of the infection was 41 ± 13.3 years, with mean lupus duration of 12.9 ± 6.7 years. Skin presentations in this review were painless to mildly painful and ranged from papules, plaques, nodules to ulcerative lesions and abscesses and few patients developed constitutional symptoms in particular fever.

NTM in lupus patients occurred after relatively long period from the initial diagnosis of lupus and after the patients had been exposed to steroids and immunosuppressants. NTM occurred in the setting of active as well as inactive lupus. The pathogen species identified in this review included mainly M. Chelonae (9 patient-events [PE]), M. Haemophilum (4 PE), M. Avium (3 PE), M. Kansasii (2 PE), M. Fortuitum (2 PE), M. Scrofulaceum (1 PE), M. Marinatum (1 PE), M. Szulgai (1 PE) and M.abscessus (1 PE). In 4 PE the culture was either negative or the specific species was not identified.

Surgical intervention in particular debridement of skin lesions were considered if needed. Empirical monotherapy therapy can be initially initiated and the final choice of antibiotics should rely on the susceptibility of the culture and clinical response. The majority of the patients' lesions improved/recovered with treatment. Nevertheless, two patients developed disseminated M. Chelonae and Fortuitum respectively and this resulted in death.

The most commonly used antibiotics in this review were ciprofloxacin, clarithromycin, ethambutol, isoniazide, rifampicin, doxycyline, amikacin, ethambutol and minocycline.

Conclusion: A high index of suspicion in lupus patients is required to diagnose NTM, as the initial presentation of NTM can mimic lupus skin manifestations. NTM should be suspected in any patient with indolent deep-nodular skin lesions, especially if routine bacterial cultures are negative.

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Efficacy of Belimumab in Systemic Lupus Erythematosus Patients with High Baseline Disease Activity. Ann E. Clarke[1], Susan Manzi[2], Michelle A. Petri[3], Richard Furie[4], Ronald F. van Vollenhoven[5], Simon Cooper[6], Z. John Zhong[6], William W. Freimuth[6] and Arthur Weinstein[7]. [1]MUHC, Montreal, QC, [2]West Penn Allegheny Health System, Pittsburgh, PA, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]North Shore-LIJ Health System, Lake Success, NY, [5]Karolinska University Hospital, Stockholm, Sweden, [6]Human Genome Sciences, Inc., Rockville, MD, [7]Washington Hospital Center, Washington, DC

Background/Purpose: To assess the efficacy of belimumab in patients with SLE who had high disease activity at baseline, as defined by SELENA-SLEDAI score ≥ 10.

Methods: In 2 randomized, double-blind, multicenter phase 3 studies, 1684 SLE patients with SELENA-SLEDAI ≥ 6 at baseline were treated with placebo, or belimumab 1 or 10 mg/kg, plus standard SLE therapy (NCT00071487/NCT00583362). In a post-hoc analysis, the SLE Responder Index (SRI) at wk 52, flares, corticosteroid use, fatigue, and the SF-36 vitality domain were examined in a subgroup of patients with baseline SELENA-SLEDAI ≥ 10.

Results: 877 patients (52%) had SELENA-SLEDAI scores ≥ 10 on entry to the BLISS trials: 299, 283, and 296 were randomized to placebo, and belimumab 1 and 10 mg/kg, respectively. Mean baseline characteristics were similar across treatment groups. In patients with SELENA-SLEDAI ≥ 10 vs ≤ 9, >80% vs 56% were anti-double-stranded−DNA positive and 55%/67% vs 34%/55% had low C3/C4 levels. In patients with SELENA-SLEDAI ≥ 10 vs all patients in the BLISS trials, 89% vs 57% had >3 organ systems involved. Belimumab 1 and 10 mg/kg significantly improved SRI response, and reduced prednisone use in high disease activity patients at wk 52 (see table). Treatment with belimumab 10 mg/kg generally resulted in a greater response than with 1 mg/kg and placebo regarding reduction in severe flare risk, and improvements in SRI response, fatigue, and SF-36 vitality at wk 52.

Efficacy in Patients With SELENA-SLEDAI Scores ≥ 10 at Baseline

Response parameter[a]	Placebo (n = 299)	Belimumab 1 mg/kg (n = 283)	Belimumab 10 mg/kg (n = 296)
SRI response: wk 52, %	44.1	58	63.2
p value		<0.001	<0.001
No new BILAG A and ≤1 new B score	65.4	73.5	74.3
p value		0.024	0.017
≥4-point reduction in SELENA-SLEDAI	48	60.4	66.2
p value		0.001	<0.001
No worsening in PGA	63.1	73.1	74
p value		0.006	0.004
Patients with ≥1 severe flare, %	28.8	21.6	18.2
Severe flare risk over 52 wk: HR (95% CI)[b]		0.73 (0.52−1.01)	0.59 (0.42−0.83)
p value		0.054	0.003
Prednisone reduction ≥25% from baseline to ≤7.5mg/day: wk 40−52, n (%)[c]	12/181 (6.6)	32/182 (17.6)	31/186 (16.7)
p value		0.002	0.004
% patients with reduction in baseline prednisone from > 7.5 to ≤7.5 mg/d at week 52	16/181 (8.8)	35/182 (19.2)	41/186 (22.0)
p value		0.007	<0.001
Mean FACIT-Fatigue score improvement: wk 52	3.38	4.76	5.12
p value		0.103	0.024
Mean SF-36 vitality score change	7.82	9.69	10.76
p value		0.196	0.044

[a] p values represent comparisons of belimumab treatment with placebo; [b]Cox proportional hazards model; [c]includes only patients with baseline prednisone >7.5 mg/d.
BILAG, British Isles Lupus Assessment Group; FACIT, Functional Assessment of Chronic Illness Therapy; PGA, Physician's Global Assessment

Conclusion: Belimumab 10 mg/kg significantly reduced disease activity, flares, corticosteroid use, and fatigue in SLE patients with high disease activity, as defined by baseline SELENA-SLEDAI scores ≥10.

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Clinical Manifestations and Predictive Factors for Response to Induction Therapy and Maintenance of Remission in ISN/RPS Class V Lupus Nephritis. Masanori Hanaoka[1], Takahisa Gono[1], Yasushi Kawaguchi[1], Hirotaka Kaneko[2], Kae Takagi[1], Hisae Ichida[1], Yasuhiro Katsumata[2], Yuko Okamoto[2], Yuko Ota[1], Sayuri Kataoka[1] and Hisashi Yamanaka[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: The pathophysiology and the content of treatment differ between International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III/IV lupus nephritis (LN) and class V LN. However, the differences in clinical manifestations have not been revealed in detail between class III/IV LN and class V LN. Moreover, predictive factors for the response to induction therapy and the maintenance of remission have not been sufficiently investigated in class V LN. The aim of this study was to clarify the clinical manifestations and predictive factors for the response to induction therapy and the maintenance of remission in class V LN compared with class III/IV LN.

Methods: 48 patients with ISN/RPS class III/IV LN and 23 patients with class V LN were consecutively enrolled at our institute from 2001 to 2010. Clinical manifestations, autoantibodies, and treatment outcomes were analyzed and compared between two subsets. We investigated the predictive factors for the response to induction therapy and the maintenance of remission.

Results: The disease duration was significantly longer (P = 0.0024), and complement component 3 was significantly higher (P = 0.0055) in the class V LN subset. The frequency of anti-dsDNA Ab positivity did not differ between two subsets. Anti-U1snRNP Ab and anti-Sm Ab positivity were significantly higher (P = 0.0054 and P = 0.012, respectively) in the class V LN subset. Patients who were anti-dsDNA Ab-positive and anti-U1snRNP Ab-negative experienced significantly more frequent complications with class III/IV LN (odds ratio 5.1, confidence interval [CI] 1.5–17.6, P = 0.010). In contrast, patients who were anti-dsDNA Ab-negative and anti-U1snRNP Ab-positive experienced significantly more frequent complications with class V LN (odds ratio 6.5, CI 1.2–35.5, P = 0.015). The combined complete and partial remission rate exhibited no significant differentiation between two subsets (82.6% in the class V LN subset and 73.3% in the class III/IV LN subset). In the non-remission subset with class V LN, the quantification of 24-hour proteinuria on induction therapy was significantly higher (P < 0.0001) than in the remission subset with class V LN. Based on the multivariate analysis, the quantification of 24-hour proteinuria was an independent predictive factor for remission in class V LN. The relapse rate exhibited no significant differentiation between two subsets (42.1% in the class V LN subset and 30.3% in the class III/IV LN subset). In the relapse subset with class V LN, the disease duration was significantly longer and the frequency of anti-Sm Ab positivity was higher than in the maintained remission subset with class V LN. Based on the multivariate analysis, the disease duration was an independent predictive factor for the maintenance of remission in class V LN.

Conclusion: LN patients who were anti-U1snRNP/Sm Ab-positive experienced more frequent complications with class V LN. In class V LN, the increased quantification of proteinuria and the longer disease duration on induction therapy were attributed to non-responder and relapsing populations, respectively. Early intervention may improve the rate of the maintenance of remission in class V LN.

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A Comparison of Systemic Lupus Erythematosus (SLE) Patients Achieving Prolonged Clinical Quiescence (PCQ) On and off Corticosteroids and/or Immunosuppressive Medications. Amanda J. Steiman[1], Dafna D. Gladman[2], Dominique Ibanez[1], Anjali Papneja[3] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [3]University of Toronto, Toronto, ON

Background/Purpose: Some patients with SLE achieve PCQ. We previously described patients achieving corticosteroid- and immunosuppressive-free PCQ. As physicians attempt to minimize patients' exposure to these medications given their associated morbidities, this study's aims were to describe patients who achieve PCQ maintained on these medications and to compare them to those maintaining medication-free PCQ.

Methods: Patients followed regularly in the Lupus Clinic from July 1970– October 2011 were identified. PCQ was defined as SLEDAI-2K=0 or =2 or 4 from active serology for ≥5 consecutive years, with visits ≤18 months apart, in patients consistently maintained on corticosteroids and/or immunosuppressives ("MED"). Charts were reviewed to qualitatively characterize the PCQ period. MED demographics and clinical course before and during PCQ were then compared to patients who achieved PCQ, defined above, but without the use of corticosteroids or immunosuppressives for its duration ("NO MED"). Descriptive statistics were used. Comparisons were made using t- and McNemar's tests.

Results: 34/1613 (2.1%) MED patients were identified. Mean MED PCQ duration was 8.5±2.9 (range 5.1–16.3) years, and ended with flare in 12 patients (35.3%). In the 22 (64.7%) patients whose PCQ did not end in flare, medications were successfully discontinued in five (14.7%), being tapered in 6 (17.6%), maintained in two (5.9%) with organ transplants necessitating ongoing immunosuppression; six (17.6%) patients were maintained on a stable regimen, with no standardized drug withdrawal algorithm specified; three patients (8.8%) were lost to follow up. 38/1613 (2.4%) NO MED patients were identified, with mean PCQ duration 11.6±6.4 (range 5.1–29.4) years. When the groups were compared, MED patients were younger at diagnosis (27.9±11.7 versus 36.1±15.2; p=0.01) and required more immunosuppressives (52.9% versus 23.7%; p=0.01) and corticosteroid (100% versus 57.9%; p<0.0001) at higher cumulative doses (42.9±39.7 versus 20.7±17.2 grams (among those requiring corticosteroids; n=22); p=0.006) prior to PCQ. There was no between–group difference in ethnicity, SLEDAI at presentation, antimalarial use, time to PCQ, organ manifestations, autoantibody profile, or SLICC damage index prior to, during, or at the last PCQ visit.

Conclusion: 2.1% of our cohort achieves PCQ of ≥5 years on corticosteroids and/or immunosuppressives; however, this group appears heterogeneous: the minority who flared, representing a group whose disease activity is merely suppressed by ongoing medication use, and the majority who tolerated/were tolerating medication withdrawal, reflective of true PCQ (as in NO MED). Further comparison between these (remission versus suppression) subgroups compared to the NO MED cohort may be instructive as each may reflect unique pathophysiology.

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Predicting Sjögren's Syndrome At Diagnosis of Systemic Lupus Erythematosus. Gabriela Hernandez-Molina[1], Tatiana Zamora-Legoff[1], Juanita Romero-Diaz[1], Carlos Alberto Nuñez-Alvarez[1], Francisco Cárdenas-Velázquez[1], Carlos Hernández-Hernández[1], Maria Luisa Calderillo[1], Martha Marroquín[1], Claudia Recillas-Gispert[1], Carmen Avila-Casado[2] and Jorge Sánchez-Guerrero[3]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]University Health Network, Toronto Canada., [3]Mount Sinai Hospital, Toronto Canada.

Background/Purpose: Sjogren's syndrome (SS) overlaps with systemic lupus erythematosus (SLE) in up to 20% of patients. Attempts to identify the characteristics of the SLE patients in whom this overlap occurs have been done in prevalent patients with long disease duration.

Aim: To identify clinical variables predicting the development of SS in SLE patients.

Methods: We included all patients from a prospective cohort of lupus of recent onset (<12 months) at enrolment. At entry, and every 3–6 months a standardized evaluation including clinical assessment and laboratory tests was

done. For SS assessment, patients undertook a sequential three phase evaluation for SS as follows: screening (six-item sicca-symptoms questionnaire, Schirmer-I and wafer tests), confirmatory (fluorescein staining test, non-stimulated whole salivary flow rate) and lip biopsy. Anti-SSA/SSB and RF (ELISA) were measured at enrollment and SS screening. SS was defined by American-European Consensus Group criteria. Statistical analysis: descriptive statistics, sensitivity (SN), specificity (SP), negative predictive value (NPV), likelihood ratio positive (LR+) and negative (LR-), logistic regression. P value <0.05.

Results: At screening for SS, the cohort comprised 105 patients. Two patients were excluded (death, hepatitis C); therefore, 93 females and 10 males were screened. Median age at lupus diagnosis and SS assessment were 25 and 30 years, respectively. Lupus duration (years) was 0.48 (0–1) at enrolment, and 4.94 years (0–6.7) at SS assessment. Although the SS status could not be defined in 14 patients, 19 patients met criteria for SS, minimum prevalence 18.5% (95% C.I. 11%–23%). All SLE/SS+ patients were females, and were older at lupus diagnosis than SLE/SS-, 30 (15–49) vs. 22 (14–54) years, P=0.003. No difference between groups was observed in lupus duration, clinical manifestations, baseline and cumulative disease activity, and damage accrual. At enrollment the prevalence of anti-SSA or anti-SSB or RF was higher in SLE/SS+ (94% vs. 61%, P= 0.006); however, individually only anti-SSA was significantly different between groups [(84% vs. 55%, P=0.02), SN 0.84, SP 0.45, NPV 0.91, LR+ 1.53 (95% C.I. 1.23–1.90), LR− 0.35 (95% C.I. 0.12–1.02). Adjusting for gender, the logistic regression analyses identified age >25 at lupus diagnosis, OR 3.8 (95% C.I. 1.19–12.4, P=0.007) and anti-SSA at baseline, OR 4.4 (95% C.I. 1.04–18.27, P=0.04) as predictors for SLE/SS+. Also, the absence of anti-SSA, anti-SSB and RF at lupus diagnosis was protective, LR− 0.14 (95% C.I. 0.02–0.95).

Conclusion: The overlap of SLE and SS occurs early during the course of lupus. Even among young patients, SLE/SS+ patients are significantly older. At lupus diagnosis, age >25 years and anti-SSA antibodies predict the overlap with SS, while the absence of anti-SSA, SSB and RF identify patients at lowest risk.

Disclosure: G. Hernandez-Molina, None; **T. Zamora-Legoff**, None; **J. Romero-Diaz**, None; **C. A. Nuñez-Alvarez**, None; **F. Cárdenas-Velázquez**, None; **C. Hernández-Hernández**, None; **M. L. Calderillo**, None; **M. Marroquín**, None; **C. Recillas-Gispert**, None; **C. Ávila-Casado**, None; **J. Sánchez-Guerrero**, None.

2245

Vitamin D Deficiency Is Associated with, but Does Not Predict, Change in hsCRP in Systemic Lupus Erythematosus (SLE). Adnan Kiani, Hong Fang and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: In the general population the cardioprotective effects of vitamin D are thought to be due to modulation of inflammatory cytokines. However, the effects of Vitamin D supplementation on inflammatory biomarkers in various trials have been inconsistent with some trials suggesting a decrease (Am J Clin Nutr 2006:83;754–9) and others finding no effect (Cytokines 2010:50;175–80). We used the NHANES (National Health and Nutrition Examination Survey) median cut off of Vitamin D at 21. We then investigated whether vitamin D was associated with or would predict change, in a major inflammatory biomarker, hsCRP, over 2 years in SLE.

Methods: 167 SLE patients (93% female, 63% Caucasian, 32% African-American, mean age 45 yrs) had measurement of hsCRP and 25 hydroxy vitamin D at baseline and at 2 years. Since distribution of hsCRP was markedly skewed, it was log transformed prior to calculating mean and performing inference.

Results: There was no difference in hsCRP or Vitamin D levels among patients with different age groups (18–30,31–49,50+) or 25-OH vitamin D levels (<21 and ≥21). However, Caucasian patients had higher 25 OH vitamin D levels compared to African-Americans (79% vs. 15%, p<0.0001). At baseline, those with above median Vitamin D had lower hsCRP. There was a decrease in mean hsCRP in both groups over 2 years, but the difference in change in the two groups was not statistically significant (p=0.78).

Table. Changes in $\log_e$ hsCRP levels, by 25-OH Vitamin D level

Measure	Mean at baseline	Mean after 2 years	Mean Change	p-value for change	Difference in change (95% CI)*	p-value for difference between groups§
Vitamin D <21 (n=78)	1.31	1.04	−0.29	0.011	0.08 (−0.26, 0.41)	0.78
Vitamin D ≥21 (n=89)	0.66	0.33	−0.37	0.0041		

* Difference in change: measure in vitamin D <21 group minus measure in vitamin D ≥21 group.
§ Adjusted for ethnicity.

Conclusion: Vitamin D deficiency was associated with higher hsCRP at baseline, but did not predict change of hsCRP over 2 years. In fact, in contrast to a previous study in the general population (Am J Cardiol 2012:226–30), which showed an increase in hsCRP levels over time with higher vitamin D levels, our study found a reduction in 25-OH vitamin D in this group, as well. Thus the behavior of vitamin D and hsCRP is different in SLE than in the general population.

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

2246

Real World Experience with Belimumab in the Management of Systemic Lupus Erythematosus (SLE): A Single Center, Observational, Post-Marketing Study. Susan S. Kim, Tanya Pavri, Kyriakos A. Kirou, Jane Salmon and Doruk Erkan. Hospital for Special Surgery, New York, NY

Background/Purpose: With the recent FDA approval of belimumab, clinicians are faced with adjusting their SLE treatment paradigm. The purpose of this study was to examine the patterns of belimumab use, as well as its tolerability and efficacy in a "real world" tertiary clinical setting.

Methods: We identified belimumab-receiving patients from our SLE Registry. We retrieved the demographics, belimumab indications, medications, ACR SLE criteria, SELENA-SLEDAI and SLICC scores, and PGA from the registry; we performed a focused infusion chart review for prophylactic-medications (acetaminophen and diphenhydramine) and infusion reactions (during or within 24 hours of the infusion). We analyzed the baseline and 3–6–9 month data in a descriptive fashion by stratifying based on baseline SELENA-SLEDAI scores (0, 1–5, ≥6), PGA scores (0–1.49, 1.5–2, 3), and prednisone dose (≤7.5, >7.5 mg).

Results: 23 patients (female: 21; mean age 38.3±12y; mean disease duration: 11.9±7.0y; mean SLICC score: 1.3±1.3) received 134 belimumab infusions (range: 1–11) between 8/11 and 6/12. All patients except one fulfilled the ACR SLE Classification Criteria; all patients were seropositive (ANA [83%] or anti-dsDNA [57%]). Indications for belimumab were active mucocutaneous disease (MC) (3), active musculoskeletal disease (MSK) (10), active MC+MSK (3), CNS lupus under remission but requiring high dose corticosteroids (CS) (2), active serositis (1), active skin ulcers (1), cutaneous vasculitis (1), cryoglobulinemia/cytopenia (1), and gastrointestinal vasculitis (1). Concomitant medications were CS 19 (83%), hydroxychloroquine 18 (78%), azathioprine 4 (17%), mycophenolate mofetil 6 (26%), and methotrexate 1 (4%). Prophylactic-medications were given to 13 (56%) patients prior to infusions; 4 (17%) experienced transient infusion reactions (itching: 1, urticarial rash: 1, headache: 1, and URI/diarrhea: 1). Table demonstrates the baseline and follow-up SELENA-SLEDAI, PGA, CS dose, dsDNA, and C3/4. One (4%) patient discontinued the medication due to lack of clinical efficacy after 2 doses. Two (8%) patients have postponed the treatment after 3 months due to hospitalizations for unrelated events (MI, MVA).

Mean±SD (#)	BL (n:23)	3-month (n:12)	6-month (n:5)	9-month (n:4)
SELENA-SLEDAI				
-BL: 0*	0 (3)	0 (2)	–	–
-BL: 1–5	3.50±1.08 (10)	3.33±1.15 (3)	–	–
-BL: ≥6	8.60±2.50 (10)	5.86±3.29 (7)	5.20±2.28 (5)**	5.50±1.91 (4)
PGA				
-Entire Group	0.92±0.69 (23)	0.55±0.47 (12)	0.54±0.45 (5)	0.75±0.65 (4)
-BL: 0–1.49	0.61±0.48 (17)	0.52±0.53 (9)	0.75±0.78 (2)	0.75±1.06 (2)
-BL: 1.5–3	1.78±0.36 (6)	0.66±0.29 (3)	0.40±0.17 (3)	0.75±0.35 (2)
Prednisone Dose				
-BL: ≤ 7.5mg	2.86±3.39 (8)	4.30±2.91 (5)	10 (1)	10 (1)
-BL: > 7.5 mg	13.17±4.06 (15)	10.71±4.50 (7)	10.00±4.08 (4)	7.92±2.60 (3)
dsDNA (+) (n/n+)	10/15 (67%)	5/10 (50%)	1/3 (33%)	0/1 (0%)
C3 Abnormal (n/n+)	9/17 (53%)	3/10 (30%)	1/3 (33%)	0/1 (0%)
C4 Abnormal (n/n+)	11/17 (65%)	6/10 (60%)	1/3 (33%)	0/1 (0%)

BL: baseline; n/n+: total # of patients with positive test/total # of patients in which the test result was available. * No disease activity at BL but history of difficulty in CS tapering; mean prednisone doses were 15.8±7.2 mg and 6.25±1.7mg at BL and 3m, respectively. ** 5 patients who completed 6m follow-up had SLEDAI scores of 9.20±2.68, 4.40±2.61, and 5.20±2.28, at BL, 3m, and 6m, respectively.

Conclusion: Our study completed in a tertiary care "real world" setting demonstrates that: a) belimumab use is not limited to patients with SELENA-SLEDAI≥6; b) infusion reaction rate is comparable to clinical trial data; and c) despite relatively small number of patients and short duration of follow-up, the results are suggestive of improved disease activity.

Disclosure: S. S. Kim, None; **T. Pavri**, None; **K. A. Kirou**, None; **J. Salmon**, None; **D. Erkan**, Human Genome Sciences, Inc., 8.

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The First Report of Desensitization to Trimethoprim/Sulfamethoxazole in Patients with Systemic Lupus Eryhtematosus. Yasuhiro Suyama[1], Mitsumasa Kishimoto[1], Hiroto Nakano[2], Ken-ichi Yamaguchi[1], Hisanori Shimizu[1], Ryo Rokutanda[1], Chisun Min[1], Yuri Ohara[1], Yoichiro Haji[1], Kazuo Matsui[2], Akira Takeda[1], Yukio Matsui[1] and Masato Okada[1]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]Kameda Medical Center, Kamogawa City, Japan

Background/Purpose: Trimethoprin-sulfamethoxazole (TMP/SMX) is the most effective and widely used prophylactic medication in immunocompromised patients. Some diseases are well-known to cause allergic reactions including human immunodeficiency virus (HIV) infection and systemic lupus erythematosus(SLE). As opposed to HIV infection, the allergic reactions in patients with SLE are often severe and result in discontinuation, which leaves the patients with high risk of serious, sometimes life-threatening infection. We examined the efficacy and safety of the TMP/SMX desensitization protocol in patients with SLE.

Methods: We conducted a retrospective cohort study in the two major urban and rural hospitals in Japan. The oral TMP/SMX desensitization protocol was applied among SLE patients who newly received TMP/SMX prophylaxis from 2009 to 2012 (Group A). The outcomes were compared with SLE patients who had been previously prescribed with usual dose of TMP/SMX prophylaxis for the first time from 1997 to 2012 (Group B). Firstly, we studied the incidence of allergic reactions to TMP/SMX prophylaxis in between Group A and B. Secondly, we assessed the risk factors for the allergic reactions using patient's demographics and laboratory data including specific antibody status. T-test and $\chi2$ test were performed to analyze these data.

Results: A total of 17 patients (2 men and 15 women, the mean age; 45.2 years old, the average dose of steroid; 160.4 mg/day of prednisone or equivalent) were enrolled for this protocol in Group A and 30 patients (3 men and 27 women, the mean age; 38.1 years old, the average dose of steroid; 26.2 mg/day of prednisone or equivalent) in Group B. Patient characteristics including sex, age, and the mean dose of steroid between groups showed no differences when compared statistically. Our analysis revealed more than half of the reduction in the incidence of allergic reactions in Group A (3/17; 17.6%) than Group B (12/30; 40%) (p = 0.114). In addition, in Group B, there was a higher positive rate of anti-SS-A/Ro antibody related to allergic reactions (83.3% in allergic reactions vs 16.7% in no allergic reactions; p = 0.019), but not with other specific antibodies. Furthermore, to compare only in SLE patients with positive anti-SS-A/Ro antibody, there were significantly fewer allergic reactions in Group A (3/13; 23.1%) than Group B (5/6; 83.3%) (p = 0.013). No patients who neither required hospitalization nor increased the dose of steroid therapy due to SLE flare related to prophylaxis were documented in both Group A and B.

Conclusion: Our findings suggested that the TMP/SMX desensitization protocol would be a simple, safe, and effective means for SLE patients to prevent allergic reactions. To our knowledge, this is the first report of attempting to desensitize allergic reactions to TMP/SMX in patients with SLE. An anti-SS-A/Ro antibody positive status might be a risk factor for allergic reactions to usual dose of TMP/SMX prophylaxis and it would also predict good candidates to initiate the desensitization protocol.

2248

Serum Phosphatidylserine-Specific Phospholipase A1 (PS-PLA1) Identified As a Novel Biomarker for Systemic Lupus Erythematosus (SLE). Tetsuji Sawada[1], Kazuhiro Nakamura[2], Ryunosuke Ohkawa[2], Aki Shoji[1], Koichiro Tahara[1], Haeru Hayashi[1], Eri Kimura[1], Koji Igarashi[3], Junken Aoki[4] and Yutaka Yatomi[5]. [1]Tokyo Medical University, Tokyo, Japan, [2]The University of Tokyo Hospital, Tokyo, Japan, [3]TOSOH Corporation, Kanagawa, Japan, [4]Graduate School of Pharmaceutical Sciences, Tohoku University, Miyagi, Japan, [5]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background/Purpose: Lysophosphatidylserine (LPS), which is a degraded form of phosphatidylserine (PS), is an acidic lyso-glycerophospholipid, similar to lysophosphatidic acid (LPA). LPS is known to mediate a number of biological processes through G protein coupled receptors, and may act as a lipid mediator in autoimmunity. LPS and LPA are generated by lyso-glycerophospholipid producing enzymes, PS-specific phospholipase A1 (PS-PLA1) and phosphatidic acid (PA) selective PLA1, known as autotaxin (ATX), respectively. The purpose of the present study is to determine the serum levels of PS-PLA1 and ATX in sera from patients with systemic lupus erythematosus (SLE), and to investigate their relationship with disease activity.

Methods: Serum levels of PS-PLA1 and ATX of 34 patients with active SLE were quantified by enzyme-linked immunoassay. As for 26 patients with SLE, serum PS-PLA1 levels after corticosteroid treatment were also measured, and their correlation with disease activity and organ damage, as evaluated by SLE Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG) index, were examined. Sera from 40 patients with active rheumatoid arthritis (RA), 23 patients with Sjogren syndrome (SjS), and 23 patients with systemic sclerosis (SSc) were utilized as disease controls.

Results: Serum PS-PLA1 levels were significantly higher in patients with SLE than those in disease controls, while serum levels of ATX were similar among all patients. In SLE patients, serum levels of PS-PLA1 were positively correlated with global SLE activity indices (SLEDAI and BILAG scores) and serum IgG levels, but negatively correlated with complement C3 levels. Regarding individual organ damage, serum PS-PLA1 levels were significantly correlated with the BILAG score for general constitutional symptoms, the mucocutaneous system, and vasculitis. Furthermore, serum PS-PLA1 decreased after immunosuppressive treatment in SLE patients.

Conclusion: The association of serum PS-PLA1 levels with SLE disease activity indicates that measurement of serum PS-PLA1 may be useful for the clinical evaluation of SLE as a novel biological marker. Specific elevation of PS-PLA1 in SLE suggests that lysophosphatidylserine (LPS) generated from PS-PLA1 may be involved in the pathogenesis of SLE.

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Comparison of Mycophenolate Mofetil and Intravenous Cyclophosphamide As Induction Therapy in Korean Patients with Lupus Nephritis. Dong-Jin Park, Kyung-Eun Lee, Tae-Jong Kim, Yong-Wook Park and Shin-Seok Lee. Chonnam National University Medical School, Gwangju, South Korea

Background/Purpose: Although intravenous cyclophosphamide (IVC) pulses are generally accepted as standard therapy for induction treatment of active proliferative lupus nephritis (LN), several clinical trials have suggested that mycophenolate mofetil (MMF) is at least as effective as IVC. The efficacy of IVC varies among racial and ethnic groups and IVC is less effective in patients of African or Hispanic descent. In contrast, MMF seems to be consistently effective in all racial/ethnic groups. Nevertheless, it is necessary to compare these two treatment modalities among different racial or ethnic groups, particularly in Asia. This study compared the efficacy of MMF and IVC as induction treatment for LN in ethnically homogeneous Korean patients.

Methods: This study enrolled 49 LN patients with available kidney biopsy specimens. Sociodemographic, clinical, laboratory, and treatment-related data at the time of kidney biopsy and during follow-up were obtained by reviewing the patients' charts. The renal biopsy specimens were reclassified according to the ISN-RPS classification, by a renal pathologist blinded to the previous classification. The renal outcome, i.e., complete response (CR), partial response (PR), and non-response (NR), after 6 and 12 months was defined according to the ACR 2006 response criteria for proliferative and membranous renal disease in clinical trials.

Results: Of the 49 patients, 28 (57.1%) were treated with IVC and 21 (42.9%) with MMF, both in combination with prednisolone. The baseline characteristics of the two groups were comparable, except that the IVC-treated patients had lower platelet counts ($p=0.026$), lower C3 levels ($p=0.007$), and higher activity scores ($p=0.021$) in the renal biopsy compared to the MMF-treated patients. CR was seen in 9 of 21 patients (42.9%) receiving MMF and 14 of 28 patients (50.0%) receiving IVC after 6 months treatment ($p= 0.450$) and in 11 of 21 patients (52.4%) in the MMF group and 13 of 28 patients (46.4%) in the IVC group at 1 year ($p= 0.745$). The number of patients achieving PR and NR did not differ significantly at 6 and 12 months between the treatment groups.

Conclusion: These findings suggest that the efficacy of oral MMF at 1 year does not differ from that of IVC in induction treatment of LN in ethnically homogeneous Korean patients. MMF may be considered first-line induction therapy for treating LN in these patients.

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2250

A Clinical Analysis of Adult Patients with Autoimmune- and Infection-Associated Hemophagocytic Lymphohistiocytosis. Min W. So[1], Bon S. Koo[1], You J. Kim[1], Yong-G Kim[1], Wook J. Seo[2], Chang-K Lee[1] and Bin Yoo[1]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Seoul Veterans Hospital, Seoul, South Korea

Background/Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening disease. Secondary HLH is associated with various clinical conditions, including infections, malignancies, and autoimmune diseases. Although many previous studies reviewed the clinical features, treatments, and outcomes of autoimmune- or infection-associated HLH, respectively, only a few studies have evaluated the differences between autoimmune- and infection-associated HLH to these factors. The purpose of our study was to identify and compare the clinical features, treatments, and outcomes of patients with secondary HLH caused by diseases other than malignancy at a single institution.

Methods: We retrospectively collected data on 33 adult patients who were diagnosed with autoimmune- or infection-associated HLH from 1997 to 2011 at a single tertiary hospital. Patients were eligible if they were over 15 years of age and met five criteria for HLH. Patients were classified as having autoimmune- or infection-associated HLH and the medical data on each patient were reviewed.

Results: Twelve patients were diagnosed as having autoimmune-associated HLH. Among the 12 patients, nine patients had SLE and three patients had adult-onset still's disease. Steroid therapy was given to all patients. Eleven patients recovered from autoimmune associated HLH. Twenty one patients were diagnosed as having infection-associated HLH. The most common infection associated with HLH was EBV (n = 19, 90.5%) followed by hepatitis A virus (n = 1, 4.8%) and parvovirus B19 (n = 1, 4.8%). Thirteen patients were treated according to the HLH protocol. Among the 21 patients, five patients underwent allogenic HCT. Only four patients survived without disease; three of the five transplant recipients and one of the 16 patients who had received no transplants. With respect to clinical characteristics, splenomegaly was more common in patients with infection-associated HLH (p = 0.010). With respect to laboratory characteristics, the platelet count and the level of ESR were lower in the infection-associated HLH group (p = 0.009 and p = 0.020). Hyperbilirubinemia was more prominent in the infection-associated HLH group (p = 0.015). Concerning treatment, patients with infection-associated HLH received the more commonly administered cyclosporine A and etoposide therapy than patients with autoimmune-associated HLH. Patients with infection-associated HLH (19.0%) had a lower survival rate than patients with autoimmune-associated HLH (91.7%).

Conclusion: Secondary HLH is a syndrome-based diagnosis as it encompasses various heterogeneous conditions. In the present study, autoimmune-associated HLH has mild disease activity and is included mild disease entity. Although there is still considerable debate regarding the ideal initial management approach for patients with autoimmune-associated HLH, corticosteroid administration alone seems to be sufficient. In secondary HLH, an exhaustive search for an underlying cause, such as infection or autoimmune disease, is warranted as the results of such research may guide treatment regimens and help predict outcomes.

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High Sensitivity C-Reactive Protein, Disease Activity and Cardiovascular Risk Factors in Systemic Lupus Erythematosus. Chi Chiu Mok[1], Daniel Birmingham[2], Ling Yin Ho[1] and Brad H. Rovin[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Ohio State University Medical Center, Columbus, OH

Background/Purpose: To study the level of high-sensitivity C-reactive protein (hsCRP) and its relationship with disease activity, damage and cardiovascular risk factors in patients with systemic lupus erythematosus (SLE).

Methods: Consecutive patients who fulfilled [3]4 ACR criteria for SLE but did not have concurrent infection were recruited. Blood was assayed for hsCRP and markers of SLE activity. Clinical activity, organ damage of SLE (SLE damage index; SDI) and cardiovascular risk factors were also assessed. Linear regression was performed for the relationship among hsCRP, SLE activity, damage and cardiovascular risk factors.

Results: 303 consecutive SLE patients were invited for this study but 14 were excluded because of evidence of active infection. Two hundred and eight-nine SLE patients were finally studied (94% women; age 39.0 ± 13.1 years; SLE duration 7.8 ± 6.7 years). The mean SLEDAI score was 4.9 ± 5.6 and clinically active SLE was present in 122(42%) patients. The mean hsCRP level was 4.87 ± 12.7mg/L, and 28(23%) patients with active SLE had undetectable hsCRP (<0.3mg/L). In contrast, 51 patients (80%) who did not have clinical or serological activity (SLEDAI score = 0; N=64) had undetectable hsCRP. Linear regression revealed a significant correlation between hsCRP and musculoskeletal (Beta=0.21), hematological (Beta=0.19), serosal (Beta=0.46) and clinical SLEDAI score (Beta=0.24), adjusting for age, sex, body mass index, creatinine and the use of various medications (p<0.005 in all). Levels of hsCRP correlated significantly with anti-dsDNA titer (Beta=0.33; p<0.001) but not with complement C3 (Beta=0.07; p=0.26). Significantly more patients with hsCRP>3.0mg/L were men and chronic smokers, and had diabetes mellitus, dyslipidemia (higher atherogenic index and total / HDL cholesterol ratio) and history of arterial thrombosis. HsCRP level correlated significantly with SDI scores in the pulmonary and endocrine system after adjustment for similar covariates.

Conclusion: hsCRP level is detectable in 77% of SLE patients with clinically active disease and correlates with SLEDAI scores, particularly serositis and in the musculoskeletal and hematological systems. Elevated hsCRP in SLE is associated with certain cardiovascular risk factors and history of arterial thromboembolism.

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2252

Epratuzumab-Treated Systemic Lupus Erythematosus Patients Report Improvements in Health-Related Quality of Life: Final Results from an Open-Label Extension Study (SL0006). V. Strand[1], K. Hobbs[2], D.J. Wallace[3], K. Kalunian[4], B. Kilgallen[5], E. Nikaï[6], W.A. Wegener[7] and D.M. Goldenberg[8]. [1]Stanford University, Palo Alto, CA, [2]Denver Arthritis Clinic, Denver, CO, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]UCSD School of Medicine, La Jolla, CA, [5]UCB Pharma, Smyrna, GA, [6]UCB Pharma, Brussels, Belgium, [7]Immunomedics Inc, Morris Plains, NJ, [8]Centre for Molecular Medicine and Immunology, Morris Plains, NJ

Background/Purpose: Epratuzumab, a monoclonal antibody targeting CD22, is in development for the treatment of systemic lupus erythematosus (SLE). Two randomized controlled trials (RCTs): ALLEVIATE 1 and 2 were prematurely terminated because of interruption of drug supply. SL0006 was an open-label extension study in which patients previously enrolled in the ALLEVIATE trials received epratuzumab.[1] Assessment of health-related quality of life (HRQoL) alongside measures of disease activity and damage is recommended in SLE RCTs and provides a comprehensive view of therapeutic responses.[2,3] This presentation reports final data from SL0006 on the effect of epratuzumab on HRQoL measured using the 36-item Short Form Health Survey (SF-36).

Methods: All patients enrolled in ALLEVIATE US sites who received randomized treatment (n = 60) and satisfied all inclusion criteria were eligible for enrollment in SL0006. Twenty-nine patients (90% female, 79% Caucasian, mean age 40 years) entered SL0006, having received placebo (n = 8), 360 (n = 17) or 720 (n = 4) mg/m^2 epratuzumab during the ALLEVIATE double-blind trials. In SL0006, all patients received 12-week cycles of 360 mg/m^2 epratuzumab; two infusions on days 1 and 8 of each cycle. SF-36 was assessed at screening and every 4 weeks thereafter. Mean changes were compared to ALLEVIATE baseline and SL0006 screening values.

Results: The table shows means and mean changes in PCS and MCS and individual SF-36 domain scores vs age- and gender-matched norms.[4] At ALLEVIATE baseline, PCS and MCS scores were approximately 2 and 1 standard deviations below normative values, respectively; domain

scores 7.9–48.5 points lower than age- and gender-matched norms, reflecting the broad impact of active SLE on HRQoL. At the SL0006 screening visit, mean changes from ALLEVIATE baseline (BL) in SF-36 PCS and 5 domain scores met or exceeded minimal clinically important differences (MCID). Throughout SL0006, these improvements were maintained or improved up to and including week 192, after which patients numbers were <50% of the screening population. Changes from ALLEVIATE baseline scores were ≥ MCID in PCS and all its domains at all timepoints, apart from RE and MH, where numerical improvements were evident and ≥ MCID at some visits. Further improvement during SL0006 was evidenced by clinically meaningful changes from the screening visit at most timepoints in PCS, RP, BP, GH, VT and SF, and at the last available visit for PCS RP, BP and SF.

Key ...

Cells shaded with this colour show <u>mean change from ALLEVIATE baseline ≥ MCID</u> (≥5.0 for SF-36 domains and ≥2.5 for PCS and MCS)

Cells shaded with this colour show <u>mean change from SL0006 screening ≥ MCID</u> (≥5.0 for SF-36 domains and ≥2.5 for PCS and MCS)

Measure...	Physical Component Summary PCS	Mental Component Summary MCS	Physical Function PF	Role Physical RP	Bodily Pain BP	General Health GH	Vitality VT	Social Function SF	Role Emotional RE	Mental Health MH
ALLEVIATE baseline (n = 29)	31.8	42.2	52.8	35.8	37.6	30.5	31.5	48.7	67.8	62.6
SL0006 (screening) (n = 29)	36.3	43.4	60.0	47.6	43.5	38.0	35.8	54.7	71.0	64.7
Week 12 (n = 29)	38.6	44.5	65.3	50.7	54.0	40.9	43.1	58.6	71.0	69.3
Week 24 (n = 25)	38.0	43.7	64.2	49.5	50.1	41.6	37.5	61.0	69.3	67.6
Week 48 (n = 29)	39.1	43.6	63.4	55.1	52.6	43.4	40.0	59.8	70.2	66.1
Week 72 (n = 22)	41.2	44.6	64.8	62.8	55.8	46.4	46.0	64.8	72.4	66.9
Week 96 (n = 22)	39.5	44.4	66.1	57.7	50.5	42.4	40.3	66.5	72.0	66.8
Week 120 (n = 19)	39.1	44.3	61.6	56.3	49.9	42.4	40.5	62.5	70.6	69.0
Week 144 (n = 21)	39.3	45.0	65.9	56.0	51.1	43.5	43.8	63.7	73.4	67.4
Week 168 (n = 18)	38.8	44.4	58.9	55.6	52.9	42.7	44.1	63.9	68.5	66.3
Week 192 (n = 18)	39.3	42.5	63.9	50.7	51.8	41.9	43.4	61.1	65.3	64.2
Last visit (n = 29)	38.3	44.2	62.4	55.6	48.6	41.2	39.9	62.9	68.4	68.5
Age- and gender-matched norms	50 ± 10	50 ± 10	85.5	84.3	71.0	69.6	54.1	81.8	85.8	70.5

Conclusion: In an open-label, single-arm extension to 2 double-blind studies, patients receiving epratuzumab reported clinically meaningful improvements in HRQoL that were sustained over approximately 4 years of treatment.

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2253

Metabolic Syndrome Is Not Only a Risk Factor for Cardiovascular Events in Systemic Lupus Erythematosus but Also Associated with Cumulative Organ Damage: A Cross-Sectional Analysis of 311 Patients. Semra Ertan-Demir[1], Bahar Artim-Esen[1], Yasemin Sahinkaya[1], Özlem Pehlivan[1], Nilüfer Alpay-Kanitez[1], Ahmet Omma[1], Burak Erer[2], Sevil Kamali[1], Ahmet Gul[1], Orhan Aral[1], Lale Ocal[1] and Murat Inanc[1]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have increased rates of cardiovascular (CV) events that are one of the major causes of mortality. In addition to the traditional CV risk factors, disease related features may contribute to accelerated atherosclerosis. The metabolic syndrome (MetS), defined by clustering of traditional CV risk factors, is reported to be increased in SLE. The aim of this study was to determine the prevalence of MetS and CV events in SLE patients and to study the link between these and SLE related factors.

Methods: Data of 311 SLE patients attending to the lupus clinic and fulfilling ACR classification criteria were collected from the records including demographic and clinical features, history of CV diseases and phenotype and characteristics of MetS as defined by the National Cholesterol Educational Programme Adult Treatment Panel III (NCEP ATP III). CV events were defined as documented coronary artery disease and cerebrovascular disease including myocardial infarction and stroke. Association with clinical features, disease duration, SLICC damage index and treatment of SLE were assessed in patients with MetS and without MetS.

Results: The mean age of the patients was 40,2± 13,4 years and (89%) were female. The mean disease duration was 112,5 ±84 months, and the mean SLICC damage score was 1,05 ± 1,5. Coronary artery disease was present in 11.1% and cerebrovascular disease was in 5.4%. The prevalence of cardiovascular events was 15.2% and of MetS was 19%. The most frequent and the least frequent criteria of MetS in SLE patients were abdominal obesity (%51,2) and hyperglycemia (%10,3) respectively. Comparing SLE patients with MetS and without MetS, age (p=0,001), cumulative damage (p<0,001), disease duration (p=0,026) and CV events (p=0,001) were associated significantly with MetS. SLE disease features and treatment modalities were not associated with MetS. CV events were related to disease duration (p=0,05), damage (p<0,001), pericarditis (p<0,001), hematologic involvement (p=0,006), lymphopenia (p<0,001), thrombocytopenia (p=0,002), neurological involvement (p<0,001) and antiphospholipid (APL) antibody positivity (p=0,008). No relationship was found between immunosuppressive drug usage or high dose corticosteroid treatment with CV events, whereas HCQ use was found protective [p= 0,005; OR: 0,32 (0,15–0,69)].

Conclusion: In SLE patients mainly consisted of young females, the prevalance of MetS was 19% and CV events was 15.2%. Mets was associated with CV events, age, disease duration and cumulative damage whereas clinical and serological features of SLE and treatment were not related to MetS. CV events was also associated with disease duration, organ damage, pericarditis, hematological involvement, neurological involvement and the presence of APL antibodies. There was a significant protective effect of HCQ from CV events in SLE. The prevention of MetS and long term use of HCQ are warranted to improve prognosis in SLE.

2254

Discoid Lupus in Patients with Systemic Lupus Erythematosus. Ghassan AlJohani, Dominique Ibanez, D. D. Gladman and Murray B. Urowitz. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Discoid lupus lesions occur in 20% of patients with SLE at some point in their disease course, and are often resistant to therapy. Atrophy, scarring, and pigmentation are often observed consequences. Recently poor response to hydroxychloroquine has been reported among SLE patients as compared with discoid lupus erythematosus (DLE) patients without SLE.

The purpose of this study was to evaluate clinical outcome of active discoid lesions in patients with SLE and examine associated features of active discoid lupus.

Methods: Patients with active discoid lupus were identified from the University of Toronto lupus clinic, a longitudinal observational cohort study of patients with SLE diagnosed on the basis of 4 ACR criteria or 3 criteria and a biopsy positive for lupus. For each patient, information on time of resolution and chronic changes of discoid lupus lesion were obtained from the database and confirmed through chart reviews. Associated features studied included demographic features, smoking, and disease activity (SLEDAI-2K). Descriptive statistics are used to describe the study population.

Results: 68 patients with active discoid lupus were identified from among 723 inception patients (9.4%). which represented 15% of the total number of patients who had any lupus rash. The age at diagnosis of SLE was 37.2 ± 11.9 years while age at diagnosis of DLE was 39.6–11.9. 59 (86.8%) were female and 41 (60.3%) were Caucasian. 30 (44.1%) patients were smokers. SLEDAI-2K was 8.66 ± 7.72 at discoid onset and adjusted mean SLEDAI was 7.51 ± 6.68. 43 (63.2%) patients were on steroid during the episode with mean steroid dose of 16.8 ± 11.6 mg/day. 56 (82.4%) were on antimalarial agents while 18 (26.5%) were on immunosuppressive agents. During their follow up 68 patients had a total of 82 episodes of DLE. Each episode lasted for 1.77 ± 2.10 years. SLE duration at discoid start is 2.3 ± 4.1 years. Pre-existing scars from previous active DLE were present in 21 (30.9%) patients while 11 (16.2%) patients developed new scars during episode and 36 (52.9%) patients never developed scars.

Conclusion: Discoid lupus is a common rash among SLE patients. SLE patients with DLE had active lupus and were taking significant doses of steroid. The duration of the discoid episode was 1.77 ± 2.10 years and 47.1% of patients developed scars.

2255

Apolipoprotein B Containing Lipoprotein Subclasses and Subclinical Atherosclerosis in Patients with Systemic Lupus Erythematosus (SLE).
Adnan Kiani[1], Hong Fang[1], Ehtisham Akhter[1], Carmen Quiroga[2], Nancy Simpson[2], Petar Alaupovic[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Oklahoma Medical Research Foundation, Oklahoma, OK

Background/Purpose: Traditional classification in lipid biology using HDL, LDL and VLDL does not provide information on lipoprotein function. Apolipoproteins, (which are protein components of plasma lipoproteins including A, B, C, D, E) with their different composition, metabolic and atherogenic properties provide a much detailed insight on lipoprotein functioning. In particular ApoB/A-1 ratio is associated with atherogenic LDL and development of cardiovascular disease. Lipoprotein function Apolipoprotein C-III and its corresponding Apolipoprotein B subclasses have been shown to be independent risk factors for cardiovascular disease in the general population (Circulation. 102:1886–92;2000 and Aterioscler Thromb Vasc Biol. 23:853–858;2003)). We explored the association between these non-traditional risk factors with subclinical measures of atherosclerosis (coronary artery calcium) in SLE.

Methods: 58 SLE patients (97% female, 58% Caucasian, 40% African-American, 2% other, mean age 44±11 yrs) had measurement of apolipoprotein and lipoproteins measured by immunoturbidimetric procedures, electroimmunoassays and immunoprecipitation. Coronary artery calcium was measured by helical CT. The p-value in the table is adjusted for age, gender, and ethnicity.

Results:

Table 1. Coronary artery calcium (CAC) and Lipoprotein Subclasses

Measures Traditional CVRF	N Normal	N Abnormal	Log_e(CAC score+1) Mean (SD) Normal	Log_e(CAC score+1) Mean (SD) Abnormal	P-value (adjusted)
Total Cholesterol (mg/dl)	42	16	0.97 (1.64)	2.20 (2.46)	0.092
Triglycerides (mg/dl)	48	10	1.14 (1.57)	2.15 (3.23)	0.20
VLDL-C (mg/dl)	41	17	1.23 (1.61)	1.52 (2.65)	0.89
LDL-C (mg/dl)	40	14	1.02 (1.66)	2.41 (2.56)	0.083
HDL-C (mg/dl)	10	44	1.17 (1.30)	1.43 (2.14)	0.39
Cardioprotective					
ApoA-I	21	37	0.80 (1.26)	1.60 (2.22)	0.15
LpA-I	38	20	1.18 (1.95)	1.57 (1.99)	0.41
LpA-I:A-II	15	43	1.08 (1.40)	1.39 (2.12)	0.39
Atherogenic					
LpB:E+LpB:C:E	39	19	1.07 (1.78)	1.81 (2.25)	0.24
ApoB	46	12	1.32 (1.82)	1.28 (2.49)	0.60
LpB	55	3	1.34 (1.99)	0.80 (1.10)	0.47
LpB:C	55	3	1.38 (1.98)	0.00 (0.00)	0.24
ApoC-III	46	7	1.30 (1.90)	2.08 (2.75)	0.60
ApoC-III-HS	23	30	0.96 (1.55)	1.75 (2.28)	0.17
ApoC-III-HP	50	3	1.4 (2.0)	1.1 (1.9)	0.76
CIII-R	–	53	–	1.41 (2.02)	–
LpA-II:B:C:D:E	36	22	1.23 (1.78)	1.44 (2.25)	0.63
ApoB/ApoA-I	44	14	1.36 (1.92)	1.14 (2.12)	0.97

Conclusion: It has been shown that apoC-III containing apoB lipoproteins are risk factors for atherosclerotic progression in rheumatoid arthritis patients (Arthritis Care Res doi:10.1002.21646;2012). In our study there was no association between any of the markers with coronary artery calcium. However, we did show that cardioprotective components including LpA-1 and ApoA-I were decreased whereas atherogenic LpA-II:B:C:D:E was increased in our patient population compared to controls. Further studies with larger sample size are warranted to confirm our findings.

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A Population of IL-21 Producing CD4+ T Cells Correlates with Disease Damage in Systemic Lupus Erythematosus (SLE) Patients.
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Background/Purpose: SLE mice models implicate IL-21, a T cell-derived cytokine, in disease pathogenesis with cytokine over-expression promoting the development of auto-antibodies and lupus-like clinical syndromes. IL-21 dysregulation has also been noted in human SLE with a subset of patients having an increased proportion of IL-21-producing CD4+ T cells. This study aims to examine the relationship between IL-21 synthesis and distinct clinical phenotypes in human SLE.

Methods: SLE patients (n = 42) fulfilling ≥ 4 ACR criteria were recruited from an established longitudinal lupus cohort. Clinical and biochemical assessment at the time of recruitment permitted calculation of disease activity (SLEDAI-2K) and SLICC damage index. Healthy age matched controls (n = 19) were also recruited. Peripheral blood mononuclear cells were isolated over a Ficoll gradient and stimulated for 4 hours with PMA/ionomycin in the presence of GolgiStop. Cells were analyzed by flow cytometry following cell surface (anti-CD3, -CD4) and intracellular staining (anti-IL-21, -IL-17). A Mann Whitney non-parametric test was used for comparisons between groups. Elevated IL-21 expression for selected CD4+ populations was defined as values ≥ 2 standard deviations above the mean for controls.

Results: A significant proportion (26.4%) of SLE patients was found to have increased levels of CD4+ IL-21 producing T cells when compared to controls. To refine this cellular population the proportion of IL-21+, IL-17+ and double positive CD4 T cells was examined. The proportion of IL-21+IL-17^{neg}CD4+ cells was significantly elevated in SLE patients when compared to controls (p = 0.03). The IL-17+IL-21^{neg}CD4+ SLE compartment was also increased but did not reach statistical significance. No differences were noted in the double positive (IL-21+IL-17+) CD4+ T cell populations. To examine the relationship between the IL-21+IL17^{neg}CD4+ population and specific clinical phenotypes patients were segregated on the basis of the proportion of IL-21+IL17^{neg}CD4+ cells into IL-21 high patients (n = 10) with an equal number of patients with the lowest IL-21 expression selected as a comparator group. No statistically significant differences between these two groups (high vs low, mean ± SD) with regards to disease activity (5.8 ± 3.5 vs 5.7 ± 6.4), anti-dsDNA antibodies (35.6 ± 39.8 vs 44.0 ± 41.9) or complement levels (0.89 ± 0.18 vs 0.98 ± 0.38) was noted. IL-21 high patients had significantly higher disease damage index (SDI, p < 0.0001) than IL-21 low individuals. As a corollary patients were stratified into quartiles based on their SDI score. Patients with the highest SDI score had statistically significant higher proportion of IL-21+ IL17^{neg} CD4+ T cells (p = 0.02) than patients in the lowest quartile.

Conclusion: These results suggest that T cell population(s) contributing to IL-21 dysregulation in SLE reside within the IL-21+ IL-17^{neg} CD4+ T cell subset. Further, as disease damage can be viewed as a surrogate marker of disease severity, this data implies that increased IL-21 synthesis may be linked to more aggressive forms of SLE.

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Association of Low Vitamin D with High Disease Activity in an Australian Systemic Lupus Erythematosus Cohort.
Kristy S. Yap[1], Alberta Y. Hoi[2] and Eric F. Morand[2]. [1]Monash Medical Centre, Clayton, Australia, [2]Monash University, Melbourne, Australia

Background/Purpose: Previous cross-sectional studies suggest that low vitamin D may be associated with higher disease activity in SLE. Vitamin D status varies with geographic location and no studies have been reported in the Southern hemisphere. The aim of this study was to determine the relationship between Vitamin D and disease activity in SLE patients in an Australian centre.

Methods: Data was collected prospectively on patients with SLE (>4 criteria) in the Monash Lupus Clinic in Melbourne Australia between January 1 2008 and January 1 2011 who had disease activity (SLEDAI-2k) and serum 25-hydroxyvitamin D concentration (VD25) measured at the same visit. Where multiple values were available, the assessment with lowest VD25 was used (n=119).

Results: Patients with VD25 in the lowest quartile had significantly higher SLEDAI (7.7±1.3) compared to those in the highest quartile (3.9±0.8, p=0.014). Accordingly, VD25 deficiency (VD25 ≤40, n=28) was associated with significantly increased SLEDAI (7.7±1.3) compared to patients with VD25 >40 (4.8±0.6, P=0.02). The relative risk of high disease activity (SLEDAI>8) for patients with VD25 deficiency was 1.6 (95% CI 1.1–2.2, P=0.002). In parallel, high disease activity was associated with significantly lower VD25 compared to patients with SLEDAI<8 (P= 0.048) or patients with inactive disease (SLEDAI<4, P=0.0073). When assessing all values, a significant negative correlation between SLEDAI and VD25 was observed (Spearman r =0.2, p =0.03). There was no association of VD25 with corticosteroid use, SLICC SLE Damage Index (SDI), or ethnicity.Vitamin D supplement use (n=53) was significantly more common among patients using corticosteroids (P=0.0001) and was associated with significantly higher VD25 (P=0.009). However, there was no association between Vitamin D supplementation and SLEDAI.

Conclusion: In a cohort of Australian patients with SLE, Vitamin D correlates negatively with disease activity. Prospective studies should examine the predictive value of Vitamin D levels and therapeutic effect of Vitamin D.

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Risk Factors for Total Joint Replacement in Systemic Lupus Erythematosus Patients with Avascular Necrosis. Jennifer Lee[1], Dae-Jun Kim[1], Jae Ho Lee[1], Seung Min Jung[1], Seung-Ki Kwok[1], Ji Hyeon Ju[2], Kyung-Su Park[1], Sung-Hwan Park[1] and Ho-Youn Kim[1]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea, [2]College of Medicine, The Catholic University of Korea, Stanford University, Seoul, Palo Alto, CA

Background/Purpose: Avascular necrosis (AVN) is a common manifestation in patients with systemic lupus erythematosus (SLE) and is associated with significant morbidity. A number of studies have been conducted to elucidate the risk factors for the development of AVN. However, clinical outcomes of AVN in patients with SLE have not been highlighted. We aimed to determine the clinical features predictive of the development of AVN in SLE patients and to elucidate the risk factors for the total joint replacement (TJR) of the affected joints in SLE patients with AVN.

Methods: The medical records of 938 patients with SLE admitted to a single center in Seoul, Korea from January 1990 to April 2012 were reviewed and 66 patients with AVN were identified. A hundred and one age-and sex-matched patients with SLE who didn't have apparent AVN were included as disease controls. The independent risk factors for the development of AVN were examined by univariate and multivariate logistic regression analyses. The timing and cumulative risk of TJR were identified by Kaplan-Meier methods. The independent risk factors for TJR were determined by univariate and multivariate Cox proportional hazards regression analyses.

Results: The prevalence AVN was 7.0%. Multivariate logistic regression analysis revealed that the independent risk factors for the development of AVN included discoid rash (odds ratio (OR) 7.861, p=0.022), lymphopenia (OR 12.316, p=0.003), cushingoid feature (OR 3.029, p=0.02). Among 66 patients with AVN, 61 had AVN of the hip, 10 had AVN of knee and 1 had AVN of shoulder. Thirty-eight patients underwent total joint replacement (TJR) surgery. In univariate analysis, male patients, bilateral joint involvement, neuropsychiatric lupus, renal involvement, advanced radiological stage of AVN (Association for Research on Osseous Circulation (ARCO) stage) at the time of diagnosis were included as predictive risk factors for TJR. In multivariate analysis, only advanced radiological stage of AVN at the time of diagnosis was included as an independent risk factor for TJR (hazard ratio 2.464, p=0.038).

Conclusion: Our results demonstrated that advanced radiological stage at the onset of AVN is an independent predictable risk factor for TJR in SLE patients with AVN.

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Limitations of Current Treatment for Systemic Lupus Erythematosus: A Patient and Physician Survey. V. Strand[1], C. Galateanu[2], S. Lobosco[3], D.S. Pushparajah[2], J. Sayers[4] and R.F. van Vollenhoven[5]. [1]Stanford University, Portola Valley, CA, [2]UCB Pharma, Brussels, Belgium, [3]Adelphi Real World Ltd., Macclesfield, United Kingdom, [4]Adelph Real World Ltd., Macclesfield, United Kingdom, [5]The Karolinska Institute, Stockholm, Sweden

Background/Purpose: Current SLE treatment regimens follow an 'add-on' paradigm: typically, therapies are added as the activity of a patient's disease increases. Most current treatments, particularly corticosteroids (CS) and immunosuppressants (IM), frequently have severe side effects that contribute to damage in SLE. This abstract reports an analysis of data drawn from a cross-sectional survey of physicians and their consulting lupus patients.

Methods: Data were extracted from the Adelphi Real World Lupus Disease-Specific Programme (DSP), a cross-sectional survey of 233 physicians and their patients conducted between December 2009 and May 2010 in the USA, France, Germany, Italy, Spain, and the UK. Each physician completed a comprehensive patient record form for their five most recently seen SLE patients. Data collected included subjective rating of disease activity, flare occurrence, treatment satisfaction, and drug classes received. Patients were invited to fill out a self-completion questionnaire, which included EQ5D and the FACIT fatigue scale. This analysis focused on three key drug classes: CS, IM, and antimalarials (AM).

Results: The Adelphi Lupus DSP survey included 886 patients, of whom 515 completed a self-assessment questionnaire. The population was 90% female with a mean age of 42 years. A total of 618 patients (70%) were classified as having mild disease activity, compared to 247 (28%) with moderate disease activity, and 21 (2%) with severe disease activity. The numbers of patients in each disease activity group flaring in the last 12 months were 138 (22.3%), 126 (51.0%), and 12 (57.1%), respectively. The proportions of patients receiving different regimens are listed in the table. SLE treatment regimens including CS (with or without other classes) were associated with more active disease (p < 0.0001) as were regimens that included ≥ 2 drug classes (p < 0.001). Patients reporting flares were more likely to be receiving ≥ 2 vs < 2 key drug classes (p < 0.001). A greater proportion of patients reported satisfaction with their treatment regimen when it did not include CS than when it did (81% vs 68%; p < 0.01). Patients receiving CS reported lower mean EQ5D than those who were not (0.731 vs 0.792; p = 0.0002). However, those receiving CS did report better fatigue levels than those who were not (35.0 vs 38.4, p = 0.0001). A greater proportion of physicians also reported more satisfaction with their patient's treatment regimen when it did not include CS (p < 0.001).

	No classes (66)	One class only (321)	Two classes (403)	All 3 classes (95)	CS only (58)	AM only (200)	IM only or IM + AM (100)	CS + IM or CS + AM (366)
Mild (618)	57 (9.2%)	270 (43.7%)	250 (40.5%)	40 (6.5%)	40 (6.5%)	183 (29.6%)	71 (11.5%)	226 (36.6%)
Moderate (247)	9 (3.6%)	45 (18.2%)	143 (57.9%)	50 (20.2%)	15 (6.1%)	16 (6.5%)	27 (10.9%)	130 (52.6%)
Severe (21)	0 (0.0%)	6 (28.6%)	10 (47.6%)	5 (23.8%)	3 (14.3%)	1 (4.8%)	2 (9.5%)	10 (47.6%)

THERAPEUTIC CLASSES (CS, AM AND IM)

Conclusion: More active disease is associated with flare in the last 12 months, ≥ 2 classes of therapy, and use of CS specifically. Unexpectedly, physicians and patients accepted moderate or high levels of disease activity while receiving multiple medications, suggesting that they had become resigned to uncontrolled disease activity. These results support the need for new therapies for SLE, and treatment algorithms incorporating such therapies.

Disclosure: V. Strand, UCB Pharma, 5; C. Galateanu, UCB Pharma, 3; S. Lobosco, Adelphi Real World Ltd., 3, UCB Pharma, 5; D. S. Pushparajah, UCB Pharma, 3; J. Sayers, Adelphi Real World Ltd., 3, UCB Pharma, 5; R. F. van Vollenhoven, Abbott Laboratories, 5, Bristol Myers-Squibb, 5, GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5, MSD, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB Pharma, 5, Abbott Laboratories, 2, Bristol Myers-Squibb, 2, GlaxoSmithKline, 2, Human Genome Sciences, Inc., 2, MSD, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, UCB Pharma, 2.

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Serum DNAse I Anti DNAse I Antibodies, CRP and Antibodies to CRP Relation to Disease Activity in Systemic Lupus Eryhtematous: Longitudinal Studies. Ramnath Misra[1], Avadesh Pratap[2], Amit Singh[1] and Amita Aggarwal[1]. [1]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Technician, Lucknow, India

Background/Purpose: Defective clearance of both nucleosomes and immune complexes has been suggested to intiate and perpetuate the disease.

Defects in DNAse I gene in mice have shown SLE like symptoms, also in humans the decreased levels and levels of DNAse I have been shown. There are few studies in SLE patients looking at these defects, a systemic study is lacking, thus we proposed to study these mechanisms.

Methods: One hundred sixtythree patients (Female: Male 13:1) were included in the study after written consent were obtained. Eightyfour patients were having active disease as measured by Systemic lupus erythematosus disease activity index (SLEDAI) core of more than 4. Sera samples were collected and stored in aliquots at −70 degree C till use. DNAse levels in sera both before and after heating at 56 degree C for 10 minutes to destroy the inhibitors of DNAse such as G protein and actin. DNAse I level were assayed in the sera of 132 patients and 52 normals individuals were done using Radial Enzyme Diffusion assay and the levels were measured using DNAse I as standard. C3, C4 and CRP were done by nephelometry. Antibodies to dsDNA and anti-DNAse I antibodies levels were levels in serum were quantitated by ELISA using commercial and in-house ELISA respectively. The levels of DNAse I, antibodies to DNAse I and CRP were correlated with SLEDAI and between each other statistically.

Results: In patients the median DNAse I levels for pre-heated serum was 2.9 (range 0–39) while the median levels for post heated serum (indicating the inhibitor free levels of DNAse I in serum) was 5.6 (range 3.9–39). In normal individuals the median levels in preheated serum was 8.5 (range 0–26) while median levels for post heated was 13.75 (range 0–39).The DNAse I levels was significantly higher ($p < 0.0001$) in inhbibitor depleted sera as compared to pre-heated ones in both patients and normals. Further, post heated DNAse I levels, was significantly, ($p < 0.0001$) reduced in patients as compared to normals. However, there was no correlation with activity status of patients as measured by SLEDAI. DNAse I levels significantly correlated with age ($r = 0.222$, $p < 0.05$). CRP, which also helps in clearing nucleosome levels in these patients were not significantly correlated with the levels of C3, C4 and anti-dsDNA antibodies levels. The median antibodies to DNAse I levels was 44.6 arbitrary unit (AU) (range 5.11–1522.08) as compared to healthy controls of 32.4 AU (range 7.77–133.08).The level of antibodies to DNAse I was higher in patients compared to normals although difference was not statistically different. Antibodies to DNAse correlated with $r = 0.18$, $p = 0.26$) DNAse I levels. There was no correlation between levels of anti-DNAse I antibodies with SLEDAI.

Conclusion: The levels of DNAse I are reduced in the SLE patients and the levels of inhibitor to DNAse I are high in serum of these patients. The levels of anti-DNAse I antibodies are positively correlated with the DNAse I levels. However, there was no correlation of these biomarkers with composite score of disease activity

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Ovarian Reserve Markers in Reproductive Age Women with Systemic Lupus Erythematosus. Olívio B. Malheiro, Carolina P. Rezende, Gilda A. Ferreira and Fernando M. Reis. Federal University of Minas Gerais, Belo Horizonte, Brazil

Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystem disease, which affects mostly women at reproductive age, and can promote premature ovarian dysfunction related to factors associated to rheumatic disease or its treatment. The assessment of indicators of ovarian reserve can determine if there are differences between these patients and the general population, prior to the establishment of the climacteric. The aim of this study was to evaluate if there are differences in ovarian reserve markers in systemic lupus erythematosus (SLE) patients compared to controls, and explore the relationship of such markers with clinical and treatment features of SLE patients, in addition to inflamatory activity (SLEDAI/ACR) and damage (SLICC/ACR-DI) disease scores.

Methods: This was a controlled cross-sectional study including 27 women with SLE and 27 controls. All participants were between 18 and 40 years, were eumenorrheic and did not use hormone therapy or hormone contraceptives in the past 6 months. Clinical data were assessed at a regular follow up visit, serum concentrations of follicle stimulating hormone (FSH) and anti-mullerian hormone (AMH), and through transvaginal ultrasound antral follicle count were assessed at early follicular phase of a subsequent menstrual cycle.

Results: Mean age of SLE patients was 30.9 years (SD±4.8) and had 102.7 months (SD±66.7) of lenth disease. We found no difference between SLE group and control group at analysis of AFC [median (interquartile interval) 7 (5–13) vs. 11 (7–12), p=0.076], FSH [6.44 (4.19–7.69) vs. 7.5 (6.03–8.09) mUI/ml, p=0.135] and AMH levels [1.23 (0.24–4.63) ng/ml vs.

1.52 (1.33–1.88) ng/ml, p=0.684]. However, AMH values in SLE group were more heterogeneous compared to control group. The presence of nephritis and the cumulative dose of cyclophosphamide were factors individually related to reduced ovarian reserve, by association with lower values of AFC and AMH. At multivariate logistic regression, control group was more likely to have higher AMH values than the SLE (OR 5.2, 95% CI 1.286–20.405, p=0.021) and in the SLE group, AMH was associated with lower maximum corticosteroid doses in the follow-up (OR 0.95, 95%CI 0.894–1.000, p=0.50). AFC was associated with lower scores of SLICC/ACR-DI (OR: 0.14, 95% CI 0.025–0.841, p=0.031).
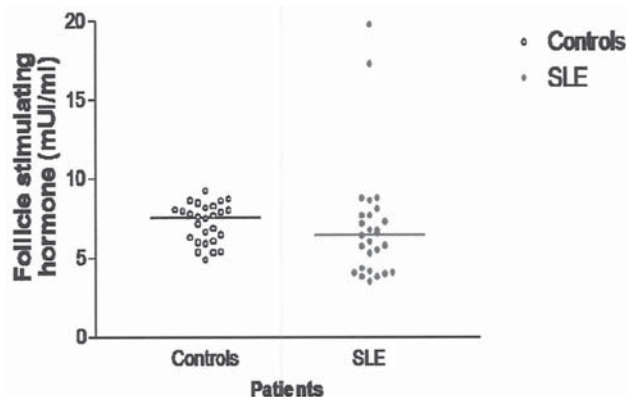
Figure. Scatters showing comparison of ovarian reserve markers in SLE patients between and controls in medians: AFC (Figure A), FSH (Figure B), and AMH (Figure C).

Conclusion: SLE patients who were eumenorrheic had average values of ovarian reserve markers similar to controls. However, AMH had a wide range of values in that group, requiring study of other markers to clarify the best clinical application for it. Ovarian function is more compromised in patients with nephritis, high cumulated dose of cyclophsphamide and higher disease damage scores.

Disclosure: O. B. Malheiro, None; **C. P. Rezende**, None; **G. A. Ferreira**, None; **F. M. Reis**, None.

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Hypogammaglobulinemia in Pediatric Systemic Lupus Erythematosus. Emilina Lim[1] and Megan A. Cooper[2]. [1]Washington University in Saint Louis- St. Louis Children's Hospital, St. Louis, MO, [2]Washington University, Saint Louis, MO

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by B cell activation, elevated serum IgG and prominent circulating immune complexes. However, hypogammaglobulinemia in SLE patients is thought to be rare and it is unclear whether this is associated with SLE or is a transient effect of immunosuppressive treatment. Approximately 1% of patients with common variable immunodeficiency (CVID) develop symptoms or laboratory abnormalities that support the diagnosis of SLE or will manifest an SLE-like syndrome. CVID can also rarely develop in patients with established SLE. We retrospectively reviewed our pediatric SLE cases at Washington University with the goal of identifying clinical and laboratory characteristics in patients with hypogammaglobulinemia.

Methods: 115 SLE cases seen in our Pediatric Rheumatology clinic from 1997–2011 were reviewed. Eighty six patients with inclusion criteria of having an IgG level within 3 months of diagnosis and more than one IgG level during follow-up were included in this study. Excluded were patients with insufficient data for SLEDAI scoring and presence of known immunodeficiency states. Hypogammaglobulinemia was defined as an IgG level <500 mg/dl (2 SD below mean for age in pediatric population) on more than two occasions. Analysis of the different variables was done using SPSS version 10 for Windows.

Results: Seven percent (6/86) of pediatric SLE patients were found to have hypogammaglobulinemia with a median onset of 27 months (0–72 months) after SLE diagnosis. There was no significant difference in the mean age of patients with and without hypogammaglobulinemia (13.66 years and 14.41 years respectively). The risk of developing hypogammaglobulinemia was 10x higher in males than female (p=0.009). There was no significant difference in the binned SLEDAI scores (≥10 and <10) between cohorts.

However, presence of lupus nephritis (p-value=0.004) and an IgG level of <1500 mg/dl at diagnosis (RR=4.88; 95% CI=1.00 – 24.97; p = 0.05) were both associated with hypogammaglobulinemia. Rituximab treatment did not significantly increase risk of developing hypogammaglobulinemia. Using multivariate analysis, male gender and an IgG level of less than 1500 mg/dl at diagnosis continued to show significant association with hypogammaglobulinemia in SLE. Double stranded DNA antibody, complement and albumin levels did not correlate with hypogammaglobulinemia. Interestingly, two patients with SLE and hypogammaglobulinemia had IgG levels less than 500 mg/dl within three months of diagnosis, suggesting that their hypogammaglobulinemia preceded or coincided with the onset of SLE. Two other patients exhibited concomitantly low IgA levels without symptoms. Two patients had recurrent sinopulmonary infections with poor to no vaccine response and required replacement IVIG treatment.

Conclusion: Immunoglobulin deficiency can co-exist with pediatric SLE independent of biologic drug treatment. Measurement of immunoglobulin levels in SLE could help identify patients at greater risk for infection that require more aggressive follow-up to reduce morbidity.

Disclosure: **E. Lim**, None; **M. A. Cooper**, None.

2263

The Association Between Prior Pregnancy Morbidity and Cardiovascular Events in Women with Systemic Lupus Erythematosus. Megan Clowse[1], Eliza F. Chakravarty[2], Jill Buyon[3] and Gerald McGwin Jr.[4]. [1]Duke University Medical Center, Durham, NC, [2]Oklahoma Medical Research Foundation, Oklahoma City, CA, [3]New York University School of Medicine, New York, NY, [4]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Adverse pregnancy outcomes have been associated with increased cardiovascular disease in healthy women. We hypothesized that women with SLE and a history of adverse pregnancy outcomes would have a higher rate of cardiovascular events.

Methods: Prior pregnancy outcomes, cardiovascular risk factors and events were collected in 2010 and 2011 through a longitudinal lupus registry. Study participants were enrolled at 17 lupus centers across North America. At enrollment, each patient reported her prior pregnancies and outcomes, including live birth, week gestation (<37 weeks indicated preterm delivery), and preeclampsia. Cardiovascular events were recorded in the SLICC-Damage Index at study entry and included prior angina or CABG, myocardial infarction, or cerebrovascular accident. Prior medical history, including a diagnosis of hypertension, diabetes, and hypercholesterolemia, current medications, and prior and current laboratory values were also reported. Univariate and multivariate analyses compared the frequency of pregnancy morbidity (a pregnancy loss, a preterm delivery, or a pregnancy with preeclampsia) among women with and without cardiovascular events. Nulliparous women were excluded from the analysis.

Results: Data are available for 602 women, of whom 316 (52.5%) had at least one prior pregnancy morbidity. The average age of SLE diagnosis and LCTC enrollment was lower for women with a pregnancy morbidity (31.2 years and 43.8 years, respectively) compared to women without a pregnancy morbidity (34.3 and 46.6 years, p<0.01). Women with a prior pregnancy morbidity were more likely to have antiphospholipid syndrome (11.1% vs 4.2%, p=0.008). The systolic blood pressure measured at enrollment, the frequency of hypertension, and the use of antihypertensive medications at LCTC enrollment were all significantly higher among women with a history of pregnancy morbidity. In contrast, the frequency of diabetes mellitus, use of anti-cholesterol medications, and hypercholesterolemia at enrollment were not significantly different between the pregnancy groups. Despite the significant increase in hypertension, the frequency of overall cardiovascular events was not significantly different between the groups: 8.23% with pregnancy morbidity vs 6.64% without pregnancy morbidity, p=0.4. A multivariate analysis demonstrated that cardiovascular events were associated with older age at LCTC enrollment, hypertension, and APS, but not race, number of pregnancies, or pregnancy morbidity.

Conclusion: Prior pregnancy morbidity is not significantly associated with cardiovascular events in this large multi-center multiethnic/racial cohort of lupus patients. This may be due to the relative young age of the cohort with the average age less than 50 years at entry. The association of pregnancy morbidity with hypertension, however, suggests that these women may be a higher risk for future cardiovascular events.

Disclosure: **M. Clowse**, UCB, 5; **E. F. Chakravarty**, None; **J. Buyon**, Exagen, 5; **G. McGwin Jr.**, None.

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Improving Outcomes for Pregnant Lupus Patients: Is There a Geographic Link? Darneesh Thornton-Johnson[1] and Daniel Albert[2]. [1]Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, [2]Dartmouth-Hitchcock Medical Center, Geisel School of Medicine, Lebanon, NH

Background/Purpose: Systemic lupus erythematosus (SLE) is stated to lead to miscarriages, preterm births, and other complications among pregnant women previously diagnosed with the disease. According to the LUMINA cohort study headed by Dr. Graciela Alarcon, this is especially true for young women of African-American or Hispanic origin as they may have a genetic predisposition and lack of resources to effectively manage the illness. Despite the landmark LUMINA findings, there remain few sources on geographic disparities experienced by lupus patients. The current literature shows potential uses for geographic analysis particularly through the process of geocoding patient zip codes and the development of Medically Underserved Areas.

Methods: The authors, in consultation with a statistician, performed a secondary data analysis using logistic regression on the STATA statistical software package. The author analyzed the following variables: zip code, age, race, income, education, preterm birth of fetus, miscarriage/spontaneous abortion frequency, mode of delivery (vaginal or c-section) and corticosteroid injection amount (re: dosage).

Continuous variables, such as age and dosage amounts, were analyzed via descriptive statistics whereas dichotomous variables were analyzed via logistic regression. It was in the logistic regression that the authors were able to find statistically significant results. The authors soon compared the statistically significant variables with US Census-designated, Medically-Underserved Areas to reveal stunning results.

Results: Data analysis gave 3 US Census-designated urban areas and 3 US Census-designated rural areas of interest. Urban areas were the following: Bessemer, Alabama; Houston, Texas; Pasadena, Texas.

Many of the patients from the aforementioned areas within the dataset have high dosages of corticosteroids and inconsistent physician visit dates-- leading to more complications. Women who are able to go to the doctor regularly while pregnant can effectively manage the lupus with less corticosteroids (as indicated in the dataset) and other drugs to have a relatively safe pregnancy. If they can't do that, the pregnancy may be more problematic.

Conclusion: Women who live in rural areas also exhibited higher rates of pregnancy complications in terms of miscarriages when taken into consideration one's age, race, educational level and income gains. A factor why rural women suffer from the effects of the illness disproportionately may be due to educational attainment, income, and geographic distance The results of this study can lead to better reproductive health outcomes that include full-term pregnancies, economically feasible treatment options, and a higher quality of life due to coordinated care that best serves their needs.

Disclosure: **D. Thornton-Johnson**, American College of Rheumatology, 2; **D. Albert**, None.

2265

Clinical Manifestations of Systemic Lupus Erythematosus Vary Based On Age of Disease Onset. Flora Simmons[1], Natasha M. Ruth[1], Gary S. Gilkeson[1] and Diane L. Kamen[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease which disproportionately affects women of child-bearing age. However, onset during childhood and late adult onset can be seen. Previous studies found that age of onset may be predictive of certain clinical manifestations and childhood-onset associated with increased mortality. The purpose of our study is to compare the clinical differences between childhood, adult, and late onset SLE within a large predominantly African American cohort.

Methods: Participants enrolled in an observational database of SLE were included in this study if they met ≥4 of 11 modified ACR Classification Criteria for SLE. Data was collected prospectively from 2003 to 2012. Demographic and clinical features were collected at baseline and updated at follow-up visits. Damage was scored using the SLICC/ACR Damage Index (SDI). Age of onset was categorized in three groups: childhood onset (<18 years old), adult onset (18 – 50 years old), and late onset (>50 years old). Chi-squared or Fisher's Exact testing was used, as appropriate, to compare

characteristics between groups. All statistical testing used a two-sided $\alpha=0.05$ level.

Results: Of the 449 patients, 91.3% were female and 80.6% were African American. Age of SLE onset varied between 2.8 and 76.6 years of age (mean 30.8 ± 13.6) and year of diagnosis varied between 1973 and 2012. Data on the demographic, clinical, and laboratory characteristics between the childhood onset (n=83), adult onset (n=317), late onset (n=41) groups is presented in Table 1.

Table 1. Patient characteristics compared between groups diagnosed with SLE in childhood (<18 years), adulthood (18–50 years), or late-adulthood (>50 years).

	Childhood Onset (n=83)	Adult Onset (n=317)	Late Onset (n=41)	p-values
Age, mean ± sd in years	13.1 ± 3.8	31.3 ± 8.5	57.2 ± 6.6	
African American (%)	78.2	84.3	58.7	* p<0.01
Sex Ratio (F:M)	8.8 (70:8)	10.6 (297:28)	14.3 (43:3)	p=NS
Malar Rash (%)	55.9	53.9	40.9	p=NS
Discoid Rash (%)	23.4	29.4	26.2	p=NS
Photosensitivity (%)	42.7	58.6	47.5	* p=0.04
Mucosal Ulcers (%)	35.7	43.6	40.9	p=NS
Arthritis (%)	76.8	85.8	81.4	p=NS
Serositis (%)	40.3	44.5	24.4	p=0.05
Renal (%)	64.8	54.6	27.3	* p<0.01
Neuro Disorder(%)	28.4	14.2	11.6	* p=0.01
Heme Disorder (%)	59.7	59.5	48.8	p=NS
Immune Disorder (%)	87.1	86.6	72.5	p=NS
ANA Positivity (%)	98.6	99.0	95.6	p=NS
SDI >1 (%)	53.9	50.8	47.8	p=NS
Mortality (%)	5.1	3.7	8.7	p=NS

Late onset patients have a higher proportion of females to males compared to childhood onset, but are significantly less likely to be African American. Childhood onset patients have the highest prevalence of renal and neurologic involvement from SLE (p-values <0.01 and 0.01 respectively) and were more likely, although not statistically significant, to have irreversible damage as reflected by the SDI.

Conclusion: These results support childhood onset SLE being a more severe form of SLE, supporting the critical need for preventive interventions early in the course of disease. Patients with earlier onset of SLE were more likely to have renal and neurologic involvement, which are leading causes of morbidity and mortality in SLE.

Disclosure: F. Simmons, None; **N. M. Ruth**, None; **G. S. Gilkeson**, None; **D. L. Kamen**, None.

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Outcome of Renal Transplantation in Lupus Patients with Positive and Negative Serology: Survival of the Graft and Patients After Transplant. Zahi Touma, Murray B. Urowitz, Dominique Ibanez and D. D. Gladman. Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Lupus nephritis (LN) occurs in 50–75% of adults with SLE and up to 20% of LN patients may advance to end stage renal disease over a 10-year period. The aims of this study were to provide an overview of the characteristics of lupus patients with renal transplantation (RT) followed in the Lupus Clinic between 1970–2012, and to determine the survival of the graft and patients after RT.

Methods: Patients with lupus have been followed prospectively at the lupus clinic since 1970. Patients attend the clinic at 2–6 month intervals and the standard protocol includes: complete history, physical and laboratory evaluation. Patients who underwent RT were identified from the database. RT outcomes included: a) nonfunctional graft requiring dialysis within ≤3 weeks, b) graft failure requiring permanent dialysis after 3 weeks, c) graft survival not requiring dialysis and d) death.

Descriptive analysis was used to study the characteristics of all patients. We grouped the patients into graft failure and graft survival. The duration of graft failure was defined as the time between RT and subsequent permanent dialysis. The duration of graft survival was defined as the time between RT and recipient death or the end of the study with functioning graft.

Results: 25 (20 F) of 1645 patients followed in the lupus cohort and of 780 with renal involvement were identified with RT. 10 (40%) were Caucasian, 7 (28%) Black, 4 (16%) Asian and 4 (16%) others. The age at

diagnosis of lupus and at transplant was 30.7 ± 13.8 and 38.1 ± 9.6 years respectively. Lupus duration at RT was 13.3 ± 7.6 years. 2 (8%) patients had a nonfunctional graft, 4 (16%) patients had graft failure (1 patient had failure <5 years and 3 ≥5 years) and 19 (76%) patients had graft survival (8 had S ≥5 years) (Table 1). Patients with graft survival were older and had longer lupus duration compared to patients with failure at the time of RT. 25% of the graft failures had positive lupus serology compared to 47% in the graft survival 1 year prior to RT.

Table 1. Characteristics if graft failure and graft survival patients.

	Graft Failure N=4	Graft survival N=19
Sex	F 75%	F 84%
Age at lupus diagnosis	25.4±7.3	24.4±8.3
Age at transplant	29.8±9.1	40.0±9.5
Lupus duration at 1st clinic visit	5.9±4.0	7.2±7.8
Lupus duration at transplant	4.5±2.1	15.5±7.1
Ethnicity		
Caucasian	1	7
Black	1	6
Asian	2	2
Others	0	4
Positive DNA in 1 year prior	1/4	5/18
Low complements in 1 year prior	1/4	9/19
Positive DNA and/or low complements in 1 year prior	1/4	9/19
Positive DNA and/or low complements in 1 year after transplant	2/3	8/19
SDI at transplant	4.0±0 (n=4)	4.6±1.9 (n=17)
Time (duration) on dialysis prior to transplant	3.9±2.4 (n=4)	5.8±5.6 (n=6)

The time to graft failure (n=4) was 5.75 ± 4.99y. In the failure group 3 patients died by 6 ± 5.19 years and one patient is still alive. In the graft survival group 3 patients died by 5.6 ± 4.6 years and one patient was lost of follow-up. Cause of death was not related to renal disease in 2patients and unknown in one patient.

Conclusion: 25 of 780 lupus nephritis patients followed at the Lupus Clinic underwent RT. The persistence of serological abnormalities at the time of RT was not associated with graft failure.

Disclosure: Z. Touma, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **D. D. Gladman**, None.

ACR/ARHP Poster Session C
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Genome-Wide Pathway Analysis of Genome-Wide Association Studies On Systemic Lupus Erythematosus. Young Ho Lee[1], Sung Jae Choi[1], Jong Dae Ji[1] and Gwan Gyu Song[2]. [1]Korea University Medical Center, Seoul, South Korea, [2]Korea Univ College of Med, Seoul

Background/Purpose: Genome-wide association studies (GWASs) have been successfully used to identify novel common genetic variants that contribute to susceptibility to complex diseases, but individual GWASs are limited in terms of identifying new loci. Thus, pathway-based analysis is required to identify further new loci that contribute to susceptibility to complex diseases. The aim of this study was to explore candidate single nucleotide polymorphisms (SNPs) and candidate mechanisms of systemic lupus erythematosus (SLE).

Methods: Two SLE GWASs datasets were included in this study. Meta-analysis was conducted using 737,984 SNPs in 1,527 SLE cases and 3,421 controls of European ancestry after quality control filtering, and ICSNPathway (identify candidate causal SNPs and pathways) analysis was applied to the meta-analysis results of the SLE GWAS datasets.

Results: The most significant result of SLE GWAS meta-analysis concerned rs2051549 in the human leukocyte antigen (HLA) region ($p = 3.36E-22$). In addition, 103 SNPs had observed p-values of less than 5×10^{-8} (genome-wide significance). In the non-HLA region, meta-analysis identified 6 SNPs associated with SLE with genome-wide significance

(STAT4, TNPO3, BLK, FAM167A, and IRF5). ICSNPathway identified five candidate causal SNPs and 13 candidate causal pathways. This pathway-based analysis provides three hypotheses of the biological mechanism involved. First, rs8084 and rs7192 à HLA-DRA à bystander B cell activation. Second, rs1800629 à TNF à cytokine network. Third, rs1150752 and rs185819 à TNXB à collagen metabolic process.

Conclusion: By applying ICSNPathway to the meta-analysis results of two SLE GWAS datasets, we identified five candidate SNPs and thirteen pathways, involving bystander B cell activation, cytokine network, and collagen metabolic processing, which may contribute to SLE susceptibility.

Disclosure: **Y. H. Lee**, None; **S. J. Choi**, None; **J. D. Ji**, None; **G. G. Song**, None.

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Hyperacetylation of Histone H4 in Systemic Lupus Erythematosus.
Yiu Tak Leung[1], Lihua Shi[2], Kelly Maurer[2], Li Song[2], Zhe Zhang[3], Michelle Petri[4] and Kathleen E. Sullivan[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, [3]Bioinformatics, Children's Hospital of Philadelphia, Philadelphia, PA, [4]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease and is characterized by multi-systemic chronic inflammation. Epigenetic processes, such as posttranslational histone modifications, can regulate gene expression without altering the underlying genomic sequence and represent important disease mechanisms that have had little attention in SLE to date. We have previously reported that histone H4 acetylation (H4ac) is globally increased across the genome in monocytes of patients with SLE as compared to in monocytes of healthy controls using a tiling array approach. In order to further characterize H4ac to determine the pathologic process responsible for the hyperacetylation, we looked for an imbalance in histone acetylatransferases (HATs) and histone deacetylases (HDACs). We further utilized flow cytometry to identify specific lysine residues hyperacetylated in SLE.

Methods: Peripheral blood monocytes (PBMCs) were obtained from 7 controls and 7 SLE patients. The patients had low SLEDAI score (mean score < 2) and were on no immune suppressive medications at the time other than low-dose prednisone. Flow cytometry for different H4 lysine acetyl groups: K5, K8, K12 and K16 were run on a FacsCalibur instrument using appropriate isotype controls. H4 acetylation was defined on both T cells and monocytes. RNA-Seq studies were performed on purified monocytes from a different set of 8 controls and 8 SLE patients to examine the differential gene expression between the groups, in order to quantify mRNA for potential HAT and HDAC enzymes responsible for histone hyperacetylation in the patients with SLE.

Results: Analysis of gene expression of HATs found that PCAF-KAT2B expression was significantly increased in SLE monocytes as compared to controls; whereas, ATF2 expression was decreased significantly in the SLE group as compared to the control group. PCAF-KAT2B can associate with IRF1 and place H4K5, H4K8, and H4K16 acetylation marks. Further examination of the RNA-Seq data revealed increased expression of genes regulated by the IRF family of transcription factors. In addition, when compared to the control group, the SLE group had significantly decreased gene expression of HDAC3, which normally functions to deacetylate all H4 lysine acetyl groups, with a preference for acetylated H4K5 and H4K12. HDAC11 expression in SLE monocytes was also significantly reduced as compared to controls. HDAC11 has been shown to negatively regulate antigen-presenting cells' production of IL-10, a cytokine that is known to have increased levels in SLE patients. Finally, using flow cytometry, we found H4K5, H4K8, and H4K16 acetylation clearly increased in SLE monocytes and H4K5 increased (but not significant statistically) in SLE T cells.

Conclusion: These data demonstrate that in addition to specific gene sets being dysregulated in SLE, global alterations to H4 acetylation occur as well. These findings parallel studies that examined CpG DNA methylation and discovered evidence of global gene demethylation. The identification of a candidate HAT provides for a potential therapeutic target.

Disclosure: **Y. T. Leung**, None; **L. Shi**, None; **K. Maurer**, None; **L. Song**, None; **Z. Zhang**, None; **M. Petri**, None; **K. E. Sullivan**, None.

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The Differences of DNA Methylome and Transcriptome Among Diverse Clinical Manifestations of Systemic Lupus Erythematosus.
Ming Zhao[1], Shuangyan Luo[1], Honglong Wu[2], Siyang Liu[2], Meini Tang[1], Wenjing Cheng[1], Qing Zhang[1], Xinhai Yu[1], Tak Mao Chan[3], Yudong Xia[2], Na Yi[2], Fei Gao[2], Li Wang[2], Ning Li[2] and Qianjin Lu[1]. [1]Second Xiangya Hospital, Central South University; Hunan Key Laboratory of Medical Epigenomics, Changsha, China, [2]Beijing Genomics Institute at Shenzhen, Shenzhen, China, Shenzhen, China, [3]Division of Nephrology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China

Background/Purpose: Aberrant DNA methylation and gene expression have been observed in systemic lupus erythematosus (SLE). However, patterns of DNA methylation and gene expression associated with different clinical manifestations of SLE patients have never been reported.

Methods: DNA methylation was profiled by methylated DNA immuno-precipitation combined with high-throughput sequencing (MeDIP-seq) and the expression of genes was analyzed through transcriptome sequencing (transcriptome-seq) in CD4^{+}T cells obtained from three groups [SLE with only skin lesion (S), SLE with skin lesion and renal disease (SK), Normal controls (N)] which constituted of four samples, respectively. Validations of DNA methylation status and expression levels of genes were performed with CD4^{+}T cells from 15 samples from each group by bisulfite sequencing and MassArray and reverse transcription quantitative PCR (RT-qPCR), respectively.

Results: According to Different Methylated Regions (DMRs) in promoter regions of genomic DNA, we identified 3056 hypo-methylated and 1965 hyper-methylated genes in S group, and 4504 hypo-methylated and 1433 hyper-methylated genes in SK group, compared with controls. Several established autoimmune-associated genes (including ITGAM, IFI44, S1PR3 and NLRP2) were confirmed to be hypo-methylated in both S and SK groups by bisulfite sequencing and MassArray, consistent with results of MeDIP-seq. Gene Ontology (GO) analysis for "biological processes" showed a significant enrichment of 86 GO terms including "induction of apoptosis" and "response to UV" in genes with DMRs in S group. Similarly, apoptosis, adherens junction and leukocyte transendothelial migration were significantly enriched via KEGG pathway analysis. Moreover, 183 GO terms were enriched significantly in SK group, including "apoptosis" and "response to DNA damage stimulus". KEGG pathway analysis revealed a significant enrichment of "renal cell carcinoma" and several autoimmune-associated pathways such as T cell receptor signaling pathway, MAPK signaling pathway and apoptosis. For differentially expressed genes, we observed 1500 up-regulated and 309 down-regulated genes in S group, and 944 up-regulated and 1552 down-regulated genes in SK group, compared with control. Over-expression of some genes including IFI44, ITGAM, S1PR3, NLRP2, C1QC and HLADRB was validated in S and SK groups using RT-qPCR, consistent with the results of transcriptome-seq. GO analysis showed that up-regulated genes were significantly enriched in immune-mediated processes including inflammation, leukocyte or complement activation. KEGG pathway analysis showed that "renal cell carcinoma" pathway was specifically enriched in down-regulated genes in SK group, suggesting aberrant DNA methylation and gene expression in this pathway may be related to lupus nephritis.

Conclusion: We characterized DNA methylome and transcriptome profiles in CD4^{+} T cells from SLE patients, and showed distinct patterns associated with different phenotypic disease manifestations.

Disclosure: **M. Zhao**, None; **S. Luo**, None; **H. Wu**, None; **S. Liu**, None; **M. Tang**, None; **W. Cheng**, None; **Q. Zhang**, None; **X. Yu**, None; **T. M. Chan**, None; **Y. Xia**, None; **N. Yi**, None; **F. Gao**, None; **L. Wang**, None; **N. Li**, None; **Q. Lu**, None.

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The DNA Methylome of Systemic Lupus Erythematosus (SLE) From Whole Peripheral Blood Mononuclear Cells (PBMCs).
Robert Shoemaker[1], Lou H. Bookbinder[2], David L. Boyle[3], Gary S. Firestein[3], Jonathan E. Lim[2] and David W. Anderson[1]. [1]NexDx, Inc., San Diego, CA, [2]NexDx, Inc., San Diego, [3]UCSD School of Medicine, La Jolla, CA

Background/Purpose: SLE is a disease where epigenetic mechanisms play a role. Methylation of DNA at CpG loci is known to influence the suppression or activation of genes that may be associated with disease pathogenesis. Methylation associated with SLE may define unique biomarkers that may serve as novel drug targets and diagnostic tools. Studies to date have focused on candidate genes or small subsets of functional genes. We

present the first >480,000 CpG differentiatal methylation analysis, covering >20,000 gene promoters, in PBMCs from SLE patients.

Methods: Genome-wide methylation analysis of 6 SLE, 6 Rheumatoid Arthritis (RA), and 4 Osteoarthritis (OA) whole PBMC preparations from females was performed on *Illumina HumanMethyl450* BeadChips. DNA was purified from Ficoll prepared whole PBMCs from clinically diagnosed patients. The Kolmogorov-Smirnov (KS) test determined differentially methylated loci (DML). Only loci with an average methylation difference > 0.10 between phenotypes were tested. KS p-values were converted to multiple hypothesis corrected q-values and loci with q-values < 0.15 were labeled as DM. Differentially methylated genes (DMG) contained at least one SLE/RA or SLE/OA DML in their promoter regions (−2.5 kb to 500 bp from transcription start site [TSS]). Pathway enrichment analysis of DMG was determined using Kyoto Encyclopedia of Genes and Genomes (KEGG) data and empirical p-values, based on 500,000 randomly generated background gene sets, which were converted to q-values.

Results: Genome-wide methylation analysis of >480,000 CpG loci identified 864 and 1,537 DML in SLE/RA and SLE/OA comparisons. Associating CpGs with TSS promoter regions narrowed these loci to 274 and 422 DMG. 71% and 65% of SLE/RA and SLE/OA CpGs were hypermethylated, respectively. Hypermethylation was found in *IL-23A, TNFRSF25,* and *PRIC285* (peroxisomal proliferator-activated receptor A interacting complex 285), genes known to regulate immune responses and inflammation. Hypomethylated CpG loci from SLE patients were identified in promoter regions associated with genes relevant to SLE, such as *IFI44L* (interferon-induced protein 44-like), *IFITM1* (Interferon-induced transmembrane protein 1) and *IL-10*. Combining SLE/RA and SLE/OA genes into a single group, we found: cytokine-cytokine receptor interaction (q-value = 0.004), rheumatoid arthritis (0.004), hematopoietic cell lineage (0.004), and cell adhesion molecules (0.010) were significantly enriched KEGG pathways where differential methylation was observed. These data suggest that epigenetic mechanisms may play an important role in SLE where aberrant regulation of key immune and inflammatory genes or pathways may contribute to SLE pathogenesis and progression.

Conclusion: This study demonstrates that the first genome-wide DNA methylation analysis of whole PBMC samples is informative. The differential methylation pattern for SLE has the potential for identification of novel biomarkers for diagnostic applications. Associated genes and pathways provide a greater understanding of the pathogenic mechanisms of SLE and potential novel therapeutic targets. These findings justify further exploration, including subsets of immune cells and healthy controls.

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Variation of Interferon-Alpha Production in Healthy Individuals and Association with Autoimmune Susceptibility Genes. Olof Berggren[1], Andrei Alexsson[1], Gunnar V. Alm[2], Ann-Christine Syvänen[3], Lars Rönnblom[1] and Maija-Leena Eloranta[1]. [1]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [2]Swedish University of Agricultural Sciences, Uppsala, Sweden, [3]Molecular Medicine, Uppsala University, Uppsala, Sweden

Background/Purpose: Many autoimmune diseases, e.g. systemic lupus erythematosus (SLE), have an activated type I interferon (IFN) system and about 40 SLE susceptibility loci, many within the type I IFN pathway, have been identified. We recently showed that the IFNα production by plasmacytoid dendritic cells (pDC) is regulated by both NK and B cells, and demonstrated a large interindividual difference in IFNα producing capacity among healthy individuals. We therefore investigated whether the capacity to produce type I IFN correlates to single nucleotide polymorphisms (SNPs) associated with different autoimmune diseases.

Methods: Plasmacytoid dendritic cells (pDC) (n = 130), B cells (n = 128) and NK (n = 66) were isolated from healthy blood donor PBMC genotyped with the 200K ImmunoChip (Illumina). PDC alone or in co-cultures with NK or B cells were stimulated with U1 snRNP- and SLE-IgG-containing immune complex (RNA-IC), herpes simplex virus or a synthetic oligonucleotide (ODN2216). The IFNα levels in the cell cultures were measured with an immunoassay after 20h. The association analysis was performed with PLINK software version 1.07. A total of 67 000 SNPs with minor allele frequency ≥20% which passed quality control were included in the analysis. The 10 most associated signals per

cell type and stimuli were selected for further analysis. The IFNα production was normalized by Box-Cox transformation and the association to the genotype was analyzed by multiple linear regression with a stepwise method (SPSS 20.0).

Results: The IFNα production by the stimulated healthy donor pDC alone or in cocultures with B or NK cells varied from <1 to 100000 U/ml. We found a strong association (p < 0.001) between the level of produced IFNα and several SNPs (24 to 194) depending on the combination of cell type and IFN inducer. The 7 most significant associations between IFNα production and specific SNPs among the 9 different combinations were located in *C1orf222, MYO9B, TOX,* between *NFYAP1* and *LGMNP1,* and *IL5RA* genes (all p ≤ 0.00003).

Further analysis on the combined effect of the 10 most significant SNPs was applied on each different IFN inducer and cell type combination. For instance, the variation in IFNα production by pDC and B cells stimulated with RNA-IC could be explained to 59% by a model including SNPs located between *ID4* and *MBOAT1,* in *BLK,* in *MOBKL2B,* in *BICC1,* between *FAM86A* and *RBFOX1,* and between *IRF8* and *FOXF1* ($p < 1 \times 10^{-18}$, $r^2 = 0.59$).

Conclusion: We found that the interindividual variation in IFNα production in healthy individuals upon stimulation with RNA containing IC as well as IFN inducers of microbial origin is associated to several autoimmune susceptibility genes. Our results may contribute to the identification of functional gene variants that directly affect the type I IFN production and IFN signature in patients with systemic autoimmune diseases. We envision that our approach using genetically characterized individuals can reveal crucial immunological targets for therapeutic intervention.

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Gene Expression Signatures in Monocytes From Primary Antiphospholipd Syndrome, Systemic Lupus Erythematosus and Lupus with Antiphospholipid Syndrome Identify Specific Pathways Involved in the Pathogenesis of Atherosclerosis and Cardiovascular Disease. Chary Lopez-Pedrera[1], Sebastiano Messineo[2], Carlos Perez-Sanchez[1], Patricia Ruiz-Limon[1], Mª Angeles Aguirre[1], Rosario M. Carretero-Prieto[1], Antonio Rodriguez-Ariza[1], Nuria Barbarroja[3], Francisco Velasco[1], Munther A. Khamashta[4], Eduardo Collantes-Estevez[1] and Mª Jose Cuadrado[4]. [1]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [2]Dipartimento di Scienze della Salute, Universitá Magna Graecia di Catanzaro, Italy., Catanzaro, Italy, [3]IMABIS and Virgen de la Victoria Hospital, Malaga, Spain, [4]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by immune-mediated inflammation in multiple organ systems. SLE, primary Antiphospholipid syndrome (APS) and secondary APS (SAPS) share several clinical features, including atherosclerosis (AT) and cardiovascular disease (CVD), but also have some unique distinguishing characteristics. The aim of this study was to identify shared and differential molecular pathways involved in the pathogenesis of AT and CVD in that autoimmune diseases.

Methods: 127 patients (42 APS, 20 SAPS and 56 SLE) and 61 healthy donors were included. Microarray expression profiling was performed in samples of monocytes from these patients and real time RT-PCR of selected genes was used to validate microarray data. Some clinical and inflammatory parameters were also obtained.

Results: Comparing to controls, the expression of 555, 1224, and 518 genes were found significantly altered in monocytes from SLE, SAPS, and APS patients, respectively. On the other hand, 1243 genes were differentially regulated in APS vs. SLE, and 605 genes in SAPS vs. SLE. Interestingly, only 220 genes were differentially regulated when comparing APS with SAPS. Approximately 25–30% of the total number of altered genes in the three diseases were related to AT, inflammation and CVD (chemoquines/cytokines and their receptors, molecules related to angiogenesis, oxidative stress, mitochondrial dynamics and metabolism, lipid metabolism and cell to cell signalling). A specific AT/CVD/Inflammation-related gene signature was found for each disease. Thus, compared to LES, APS showed alterations in mitochondria biogenesis and function, oxidative stress and antioxidant defense. Besides the interferon signature found SAPS and SLE patients, a number of genes mediating atherosclerotic/inflammatory signalling were found further altered in SAPS. Multivariate analysis showed that IgG aCL titers, which are known risk factors for AT and CVD events in SLE,

independently predicted both atherosclerotic and thrombosis in SAPS. Moreover, a higher percentage of SAPS showed increased carotid intimate media thickness than LES patients. We further found a significant correlation of IgG-aCL titers with circulating levels of inflammatory molecules (tPA, MCP-1, TNFα, and IL-2).

Conclusion: 1) Gene expression profiling allows the segregation of APS, SAPS and SLE, with specific signatures explaining the pro-atherosclerotic, pro-thrombotic and inflammatory changes in these highly related autoimmune diseases. 2) The identification of key genes regulating specific pathophysiologic pathways will permit the development of targeted therapies for each autoimmune condition. Supported by JA0246/2009, P08-CVI-04234, and PS09/01809.

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Functional Genetic Polymorphisms in Immunoglobulin-Like Transcript 3 Are Associated with Decreased Surface Expression On Dendritic Cells and Increased Serum Cytokines in Lupus Patients. Mark A. Jensen, Karen C. Patterson, Akaash A. Kumar, Marissa Kumabe, Beverly S. Franek and Timothy B. Niewold. University of Chicago, Chicago, IL

Background/Purpose: Hyperactivity of the type I interferon (IFN) pathway is involved in the pathogenesis of systemic lupus erythematosus (SLE). Immunoglobulin like transcript (ILT3) is an immunohibitory transmembrane molecule which is induced by type I IFNs. ILT3 is expressed by plasmacytoid dendritic cells (PDCs), monocytoid dendritic cells (MDCs), and monocytes/macrophages. Given the pathogenic role of IFN in SLE, we hypothesized that the IFN-induced immunosuppressive ILT3 receptor may be dysfunctional in human SLE.

Methods: 132 European-derived and 79 Hispanic-American SLE patients were genotyped for two coding-change single nucleotide polymorphisms (SNPs) predicted to interfere with protein folding in ILT3 (rs11540761 and rs1048801). 116 control DNA samples and sera from healthy controls were also studied. We detected associations between ILT3 genotype and serum cytokine profiles. ILT3 expression levels on PDCs and MDCs from 18 patients and 10 controls were studied by flow cytometry.

Results: The rs11540761 SNP in the extracellular region was associated with decreased cell surface expression of ILT3 on circulating MDCs and to a lesser extent PDCs in SLE patients. The cytoplasmically located rs1048801 SNP was not associated with a change in DC expression of ILT3. Both SNPs were significantly and independently associated with increased levels of serum type I IFN activity in SLE patients. The rs1048801 SNP was also associated with increased serum levels of TNF-α.

Conclusion: Loss-of-function polymorphisms in ILT3 are associated with increased inflammatory cytokine levels in SLE, supporting a biological role for ILT3 in SLE.

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Genes Associated with Systemic Lupus Erythematosus Show Evidence of Selection in the Gullah African American Population. Paula S. Ramos[1], Satria Sajuthi[2], Yiqi Huang[3], Diane L. Kamen[4], Jasmin Divers[2], Kenneth M. Kaufman[5], John B. Harley[5], Robert P. Kimberly[6], Carl D. Langefeld[2], Michèle M. Sale[3], W. Timothy Garvey[6] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]University of Virginia, Charlottesville, VA, [4]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC, [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: In spite of its higher prevalence and severity, little is known about the genetic etiology of systemic lupus erythematosus (SLE) in African Americans (AA). Given this greater prevalence and the increasing evidence of selection at loci associated with human diseases, identification of alleles under selection may provide insight into the susceptibility to SLE. The Gullah are an AA population with limited and well defined ancestral diversity. The shorter genetic distance between the Gullah and Sierra Leonean (SL) suggests that population genetic signals, such as regions under recent selection,

may be more easily detected in the Gullah than in other AA populations. Since population-specific selection may cause allele frequency differences, the goal of this study was to identify regions with minor allele frequency (MAF) differences between Gullah and SL that may increase the risk of SLE in AA.

Methods: We had available 120 Gullah and 400 SL samples, all unaffected, genotyped on the Illumina 1M and **Affymetrix** SNP Array 6.0, respectively. After stringent quality control was applied to each population, 185,569 SNPs common to both arrays with MAF>5% were used to compute the significance of the MAF differences between the two populations. In order to exclude spurious signals, only regions where at least two SNPs in linkage disequilibrium showed significant Bonferroni-adjusted MAF differences were considered.

Results: Amongst the regions where multiple SNPs showed significant MAF differences between the Gullah and SL (P<E-06), some are associated with SLE in Caucasians. These include the MHC, which was previously shown to be under selection in other populations, as well as PTPN22 and TNIP2. Several other regions associated with SLE in Caucasians showed suggestive MAF differences. The region showing the most significant MAF differences was that of the complement-regulatory *CSMD1* gene, which has been associated with, among other traits, emphysema, multiple sclerosis, and insulin resistance in AA. Overall, our results confirmed an enrichment of genes involved in immunity and defense (BP00148; P=0.0076).

Conclusion: We have identified several regions with significant allele frequency differences between the Gullah and SL, suggesting that population-specific selective pressures may be operating at these loci. Given the increased prevalence of SLE in AA and the homogeneity of the Gullah, identification of these regions in the Gullah has the potential to elucidate the etiology of SLE in AA.

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NR1H3 (LXR alpha) Gene Polymorphisms Are Associated with Systemic Lupus Erythematosus in Koreans. Ja-Young Jeon, Hyoun-Ah Kim and Chang-Hee Suh. Ajou University School of Medicine, Suwon, South Korea

Background/Purpose: Liver X receptorsare established sensors of lipid and cholesterol homeostasis. The recent studies have reported that LXRs are involved in regulation of inflammation and immune responses. We attempted to identify single nucleotide polymorphisms (SNPs) of the NR1H3 and NR1H2 genes, associated with the susceptibility to SLE in Korean populations.

Methods: Blood samples were collected from Korean SLE patients (n=300) and normal healthy controls (NC, n=217). Also, replication samples were collected from Korean SLE patients (n=160) and NC (n=143). SNPs were genotyped using SNaPSHOT assay. The promoter activity was analyzed by luciferase reporter assay in Hep3B cells and COS-7 cells. To investigate the effects of the stimulation, we used a functional assay of transcriptional activity and B cell proliferation assay. To investigate whether the genetic polymorphism changed a transcription factor binding, we performed an electrophoretic mobility shift assay.

Results: We have identified five polymorphisms (-1851 T>C and -1830 T>C in the promoter region, -1003 G>A, -840 C>A and -115 G>A in the intron 1 region) including one novel SNPs (-1003 G>A) in the NR1H3 gene. Two SNPs in the NR1H3 gene, -840 C>A and -115 G>A, showed the complete linkage disequilibrium. There was significant difference in the -1830 T>C polymorphism (co: p=0.001), -1003 G>A polymorphism (co: p=0.002), -115 G>A polymorphism (co: p<0.001) between SLE and NC. These results were consistent with those of replication samples. Three common haplotypes for four polymorphisms were constructed: HT1 [TTGG], HT2 [CTGG] and HT3 [TCAA]. There was significant difference between SLE and NC in the observed haplotype HT1 [TTGG] (co: p=0.033) and HT3 [TCAA] (co: p=0.008). In the -1830 T>C polymorphism, arthritis was significantly more common in the SLE patients with the -1830 C allele (p=0.005). The -1003 G>A polymorphism was significantly associated with oral ulcer (p=0.039), arthritis (p=0.006), anti-dsDNA (p=0.041) and elevated triglyceride (p=0.007). The -115 G>A polymorphism was significantly associated with oral ulcer (p=0.024), arthritis (p=<0.001) and elevated triglyceride (p=0.011). Luciferase activity of the constructs containing -1830 Cand -1003 A was lower than that of the constructs containing -1830 T and -1003 G (p=0.009 and p=0.030, respectively). Moreover, promoter activity of the -1830 C and -1003 A was less enhanced when compared to that of the -1830 T and -1003 G in GW3965 and T0901317 treated cells (p=0.034 and p<0.001, respectively). Proliferation of -1830 TC type was increased when compared to that of -1830 TT type in basal,

GW3965 and T0901317 treated B cells from SLE patients (p=0.011, p= 0.040 and p=0.017, respectively). We found that transcription factor GATA-binding protein 3 (GATA3) protein preferentially bound the −1830 T promoter.

Conclusion: These results suggest that the NR1H3 gene genetic polymorphisms may be associated with disease susceptibility and clinical manifestations of SLE in Korean population. Specially, −1830 T>C polymorphism within NR1H3 promoter region may be involved in regulation of NR1H3 expression.

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Signature of Circulating Micro-RNA in Systemic Lupus Erythematosus.

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Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by chronic inflammation sustained by a type I interferon response. The diagnostic value of circulating micro-RNA (miRNA) signatures in SLE has not been systematically evaluated and compared to healthy controls and other autoimmune conditions.

Methods: We quantified 45 mature miRNAs in 409 plasma samples from clinically well-characterized SLE patients, healthy controls, and controls with other systemic autoimmune diseases (RA and vasculitis) and immunosuppressed patients (kidney transplant recipients). SLE risk probability scores were modeled by logistic regression and validated in independent cohorts.

Results: Highly significant changes in 7 specific miRNAs were identified and validated independently. Up-regulated miRNAs were miR-142-3p and -181a and down-regulated miRNAs were miR-106a, -17, -20a, -92a, and -203. Four of five down-regulated miRNAs represent members of the polycistronic miR-17–92 family, and, together with miR-223, were significantly lower in SLE patients with active nephritis than in patients without nephritis. A predictive model for the SLE diagnosis based on 2 miRNAs discriminated SLE from controls (AUC=0.89) when validated independently (accuracy: 76%, $p<2\times10^{-9}$). Using a 4 miRNA model SLE cases was grouped statistically significantly different from disease controls except for vasculitis samples.

Conclusion: We find consistent changes of circulating miRNA profiles in SLE patients compared with healthy controls and disease controls. All 7 validated differently expressed miRNAs target genes in the TGF-b signaling pathway. Other targets imply regulation of apoptosis, cytokine-cytokine receptors, T-cell development, and cytoskeletal organization. A four-miRNA signature was diagnostic for SLE, and patients with active nephritis showed specific subset miRNA profiles. The findings highlight possible deregulated pathways in SLE and suggest that circulating miRNA signatures may potentially be used diagnostically and for monitoring purposes in SLE.

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Familial Aggregation and Heritability of Systemic Lupus Erythematosus in Taiwan: A Nationwide Population Study.

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Background/Purpose: The aims of the present study were to estimate relative risk (RR) of systemic lupus erythematosus (SLE) in individuals with affected relatives in comparison with those without family history of the disease. We also estimated the heritability of SLE in the general population in Taiwan.

Methods: Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of data collected from 11,449,138 men and 11,800,070 women in 2010. Cases of SLE were defined as those receiving catastrophic illness certificates for SLE. The identification of first-degree relatives of each individual was determined using the NIHRD registry for beneficiaries. This specifies relationships between the insured person who paid the insurance fee and his/her dependents, allowing first-degree relatives (father, mother, son, daughter, brother, sister, twin) to be identified directly. Full siblings were identified as individuals who shared the same parents. Twins were full siblings who shared the same date of birth. The marginal Cox proportional hazard model with an equal follow-up time was used to estimate RR (95% confidence interval [CI]), accounting for shared environment and case clustering within families with robust variance, and adjusting for age and sex. Heritability (h^2) was estimated using the multifactorial polygenic model.

Results: There were 2,029 men (0.02%) and 17,200 women (0.15%) who had SLE in 2010. The prevalence of SLE was higher in individuals with affected first-degree relatives (1.16%) than those without (0.08%). The overall familial RR was 15.68 (95% CI, 13.66–18.00). The RRs (95% CIs) for an individual with an affected twin, sibling, offspring and parent were 30.00 (17.82–50.51), 24.69 (19.13–31.85), 11.26 (9.10–13.93) and 14.24 (12.07–16.80), respectively. The RR (95% CI) increased with the number of affected first-degree relatives, from 15.61 (13.59–17.93) and 36.12 (9.10–143.46) for one and two or more affected relatives. The heritability of SLE was 0.72 (95% CI, 0.66–0.79).

Conclusion: This population-based study confirms strong familial aggregation and high heritability of SLE. We provided solid evidence for the significance of genetic factor in SLE susceptibility.

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Single Nucleotide Polymorphisms (SNPs) of Integrin-á-M (ITGAM) Are Associated with Susceptibility to Systemic Lupus Erythematosus (SLE) in an Asian Lupus Cohort.

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Background/Purpose: SLE is a systemic autoimmune disease where lupus nephritis (LN) is a major cause of morbidity and mortality. Integrin-a-M (ITGAM) is critical for the adherence of neutrophils to stimulated endothelium and phagocytosis of complement coated particles. Recently, a variant of exon 3 (rs1143679) of ITGAM was found to be associated with susceptibility to SLE and LN in several ethnic groups including oriental Chinese and Thai populations. Our aim was to examine the potential association of ITGAM SNPs in our local SLE patients.

Methods: Custom-designed arrays were employed to study 201 SNPs covering the approximately 140kb of the ITGAM-ITGAX region in 293 Singapore SLE patients vs. 243 Asian controls. All patients satisfied the 1997 ACR revised SLE criteria. In total 147 SNPs of ITGAM-ITGAX were included in analysis. Significance difference in allelic frequencies of each SNP was examined by gPLINK 1.062 software with Bonferroni adjustment for multiple testing corrections.

Results: 13 SNPs spanning from 5' upstream of ITGAM to intron 5 of ITGAX showed significant association ($p<3.4\times10^{-4}$). The strongest association was detected at rs4561481 in the 5' upstream of ITGAM (OR=1.77 [1.34–2.32], $p=4.2\times10^{-5}$). The previously identified functional SNP of ITGAM (rs1143679, R77H) in European ancestry and African-American populations has shown a strong association for the risk allele (A). However, we observed a low frequency of the risk allele (A) in our patients (1.4% in SLE vs 0.2% in controls; p=0.039, OR=6.7 [0.83–53.42]), and its association with disease susceptibility did not remain significant after Bonferroni correction. To localize the underlying causal variant, linkage equilibrium (LD) analysis was examined among these 13 SNPs which were located in a strong LD block (r^2=0.92–1.0), and the conditional association could not be applied to further distinguish the independent association in our SLE cohort.

Signficiant Disease Association of 13/15 ITGAM SNPs from a Singapore SLE Cohort (n=293 Singapore SLE vs 243 controls)

SNP	BP	Test Allelle	Frequency SLE	Control	P value	OR (95%CI)
rs4561481	31167054	G	0.338	0.224	4.2E-05	1.77 (1.34–2.32)
rs8051304	31167513	C	0.336	0.224	5.4E-05	1.75 (1.33–2.30)
rs889551	31167923	A	0.323	0.216	1.0E-04	1.73 (1.31–2.28)
rs4889640	31171768	C	0.336	0.228	1.1E-04	1.71 (1.30–2.24)
rs889549	31174452	C	0.335	0.226	9.5E-05	1.72 (1.31–2.26)
rs11645526	31175740	A	0.335	0.228	1.3E-04	1.70 (1.29–2.23)
rs8057320	31177052	C	0.335	0.229	1.5E-04	1.70 (1.29–2.22)
rs7193943	31178564	G	0.336	0.228	1.1E-04	1.71 (1.30–2.24)
rs11865830	31179046	G	0.335	0.222	4.9E-05	1.76 (1.34–2.31)
rs3764327	31180630	T	0.335	0.228	1.3E-04	1.70 (1.29–2.23)
rs7196256	31181031	T	0.335	0.229	1.5E-04	1.70 (1.29–2.22)
rs3815801	31184438	C	0.331	0.226	1.5E-04	1.69 (1.29–2.22)
rs2359661	31188648	A	0.345	0.239	1.5E-04	1.68 (1.28–2.20)
rs1143679*	31184312	A	0.014	0.002	3.9E-02	6.66 (0.83–53.42)
rs41477949*	31194928	T	0.021	0.008	9.8E-02	2.53 (0.81–7.89)

*p value = Not significant after bonferroni correction.

Conclusion: All the 13 SNPs of ITGAM were associated with increased susceptibility to SLE. The most significant SNP was rs4561481, but not the previously identified functional SNP of ITGAM (rs1143679), suggesting contribution of other ITGAM variants to SLE in our cohort.

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Genetic Markers for Circulating Vitamin D and the Associations with Risk of Systemic Lupus Erythematosus. Linda T. Hiraki[1], Adrienne H. Williams[2], Arun-Prasad Manoharan[3], Peter Kraft[4], Carl D. Langefeld[5], Robert R. Graham[6] and Elizabeth W. Karlson[7]. [1]Brigham and Women's Hospital, Harvard School of Public Health, Boston, MA, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Genentech, Inc., [4]Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, [5]Department of Biostatistical Sciences, Wake Forest University Health Sciences, Winston-Salem, NC, [6]Genentech, Inc., South San Francisco, CA, [7]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex, life threatening autoimmune disease and a presumed consequence of susceptibility genes interacting with environmental exposures. Vitamin D deficiency has been implicated as an etiologic factor in several autoimmune diseases including SLE. Studies of common single nucleotide polymorphisms (SNPs) in the genes influencing circulating 25-hydroxyvitamin D (25(OH)D) levels (eg: vitamin D receptor, the 1-alpha hydroxylase enzyme and vitamin D binding protein) have demonstrated associations with type 1 diabetes, autoimmune thyroid disease and multiple sclerosis. Few studies to date have examined these genes in predicting SLE. We hypothesized that variations in vitamin D related genes are associated with SLE susceptibility.

Methods: Vitamin D associated SNPs were identified and meta-analyzed from SLE genome wide association studies (GWAS) in two large consortia, the International Consortium on the Genetics of Systemic Lupus Erythematosus (SLEGEN) (720 cases, 2302 controls) and Genentech (1225 cases and 4683 controls). Genotyping was done using the Illumina 550K among Genentech individuals and the Illumina 317K in SLEGEN. We imputed 550K SNPs among SLEGEN individuals using Impute and retained those SNPs with a confidence score > 0.9 and an information score > 0.5. We examined individual SNP associations with SLE risk as well as a genetic risk score (GRS) comprised of four 25(OH)D GWAS associated SNPs (rs2282679, rs3829251, rs2060793, rs6013897) in *GC, DHCR7/NADSYN1, CYP2R1, CYP24A1* genes. We meta-analyzed individual study results using an inverse variance weighted approach, as implemented in the software METAL. We performed gene based tests of 29 vitamin D associated genes identified by literature review, using the versatile gene-based association study (VEGAS).

Results: We did not observe a significant association between four 25(OH)D GWAS associated SNPs and SLE or with an additive GRS comprised of those 4 SNPs (OR 0.99 (95% CI 0.93, 1.07)). Of the 29 vitamin D genes interrogated using VEGAS, *TNF* was found to be significantly associated (p<10–5), as was *CASR* (p=0.002), *SHBG* (p=0.003), *MED1* (p=0.02) and *SMAD3* (p=0.03). However the four GWAS significant 25(OH)D gene regions were not found to be statistically significantly associated with SLE.

Conclusion: We did not observe a direct association between genetic markers of vitamin D and SLE risk. Further investigation into the mechanism by which vitamin D acts on SLE disease risk would provide insight into the pathogenesis and progression of disease.

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Serum Metabolomics As a Novel Diagnostic Approach for Systemic Lupus Erythematosus. Jun Saegusa[1], Yasuhiro Irino[1], Masaru Yoshida[1], Shino Tanaka[1], Yoshinori Kogata[1], Goichi Kageyama[1], Seiji Kawano[1], Goh Tsuji[2], Shunichi Kumagai[2] and Akio Morinobu[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Shinko Hospital, Kobe, Japan

Background/Purpose: Metabolomics, or metabolome analysis, is the comprehensive study of low-molecular-weight metabolites. The metabolome represents the metabolite profiles of all the cellular processes in a cell, tissue, organ, or organism. Notably, because the metabolome is the last step in the omics cascade before the phenotype, alterations in the levels of metabolites may better reflect the physiological and pathological characteristics of a disease than changes in gene or protein expressions. It is now apparent that cell metabolism has a tremendous impact on the function of various immune cells. In this study, we evaluated the differences in the serum metabolome between systemic lupus erythematosus (SLE) patients and healthy subjects, using gas chromatography/mass spectrometry (GC/MS), and sought to identify candidates for metabolic biomarkers.

Methods: Serum samples were obtained in the morning from fasting human patients with SLE (n=26) and healthy volunteers (n=26). Serum metabolite profiling was performed by GC/MS. The metabolic profiles of the patient and control groups were compared using multivariate statistical analysis.

Results: Sixty-two metabolites were detected in the serum. The level of 24 of them was significantly different in SLE patients compared to healthy controls. The 2D-plots of the principal component analysis (PCA) scores for all 62 metabolites showed distinct clustering for the two subject groups. The corresponding 2D-PCA- and partial least squares-discriminant analysis (PLS-DA)-loading plots revealed that variations in the levels of glutamic acid, ornithine, urea, tyrosine, and glycerol greatly contributed to the observed separation of the metabolomics profiles of the SLE patients and healthy controls. Furthermore, we demonstrated that the serum levels of glutamic acid and ornithine were significantly correlated with the SLE activity index (SLEDAI) score in the patient group.

Conclusion: Our study suggests that GC/MS-based serum metabolomics can serve as a novel diagnostic and monitoring tool for SLE, and that the pattern of variation in metabolite levels may be useful for understanding the pathophysiology of SLE and establishing novel therapeutic strategies.

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Tartrate-Resistant Acid Phosphatase Deficiency in the Predisposition to Systemic Lupus Erythematosus. Jie An[1], Tracy A. Briggs[2], Nalini Agrawal[1], Alice Wiedeman[1], Laurence Chaperot[3], Joel Plumas[3], Yanick J. Crow[2] and Keith B. Elkon[1]. [1]University of Washington, Seattle, WA, [2]University of Manchester, Manchester, United Kingdom, [3]Immunobiology & Immunotherapy of Cancers, La Tronche, France

Background/Purpose: The enzyme tartrate-resistant acid phosphatase (TRAP) is highly expressed in osteoclasts. One of the main substrates for TRAP in bone matrix is osteopontin (OPN). Biallelic mutations in the gene, ACP5, that encodes TRAP, result in an immuno-osseous disease called spondyloenchondrodysplasia (SPENCD). In addition to bone and neurological abnormalities, SPENCD patients also develop autoimmune disorders such as systemic lupus erythematosus (SLE). Of note, SPENCD patients demonstrate evidence of increased interferon-alpha (IFN-α) production in their

blood. Since very little is known about the function of TRAP in immune cells, the objectives of our study were to determine whether OPN is a substrate for TRAP and to define the consequences of TRAP deficiency in immune cells.

Methods: Co-localization of TRAP and OPN was determined by confocal microscopy and also by immunoprecipitation and western blot analysis (IP-western). TRAP overexpression or knockdown was performed by transfection with cDNA or shRNA, respectively. Expression of IFN-α and IFN signature genes (ISGs) were determined by enzyme-linked immunosorbent assay (ELISA) and quantitative PCR (qPCR). Phosphatase activity was quantified by Biomol Green fluorimetry.

Results: We observed that TRAP co-localized with OPN in early endosomes and the Golgi in both primary macrophages as well as in plasmacytoid dendritic cells (pDC). Co-localization was confirmed biochemically: following co-transfection of cDNAs encoding TRAP and OPN in 293 cells, we reciprocally co-immunoprecipitated TRAP and OPN as determined by western blots. Also, in macrophages, anti-TRAP antibody immunoprecipitated both TRAP and OPN, indicating that they interacted with each other in primary non-transfected cells. To confirm that OPN was indeed a substrate for TRAP, we observed that recombinant human TRAP dephosphorylated OPN by the release of free phosphate in an *in vitro* assay. To relate the functional significance of TRAP deficiency to IFN-α production, we knocked down the expression of TRAP in pDC. We observed that TRAP specific shRNA, but not scrambled shRNA, increased the expression of IFN-α and IFN signature genes (ISGs).

Conclusion: Taken together, these findings indicate that TRAP and OPN co-localize and that OPN is a substrate for TRAP in immune cells. Significantly, TRAP deficiency in pDC leads to increased IFN-α production providing an explanation for why TRAP mutations lead to a lupus-like disease in SPENCD patients.

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Low Gene Copy Number for C4, C4A and C4B Is a Strong Risk Factor for Developing Systemic Lupus Erythematosus in Childhood. Luis Eduardo C. Andrade[1], Kaline M.C. Pereira[2], Atila G. A. Faria[3], Bernadete Liphaus[4], Adriana A. Jesus[5], Clovis Silva[6] and Magda Carneiro-Sampaio[5]. [1]Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo and Fleury Health and Medicine Laboratories, Sao Paulo, Brazil, [3]Sao Paulo, Brazil, [4]Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [5]Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil, [6]MD; PhD, São Paulo-SP, Brazil

Background/Purpose: C4 is an important component of the Complement system and plays an essential role in the activation cascade of the classical Complement pathway. Complete C4 deficiency is among the strongest genetic risk factors for systemic lupus erythematosus (SLE). There are two C4 circulating isoforms (C4A and C4B) encoded by C4A and C4B genes, respectively, that differ by only five nucleotides. C4A protein is involved in the clearance of immune complex and apoptotic debris while C4B protein is relevant in the opsonization of microbes. C4A and C4B genes are located at a gene cassette within the MHC class III region and depict gene copy-number variation (CNV). The number of C4A copies may be related to the susceptibility to SLE. This study aimed to investigate the impact of the C4A and C4B gene CNV on juvenile SLE.

Methods: We evaluated 90 children and 170 adults with SLE (meeting SLE ACR criteria) sequentially retrieved from the rheumatology outpatient clinic. Two hundred healthy individuals (HI) without evidence of autoimmune diseases were retrieved among blood bank donors. Peripheral blood leukocyte DNA was amplified by quantitative real-time PCR (qPCR) with primers for C4 gene and sequence specific TaqMan® probes for C4A (5′ FAM-ACCCCTGTCCAGTGTTAG-MGB 3′) and C4B (5′ FAM-ACCTCTCTCCAGTGATAC-MGB 3′). Gene copy number (GCN) was determined by the delta-delta cycle threshold (DDCT) method.

Results: Children with SLE had lower GCN of total C4 (mean total C4=3.1; 95% CI=2.8–3.4), C4A (mean C4A=1.7; 95% CI=1.5–1.9) and C4B (mean C4B=1.5; 95% CI=1.3–1.6) than HI (C4=4.3 with 95% CI=4.1–4.5, p<0.001; C4A=2.3 with 95% CI=2.2–2.5, p<0.001; C4B=2.0 with 95% CI=1.8–2.1; p<0.001). The frequency of SLE children with total C4 low GCN (<4 copies) was significantly higher than in HI (SLE=59% versus HI=28%; OR=3.68; 95% CI=2.19–6.20; p<0.001). The same was observed for C4A low GCN (<2 copies) (SLE=52% versus HI=18%; OR=4.98; 95% CI=2.88–8.62; p<0.001) and C4B low GCN (SLE=60% versus HI=31%; OR=3.26; CI=1.95–5.47; p<0.001). The association between adult SLE and low GCN for total C4 (OR=2.03; 95% CI=1.32–3.13; p=0.001), C4A (OR=2.36; 95% CI=1.46–3.81; p<0.001) and C4B (OR=1.13; CI=0.73–1.74; p=0.593) was less pronounced than observed in juvenile SLE. Moreover, there was an association between cardiovascular damage and low GCN for C4 and C4A. 81% of SLE children with cardiovascular damage had less than 4 copies of C4 against 51% of the children without cardiovascular manifestation (OR=4.13; CI 95%=1.02–16.68; p=0.047). The same was observed for C4A (81% of those with cardiovascular damage had <2C4A against 44% of those with no heart involvement; OR=5.54; CI 95%=1.37–22.32; p=0.016).

Conclusion: Low GCN for total C4, C4A and C4B is associated with an increased risk for developing systemic lupus erythematosus and this association is stronger in childhood than in adults. Furthermore, low GCN for C4 and C4A seems to be a risk factor of cardiovascular damage in juvenile SLE.

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Preferential Association of Complement Receptor 2 Variants with Anti-dsDNA Autoantibodies in Systemic Lupus Erythematosus. Brendan M. Giles[1], Jian Zhao[2], Kara M. Lough[1], Patrick M. Gaffney on behalf of LLAS2[3], Marta E. Alarcon-Riquelme on behalf of BIOLUPUS[4], Elizabeth E. Brown on behalf of PROFILE[5], Lindsey A. Criswell[6], Gary S. Gilkeson[7], Chaim O. Jacob[8], Judith A. James[9], Joan T. Merrill[3], Kathy L. Moser[3], Timothy B. Niewold[10], R. Hal Scofield[3], Timothy J. Vyse[11], John B. Harley[12], Kenneth M. Kaufman[3], Jennifer A. Kelly[3], Carl D. Langefeld[13], Jeffrey C. Edberg[14], Robert P. Kimberly[5], Daniela Ulgiati[15], Betty P. Tsao[16] and Susan A. Boackle[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [5]University of Alabama at Birmingham, Birmingham, AL, [6]University of California San Francisco, San Francisco, CA, [7]Medical University of South Carolina, Charleston, SC, [8]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [9]Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK, [10]University of Chicago, Chicago, IL, [11]King's College London, Guy's Hospital, London, United Kingdom, [12]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [13]Wake Forest School of Medicine, Winston-Salem, NC, [14]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [15]University of Western Australia, Perth, Western Australia, Australia, [16]UCLA School of Medicine, Los Angeles, CA

Background/Purpose: Complement receptor 2 (CR2/CD21) is primarily expressed on B cells and follicular dendritic cells (FDC) and is required for normal humoral immune responses. We have previously identified *CR2* variants associated with systemic lupus erythematosus (SLE) susceptibility. To understand how *CR2* might contribute to disease development, we explored the association of *CR2* polymorphisms with specific clinical manifestations of SLE.

Methods: We genotyped 49 *CR2* single-nucleotide polymorphisms (SNPs) and assessed them for association with 14 clinical manifestations of SLE in 7,427 European-Americans (EA) cases and controls. We imputed genotypes for untyped SNPs, identified functional implications of associated SNPs, and evaluated haplotype-associated RNA and protein expression profiles in primary B cells from healthy control subjects.

Results: We detected a strong association between *CR2* SNPs and anti-dsDNA autoantibodies in EA SLE subjects, and identified two SNP haplotypes independently associated with the absence (H1: 7.0% vs. 10.4%, $P=1.2\times10^{-5}$) and presence (H2: 5.8% vs. 3.8%, $P=7.0\times10^{-4}$) of anti-dsDNA autoantibodies. The H1 haplotype contained imputed SNPs extending into the proximal complement receptor 1 (*CR1/CD35*) gene. Three phenotypes were found in healthy control subjects with the H1 haplotype compared to the H2 haplotype: 1) decreased mRNA levels for the *CR2* long isoform (p=0.0293), which is expressed primarily on FDC, 2) increased expression of CR1 (p=0.0353), and 3) positive correlation of surface CR2 with ligand binding capacity (H1: p=0.0311; H2: p=0.2967).

Conclusion: These data indicate that *CR2* haplotypes are preferentially associated with anti-dsDNA autoantibodies and may modify both B cell and FDC responses. The association of imputed *CR1* SNPs and altered B cell CR1 expression suggest that an extended haplotype encompassing both genes is responsible. Anti-dsDNA antibodies fluctuate with lupus disease activity, are associated with more severe disease, and are among the last autoantibodies to appear prior to the onset of clinical symptoms. Therefore, understanding the mechanisms by which they are regulated has important therapeutic implications.

*These authors contributed equally to this work.

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Epigenetic Profiling in Monozygotic Twins Discordant for Systemic Lupus Erythematosus Reveals Prominent Hypomethylation of Interferon-Inducible Genes. Paula S. Ramos[1], Timothy D. Howard[2], Miranda C. Marion[2], Satria Sajuthi[2], Jennifer A. Kelly[3], Kathy L. Moser[3] and Carl D. Langefeld[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune inflammatory disease. In addition to genetic and environmental influences, the discordance rate between monozygotic (MZ) twins suggests a role for epigenetic factors in disease. The analysis of MZ twins represents the ideal design to assess the role of epigenetic factors in disease etiology. Here, we report the results of a genome-wide analysis of DNA methylation on 3 MZ twin pairs discordant for SLE.

Methods: Genomic DNA was extracted from peripheral blood of 3 MZ twin pairs discordant for SLE. DNA methylation profiling was performed using the Illumina Infinium HumanMethylation450 BeadChip. Probes with a detection P-value$<$1.0E-05 were excluded. In order to identify differentially methylated genes between unaffected and affected twins, a paired *t*-test on the probe-specific β-values was computed and significance was assessed as the intersection of meeting an FDR threshold (1.06×10E-7) and mean DNA methylation difference ($\Delta\beta$)$>|0.10|$.

Results: Global hypomethylation of interferon-inducible genes was observed in the affected twins. Analysis of the top loci using Gene Ontology suggested an enrichment of epigenetic changes in genes involved in response to biotic stimulus (GO:0009607; P(Benjamini)=0.0077) and response to virus (GO:0009615; P(Benjamini)=0.021), and their functional annotation using Panther revealed an enrichment of two biological processes, immunity and defense (BP00148; P(Benjamini)=0.0044) and interferon-mediated immunity (BP00156; P(Benjamini)=0.032). The top hypomethylated sites in the affecteds were located in several interferon-inducible genes, including MX1 ($\Delta\beta = -0.47$, $P=6.59$E-13), IFI44L ($\Delta\beta = -0.29$, P=1.58E-14), and IFITM1 ($\Delta\beta = -0.25$, P=4.41E-40). Other significant loci included the polymerase PARP9 (P=6.74E-126, $\Delta\beta = -0.37$), the cytidine kinase CMPK2 ($\Delta\beta = -0.33$, P=7.98E-08), and the cyclic nucleotide phosphodiesterase PDE7A genes ($\Delta\beta = -0.35$, P=1.21E-09).

Conclusion: These data support a role for DNA methylation differences in mediating susceptibility to SLE. Furthermore, these observed hypomethylation of interferon-inducible genes offers a mechanistic explanation for the well know overexpression of interferon-inducible genes observed in patients with SLE and other autoimmune diseases.

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Systemic Lupus Erythematosus RNA-Seq: Endogenous Retroviral Group K Overexpression in Monocytes. Lihua Shi[1], Zhe Zhang[2], Michelle Petri[3] and Kate Sullivan[4]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Bioinformatics, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]THe Children's Hospital of Philadelphia, Philadelphia, PA

Background/Purpose: Gene expression studies of peripheral blood mononuclear cells in SLE have consistently shown an interferon signature. We previously examined monocytes from SLE patients to understand the impact of interferon expression on the cell that is integral to atherosclerosis and renal disease. In that study, we also found a gene expression signature consistent with interferon exposure. Various triggers of interferon expression have been identified and endogenous retroviral elements have been considered as a possible nucleic acid stimulus. Older literature on endogenous retroviruses in SLE identified intracisternal A-type particles reminiscent of retroviruses and frequent identification of anti-retroviral antibodies. Nevertheless, there has been little direct demonstration of altered expression of endogenous retroviral elements. To better understand the altered gene expression and to examine non-coding RNAs, which are poorly represented on arrays, we performed RNA-seq.

Methods: RNA-seq on the SOLiD platform was performed on RNA from monocytes from 8 SLE patients and 8 age/gender-matched controls. Reads were aligned and mapped using BioScope. The biological samples were scored to define variability by calculating the sample-sample correlation. Group comparison statistics and FDR calculation were used to identify regions with significant RPKM group-based variations. To minimize confounders, we selected patients with a low disease activity and minimal medications.

Results: Again, we saw evidence of interferon exposure. We also noted a dramatic enrichment of genes regulated by the IRF family of transcription factors. Among the most highly expressed transcripts were non-coding RNAs, anti-sense RNAs and micro-RNAs, suggesting that array studies have captured but one facet of the transcriptome. The use of RNA-seq also enabled us to look at highly repetitive transcripts such as LINE and Alu elements. Although unmappable, the total read depth was analyzed. Amongst all repetitive elements, the ERVK family was found to be 3X overexpressed in SLE monocytes relative to the controls. Other engogenous retroviral elements were expressed at comparable levels in SLE patient and controls.

Conclusion: The ERVK family of endogenous retroviruses is unusual in that it can encode gag, env, pol, reverse transcriptase and integrase proteins. Retroviruses have been implicated in murine lupus but data on human endogenous retroviruses have been limited. The recognition of the important role of TREX1 in limiting retroviral DNA induction of interferons has supported a role for retroviruses in human SLE but until the advent of next generation sequencing, it was difficult to identify specific families. This study identified many non-coding RNAs both over-expressed and under-expressed, often by 20–50-fold. Unexpectedly, the ERVK family was over-expressed out of proportion to other endogenous retroviruses, suggesting that this family may be selectively de-repressed. De-repression of ERVK elements could contribute to interferon production via accumulation of viral RNAs.

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ACR/ARHP Poster Session C
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's –
Pathogenesis, Animal Models and Genetics
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Dysregulated Discoidin Domain Receptor 2-Microrna 196a-Mediated Negative Feedback Against Excess Type I Collagen Expression in Scleroderma Dermal Fibroblasts. Katsunari Makino, Masatoshi Jinnin, Jun Aoi, Ikko Kajihara, Takamitsu Makino, Keisuke Sakai, Satoshi Fukushima, Yuji Inoue and Hironobu Ihn. Kumamoto University, Kumamoto, Japan

Background/Purpose: Systemic sclerosis (SSc) is characterized by the excess deposition of collagen in the skin, due to intrinsic transforming growth factor (TGF)-β activation. The discoidin domain receptor 2 (DDR2) is a transmembrane receptor belonging to the receptor tyrosine kinase family. DDR2 is mainly detected in mesenchymal cells and responds to collagen types I, II, III and X. This study was undertaken to clarify the expression pattern of DDR2 in SSc and the role in the pathogenesis of SSc.

Methods: DDR2 expression was evaluated by immunoblotting, immunohistochemistry and real-time PCR. The knockdown or overexpression of DDR2 was performed using siRNA or lentiviral transfection. The microRNA expression was evaluated by real-time PCR. The knockdown or overexpression of microRNA in dermal fibroblasts was performed using microRNA inhibitor or mimic.

Results: The expression of DDR2 mRNA and protein was significantly decreased in SSc cultured dermal fibroblasts, which was recovered after knockdown TGF-β. The knockdown of DDR2 in normal fibroblasts induced microRNA-196a expression, which led to type I collagen down-regulation, thus indicating that DDR2 itself has a negative effect on microRNA-196a expression and that it induces type I collagen expression. In SSc fibroblasts, however, the DDR2 knockdown did not affect TGF-β signaling and microRNA-196a expression. The microRNA-196a levels were significantly decreased in normal fibroblasts treated with TGF-β and in SSc fibroblasts. Taken together, these findings indicate that, in SSc fibroblasts, the intrinsic TGF-β stimulation induces type I collagen expression and down-regulates DDR2 expression. This probably acts as a negative feedback mechanism against excess collagen expression, since a decreased DDR2 expression is supposed to stimulate the microRNA-196a expression and further change the collagen expression. However, in SSc fibroblasts the microRNA-196a expression was down-regulated by TGF-β signaling.

Conclusion: DDR2-microRNA 196a-mediated negative feedback against excess type I collagen expression is impaired in SSc fibroblasts. Its impairment may be involved in the pathogenesis of SSc. Investigations of the overall regulatory mechanisms of fibrosis by DDR2 and microRNAs may lead to new therapeutic approaches for this disease.

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Altered Regulation of Metabolic Pathways in Systemic Sclerosis Evidenced by Metabolomics. Emmanuel Chatelus, Jacques-Eric Gottenberg, François-Marie Moussallieh, Christelle Sordet, Arnaud Theulin, Alain Meyer, Jean-Francois Kleimann, Jean Sibilia and Izzie Jacques Namer. Strasbourg University Hospital, Strasbourg, France

Background/Purpose: High throughput study of metabolic pathways might help identify new biomarkers and therapeutic targets in autoimmune diseases. Systemic sclerosis (SSc) currently lacks prognostic biomarkers and efficacious and specific treatments. We therefore assessed serum levels of 40 metabolites in patients with SSc and healthy controls using high-resolution magic-angle spinning (HRMAS) proton magnetic resonance spectroscopy.

Methods: The blood samples of 38 successive patients with SSc (median age (range) 62 years (25–85); disease duration 8 years (1–22); limited cutaneous SSc: 62%; diffuse cutaneous SSc: 38%) and 39 healthy controls were analysed in this study. After cryopreservation at $-80°C$, the samples were studied with HRMAS proton magnetic resonance spectroscopy (1H-MRS). Spectra were recorded on a Bruker Avance III 500 spectrometer operating at a proton frequency of 500 MHz. The speed revolution of the tube was 3000 Hz. The 1D MR spectra were acquired during 15 min (between 0.5 and 4,7 ppm). Unsupervised clustering was performed using principal component analysis (PCA).

Results: Unsupervised clustering of the 38 samples allowed to discriminate all patients with SSc from healthy controls ($R^2Y=0.76$ and $Q^2=0.67$ (figure 1)). Interestingly, 3 metabolites were significantly more expressed in SSc blood samples than in healthy controls: acetone, acetate and formate (median 10.7 vs 8.1 μmol/l, $p<0.05$; 21.8 vs 5.4 μmol/l; $p<0.05$; 28.6 vs 7.9 μmol/l, $p<0,05$ respectively).
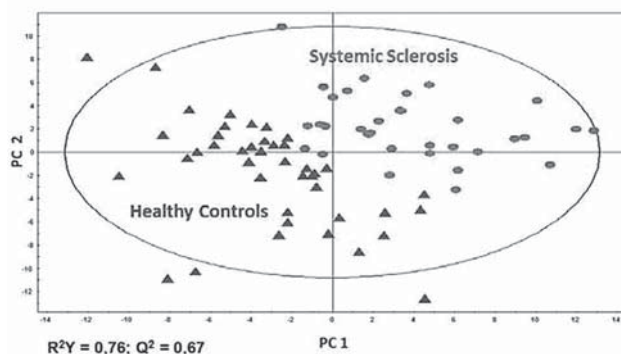
Figure 1. PCA scored plot based on NMR spectra of blood samples obtained from systemic sclerosis patients (red dot) and healthy controls (blue triangle).

Conclusion: This first high-throughput analysis of metabolic pathways disclosed a specific metabolomic signature of SSc allowing to discriminate all patients from controls. This new and very potent means of metabolic analysis may help to increase our knowledge on the pathogenesis of SSc, identify biomarkers, and new therapeutic targets.

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The Role of TCR Vä1[+] NKT Cells in Systemic Sclerosis Patients with Interstitial Pneumonitis. Seiji Segawa, Daisuke Goto, Masanobu Horikoshi, Shinya Hagiwara, Naoto Umeda, Hiroshi Ogishima, Yuya Kondo, Hiroto Tsuboi, Makoto Sugihara, Taichi Hayashi, Yusuke Chino, Isao Matsumoto and Takayuki Sumida. University of Tsukuba, Tsukuba City, Japan

Background/Purpose: Interstitial pneumonia (IP) is one of the critical complications in patients with several autoimmune diseases. However, the exact mechanism of IP remains elusive. Recently, the pathological role of gd T cells was reported in several IP mice models. Previous our data showed that IP in Interleukin (IL)-2 plus IL-18 induced mice was similar to human IP. In this mice, $\gamma\delta$NKT cells exacerbated IL-2 plus IL-18 induced lung inflammation via the production of IFN-γ. Thus, to examine whether Vd1^{+} NKT cells play a crucial role, we carried out the number and function of TCR Vδ1[+]NKT cells in systemic sclerosis patients with IP.

Methods: 1) PBMCs were isolated from healthy controls (HC, n=22) and patients with rheumatoid arthritis (RA, n=17), systemic sclerosis (SSc, n=35), and polymyositis/dermatomyositis (PM/DM, n=14). We examined the proportion of TCR Vδ1[+]NKT cells in PBMCs by flow cytometry (FCM). 2) We examined the proportion of TCR Vδ1[+]NKT cells in patients with autoimmune disease plus IP. 3) We analyzed the correlation between the proportion of TCR Vδ1^{+}NKT cells in PBMCs and serum KL-6 values. 4) CD161^{-} Vδ1^{+} $\gamma\delta$T and CD161^{+} Vδ1^{+} $\gamma\delta$T cells (TCR Vδ1^{+}NKT cells) in PBMCs were sorted out from HC (n=3). We performed GeneChip analysis using those two cell populations.

Results: 1) The proportion of TCR Vδ1[+]NKT cells in PBMCs from SSc patients (mean±SEM, 0.55±0.13%) was significantly higher than that of HC (0.23±0.09%, $p<0.05$), whereas RA (0.38±0.12%) and PM/DM patients (0.23±0.11%) were not. 2) In SSc patients, the proportion of TCR Vδ1[+]NKT cells in PBMCs from IP-negative subjects (1.03±0.32%) was significantly higher than that of IP-positive subjects (0.28±0.07%, $p<0.05$). In RA and PM/DM patients, there was no difference between IP-negative and IP-positive subjects. 3) In IP-positive SSc patients, results showed a negative correlation between serum KL-6 values and the proportion of TCR Vδ1^{+} NKT cells ($r=-0.464$, $p<0.05$). In IP-positive PM/DM patients, there were no any correlations. 4) We found highly expressed 192 genes in TCR Vδ1^{+} NKT cells compared to CD161^{-} Vδ1^{+} $\gamma\delta$T cells. One of 192 genes was CCL3 chemokine associating with SSc and IP. Exactly, the CCL3 mRNA was significantly increased in TCR Vδ1[+]NKT from SSc patients by real time PCR methods ($p<0.05$).

Conclusion: TCR Vδ1^{+} NKT cells might play a crucial role in the generation of IP in patients with SSc.

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2289

Adiponectin Has Potent Anti-Fibrotic Effects Mediated Via AMP Kinase: Novel Target for Fibrosis Therap. Feng Fang[1], Lei Liu[2], Yang Yang[2], Jun Wei[1], Swati Bhattacharyya[1], Ross Summer[3], Boping Ye[2] and John Varga[1]. [1]Northwestern University, Chicago, IL, [2]China Pharmaceutical University, Nanjing, China, [3]Boston University, Boston, MA

Background/Purpose: Fibrosis in scleroderma is associated with transforming growth factor-β (TGF-β) signaling activation, collagen deposition and myofibroblast accumulation. Peroxisome proliferator activated receptor gamma (PPAR-γ) inhibits profibrotic responses, while regulates adiponectin production. Our recent studies demonstrated that adiponectin levels were reduced in patients with diffuse cutaneous scleroderma, and inversely correlated with disease activity, severity and duration. However, the function and molecular signaling of adiponectin during fibrogenesis are still unknown.

Methods: Collagen and α-smooth muscle actin (α-SMA) gene expression and TGF-β signaling by recombinant adiponectin, AICAR and metformin were examined by real-time qPCR, Western blot, immunofluorescence microscopy and transient transfection assays. AdipoR1 expression on skin fibroblasts was determined by real-time qPCR. Gene expression changes were examined using microarrays.

Results: In skin fibroblasts, recombinant adiponectin inhibited the basal and TGF-β-stimulated collagen and alpha-smooth muscle actin mRNA and protein expression at dose-depend manner, while RNAi knockdown of adiponectin sensitized TGF-β-stimulated fibrotic responses. Similarly, metformin and AICAR, two agonists of 5' adenosine monophosphate (AMP)-activated protein kinase, inhibited fibrotic responses. AMPK antagonist compound C impaired the anti-fibrotic effects of adiponectin. In adiponectin-null fibroblasts, PPAR-γ ligand PGJ$_2$ failed to inhibit TGF-β-stimulated fibrotic responses. In addition, adiponectin completely abrogated the profibrotic effects of lipopolysaccharide (LPS, a potent ligand of Toll-like receptor 4 (TLR4) with profibrotic effects). Furthermore, the adiponectin receptor 1 showed reduced expression in scleroderma skin biopsies, suggesting the defective adiponectin signaling in scleroderma.

Conclusion: Our results indicate adiponectin plays an important homeostatic role in negative regulation of collagen deposition and myofibroblast accumulation. The anti-fibrotic effects associated with pharmacological PPAR-γ ligands are at least in part due to the activation of the adiponectin signaling pathway. Restoring the adiponectin signaling axis in fibroblasts might represent a novel pharmacological approach to controlling fibrosis.

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Type I Interferon Associated Gene *IRF7* in the Pathogenesis of Fibrosis in Systemic Sclerosis (SSc). Minghua Wu[1], Michael R. Blackburn[2], Shervin Assassi[1], Xiaochun Liu[1], John D. Reveille[1], Filemon K. Tan[1], Sandeep K. Agarwal[3] and Maureen D. Mayes[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]The University of Texas Medical School at Houston, Houston, TX, [3]Baylor College of Medicine, Houston, TX

Background/Purpose: Fibrosis in Systemic Sclerosis is characterized by excessive collagen production and accumulation in the skin and lungs. It has been increasingly appreciated that a substantial number of SSc patients display a type I interferon (IFN) signature. Microarray studies support a pivotal role of type I IFN in the pathophysiology of connective tissue diseases. Type I IFN and associated gene signatures might serve as a marker for more severe disease. Interferon regulatory factors (IRFs) are characterized as transcriptional regulators of type I IFNs and IFN-inducible genes. Interferon regulatory factor 7 (IRF7) polymorphisms are associated with many autoimmune diseases including SSc. However, no specific mechanism for its involvement in SSc has been identified.

Methods: Healthy adult dermal fibroblasts and SSc fibroblasts were studied in parallel. Scleroderma and normal skin biopsies (61 SSc patients and 36 healthy controls) were used for microarray studies to quantitate IRF7 levels and for immunohistochemistry (IHC) analyses (6 SSc patients and 5 healthy controls) to determine expression pattern of IRF7. In addition to patient samples, IRF7 was examined in bleomycin induced scleroderma mouse model. Lesional murine skin tissues were examined by microarray and immunohistochemistry analysis.

Results: IRF7 protein levels were significantly elevated in explanted SSc skin fibroblasts and skin tissues from patients with SSc compared to healthy controls. Microarray studies showed that IRF7 mRNA levels were up-regulated in skin and monocytes from SSc patients. TGF-β, PolyI(c) and IFN-α caused a time- and dose-dependent increase in IRF7 protein and mRNA expression in normal and SSc skin fibroblasts. IRF7 protein and mRNA levels were found to be up-regulated in skin from the bleomycin induced mouse model of scleroderma.

Conclusion: Up-regulation of IRF7 in SSc might contribute to amplification or persistence of the IFN driven inflammatory response and TGF-β-driven fibrotic response. Blocking IRF-7 may therefore represent a novel therapeutic strategy in SSc.

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Enhanced Release of S100A9 and Hepatocyte Growth Factor by the Epidermis in Systemic Sclerosis. Joanna Nikitorowicz Buniak[1], Christopher P. Denton[2], David J. Abraham[1] and Richard J. Stratton[1]. [1]UCL Medical School, London, United Kingdom, [2]UCL, London, United Kingdom

Background/Purpose: Systemic sclerosis (SSc) is a severe disease of unknown aetiology characterised by cellular injury and activation in early stage, followed by autoimmunity and fibrosis. Much of the work is focused on the fibroblasts however, keratinocytes are known to be able to secrete chemo-attracting agents, as well as growth factors influencing phenotype and proliferation rate of fibroblasts. We have recently shown that SSc epithelial cells exhibit an activated phenotype similar to wound healing. Data from hypertrophic scaring and keloids demonstrate that epidermis can promote dermal fibrosis. Therefore, we decided to look for evidence that in SSc injured epidermal cells are releasing chemokines and cytokines capable of recruiting immune cells to the skin and promoting fibrosis.

Methods: Forearm biopsies were taken from 12 healthy controls and 12 SSc patients. Dermis and epidermis were separated using trypsin/EDTA and the explants incubated overnight in serum free media. The conditioned media were then collected and analysed using Legend PLEX (BioLegend) for presence of G-CSF, GM-CSF, VEGF, PDGF-AA, PDGF-BB, MCP-1, FGF-2, IL-8, IL-6, IL-1α, IL-1β, and IL-1ra. Additionally, HGF, CCL20 and S100A9 were measure by ELISA (R&D Systems). Moreover, immunohistochemistry was performed on skin biopsies of 6 dcSSc and 6 healthy controls using antibodies against S100A9, S100A8, loricrin and involucrin. The epidermal thickness and cell area were also measured. The statistical analysis was performed using Wilcoxon rank-sum test.

Results: The conditioned media analysis revealed significantly higher levels of HGF ($p<0.005$) and S100A9 ($p<0.05$) released by SSc epidermis. Also increased levels of FGF-2, VEGF-A and PDGF-AA and IL-8 found in the SSc epidermis conditioned media showed a trend towards significance. Staining of skin sections confirmed much higher levels of S100A9 in SSc present throughout the epidermis, compared to positive staining in the healthy skin only around epidermal appendages. The SSc epidermis showed significant increase in thickness ($p<0.05$) and hypertrophic cells in basal ($p<0.005$) and spinous layers ($p<0.005$). The expression of involucrin and loricrin was also altered.

Conclusion: The epidermis provides a potential source of chemokines in SSc. High levels of pro-inflammatory S100A9 released by SSc dermis might contribute to the inflammation and therefore skin fibrosis. The abnormal thickness, hypertrophic keratinocytes and altered expression of differentiation markers in SSc epidermis suggest changes in terminal differentiation and signalling. The increase in HGF release by SSc epidermis is consistent with our previous report of enhanced c-Met activation in SSc epidermis and, indicates autocrine stimulation that could be responsible for the changes observed. However, more investigations are required to fully explore the mechanisms underlying S100A9 and c-Met/HGF signaling and they role of in skin fibrosis.

Disclosure: **J. Nikitorowicz Buniak**, None; **C. P. Denton**, None; **D. J. Abraham**, None; **R. J. Stratton**, None.

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Increased Synthesis of Leukotrienes by Peripheral Blood Mononuclear Cells Is Associated with More Severe Disease and Worse Prognosis in Patients with Systemic Sclerosis. Otylia M. Kowal-Bielecka[1], Anna Lapinska[2], Marek Bielecki[3], Oliver Distler[4], Izabela Domyslawska[1], Lech Chyczewski[2], Stanislaw Sierakowski[1], Steffen Gay[5] and Krzysztof Kowal[6]. [1]Department of Rheumatology and Internal Medicine, Medical University in Bialystok, Bialystok, Poland, [2]Department of Medical Pathomorphology, Medical University in Bialystok, Bialystok, Poland, [3]Department of Orthopedics and Traumatology, Medical University in Bialystok, Bialystok, Poland, [4]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [5]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, Zurich, Switzerland, [6]Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland

Background/Purpose: Eicosanoids are a group of arachidonic acid-derived lipid mediators which play a key role in the regulation of inflammatory response and connective tissue remodeling. Different classes of eicosanoids exert different, often opposing roles. Leukotrienes (LTs), synthesized

through the action of 5-lipoxygenase, are considered pro-inflammatory and pro-fibrotic mediators, while 15-lipoxygenase-derived products, 15-hydroxyeicosatetraenoic acid (15-HETE) and lipoxins, possess anti-inflammatory and anti-fibrotic properties, in part due to antagonizing action of LTs.

We undertook this study to investigate the role of eicosanoids in the pathogenesis of SSc trough evaluation of 1). the profile of eicosanoids synthesized by peripheral blood mononuclear cells (PBMC) and 2). relationships between eicosanoid profile of PBMC and clinical features and progression of the disease in patients with SSc.

Methods: Leukotriene B4 (LTB4), cysteinyl leukotrienes (CysLTs), and 15-HETE were measured by ELISA in the supernatants from ionophore-stimulated PBMC of 39 patients with SSc and 24 age- and sex-matched healthy controls (HC). Only patients, who had not received immunosuppressive drugs, aspirin or other NSAIDs before the study, were included. Follow-up data were available in 25 SSc patients (mean $+/-$ SD follow-up time: 34 $+/-$ 18 months). Disease progression was defined as death due to SSc-related organ complication, development of a new or progression of pre-existing SSc-related organ involvement.

Results: Concentration of LTB4 was significantly higher in PBMC cultures from patients with SSc (640 $+/-$ 518 pg/mL/10^5cells) as compared with HC (353 $+/-$ 216 pg/mL/10^5cells, p<0.05). Higher LTB4 levels were associated with the presence of diffuse SSc and pulmonary fibrosis. No significant differences could be found in the concentrations of CysLTs or 15-HETE between SSc patients and HC (data not shown). The 15-HETE/LTB4 and 15-HETE/CysLTs ratios were lower in SSc patients (13 $+/-$ 11 and 20 $+/-$ 19, respectively) as compared with HC (26 $+/-$ 28, p<0.05, and 26 $+/-$ 17, p=0.08, respectively),

In 7 SSc patients who experienced subsequent progression of the disease baseline concentration of CysLTs was significantly higher (452$+/-$ 197 pg/mL/10^5cells) while 15-HETE/LTB4 (6.9 $+/-$ 9.3) and 15-HETE/CysLTs (8.1 $+/-$ 6.0) ratios – significantly lower as compared with the remaining 18 with stable disease (276$+/-$ 139 pg/mL/10^5cells, 13.2$+/-$ 10.7, and 18.9$+/-$ 11.6, respectively, p<0.05 for all). Although LTB4 concentration was higher in patients who progressed over time (918$+/-$ 665 pg/mL/10^5cells) as compared with those with stable disease (569$+/-$ 549 pg/mL/10^5cells), the difference was not significant (p=0.1).

Conclusion: The results of our study indicate that increased synthesis of LTs, which is not balanced by sufficient synthesis of 15-lipoxygenase derived eicosanoids, might be involved in the pathogenesis and progression of SSc. Consequently, inhibition of LTs synthesis or action might represent a new, promising target in the treatment of SSc.

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Interleukin-17A Positive Cells Are Increased in Systemic Sclerosis Skin and Their Number Is Inversely Correlated to Skin Thickness.
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Background/Purpose: T cell producing IL-17A are increased in the peripheral blood of individuals affected by systemic sclerosis (SSc). We asked the question whether IL-17A-producing cells are present in affected SSc skin and whether they exert any role in myofibroblasts induction.

Methods: Bioptic material was obtained from the involved skin of 8 SSc and 8 healthy donors (HD) undergoing plastic surgery. We adopted an immunohistochemistry and multicolor immunofluorescence approach to identify and quantify in vivo IL-17A+, IL-4+, CD3+, tryptase+, alpha-smooth muscle (aSMA)+, myeloperoxidase+, CD1a+ cells. Dermal fibroblasts cell lines were generated from all biopsies. Quantitative PCR, western-blot, and solid phase assays used to quantify aSMA, and matrix metalloproteinase-1 (MMP1) production by cultured fibroblasts.

Results: IL-17A+ cells were significantly more numerous in SSc than HD skin (p=0.004) and present in both superficial and deep dermis. Most of these cells (>60%) were tryptase+ mast cells and between 10 to 20% Th17 cells. Some IL-17A+, but no IL-4+ cells were found adjacent to aSMA+ cells.

fibroblasts. However, IL-17A did not induce aSMA-expression in cultured fibroblasts and decreased aSMA-expression induced by transforming growth factor-beta, while directly enhancing MMP-1 production. Furthermore, the frequency of IL-17A+ cells was higher in the skin of SSc individuals with lower global skin thickness score.

Conclusion: IL-17A+ cells belonging to the innate and adaptive immune system are numerous in SSc skin where IL-17A participates to inflammation and exerts an inhibitory activity on myofibroblast differentiation. These data are consistent with a direct negative regulatory role for IL-17A in the development of dermal fibrosis in humans.

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The Histone Deacetylase SIRT1 Is Anti-Fibrotic and Mediates Resveratrol Effects.
Roberta G. Marangoni[1], Archit Ghosh[1], Jun Wei[2] and John Varga[3]. [1]Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern University Medical School, Chicago, IL

Background/Purpose: Fibrosis in scleroderma is associated with increased collagen synthesis driven by TGF-β and associated epigenetic modifications. The Class III histone deacetylase SIRT1 has anticancer and anti-inflammatory properties in vitro and in vivo, and its expression and activation are induced by the natural phytoalexin resveratrol. We investigated SIRT1 function and regulation by resveratrol during fibrogenesis.

Methods: *SIRT1* expression in scleroderma skin biopsies was analyzed in published microarray dataset. The effects of resveratrol on fibrotic responses were evaluated by real-time qPCR, Western analysis, immunefluorescence, transient transfection, collagen gel contraction and cell migration assays. SIRT1 modulation of TGF-β signaling was examined using the pharmacological SIRT1 inhibitors splitomicin and nicotinamide.

Results: Analysis of published microarray datasets revealed significant reduction of *SIRT1* mRNA levels in skin biopsies from patients with diffuse cutaneous scleroderma n=11, p<0.001). Resveratrol induced the activity of SIRT1 in explanted normal skin fibroblasts. Moreover, resveratrol blocked the stimulation of collagen gel contraction and cell migration induced by TGF-β, and abrogated TGF-β–induced collagen and α-smooth muscle actin expression, and Smad2/3-dependent transcriptional activity, in a dose-dependent manner. Ectopic SIRT1 by itself was sufficient to abrogate TGF-β stimulated collagen expression, whereas pharmacological inhibition of SIRT prevented the anti-fibrotic activities of resveratrol.

Conclusion: Resveratrol abrogates canonical TGF-β signaling and suppresses fibrotic responses via the histone deacetylase and essential metabolic regulator SIRT1. Reduction of *SIRT1* in scleroderma skin biopsies suggests its role in regulating fibrogenesis. Accordingly, we propose that SIRT1 is a novel target for anti-fibrotic therapy, and pharmacological enhancement of the SIRT1 expression or activity might have a therapeutic potential in scleroderma.

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Caveolin-1 Deficiency Induces Spontaneous Endothelial-to-Mesenchymal Transition (EndoMT) in Murine Pulmonary Endothelial Cells *in Vitro*.
Zhaodong Li[1], Peter J. Wermuth[1], Bryan Benn[1], Michael P. Lisanti[2] and Sergio A. Jimenez[1]. [1]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA, [2]Jefferson Stem Cell Biology and Regenerative Medicine Center, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background/Purpose: Recent studies demonstrated that the phenotypic transition of endothelial cells (EC) into activated mesenchymal cells, a process known an endothelial-to-mesenchymal transition (EndoMT), may be crucial in the development of tissue and organ fibrosis in fibrotic diseases such as Pulmonary Fibrosis and Systemic Sclerosis (SSc). Furthermore, it was previously demonstrated that TGF-β induces EndoMT in murine lung EC in vitro. Owing to the important role of caveolin-1 (cav-1) in TGF-β receptor internalization and TGF-β signaling

the role of cav-1 in induction of EndoMT in murine lung EC was investigated.

Methods: Pulmonary EC were isolated from wild-type (WT) and cav-1 knockout (cav-1 KO) mice employing sequential immunomagnetic selection with anti-CD31 and anti-CD102 antibodies followed by in vitro culture and treatment with TGF-β1. EndoMT was assessed by immuno-fluorescence for α-smooth muscle actin (α-SMA) and by Western blot analysis for α-SMA and type I collagen. Induction of the transcriptional repressor, Snail 1, was assessed by real time PCR. The same studies were performed in cav-1 KO pulmonary EC following restoration of functional cav-1 domains employing a cell permeable cav-1 scaffolding domain peptide.

Results: Pulmonary EC from cav-1 KO mice displayed high levels of spontaneous α-SMA and type I collagen expression which increased following TGF-β treatment. There was a remarkable increase in sponta-neous Snail 1 expression. Spontaneous and TGF-β1-stimulated EndoMT were abrogated by restoration of functional cav-1 domains.
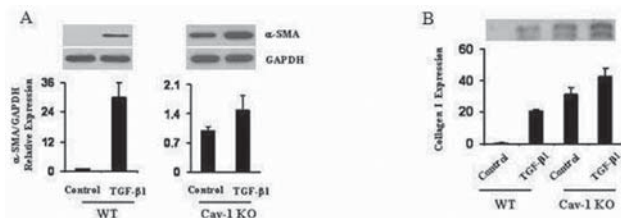
Spontaneous and TGF-β1 stimulated EndoMT in cav-1 KO primary pulmonary EC. **A.** Pulmonary EC from WT and cav-1 KO mice were cultured in media alone (control) or with 10 ng/ml TGF-β1 for 72h, protein from cell lysates was electrophoresed and probed in Western blots for α-SMA. **B.** Culture media from the same samples were analyzed by Western blot for type I collagen.

Conclusion: Cav-1 plays an important role in the regulation of EndoMT by abrogating spontaneous and TGF-β-induced EndoMT and EndoMT-mediated generation of activated myofibroblasts. Since reduc-tion of cav-1 expression is an important molecular abnormality present in SSc lung and dermal fibroblasts the results indicate that exaggerated spontaneous and TGF-β induced EndoMT caused by cav-1 deficiency may play a crucial role in the pathogenesis of SSc tissue fibrosis and vasculopathy.

Disclosure: Z. Li, None; **P. J. Wermuth**, None; **B. Benn**, None; **M. P. Lisanti**, None; **S. A. Jimenez**, None.

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Platelet Release Products Mediate Endothelial Apoptosis: A Possible Role for Thrombospondin 1- CD36 Pathway in SSc-Endothelial Apoptosis. Bashar Kahaleh and Yongqing Wang. University of Toledo, Toledo, OH

Background/Purpose: Sequential pathologic observations in the early stages of SSc demonstrated evidence for platelet aggregation and binding to blood vessels that is generally followed by vascular effacement and the development of SSc vasculopathy. In this study we thought to investigate the effects of platelet constituents on microvascular endothelial cells (MVEC) apoptosis. We particularly investigated the role of thrombospon-din 1 (TSP1) as a possible platelet derived signal since it is a potent angiogenic inhibiter, it can mediate endothelial apoptosis and activate TGF-β and is reported to be overexpressed in SSc. Furthermore, we investigated the role of CD36 in MVEC apoptosis since TSP1 vascular effects are known to results from its binding to CD 36 receptors.

Methods: MVEC were isolated from involved SSc skin and from match healthy control subjects. Platelets were collected from healthy subjects, sonicated, ultracentrifuged and the resulting supernatant (PLSN) was used in MVEC cultures. MVEC apoptosis was evaluated by *TUNEL* and active caspases-3 staining. CD 36 expression in MVEC was measured by quantitative RT-PCR and CD36 expression was knocked down using CD36 *specific siRNA.*

Results: The following results were observed in this study:

1. Addition of PLSN to MVEC cultured in 0.5% serum concentration resulted in a dose dependent apoptosis of MVEC. SSc-MVEC were more susceptible to apoptosis than control MVEC, thus at 20%

PLSN concentration, MVEC apoptosis was 20% $\pm$ 5 and 48% $\pm$ 8 in control vs SSc MVEC respectively (mean $\pm$ SD of three cell lines).

2. Addition of TSP1 neutralizing antibody to PLSN significantly reduced PLSN induced MVEC apoptosis, suggesting that TSP1 in PLSN mediate MVEC apoptosis.

3. CD 36 expression levels were significantly higher in SSc MVEC than in control MVEC (7.4 $\pm$ 2.3 folds, mean $\pm$ SD of 3 cell lines)

4. CD36 knock down using CD36 specific *siRNA* but not ir-*siRNA* resulted in > 90% decrease in CD36 expression and the inhibition of TSP1 and PLSN induced MVEC apoptosis.

Conclusion: Platelets interaction with MVEC results in MVEC apoptosis. This effect is largely mediated by interaction of TSP1 with CD36. SSc-MVEC are more susceptible to this effect possibly because of an upregulated CD36 expression in SSc-MVEC. The data propose the platelet as a possible source for the initial MVEC apoptotic signal in the early stages of SSc vasculopathy and suggest TSP1 as a crucial player in SSc pathogenesis in view of its abundance in SSc and its documented role in the genesis of vasculopathy and tissue fibrosis

Disclosure: B. Kahaleh, None; **Y. Wang**, None.

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Decrease Activity of DNA Demethylase in SSc Fibroblast and Micro-vascular Endothelial Cells: A Possible Mechanism for Persistence of SSc Phenotype. Bashar Kahaleh and Yongqing Wang. University of Toledo, Toledo, OH

Background/Purpose: DNA methylation is one of the best-characterized epigenetic modifications that have been implicated in numerous biologic and pathologic processes. It is initiated by DNA methyltransferases (DNMT) 3a and 3b and maintained in subsequent cellular generations by the maintenance enzyme DNMT1. Despite its role in long-term gene silencing, DNA methylation is now believed to be a dynamic process as active DNA demethylation has been observed in certain experimental systems. Thus, during cellular division a competition between DNMT1 and DNA demethylase determine the maintenance or the reversal of DNA methylation in the daughter cells. The molecular identity of DNA demethylase remains elusive but its activity can be measured by functional assay. DNMT1 expression is upregulated in SSc microvascular endothelial cells (MVEC) and fibroblasts (FB) in associa-tion with persistence of DNA methylation of the NCpG islands in the promoter region of key underexpressed genes (i.e. *Fli1* and *NOS3*). Thus we thought in this study to examine the activity of DNA demethylase in SSc and control cells and the role of microRNA (miRNA) in the regulation of DNA demethylase activities.

Methods: MVEC and FB were isolated from involved SSc skin and control subjects. DNMT1 expression levels were determined by qRT-PCR and by western blot analysis. DNA demethylase activity was measured in nuclear extracts using the EPI Quik™ DNA Demethylase Activity/ Inhibition Assay Kit. Small RNA molecules including miRNA were isolated from SSc and control MVEC and FB using PureLink miRNA isolation kit. The effects of miRNA on DNA demethylase activity was examined in SSc and control cells by transfecting the cells with SSc and control miRNA.

Results: The following results were observed in this study:

1. DNMT1 expression levels were significantly upregulated in SSc cells (mean 3.2 and 2.8 folds in MVEC and FB respectively vs control cells, mean 3 cell lines each).

2. DNA demethylase activity was significantly reduced in SSc cells (42% and 51 % in MVEC and FB respectively vs control cells, mean 3 cell lines each)

3. The knockdown of DNMT1 using DNMT1 specific *siRNA* did not affect demethylase activity.

4. Transfection of SSc cells with control miRNA results in decrease expression of DNMT1 and increase activity of DNA demethylase, while the transfection of control cells with SSc miRNA resulted in upregulation of DNMT1 and reduced DNA demethylase activity.

5. SSc MVEC and FB transfection with control miRNA normalized abnormal gene expression profile.

Conclusion: This study demonstrates upregulation of DNMT1 and diminished activities of DNA demethylase in SSc MVEC and FB and that

DNA demethylase activity is regulated by miRNA. The characterization of the molecular mechanisms that target both DNA methylation and demethylation is essential for understanding the emergence and persistence of the pathologic phenotype exhibited by SSc cells.

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The Arachidonate 5-Lipoxygenase Activating Protein (*ALOX5AP*) Polymorphism Is Associated with Risk of Scleroderma-Related Interstitial Lung Disease: A Multicenter Study From the EULAR Scleroderma Trial and Research Group.

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Background/Purpose: Systemic sclerosis (SSc, scleroderma) is an autoimmune disease characterized by chronic inflammation, vascular injury and profound fibrosis of the skin and internal organ. Leukotrienes (LTs) are a family of arachidonic acid-derived lipid mediators which play a key role in the regulation of inflammation, vascular function and connective tissue remodeling. Studies in humans have shown that increased synthesis of LTs takes places in SSc. However, the mechanisms responsible for overproduction of LTs in SSc remain unclear. The arachidonate 5-lipoxygenase activating protein (ALOX5AP) plays a key role in the regulation of synthesis of LTs through presenting arachidonic acid to 5-lipoxygenase.

In the present study we hypothesized that single nucleotide polymorphisms (SNPs) of *ALOX5AP* might confer risk of SSc and/or SSc-related organ involvement.

Methods: Seven SNPs of *ALOX5AP* (rs17222814, rs17216473, rs10507391, rs4769874, rs9551963, rs9315050, and rs7222842) were genotyped in a cohort of 977 patients with SSc and 539 healthy controls from European centers collaborating within the EULAR Scleroderma Trials and Research (EUSTAR) group. SSc patients were classified as having diffuse or limited SSc, according to the Medsger and LeRoy criteria. Clinical characteristics of SSc patients included the presence of SSc-related interstitial lung disease (SSc-ILD, based on chest X-ray/HRCT), pulmonary hypertension (SPAP > 45 mmHg in echocardiography), scleroderma renal crisis and digital ulcers.

In 14 SSc patients concentrations of cysteinyl leukotrienes and leukotriene B4 were measured in the supernatants of ionophore-stimulated peripheral blood mononuclear cells (PBMC) by means of commercially available EIA kits (Cayman Chemicals, MI, USA).

Results: Significant association was found between rs10507391 polymorphism (T/A) of the *ALOX5AP* and the risk of SSc (Odds Ratio; 95%CI: 1.26; 1.0655–1.49, p=0.0078) and SSc-ILD (OR;95%CI: 1.4224; 1.1621– 1.7412, p=0.0007). However, only the latter association remained significant when corrected for multiple testing (p=0.005).

PBMC from SSc carriers of rs10507391 allele A (N=5) synthesized greater amounts of cysteinyl leukotrienes (433 +/− 215 pg/mL/10^5 cells) as compared with PBMC from SSc patients with rs10507391 TT genotype (N=9, 261 +/− 99 pg/mL/10^5 cells, p<0.05). Synthesis of leukotriene B4 was comparable between the two groups (995 +/− 547 pg/mL/10^5 cells vs 790 +/− 756 pg/mL/10^5 cells, p=0.9).

No significant associations could be found between the remaining SNPs of *ALOX5AP* and the presence of SSc or SSc-related internal organ involvement.

Conclusion: The results of our study indicate, for the first time, that the genetic variants of *ALOX5AP* might play a role in the development of SSc-related pulmonary fibrosis. Moreover, our results might raise the possibility of developing genotype-specific therapy for SSc-related lung involvement. This appears particularly attractive since antileukotriene therapies are already in use in humans.

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Acroosteolysis Is Associated with Increased Propensity for Osteoclast Formation and Higher VEGF Levels in the Peripheral Blood of Systemic Sclerosis Patients.

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Background/Purpose: Acroosteolysis (AO) secondary to bone resorption of distal phalanges affects up to 20% of systemic sclerosis (SSc) patients leading to shortening of the digits, impaired hand function, and disability. AO pathophysiology is not known, but chronic hypoxia secondary to SSc vasculopathy may be a contributing factor. In this study, we sought to define whether the propensity for osteoclast formation is increased in peripheral blood mononuclear cells (PBMCs) of SSc patients with AO compared to controls, and whether this may be associated with levels of the hypoxia-driven vascular endothelial growth factor (VEGF).

Methods: PBMCs obtained from 26 SSc patients (11 with and 15 without AO) and 14 healthy controls were cultured in 96- well plates in the presence of receptor activator of nuclear factor-kappaB ligand (RANKL) and M-CSF. After 9 days, osteoclast-like tartrate resistant acid phosphatase (TRAP)-positive multinucleated giant cells (MNGs) were counted. MNGs formation was also assessed after VEGF (10 ng/ml) priming for 24 hours. Plasma VEGF levels were measured using an electrochemiluminescence platform (Meso Scale Discovery).

Results: SSc patients with AO formed significantly more TRAP+ MNGs at day 9 than SSc patients without AO (142.4 ± 69.6 vs. 27.2 ± 17.6 MNG/well, P < 0.01), whereas no difference was noted between SSc without AO and controls (27.2 ± 17.6 MNG/well vs. 18.7 ± 27.0 MNGs/well, P=NS). Priming with VEGF at 10 ng/ml for 24 hours significantly increased TRAP+MNGs formation by 5.3 fold (P=0.002). In plasma of SSc patients with AO, VEGF levels were significantly higher than in SSc patients without AO (165.3 ± 80.2 vs. 88.1 ± 38.1 pg/ml, P<0.05). Strikingly, plasma VEGF levels correlated with TRAP+MNG formation (Spearman rho=0.386, P=0.05).

Conclusion: AO is associated with an increased propensity of peripheral blood cells to form osteoclasts and this seems to be partly driven by higher VEGF plasma levels. Effective control of hypoxia and inhibition of terminal mediators of osteoclastogenesis may be an effective strategy to prevent and treat AO in SSc patients.

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The Effects of Salvianolic Acid B in Fibrotic Models *in Vivo* and *in Vitro*.

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Background/Purpose: Scleroderma or systemic sclerosis (SSc) is characterized by the fibrosis of skin and visceral organs. Salvianolic acid B (SAB) is an important water-soluble ingredient extracted from Danshen, a kind of Chinese medicinal herbs. Clinical data showed there were good curative effects and low side-effects on SSc with a compound prescription of traditional Chinese medicine including Danshen. Furthermore, SAB has been

proved its efficacy in treating chronic liver fibrosis. Our aim is to examine whether SAB can attenuate fibrosis in the activated fibroblasts from SSc patients and fibrotic mouse models.

Methods: For *in vitro* studies, dermal fibroblasts trains were cultured from skin biopsies of SSc patients which constitutively over-expressed collagen genes. Cell growth was measured with the xCELLigence system to evaluate the effects of SAB on fibroblasts. Real-time quantitative RT-PCR was used to examine the transcript levels of collagen. The levels of Smad3 and p-Smad3 were assayed by Western blot. For *in vivo* studies, C57BL/6 female mice of 6–8 weeks (n = 5 for each treatment) were injected with bleomycin through tracheal cutting to induce pulmonary fibrosis. SAB was feed daily for 10 or 24 days from the third day before bleomycin (BLM) instillation for the Group of Prevention Study (P) or the Group of Prevention &Treatment Study (P&T), respectively. The total cell counts in BALF (broncho alveolar lavage fluid) were used to evaluate the inflammatory status. HE and Masson's trichrome stains, gene expression analysis and Sircol assay were used to assess the effects of drug treatments on inflammatory and fibrotic changes. Immunohistochemistry was also performed to examine the α-SMA positive cells.

Results: ≤°For *in vitro* studies, SAB suppressed fibroblasts proliferation and decreased the synthesis of collagen mRNA in SSc dermal fibroblasts efficiently. Additionally, SAB attenuated TGF-β1-induced Smad3 phosphorylation in normal dermal fibroblasts. In the mouse model of pulmonary fibrosis, SAB significantly reduced the total cell counts in BALF in the P group, indicating the amelioration of inflammation. Furthermore, SAB potently reduced the number of myofibroblasts, the mRNA level of collagen and the collagen content in both the P group and P&T group. HE stain of mouse lung tissues further showed a significant disruption of the alveolar units and infiltration of inflammatory cells in the lungs induced by BLM, while SAB treatment improved the disruption of the alveoli with less infiltrating inflammatory cells in the P group [Figure 1].

Conclusion: SAB inhibited fibroblasts proliferation and collagen gene expression in a Smad3 dependent signaling pathway. Administration of SAB could reduce inflammation and fibrosis in mouse lungs induced by BLM. Therefore, SAB is a promising candidate for the treatment of SSc.
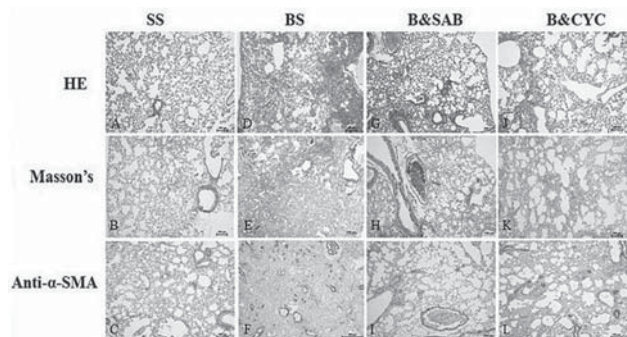
Figure 1. Examination of lung tissues from mice with different treatments. SS: tissues injected with saline and fed with saline; BS: tissues injected with BLM and fed with saline; B&SAB: tissues injected with BLM and fed with SAB; B&CYC: tissues injected with BLM and fed with CYC (Cyclophosphamide, being used as a positive control). Compared with negative control(A-C), mice showed increased collagen content, a disruption of the alveolar units and infiltration of inflammatory cells in the lungs induced by BLM by Masson's trichrome (D) and HE staining (E). Immunochemistry analysis with α-SMA antibody revealed increased numbers of myofibroblasts (F). Administration of SAB (G-I) or CYC (J-L) could reduce the inflammation and fibrosis induced by BLM.

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The Interferon Type I Signature Is Increased in Monocytes From Systemic Sclerosis Patients. Zana Brkic[1], Lenny van Bon[2], Cornelia G. van Helden-Meeuwsen[1], Madelon C. Vonk[3], Hanneke Knaapen[3], Wim van den Berg[3], Paul L. Van Daele[1], Virgil A. Dalm[1], Timothy Radstake[2] and Marjan A. Versnel[1]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]University Medical Center Utrecht/Radboud University Nijmegen Medical Center, Utrecht/Nijmegen, Netherlands, [3]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Background/Purpose: Systemic sclerosis (SSc) is a complex fibrosing disease of unknown etiology. The past decade clear indications for an aberrant immune system have been revealed. SSc is classified either as limited (lSSc) or diffuse cutaneous (dSSc), of which the latter is more severe with excessive involvement of the skin. Although the pathogenesis of SSc is largely unknown, the past few years it has been appreciated that a substantial part of the SSc patients display an Interferon (IFN) type I signature. In this study we assessed the prevalence of such an IFN type I signature in monocytes in a cohort of SSc patients from two clinics in the Netherlands and correlated the IFN type I signature with disease manifestations.

Methods: 41 patients with SSc were included and 25 healthy controls (HC). Patients were stratified as having lSSc (n=25) or dSSc (n=16), and further divided into patients with late (> 3 years) or early disease (<3 years). Expression levels of 11 IFN type I inducible genes, which were previously detected by us in CD14+ monocytes from Sjögren patients, were assessed using real time quantitative PCR. Expression levels were next submitted to a principal component analysis to identify correlated groups of genes.

Results: of factor analysis showed that 4 genes (IFI44L, IFITM1, IFIT1 and MX1) explained 95% of the total variance of the 11 genes, and we therefore adopted overexpression of these 4 genes as our operational definition of positivity for an IFN type I signature. Expression levels of these 4 genes were used to calculate IFN type I scores for each subject. SSc patients positive for the IFN type I signature (IFN score≥10) and patients negative for the signature (IFN score< 10) were then compared for clinical disease manifestations.

Results: IFN type I signature was present in 29% of SSc patients compared with 0% of HC. Stratifying the patients in lSSc and dSSc, we found the IFN type I signature to be present in 24% of lSSc patients and 38% of dSSc. Further dividing the patients into early and late SSc, we observed a statistically significant increase in IFN scores in the early diffuse SSc group compared with HC (P<0.001). SSc patients positive for the IFN type I signature were also significantly younger compared with the patients negative for the signature (p=0.008). Moreover SSc patients with the presence of anti-RNP had significantly higher IFN scores compared to patients without anti-RNP antibodies (P=0.003). In contrast to the presence of anti-RNP antibodies, SSc patients positive for anticentromere antibodies (9 out of 38 patients) were all negative for the IFN type I signature. Studying anti-topoisomerase and anti-SSA antibodies, we observed a trend of higher IFN scores in the patients with these autoantibodies, however no significant differences were detected. When stratifying patients according to the presence of digital ulcers, lung fibrosis, pulmonary hypertension or Raynauds's phenomenon, no differences in IFN scores were observed.

Conclusion: The monocyte IFN type I signature is present in about 1/3 of SSc patients and mainly in the early diffuse SSc group with anti-RNP autoantibodies. Such patients might benefit from treatment blocking the IFN type I production or activity.

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Secreted Frizzled-Related Protein 4 Induces a Profibrotic Phenotype in Systemic Sclerosis Fibroblasts by Activating a Non-Canonical WNT Signaling Pathway. Justin Gillespie[1], Paul Emery[2] and Francesco Del Galdo[3]. [1]University of Leeds, Leeds, United Kingdom, [2]Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom

Background/Purpose: Systemic Sclerosis (SSc) is a chronic fibrotic disease involving autoimmune activation, fibroproliferative vasculopathy and tissue fibrosis of skin and multiple internal organs. Several studies have indicated that activation of WNT/β-catenin signaling pathway plays an important role in the pathogenesis of tissue fibrosis. Intriguingly, tissue expression studies on SSc skin show both upregulation of canonical WNT ligands[1,2] and consistent upregulation of a putative WNT antagonist, Secreted Frizzled-Related Protein 4 (SFRP4) both at mRNA at protein level[3,4].

Objectives: To determine the role of SFRP4 in modulating WNT signaling and the profibrotic phenotype of SSc fibroblasts.

Methods: Immortalized primary control and SSc fibroblasts were cultured in 10% DMEM and starved in 0.5% DMEM for 24hrs prior to stimulation with recombinant WNT-3a, WNT-5a (100ng/ml) and/or SFRP4 (70ng/ml). Gene expression was quantified by SYBR green QPCR. Canonical WNT signaling activation was assessed by TOPflash TCF/LEF luciferase

reporter activity. Whole cell lysates were used to assess protein expression by Western Blot and c-Jun phosphorylation by Phospho-c-Jun ELISA (Cell Signaling Technology, UK). Mean ± SEM of 4 independent experiments were analyzed using Graph Prism 5.0.

Results: Basal SFRP4 gene expression in SSc fibroblasts was increased on average by 264% compared to normal controls [$P<0.0001$]. Stimulation with WNT-3a upregulated *SFRP4* expression by 56% [$P<0.001$]. WNT-3a upregualted *COL1A1 and α-SMA* gene expression by 160% [$P<0.001$] and 230% [$P<0.0001$] in SSc fibroblasts, in contrast to 18% [$P<0.05$] and 72% [$P<0.01$] in normal fibroblasts, respectively. Consistent with canonical WNT signaling activation, WNT-3a caused an upregulation of *axin-2* by 200% [$P<0.0001$] in SSc and 90% [$P<0.001$] in normal fibroblasts. TOPflash activity was also increased [$P<0.0001$] by 44% and 38%, respectively. Co-stimulation with SFRP4 showed no inhibitory activity of the WNT-3a effects. However, SFRP4 treatment alone was able to induce both *COL1A1* by 43% [$P<0.01$] and *α-SMA by* 46% [$P<0.001$] only in SSc fibroblasts without any significant changes in either *axin-2* expression or TOPflash activity. Similarly, stimulation with WNT-5a, a classic non-canonical WNT ligand, increased *COL1A1* in SSc fibroblasts by 42% [$P<0.0001$] without any increase in *axin-2* expression or TOPflash activity. Additionally, SSc fibroblasts treated with SFRP4 showed an increase in c-Jun phosphorylation reaching maximum levels at 10min by 167% [$P<0.001$] and again at 24hrs by 184% [$P<0.0001$].

Conclusion: Increased SFRP4 in SSc may contribute to the fibrotic process through non-canonical WNT activation instead of functioning as a WNT inhibitor. The molecular events underlying this paradox response of SSc fibroblasts may reveal insightful mechanisms in the pathogenesis and perpetuation of the fibrotic response in SSc.

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Confirmation of *TNIP1* As a Susceptibility Locus for Systemic Sclerosis in a Large Multicentre Study.

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Background/Purpose: Systemic sclerosis or scleroderma (SSc) is a complex autoimmune disorder that affects the connective tissue causing fibrosis in the skin and different internal organs. A recent genome-wide association study (GWAS) in European SSc patients identified three *loci* as novel genetic risk factors for the disease (*RHOB, PSORS1C1* and *TNIP1*). The latter two have a well-known role in autoimmune disease genetic susceptibility. *PSORS1C1* (Psoriasis susceptibility 1 candidate 1) is located in the vicinity of HLA class I region and has been identified as a psoriasis genetic risk factor. Polymorphisms in *TNIP1* (TNFAIP3 interacting protein 1) have been related to a number of autoimmune disorders and the protein encoded by this gene is involved in the NF-$\kappa\beta$ signaling pathway. The aim of our study was to replicate the previously mentioned findings in a large multicentre independent SSc cohort of Caucasian ancestry.

Methods: 4,389 SSc patients and 7,611 healthy controls from different European countries and the US were included in this study. Six single nucleotide polymorphisms (SNPs): rs342070, rs13021401 (*RHOB*), rs2233287, rs4958881, rs3792783 (*TNIP1*) and rs3130573 (*PSORS1C1*) were analyzed. Plink was used for the statistical analyses. Overall significance was calculated by pooled-analysis of all the cohorts. Haplotype analyses and conditional logistic regression analyses were carried out to further explore the genetic structure of the tested *loci*.

Results: Pooled-analyses of all the analyzed SNPs in *TNIP1* revealed significant association with the whole disease (rs2233287 $P_{MH}=1.94\times10^{-4}$ OR $= 1.19$; rs4958881 $P_{MH}= 3.26\times10^{-5}$ OR $= 1.19$; rs3792783 $P_{MH}= 2.16\times10^{-4}$ OR $= 1.19$). These associations were maintained in all the considered subgroups. *PSORS1C1* comparison showed association with the complete set of patients and all the subsets except for the ACA+ patients. However, the association was dependent on different HLA class II alleles. The variants in the *RHOB* gene were not associated with SSc or any of its subsets.

Conclusion: Our data confirmed the influence of *TNIP1* on an increased susceptibility to SSc and reinforced this *locus* as a common autoimmunity risk factor.

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Differential Association of *IRAK1* and *MECP2* with Specific Systemic Sclerosis Phenotypes.

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Background/Purpose: Systemic sclerosis (SSc) is a fibrotic autoimmune disease that represents a clear example of a sex biased immune disorder. The X-chromosome gene *IRAK1* has been associated with SSc and systemic lupus erythematosus (SLE), being an interesting candidate to explain this sexual dimorphism. However, *IRAK1* is in the same haplotypic block as *MECP2* on Xq28, and recent studies suggest that functional genetic variants of the latter locus may explain the association signals with SLE observed in *IRAK1*. We aimed to evaluate whether the SSc-associated *IRAK1* polymorphism rs1059702 (Phe196Ser) is the causal variant of the Xq28 association or whether it reflects another association signal from the nearby *MECP2*.

Methods: Only women were included in the study. We analysed a total of 3065 SSc patients and 2630 healthy controls from five independent Caucasian cohorts (Spain, USA, Germany, The Netherlands, and UK). A tagging strategy was used to select four taggers that cover all the common genetic variation within *MECP2* (r2≥0.8) in the CEU population of the HapMap database (rs3027935, rs17435, rs5987201 and rs5945175). We also included the SSc-associated *IRAK1* genetic variant rs1059702. The genotyping was performed with predesigned TaqMan assays. Plink was used for the statistical analyses. *P*-values were corrected for multiple testing using FDR.

Results: *IRAK1* rs1059702 was associated with diffuse cutaneous SSc (dcSSc; P_{FDR}=4.12×10−3, OR=1.27), and trends of association were evident in the global SSc/control (P_{FDR}=0.070, OR=1.13) and anti-topoisomerase positive (ATA+)/control (P_{FDR}=0.087, OR=1.23) comparisons, consistent with previously published data. Similarly, the *MECP2* rs17435 variant reached statistical significance after comparing the global disease group and dcSSc subgroup with the control population (P_{FDR}=2.68×10−3, OR=1.19, and P_{FDR}=5.26×10−4, OR=1.30, respectively). Conditional logistic regression analyses showed that the association of *IRAK1* rs1059702 with dcSSc was explained by that of *MECP2* rs17435, because only the latter remained significant after conditioned to each other (rs1059702 conditioned P=0.786; rs17435 conditioned P=0.049). However, the analysis of pulmonary fibrosis (PF) data suggested that *IRAK1* rs1059702 was consistently associated with this feature, since statistical significance was observed when comparing PF+ vs controls (P_{FDR}=0.039, OR=1.30) and PF+ vs PF- (P=0.025, OR=1.26), but not PF- vs controls (P=0.574, OR=1.04).

Conclusion: Our data suggest the existence of two independent signals within the Xq28 region, one located in *IRAK1* associated with PF, and another in *MECP2* associated with dcSSc.

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A Putative Role for the TGFβ Accessory Receptors Betaglycan and Endoglin in pulmonary Complications of Scleroderma. Sarah L. Trinder, Adrian Gilbane, Markella Ponticos, Johanna Donovan, Christopher P. Denton, David J. Abraham and Alan M. Holmes. UCL, London, United Kingdom

Background/Purpose: In scleroderma (SSc) pulmonary complications such as fibrosis and pulmonary hypertension represents a significant cause of mortality. The ability of TGFβ1 to act as a potent pro-fibrotic mediator is well established, potently inducing the expression of numerous fibrogenic genes including type I collagen and CCN2. Cellular responses to TGFβs are markedly regulated by the accessory receptors betaglycan and endoglin. Here we sought to investigate the expression and cellular effects of these accessory receptors in SSc pulmonary fibroblast function.

Methods: Pulmonary fibroblasts explant cultured from SSc patient with lung complications were assessed for the expression of the TGFβ accessory receptors betaglycan/TGFβRIII and endoglin by Q-PCR and western blot. TGFβ accessory receptor expression was further determined by immunohistochemistry on pulmonary lung sections. The cellular effect of altered expression of these receptors on fibrogenic genes through transient over-expression in pulmonary fibroblasts were assessed by Q-PCR and western blot.

Results: SSc lung fibroblasts exhibited a marked elevated expression in betaglycan and endoglin. Immunohistochemical analysis demonstrated a similar elevated expression of these receptors. Consistent with a pathological role of betaglycan and endoglin, over-expression of these accessory receptors led to altered cellular responses to TGFβ, as assessed by the expression of the fibrogenic genes CCN2, collagen type I and aSMA.

Conclusion: These data demonstrate elevated expression of the TGFβ accessory receptors betaglycan and endoglin on SSc pulmonary fibroblasts. An altered accessory receptor repertoire led to a marked change in the expression of known pro-fibrotic genes, including collagen type I and CCN2. Thus altered expression of TGFβ accessory receptors may play a significant role in the pro-fibrotic phenotype exhibited by SSc pulmonary fibroblasts.

Disclosure: **S. L. Trinder**, None; **A. Gilbane**, None; **M. Ponticos**, None; **J. Donovan**, None; **C. P. Denton**, None; **D. J. Abraham**, None; **A. M. Holmes**, None.

2306

Intratracheal Instillation of Omniscan in an Adenine-Induced Model of Chronic Renal Failure: A New Model of Nephrogenic Systemic Fibrosis. Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center-,Thomas Jefferson University, Philadelphia, PA

Background/Purpose: Nephrogenic Systemic Fibrosis (NSF), a generalized progressive fibrotic disorder, occurs in some patients with renal insufficiency exposed to various gadolinium based contrast agents (Gd-

BCA). Currently, there is no animal model for human NSF. Some studies using subtotal nephrectomized rats described cutaneous lesions characterized by slight dermal fibrosis and increased infiltration of CD34+ cells following systemic GdBCA administration. These lesions, however, failed to reproduce the severe dermal and tissue fibrosis and other histomorphological changes characteristic of human NSF. One possible reason for this is that although subtotal nephrectomy replicates the decreased filtering capacity of human chronic renal failure, it fails to induce numerous other features that may be necessary for NSF development. In this study, we treated mice with adenine-induced renal failure by intratracheal instillation of the GdBCA Omniscan to develop a more relevant model of NSF.

Methods: Chronic renal failure was induced in C57BL6/J mice by ad libitum feeding of standard rodent diet supplemented with 3% adenine for 30 days. A single dose of either the GdBCA Omniscan (25 μL of a 0.5 M solution) or an equal volume of normal saline was administered to mice with normal renal function (controls) or with chronic renal failure by intratracheal instillation. Mice were sacrificed 28 days post-instillation and tissues were isolated for analysis by histological examination (hematoxyllin/eosin and Masson's trichrome stains. Assays of collagen content to assess the severity of tissue fibrosis were performed employing a standard hydroxyproline assay of hydrolyzed tissue samples.

Results: Histopathology studies showed mononuclear cell infiltration and fibrosis in lungs isolated from adenine-fed mice instilled with Omniscan but not in lungs from mice with normal renal function instilled with Omniscan nor in mice with either normal or ablated renal function instilled with saline. The pattern of fibrosis was predominantly peribronchial although substantial diffuse interstitial fibrosis was also observed. Hydroxyproline content was increased ~3 fold in the lungs of renal failure mice treated with Omniscan compared to mice in all other treatment groups.

Conclusion: The present study demonstrates for the first time the ability to induce significant tissue fibrosis and increased collagen deposition in mice with adenine induced renal failure exposed to the gadolinium contrast agent Omniscan. This inducible model of tissue fibrosis will be a valuable tool in studying the pathogenesis of NSF and other chemically-induced fibrotic disorders.

Disclosure: **P. J. Wermuth**, None; **S. A. Jimenez**, None.

2307

Role of Endosomal and Cell Membrane Toll-Like Receptors in Keratinocyte Activation by Systemic Sclerosis Autoantibodies. James M. Watson[1], Joanna Nikitorowicz Buniak[1], Xu Shiwen[2], David J. Abraham[1], Christopher P. Denton[3] and Richard J. Stratton[1]. [1]UCL Medical School, London, United Kingdom, [2]Royal Free Hospital, London, United Kingdom, [3]Royal Free and University College Medical School, London, United Kingdom

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune rare connective tissue disorder of unknown aetiology, heterogeneous clinical manifestations and an often progressive course which includes skin changes which are partly mediated by keratinocytes. It is proposed that immunoglobulin from patients with SSc causes activation of toll like receptors (TLR) 2 and 3.

Methods: Initially, patient IgG samples which had previously been shown to up-regulate interleukins in HaCat immortalised keratinocytes were studied. More patient samples of IgG were then purified using a protein A column and TLR2 and TLR3 activation was measured using the HEK cell line which was co-transfected with either the hTLR2 or hTLR3 gene, and a secreted embryonic alkaline phosphatase (SEAP) gene. Concentrations of IgG used were 1000, 100, 10, 1 and 0.1 μg/mL.

Results: Initial assessment of signalling downstream of TLRs gave variable results but some SSc samples induced nuclear translocation of NFκB (RelA)..

A total of 21 diffuse and limited SSc samples with 5 control samples were used. 13 SSc samples showed an increase in TLR2 signalling, whilst 3 SSC samples showed an increase in TLR3 signalling. No healthy control samples showed an increase in expression of TLR 2 or 3. On statistical analysis the data was grouped by disease type. At all concentrations studied p values were statistically significant showing an increase in TLR activity compared to healthy samples except for one, see figure 1 and 2.
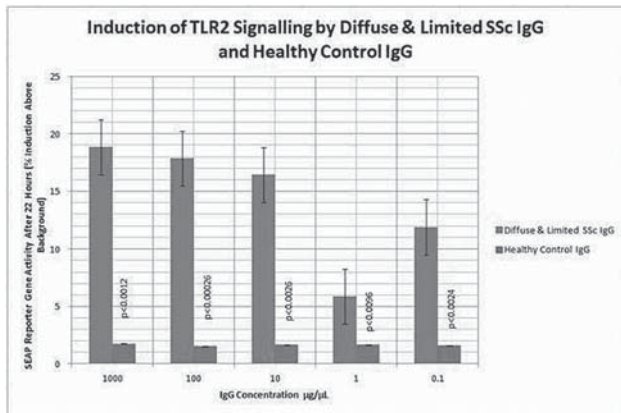
Figure 1. Induction of TLR2 Signalling by Diffuse & Limited SSc IgG and Healthy Control IgG

HEK2 cells were exposed to Diffuse & Limited SSc (n = 21 patient samples) and control IgG (n = 5 control samples) at various concentrations for 24 hours. Treatment with Diffuse & Limited SSc IgG lead to induction of SEAP greater than healthy control IgG. Student's t-test p values for Diffuse & Limited SSc vs control values shown.
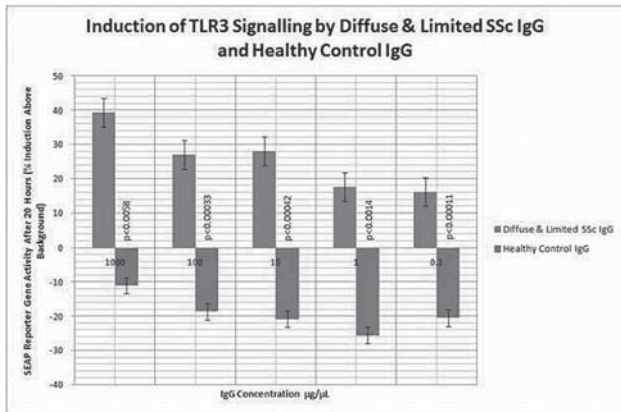
Figure 2. Induction of TLR3 Signalling by Diffuse & Limited SSc IgG and Healthy Control IgG

HEK3 cells were exposed to Diffuse & Limited SSc (n = 21 patient samples) and control IgG (n = 5 control samples) at various concentrations for 20 hours. Treatment with Diffuse & Limited SSc IgG lead to induction of SEAP greater than healthy control IgG. Student's t-test p values for Diffuse & Limited SSc vs control values shown.

Conclusion: In conclusion SSc IgG induces TLR2 and TLR3 far more than healthy control IgG which may dampen the TLR2 and TLR3 response somewhat. The autoantibody component in SSc IgG that causes this is unknown. Further work will attempt to confirm the mechanism of TLR 2 and 3 activation.

Disclosure: **J. M. Watson**, None; **J. Nikitorowicz Buniak**, None; **X. Shiwen**, None; **D. J. Abraham**, None; **C. P. Denton**, None; **R. J. Stratton**, None.

2308

CD11c^{+} Cells Are Necessary for Myofibroblast Maintenance in Bleomycin-Induced Cutaneous Fibrosis. Jennifer J. Chia[1], Sha Tian[2] and Theresa T. Lu[2]. [1]Weill Cornell/Rockefeller/Sloan-Kettering Tri-Institutional MD-PhD Program, New York, NY, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: Systemic sclerosis (SSc) is a heterogeneous connective tissue disease that has significant mortality and morbidity secondary to internal and cutaneous fibrosis. Though the exact pathogenesis remains poorly understood, fibroblast and myofibroblast activation are thought to be key contributors to the fibrotic process. Dendritic cells (DCs) can modulate mesenchymal cell activity in lymph nodes, and we hypothesized that they may also have a role in modulating the fibroblasts activity in skin fibrosis.

Methods: We induced fibrosis by injecting bleomycin (BLM, $20\mu g$) subcutaneously into 3 adjacent points on shaved back skin for 17 or 28 days. After sacrifice, we took 3x 8mm biopsy punches of affected tissue for histology, flow cytometry and RNA extraction. Primary fibroblasts were derived from wild type, untreated mouse ears and used at passage 1. Bone marrow-derived DCs (BMDCs) were isolated from wild type, untreated bone marrow cultured in the presence of GM-CSF.

Results: By immunohistochemistry, we observe the association of CD11c^{hi} cells and alpha-smooth muscle actin^{+} (SMA^{+}) myofibroblasts after BLM treatment. Using CD11c-DTR transgenic mice that allow for inducible depletion of CD11c^{+} cells, we depleted CD11c^{hi} cells after 15 days of BLM treatment. CD11c^{hi} cell depletion resulted in disappearance of SMA^{+} cells and over 2-fold decrease in TGFb1 transcription in total skin, suggesting that dendritic cells are required to maintain myofibroblasts and TGFb1 levels in fibrotic skin. Culturing BMDCs with primary fibroblasts resulted in increased SMA[+] and SMA[−] fibroblast numbers, as well as increased SMA expression in SMA^{+} cells, suggesting that dendritic cells are sufficient to promote fibroblast and myofibroblast proliferation and activation.

Conclusion: These results suggest a scenario whereby dendritic cells in fibrotic skin contribute to fibrosis in part by promoting the proliferation and activation of fibroblasts and myofibroblasts, perhaps via their expression of TGFb1.

Disclosure: **J. J. Chia**, None; **S. Tian**, None; **T. T. Lu**, None.

2309

Increased Levels of Ser 181 Phosphorylated SOX9 in SSc Dermal Fibroblasts: A Novel Participant in the Pathogenesis of SSc Fibrotic Process. Sonsoles Piera-Velazquez, Jolanta Fertala and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center,Thomas Jefferson University, Philadelphia, PA

Background/Purpose: SOX9, a high mobility group (HMG) transcription factor is a master regulator of chondrogenesis and is essential for the maintenance of the chondrocyte-specific phenotype regulating the expression of various chondrocyte-specific gene products including type II collagen and COMP. We recently performed an analysis of the kinome of human dermal fibroblasts and demonstrated that these cells contained high levels of SOX9 phosphorylated at serine residue 181 (Ser181 phosphoSOX9). Recent studies on liver fibrosis and segmental glomerulosclerosis have suggested that SOX9 may participate in tissue fibrosis. Therefore, we explored here the involvement of Ser181 phosphoSOX9 in the fibrotic process of Systemic Sclerosis (SSc) employing cultured SSc dermal fibroblasts in vitro.

Methods: Dermal fibroblasts were obtained from skin samples from normal individuals and from clinically affected and non-affected forearm skin from patients with diffuse SSc of recent onset. Ser181 phosphoSOX9 levels were assessed by Western blot analysis of cell lysates of confluent dermal fibroblast cultures employing a phospho-specific antibody that recognizes a SOX9 epitope containing a phosphorylated Ser 181 residue. Gene expression analyses were performed by real time PCR employing specific primers. Collagen production was assessed by Western blots of fibroblast culture media. The effects of TGF-β treatment on Ser181 phosphoSOX9 were assessed in confluent cultures in the presence or absence of TGF-β1 (10ng/mL) for 24h. The intracellular kinases responsible for SOX9 phosphorylation were examined by inhibition with specific small molecule kinase inhibitors.

Results: Dermal fibroblasts from SSc patients displayed marked elevation of Ser181 phosphoSOX9 levels in comparison with normal fibroblasts. Furthermore, fibroblasts cultured from clinically affected SSc skin had significantly greater levels of Ser 181 phosphoSOX9 than fibroblasts cultured from clinically non-affected skin from the same patients. TGF-β caused a potent stimulation of SOX9 phosphorylation in normal fibroblasts but only minor stimulation in SSc fibroblasts. The stimulation of SOX9 phosphorylation by TGF-β was inhibited by small molecule inhibitors targeting PKC-delta and Rho Kinase. Inhibitors of PI3 Kinase and other kinases were not effective. The levels of the Type I collagen production changed in parallel with the changes in Ser181 phosphoSOX9 levels.

Conclusion: The results indicate that Ser181 phosphoSOX9 may participate in the molecular mechanisms responsible for the exaggerated fibrotic process in SSc and suggest that PKC-delta and Rho Kinase, the specific kinases responsible for SOX9 phosphorylation, may provide novel therapeutic targets for SSc and other fibrotic disorders involving Ser181 phosphoSOX9.

Disclosure: S. Piera-Velazquez, None; **J. Fertala**, None; **S. A. Jimenez**, None.

2310

Enhancement of CRACM1 Expression in Functionally Aberrant Naïve CD4^{+} T Cells in Active Rheumatoid Arthritis. Shuang Liu[1], Shohei Watanabe[2], Miyuki Kuno[3], Hiromasa Miura[2] and Kazutaka Maeyama[1]. [1]Informational Biomedicine, Ehime University Graduate School of Medicine, Toon-shi, Ehime, Japan, [2]Ehime University Graduate School of Medicine, Toon, Japan, [3]Osaka City University Graduate School of Medicine, Osaka, Japan

Background/Purpose: Lymphocytes from rheumatoid arthritis (RA) patients have been reported to exhibit increased basal intracellular Ca^{2+} concentrations compared with the lymphocytes of healthy controls. A precise molecular explanation for the enhanced Ca^{2+} influx in T cells has not yet been established. To explore the molecular basis of the irregular Ca^{2+} influx in RA T cells, we performed a cross-sectional study to characterise the expression levels and functional status of Ca^{2+} release-activated Ca^{2+} (CRAC) channels in peripheral naïve CD4^{+} T cells from 50 RA patients, 50 osteoarthritis (OA) patients and 15 healthy donors.

Methods: To determine whether CRACM1 channels contribute to the abnormal behavior of T cells in RA, CRACM1 expression was evaluated by western blotting and immunofluorescence analysis. We also measured Ca^{2+} influx and CRAC currents in naïve CD4^{+} T cells, as well as cytokine release by activated naïve CD4^{+} T cells, for each of the three groups.

Results: 1.Intracellular Ca^{2+} influx is up-regulated in naïve CD4^{+} T cells from RA patients and is associated with RA disease activity.2.CRACM1 channel function is increased in T cells from active RA patients. 3.CRACM1 expression in naïve CD4^{+} T cells is higher in active RA patients than in OA patients and healthy donors.

Conclusion: Functionally aberrant naïve CD4^{+} T cells from active RA patients exhibited an increase in Ca^{2+} influx, as well as up-regulated CRACM1 protein expression and function, indicating that CRACM1 might represent a new molecular target for novel RA therapies.

Disclosure: S. Liu, None; **S. Watanabe**, None; **M. Kuno**, None; **H. Miura**, None; **K. Maeyama**, None.

2311

Total Glucosides of Paeony Th1 and Th17 Cell Differentiation by Blocking STAT1 and STAT3 Activation *in Vivo*. Ningli Li[1] and JP Lin[2]. [1]Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Shanghai, China

Background/Purpose: Th1 and Th17 cells play very importent role in the lesions of human rheumatoid arthritis (RA). Total glucoside of paeony (TGP), an active compound extracted from Paeony root, has been used in therapy for RA and other autoimmune diseases. However the molecular mechanism of TGP in prevention of Th1 and Th17 differentiation remains unclear.

Methods: Collagen-induced arthritis (CIA) mice were used as the RA animal model to test the therapeutic effect of TGP as well as its effect on Th1 and Th17 differentiation *in vivo*. Expression of cytokines was measured by ELISA, real-time PCR. Th1 and Th17 population were identified by flow cytometry, STATs activation was analyzed by western blotting.

Results: In this study, we found that TGP treatment significantly decreased clinical inflammatory score of CIA. Percentage and number of Th1 and Th17 cells in TGP-treated CIA CD4+ T cells decreased signifi-

cantly compared with that of without TGP treatment. Moreover, investigation revealed that CIA-treated with TGP decreased expression of T-bet and RORgt in CD4+ T cells. But we did not found regulatory T cells (Treg) was altered in TGP treatment CIA mice. Furthermore, we found that TGP treatment inhibited IL-12 and IL-6 expression, meanwhile, activation of STAT1 and STAT3 was inhibited in TGP-treated CIA mice consistently.

Conclusion: Taken together, these findings indicate that TGP inhibits inflammation and autoimmunity in RA patients possibly by reducing Th1 and Th17 cell differentiation.

Disclosure: N. Li, None;

2312

Senescent T Cells Promote Bone Loss in Rheumatoid Arthritis. Johannes Fessler, Rusmir Husic, Elisabeth Lerchbaum, Verena Schwetz, Claudia Stiegler, Barbara Obermayer-Pietsch, Winfried B. Graninger and Christian Dejaco. Medical University Graz, Graz, Austria

Background/Purpose: To study the influence of aged CD28^{−} T cells on systemic osteoporosis in rheumatoid arthritis (RA) patients.

Methods: Prospective, cross-sectional study on 100 patients with RA [mean age 61.9 ($\pm$SD 11.2), 75% female, median time since diagnosis 162.4 (range 0–552) months, SDAI 12.7 ($\pm$SD9.3), 81% and 50% received synthetic and/or biologic DMARDs, respectively; 24% used corticosteroids, 16% were treated with bisphosphonates]. Bone mineral density (BMD) was determined by lumbar spine (LS) and total hip DEXA and laboratory markers of bone metabolism included bone specific alkaline phosphatase, osteocalcin, osteoprotegerin, β-crosslaps and soluble RANKL. PBMCs were retrieved at the same day of BMD measurement and were stained with anti-RANKL, CD3, CD4, CD8, CD45RA, CD45RO and/or CD28 mAbs to measure surface expression of RANKL on T cells and to determine the prevalence of T cell subsets by flow cytometry. *In vitro*RANKL regulation assays were performed using human TNF-α (100ng/ml), IL-6 (100ng/ml), IL-15 (100ng/ml) or solid-phase anti-CD3 (10ng/ml).

Results: A reduced BMD as determined by DEXA was found in 63% of RA patients (13% with osteoporosis, 50% with osteopenia). The prevalences of aged CD4^{+}CD28^{−} and CD8^{+}CD28^{−} T cells inversely correlated with T-scores of LS (corr$_{coeff}$=−0.235, p=0.028 and corr$_{coeff}$=−0.266, p=0.012, respectively) and hip (corr$_{coeff}$=−0.235, p=0.025, corr$_{coeff=}$−0.253, p=0.016 respectively). Patients with a T-score below −1.0 tended to have higher prevalences of circulating CD4^{+}CD28^{−} (2.2% [0.1–41.2] vs. 0.5% (0–17.6), p=0.065) and CD8^{+}CD28^{−}T cells [44.8% $\pm$ 20.7 vs. 37.4% $\pm$ 20.1, p=0.134] than patients with normal bone mass. No association was found between frequencies of aged T cells and blood parameters of bone metabolism.

RANKL expression was higher in CD4^{+}CD28^{−} T cells (3.8% [0.2–57.9]) compared to naïve CD4^{+}CD28^{+}CD45RA^{+} (2.2% [0.2–30.5], p<0.001) and memory CD4^{+}CD28^{+}CD45RO^{+} (2.8% [0.2–38], p=0.009) T cells. In the CD8^{+}T cell population surface expression of RANKL was higher on memory (4.4% [0.5–44.5]) compared to naïve (3.3% [0.5–41.3], p<0.001) and aged T cells (2.2% [0–20.1], p<0.001).

In cell culture experiments IL-15 and anti-CD3 stimulation increased RANKL expression on all T cell subsets. IL-15 stimulation showed largest effects on memory CD4^{+} and CD8^{+} T cells [4.5-fold and 6-fold higher expression, respectively compared to unstimulated cells, p<0.05] compared to aged [3.9-fold and 5-fold, respectively, p<0.05] and naïve T cells [1.5-fold and 3.8-fold, respectively, p<0.05]. Also, activation by anti-CD3 had the largest effect on RANKL expression on memory CD4^{+} and CD8^{+}T cells [7.8-fold and 7.5-fold, respectively, p<0.05] compared to naïve [5.2-fold and 4.7-fold, respectively, p<0.05] and aged cell subsets [2.9-fold and 3.2-fold, respectively, p<0.05]. IL-6 and TNF-α had no effect on RANKL.

Conclusion: Aged CD28^{−} T cells are linked with the occurrence of systemic bone loss in RA. Increased expression of RANKL on CD4^{+}CD28^{−} T cells compared to other T cell subsets is compatible with direct stimulation of osteoclastogenesis by aged T cells in RA.

Disclosure: J. Fessler, None; **R. Husic**, None; **E. Lerchbaum**, None; **V. Schwetz**, None; **C. Stiegler**, None; **B. Obermayer-Pietsch**, None; **W. B. Graninger**, None; **C. Dejaco**, None.

Tuesday, November 13

2313

The Autoantibody-Inducing CD4 T Cell (*ai*CD4 T cell) Belongs to CCR4^{+}CD45RB^{lo}122^{lo} CD4 Subpopulation: A Novel 'Self-Organized Criticality Theory' Explains the Cause of Systemic Lupus Erythematosus (SLE). Yumi Miyazaki[1], Ken Tsumiyama[2] and Shunichi Shiozawa[2]. [1]Kyushu University Beppu Hospital/Kobe University Graduate School of Health Sciences, Beppu/Kobe, Japan, [2]Kyushu University Beppu Hospital, Beppu, Japan

Background/Purpose: We found that systemic lupus erythematosus (SLE) was induced experimentally by repeatedly immunizing the mice normally not prone to autoimmune diseases by any exogenous antigen so far examined (Tsumiyama K. *et al.* PLoS ONE 4(12):e8382, 2009). We have then proposed a novel 'self-organized criticality theory' that takes place when host's immune system is overstimulated by repeated exposure to antigen to levels that surpass the immune system's stability limit, i.e., self-organized criticality. The autoreactive lymphocyte clones, which we name autoantibody-inducing CD4 cells (*ai*CD4 T cells) are newly generated *via de novo* T cell receptor (TCR) revision from thymus-passed non-autoreactive clones at peripheral lymphoid organs. They not only stimulated B cells to generate varieties of autoantibodies but also helped final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce tissue injuries identical to SLE. We here tried to identify the phenotype of *ai*CD4 T cell, and show that *ai*CD4 T cell belongs to CCR4^{+}CD45RB^{lo}122^{lo} CD4 subpopulation.

Methods: BALB/c were repeatedly immunized with ovalbumin (OVA), keyhole limpet hemocyanin (KLH) or staphylococcal enterotoxin B (SEB). RF, anti-Sm and anti-dsDNA antibodies were measured using ELISA. To assign CD number on the *ai*CD4 T cell, expression of effector/memory markers were studied in the CD4 T cell of repeatedly immunized mice. These CD4 T cells were isolated referring to CD45RB, CD27 and CD122 markers, and fractionated cells were adoptively transferred into naïve recipients. Autoantibodies in sera of recipient mice were measured 2 weeks after cell transfer. Further, we performed microarray analysis (Whole Mouse Genome Microarray; Agilent Technologies) to investigate gene expression of CD45RB^{lo}122^{lo} CD4 T cell, and flow cytometry of CD45RB^{lo}122^{lo} CD4 T cell to study protein expression profiles of *ai*CD4 T cell in the mice immunized 12x with OVA.

Results: Upon repeated immunization 12x with OVA, KLH or SEB, varieties of autoantibodies including RF, anti-Sm and anti-dsDNA antibodies were generated. Simultaneously, CD45RB^{lo}, CD27^{lo} and CD122^{hi} CD4 T cells were significantly expanded as compared with control mice upon repeated immunization with either OVA, KLH or SEB. Adoptive transfer of fractionated CD4 cells with either CD45RB, CD27 or CD122 markers of the mice immunized 12x with OVA showed that both CD45RB^{lo} CD4 T cell and CD122^{lo} CD4 T cells were capable of inducing autoantibodies in the naïve recipients. However, CD27 marker was irrelevant for inducing autoantibodies. Consequently, we transferred CD45RB^{lo}122^{lo} CD4 T cells into naïve mice and found that both RF and anti-dsDNA antibody were indeed significantly increased. In microarray analyses, we compared the gene expression profile between CD45RB^{lo}122^{lo} CD4 T cell and the rest of CD4 T cell subsets after immunization 12x with OVA. We found that chemokine (C-C motif) receptor 4 (Ccr4) was increased $\times$ 4 in the CD45RB^{lo}122^{lo} CD4 subsets. Surface expression of CCR4 protein was also similarly significantly increased in this subset.

Conclusion: The *ai*CD4 T cell that induces SLE belongs to a CCR4^{+}CD45RB^{lo}122^{lo} CD4 subpopulation.

Disclosure: Y. Miyazaki, None; **K. Tsumiyama**, None; **S. Shiozawa**, None.

2314

Correlation Between Abatacept and Rheumatoid Factor – Can Rheumatoid Factor Be a Predictive Factor for Abatacept? Tomonori Kobayakawa[1], Masatoshi Hayashi[1], Toshihisa Kanamono[1], Atsushi Kaneko[2], Toshihisa Kojima[3] and Naoki Ishiguro[4]. [1]Nagano Red Cross Hospital, Nagano, Japan, [2]Nagoya Medical Center, Nagoya, Japan, [3]Nagoya University, School of Medicine, Nagoya, Japan, [4]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan

Background/Purpose: Abatacept (ABT), a T-cell selective costimulatory regulator, went on the market in Japan in September 2010, with a number of reports issued on its effectiveness since. However, no report has been made on the correlation between ABT and rheumatoid factor (RF). We examined the correlation between ABT and RF.

Methods: Among the 143 patients with rheumatoid arthritis who were given ABT at Tsurumai Biologics Communication between September 2010 and August 2011, 89 cases whose RF was measured before and after the ABT administration with week 24 follow-up observation. The subjects were sorted into two groups according to the Simplified Disease Activity Index at week 24 after ABT administration: a good response (GR) group (n=35) that exhibited remission and low disease activity and a poor response (PR) group (n=54) that exhibited moderate and high disease activity. The correlation between the ABT responsiveness and the RF was examined for these groups. In addition, the cases with high disease activity at week zero were selected for a sub-analysis to determine the correlation between the change in disease activity and RF at 24 weeks and the correlation between the effect of ABT and RF at week 24 in terms of the duration of disease, whether or not methotrexate was concurrently used, and the history of pre-biologics administration.

Results: The percentage of men was higher and the disease activity tended to be lower at week zero in the GR group. The RF was 148.5 mg/dl and 341.1 mg/dl at week zero for the GR group and the PR group and 126.8 mg/dl and 194 mg/dl at the 24th week, respectively. In the group consisting only of subjects with high disease activity, the subjects whose disease activity had improved low at week 24 displayed significantly lower RF values at both week zero and week 24 than those whose disease activity had not improved at week 24. The sub-analysis revealed that the bio naive patients who had experienced a crisis less than two years earlier had a significantly lower RF value at week zero and maintained the low level through to week 24. No significant difference was observed in RF change over time between those with and without concurrent methotrexate administration.

Table 1. Baseline characteristics of two groups that the RA patients treated with ABT who were enrolled in the present study

	GR group (n = 35)	PR group (n = 54)	P value
Age, years (mean ± SD)	64.5 ± 9.6	63.9 ± 11.2	0.9376
Female, (%)	23 (67%)	46 (85%)	0.0316
RA duration, years (mean ± SD)	11.4 ± 12.1	12.0 ± 11.1	0.3545
Stage (I/II/III/IV)	9/7/10/9	2/14/26/12	0.0131
Class (1/2/3/4)	7/14/13/1	2/26/25/1	0.0936
MTX use (%)	21/35 (60%)	32/54 (59%)	0.9446
MTX dose, mg/w (mean ± SD)	7.3 ± 2.6	7.1 ± 1.9	0.8807
PSL use (%)	20/35 (57%)	31/54 (57%)	0.9803
PSL dose, mg/day (mean ± SD)	4.1 ± 2.2	4.8 ± 3.1	0.7962
Bio naïve/2nd/3rd/4th/5th	23/5/6/1/0	21/14/13/4/2	0.1361
DAS28ESR	4.68 ± 1.30	5.65 ± 1.30	0.0006
SDAI	18.6 ± 11.7	28.9 ± 14.2	0.0001
MMP-3	161.3 ± 117.2	258.2 ± 311.4	0.0319

GR Good response, PR poor response, RA Rheumatoid arthritis, MTX methotrexate, PSL prednisolone, DAS28ESR 28 joint disease activity score and erythrocyte sedimentation rate, SDAI simplified disease activity index, MMP-3 matrix metalloproteinase-3

# P<0.05 Un-Paired t test * VS. Baseline P<0.05 Paired t test
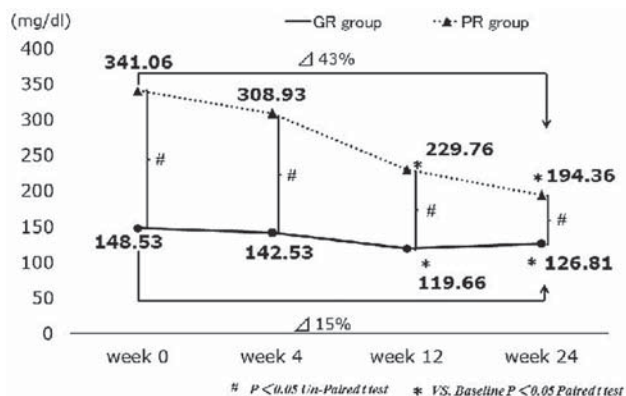
Conclusion: We conclude that the lower the RF was at the time of ABT administration, the more effective it was. The RF tended to be lower for the bio naive subjects who had experienced a crisis less than two years earlier. The RF can be a predictive factor for ABT.

Disclosure: T. Kobayakawa, None; **M. Hayashi**, None; **T. Kanamono**, Santen Pharmaceutical, 2; **A. Kaneko**, None; **T. Kojima**, None; **N. Ishiguro**, Abbott Japan, Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma, Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd., 2, Abbott Japan, Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma, Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd., 8.

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Foxp3^{+} Treg Cells Decreased in Overexpression of T-Bet in PD-1 Deficient Mice. Masahiro Tahara[1], Yuya Kondo[1], Hiroto Tsuboi[1], Satoru Takahashi[2], Isao Matsumoto[1] and Takayuki Sumida[1]. [1]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan, [2]Department of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba, Tsukuba city, Ibaraki, Japan

Background/Purpose: Programmed cell Death-1 (PD-1) plays an important role in peripheral T cell tolerance, therefore PD-1 deficient (PD-1 KO) mice develop strain-specific autoimmune phenotypes. C57BL/6 (B6) background PD-1 KO mice develop glomerulonephritis after 24–48 weeks of age, which is similar to human endocapillary proliferative glomerulonehiritis observed in lupus nephritis. The differentiation of Th cells in PD-1 KO mice was not fully elucidated. The purpose of this study is to clarify the effect of T cell specific T-bet overexpression on autoimmune disease in PD-1 KO mice.

Methods: 1) T-bet overexpressing PD-1 KO mice were generated by crossing T-bet transgenic (T-bet Tg) mice under the promoter of CD2 gene with PD-1 KO mice (PD-1 KO × T-bet Tg mice; P/T mice). 2) In wild-type (WT) mice, PD-1 KO mice, T-bet Tg mice and P/T mice, the pathological evaluation of the kidneys was performed with H·E, PAS and PAM staining at 6–8 weeks of age. Deposition of IgG and C3 in kidneys was analyzed with immunofluorescence staining. 3) The histological analyses were evaluated on the heart, spleen, mesenteric LN, lung, liver, pancreas, salivary gland and lacrimal gland with H·E staining and immunofluorescence staining in WT mice, PD-1 KO mice, T-bet Tg mice and P/T mice. 4) Proportion of lymphocytes subset and cytokine production by CD4^{+} T cells in spleen was analyzed by FACS. 5) FACS analysis was performed to evaluate transcription factor expression on CD4^{+} T cells in spleen.

Results: 1) Most of P/T mice died within 10 weeks. 2) Glomerulonephritis was not observed in WT mice, PD-1 KO mice, T-bet Tg mice and P/T mice. Deposition of IgG and C3 was observed in glomeruli in PD-1 KO mice, but not in WT mice, T-bet Tg mice and P/T mice. 3) Splenomegaly and infiltration of mononuclear cells in liver were observed only in P/T mice. Immunofluorescence staining revealed that infiltrating cells were CD3^{+} T cells. 4) FACS analysis showed that the total cell number was increased in P/T mice ($15.3 \pm 3.11 \times 10^7$cells), compared with WT mice ($6.41 \pm 0.81 \times 10^7$cells, $P<0.05$ by Mann-Whitney U-test), PD-1 KO mice ($8.46 \pm 1.77 \times 10^7$cells, $P=0.086$) and T-bet Tg mice ($7.12 \pm 2.32 \times 10^7$cells, $P=0.086$), and IFN-γ production on CD4^{+} T cells observed in P/T mice ($20.5 \pm 3.42\%$) was higher than that in WT mice ($3.56 \pm 0.63\%$, $P<0.05$) and PD-1 KO mice($6.85 \pm 1.17\%$, $P<0.05$). 5) Percentage of Foxp3^{+} cells in CD4^{+} Treg cells was significantly decreased in P/T mice ($2.47 \pm 1.31\%$), compared with WT mice ($13.4 \pm 1.39\%$), PD-1 KO mice ($16.9 \pm 2.15\%$) and T-bet Tg mice ($19.1 \pm 2.55\%$) ($P<0.05$).

Conclusion: In P/T mice, the reduced percentage of Foxp3^{+}CD4^{+} Treg cells induced systemic inflammation, resulting in short-life span.

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Generation of CD4^{+} Follicular Helper T cells by Complement and Immune Complexes. Anil K. Chauhan[1], Richard DiPaolo[2] and Terry L. Moore[1]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis, MO

Background/Purpose: Complement opsonized immune complexes (ICs) are key players of disease pathology. We showed in systemic lupus erythematosus (SLE), ICs and complement (C′) drive activation and differentiation of naïve CD4^{+} cells into the T effector population. We also established activation-induced expression of FcγRIIIA in naïve CD4^{+} population that is partly responsible for this activation. To further understand the role IC and C′ mediated activation in the development of autoantibody secreting plasma cells, we examined the development of Bcl6^{+}PD1^{+}CXCR5^{+} follicular helper cells (T$_{FH}$). We asked whether ICs play a role in cognate contact between T$_{FH}$ cells and naïve B cells in pre germinal centers (GC) and/or in secondary GC that could lead to the formation B memory and/or plasma cells.

Methods: Peripheral human naïve CD4^{+} T cells were stimulated in vitro using ICs and the late complement complex C5b-9. They were grown in the presence of IL-6 and IL-21. Post 72 h, cells were analyzed by flow for the expression of Bcl6, PD1, and CXCR5. RNA expression was quantified using QT-PCR. To analyze whether ICs facilitate the contact among CD4^{+}T cells, we used an autoimmune gastritis mouse model (TxA23 TCR-Tg). In this model, the T and B cells association was analyzed by flow staining for a cell specific marker in the presence of Alexa Fluor 647 labeled ICs and GC reaction by staining with anti-GL-7.

Results: Antigen-specific B cell memory progressively develops under the cognate guidance of T$_{FH}$ cells, following initial priming and secondary antigenic challenge. Cognate contact of naïve B cells with T$_{FH}$ initiates immunoglobulin class switching and naïve B cell differentiation into plasma cells outside the GC. Such cell contacts also induce GC reaction. Our previous work established the presence of FcγRIIIA on CD4^{+} T cells, which upon ICs engagement produced IFN-g. It also, showed T cell activation. The naïve CD4^{+} T cell activation by ICs and C5b-9 showed three-fold increase in expression CXCR5^{+}Bcl6^{+} T cell population. This was comparable to anti-CD3 and anti-CD28 stimulation. However, CD4^{+}IC^{+} gated population showed 52% cells that were CXCR5^{+}PD1^{+}Bc6^{+}, in response to ICs and C5b-9 activation compared to 20% using anti-CD3 and anti-CD28. These results suggest that naïve CD4^{+} cells upon activation with ICs and C5b-9 express T$_{FH}$ markers and receptors that bound to ICs. To further establish the role of these cells in starting the formation of GC reaction, we used TxA23 TCR-Tg mice that demonstrate formation of ectopic GCs. Cells obtained from spleen/lymph nodes of these mice with disease activity upon staining with anti-CD4, anti-CD19, and labeled ICs showed 39% of CD4^{+}; 34.8 % of CD19^{+} and 6.2 % of cells that were CD4^{+}CD19^{+}. The CD4^{+}CD19^{+} showed a very high percentage of cells (83.9%) that bound to ICs, compared to 4% CD4^{+} cells and 43% CD19^{+} B cells. The side scatter of CD4^{+}CD19^{+}was two fold higher suggesting a large size. This suggests the formation of T and B cell conjugates by ICs.

Conclusion: These results thus suggest an important role for ICs and complement in generation of T$_{FH}$ cells and formation of secondary GCs.

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Protein Phosphatase 5 (PP5) Regulates Methylation Sensitive Gene Expression in CD4+ T Cells. Dipak R. Patel, Gabriela Gorelik and Bruce C. Richardson. University of Michigan, Ann Arbor, MI

Background/Purpose: CD4+CD28- T cells are enriched in chronic inflammatory diseases like rheumatoid arthritis (RA) and lupus. They are cytotoxic and resistant to apoptosis. Compared to CD28+ cells, CD28- CD4 T cells over-express killer immunoglobulin-like receptors (KIRs), perforin, and other molecules that are expected to contribute to their pro-inflammatory phenotype. These genes are regulated by DNA methylation, so they are over-expressed by CD4 T cells that are demethylated in vitro. This is a result of decreased signaling through the ERK and JNK pathways. This consequently decreases activity of the DNA methyltransferase enzymes (DNMTs) responsible for DNA methylation. Protein phosphatase 5 (PP5) is a stress induced regulator of gene expression in multiple signaling pathways, including ERK, JNK, and those involved in aging. It is expressed in CD4+CD28-, but not CD4+CD28+ T cells. We hypothesized that PP5 is over-expressed in CD4+ T cells in patients with RA and lupus, and that over-expressing PP5 in CD4 T cells from healthy donors will induce expression of methylation sensitive genes unique to CD4+CD28- T cells.

Methods: CD4+ T cells were isolated from healthy controls and patients with RA and lupus, and PP5 mRNA expression was measured by RT-PCR. To study the effects of PP5 on methylation sensitive genes, PBMCs from healthy donors were stimulated with phytohemagglutinin (PHA) and cultured for 3 days with IL-2. CD4+ T cells were then isolated by negative selection, transfected (Amaxa Nucleofector) with constructs encoding GFP and PP5 or GFP alone, and cultured an additional 24–72 hours. Expression of DNMT1, KIR, and perforin was assessed by RT-PCR in sorted CD4+GFP+ T cells. DNMT1 expression was measured 24 hours after transfection, and KIR and perforin were analyzed 72 hours after transfection. KIR protein expression was also measured by flow cytometry with unsorted cells 72 hours after transfection.

Results: Compared to CD4+ T cells from healthy controls, PP5 mRNA is over-expressed in CD4+ T cells from patients with lupus (1.97 fold change ± 0.18 SEM, $p=0.03$) and RA (1.6 ± 0.2, $p=0.06$). When transfected into CD4+ T cells from healthy donors, PP5 increased KIR mRNA expression (2DL4 gene, 2.4 ± 0.7, $n=3$, $p=0.04$) and CD70 mRNA expression (1.38 ± 0.07, $n=3$, $p=0.03$). PP5 transfection also increased the percentage of cells expressing KIR proteins on their surface ($33 \pm 7\%$ with control vs. $62 \pm 7\%$ with PP5, $n=7$, $p<0.01$). Finally, PP5 caused a corresponding $20 \pm 8\%$ decrease ($n=3$, $p=0.05$) in DNMT1 mRNA expression.

Conclusion: CD4+CD28− T cells, which are enriched in RA and lupus, over-express methylation sensitive genes that contribute to their pro-inflammatory phenotype. These data demonstrate, for the first time, that protein phosphatase 5 (PP5) contributes to the regulation of methylation sensitive genes in CD4+ T cells. Specifically, PP5 increases expression of KIR and perforin, and it decreases expression of DNMT1. Its effects on other methylation sensitive genes, including CD70 and IFN-g, are currently being studied. PP5 has not been studied in T cells before, and it potentially links aging and DNA methylation with the pathogenesis of multiple rheumatologic disorders.

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Reduced Thymus Function and Accelerated T-Cell Aging in Patients with Axial Spondylarthritis. Christian Dejaco[1], Wolfgang Schwinger[1], Andrea Raicht[1], Rusmir Husic[1], Johannes Fessler[1], Christoph G. Ammann[2], Christina Duftner[3], Winfried B. Graninger[1] and Michael Schirmer[4]. [1]Medical University Graz, Graz, Austria, [2]Medical Uiversity Innsbruck, Innsbruck, Austria, [3]Hopital Elisabethinen, Klagenfurt, Austria, [4]Innsbruck Medical University, Innsbruck, Austria

Background/Purpose: To investigate thymic T-cell output, senescence of circulating T-cell subsets and changes of T cell subsets in patients with axial spondylarthritis (aSpA). **Results** are compared with data from rheumatoid arthritis (RA) patients and healthy controls (HC).

Methods: Patients with aSpA (n=26; 26.9% female, mean BASDAI 3.2 ±2.1), RA (n=20; 60.0%, mean SDAI 10.2 ±10.2) and HC (n=24; 70.8%) were prospectively enrolled. Naïve and memory CD4+ and CD8+ T-cell subsets were isolated by MACS-technology. DNA was extracted by QIAamp DNA isolation Kit. TREC Analysis was performed with LC 480 Probes Master using established oligonucleotides as primers. Telomere length analysis was performed using LightCycler FastStart DNA Master SYBR Green I with published oligonucleotides as primers for telomere length or for the single copy gene 36B4 as normalizing sequence. The telomere length was calculated by comparison of sample result with a positive control with known telomere length (HEK293 with 5 kbp). FACS analyses were performed on fresh PBMCs in a separate cohort of 25 patients and 24 HC.

Results: aSpA (median age 37.0, range 21.8–69.7 years) and RA (37.0, 21.4–73.6 years) patients did not differ from HC (35.3, 23.3–54.3 years) regarding age and disease duration (aSpA: mean 7.7±6.8, RA 6.4±5.1 years, each with p>0.2). Percentages of circulating TH17, naïve CD45RA+ and memory CD45RO+ CD4+/CD8+ T-cells as well as CD4+FOXP3+ Treg cells did not differ between aSpA patients and healthy controls.

Reduced thymus function as indicated by a lower TREC content in naïve CD3+CD4+CD45RA+ and CD3+CD8+CD45RA+ T-cells was found in aSpA (median 483 copies/ng DNA, range 33–5033 and 462, 15–4467, respectively) and RA patients (355, 0–162800 and 296, 0–71800, respectively) compared to HC (2304, 0–64444 and 2558, 0–103091, respectively; p<0.05 for comparisons between aSpA or RA patients and HC). Trends for an inverse correlation between TREC content in naïve CD4+ or CD8+ T-cells and age were found among RA patients and HC (corr$_{coeffs}$ ranging from −0.30 to −0.53, p<0.2 for each analysis) but not among aSpA patients (corr$_{coeffs}$ −0.01–0.07). Shortened telomeres were found in naïve CD45RA+CD4+ and CD8+ (6.24, 5.76–8.13 and 6.15, 5.33–7.56, respectively) as well as memory CD45RO+CD4+ and CD8+ T-cell subsets (5.99, 5.51–8.46 and 6.21, 5.50–7.79, respectively) from aSpA patients compared to HC (CD4+CD45RA+: 7.17, 3.65–8.67, CD8+CD45RA+: 6.99, 3.83–8.47; CD4+CD45RO+: 6.99, 3.70–8.32 and CD8+CD45RO+: 7.20, 3.87–8.06; p<0.05 for each comparison) whereas differences between RA patients and HC concerning telomere length of T-cell subsets did not reach statistical significance.

Conclusion: Thymic T-cell renewal is impaired in aSpA patients. Consequently, increased peripheral T-cell turnover compensates for failing thymus to maintain T-cell homeostasis leading to accelerated telomere erosion and the accumulation of early aged T-cells.

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T Follicular Helper Cell and Regulatory T Cell Frequencies Are Affected by B Cell Depletion in Patients with Granulomatosis with Polyangiitis. Yuan Zhao[1], Jessica Thomas[1], Shirish Sangle[2], Pamela M.K Lutalo[3], Lee Meng Choong[4], Jennifer R. Tyler[1], Jo Spencer[1], Timothy Tree[1] and David P. D'Cruz[2]. [1]School of Medicine, King's College London, London, United Kingdom, [2]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [3]Louise Coote Lupus Unit, St Thomas Hospital, London, United Kingdom, [4]St Thomas' Hospital, London, United Kingdom

Background/Purpose: Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is a rare and sometimes fatal systemic autoimmune disease. Anti-neutrophil cytoplasmic antibodies (ANCAs) specific for proteinase 3 (PR3) are associated with GPA. Remissions in GPA can be achieved through B cell depletion therapy. However, the mechanism is not yet clear.

Methods: The frequencies of T follicular helper cells (TFH) and regulatory T cells (Treg) from 27 GPA patients including 9 rituximab treated patients and 10 healthy controls were studied by flow cytometry. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) and clinical data was collected in all patients. The functional capacity of Tregs was assessed by in vitro co-culture assays.

Results: The average (range) age was 51 (25–83), and disease duration was from less than 1 year up to 25 years. The mean BVAS scores in rituximab treated patients and those on conventional therapy were 5.56 and 9.67 respectively. We observed an increased frequency of TFH (P=0.0013) and a reduced frequency of antigen experienced Treg (P<0.0001) in peripheral blood from GPA patients on conventional therapies but not in those treated with rituximab compared to healthy controls (figure A & B). The frequencies of TFH and Treg were significantly inversely correlated (P=0.0059, figure C). Furthermore, the ratio of TFH to Treg was significantly higher in GPA patients on conventional therapies (average 9.07) than in GPA patients treated with rituximab (average 2.43; P=0.0002), who were clinically improved or controls (figure D). Whereas Tregs were numerically reduced in individuals with GPA on conventional therapy (average 5.03%, P=0.0009), the suppressive capacity of Tregs on a per cell basis is not significantly altered in these individuals compared to healthy controls (P=0.23).
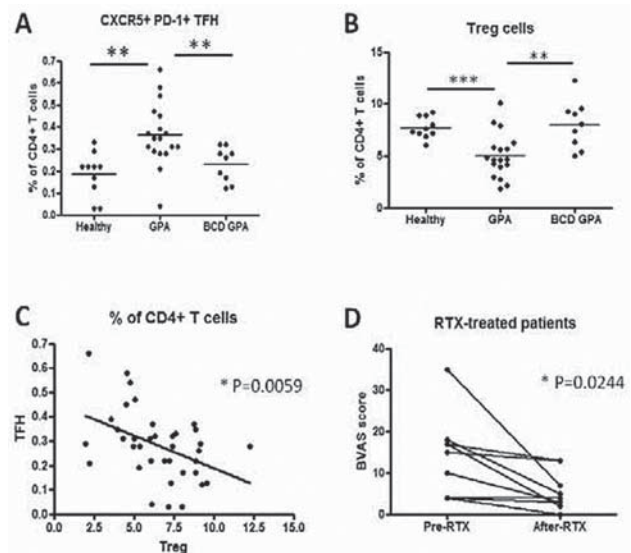
Conclusion: Our study demonstrates increased TFH cells and decreased antigen experienced Treg cells in GPA patients on conventional therapies compared to controls. Patients undergoing B cell depletion therapy were indistinguishable from controls. The negative correlation between TFH and Treg cells implies that the balance between T cell subsets and its B cell dependence impact on disease activity in GPA.

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Superantigen Induces IL-17 Production From Extremely Polarized Th1 Clones. Kentaro Yomogida[1], Yuan K. Chou[1] and Cong-Qiu Chu[2]. [1]Oregon Health & Science University, Portland, OR, [2]Oregon Health & Science Univ and Portland VA Medical Center, Portland, OR

Background/Purpose: Differentiation of naïve CD4^{+} T cells is considered to be an irreversible event and, in particular, the plasticity is thought to be completely lost in Th1 subset *in vitro* after multiple stimulations. Superantigens produced by different types of pathogens have been linked to autoimmune diseases. Superantigen-stimulation does not prime an adaptive immune response but causes a massive production of cytokines by CD4^{+} T cells. We hypothesized that superantigens are capable of stimulating Th1 cells to produce inflammatory cytokine, IL-17.

Methods: MOG$_{35-55}$-specific and herpes simplex virus (HSV)-specific CD4^{+} T cell clones were established from PBMC of healthy individuals. These CD4^{+} T cell clones were stimulated by each antigen respectively under Th17 polarizing conditions (with addition of IL-1, IL-6, TGF-beta, anti-IL-12 and anti-IFN-*f*ngamma) or cultured with bacterial superantigens, SEB or TSST-1. IL-17 and IFN-gamma production was determined by ELISA, double-color ELISPOT and intracellular cytokine staining.

Results: Upon repeated Ag-specific stimulation, Th1 clones proliferated specifically to MOG$_{35-55}$ and HSV respectively and produced IFN-gamma and IL-2, but did not produce IL-17. Various Th17-polarization conditions including co-stimulation with IL-1, TNF, IL-6, IL-23, TGF-beta in combination with anti-IL-12 and anti-IFN-gamma antibodies did not induce measurable IL-17 from these Th1 clones. However, superantigen-stimulation promoted both clones to produce IL-17 at a range of $0.5 - 1$ ng/1×10^5 cells. Combination of SEB and TSST-1 showed additive effect on IL-17 production by Th1 clone cells where IL-17 level was greater than 2 ng/1×10^5 cells. Using double-color ELISPOT assay, we found 30% of IFN-gamma-producing cells were positive for IL-17, suggests that superantigens promoted IL-17 production from highly polarized Th1 cloned cells. Interestingly, IL-17 production by these Th1 clones was blocked by anti-HLA class II or anti-TCR alpha/beta chain antibodies.

Conclusion: We have demonstrated that highly polarized Th1 clones can produce a significant amount of IL-17 in response to superantigen stimulation. Infections have been linked to exacerbation of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. Stimulating Th1 cells to produce IL-17 by superantigens of infecting pathogens may be responsible.

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Interleukin 12 Is Involved in an Interferon Type I Signature Through Crosstalk of CD4^{+} T Cells and Plasmacytoid Dendritic Cells. Corinne Miceli-Richard[1], Nicolas Gestermann[2], Federico Simoneta[2], Saida Boudaoud[2], Gaetane Nocturne[3], Yann Lecluze[4], Christine Bourgeois[2] and Xavier Mariette[3]. [1]Université Paris-Sud, Le Kremlin Bicêtre, France, [2]INSERM U1012, Le Kremlin Bicêtre, France, [3]Université Paris-Sud, Le Kremlin Bicetre, France, [4]Villejuif, France

Background/Purpose: STAT4 is a transcription factor involved in T_H1 polarization characterized by type II interferon (IFN) (or IFN-g) secretion and specifically activated by interleukin 12 (IL-12) binding on its receptor. Polymorphisms of STAT4 have been associated with rheumatoid arthritis, in which IFN-g may play a key role, but also with primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE), which are characterized by a type I IFN (IFN-a and IFN-β) signature. Moreover, a strong correlation was found between *STAT4* mRNA and type I IFN-induced gene mRNA expression in pSS. We aimed to elucidate the extent to which STAT4 could be involved in the type I IFN signalling pathway by investigating the effect of CD4^{+} T cells stimulation with IL-12 on the type 1 IFN signature.

Methods: CD4^{+} T cells (isolated by magnetic beads or cell sorting) from healthy controls were activated with anti-CD3 and anti-CD28 +/− IL-12, and then mRNA was extracted. CD4^{+} T cells and plasmacytoid dendritic cells (pDCs) were cultured with supernatants from CD4^{+} T cells under various conditions. mRNA expression of interferon-induced protein with tetratricopeptide repeats 1 (IFIT-1), interferon-induced transmembrane protein 1 (IFITM1), and protein kinase R (PKR), reflecting type I IFN signature, was analysed by quantitative PCR. Profiles of cytokines secretion by unstimulated CD4^{+} T cells compared with IL-12 stimulated CD4^{+} T cells was assessed using a 27-plex LUMINEX technology.

Results: CD4^{+} T cells isolated by magnetic beads showed upregulated type I IFN-induced genes after IL-12 stimulation in healthy controls: IFIT-1

(n=13) (p=0.0007), IFITM1 (n=6) (p=0.06) and PKR (n=6) (p=0.035). This effect was mediated by the secretion of type 1 IFN since it was abrogated by anti-IFNAR antibodies. Highly purified cell-sorted CD4^{+} T cells did not show any type I IFN signature under the same culture conditions, which suggests that a CD4^{+} cellular partner was excluded by cell sorting. This cellular partner was demonstrated to be pDCs, which express a low level of CD4. IL-12 alone did not induce a type I IFN signature in pDCs. CD4^{+} T cells–pDC crosstalk was necessary to induce this type I IFN signature after IL-12 stimulation of CD4^{+} T cells. GMCSF was highly induced in the supernatant of IL12-stimulated CD4^{+} T cells compared with unstimulated CD4^{+} T cells. Thus, IL-12-induced GM-CSF secretion by T cells might be a good candidate to induce the secretion of type 1 IFN by pDC.

Conclusion: IL-12 specifically induces type 1 IFN and a type I IFN signature through CD4^{+} T-cell–pDC crosstalk possibly via GM-CSF induction. These results could explain the implications of *STAT4* polymorphisms in type I IFN-dependent autoimmune diseases. Our data confirm that type I and II IFN-mediated autoimmune diseases are not in opposition and emphasizes the important role of IL-12. Thus, RA in one hand and SLE and pSS in another hand might be the "yin" and "yang" of activation by IL-12, which can stimulate both type I and type II IFN pathways pathways.

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Dynamic Regulation of T Follicular Helper Cell Differentiation Through STAT Signaling. Shingo Nakayamada[1], Yuka Kanno[2], Golnaz Vahedi[2], John J. O'Shea[2] and Yoshiya Tanaka[1]. [1]First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD

Background/Purpose: T follicular helper (Tfh) cells are a new subset of T cells that regulate B cell function and exert an important role in the pathogenesis of *autoimmune diseases*. However, their relationship with other helper lineages and the mechanisms that direct their specification are incompletely understood. As STAT family transcription factors play pivotal roles in specifying T cell lineages, we investigated the roles of STAT proteins in Tfh cell differentiation.

Methods: Naive CD4+ T cells isolated from wild type and STAT deficient mice were activated and cultured with various cytokines. Cytokine production and expression of cell surface molecules and transcription factors were assessed by flow cytometry and qPCR. Genome-wide targets of STATs and epigenetic modifications in Tfh-like cells were evaluated by chromatin immunoprecipitation sequencing (ChIP-seq) and DNaseI hypersensitivity sequencing (DNase-seq). Expression levels of mRNA were determined by microarray analysis.

Results: IL-12 acting STAT4 directly induced IL-21- and IFN-γ-producing cells, which share features of both Tfh and Th1 cells. Although IL-4 acting STAT6 had no effect for induction of IL-21 and IFN-g, IL-6 acting STAT3 generated cells that express IL-21 and not IFN-g. STAT4-indued IL-21 in turn acted through STAT3 in a positive feedback loop to maximize IL-21 production. Using ChIP-seq and DNase-seq, we found that both STAT3 and STAT4 directly bound to multiple genes involved in Tfh cell development including *Il21* and *Bcl6*, regulating gene expression and epigenetic modifications. Thus, STAT3 and STAT4 redundantly serve to induce IL-21, Bcl6 and other Tfh cell molecules. However, STAT4 also induced the transcription factor T-bet that repressed *Bcl6,* thereby attenuating the Tfh-like phenotype. IFN-γ-dependent activation of STAT1 induced T-bet, which produced a biphasic effect: early on it promotes, but later it inhibits, Tfh-like phenotype. Finally, the *Bcl6* locus remained accessible in fully polarized effector T cells, suggesting that although Bcl6 expression can vary with different states of differentiation; this locus remains poised for transcription even in the absence of active transcription.

Conclusion: These results highlight the importance of STAT-mediated gene regulation, which underlies plasticity of Tfh cells. Like Th17 cells, Tfh cells are a fluid subset and their differentiation represents a dynamic balance of signals mediated by STATs. Thus, modulation of STAT-mediated gene regulation in Tfh cells should offer opportunities for the treatment of autoimmune diseases.

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A Genetic Polymorphism on New Zealand Black Chromosome 1 Is Associated with Abnormal Dendritic Cell Function Leading to Expansion of T_H1, T_H17 and T Follicular Helper (T_{FH}) Cells. Nafiseh Talaei[1], Carolina Landolt-Marticorena[2], Babak Noamani[1], Evelyn Pau[1], Nan-Hua Chang[1] and Joan E. Wither[1]. [1]Toronto Western Research Institute, University Health Network, Toronto, ON, [2]University Health Network, Toronto, ON

Background/Purpose: We have previously shown that B6 mice with an introgressed homozygous New Zealand Black chromosome (c) 1 interval (70 to 100 cM) develop high titres of antinuclear antibodies and severe glomerulonephritis (GN), with approximately 40% of the mice dying by 8 months age. Using subcongenic mice with shorter intervals in this region we found that expansion of T_H1, T_H17, and T_{FH} cell populations was closely associated with the severity of GN. We further showed, using ovalbumin (OVA) as an exogenous antigen, that this was an intrinsic aspect of their immune system, resulting from a combination of T and non-T cell defects. In this report, we have investigated the role of dendritic cells (DC) in this expansion.

Methods: OVA-specific T cells from B6 or c1(70–100), c1(88–100), or c1(96–100) congenic OT-II TCR transgenic mice were adoptively transferred into B6.Thy1.1 or c1(70–100).Thy1.1 mice. Mice were immunized with OVA emulsified in CFA, sacrificed 2 weeks later, and the proportion of various splenic T cell subsets determined by flow cytometry, gating separately on Thy1.1[+] (recipient) and Thy1.2[+](transferred) T cells. Bone marrow-derived dendritic cells (DC) isolated from 8wk old c1(70–100), c1(88–100) and c1(96–100) congenic, and B6 control mice were cultured in the presence of LPS, imiquimod or CpG, or pulsed with OVA and co-cultured with naïve OT-II T cells. Production of cytokines (IL-12, IL-23, IL-6) by stimulated DC was analyzed by ELISA or flow cytometry.

Results: Adoptive transfer experiments revealed that the increased IFN-γ and IL-17 secreting cell differentiation in c1(70–100) congenic mice arises in part from intrinsic T cell defects localizing to the NZB c1 96–100 cM and 88–96 cM intervals, respectively. However, OT-II T cells from all mouse strains examined demonstrated enhanced differentiation to T_H1, T_H17, and T_{FH}populations when transferred into c1(70–100).Thy1.1 as compared to B6.Thy1.1 mice. This finding suggested that the increased differentiation of these T cell subsets in c1 congenic mice was also dependent upon cellular and/or cytokine cues provided by the c1(70–100) environment. Since, DC play an important role in the antigen presentation and cytokine secretion that directs T cell responses, DC function was contrasted in the various mouse strains. Following TLR stimulation, DC from c1(70–100) mice expressed significantly higher levels of MHC and co-stimulatory molecules, and secreted higher amounts of pro-inflammatory cytokines such as IL-6 and IL-12. Consistent with altered DC function, OVA-pulsed DC from c1(70–100) mice induced significantly increased differentiation of naïve OT-II cells to IFN-γ, IL-17 or IL-21 secreting cells as compared to B6 DC.

Conclusion: Our results suggest that a genetic polymorphism in the 70–88 cM interval of NZB c1 congenic mice alters DC function and acts together with intrinsic T cell defects to promote the expansion of T_H1, T_H17 and T_{FH} cells in c1(70–100) mice, resulting in severe GN.

Disclosure: N. Talaei, None; **C. Landolt-Marticorena**, None; **B. Noamani**, None; **E. Pau**, None; **N. H. Chang**, None; **J. E. Wither**, None.

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An Essential Role for TNF and PD-L1 in the Generation of Human CD8+CD25+Foxp3+ Regulatory T Cells That Are More Protective *in Vivo* Than CD4regs. David A. Horwitz, Stephanie Pan, Julie Wang and Song G. Zheng. Keck School of Medicine of USC, Los Angeles, CA

Background/Purpose: In addition to rare thymus-derived CD8+ regulatory/suppressor cells (CD8regs), several subsets of peripherally derived CD8regs have been described. We have recently induced ex-vivo a human CD8 subset that displays TNFR2 and PD-L1 and here consider whether these receptors are important in the generation and function of these CD8regs.

Methods: Naïve CD8+ cells were stimulated with anti-CD3/28 coated beads + IL-2 and TGF-β for 6 days. CD8regs were sorted into separated into TNFR2+, PD-L1+, double + and double - cells, and the suppressive activity of each subset assessed. In some experiments TNFR2 signaling was blocked by neutralizing TNF with TNFR-Fc (Enbrel), and effects of ligating PD-L1 with anti-PD-L1 were assessed. *In vivo* CD8reg activity was assessed by protection of NOD SCID CD8 chain−/− (NOG) mice from GVHD caused by human PBMC.

Results: The CD8regs expressed Foxp3, CD25^{high}, CD122^{high}, TNFR2 and CD103, and displayed the negative co-stimulatory receptors PD-1, PD-L1, Tim-3 and CTLA-4. TGF-β enhanced expression of. Foxp3, PD-1 and CD103, and inhibited CD80, CD86 and granzymes. Most remained naïve CD45RA+ cells. CD8regs produced both IL-2 and TNF. CD8regs preferentially targeted allogeneic cells both *in vitro* and *in vivo*. While we and others reported that both expanded natural and induced CD4regs doubled survival of NOG mice from GVHD, protection by CD8regs was 2 fold greater.

Sorted TNFR2+ PD-L1+ cells suppressed the proliferation of CD4+CD25- cells markedly greater than sham sorted cells. Single positive cells had activity similar to controls, but double negative cells lacked activity. Studies with TNFR-Fc and anti-PD-L1 suggested TNF significantly enhanced CD8 cell PD-L1 expression. Both agents inhibited Foxp3 expression. Neither affected activation (CD25 expression), but adding TNFR-Fc doubled the expansion of CD8 cells while anti-PD-L1 completely blocked expansion. Blocking TNF signaling resulted in a dose-related decrease in suppressive function of the CD8regs generated. By contrast, ligating PD-L1 with anti-PD-L1 doubled the suppressive activity of the CD8regs induced, and also doubled activity when added to the suppressor cell assay. Treating CD8regs with anti-IL-10R or a TGF-βR1 signaling inhibitor decreased GVHD protection *in vivo*, but both TNF-Fc and anti-PD-L1 lacked this effect.

Conclusion: These polyclonal CD8regs have a unique phenotype associated with remarkable *in vivo* suppressive activity. They display the negative co-stimulatory marker profile characteristic of chronically stimulated, "exhausted" CD8 cells, but differ in that they also express bright IL-2R, TNF-R2, CD103 and remain naive. Although anti-PD-L1 blocks the inhibitory co-stimulatory effects of PD-L1 expressed by APC and tumor cells, we found that anti-PD-L1 had the opposite effect on PD-L1 expressed CD8regs by enhancing both generation and suppressive function. Enhancement of CD8 PD-L1 expression by TNF via TNFR2 can be considered compensatory to this cytokine's pro-inflammatory effects. The inhibitory effects of TNFR-Fc on CD8reg generation, and the opposite effect of anti-PD-L1 may affect the clinical outcome of these agents when they are used in autoimmune diseases or cancer.

Disclosure: D. A. Horwitz, Athelos, 2; **S. Pan**, None; **J. Wang**, None; **S. G. Zheng**, None.

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PD-1 Signaling Promotes Suppressive Function of CD4^{+} Regulatory T Cells in (New Zealand Black × New Zealand White) F_1 Lupus-Prone Mice in a Dose-Dependent Manner. Maida Wong, Antonio La Cava and Bevra H. Hahn. University of California, Los Angeles, Los Angeles, CA

Background/Purpose: Programmed death-1 (PD-1) has been regarded as a negative regulatory signal in T cells. Our laboratory has shown that PD-1 is important in T cell regulation of autoimmunity, as treatment with neutralizing anti-PD1 Ab increased regulatory T cell function and dramatically delayed SLE onset in young BWF_1 females. We hypothesized that tight regulation of PD-1 signaling is required for maintenance of functional $CD4^+T_{reg}$ and subsequent control of autoimmunity in BWF_1 mice, and that regulatory capacity of the cells is sustained at least in part by resistance to apoptosis, resulting in $CD4^+T_{reg}$ survival, when PD-1 is expressed at a certain level – neither absent nor high.

Methods: A neutralizing Ab against PD-1 or control isotype-matched IgG were injected i.p. into BWF_1 mice. Foxp3 and PD-1 expression were assessed by flow cytometry. Splenocytes from these animals were isolated for *in vitro* culture, and anti-PD-1 Ab at various concentrations were added *in vitro* to test for B cell apoptosis by Annexin V and 7-AAD, and $CD4^+CD25^-$ helper T cell (T_h) proliferation by CFSE. AutoAb production of anti-dsDNA and total IgG was tested by ELISA in the supernatant.

Results: Blocking the full expression of PD-1 *in vivo* resulted in induction of $CD4^+CD25^+Foxp3^+T_{reg}$ with reduced, but not absent, PD-1 expression. These PD-1^{lo}$CD4^+T_{reg}$, compared to $CD4^+T_{reg}$ with PD-1^{hi} expression, had increased ability to induce B cell apoptosis and to suppress T_h proliferation. The PD-1^{lo}$CD4^+T_{reg}$ suppressed syngeneic B cells production of anti-dsDNA and IgG. Apoptosis was significantly lower in the PD-1^{lo}$CD4^+T_{reg}$. *In vitro* PD-1 blockade confirmed that tight regulation of PD-1 expression is important in maintaining $CD4^+T_{reg}$ suppressivity. By adding anti-PD-1 Ab >25 hg/ml *in vitro*, PD-1^{lo}$CD4^+T_{reg}$ from mice with *in vivo* PD-1 blockade lost their ability to induce B cell apoptosis and suppress T_h proliferation. On the other hand, PD-1^{hi}$CD4^+T_{reg}$ from the isotype controls became more suppressive with the presence of anti-PD-1 Ab *in vitro*, until its concentration was > 75hg/ml. The concentration of anti-PD-1 Ab did not affect the survival of $CD4^+T_{reg}$.

Conclusion: PD-1 expression is central in the ability of $CD4^+T_{reg}$ to suppress autoimmunity; their PD-1 expression has to be finely tuned to permit $CD4^+T_{reg}$ to survive and retain suppressive capacities. One mechanism by which PD-1 sustains $CD4^+T_{reg}$ is by reducing their susceptibility to apoptosis.

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Discovery of a Highly Potent, Selective Reversible Covalent Inhibitor of JAK3 Kinase. Ronald J. Hill[1], Angelina Bisconte[1], J. Michael Bradshaw[1], Ken Brameld[2], Eun Ok Kim[1], Xiaoyan Li[2], Tim Owens[2], Erik Verner[2] and David M. Goldstein[2]. [1]Principia Biopharma, South San Francisco, CA, [2]Principia Biopharma

Background/Purpose: Targeting of the JAK-STAT pathway has been shown to be efficacious for treatment of patients with rheumatoid arthritis through the successful use of pan-JAK inhibitors in clinical trials. To date, lack of selective JAK3 inhibitors has hindered the assessment of the role of JAK3 in autoimmune disorders. A JAK3 inhibitor has the potential benefit of alleviating undesirable side effects of JAK1 and JAK2 inhibition such as dyslipidemia and suppression of hematopoiesis, respectively. A new approach is presented to achieve potent, selective and durable inhibition of JAK3 by application of Principia's reversible covalent platform targeting a cysteine residue in the active site of JAK3 that is absent from other JAK family members. Ability of these inhibitors to block IL-2 and IL-4 signaling is presented.

Methods: Enzyme potencies were measured using the Caliper platform at Nanosyn Inc. (Santa Clara, CA). IL-2 stimulated phospho-STAT5 was measured in Ficoll separated human peripheral blood mononuclear cells (PBMCs) by flow cytometry. IL-4 stimulated STAT6 activation was measured in Ramos B cells based on a STAT6 reporter assay (Invitrogen, Madison, WI). Kinase profiling was performed at DiscoveRx (San Diego, CA).

Results: We have developed a series of molecules that are highly potent and selective for JAK3. Compound 1 inhibited JAK3 enzymatic activity with an IC_{50} of 0.5 ± 0.3 nM, but not JAK1, JAK2, or TYK2 up to a concentration of 5 uM. The selectivity among other kinases within the Cys sub-family was also high with no inhibition exceeding 60% at 1 uM. Profiling against a panel of 442 kinases confirmed the exceptional selectivity of the series. Compound 1 forms a durable yet reversible Cys interaction with JAK3 in biochemical assays with a dissociation half-life of 9 hours.

In cell-based assays, Compound 1 completely inhibited IL-2 stimulated STAT5 phosphorylation ($IC_{50} = 206 \pm 11$ nM) in hPBMCs, IL-4 stimulated STAT6 phosphorylation ($IC_{50} = 58 \pm 10$ nM) in Ramos B cells and IL-2 driven IFNgamma secretion ($IC_{50} = 248 \pm 8$ nM) in hPBMCs. IL-6 stimulated STAT3 phosphorylation was not inhibited up to 5 uM indicating complete cellular selectivity for JAK3 over JAK1. In addition, NFAT activation downstream of TCR stimulation in Jurkat T cells was not blocked.

Conclusion: Compound 1 is a potent, selective and durable inhibitor of JAK3 and has the potential to be an efficacious treatment for rheumatoid arthritis or other T cell driven diseases with a potential for differentiation from pan-JAK inhibitors.

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CGEN-15001, a Novel Negative Costimulatory Fusion Protein Is Effective in the Collagen-Induced Arthritis Mouse Model of Rheumatoid Arthritis. Iris Hecht[1], Kay McNamee[2], Ilan Vaknin[1], Anat Oren[1], Joseph R. Podojil[3], Galit Rotman[1], Eyal Neria[1], Stephen D. Miller[3] and Richard O. Williams[2]. [1]Compugen Ltd., Tel Aviv, Israel, [2]Oxford University, London, United Kingdom, [3]Northwestern University, Chicago, IL

Background/Purpose: CGEN-15001 is a recombinant Fc fusion protein consisting of the extracellular domain of CGEN-15001T, a protein predicted to be a member of the B7/CD28 costimulatory family. CGEN-15001T was identified using a proprietary discovery platform based on shared bioinformatic characteristics with known members of this family. The immunomodu-

latory effect of CGEN-15001 on T cell activity and its efficacy in the murine collagen-induced arthritis (CIA) model were evaluated.

Methods: Murine naïve CD4+ T cells were activated with plate bound anti-CD3 and either CGEN-15001 or control proteins. The effect of CGEN-15001 on activation marker expression and cytokine secretion was evaluated after 48hrs of incubation, while effects on cell division and apoptosis were evaluated after 96hrs. The effect of CGEN-15001T was studied using a similar experimental system utilizing HEK-293 transfected cells expressing CGEN-15001T or empty vector.

To study the effects of CGEN-15001 on T cell proliferation and differentiation, CD4+ T cells from DO11.10 mice were activated with $OVA_{323-339}$ plus irradiated APCs in the presence of Th driving conditions and either CGEN-15001 or control Ig. Proliferation was evaluated after 72hrs and cytokine secretion after 96hrs.

To study the effect of CGEN-15001 in the CIA model, DBA/1 mice (n=7–10/group) were immunized with type II bovine collagen in complete Freund's adjuvant. Mice were injected intraperitoneally with CGEN-15001, TNFR-Ig, CTLA4-Ig or Ig control at 100ug/mouse, three times/week for 10 days. Treatment started at onset of clinical arthritis and mice were scored daily for arthritis severity. On day 10 of arthritis, mice were sacrificed and paws were removed for histological analysis.

Results: CGEN-15001 as well as stably expressed CGEN-15001T, inhibited T cell activation demonstrated by inhibition of proliferation, inflammatory cytokine secretion and expression of early activation markers. CGEN-15001 elicited its immunomodulatory activity by skewing immune response from Th1/Th17 to Th2.

In the CIA model, CGEN-15001 demonstrated potent therapeutic efficacy when administered to mice with existing disease. Treatment with CGEN-15001 resulted in significant inhibition of clinical symptoms including joint swelling, erythema, and stiffness compared to mice treated with Ig control. Histological analysis of the diseased joints showed reduced inflammation and joint erosion compared to the control.
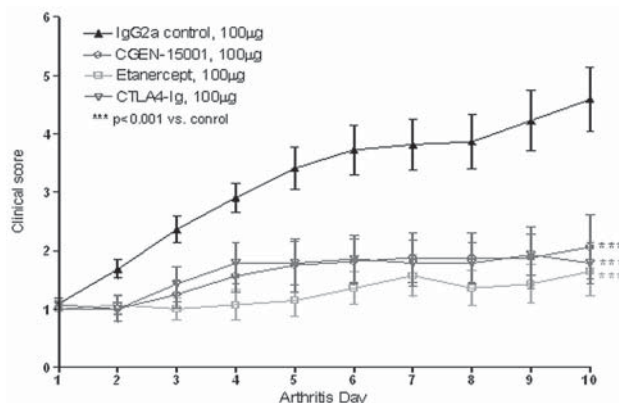
Conclusion: These results as well as data showing long term efficacy of CGEN-15001 in murine models of multiple sclerosis, support the therapeutic potential of CGEN-15001 in the treatment of rheumatoid arthritis and other autoimmune diseases. The therapeutic use of negative co-stimulators to keep the immune system in check promises to provide an efficacious and safe approach to the treatment of autoimmune diseases.

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A Novel Method for Quantitative and Functional Analysis of Autophagy Using Flow Cytometry in Activated Human Primary T Cells. Ryu Watanabe, Hiroshi Fujii, Yukiko Kamogawa, Kyohei Nakamura, Tsuyoshi Shirai, Yumi Tajima, Shinichiro Saito, Tomonori Ishii and Hideo Harigae. Tohoku University, Sendai, Japan

Background/Purpose: Autophagy is an evolutionally conserved self-degradation system. In this process, an isolation membrane engulfs cytoplasmic materials and organelles to form an autophagosome. The autophagosome then fuses with the lysosome, leading to the degradation of the enclosed materials to recycle or energy production. Autophagy is considered to play important roles in activated T cells to counteract various cellular stresses, and it would

be a potential therapeutic target in chronic inflammatory diseases. Although several methods to measure autophagy were developed, it is not easy to quantify autophagic activity in small number of human primary cells. The aim of this study is to develop a high sensitive and high throughput method for quantitative and functional analysis of autophagy in human primary T cells using flow cytometry.

Methods: Human naïve and effector memory CD4+ T cells were isolated from peripheral blood and stimulated with anti-CD3 and anti-CD28 antibody. Two days after stimulation, GFP-LC3 fusion protein which can function as an autophagy sensor was overexpressed in human activated T cells using retroviral vector system. To inhibit autophagy, dominant negative form of ULK1 (ULK1-DN) was overexpressed in human activated T cells. Autophagic activity and cell death were quantified in naïve and effector memory CD4+ T cells.

Results: Using Western blotting and electron microscopy, we confirmed that autophagy was induced in activated T cells and the reduction of fluorescence intensity of GFP-LC3 correlated with autophagy (Fig.1). Compared to naïve T cells, effector memory T cells had significantly lower autophagic activity (p=0.025) and were susceptible to apoptotic cell death (p=0.01). Overexpression of ULK1-DN inhibited autophagic flux and induced more apoptotic cell death in naïve and effector memory T cells. In these autophagy-defective naïve CD4+ T cells, mitochondria volumes and reactive oxygen species were increased. In contrast, enhancement of autophagy by rapamycin reduced apoptotic cell death in naïve and effector memory CD4+ T cells.
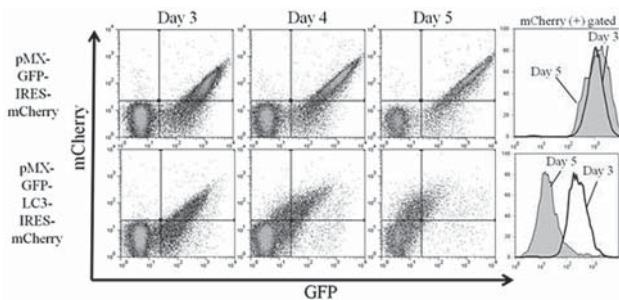
Fig 1. The GFP-LC3 fluorescence intensity was reduced in activated T cells, indicating that autophagy was induced in activated human primary T cells.

Conclusion: We established a novel method for measuring autophagic flux in activated human primary T cells. Using this assay, we first identified that effector memory CD4+ T cells had lower autophagic activity than naïve CD4+ T cells and this lower autophagic activity may contribute to more apoptotic cell death in effector memory CD4+ T cells. This novel method is helpful to examine pathological roles of autophagy and investigate autophagy as a potential therapeutic target in collagen diseases.

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Increase of CD4$^+$CD25$^+$FoxP$_3$$^+$ T Cell in Patients with Systemic Sclerosis Could Secret IL-17 with Dysfunction of Immunosuppression. Xinjuan Liu[1], Na Gao[1], Mengtao Li[1], Dong Xu[1], Yong Hou[1], Qian Wang[1], Guohua Zhang[1], Qiuning Sun[1], Henghui Zhang[2] and Xiaofeng Zeng[1]. [1]Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China, [2]Peking University, People's Hospital, Beijing, China

Background/Purpose: Immune unbalance between Th17 and regulatory T cells (Treg) is a characteristic of systemic sclerosis (SSc). The functional heterogeneity and differentiation dynamics can be clearly shown by separating Treg cells into three subsets based on the expression of FoxP$_3$ and CD45RA. The aim of this study was to investigate subsets levels of Treg from the patients with naive SSc and assess their roles in the immune balance between Treg and Th17.

Methods: Peripheral blood from 31 patients with SSc and 33 health controls were collected. Peripheral blood mononuclear cells (PBMCs) were prepared and analyzed for the expression of CD4, CD25, CD45RA, CTLA-4, CD69, CD279, GITR, FoxP3 and IL-17 with flow cytometry. Measuring Treg suppressive capacity against proliferation of CD4$^+$CD25$^-$ T cells in

coculture experiments by a CFSE based. The expression of FoxP$_3$, CTLA-4, IL-17A and RORC mRNA were studied with real-time PCR.

Results: (1)The frequency of CD4$^+$CD25$^+$FoxP$_3$$^+$Treg cells were significantly elevated in patients with SSc (3.62±1.14) compared with controls (1.97±0.75, P<0.001), but the expression of CTLA-4 and its mRNA were lower in Treg cells of SSc patients compared with control with diminished immunosuppression capacity.

(2) In the patients with SSc, the frequency of CD45RA$^-$FoxP$_3$^{high} activated Treg cells (aTreg,FrII) were lower than control (0.25±0.16 vs 0.66±0.41 among CD4+, P<0.001; 12.42±5.23 vs 30.01±1.74 among Treg, P<0.001),CD45RA$^-$FoxP3^{lo} T cell (FrIII) were higher than control(6.23±2.29 vs 2.90±0.91 among CD4+, P<0.001; 73.71±9.62 vs 57.96±9.90 among Treg, P<0.001),There were no significant difference in two groups with CD45RA$^+$FoxP3^{lo}Treg cells (rTreg,FrI),which were relatively lower in Treg cells (1.87±0.94 vs 1.63±0.97 among CD4+, P=0.320; 23.19±10.60 vs 29.63±11.77 among Treg, P=0.025).

(3)In the patients with SSc, immunosuppressive capacity of aTreg and rTreg cells were diminished,FrIII cells had no immunosuppressive capacity neither in the patients with SSc nor with control; in the patients with SSc, the expression of CTLA-4 in the surface of FrII and FrIII cells were decreased significantly (P<0.001,respectively), and CTLA-4 mRNA expression in FrII were decreased.

(4) The expression of IL-17 were higher in FrIII cells than FrI and FrII cells in both groups (P<0.001,respectively),but there were no difference of FrIII between these two groups; Th17 cells were increased in the patients with SSc (P<0.001); in the patients with SSc, CD25$^+$FoxP$_3$$^+$IL17$^+$cells among CD4$^+$ cells were increased(0.075±0.032 vs 0.049±0.027, P=0.029),but no difference of CD25$^+$FoxP3$^+$IL17$^-$with control; the expression of IL-17A and RORC mRNA were increased in the FrIII cells of SSc patients(P<0.001,respectively).

Conclusion: Decreased aTreg with functional deficiency and increased CD45RA$^-$FoxP$_3$^{lo} T cells could explain increased Treg with dysfunction in the patients with SSc, which were the reasons of unbalance of Treg and Th17 cells in the patients with SSc too. Increased Treg cells were not the real regulatory T cells, but non-suppressive CD45RA$^-$FoxP$_3$^{lo} cells, which is the main provider for FoxP$_3$$^+$IL-17$^+$ cells without immunosuppressive capacity.

Disclosure: X. Liu, None; **N. Gao**, None; **M. Li**, None; **D. Xu**, None; **Y. Hou**, None; **Q. Wang**, None; **G. Zhang**, None; **Q. Sun**, None; **H. Zhang**, None; **X. Zeng**, None.

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Mucosal-Associated Invariant T Cells Are Inactivated by IFNα and Reduced in Systemic Lupus Erythematosus. Asako Chiba[1], Naoto Tamura[2], Ran Matsudaira[2], Takashi Yamamura[1], Yoshinari Takasaki[2] and Sachiko Miyake[1]. [1]National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan, [2]Juntendo University School of Medicine, Tokyo, Japan

Background/Purpose: Mucosal-associated invariant T (MAIT) cells are a subset of innate-like lymphocytes which are restricted by the MHC-related molecule-1 (MR1) and express an invariant TCRα chain:Vα7.2-Jα33 in humans and Vα19-Jα33 in mice with a limited set of Vβ chains. Although the function of MAIT cells is not well known, like other innate-like lymphocytes, MAIT cells have been suggested to play both proinflammatory and regulatory roles in autoimmune models. We previously demonstrated that MAIT cells exerted a suppressive activity on T cells and the frequency of MAIT cells was reduced in patients with multiple sclerosis. In this study, we sought to investigate mechanisms by which MAIT cells are activated/inactivated and whether MAIT cells are relevant to other human autoimmune diseases including systemic lupus erythematosus(SLE).

Methods: Whole blood samples or peripheral blood mononuclear cells (PBMC) of SLE patients as well as healthy volunteers were stained with anti-human monoclonal antibodies(mAb) against CD3, $\gamma\delta$TCR, invariant Vα7.2TCR, and CD161 and analyzed by FACS. MAIT cells were identified as CD3$^+$$\gamma\delta$TCR$^-V\alpha$7.2TCR$^+$CD161^{high}cells. PBMC or FACS sorted MAIT cells were labeled with CellTrace Violet dye and stimulated with anti-CD3mAb and anti-CD28mAb or various types of cytokines. 6–7 days later, the cell proliferation was analyzed by FACS.

Results: As previously demonstrated, the frequency of MAIT cells of healthy controls was about 5% among T cells. The percentages of MAIT cells of SLE patients were 10-fold lower compared with those of healthy subjects. MAIT cells proliferated upon TCR stimulation when cultured with other PBMC. However, sorted MAIT cells failed to respond to anti-CD3mAb and anti-CD28mAb stimulation. MAIT cells and $\gamma\delta$T cells were activated and proliferated by IL-15 even without exogenous TCR stimuli. MAIT cell

proliferation was markedly suppressed by IFNα, but IFNα had little effect on TCR-stimulated γδT cell proliferation.

Conclusion: This study demonstrates that MAIT cell activation greatly depends on cytokines. As IFNα is known to be related to the pathogenesis of SLE, the abnormal balance of cytokines may be responsible to the reduced frequency of MAIT cells in SLE.

Disclosure: **A. Chiba**, None; **N. Tamura**, None; **R. Matsudaira**, None; **T. Yamamura**, None; **Y. Takasaki**, None; **S. Miyake**, None.

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The Effects of Anti–Tumor Necrosis Factor Agents On the Expansion of T Helper-Type 17 Cells Driven by Lipopolysaccharide-Stimulated Monocytes. Gianluca Fossati[1], Louise Healy[1] and Andrew Nesbitt[2]. [1]UCB Pharma, Slough, United Kingdom, [2]UCB Pharma, SLough, United Kingdom

Background/Purpose: T helper-type 17 (Th17) cells are proinflammatory CD4+ cells characterized by the production of Interleukin-17 (IL-17).There is evidence that IL-17 and other cytokines which Th17s produce such as IL-21 are involved in the pathogenesis of RA.[1] Lipopolysaccharide (LPS)-stimulated monocytes can promote differentiation of CD4+ cells into Th17 cells and produce IL-17 in vitro.[2] This study examined the effect of 4 anti–tumor necrosis factor (TNF) agents (adalimumab, etanercept, infliximab, and certolizumab pegol) on the expansion of CD4+CD45RO+ memory T cells into Th17 cells driven by LPS-stimulated monocytes.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from healthy volunteers. Monocytes and CD4 + T cells were purified from the PBMC by positive and negative selection, respectively. CD4+CD45RO+ memory T cells were enriched from the CD4+ T cell fraction by positive selection. Purified monocytes and memory T cells were co-cultured at a 1:1 ratio for 7 days with CD3/CD28 Human T-Activator Dynabeads with and without 1 μg/mL LPS. Cells were cultured in the presence and absence of the 4 anti-TNF agents at 10 μg/mL. After 7 days the CD4+ T cells were stained for intracellular Interferon γ (IFNγ) and IL-17A and analyzed by flow cytometry. IL-17A and IL-17F secretion into the supernatant was determined by ELISA.

Results: CD4+ T cells positive for IL-17A were increased from 5.7% in the control co-cultures without LPS to 20.5% with LPS (mean of 2 experiments). The frequency of IFNγ-positive CD4+ T cells showed a smaller increase from 4.4% to 10.6% when LPS was added. IL-17A and IFN-γ were expressed largely by different cells, suggesting the expansion of both Th17 and Th1 T-helper subsets. The frequency of IL-17A-producing CD4+ T cells in co-cultures of monocytes and memory T cells plus LPS in the presence of the 4 anti-TNF agents were roughly 2.5 -fold lower than the LPS-positive control cultures generated in the absence of anti-TNF agents (mean of 4 experiments). Cells exposed to the 4 anti-TNF agents showed a similar level of CD4+ cells producing IL-17A and IFNγ. The level of IL-17A secreted into the supernatant decreased from 580 pg/mL in the LPS positive control to 180 pg/mL in co-cultures generated in the presence of the 4 anti-TNF agents. IL-17F decreased from approximately 8 ng/mL to 2 ng/mL in the LPS control and the anti-TNF exposed cultures, respectively (mean of 4 experiments). There were no significant differences in the concentration of IL-17A or IL-17F from co-cultures exposed to the 4 different anti-TNF agents.

Conclusion: The increased frequency of IL-17+ T cells and secretion of IL-17A and IL-17F suggest that LPS-activated monocytes support the expansion of Th17 cells present within the memory pool. Exposure to anti-TNF agents inhibited Th17 expansion and IL-17A production. This suggests that part of the mode of action of anti-TNF agents may be to reduce Th17 expansion and, as a consequence, IL-17A and IL-17F concentration. It is unclear whether soluble TNF or membrane TNF is responsible for this activity.

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2. Evans H, et al. Proc Natl Acad Sci U S A. 2009;106:6232–6237.

Disclosure: **G. Fossati**, UCB, 3; **L. Healy**, UCB, 3; **A. Nesbitt**, UCB, 1, UCB, 3.

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Suppression of PP2Ac Causes DNA Hypermethylation Through Enhanced Pmek/Perk Activity in T Cells. Katsue S. Watanabe[1], Kamalpreet Nagpal[2] and George C. Tsokos[2]. [1]Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background/Purpose: Although many reports have focused on the impaired MEK-ERK signaling pathway in T cells from systemic lupus erythematosus (SLE) patients which results in suppression of DNA methyltransferase (DNMTs) expression and induction of gene transcription of methylation-sensitive genes, the involved mechanisms are still unclear. Here we investigated whether the catalytic subunit of protein phosphatase 2A (PP2Ac) which is overexpressed in SLE T cells contributes to inhibition of MEK-ERK signaling and DNA methylation.

Methods: Human peripheral CD3 positive T cells from normal subjects were treated with the selective chemical inhibitor, okadaic acid (OA) or transfected with siPP2Ac to achieve sufficient suppression of the PP2Ac enzymatic activity. After stimulation with PMA and ionomycin, DNA, RNA and protein were extracted. The ratio of phosphorylated over total MEK and ERK protein were determined by western blotting. The enzyme activity of DNMTs and the level of global DNA methylation status were calculated by ELISA. The transcription level of two methylation sensitive genes, CD70 and CD11a was quantified by real time RT-PCR.

Results: Chemical suppression or siRNA silencing of PP2Ac in T cells resulted in sustained phosphorylation of MEK and ERK following stimulation with PMA and ionomycin compared to T cells in which PP2Ac was not manipulated. PP2Ac suppression resulted in increased DNMT enzymatic activity of DNMT, DNA hypermethylation and decreased expression of methylation-sensitive genes.

Conclusion: Our results demonstrate that PP2A regulates DNA methylation levels by influencing the phosphorylation levels of the MEK/ERK pathway. We propose that enhanced PP2Ac in SLE T cells may dephosphorylate and activate the upstream signaling pathway of DNMT and disturb the tight control of methylation-sensitive genes such as CD70 and CD11a which are involved in SLE pathogenesis. In addition, based on our previous report that PP2Ac itself is regulated though DNA methylation around a cAMP response element (CRE) binding site located in the proximal promoter, and therefore PP2A may represent a potent accelerator of DNA demethylation through an additional positive feedback mechanism.

Disclosure: **K. S. Watanabe**, None; **K. Nagpal**, None; **G. C. Tsokos**, None.

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A Novel Subset of CD4 T Cells That Provides Help for Human Memory B Cell Responses. Sang T. Kim, Jin Young Choi, Begona Lainez and Joseph E. Craft. Yale University School of Medicine, New Haven, CT

Background/Purpose: Follicular helper T (Tfh) cells provide help to B cells in germinal centers (GCs) of secondary lymphoid organs (SLOs) following primary antigen (Ag) challenge, with formation of memory B and long-lived plasma cells. Memory B cells can be recalled in secondary responses upon Ag rechallenge, with generation of short-lived plasmablast or secondary GCs with further rounds of B cell maturation. Human memory B cells function better *in vitro* with T cell help; however, the nature of the T cells that provide such help is unclear, with the role of Tfh cells, if any, not known. Our goal is to identify and characterize human memory B helper T cells.

Methods: Tonsils were obtained from tonsillectomies (2–18 y) done at Yale New Haven Hospital, with cells used for flow cytometry, qPCR, and cytokine analyses. Autologous CD4 T cell and B cells were co-cultured for immunoglobulin (Ig) production, as a readout for T dependent B cell maturation. Confocal microscopy was performed to localize memory B cells and helper T cells.

Results: We found that human Tfh cells, as defined by classical flow cytometry markers (CXCR5hi PD-1hi), can be subdivided into two groups based upon expression of P-selectin glycoprotein ligand-1 (PSGL-1), a cell surface protein that in synergy with the T cell homing marker (CCR7) dictates residence in the T cell zone of SLOs. PSGL-1lo CXCR5hi PD-1hi cells reside in B cell follicles as Tfh cells, whereas we found by confocal microscopy that PSGL-1hi CXCR5hi PD-1hi cells reside in T cell zones outside B cell follicles. We defined the latter PSGL-1hi CXCR5hi PD-1hi cells as triple hi cells (Thi), finding that except for their location in T cell zones and PSGL-1 expression, they shared with GC-resident Tfh cells a similar surface marker profile. Yet, by contrast to Tfh cells, Thi cells expressed more CCR7 with lower expression of the follicular homing marker CXCR5, findings consistent with their T zone location. Bcl6, the master transcriptional regulator for Tfh cells, was expressed in both populations at equivalent levels, but expression of Blimp1, a regulator of effector T cell development, was higher in Thi cells. Tfh cells and Thi cells produced comparable levels of IL-21; however, Tfh cells produced more IL-4 while Thi cells exclusively produced IL-10, with the latter important in provision of B cell help. Memory B cells produced more Ig when co-cultured with Thi cells than other CD4 subsets, with such help

contact dependent and reliant upon CD40L, IL-21, and IL-10; moreover, Thi cells preferentially associated with memory B cells as T-B cell couplets in flow cytometry compared to Tfh cells. Confocal microscopy showed co-localization of Thi cells and memory B cells at the T-B border. Thi cells were also found in human spleens.

Conclusion: We have identified a population of B T helper T cells in SLOs that promote maturation of memory B cells in a cytokine- and contact-dependent manner, with localization at the border of the T cell zone and B cell follicles in SLOs. They are distinct from classical GC-resident Tfh cells, and are likely critical for antibody recall responses. Their further characterization should pave the way for new understanding of human immune memory responses in normal and autoimmune subjects.

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T-Cell Cross Reactivity with Citrullinated Antigen and *P. Gingivalis* Membrane Antigen Following Infection with *P. Gingavalis* and/or Injection of Citrullinated Mouse Type II Collagen in DBA/1J Mice. Michael J. Duryee[1], Anand Dusad[1], Carlos D. Hunter[1], Ke Ren[1], Dong Wang[2], James R. O'Dell[3], Lynell W. Klassen[3], Ted R. Mikuls[4] and Geoffrey M. Thiele[3]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Univ of Nebraska Medical Ctr, Omaha, NE, [3]Univ of Nebraska Med Ctr, Omaha, NE, [4]Omaha VA and University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Recently, periodontal disease (PD) has been associated with the risk and progression of RA. Patients with RA complicated by PD have been shown to have higher anti-citrullinated protein antibody (ACPA) levels, which have also become predictive markers of the disease and its severity. Previous studies have demonstrated that RA can be induced in mice following oral infection with *P. gingivalis (P. ging)*, a major cause of PD. However, these studies never demonstrated antibody or T-cell responses to citrullinated antigens. Therefore, it was the purpose of this study to determine whether infection with *P. ging* can induce RA and if these responses induce antibodies and/or T-cell responses to select citrullinated antigens in DBA/1J mice.

Methods: DBA/1J mice were subjected to sulpha-methoxazole in their water for 10 days and then gavaged with *P. ging* 3 times over a 1 week period. Control mice were subjected to antibiotics in the absence of *P. ging* and injected with mouse type II collagen collagen (Col). Also, mice were immunized with citrullinated Col (Cit-Col) in parallel as previously published. Animals were evaluated weekly for inflammation of the joints for 6 weeks and sacrificed followed by serum and spleen collection. The $CD4^+$ T cells were then isolated and proliferated against Col, Cit-Col or *P. ging* outer membrane antigen (PGMA). Serum was tested for the presence of antibody to PGMA and ACPA, the latter using a second generation anti-CCP assay.

Results: At week 6, mice gavaged with *P. ging* had a significant increase in inflammation as assessed by paw thickness (2.883 mm) and scoring (3.25) compared to the respective controls (2.543 mm) and (1.6); P≤0.01 between groups. Similar results were demonstrated for the Cit-Col groups, 2.868 mm and 3.25 (P≤0.001vs. controls). There was nearly a 2-fold increase in serum ACPA in the *P. ging* infected mice (11.2 U/ml) compared to no infection (6.89 U/ml) (p=0.002). The Cit-Col injected animals showed an ACPA response of 10.8 U/ml which was significantly different from controls (P=0.02). Antibody to PGMA was significantly higher in both the *P. ging* infected animals (4.101 µg/ml) and the Cit-Col (2.714 µg/ml) injected mice compared to controls (1.201 µg/ml) (P≤0.01 for both groups). $CD4^+$ T-cells from *P. ging* infected mice proliferated to both Cit-Col (5.34 stimulation index (SI)) and to PGMA (16.68 SI) compared to controls which had SI's of (0.160) and (0.704) respectively P≤0.001. T-cells from mice immunized with Cit-Col proliferated to Cit-Col at (3.950 SI) and to PGMA at (4.829 SI). This proliferative response was not observed with exposure of T-cells from both *P.ging* or Cit-Col injected mice to *P.intermedia* (an alternative cause of PD) membrane antigen.

Conclusion: These data show that following infection with *P. ging*, DBA/1J mice develop an inflammatory arthritis that is characterized by the expression of ACPA. Furthermore, T-cells from mice immunized with Cit-Col or infected with *P. ging* showed increased proliferation to both Cit-Col and PGMA. This suggests a cross reactivity between the PGMA and the citrullinated antigen. These studies begin to provide some insight into mechanisms linking *P. ging* with RA pathogenesis.

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Increased TSLP Expression in Joints of Rheumatoid Arthritis Patients Causes Increased Activation of Intra-Articular Myeloid Dendritic Cells with Enhanced Th1 and Th17 Cell Activity. F.M. Moret, C.E. Hack, T.R.D.J. Radstake, J.W.J. Bijlsma, F.P.J.G. Lafeber and J.A.G. van Roon. University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: Thymic stromal lymphopoietin (TSLP) is well known for its potent activation of myeloid dendritic cells (mDCs) to induce Th2-mediated immune responses. Administration of TSLP in a collagen-induced arthritis model was expected to inhibit Th1 and Th17-driven arthritis by the induction of Th2 activity. However, this resulted in an enhanced severity of inflammation and joint destruction. Additionally, prevention of TSLPR signalling strongly reduced Th17-driven experimental arthritis and immunopathology. The present study determined the levels of TSLP and numbers of TSLPR-expressing mDCs in joints of rheumatoid arthritis (RA) patients as compared to peripheral blood (PB) and studied the capacity of TSLP to induce mDC-dependent T-cell activation.

Methods: TSLP was measured in synovial fluid (SF) of patients with RA (n=50) and osteoarthritis (OA, n=24) by ELISA. CD1c mDC numbers and TSLPR expression on these cells were assessed by FACS analysis in paired samples of SF and PB from RA patients (n=9). CD1c mDCs, isolated from PB as well as SF of RA patients (n=6), were stimulated with TSLP for 20 hours and cytokine production was measured by multiplex immunoassay (measuring 51 cytokines). Washed TSLP-activated CD1c mDCs from PB (n=11) and SF (n=5) were added to autologous CD4 T cells in the absence of additional stimuli, cultured for 6 days and subsequently proliferation was measured. Additionally, T-cell cytokine production was measured (by ELISA) upon restimulation with ionomycin/PMA.

Results: TSLP levels in SF of RA patients were significantly increased compared to OA patients (mean 297 vs. 80 pg/ml, resp., p<0.01). mDCs numbers from SF were significantly increased compared to PB (5.0% vs. 0.6%, resp., p<0.01) and expressed increased levels of TSLPR (MFI 24 vs. 15, resp., p<0.01). TSLP significantly stimulated the production of chemokines TARC and MIP1α by mDCs from PB and SF (TARC: PB from 1 to 42 pg/ml, p<0.05 and SF from 26 to 186 pg/ml, p<0.05; MIP1α: PB from 1268 to 5486 pg/ml, p<0.05 and SF from 2776 to 3733 pg/ml, p<0.05). Upon incubation with TSLP, TSLPR-expressing mDCs from PB potently stimulated proliferation of autologous CD4 T cells as compared to unstimulated mDCs (ratio T cell:DC 5:1, from 1503 to 16036 cpm, p<0.01). However, TSLP-mDCs from SF had a strongly increased capacity to activate CD4 T cells (ratio T cell:DC 5:1, from 26395 to 57387 cpm, p<0.05). Enhanced proliferation was associated with increased production of IFNγ (ratio T cell:DC 5:1, PB from 179 to 655 pg/ml, p<0.01 and SF from 601 to 1867 pg/ml, p<0.05), IL-17 (PB from 39 to 353 pg/ml, p<0.05 and SF from 363 to 1382 pg/ml, p<0.05), and IL-4 (PB from 17 to 246 pg/ml, p<0.01 and SF from 193 to 775 pg/ml, n.s.).

Conclusion: Our data indicate that increased intra-articular TSLP concentrations in RA potently activate TSLPR-expressing mDCs from SF to secrete enhanced levels of proinflammatory mediators causing T cell chemotaxis and to potently increase arthritogenic T cell activation. This suggests that TSLP and TSLPR-expressing mDCs could both play an essential role in the immunopathology of RA.

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Elevated Frequency of Synovial Interleukin-21$^+$ CD4$^+$ T Cells Co-Expressing Tumor Necrosis Factor-a in Rheumatoid Arthritis. Maria C. Lebre[1], Pedro L. Vieira[2], Saïda Aarrass[1], Thomas Newsom-Davis[2], Paul P. Tak[3] and Gavin R. Screaton[2]. [1]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam The Netherlands, Amsterdam, Netherlands, [2]Imperial College London, London, United Kingdom, [3]Academic Medical Center, University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting synovial tissue in multiple joints. The inflammatory process in RA is regulated by several cytokines, especially TNF, which is produced not only by macrophages and dendritic cells (DC) but also by activated antigen-specific CD4$^+$ T helper cells. IL-21 is a T cell-derived cytokine that has been implicated in several autoimmune diseases, including RA. Both activated CD4$^+$ T cells and T follicular helper cells (TFh) secrete

this inflammatory cytokine. IL-21 regulates T helper 17 cells and antibody production by B cells and induces osteoclastogenesis, mechanisms that contribute to RA pathology. In addition IL-21R blockade ameliorates arthritis in mice. Taking into account the recent literature we investigated whether IL-21 might play a role in RA.

Methods: Expression of surface markers and cytokine production at the single cell level in peripheral blood (PB) and matched synovial fluid (SF) from RA (n=13) and psoriatic arthritis (PsA, n=6) patients, as compared to PB of healthy control (HC) subjects (n=17), was evaluated by flow cytometry following PMA/ionomycin stimulation ex-vivo. IL-21 concentrations were assessed by ELISA in cell-free SF samples of RA (n=15), PsA (n=14) and OA (n=5) patients and in 6 days supernatants of RA (n=6) and spondyloarthropathy (SpA, n=5) synovial biopsy cultures. In addition we dissected the in vitro requirements for the differentiation of human IL-21-secreting CD4+ T cells from naive T cells.

Results: We observed significant expansions of $CD4^+$ T cells secreting IL-21 in RA SF compared to matched PB (p<0.0001). Interestingly, while the % of IL-21$^+$ CD4$^+$ T cells in PB did not differ between RA, PsA and HC, the % of both total IL-21$^+$ and IL-21$^+$TNF-a$^+$ CD4$^+$ T cells in RA SF were significantly increased compared to PsA (p=0.0140 and p=0.0038, respectively). The % of IL-21$^+$ CD4$^+$ T cells in RA PB was positively correlated with DAS28 (r=0.592, p=0.033), serum anti-cyclic citrullinated peptide (anti-CCP) antibodies (r=0.788, p=0.001) and rheumatoid factor (RF; r=0.691, p=0.009). In addition, the % of IL-21$^+$ CD4$^+$ T cells in anti-anti-CCP$^+$ or RF$^+$ patients was significantly higher compared to anti-CCP$^-$ (p=0.03) and RF$^-$ (p=0.01) patients respectively. The levels of IL-21 present in SF did not differ between RA and PsA but there was trend towards elevated levels of this cytokine in RA SF compared to OA SF (p=0.06). RA synovial biopsies released significantly higher levels of IL-21 compared to SpA (p=0.03). Synovial IL-21-secreting CD4$^+$ T cells did not phenotypically fit the TFh cell paradigm in that they did not express CXCR5. In humans, differentiation of naive CD4$^+$ T cells into IL-21-secreting cells in vitro was preferentially driven by IL-21 and/or IL-6 in the additional presence of transforming growth factor-β.

Conclusion: IL-21 and IL-21 blocking therapy is now being tested in a number of diseases. The results of this study enhance the rationale for a trial of IL-21 blockade in RA where it may provide a useful adjunct in those patients refractory to or unable to tolerate anti-TNF therapy.

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Therapeutic Promotion of CD8 CTL by CpG Oligodeoxynucleotides (ODN) in an Induced Model of Lupus. Maksym Puliaiev, Kateryna Soloviova and Charles S. Via. Uniformed Services University of Health Sciences, Bethesda, MD

Background/Purpose: In addition to TcR signaling and costimulation, CD8 T cells require a third signal to mature into effector cytotoxic T lymphocytes (CTL). In pathogen models, interferon alpha (IFN-a) and IL-12 can serve as signal 3. In the parent-into-F1 (P->F1) model, there are no exogenous pathogens yet B6->B6D2F1 mice exhibit robust donor anti-host CD8 CTL resulting in >90% elimination of host splenocytes i.e. acute graft-vs.-host disease (GVHD). Transfer of the DBA parent (DBA->F1) results in DBA CD4-driven host B cell expansion and lupus (chronic GVHD) due to a failure of CD8 CTL supporting the idea that promoting CD8 CTL by enhancing signal 3 molecules may be beneficial in lupus.

Methods: Following donor cell transfer, host splenocytes were analyzed by real time PCR and flow cytometry. To promote signal 3 molecules, three TLR-9 simulating CpG ODNs (2006, 1826 or 2336) were administered to DBA->F1 mice (100 micrograms i.p.) during the first 5 days after transfer.

Results: For untreated DBA->F1 mice, there was no significant elevation of IL-12 gene expression and transient, low level (5–10 fold) elevations of IFN-a inducible (IFI) genes (MX-1, OAS-1) during the first two weeks after donor transfer. Long term, IFI gene expression in the setting of severe lupus renal disease was similarly low level for DBA->F1 mice. DBA->F1 mice receiving CpG ODN s exhibited a robust donor anti-host CD8 CTL response and profound host B cell elimination at two weeks for CpGs 2006 and 1826. CpG 2336 prevented chronic GVHD associated host B cell expansion but did

not significantly reduce B cells below normal F1 values. Only CpGs 2006 and 1826 induced strong (30–60 fold) IL-12 and IFI-gene expression at 6 hours after administration to normal F1 mice supporting the idea that the ability of a TLR9 CpG ODN to induce CTL is related to its ability to induce signal 3 molecules IL-12 and/or IFN-a. Surprisingly, we found no evidence that either IL-12 or IFN-a are critical for the robust CD8 CTL response in B6->F1 mice. Acute GVHD phenotype was not significantly altered in BDF1 mice by transferring B6 donor T cells deficient in either IFN-a receptor or IL-12 receptor beta nor by treating with anti-IL-12 mAb however disease could be blocked by transferring B6 donor T cells deficient in TNF receptor 2 (TNFR2) but not TNFR1.

Conclusion: These results support the conclusion that in the absence of pathogens, failure of down regulatory CD8 CTL permits CD4 T cell driven lupus. Conversely, induction of IL-12 and/or IFN-a can rescue defective CD8 CTL in DBA->F1 mice and abort lupus raising the possibility that CTL promotion may be worthy of further study as a potential lupus treatment. Our results demonstrating a critical role for TNF in CD8 CTL responses in the absence of pathogens raise concerns that therapeutic TNF blockade in humans may impair CD8 CTL responses to non-pathogens (tumors, autoantigens) and raise the risk of certain tumors and humoral autoimmunity as described for some TNF-blocking agents.

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1,25(OH)$_2$D$_3$ Modulates the Migration Pattern of Th17 Cells From Patients with Rheumatoid Arthritis. Wendy Dankers[1], Jan Piet van Hamburg[2], Patrick S. Asmawidjaja[1], Nadine Davelaar[3], Hoyan Wen[1], Anne-Marie Mus[1], Edgar Colin[2], Johannes van Leeuwen[1], Johanna M.W. Hazes[4] and Erik Lubberts[1]. [1]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [2]Erasmus MC, Rotterdam, Netherlands, [3]Erasmus MC, University Medical Center, Rotterdam, Rotterdam, Netherlands, [4]Erasmus Medical Center, Rotterdam, Netherlands

Background/Purpose: Vitamin D has suppressive effects on autoimmune diseases, such as rheumatoid arthritis (RA). Within these diseases, T-helper-17 (Th17) cells have been implicated to play a crucial role in the development and progression of persistent inflammation. Recently, we have shown that Th17 cells are able to activate synovial fibroblasts of patients with RA (RASF) resulting in a pro-inflammatory feedback loop. This leads to increased production of pro-inflammatory cytokines and tissue-degrading enzymes. We have found that the active vitamin D compound, 1,25(OH)$_2$D$_3$, has direct suppressive effects on Th17 cells from patients with early RA. In addition 1,25(OH)$_2$D$_3$ is capable of inhibiting the pro-inflammatory feedback loop between Th17 cells and RASF. The objective of this study is to identify molecular targets of 1,25(OH)$_2$D$_3$ signaling underlying this suppressive action of 1,25(OH)$_2$D$_3$ in Th17 cells.

Methods: Primary Th17 cells were sorted from peripheral blood of treatment naïve patients with early RA. They were cultured with or without 1,25(OH)$_2$D$_3$ alone or together with RASF. From these cultures gene-expression profiles were generated. Expression of genes of interest was confirmed by Q-PCR and/or specific ELISA.

Results: In the presence of 1,25(OH)$_2$D$_3$, protein expression of Th17 associated cytokines IL-17A and IL-22 was inhibited, while in contrast the anti-inflammatory cytokine IL-10 was induced. These findings were supported by the gene-expression profiles from these cultures. Furthermore, 1,25(OH)$_2$D$_3$ inhibited transcription of the cytokine receptors IL-23R and IL-7R, which are involved in Th17 survival and proliferation. Chemokines CCL20 and CXCL10 were down-regulated and chemokine receptors CCR2, CXCR6, CXCR3 and CCR10 were up-regulated. Importantly, Rorγt, which is critically involved in Th17 differentiation and function and the cell-size regulator and oncogene c-Myc were down-regulated by 1,25(OH)$_2$D$_3$.

Conclusion: From these findings, we concluded that 1,25(OH)$_2$D$_3$ modulates the expression of genes involved in cytokine production, proliferation, and migration of Th17 cells. These data indicate that 1,25(OH)$_2$D$_3$ not only suppresses Th17 cell activity but also regulates Th17 phenotype stability and migration of these cells to sites of tissue inflammation in RA.

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Lowering Fli1 Levels Decreases the Levels of Lipid Mediators in the Kidneys and T Cells of MRL/Lpr Lupus Prone Mice. Marlene Bunni[1], Zainab Amani[1], Andrew Mather[1], Jennifer Berglind Schepp[1], Leah Siskind[1] and Tamara K. Nowling[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC

Background/Purpose: The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Lowering the global levels of Fli1 in two lupus mouse models significantly improved kidney disease and prolonged survival. Lowering the levels of Fli1 in hematopoietic cells in MRL/lpr lupus mice resulted in significantly improved kidney disease. The mechanism(s) by which Fli1 exerts this protective effect is unknown. The glycosphingolipid lactosylceramide (LacCer) is a ganglioside precursor to which sialic acid (SA) residues are added by ganglioside synthases or removed by sialidases. Loss of SA residues from gangliosides on the surface of podocytes is linked to proteinuria in glomerulonephritis and lipids with distinct chain lengths are thought to possess distinct biological activities. We demonstrate that lowering Fli1 levels decreases the levels of LacCer and the sialidase Neu1 in the kidney cortex and in T cells of MRL/lpr lupus prone mice. We present additional data demonstrating that Fli1 regulates Neu1 promoter activity in T cells.

Methods: Kidney and/or spleen were harvested from 17–19 week-old MRL/MpJ mice and MRL/lpr Fli1+/+ and Fli1+/− mice. T cells were isolated by negative selection from spleen and left unstimulated or stimulated with anti-CD3/CD28. Supercritical Fluid Chromatography coupled with tandem mass spectrometry was performed on kidney cortex homogenates and isolated T cells to quantify LacCer. Gene expression was analyzed by real-time RTPCR on RNA isolated from kidney cortex and T cells. Immunohistochemistry for LacCer was performed on frozen kidney sections. Neu1 promoter activity was examined by co-transfection of Neu1 promoter/reporter constructs and a Fli1 expression construct in human and mouse T cell lines.

Results: Diseased MRL/lpr mice express a significant 2.5-fold increase in the major LacCer species C16 in the kidney compared to age-matched MRL/MpJ, which do not exhibit kidney disease. MRL/lpr mice that are heterozygote for Fli1 (Fli1+/−) express a significant 2-fold decrease in LacCer C16 in the kidney compared to wild-type age-matched MRL/lpr mice. Similarly, a significant reduction in LacCer staining in cells of the glomeruli is observed by immunohistochemistry. Neu1 expression is significantly elevated 40-fold in the MRL/lpr compared to the MRL/MpJ kidney cortex, but is not significantly different in the MRL/lpr Fli1+/− compared to the wild-type MRL/lpr kidney cortex. Interestingly, Neu1 is reduced 3–4-fold and LacCer levels are significantly reduced 2.5-fold in T cells isolated from Fli1+/− compared to Fli1+/+ MRL/lpr mice. Over-expression of Fli1 results in a dose-dependent increase in Neu1 promoter activity in activated T cells.

Conclusion: Our results demonstrate that one mechanism by which reducing Fli1 levels may be protective in lupus kidney disease is to decrease LacCer levels through the regulation of Neu1 expression. We speculate that Fli1 regulates Neu1 expression in T cells that may act on gangliosides intra- (within the T cell) and inter- (on neighboring kidney cells upon infiltration in the kidney) ceullarly.

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A Numeric Expansion of Invariant Natural Killer T Cells Protects Against the Progression of Fatal Autoimmunity in Lupus-Prone Mice. Yuriy Baglaenko[1], Nan-Hua Chang[1], Evelyn Pau[2], Christina Loh[1] and Joan E. Wither[1]. [1]Toronto Western Research Institute, University Health Network, Toronto, ON, [2]Toronto Western Hospital, University Health Network, Toronto, ON

Background/Purpose: Previous studies from our lab have shown that the introgression of a NZB chromosome 1 (c1) interval extending from 135 to 179 Mb onto the non-autoimmune C57BL/6 (B6) background results in increased B and T cell activation, elevated anti-nuclear antibodies (ANA), and fatal kidney disease. Similar introgression of a NZB c4 interval with mapped susceptibility loci extending from 30 to 150Mb onto the B6 background

resulted in the expansion of splenic invariant Natural Killer T (iNKT) and CD5^{+} B cells in the absence of autoimmunity. To define the role of NZB c4 in autoimmunity, bicongenic (c1c4) mice were produced with both NZB c4 and c1 intervals. Despite the presence of c1 autoimmune augmenting genes, c1c4 mice had reduced renal disease, increased survival, and a shift towards less pathogenic IgG1 autoantibodies. Interestingly, bicongenic mice had retained an expansion of splenic iNKT cells. Recent studies have shown that activated iNKT cells can rapidly secrete large quantities of Th1 or Th2 cytokines, thereby altering the progression and initiation of autoimmunity. In this study we sought to define the role of iNKT cells in the suppression of spontaneous autoimmunity.

Methods: NKT cells were stimulated *in vivo* by intravenous injection with 2μg of α-GalCer. Cellular phenotypes were examined by flow cytometry of de novo splenocytes. Intracellular production of IFNγ, IL-17, and IL-4 was measured by flow cytometry following 4 to 5 hour stimulation with PMA and Ionomycin.

Results: The functional capacity of NKT cells was examined by *in vivo* stimulation with α-GalCer. Following activation, there was a significant decrease in the frequency of IFNγ and IL-4 producing splenic iNKT cells in c1 and c1c4 mice when compared to B6 and c4 controls. However, the expansion of splenic iNKT cells normalized the total number of IFNγ and IL-4 producing iNKT cells in c1c4 mice to B6 levels. In order to more conclusively define the role of iNKT cells in initiation and progression of spontaneous autoimmunity, CD1d knockout mice were bred onto the suppressed bicongenic background. Characterization of aged CD1d knockout bicongenic mice, that lack NKT cells, revealed an increase in germinal center B cells, memory/effector T cells, and IL-17 or IFNγ producing T cells when compared to bicongenic mice. The CD1d knockout had no impact on the number of IL-10 producing CD5^{+}B cells.

Conclusion: These data suggest that suppressed bicongenic mice have a normalization of iNKT cell cytokine production through a numeric expansion. Furthermore, knockout of NKT cells on the suppressed background resulted in an increase in cellular activation suggesting a protective role for iNKT cells in the pathogenesis of spontaneous autoimmunity.

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Exacerbation of Collagen-Induced Arthritis by an Anti-CD3 Antibody Targeting Aminoterminal-Deficient CD3ε. María J. Pérez-Lorenzo[1], Elena Gonzalo[1], José M. Rojo[2], María Galindo[1], Jose L. Pablos[1] and Gabriel Criado[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Centro de Investigaciones Biológicas-CSIC, Madrid, Spain

Background/Purpose: We have previously characterized naturally occurring forms of CD3e that lack the aminoterminal region (DNH2-CD3e) and are bound with high avidity by the YCD3-1 antibody (Criado et al., Eur J. Immunol 30, 1469). The presence of high levels of DNH2-CD3e results in weaker TCR-CD3 interactions and increased TCR mediated signalling and functional responses. To understand the potential contribution of DNH2-CD3e to arthritis development, we have evaluated disease progression and functional responses in collagen-induced arthritis after treatment with YCD3-1 antibody.

Methods: Arthritis was induced in 8–10 weeks old male and female DBA/1 mice by intradermal immunization with 200 mcg of chicken type II collagen (CII) in Complete Freund Adjuvant (CFA). Mice were treated on the day of arthritis onset with YCD3-1 or control rat IgG2$_b$ (50 mcg/mouse) and arthritis severity was evaluated daily during ten days. Effect of anti-CD3 treatment in vivo was assessed by flow cytometry to detect Treg (FoxP3^{+}), Th1 (IFNg[+]) and Th17 (IL17^{+}) CD4 T cells in lymph nodes. To analyze T cell responses in vitro, lymph node cells were stimulated with CII, proliferation was measured by incorporation of the colorimetric reagent WST-1 and IFNg and IL17 levels were quantified by ELISA. Serum levels of anti-CII antibodies were determined by ELISA. Statistical differences were analyzed by ANOVA and Mann-Whitney U-test using GraphPad Prism software. P values < 0.05 were considered significant.

Results: Treatment of CIA mice with YCD3-1 increased disease severity in female DBA/1 mice compared to control-treated mice. Differences appeared the first day after treatment and reached statistical significance on day five and later (Figure 1). A similar trend was observed in arthritic males, although differences did not reach statistical significance. Levels of anti-CII antibodies were not affected by YCD3-1 treatment.
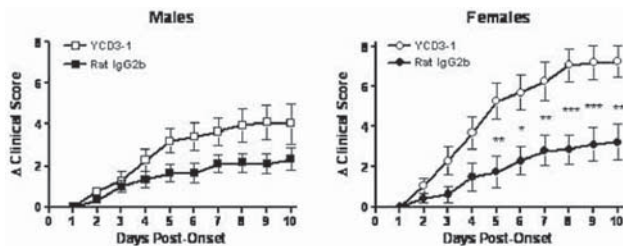
Figure 1. Severity of CIA in male and female DBA/1 mice treated with YCD3-1 anti-CD3 antibody.

Analysis of CD4 T cell populations in YCD3-1 treated mice showed an enrichment in FoxP3^{+} Treg cells (16.85 ± 4.7 % vs 10.25 ± 2.57% in control mice, **P= 0.003). IFNg and IL17 producing cells were also increased (IFNg: 2.77 ± 2.07 % vs 0.79 ± 0.25 %, **P= 0.003; IL17: 1.74 ± 1.01 % vs 0.64 ± 0.23 %, ***P= 0.0003). Ratio of Treg to Th17 cells was reduced (10.91 ± 3.18 % vs 17.95 ± 7.21 %, P= 0.04). No significant differences were observed in Treg/Th1 ratio. In vitro stimulation with CII caused higher proliferation and production of IFNg and IL17 in lymph node cells from anti-CD3 treated mice.

Conclusion: Targeting DNH2-CD3e in vivo reduces Treg/Th17 ratio and exacerbates collagen induced arthritis. Our results suggest that DNH2-CD3e can contribute to arthritis progression.

Disclosure: M. J. Pérez-Lorenzo, None; E. Gonzalo, None; J. M. Rojo, None; M. Galindo, None; J. L. Pablos, None; G. Criado, None.

2342

Synovial Tissue Analysis in the Pre-Clinical Phase of Arthritis: T-Cell Infiltration Preceding the Development of Arthritis. Maria J. H. de Hair[1], Marleen G. H. van de Sande[1], Tamara H. Ramwadhdoebe[2], Robert B. M. Landewé[3], Christiaan van der Leij[4], Mario Maas[4], D. van Schaardenburg[5], Danielle Marie Gerlag[1], Lisa G.M. van Baarsen[2] and Paul P. Tak[6]. [1]Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Division of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [4]Department of Radiology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [5]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [6]Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: We have previously shown in a pilot study that there is no evident synovial inflammation in autoantibody-positive individuals who are at risk of developing rheumatoid arthritis (RA), compared to healthy controls. Here, we investigated in a larger, prospective cohort whether subtle changes in the synovium are associated with the development of clinically manifest arthritis in RA-prone individuals.

Methods: Fifty-five IgM rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) positive individuals, without evidence of arthritis upon physical examination who are at risk for developing RA, were included in the study. All individuals underwent MRI and arthroscopic synovial biopsy sampling of a knee joint at inclusion, and were prospectively followed for arthritis development. Biopsies were analysed by immunohistochemistry using antibodies for T cells (CD3, CD4, and CD8), B cells (CD22), fibroblast-like-synoviocytes (CD55), plasma cells (CD138), von Willebrand Factor and citrullinated fibrinogen. Proportional hazard regression analysis was performed to investigate associations of (combinations of) variables with onset of arthritis over time.

Results: After a median follow-up time of 13 (IQR 6–27, range 1–47) months, 15 individuals (27%) developed arthritis. Synovial expression of CD3+ T cells was associated with arthritis development (Hazard ratio: 2.8; 95% confidence interval: (0.9 to 9.1; p=0.088)), although not statistically significant. Combined with ACPA-positivity CD3 expression was highly associated with arthritis development (double-positive vs. single-positive or double-negative (HR (95%CI): 4.0

(1.4 to 11.4); p=0.010)). The expression of other inflammatory cell markers as well as MRI-findings were not associated with arthritis development.

Conclusion: The results presented here suggest that synovial T cell infiltration might play a role in arthritis development in autoantibody-positive individuals who are at risk of developing RA.

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The Therapeutic Antibody Tregalizumab (BT-061) Induces Activation of Regulatory T Cells by Engaging a Unique CD4 Mediated Signaling That Strongly Differs From Signaling Events Induced by Standard Anti-CD4 Antibodies. Bianca Helling[1], Benjamin Daelken[1], Holger Wallmeier[2], Silke Aigner[1], Chantal Zuber[1], Martin Koenig[1], Andre Engling[1], Frank Osterroth[1], Niklas Czeloth[1] and Christoph Uherek[1]. [1]Biotest AG, Dreieich, Germany, [2]Condor Scientific Computing & Consulting, Sulzbach, Germany

Background/Purpose: The humanized CD4 specific monoclonal antibody (mAb) tregalizumab is currently being tested in phase II clinical trials in Rheumatoid Arthritis. In contrast to other anti-CD4 antibodies, tregalizumab is able to activate the suppressive properties of regulatory T cells (Tregs). Since tregalizumab was the first and only humanized anti-CD4 antibody described to be able to activate Tregs we asked for the underlying reason for this specific and unique functionality. To elucidate on the mode of action of this mAb, we focused on the signaling pathways engaged by tregalizumab.

Methods: Signaling events after cross-linking of tregalizumab, other anti-CD4 antibodies (RPA-T4, MT310, QS4120 or B-A1) or anti-CD3 (OKT-3) treatment were analyzed using intracellular staining of phosphorylated proteins (Lck, ZAP-70, LAT, SLP-76, PLC-gamma, MEK, Itk, ERK, PKC, MAPK and NF-kappaB). Furthermore, the ability of tregalizumab to induce suppressive properties in Tregs was evaluated using a mixed lymphocyte reaction system. Other CD4 antibodies were included as controls. Additionally, the binding mode of tregalizumab to soluble CD4 was resolved by co-crystallization and subsequent x-ray crystallography with a resolution of 2.9 angstrom.

Results: Upon binding of tregalizumab to the CD4 molecule on T cells and subsequent cross-linking, an intracellular signal was induced. As described for anti-CD3 or other anti-CD4 antibodies, phosphorylation of the CD4 associated kinase Lck was observed. Nonetheless, significant signaling strength differences were observed between the different antibodies. Although tregalizumab induced the lowest phosphorylation signal on Lck, further downstream molecules were also activated. Tregalizumab mediated signaling additionally led to phosphorylation of ZAP-70, LAT, SLP-76, PLC-gamma and MEK, thus engaging several components of the T cell receptor pathway. However, tregalizumab induced no phosphorylation of Itk, ERK, PKC, MAPK and NF-kappaB as observed for anti-CD3 treatment or other anti-CD4 antibodies tested. Although inducing the weakest signal of all anti-CD4 antibodies, only tregalizumab was able to induce full functional activation of Tregs via CD4.

The new mode of action of tregalizumab may be explained by the special binding epitope. While all other tested anti-CD4 antibodies bound to domain 1 of CD4, the crystal structure of tregalizumab in complex with CD4 revealed binding to domain 2.

Conclusion: In summary, we hypothesize that binding to domain 2 of CD4 may be the underlying reason for inducing weak but unique signaling in CD4 T cells that is sufficient to activate the function of Tregs without activation of T effector cells. Thus, tregalizumab represents a unique and novel mode of action for treatment of autoimmune diseases with insufficient Treg activity. A phase IIb clinical trial is currently ongoing in Rheumatoid Arthritis in european countries to further evaluate clinical use of tregalizumab (Biotest Study 979).

Disclosure: B. Helling, Biotest AG, 3; B. Daelken, Biotest AG, 3; H. Wallmeier, Biotest AG, 5; S. Aigner, Biotest AG, 3; C. Zuber, Biotest AG, 3; M. Koenig, Biotest AG, 3; A. Engling, Biotest AG, 3; F. Osterroth, Biotest AG, 3; N. Czeloth, Biotest AG, 3; C. Uherek, Biotest AG, 3.

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Transcriptional Regulation of Garp Expression. Sonja Haupt, Qihui Zhou, Johannes Thomas Kreuzer, Simon Herrmann, Hendrik Schulze-Koops and Alla Skapenko. University of Munich, Munich, Germany

Background/Purpose: Regulatory T cells (Tregs) contribute to immune tolerance and play a pivotal role in the prevention of autoimmune diseases such as rheumatoid arthritis (RA). In active RA, the suppressive function of Tregs is markedly reduced. Recently, a membrane-associated molecule, glycoprotein A repetitions predominant (GARP), has been identified to be specifically expressed on Tregs in response to activation. While the function of GARP is not completely understood, diminution of GARP expression attenuates the suppressive capacity of Tregs. Therefore, we hypothesized that diminished expression of GARP on the surface of Tregs in RA patients might be responsible for their reduced suppressive function. To provide insight, we investigated in detail the molecular mechanisms of GARP transcription and analyzed GARP expression on Tregs from RA patients.

Methods: To delineate transcriptional mechanisms of GARP expression, human GARP promoter sequences and several CNS regions were cloned into reporter vectors. Their transcriptional activity in response to different stimuli was assessed. To analyze the chromatin configuration state in primary Tregs, chromatin immunoprecipitation of GARP promoters and CNS regions in activated and non-activated Tregs was performed. In order to investigate GARP expression, CD25$^+$ and CD25$^-$ CD4 T cells were purified from peripheral blood, and GARP expression was compared between eight RA patients with early active disease (disease duration 3.0 ± 2.4 months, DAS28 5.2 ± 1.2) and an age- and gender-matched healthy cohort.

Results: Two different transcript variants under the control of different promoters (denoted as promoter 1 and 2) are encoded by the GARP gene. Whereas GARP promoter 1 activity was dependent on TCR stimulation and the presence of Forkhead box protein 3 (Foxp3), the master transcription factor of Tregs, Foxp3 and retinoic acid synergistically induced transcription from GARP promoter 2 in a concentration dependent manner. Histone modifications in both promoter regions and in an upstream located CNS changed towards a more accessible chromatin configuration upon T cell activation. When GARP expression was analyzed in primary T cells, only CD25$^+$ Foxp3-expressing CD4 T cells upregulated GARP, confirming Treg specificity of GARP expression and its Foxp3 dependency. The upregulation of GARP expression upon stimulation was however less pronounced on Tregs from RA patients as compared to healthy controls.

Conclusion: Thus, GARP expression is attenuated in RA patients. As transcriptional activity of the GARP gene is initiated by coordinate action of TCR stimulation, Foxp3 and retinoic acid on two promoters and one CNS region, alterations of these control mechanisms in RA might cause diminished GARP expression and subsequently might result in the reduced suppressive capacity of Tregs in RA.

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HRES-1/RAB4-Mediated Loss of DRP1 Inhibits Mitophagy, Promotes Accumulation of Mitochondria and Serves As Target for Treatment in SLE. Tiffany Telarico[1], David Fernandez[1], Zachary A. Oaks[2], Gergely Talaber[2], Mark Haas[3], Michael P. Madaio[4] and Andras Perl[5]. [1]SUNY Upstate Medical University, Syracuse, NY, [2]SUNY, Syracuse, NY, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Medical College of Georgia, Augusta, GA, [5]Upstate Medical University, Syracuse, NY

Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) exhibit accumulation of mitochondria and activation of the mammalian target of rapamycin (mTOR). Although mTOR has been implicated in blocking of autophagy and may account for increased mitochondrial mass, paradoxically, blockade of mTOR with rapamycin failed to reduce mitochondrial mass in lupus T cells. mTOR interacts and co-localizes with the small GTPase HRES-1/Rab4 on endosomes that carry autophagocytic cargo, including mitochondria, to lysosomes. Therefore, we investigated whether HRES-1/Rab4, that is over-expressed in lupus T cells, may mediate the accumulation of mitochondria and whether its inhibition by geranylgeranyl transferase inhibitor, 2-[3-pyridinyl]-1-hydroxyethylidene-1,1-

phosphonocarboxylic acid (3-PEHPC) can influence the development of disease in lupus-prone mice.

Methods: Microarray and confirmatory western blot as well as glutathione-S-transferase pull-down assays were used to map the interactome of HRES-1/Rab4 in human peripheral blood lymphocytes. Expression of Rab4, the murine homolog of HRES-1/Rab4, and its interacting partners were assessed with respect to mitochondrial mass and mTOR activity in the thymus and spleen cell subsets of lupus-prone MRL/lpr and C57BL/6, MRL/MpJ, and Black 6/lpr control mice at ages of 4 and 8 weeks. MRL/lpr mice were treated with 125 μg/kg 3-PEHPC or 1 mg/kg rapamycin in comparison to solvent controls for 10 weeks, beginning at 4 weeks of age. Disease development was monitored by antinuclear antibody (ANA) production and proteinuria. At the time of sacrifice, nephritis was assessed by histopathology, serum cytokine levels were measured by ELISA, gene expression in splenocyte subsets was measured by western blot, and mitochondrial homeostasis was evaluated by flow cytometry. Statistical analyses were done by t-tests and ANOVA, with $p<0.05$ considered significant.

Results: HRES-1/Rab4 was found to directly interact with Drp1and its overexpression caused the depletion of Drp1 in human Jurkat cells ($p=0.01$) and mouse splenocytes ($p=0.03$). Rab4A was over-expressed in MRL/lpr thymocytes at 4 weeks ($p=0.0002$). Drp1 is reduced in MRL/lpr T cells at 4 weeks ($p=0.007$). MRL/lpr mice exhibited increased mitochondrial mass in thymocytes ($p=0.02$) at 4 weeks and in splenocytes ($p=0.01$) at 8 weeks of age. At 14 weeks of age, treatment with 3-PEHPC increased Drp1 ($p=0.03$) and reduced mitochondrial mass in MRL/lpr T cells ($p=0.02$), reduced ANA production ($p=0.021$), reduced proteinuria ($p=0.00004$), and reduced nephritis scores in MRL/lpr mice ($p<0.001$). Unlike 3-PEHPC, rapamycin reduced mTOR activity ($p<0.05$) but failed to affect mitochondrial mass. IL-10 production was reduced by 3-PEHPC ($p=0.04$), while rapamycin reduced production of IFN-γ ($p=1 \times 10^{-5}$) and IL-17A ($p=0.01$).

Conclusion: These data reveal a pathogenic role of Drp1 depletion and identify the regulation of mitophagy by HRES-1/Rab4 as a promising target for treatment in SLE.

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MHC II-Independent Regulation of Intestinal Tregs. Lisa L. Korn and Terri M. Laufer. University of Pennsylvania, Philadelphia, PA

Background/Purpose: Regulatory T cells (Tregs) are critical to prevent autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis. Like all CD4+ T cells, CD4+ Tregs expressing the transcription factor Foxp3 develop in the thymus, though Tregs also are generated in the periphery from naïve CD4+ T cells. T cell receptor (TCR)-major histocompatibility complex class II (MHC II) signals are necessary for thymic Treg generation and provide antigen-specific signals in the periphery. Yet the role of MHC II signals in peripheral Treg maintenance has remained unclear, or in cases of tissue sites such as intestine, unstudied.

Methods: To dissect the role of MHC II in intestinal Treg maintenance, we examined K14/Abb (K14) mice that have MHC II restricted to cortical thymic epithelium but lack peripheral TCR-MHC II interactions.

Results: Intestinal Treg frequency was increased in mice lacking peripheral expression of MHCII. Treg proliferation was equivalent in the intestinal lamina propria of young K14 and wild type mice; however, proliferation of conventional T cells was MHC II-dependent. The initial MHC II-independent Treg accumulation was not due to increased homing directly from the thymus, as intestinal Tregs in young K14 mice were not enriched for recent thymic emigrants (RTEs). Intestinal Tregs were maintained in adult K14 mice when, in contrast to young mice, Treg and Tconv proliferation and turnover were similar to wild type. In all adult mice the intestine contained no Treg RTEs. However, depletion of microbial gut flora by antibiotics in adult K14 mice partially restored the Treg frequency to wild type levels.

Conclusion: These data suggest that the intestine specifically contains a niche for regulatory T cells that does not require MHC II signals to be filled, but may rely on MHC II-independent, intestinal flora-derived signals to be subsequently maintained. These cells may represent a tissue-specific mechanism to prevent autoimmunity.

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Specificity of the New American College of Rheumatology/European League Against Rheumatism Classification Criteria for Polymyalgia Rheumatica in Comparison with the Former Ones: A Single Centre Study. Pierluigi Macchioni[1], Luigi Boiardi[2], Mariagrazia Catanoso[2], Giulia Pazzola[2] and Carlo Salvarani[3]. [1]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [3]Arcispedale S Maria Nuova. IRCCS, Reggio Emilia, Italy

Background/Purpose: To evaluate the specificity of the new ACR/EULAR classification criteria for PMR in a consecutive series of outpatients attending an early arthritis clinic (EAC).

Methods: All patients attending our outpatients EAC are followed according to a standardized protocol which include clinical examination, determination of laboratory parameters, quality of life questionnaires and ultrasound (US) examination of shoulders, hips, hands and feet. In this 3-year prospective study we included consecutive patients aged > 50 years followed for at least 12 months. Patients entered the study if they had a definite diagnosis of non-PMR inflammatory joint condition confirmed at 12 month follow-up period according to rheumatologist opinion (PM). The PMR group consisted of 136 recent onset, consecutive patients seen in our rheumatological centre during a 5 year period. C statistic were utilized to compare the new ACR/EULAR classification criteria with some of the former diagnostic/classification criteria (Hunder's, Jones's, Bird's, Healey's criteria).

Results: One hundred and twenty-eight non PMR patients entered the study (mean age 64.2+9.9y, female 70.3%, mean disease duration at first visit 12.47+9.0 w, mean ESR 35.13+25.3 mm/1sth, mean CRP 2.04+2.48 mg/dl). After one year of follow up their diagnosis was: rheumatoid arthritis (RA) 96 pts, spondyloarthropaty 32 pts.

Table 1 shows the specificity and area under the curve (AUC) of the receiver operating characteristic curves when conditions were met in the total group and in the RA patients group(*).

Specificity and AUC in the total group and in the rheumatoid arthritis patients group(*)

PMR diagnostic/ classification criteria	Specificity (128 total cases)	AUC (SE)	Specificity* (96 RA patients)	AUC* (SE)
ACR/EULAR	81.5	0.872 (.029)	79.7	0.863 (.031)
US-ACR/EULAR	91.4	0.917 (.023)	89.9	0.910 (.025)
HEALEY	80.2	0.799 (.033)	78.3	0.773 (.035)
HUNDER	79.0	0.777 (.034)	78.3	0.789 (.036)
BIRD	72.8	0.742 (.036)	72.5	0.740 (.038)
JONES	96.7	0.810 (.030)	98.6	0.816 (.030)

Conclusion: In a series of outpatients attending our EAC the new ACR/EULAR PMR classification criteria have a better specificity as compared to the previous criteria (except for Jones's one). US shoulders and hips examination increases the specificity of the new ACR/EULAR criteria.

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Plasma Fibrinogen Better Identifies Persistent Disease Activity in Polymyalgia Rheumatica Than Either ESR or CRP. EM McCarthy[1], Paul A. MacMullan[1], S. Al-Mudhaffer[1], Anne M. Madigan[1], S. Donnelly[1], C. J. McCarthy[1], Dermot Kenny[2], Eamonn S. Molloy[3] and G M. McCarthy[1]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]RCSI, Dublin 2, Ireland, [3]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: In PMR careful tailoring of the glucocorticoid dosage to the patients needs is crucial to avoid the risk of treatment-related adverse effects and the disability associated with uncontrolled inflammation. The ESR and CRP are standard assays used to guide assessment of disease activity. Studies have demonstrated a discordance between ESR and CRP of 28% making assessment of disease activity a diagnostic challenge. Any biomarker that accurately reflects disease activity in PMR, thereby facilitating appropriate adjustment of glucocorticoid dose would be welcomed. Previously we have demonstrated that plasma fibrinogen is more specific for the confirmation of response to treatment than either ESR or CRP. Here we prospectively compare the ability of the biomarkers ESR, CRP and fibrinogen to distinguish between disease remission and disease activity in PMR.

Methods: 25 patients with newly diagnosed PMR and 35 patients with a known diagnosis were assessed at baseline and 6 weeks. Patients were divided into disease remission(Group 1) or persistent disease activity(Group 2),based on the Polymyalgia Rheumatica Activity Score (PMR-AS). A PMR-AS < 1.5 indicates disease remission with a PMR-AS >1.5 reflecting persistent disease activity. Plasma fibrinogen, CRP and ESR were assayed. An ESR value of 20mm/hr and CRP of 6mg/L(lab normal <5mg/l) were considered the upper limit for detection for remission. The upper limit of the lab normal for Fibrinogen(4g/L) was used. Sensitivity, specificity, positive predictive values and likelihood ratios was calculated for all biomarkers.

Results: Data was available from 120 patient visits. Mean age was 71.8 years.Demographic data was similar between groups. A significant difference was observed in steroid dose between groups(10mg v 3.5mg p<.001).

All biomarkers were significantly higher in those with persistent disease activity(Group 2) compared to those in remission(Group 1)(p<.0001).

Overall 24 patients were defined as being in remission as per the PMR-AS. Of these 23/24 had a normal plasma fibrinogen with 18/24 having a normal ESR and 16/24 a CRP < 6mg/L. The specificity, sensitivity, positive predictive values and likelihood ratios for the different biomarkers are shown in the table below.

	Specificity	Sensitivity	PPV	Likelihood Ratio	Fischers Exact Test
Fibrinogen	96%	34%	.97	8.2	P=.002
CRP	67%	68%	.88	2.04	P=.004
ESR	75%	43%	.87	1.7	P=.16

Plasma fibrinogen was more specific than ESR and CRP for differentiating between disease remission and disease activity. It also demonstrated a superior positive predictive value and likelihood ratio than ESR and CRP for identifying patients with persistent disease. The ESR showed no significant ability to distinguish between disease remission and activity (p=.16).

Conclusion: Elevated plasma fibrinogen more accurately indicates that patients have persistent disease activity than either the ESR or CRP. Measurement of fibrinogen may therefore help treating physicians more accurately identify patients' disease status and guide decisions with regards to glucocorticoid dosage.

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Corticosterois Therapy Restored Treg/Th17 Balance in Patients with Polimyalgia Rheumatica. Lorena Alvarez-Rodriguez[1], Marcos Lopez-Hoyos[1], Jaime Calvo-Alen[2], Elena Aurrecoechea[3], Teresa Ruiz Jimeno[3], Ignacio Villa[3], Carmen Gonzalez-Vela[1] and Victor M. Martinez-Taboada[1]. [1]Hospital Universitario Marques de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Universitario Sierrallana, Torrelavega, Spain, [3]Hospital de Sierrallana, Torrelavega, Spain

Background/Purpose: To characterize the levels of circulating T regulatory cells (Tregs) and Th17 cells in polymyalgia rheumatica (PMR).

Methods: The study included 46 patients with active untreated PMR and 12 age-matched healthy controls (HC). Thirty one PMR patients were also studied after disease control with corticosteroid (CS) therapy. As disease controls, 9 patients with giant cell arteritis (GCA) and 14 with elderly onset rheumatoid arthritis (EORA) were also included. Analysis of circulating regulatory T cells and TH17 cells were performed by flow cytometry. The suppressive capacity of peripheral Tregs was assessed by CFSE at a 1:1/Teffector ratio after polyclonal activation with anti-CD3 and anti-CD28.

Results: The frequency of $CD4^+CD25^{hi}FoxP3^+CD127^{-/low}CD27^+$ in the peripheral blood of active PMR was not significantly different from HC. However, patients with EORA showed marginally significant lower levels than HC ($p=0.048$) and GCA ($p=0.048$) patients. Therapy with CS showed no significant effect on the frequency of Tregs during the course of disease. The frequency of $CD4^+IL17^+IFN^+$ and $CD8^+CD28^-CD27^+$ cells was similar in all the study groups. The frequency of Th17 cells ($CD4^+IL17^+IFN^-$ and $CD4^+IL17^+CCR6^+$) was significantly higher in the peripheral blood of patients with PMR compared to HC ($p=0.037$) and

decreased after disease control with CS therapy ($p=0.031$). No significant differences between PMR and the other disease controls were found. Consequently, the ratio Tregs/Th17 was significantly decreased in patients with active PMR ($p=0.024$) and restored to normal after disease control. Moreover, the suppressive capacity of Tregs was slightly increase in PMR patients compared to HC ($p=0.047$).

Conclusion: Active PMR is associated with increased frequency of Th17 cells that is corrected after CS therapy. The frequency of Tregs does not change in PMR. Thus, the onset of PMR seems to be associated with increased inflammatory cells with not counterbalance by regulatory cells.

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Similarities Exceeds Differences in the Pattern of Joint and Vascular Positron Emission/Computed Tomography Uptake in Polymyalgia Rheumatica and Giant Cell Arteritis.

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Background/Purpose: Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two frequent overlapping diseases. The purpose of this work is to examine the relationship between these conditions by analysis of CT/PET findings.

Methods: Eighty consecutive patients (64 PMR diagnosed according to Bird's criteria, 16 GCA diagnosed according to the ACR criteria, of whom 10 also had PMR) underwent simultaneous FDG-PET and CT imaging from the skull base to the knee using an integrated PET/CT scanner (Hirez; Siemens Medical Solutions, Knoxville TN, USA), after recording demographic, clinical and laboratory data. Arterial and joint uptake were scored relative to liver uptake as 0=no uptake present, 1=lower than liver uptake, 2=similar to liver uptake, 3=higher than liver uptake. All the values were further subdivided into "positive" (scores 2 and 3) and "negative" (scores 0 and 1). Fifty-five patients were women, median age was 74 years (range 50–90 years), median disease duration was 3 months (range 0.5–11 months), median morning stiffness was 52 minutes (range 0–420 minutes), median C-reactive protein (CRP) was 36 mg/L (range 2–106 mg/L). Eighty age-matched controls were enrolled, who underwent PET/CT for suspected neoplastic disease, but without autoimmune conditions or previous chemiotherapy, radiotheraphy, and glucocorticoid treatment.

Results: Shoulders showed more frequently increased uptake (65 patients or 81.3%, bilateral in 57) (table 1), followed by the trochanteric bursae (60 patients or 75%, bilateral in 50). Among the studied arteries, an increased uptake was seen at the aortic arch and in the ascending aorta in 35 patients (43.8%). Patients had more frequently increased uptake than controls in all arterial and joint sites, except the coxofemoral joints. Among patients groups, a significant difference in uptake frequency was seen in trochanteric bursae (PMR>GCA, p=0.05), in carotid arteries (GCA>PMR, p=0.001), and in abdominal aorta (PMR+GCA>PMR, p=0.04)

Table 1. Distribution of uptake sites in patients groups and controls

	PMR n (%)	PMR+GCA n (%)	GCA n (%)	Controls n (%)	p (PMR vs. PMR+GCA vs. GCA)	p (patients vs. controls)
Patients	64	10	6	80		
Shoulders	55 (86)	8 (80)	2 (33)	14 (17)	0.07	<0.0001
Sternoclavear	32 (50)	7 (70)	3 (50)	0	0.5	<0.0001
Trochanteric bursae	50 (78)	8 (80)	2 (33)	4 (5)	0.05*	<0.0001
Coxo-femoral	5 (8)	0	0	4 (5)	0.5	0.6
Ischiatic bursae	46 (72)	7 (70)	2 (33)	0	0.1	<0.0001
Cervical interspinous bursae	6 (9)	2 (20)	1 (17)	0	0.55	<0.008
Lumbar interspinous bursare	28 (44)	5 (50)	2 (33)	0	0.8	=0.0001
Carotid arteries	4 (6)	2 (20)	4 (67)	1 (1)	0.001**	<0.0001
Subclavian arteries	11 (17)	3 (30)	3 (50)	0	0.1	<0.0001
Aortic arch	26 (41)	5 (50)	4 (67)	0	0.4	<0.0001
Ascending aorta	25 (39)	5 (50)	5 (83)	1	0.1	<0.0001
Descending aorta	22 (34)	4 (40)	4 (67)	1 (1)	0.3	<0.0001
Abdominal aorta	7 (11)	4 (40)	2 (33)	0	0.04***	<0.0001
Iliac arteries	4 (6)	2 (20)	1 (2)	1 (1)	0.3	0.03
Femoral arteries	20 (31)	3 (30)	3 (50)	0	0.6	<0.0001

*=PMR>GCA; **=GCA>PMR; ***=PMR+GCA>PMR.

Conclusion: With the limitation of the small number of GCA patients included and of the absence of histological data on the temporal arteries of PMR patients, our study suggests that in PMR and GCA similarities exceed differences. These conditions could be different forms of the same disease. PET/CT, a minimally invasive technique, is an effective and objective method to evaluate inflammation in PMR/GCA, optimally discriminating patients with PMR/GCA complex from controls.

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Correlation Between Hypoechoic Halo of the Temporal Arteries and Clinical, Laboratory, and Temporal Artery Biopsy Findings in Patients with Giant Cell Arteritis.

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Background/Purpose: The presence of a hypoechoic halo of the temporal arteries on Color-Doppler sonography (CDS) has high specificity and acceptable sensitivity for the diagnosis of giant cell arteritis (GCA). However, it is unclear whether patients with a positive halo sign differ from those without such a sign. The aim of our study was to evaluate the correlations between the presence of a hypoechoic halo, on the one hand, and clinical, laboratory, and histological parameters, on the other, in patients with biopsy-proven GCA.

Methods: We analyzed the clinical records of 105 consecutive patients with biopsy-proven GCA (including those with transmural cell infiltration, small-vessel vasculitis and vasa vasorum vasculitis of the temporal arteries) who underwent CDS of the temporal arteries before temporal artery. Mean age was 74 ± 8 years, while females were 72.4%. A hypoechoic halo larger than 0.4 mm around the temporal artery lumen on CDS was considered positive. Correlations were sought by chi-square test or Fisher's exact test as appropriate using SPSS version 18.0.

Results: The presence of a hypoechoic halo significantly correlated with jaw claudication (58.8% vs 25.9%; p=0.001, odds ratio [OR] 4.1, 95% confidence interval [CI] 1.8–9.3), abnormalities of temporal artery on clinical examination (67.3% vs 46,9; p=0.041, OR 2.3 [CI 1.0–5.3]), elevated erythrocyte sedimentation rate [91.5% vs 59.2%; p=0.001, OR 7.4 [CI 2.3–23.94], and the presence of giant cells on temporal artery biopsy [66.7% vs 29.4%; p=0.0001, OR 4.8 [CI 2.0–11.4]. In addition, patients with a hypoechoic halo had higher levels of blood platelets (396875 +116274 vs 327954 + 103181; p= 0.005, unpaired two-tailed t-test). However, no correlation was found between the presence of a ultrasonographic halo and visual loss.

Conclusion: These provide evidence for a close correlation between the presence of a hypoechoic halo on CDS of the temporal arteries and jaw claudication, giant cells on temporal artery biopsies, and elevated levels of erythrocyte sedimentation rate in patients with GCA. In contrast, a positive halo sign did not predict visual loss.

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Temporal Artery Biopsy Culture in Tridimensional Matrix. *in Vitro* **Model for Functional Studies in Giant-Cell Arteritis.** Marc Corbera Bellalta[1], Ester Planas Rigol[1], Ester Lozano[1], Marco A. Alba[2], Itziar Tavera-Bahillo[1], Sergio Prieto-González[1], Georgina Espígol Frigolé[1], Montserrat Butjosa[1], José Hernández-Rodríguez[1], Ana García-Martínez[2] and Maria C. Cid[2]. [1]Hospital Clinic University Barcelona, Barcelona, Spain, [2]Vasculitis Research Unit. Hospital Clínic. University of Barcelona. IDI-BAPS, Barcelona, Spain

Background/Purpose: GCA is the most frequent systemic vasculitis in Europe and North America. In spite of the initial response to glucocorticoid treatment more than 60% of patients relapse when glucocorticoids are tapered indicating the need for more effective therapies. Search for therapeutic targets in GCA is hampered by the lack of an animal model to assess the consequences of therapeutic intervention. Subcutaneous engraftment of temporal artery fragments into the SCID mice is the only existing functional system (Brack et al, J Clin Invest 1997) to assess the effects of intervention. However it is costly, complex and only a limited number of conditions can be evaluated. We previously described a temporal artery culture model (Arthritis Rheum 2008 (suppl) 58:9; S929-S929), and the effects of the some cytokine blockade on cultured GCA arteries. Our purpose is to explore changes induced by corticosteroids on the expression of inflammatory mediators between control arteries, treatment naïve GCA arteries and GCA arteries treated with dexamethasone

Methods: Fresh temporal artery sections surgically removed for diagnoses purposes from 20 GCA patients and 18 controls were embedded in the reconstituted basement membrane Matrigel™ and cultured for 10 days as described (Arthritis Rheum 2008 (suppl) 58:9; S929-S929). Cultured sections were treated with medium alone or with medium supplemented with 0.5mg/ml of dexamethasone. IFNg, TNFα, IL-1β, IL-6, CD3, CD20 and CD68 mRNA were measured in recovered sections by quantitative real-time PCR (Applied Biosystems). Proinflammatory cytokine secretion was also measured in the supernatant fluid by immunoassay (R&D Systems)

Results: As expected, cultured inflamed arteries produced remarkable amounts of proinflammatory cytokine mRNAs (IFNg, TNFα, IL-1β, and IL-6) compared with control biopsies. Moreover, mRNA expression of CD3, CD20 and CD68 cell markers was significantly increased in biopsies from patients compared with controls. Glucocorticoid treatment of the GCA biopsies for 10 days markedly reduced mRNA expression of all cytokines and cell markers. At the protein level we found a significant decrease in IL-1β, TNFα and IL-6 which was less marked for IFNg. Our model reproduces previous results obtained in other functional systems or in cross-sectional or serial comparison of biopsies obtained from patient naïve versus treated patiens (Visvanathan S, Rheumatology 2011)

Conclusion: Our temporal artery culture system in tridimenional matrix is viable and is a suitable model to evaluate functional changes in biomarker expression and secretion after intervention. This model has several advantages compared with the SCID mice engraftment: it is simpler and cheaper, it allows continuous assessment of viability, the analysis of more conditions per specimen and the assessment of proteins in the supernatant fluid. Unfortunately, as in the SCID mice, disease outcomes cannot be assessed in our model.

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TLR2 Activation by Acute Serum Amyloid A Induces Pro-Inflammatory Mechanisms in a Novel Ex Vivo Temporal Artery Explant Culture/ Model of Giant Cell Arteritis. Peadar Rooney[1], Danielle Molloy[1], Jennifer McCormick[1], Mary Connolly[1], Sinead M. Miggin[2], Ashwini Maratha[2], Douglas J. Veale[3], Conor Murphy[4], Eamonn S. Molloy[3] and Ursula Fearon[5]. [1]Dublin Academic Medical Centre, Dublin, Ireland, [2]Immune Signalling Laboratory, Maynooth, Ireland, [3]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [4]Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [5]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Giant cell arteritis (GCA) is the most common form of primary vasculitis. The pathogenesis of this disease is characterised by disregulated angiogenesis and inflammatory infiltration, however the causative mechanisms involved in regulating these processes have yet to be elucidated. This study examines the role of acute serum amyloid A (A-SAA), TLR2 activation and the downstream Notch signalling pathway in mediating the pro-inflammatory response in GCA.

Methods: A-SAA expression in Temporal artery (TA) sections from GCA patients was assessed by immunohistology. *Ex vivo* TA explant cultures were established from GCA patients, and the effect of pro-inflammatory stimuli A-SAA (10μg/ml) and a TLR2 agonist Pam3CYSK4 (1μg/ml) on Ang2, MMP2, MMP9, IL-6 and IL-8 was quantified by ELISA and gelatin zymography. Spontaneous release of A-SAA from *ex vivo* TA explant cultures was quantified by ELISA. Furthermore, myofibroblast outgrowth from TA explants was assessed using matrigel assays over a time course of 1–15 days. A-SAA induced TA explant and microvascular endothelial cell function in the presence of Notch-1 inhibition (γ-secretase inhibitor (DAPT)) or anti-TLR2 was assessed by gelatine zymography, angiogenic assays and ELISA. The effect of conditioned media from TA explants on Human embryonic kidney (HEK) -TLR2 cells was quantified by NFkb luciferase reporter assays.

Results: A-SAA expression was demonstrated in the advential and intimal regions, particularly localised to endothelial cells. High A-SAA levels (386 +/− 191 pg/ml) were spontaneously released from TA explants cultures. *Ex-vivo* TA explant cultures spontaneously released pro-inflammatory mediators, maintained cell viability and histological morphology, reflecting the *in vivo* microenvironment. A-SAA and Pam3CSK4 induced expression of instability growth factor Ang2 (p<0.05), IL-8 (p<0.05), IL-6 (p<0.05) and MMP2 and MMP 9. A-SAA and Pam3CSK4 induced myofibroblast outgrowths from TA explants embedded in matrigel over a time course of 1–15 days. In parallel, Ang2, MMP2/9 and pro-inflammatory chemokine IL-8 were induced in myofibroblast outgrowth cultures in response to A-SAA, and to a lesser extent Pam3CSK4. A-SAA induced Ang2, IL-8, IL-6 were significantly decreased in the presence of Notch inhibitor DAPT. Furthermore anti-TLR2 inhibited the effects of A-SAA on endothelial cell function. Finally conditioned media from TA explants significantly induced TLR2 activation through induction of NFκb activation, suggesting the presence of a TLR2 ligand in the inflamed microenvironment.

Conclusion: A-SAA-induced pro-inflammatory events in GAC are mediated through Notch signaling and the TLR2 activation. A better understanding of A-SAA/TLR2-mediated inflammatory pathways may lead to novel treatment strategies for RA.

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The Prevalence of Low Bone Mineral Density in Patients with New Onset Giant Cell Arteritis. Do They Get Appropriate Bone Protective Treatment? Andreas P. Diamantopoulos and Glenn Haugeberg. Hospital of Southern Norway HF, Kristiansand, Norway

Background/Purpose: Giant cell arteritis (GCA) is a common form of vasculitis mainly affecting individuals older than 50 years with a mean onset age of 69 years. The prevalence of osteoporosis in postmenopausal women is high and increases with age. The recommended standard treatment for GCA is high doses of glucocorticosteroids which over weeks are reduced to lower maintenance doses. The aim of this study was to examine the prevalence of reduced bone mineral density (BMD) in patients with a new onset GCA and to examine if these patients were treated adequately according to the American College of Rheumatology (ACR) 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis.

Methods: Patients diagnosed at our outpatient clinic with GCA from January 2010 to May 2012 were retrospectively assessed. The majority of patients were examined by dual energy X-ray absorptiometry (DXA) in spine and hips. The WHO definition was applied to define osteoporosis (T-score ≤−2.5 SD at femoral neck and/or lumbar spine L1–4) and osteopenia (T-score <-1 and >-2.5 SD). Treatment data were also recorded.

Results: A total of 36 patients were diagnosed with GCA (27 females, 9 males). Two patients were excluded due to known osteoporosis. From the 34 remaining patients (25 females and 9 males) DXA measurement was performed in 27 (23 females and 4 males) patients at the time of the

initial evaluation. A total of 21 patients (78%) had reduced BMD (osteoporosis in 13 females and osteopenia in 3 males and 5 females). Treatment with bisphosphonates was initiated in 14 out the 21 patients (67%) with reduced BMD (11 patients with osteoporosis and 3 patients with osteopenia) who according to the ACR guidelines were recommended treatment. All patients with osteoporosis and osteopenia received calcium and vitamin D supplementation.

Conclusion: More than 75% of the DXA examined patients had reduced BMD and thus were in need for osteoporosis treatment with bisphosphonates according to the ACR 2010 recommendations for glucocorticoid-induced osteoporosis. Despite the clear guidelines 1 out of 3 GCA patients were in our patient cohort not treated properly. Our data emphasizes the need for increased awareness of osteoporosis and osteopenia in these patients which are at high risk for future fractures.

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Increase in Duration and Cumulative Dose of Glucocorticoid Therapy in Recent Decades: Observations From a Population-Based Cohort of Patients with Giant Cell Arteritis. P. Deepak Udayakumar, Tanaz A. Kermani, Kenneth J. Warrington, Cynthia S. Crowson and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Systemic glucocorticoid (GC) therapy is the first line treatment for giant cell arteritis (GCA). Patients with GCA are often counseled that therapy will be needed for 1 to 2 years, but in recent years it has been recognized that GCA is a chronic disease requiring long-term therapy and monitoring. We sought to evaluate the duration and cumulative dose of GC therapy in a population based cohort of patients with GCA diagnosed 1980–2004 compared with 1950–1979.

Methods: We retrospectively reviewed a population-based incidence cohort of GCA patients diagnosed between 1950 and 2004. All subjects were longitudinally followed through all available community medical records until death, migration or December 31, 2009. Data was collected regarding dosing and duration of GC use. Kaplan-Meier methods were used to estimate the time to discontinuation of GC and log rank tests were used for comparisons between time periods.

Results: The study population included 204 patients. Mean age was 76 years and 163 (80%) were female. Median follow-up was 8.8 years with 1,996 total person-years. Mean erythrocyte sedimentation rate at diagnosis was 79.2 mm/hr. Temporal artery biopsy was positive in 176 (86%) patients.

The mean starting dose of prednisone was 53.2mg/day in 1980–2004 and 54.8 mg/day in 1950–1979 (p=0.79). Prednisone dose of <10 mg/day for 6 months was reached in 34%, 81% and 98% patients by 1, 2 and 5 years from GCA incidence date respectively in patients diagnosed between 1980–2004 compared to 52%, 88% and 100% respectively among patients in the 1950–1979 cohort (p=0.003). In the 1980–2004 cohort, only 14% permanently discontinued GC use by 1 year from GCA incidence date, 41% by 2 years and 75% by 5 years compared to 40%, 64% and 76% respectively in the 1950–1979 cohort (p=0.032).

The median time to reach a prednisone dose of <10mg/day was about 6.5 months in 1980–2004 versus 3.2 months in 1950–1979 (p <0.001). The mean cumulative dose of prednisone by 1 year after incidence of GCA was 6.1 gm in 1980–2004 versus 4.1 gm in 1950–1979 (p < 0.001). Mean cumulative dose by 5 years was 10.3 gm in 1980–2004 versus 7.8 gm in 1950–1979 (p=0.007).

Conclusion: Patients diagnosed with GCA in recent decades were on GC for a longer duration and received higher cumulative doses. As well, a significantly higher proportion of patients remain on GC therapy even beyond 5 years following diagnosis. The reasons for the secular trend in longer duration and higher doses of GC for treating GCA are unclear, but may relate to recognition that GCA a more chronic disease with late sequelae such as large vessel disease than previously recognized, increasing the concern for GC associated adverse effects in these patients.

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Visual Manifestations in Giant Cell Arteritis: Trend Over Five Decades. Abha G. Singh[1], Cynthia S. Crowson[1], Tanaz A. Kermani[2], Cornelia M. Weyand[3], Eric L. Matteson[1] and Kenneth J. Warrington[1]. [1]Mayo Clinic, Rochester, MN, [2]University of California Los Angeles, Los Angeles, [3]Stanford University School of Medicine, Stanford, CA

Background/Purpose: Cranial ischemic complications, particularly permanent visual loss, are catastrophic complications of giant cell arteritis (GCA). Corticosteroids have been used to decrease the risk of vision loss but it is unclear if the rate of visual complications has changed in recent decades. We examined trends in visual manifestations in GCA over the last 5 decades.

Methods: We reviewed the medical records of a population-based cohort of patients with GCA meeting ACR classification criteria, diagnosed between 1950 and 2004. We characterized the clinical, ophthalmological and laboratory features of patients with visual manifestations and compared them with patients who did not develop visual complications. Trends of visual manifestations in GCA over time were examined using logistic regression model adjusted for age and sex.

Results: 204 cases of GCA were identified (mean age 76.0 ± 8.2 years, 80% female) of which 47 had visual manifestations attributable to GCA at presentation. Blurred vision (15%) and diplopia (5%) were the most common visual symptoms. Ischemic optic neuropathy (ION) was the predominant ophthalmologic diagnosis (17/204, 8%). Nine patients (4.4%) suffered complete loss of vision. As compared to patients with GCA without visual manifestations at presentation, patients with visual manifestations were more likely to have associated jaw claudication (59/157 v.s 26/47, p =0.04), but were similar with regard to other clinical (age, smoking status, headache, scalp tenderness, constitutional symptoms, frequency of polymyalgia rheumatica) and laboratory features.

Recovery from visual symptoms was less likely in patients with complete vision loss as compared to those with blurred vision alone [Hazard ratio, 95% Confidence Interval (HR, 95% CI): 0.20 (0.06–0.63), p<0.01], and in patients with ION or central retinal artery occlusion as compared to other diagnoses [HR (95% CI): 0.22(0.10–0.49), p<0.001].

Over a period of 55 years, there has been a significant decline in the incidence of visual symptoms (figure) and ION [1950–1979 vs 1980–2004: 9/61 (15%) vs 8/143 (6%), p=0.03] with time. Additionally, patients diagnosed more recently were more likely to have recovery from visual symptoms than patients diagnosed in earlier years [HR (95% CI): 1.34 (1.06–1.71) per 10 year increase in calendar year, p=0.016].
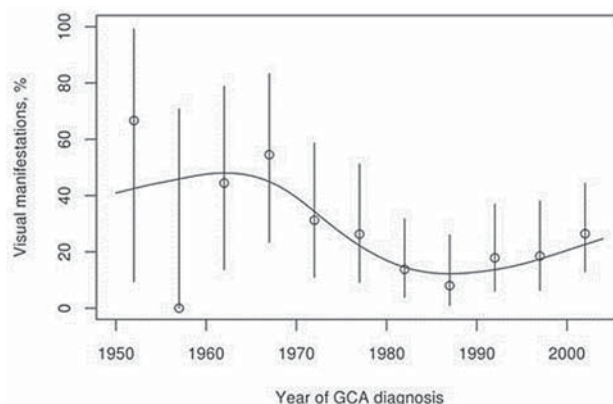
Figure. Incidence of visual manifestations (adjusted for age and sex) among 204 patients with giant cell arteritis declined over time (p=0.02). Point estimate and 95% confidence interval for each 5 year time period are displayed.

Conclusion: In this population-based cohort study of patients with GCA we found that the incidence of visual symptoms and ION has declined over the past 5 decades, and chances of recovery from visual symptoms have improved. Reasons for this improvement are unclear but may relate to increased disease awareness, earlier diagnosis and timely initiation of treatment.

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Relapses in Patients with Giant-Cell Arteritis: Prevalence, Characteristics and Associated Clinical Findings in a Prospectively Followed Cohort of 106 Patients. Marco A. Alba[1], Ana García-Martínez[1], Itziar Tavera-Bahillo[1], Sergio Prieto-González[1], Montserrat Butjosa[2], Georgina Espígol[3], Marc Corbera[3], Ester Planas[3], Jose Hernandez-Rodriguez[4] and Maria C. Cid[1]. [1]Vasculitis Research Unit. Hospital Clínic. University of Barcelona. IDI-BAPS, Barcelona, Spain, [2]Hospital Clinic University Barcelona, Barcelona, Spain, [3]Vasculitis research unit. Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain, [4]Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain

Background/Purpose: In spite of the satisfactory initial response to glucocorticoid treatment, patients with giant cell arteritis (GCA) frequently experience relapses during follow-up. The objectives of this study were 1) To investigate the prevalence and characteristics of relapses in a prospectively followed cohort of patients with GCA. 2) To determine whether clinical or analytical findings at presentation may predict relapses and 3) To analyze whether a relapsing course is associated with higher cumulated GC doses and more prolonged treatment periods.

Methods: Between 1995 and 2007, 187 patients were diagnosed with biopsy-proven GCA at our institution. Among them, 106 patients fulfilled the following inclusion criteria: prospective treatment by the authors according to uniform criteria and prospective follow-up for at least 4 years. GCA features and blood tests at diagnosis (acute phase reactants, blood cell counts and liver function tests), ischemic complications, relapses, and prednisone doses for at least 4 years. Relapses were defined as reappearance of disease related symptoms accompanied by elevation of acute-phase reactants that required treatment adjustment. Type of relapse was defined as PMR, cranial symptoms, severe cranial ischemic complications or systemic disease (anemia, fever and/or weight loss). Chi-square test, student T test and Kaplan-Meyer survival analysis/log-rank test were used for statistical comparison.

Results: During the follow-up period (mean 7.6 ± 3.3 years), 66 (62%) patients experienced at least 1 relapse and 38 (36%) 2 or more. Relapses consisted of PMR in 33 (50%), cranial symptoms in 19 (29%), systemic complaints in 13 (19.5%) and cranial ischemic complications in 1 (1.5%). Mean time (in weeks) to first relapse was 72 ± 71 (11–339). There were no differences in clinical findings or blood test results at presentation between patients who relapsed and those who achieved sustained remission. However, 23 (60.5%) of patients with ≥ 2 relapses had a strong systemic inflammatory response at presentation (defined as at least 3 of the following fever >38°C, weight loss >5 kg, hemoglobin < 11 gr/L or ESR >85 mm/hour) which was present in only 5 (18%) of the remaining patients (p=0.001). Patients with ≥ 2 relapses presented significantly higher levels of ESR and C-reactive protein at 6 months and lower concentrations of hemoglobin at baseline, at 6 months (all p<0.01) and at 24 months (p=0.045). Patients with relapses required longer periods of time to reach a stable maintenance dose of prednisone <10mg/day (67±58 weeks vs 31±21, p<0.001), <5mg/day (159±106 vs 89±42, p<0.001) and to completely discontinue GC treatment (237±124 vs 157±59 p=0.005). In addition, cumulative prednisone dose at one year was significantly different between both groups (6.2±1.7 gr vs 5.4±0.7, p=0.01).

Conclusion: More than 60% of patients with GCA experience at least one relapse and 36% have multiple relapses. Relapses usually consist of PMR. Those with multiple relapses have stronger systemic inflammatory response at presentation. A relapsing course is associated with higher and prolonged GC requirements underlining the need for more effective treatments for GCA.

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Large Vessel Giant Cell Arteritis: A Cohort Study. Francesco Muratore[1], Tanaz A. Kermani[2], Cynthia S. Crowson[3], Abigail B. Green[3], Eric L. Matteson[3] and Kenneth J. Warrington[3]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]University of California Los Angeles, Los Angeles, [3]Mayo Clinic, Rochester, MN

Background/Purpose: A subset of patients with giant cell arteritis (GCA) has large vessel (LV) involvement. We sought to identify baseline variables that distinguish patients with GCA with subclavian artery involvement (LV-GCA) from those with cranial disease (C-GCA), and to compare treatment, long term follow-up and prognosis of these two subtypes of GCA.

Methods: All patients over age 50 years with radiographic evidence of subclavian LV-GCA diagnosed between January 1, 1999 and December 31, 2008 were identified in this retrospective study. These were compared to a cohort of patients with biopsy-positive C-GCA diagnosed in the same period.

Results: The study included 120 patients with radiographic evidence of LV-GCA and 212 patients with C-GCA. LV-GCA was noted at GCA diagnosis in 90 patients, and after GCA in 30 patients (mean time 2.6 years from diagnosis of GCA). Temporal artery biopsy (TAB) was performed in 79 patients with LV-GCA, and was positive in 41 (52%). In addition to subclavian vasculitis, 56% of LV-GCA cases had radiographic evidence of thoracic aortic involvement (thickening or aneurysm/ectasia).

Compared to patients with C-GCA, patients with LV-GCA were younger (mean age 68.2 + 7.5 years vs 75.7 + 7.4, p <0.001), more likely to have a prior history of PMR (26% vs 15%, p = 0.01) and had longer duration of symptoms at GCA diagnosis (median 3.5 months vs 2.2 months p <0.001). Cranial symptoms (41% vs 83%, p <0.001) and vision loss (4% vs 11%, p = 0.04) were less frequent in LV-GCA compared with C-GCA. Upper extremity claudication (52% vs 0%, p <0.001), Raynaud's phenomenon (11% vs 0%, p <0.001), vascular bruits (38% vs 9%, p <0.001) and abnormal pulse exam (60% vs 14%, p <0.001) were more frequent in LV-GCA compared to C-GCA. There were no differences in cardiovascular risk factors, sex distribution and ESR/CRP between the 2 cohorts. ACR classification criteria for GCA were satisfied in 39.2% of LV-GCA and in 95.3% of C-GCA patients (p <0.001). Patients in the C-GCA cohort met a median of 4.0 ACR criteria for GCA, while the LV-GCA patients met only a median of 2.0 criteria (p <0.001).

103 patients with LV-GCA and 167 patients with C-GCA had a follow-up period longer than 6 months (median follow up 3.6 and 4.6 years respectively). Relapse rate was significantly higher (48.6 vs 29.8/100 person-yrs, p <0.001) and time to first relapse was shorter (median 0.8 vs 1.2 yrs, p = 0.005) for LV-GCA compared with C-GCA. The cumulative corticosteroid (CS) dose at 1 year was higher (11.4 + 5.9 grms vs 9.1 + 3.7, p <0.001) and the time to discontinuation of CS therapy was longer (median 4.5 vs 2.2 yrs, p <0.001) in LV-GCA. At 5 years of follow-up, the rate of incident aortic aneurysm was higher in LV-GCA (1.5% vs 0.3%, p = 0.005) compared with C-GCA. Rate of incident stroke was similar in the 2 GCA cohorts.

Conclusion: In this large study, patients with LV-GCA presented less often with cranial symptoms and more often with findings of large-vessel insufficiency. Although patients with LV-GCA had a lower rate of vision loss, they had a higher relapse rate, greater CS requirements and an increased incidence of aortic aneurysm compared with C-GCA. The ACR criteria for GCA are inadequate for the classification of patients with LV-GCA.

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Outcome of Aortic Involvement in GIANT CELL Arteritis (GCA) After 1-Year Follow-up: Prospective Study in 35 Patients Using Computed Tompography Angiography (CTA). Sergio Prieto-González, Pedro Arguis, Ana García-Martínez, Itziar Tavera-Bahillo, Marc Corbera-Bellalta, Marco A. Alba, Georgina Espígol-Frigolé, Ester Planas-Rigol, José Hernández-Rodríguez and Maria C. Cid. Vasculitis Research Unit. Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain

Background/Purpose: 65% of patients with newly diagnosed, biopsy-proven GCA showed radiologic finding of aortitis using CTA in a prospective study of 40 patients.

By segments, the involvement was as follows: ascending aorta 30%, aortic arch 57,5%, descending thoracic aorta 57,5%, and abdominal aorta 47,5%. Moreover, 15% of patients already had aortic dilation at the time of diagnosis.

The objective of our study was to prospectively evaluate the outcome of aortic involvement by comparing CTA findings at the time of diagnosis and those obtained after 1 year of treatment in the same patient cohort.

Methods: All the patients included in the first study were prospectively treated and followed by the investigators according to a defined protocol, and a new CTA were performed after 1 year of treatment. Vessel wall thickness

and vessel diameter at the aforementioned four aortic segments were evaluated. Aortitis was defined as circumferential aortic wall thickness ≥2 mm with or without contrast enhancement of the vessel wall observed in zones without adjacent atheroma.

Results: Five out of the 40 patients were lost to follow-up or declined a new CTA, so follow-up CTA has been completed in the remaining 35 patients. CTA findings of aortitis were still present in 16 (72% of the patients who initially had aortitis). Nevertheless, significant reduction in mean wall thickening was detected in all of the aortic segments: ascending aorta (1,51±0,81 vs 1,22±0,59 mm, p=0,018), aortic arch (2,31±1,02 vs 1,77± 0,87 mm; p=0,002), descending thoracic aorta (2,74±1,06 vs 2,02±0,95 mm; p<0,001), and abdominal aorta (1,68±0,8 vs 1,31±0,6 mm; p=0,012). None of the 35 patients evaluated developed new lesions in previously unaffected areas and no patients lacking aortitis in the first CTA developed new aortic involvement. Similar to the first evaluation, aortic arch and descending thoracic aorta were the most affected segments, followed by the abdominal aorta and ascending aorta, respectively. Interestingly, aortic diameters remained stable, and no patients developed new aortic dilation or increase in previous dilations.

Conclusion: CTA signs of aortitis persisted in 72% of the patients who presented initial aortic inflammation after one year of steroid treatment. Nevertheless, aortic thickening significantly decreased and there were no changes in aortic diameters during this period of time. In order to rule out clinical significance of these inflammatory findings and their possible relationship with dilatation longer follow-up is mandatory.

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Prevalence, Management and Outcomes of PET Positive Large Vessel Vasculitis in Difficult to Treat PMR and GCA Patients. Pravin Patil[1], Shaifali Jain[1], Katerina Achilleos[1], Tochukwu Adizie[1], Mark Williams[1], Matthew Tam[1] and Bhaskar Dasgupta[2]. [1]Southend University Hospital, Westcliff on sea, United Kingdom, [2]Southend University Hospital, Westcliff-on-Sea, United Kingdom

Background/Purpose: Management of PMR and GCA can be challenging in patients with persistently elevated inflammatory markers, prominent constitutional symptoms and inadequate steroid response. We undertook an audit in such difficult to treat cases of the utility of FDG-PET CT scanning and outcomes of therapeutic decisions subsequently made.

Methods: We report a retrospective case notes review of 52 rheumatology patients with active PMR, GCA despite optimal steroid/ methotrexate therapy or patients with an unexplained systemic illness who had PET-CT from 2008–2012. FDG uptake was graded on a 4-point scale and grade 2 or more was accepted as positive.

Results: Of the 52, 68 % were female (median age 70, range 57–89), 23 PMR and 20 had GCA (12 biopsy positive). 63 % PMR and GCA patients were on steroids. The average dose of Prednisolone prior to PET scan was 6mg daily in PET positives compared to 21mg daily in PET negative patients.

Large vessel vasculitis (LVV): 15 had avid FDG uptake in the subclavian, aortic and axillary arteries, suggesting presence of LVV. All had constitutional symptoms notably night sweats, weight loss and lethargy. The average CRP in patients with LVV was 112mg/dl (range 13–403). Where PET scans were negative, the average CRP was 19 (1–48). There was no significant difference in gender, incidence of PMR, GCA, and resistance to treatment in both groups. 8 out of 9 with LVV who had abdominal CT scan were found to have inflammatory aortitis (soft tissue vascular cuffing) on retrospective CT review. All patients with LVV had successful clinical response to escalation of immunosuppression with 4–6 weeks post treatment mean CRP of 7 (1–26). 78% were treated with high dose Predinisolone and Leflunomide (53%). 4 patients required treatment with Tocilizumab (TCZ). 1 patient with retroperitoneal fibrosis and LVV associated with pan aortitis was treated with Rituximab. All patients on TCZ showed reversal of FDG avidity, normalized CRP, reduction of prednisolone to < 90% pre TCZ dose and 1 showed re-vascularisation of axillary artery stenosis on follow up CT angiography and ultrasound.

Non LVV findings on FDG PET: 2 patients had uptake in sterno-clavicular and sacroiliac joints suggestive of SpA. One patient with connective tissue disease overlap had symmetrical uptake in shoulders consistent with inflammatory arthritis. In 2 patients with atypical clinical presentation the diagnosis of PMR was confirmed with bursal & entheseal uptake in the shoulder/hips. In 3 cases FDG PET revealed cancer (pancreas 2, metastatic breast 1).

Conclusion: LVV is a common finding in both PMR and GCA exhibiting lack of steroid response, constitutional symptoms and raised inflammatory markers. Abdominal CT scan may provide important diagnostic clues of aortitis which can be confirmed on FDG-PET scan. Scan results are influenced by dose of steroid intake and we suggest prednisolone no higher than 7.5 –10mg daily a week prior to the scan. Patients on higher doses may have false negative scans. FDG PET can also reveal occult malignancies or confirm the PMR diagnosis. Novel agents like leflunomide and tocilizumab provide targeted and effective therapy in refractory patients with reversal of FDG avidity on and re-vascularisation on repeat scans.

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Misdiagnosis of Giant Cell Arteritis Presenting As Fever of Unknown Origin. Chiara Stagnaro, Rosaria Talarico, Claudia Ferrari, Anna d'Ascanio and Stefano Bombardieri. Rheumatology Unit, University of Pisa, Pisa, Italy

Background/Purpose: Giant cell arteritis (GCA) represents the most common primary vasculitis of the elderly, that usually involves large and medium sized arteries. The wide spectrum of clinical manifestations can extensively vary, from cranial symptoms, such as headache, jaw claudication or visual alterations, to constitutional symptoms, like fever, weight loss or asthenia. Fever of unknown origin (FUO) may sometimes represent the initial symptom of GCA and when it is not associated with other typical GCA features, unfortunately the diagnosis can be delayed. The primary aim of this study was to evaluate the prevalence of GCA presenting as FUO. The secondary aims were: to identify delays in recognizing patients with GCA presenting as FUO and to explore any potential differences between the subset of GCA patients characterised by the presence of FUO at the onset, and the other patients of the cohort.

Methods: Epidemiological and clinical data of 180 GCA patients followed in the last 15 years in our Unit were analysed. We quantified the latency period between the onset of signs and symptoms and the final diagnosis of GCA in terms of months.

Results: One hundred and thirty-five patients (13 males and 122 females, mean ± SD age at the onset 75±6 years, mean follow-up 8 years) had shown at the onset signs and symptoms suggestive of GCA (new onset headache and/or scalp pain 78%, jaw claudication 36%, vision loss 33%, abnormal temporal artery on examination 32%, dizziness 29%) while 45 patients (9 males and 36 females, mean age at the onset 67±2 years, mean follow-up 6 years) were sent to our attention because of FUO onset and an increase of erythrocyte sedimentation rate and C-reactive protein not otherwise justified. After an extensive work-up aimed at excluding any kind of infection, malignancy or hematological disorder, we performed temporal artery biopsy (TAB) in all patients presenting as FUO, that resulted positive in 52% of cases. Moreover, (18)F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) was performed in 29 cases and was positive in 27. The main PET alterations reported were characterized by a (18)FDG uptake of the aortic arch and its major branches, including the carotid, subclavian, thoracic aorta and, less frequently, the abdominal aorta. The mean latency period between the onset of FUO and the diagnosis of GCA was 7±2 months, which was significantly higher compared with the mean latency period between the onset of signs and symptoms suggestive of GCA and the definitive diagnosis (3±1 months) in the other patients of the cohort. No difference was noted between the 2 groups, except for the mean age at the onset, which seems to be earlier in GCA patients presenting with FUO.

Conclusion: GCA patients presenting with constitutional symptoms may sometimes represents a diagnostic challenge and our results confirm that FUO must to be carefully investigated in elderly patients. In fact, there are major delays in the recognition of GCA patients presenting with FUO, and it partially seems to be due to the long diagnostic work-up before performing a rheumatologic evaluation.

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Evaluation of Disease Activity Using FDG PET-CT in Patients with Large Vessel Vasculitis. Giulia Pazzola[1], Luca Magnani[1], Luigi Boiardi[1], Nicolo Pipitone[1], Annibale Versari[1], Debora Formisano[1], Olga Addimanda[1], Riccardo Meliconi[2], Lia Pulsatelli[3], Gianluigi Bajocchi[1], Pierluigi Macchioni[1], Maria Grazia Catanoso[1], Niccolò Possemato[1], Ilaria Padovano[1], Alberto Lo Gullo[1] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Istituto Ortopedico Rizzoli, University of Bologna, Bologna, Italy, [3]Istituto Ortopedico Rizzoli, Bologna, Italy

Background/Purpose: 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computerized tomography (CT) [PET/CT] has been proposed as a useful tool to diagnose and monitor activity of large vessel vasculitis (LVV), but its precise role remains debated. The objective of this study was to determine the value of PET-CT in the assessment of disease activity in LVV. To this end, PET/CT findings were correlated with clinical indices including ITAS (Indian Takayasu activity score) and Kerr/National Institute of Health, serum acute-phase reactants (ESR, CRP) levels as well as interleukin-6 (IL-6) and the soluble IL-6 receptor (sIL-6R).

Methods: 78 patients with LVV (giant cell arteritis, Takayasu arteritis or idiopatic aortitis) underwent a total of 204 PET/CT scans. PET/CT scans were reviewed by a nuclear medicine physician without knowledge of clinical information. Vascular uptake was graded using a 4-point semiquantitative scale where grade 0=no uptake, grade 1=less than liver uptake, grade 2=similar to liver uptake, grade 3=higher than liver uptake. Visual analysis was performed on 14 vessel segments. PET/CT scans were considered negative if vascular FDG uptake was grade 0–1, moderately positive if vascular uptake was grade 2, and markedly positive if vascular uptake was grade 3 in at least one vessel. ITAS, Kerr/NIH scores, ESR, CRP, IL-6 and sIL-6R values were obtained within 20 days of PET/CT scans.

Results: 43% of 204 PET-CT were negative, 31% were moderately positive, and 26% were markedly positive. We found a significant association between the intensity of the uptake and both ESR and CRP levels. Significantly higher ESR values were observed in the patients with markedly positive PET/CT (49.4 + 36.5 mm/1st h) compared with those with moderately positive (27+ 21 mm/1st h, p = 0.0001) and inactive scans (22.7 + 15.9 mm/1st h, p=0.0001), respectively. CRP levels were 0.8+1.0 mg/dL in patients with inactive scans, 1.3+ 2.2 mg/dL in patients with moderately positive (p=0.001) and 3.0 + 3.6 in patients with markedly positive scans (p = 0.0001). Significantly higher levels of IL-6 were measures in patients with markedly positive scans (10.0 + 8.9 pg/ml) compared to those with inactive scans (8.1+18.5 pg/ml, p=0.013). No association was found between sIL-6R levels and intensity of vascular FDG uptake. However, there was a significant association between the intensity of vascular FDG uptake and both ITAS and Kerr/NIH scores.

Patients with markedly positive scans had more frequently (50%) active vasculitis according to the ITAS compared with those with moderately active (31.7%) and inactive scans (28.1%) (p=0.003). Likewise, vasculitis was judged to be active according to the Kerr/NIH index in 50% of patients with markedly positive scans, 22% of those with moderately positive scans, and 14.6% with inactive scans (p=0.0001).

Conclusion: Our findings show a strong association between vascular FDG uptake and clinical activity and traditional inflammatory markers. A weaker association was found between vascular FDG uptake and IL-6 levels. These data suggest that PET/CT may be a useful tool for evaluating disease activity in patients with LVV.

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Assessment of Disease Activity in Large Vessel Vasculitis: Initial Results of an International Delphi Exercise. Sibel Z. Aydin[1], Haner Direskeneli[2], Eric L. Matteson[3] and Peter A. Merkel[4]. [1]Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey, [2]Marmara University, School of Medicine, Istanbul, Turkey, [3]Mayo Clinic, Rochester, MN, [4]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Assessment of disease activity in large vessel vasculitis (LVV) is challenging. The lack of specific, validated outcome measurements for both Takayasu's (TAK) and giant cell arteritis (GCA) affects clinical care and research in these diseases.

Methods: The Delphi survey was sent out to >300 experts by e-mail. Experts were chosen from different specialties based on their interest in LVV and previous involvement in vasculitis clinical research. Experts from countries with high prevalence of either TAK or GCA were especially recruited. The first round included 99 items on a 5-point scale aiming to cover all potential disease manifestations. Items accepted or rejected by >70% of the voters are not advanced to subsequent rounds.

Results: 116 experts completed the survey and included physicians from 23 countries in Asia, Australia, Europe and North and South America. Most of the vascular/cardiovascular items (e.g. bruits, new loss of pulse, claudication) were accepted by >70% of experts for TAK; ocular findings (e.g. visual loss, blurred vision, retinal vasculitis) were considered high-priority outcomes for GCA. Vascular imaging (CT, MRI, PET, or ultrasound) was accepted for both TAK and GCA. SF36 and patient global assessment were widely accepted as tools for patient-reported outcomes in both diseases. Disease Extent Index-Tak (DEI.Tak) was the only composite index accepted by the majority for TAK. Only ESR and CRP were suggested as biomarkers in TAK, whereas hemoglobin level was also supported in GCA. Findings rejected by >70 % of the experts were erythema nodosum for TAK and pulmonary assessments for GCA. Many items were endorsed by a majority of experts but did not reach the 70% threshold for final acceptance; it is expected that additional items will reach the 70% threshold in subsequent Delphi rounds. Several new items were proposed by participants (e.g. IL-6 levels and novel patient reported outcome measures) that will be considered in subsequent rounds.

The majority of experts (63%) voted for aiming to have a common tool for both TAK and GCA but also develop additional tools specific for each disease. 25% felt the two diseases were unsuitable for common outcome measures.

Conclusion: This exercise points out the similarities and differences from experts' perspective for assessing clinical activity in TAK and GCA. The completion of the Delphi will produce a consensus-driven set of outcomes to study prospectively with the long-term goal of developing a core set of validated outcomes for LVV. Based on these data it is anticipated that such a set of outcomes will include many data elements common to both diseases, supplemented by disease-specific items for TAK and GCA. Continued international collaborative work will be required to advance this research for these diseases.

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CROSS-Sectional Assessment of Damage in Takayasu Arteritis with A Validated Tool. Ahmet Omma[1], Burak Erer[1], Omer Karadag[2], Neslihan Yilmaz[3], Fatma Alibaz-Oner[3], Fatih Yildiz[4], Melike Kalfa[5], Gezmis Kimyon[6], Sedat Kiraz[2], Haner Direskeneli[3], Eren Erken[4], Kenan Aksu[5], Ahmet Mesut Onat[6], Ahmet Gul[1], Lale Ocal[1], Murat Inanc[1] and Sevil Kamali[1]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Hacettepe University, Faculty of Medicine, Ankara, Turkey, [3]Marmara University, Faculty of Medicine, Istanbul, Turkey, [4]Cukurova University, Faculty of Medicine, Adana, Turkey, [5]Ege University, Faculty of Medicine, Izmir, Turkey, [6]Gaziantep University, Faculty of Medicine, Gaziantep, Turkey

Background/Purpose: Takayasu arteritis (TA) is a large vessel vasculitis with a chronic course, usually causing damage by the time of diagnosis. To our knowledge, there is no reported study assessing the damage related to TA itself or treatment. We aimed to evaluate the damage cross-sectionally in TA patients with Vasculitis Damage Index (VDI), a generic tool developed for systemic vasculitides.

Methods: A collection of 165 TA patients (146 female) fulfilling ACR criteria and followed-up more than 6 mo from 6 centers in Turkey, were enrolled into the study. All patients underwent detailed examination including eye, vascular imaging, echocardiography and bone dansitometry. Clinical, angiographical and treatment characteristics and damage items of VDI were recorded using a standardized protocol. Disease activity and quality of life (QoL) were evaluated by Kerr criteria and SF-36, respectively. TA patients with persistant disease activity ≥6 mo were considered as resistant. The correlation between VDI scores and disease duration, cumulative glucocorticoid (GC), cyclophosphamide (CYC) duration and doses, and mental (MCS) and physical (PCS) component summary scores of SF-36 were analysed by Pearson correlation test. VDI scores according to the disease resistance and

poor QoL (MCS and PCS scores <50) were compared by Mann Whitney U test.

Results: The mean age, follow-up time and disease duration were 40 ± 12 years, 74 ± 73 mo and 95 ± 91 mo, respectively. Type I (51%) was the most common type of vascular involvement. Cumulative doses / duration of GC and CYC were $10,6 \pm 9,6$ g / 64 ± 60 mo and $2 \pm 5,5$ g / $2,3 \pm 6,5$ mo, respectively; 39% of them had resistant course. Major vessel stenosis, absent pulses, claudication were demonstrated in ≥50% of TA patients, as damage items. Osteoporosis (22%) and cataract (12%) were the main treatment related damages. Cumulative VDI scores in TA cohort were found to be 4.3 ± 2.2, mainly (3.8 ± 1.9) due to disease itself. MCS and PCS scores were calculated as 43 ± 10 and 38 ± 11, respectively. Poor SF-36 MCS scores were demonstrated in 70% and PCS scores in 80% of the patients. VDI scores were found to be correlated with disease duration ($p<0.01$, $r= 0.27$), cumulative doses of GC ($p<0.01$, $r= 0.29$) and CYC ($p=0.02$, $r= 0.20$) and duration of GC ($p<0.01$ $r= 0.37$). A negative correlation was observed between the VDI and both MCS ($p=0.007$, $r=-0,21$) and PCS scores ($p<0.001$, $r=-0.36$). The higher VDI scores were detected in the subgroup of patients PCS <50 ($4,8 \pm 2,2$ vs $2,9 \pm 1,5$, $p<0.001$).

Conclusion: Cross-sectional analysis of this TA cohort with a long disease duration revealed vascular damage scores comparable to the scores of severe systemic necrotizing vasculitides. Majority of TA patients had disease related damage, characterized by peripheral vascular involvement. The longer disease duration and higher GC and CYC exposure were significantly associated with the damage. The severe damage scores (≥5) were observed in TA patients with poor health quality.

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Asymptomatic Myocardial Ischemic Disease in Takayasu's Arteritis.
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Background/Purpose: Cardiac involvement in Takayasu's arteritis (TA) is a leading cause of death. Previous studies reported a high incidence of myocardial involvement using exercise thallium-201 scintigraphy whereas macrovascular coronary lesions are not frequent in coronary angiography.

Objective: The aim of the present study is to evaluate coronary microvascular dysfunction in TA using dipyridamole thallium-201 myocardial scintigraphy.

Methods: Twenty five consecutive patients with TA [median (IQR) age 48 (36–60) years, with 18 (72%) females, and median duration of disease between diagnosis and enrollment 7 (3–11) years] were prospectively examined by 201Tl myocardial scintigraphy at rest and after dipyridamole induced stress.

Results: Among 25 TA patients, 21 (84%) had abnormal scintigraphic findings and 4 (16%) had normal myocardial perfusion. Using 17-segments model for quantitative image analysis, dipyridamole significantly improved resting 201Tl myocardial perfusion in 14/23 patients (60.9% with reversible defects in at least 3 segments) versus 9/23 (39.1% with permanent defects or reversible defects in less than 3 segments). We were able to examine coronary artery stenoses in 11 patients including 10 patients with thallium perfusion abnormalities. Among patients with thallium perfusion abnormalities, significant coronary artery stenoses were present in only 2/11 (18.2%) patients. No significant difference was found between TA patients with normal and abnormal myocardial perfusion scintigraphy in terms of cardiovascular risk factors or characteristics of TA.

Conclusion: Our results demonstrate a high incidence of myocardial involvement in TA patients mainly related to microcirculation impairment. This clearly demonstrate that this large vessel vasculitis, also affect vessels of small size. Systematic cardiac evaluation including dipyridamole thallium-201 stress myocardial scintigraphy is required to properly identify TA patients with asymptomatic myocardial involvement. Further studies are needed to determine whether myocardial findings using dipyridamole thallium-201 stress myocardial scintigraphy have an impact on the prognosis and treatment strategy.

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Aortic and Coronary Calcifications in Takayasu Arteritis.
Emire Seyahi[1], Ayca Ucgul[2], Serdal Ugurlu[1], Canan Akman[3], Deniz Cebi Olgun[3], Sebahattin Yurdakul[1] and Hasan Yazici[1]. [1]Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, [2]University of Istanbul, Cerrahpasa Medical Faculty, Istanbul, Turkey, [3]Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey

Background/Purpose: We had previously shown, similar to patients with systemic lupus erythematosus (SLE), patients with Takayasu arteritis (TAK) had significantly more atherosclerotic plaques in the carotid arteries compared to the healthy controls (1). Moreover, we had observed that atherosclerotic plaques were more common in areas where arteritis was more prominent, implying that atherosclerosis in TAK might be mainly due to local inflammation.

In this study, we aimed to investigate the presence of coronary artery (CAC) and thoracic aorta calcifications (ToAC) using multi-detector computed tomography (MDCT) in a larger cohort of TAK patients and controls. We again investigated the frequency of atherosclerotic plaques in the carotid arteries. These investigations enabled us to compare atherosclerotic lesions in different vessel beds in patients with TAK and controls and thus to test the hypothesis that atherosclerosis observed in TAK is primarily due to local factors.

Methods: We studied 47 female with TAK (mean age: 37.4 ± 8.0 SD years), 43 patients with SLE (mean age: 39.3 ± 8.1 years) and 70 healthy controls (mean age: 40.2 ± 5.2 years). Calcification in the coronary arteries and thoracic aorta was measured using MDCT. Carotid artery plaques (CAP) were assessed using B-Mode ultrasonography.

Results: Table 1 demonstrates the odds ratios for the surrogate markers of atherosclerosis among the study groups with healthy controls being the reference group. The OR for having atherosclerotic plaques was considerably higher (9 vs 4) among the SLE patients as compared to the TAK patients while the frequency of CAC was significantly increased only among patients with SLE compared to the healthy controls. However, ToAC and CAP were significantly more common among both TAK and SLE patients compared to the healthy controls. Calcification in the thoracic aorta was present in 45 % of TAK patients and its morphology was different than that observed in SLE. It was mostly circumferential in TAK, whereas punctuate or linear in SLE. As reported previously, similar to SLE patients, TAK patients were found to have increased risk for CAP. Moreover, among TAK patients CAC, ToAC and CAP were more likely to be seen in places where primary vasculitic lesions were frequent (coronary artery involvement: 67% vs 7 %, CAC (+) vs CAC (−), respectively, p =0.027; thoracic aorta involvement: 52 % vs 19 %, ToAC (+) vs ToAC (−), respectively, P= 0.029, and carotid artery involvement: 92 % vs 69 %, CAP (+) vs CAP (−), respectively, P=0.146).

Table. Prevalence and the odds ratios of CAC, ToAC and CAP

	Study groups	Patients with, n (%)	OR (95 % CI)	P value
CAC	TAK, n =47	5 (11)	4.0 (0.8–21.8)	0.104
	SLE, n =43	9 (21)	9.0 (1.8–44.0)	0.007
	HC, n =70	2 (3)	−	−
ToAC	TAK, n =47	21 (45)	27.5 (6.0–125.5)	<0.001
	SLE, n =43	10 (23)	10.3 (2.1–49.7)	0.004
	HC, n =70	2 (3)	−	−
CAP	TAK, n =47	12 (23)	3.1 (1.1–8.6)	0.030
	SLE, n =43	12 (28)	3.5 (1.2–9.7)	0.017
	HC, n =70	7 (10)	−	−

Conclusion: Unlike what is observed in SLE, atherosclerosis in TAK seems to be influenced by local rather than systemic factors.

Reference:
1) Seyahi E, et al. Atherosclerosis in Takayasu arteritis. Ann Rheum Dis 2006; 65: 1202–7.

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Presence of Fibromyalgia and Fatigue Is Not Increased in Patients with Takayasu's Arteritis. Fatma Alibaz-Oner, Meryem Can, Birkan Ilhan, Ozge Polat and Haner Direskeneli. Marmara University, School of Medicine, Istanbul, Turkey

Background/Purpose: Takayasu's arteritis (TAK) is a large-vessel vasculitis of the aorta and its major branches. To our knowledge, no data is reported about the frequency of Fibromyalgia Syndrome (FM), in TAK. We aimed to investigate the frequency of FM in TAK, defined according to the new 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia. The correlation between ACR-1990 and 2010 FM criterias and the effect of patient-reported outcomes (PROs) such as Health Assessment Questionnaire (HAQ), Multidimensional Assessment of Fatigue Scale (MAF), *Short-Form 36*-item survey (*SF-36) and hospital* anxiety and depression scales (HADS) on FM were analyzed.

Methods: We studied 51 patients with TAK (F/M: 47/4, mean age: 42.3 years), 50 (F/M: 35/15, mean age: 40.89 years) healthy controls (HC). All patients were examined for FM tender points by two observers (kappa: 0.648) and asked to complete new ACR 2010 FM questionnaire for FM (ref1). *SF-36, MAF* and HADS were used to assess quality of life together with HAQ. Seventeen patients were re-evaluated 6 months later.

Results: Six(11,7%) patients with TAK and 5 HC (10%) met the ACR-2010 FM criteria, whereas only 3(5,8%) TAK patients and no controls (0%) met the 1990 Criteria. No significant differences regarding the FM frequency were present according to both ACR-2010 and 1990 FM criterias between TAK and HC. No differences were also observed for the 2 subscales of 2010 criteria, the Widespread Pain Index(WPI) and the Symptom Severity scale (SSS) scale among the groups. Fourteen patients (33,3%) were clinically active. FM presence was also similar between active and inactive patients (p=0,188). The results of PROs were showed in Table 1. WPI correlate significantly with tender points (r=0,477, p<0,001), MAF (r=0,623, p<0,001), HAQ (r=0,477, p<0,001), anxiety (r=0,458, p<0,001), depression (r=0,378, p<0,001), PCS (r=−0,586, p<0,001) and MCS (r=−0, 335, p<0,001). SSS correlate significantly with tender points (r=0,477, p<0,001), MAF (r=0,775, p<0,001), HAQ (r=0,437, p<0,001), anxiety (r=0,557, p<0,001), depression (r=0,438, p<0,001), PCS (r= −0,593, p<0,001) and MCS (r=−0,531, p<0,001). During follow-up, no significant differences between baseline and 6.month were observed in terms of frequency of FM, MAF, HAQ, HADS, PCS and MCS.

Table 1. Results of the patient-reported outcomes in TAK and controls

	Takayasu'sarteritis (n=51)	Healthy controls (n=50)	P values
MAF	18,5 (0–49,7)	17,5 (0–38,6)	0,282
Anxiety scale score	5 (0–21)	5 (0–18)	0,533
Depression scale score	3 (0–21)	3 (0–14	0,529
HAQ	0,15 (0–2,35)	0 (0–0,8)	**<0,001**
PCS	46,9 (17,5–61,7)	53,4 (30,4–100)	**0,003**
MCS	46 (22,4–65,4)	49,9 (20,8–100)	0,350

Conclusion: The frequency of FM is similar to general population in patients with Takayasu arteritis. However, although other PROs also does not differ from HC, the new FM criteria subscales WPI and SSS significantly correlated with scales such as SF-36, MAF, anxiety and depression scale and HAQ in TA, suggesting that in a minority of patients with FM and TA, PROs are affected with FM presence.

1. Wolfe F, Clauw DJ, Fitzcharles MA, et all. The ACR preliminary diagnostic criteria forfibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010 May;62(5):600–10.

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Tocilizumab in Refractory Takayasu's Arteritis: 7 Patients Followed At a Single Italian Centre. Enrico Tombetti, Elena Baldissera, Stefano Franchini, Patrizia Aiello, Francesca Motta, Barbara Gulgielmi and Maria Grazia Sabbadini. Vita-Salute San Raffaele University, Milan, Italy

Background/Purpose: Takayasu arteritis (TA) is a rare chronic-relapsing vasculitis involving primarily the aorta and its major branches.TA is associated with considerable morbidity and mortality. Therapy is based on corticosteroids (CS) but steroid-sparing immunosuppressive drugs are required in most patients to minimize CS adverse events and to control progressive vascular disease. However, about 25% of patients relapse when CS are tapered. In this setting, previous works showed that tocilizumab (TCZ), an humanized anti-IL6 receptor antibody may be useful.

Objectives: To evaluate the safety and efficacy of TCZ in the treatment of refractory TA.

Methods: We retrospectively studied 7 TA patients (pts) treated with TCZ (8 mg/kg monthly) between 2010 and 2012 at a single academic Italian center. All pts satisfied ACR criteria for TA classification and had active refractory TA. Treatment efficacy was evaluated as: i) reduction of signs and symptoms of active disease, ii) steroid sparing activity (assessed as reduction in the average daily dose measured within the 12 month period preceding each medical evaluation, iii) angio-MRI assessment of vascular lesions evolution, iv) decrease in CRP and ESR.

Results: All 7 pts were female, with a median age at the beginning of TCZ therapy of 35 years (range 32–46), median duration of disease 66 months (range 17–101). Before TCZ therapy, they were taking a median of 4 (range 1–8) immunosuppressive agents. Four pts had been previously treated with anti-TNF agents. Median FU on TCZ therapy was 14 months (range 9–24). Mean duration of CS therapy before TCZ was 37 months. Two pts did not show signs or symptoms of active disease during FU while in 3 pts satisfied NIH criteria of active disease. During FU, average prednisone daily dose decreased from a median value of 8.3 mg (range 5.9–29) to 8.0 mg (range 5.0–16): however, the dose could be reduced more than 3 mg/day in 4 patients. The median number of vascular lesions was unchanged (8, range 4–12) at baseline and at the end of FU. In one pt vascular lesions improved during FU and in another did not progress, while in the other 5 pts there was worsening of at least one vascular lesion. Median values of ESR and CRP decreased from 34 (range 8.0–76) to 4.0 (range 2.0–45) mm/h and from 13 (range 10–35) to 2.0 (range 1.0–44) mg/l, respectively. TCZ was stopped in 4 pts because of suboptimal disease control. During FU one pt had severe pneumonia, requiring TCZ interruption, another had relapsing upper respiratory infections and a third developed pytiriasis rosea, that subsided after TCZ interruption.

Conclusion: In this study of refractory TA, TCZ showed efficacy only in a minority of pts. Our data do not confirm the positive results of TCZ therapy reported in previous studies. However, our pts may have had more severe disease, as suggested by the higher number of immunosuppressive agents at baseline compared to previous reports. Finally, it should be noted that ESR and CRP do not appear to correlate reliably with disease activity during TCZ therapy. Further studies are necessary to better define the role of TCZ in TA therapy.

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Aspects of Innate Immunity in Behçet′s Disease: A Model of Auto-inflammatory Disease? Sandro F. Perazzio[1], Paulo Vitor Soeiro Pereira[2], Alexandre Wagner S. de Souza[3], Antonio Condino-Neto[2] and Luis Eduardo C. Andrade[4]. [1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]USP, São Paulo, Brazil, [3]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [4]Universidade Federal de São Paulo, Sao Paulo, Brazil

Background/Purpose: Behçet's disease (BD) is a systemic vasculitis of unknown etiopathogenesis. Increased neutrophil activation has been previously shown in BD patients and it is unclear whether neutrophil activation occurs constitutively or if it is secondary to a yet unknown stimulus or some serum or tissue soluble factor. The hypersensitivity to *Streptococcus sanguinis* antigens suggests that infectious agents may play a role in BD pathogenesis. Recently, it has been postulated that BD may be a form of auto-inflammatory disease. The present study investigated several aspects of

cellular activation in neutrophils and peripheral blood mononuclear cells (PBMC) of patients with active and inactive BD.

Methods: four study groups were analyzed: active BD (aBD; n=17), inactive BD (iBD; n=26); septic patients (SP; n=10); healthy controls (HC; n=10). BD activity was established as Behçet's Disease Current Activity Form simplified (BDCAFs) score[3]2. Flow cytometry analysis evaluated phagocytosis (zymosan particles, *Stretococcus pneumoniae* and *Candida albicans)* and the oxidative metabolism before and after stimulation with phorbol myristate acetate (PMA). The shedding of CD62L was determined after stimulation of TLR-2, -3, -4, -5, -7. Microbicidal activity against *Streptococcus* and *Candida* was determined by means of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction and absorbance read by ELISA. The supernatant of PBMC cultures under TLR or microbial stimuli were used for determination of TNFa, IFNg, IL-12p70, IL-23, IL-6 and IL-10 by ELISA. The supernatant of neutrophil cultures under PMA, LPS or microbial stimuli were used for determination of IL-1$_\beta$ and IL-8.

Results: There was no difference in medication use between aBD and iBD. Phagocytosis, microbial killing activity and oxidative burst assays in PMN and monocytes showed no difference among the four groups. The activated monocyte index of shedding assay showed higher activation by TLR3 in iBD (31±28%, p=0.022) and aBD (27±20%, p=0.029) than in SP (3.4±25%). In contrast, the activation by TLR7 was lower in iBD (27±23%, p=0.022) and aBD (32±27%, p=0.029) than in SP (74±39%). BD monocytes did not differ from HC monocytes regarding activation via TLR stimuli. Neutrophils from aBD produced less IL-1β after stimulus with *S. pneumoniae* (68±61 pg/mL) than HC (273±174 pg/mL, p=0.05) and showed a trend for lower values comparing to iBD (175±93 pg/mL, p=0.076). There was no difference in the production rate of other cytokines.

Conclusion: These results showed that phagocytes in BD are not constitutively activated. This negative evidence suggests that the marked involvement of neutrophils in BD pathophysiology may be caused by some kind of stimuli produced by other cells at or close to the target tissues. Thence, further studies should address proteomic analyses of the serum and samples from target tissues in BD in an attempt to identify possible metabolic pathways involved in neutrophil activation in BD.

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A Genome-Wide DNA Methylation Study Identifies Significant Epigenetic Changes Across the Genome and in Multiple HLA Loci in Behçet's Disease.

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Background/Purpose: Behcet's disease (BD) is a systemic vasculitis of poorly understood etiology. Herein, we study the DNA methylome in BD for the first time and identify significant DNA methylation changes in this disease.

Methods: We studied six untreated newly diagnosed male patients with BD and six age-, sex-, and race-matched controls. Monocytes and CD4+ T cells were purified using magnetic bead separation from PBMCs. DNA was extracted from each cell subset and treated with sodium bisulfite. Genome-wide DNA methylation changes were assessed using the Illumina Infinium HumanMethylation450 BeadChip arrays. This platform allows for the interrogation of over 485,000 CpG sites within the entire genome. Percent methylation of each CpG site and differential methylation between patients and controls were determined using GenomeStudio. False discovery rate of ≤5% was applied to correct for multiple testing. Further, only CpG sites with a differential methylation score between patients and controls ≥75 ($P \leq 5\times10^{-8}$), and a methylation difference of at least 1.2-fold were included in the analysis. Pathway and gene ontology analysis was performed using Ingenuity.

Results: A total of 343 hypomethylated and 337 hypermethylated CpG sites, and 232 hypomethylated and 254 hypermethylated CpG sites, were identified in BD monocytes and CD4+ T cells, respectively. The most significant DNA methylation change detected was hypomethylation in multiple CpG sites located within the *HLA-C* gene in both monocytes (7.9-fold) and CD4+ T cells (8.2-fold) in patients compared to controls. Differential

DNA methylation between patients and controls, consistent in the two cell subsets, was also observed in *HLA-DPB1, HLA-DPB2, HLA-DQA1, HLA-DQA2, HLA-DRB1, HLA-DRB6,* and *HLA-G.* Other hypomethyled loci in BD include *NOP10* (monocytes, 3.2-fold; CD4+ T cells, 4.2-fold), and *SPDEF* (monocytes, 2.3-fold; CD4+ T cells, 2.2-fold). Hypermethylated loci include *IL17RA* (monocytes, 4.0-fold; CD4+ T cells, 2.2-fold), *MMP27* (monocytes, 3.8-fold; CD4+ T cells, 2.0-fold), *MRPL1* (monocytes, 2.1-fold; CD4+ T cells, 5.7 fold), and *SLC37A1* (monocytes, 2.0-fold; CD4+ T cells, 1.9-fold). Canonical pathway analysis of differentially methylated genes highlights the antigen-presentation pathway (monocytes, $P=1.1\times10^{-6}$; CD4+ T cells, $P=4.02\times10^{-11}$). Indeed, transcription factor binding site analysis demonstrates enrichment of CIITA binding sites in differentially methylated genes (monocytes, $P=1.22\times10^{-3}$; CD4+ T cells, $P=4.52\times10^{-4}$). Cytotoxic T cell-mediated apoptosis, allograft rejection signaling, graft-versus-host disease signaling, and OX40 signaling, are also enriched pathways. Network analysis also highlights type-I interferon and NFkB signaling.

Conclusion: We performed a genome-wide DNA methylaltion study in BD using two distinct cell populations. Our data demonstrate significant genome-wide epigenetic differences between BD patients and healthy age-, sex-, and race-matched controls. We identified differential DNA methylation in the HLA locus in BD, and hypothesize that BD-associated risk alleles in the HLA might induce disease susceptibility, at least in part, by tagging a DNA methylation change.

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The Unmet Need in Behcet's Disease: Most Patients Are Not in Complete Remission in the Long-Term Follow-up.

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Background/Purpose: The nature of Behcet's disease (BD) as a multisystemic disorder with a remitting-relapsing course is unsufficiently explored. As complete remission should be aimed in all inflammatory diseases, we investigated the frequency of complete remission in routine practice in BD.

Methods: In this retrospective study, 130 patients with BD (F/M: 67/63, mean age: 43.23±11,7 years) classified according to ISG criteria were included. The demographic and clinical data for active organ manifestations and treatment protocols were evaluated, both for the current visit and in the last month. Patients having at least one of any disease manifestations were categorized as active.

Results: A total of 857 visits of 130 patients were overviewed**.** Mean visit number was 6,5± 2,7 (range:1–10) and mean follow-up duration was 53,54±41,79 months (3–162). Sixty-one patients (46,9%) were of mucocutaneus type, whereas 69 patients (53,1%) had major organ involvement. When all visits combined, 16–49% of the patients were using immunosuppressives (IS), whereas 30–62,3% was under non-IS therapies such as colchicine or NSAIDs. There was also a group of noncompliant patients (6–53,8%) without any treatment. Patients were clinically active in 67% (n=575) of the total visits (n=857). Mean frequency of clinical activity was 61,9% (53,7–87,7), which increased to 77,2% (64,2– 90) when the month before the visit was also included. The major cause of the activity was aphthous ulcers (44,1–74,6%) with other mucocutaneous manifestations also commonly present (Genital ulcer: 4,5–33,8 %, erythema nodosum: 7,5–30%, papulopustular lesions: 16,3–39,2%, arthritis: 19,9–33,3%, uveitis: 0–7,7% and vascular involvement: 2,3–12,3%). No difference was observed between the frequency of activity of patients having ISs or non-IS therapies.

Conclusion: Although complete remission is the current, primary target in inflammatory rheumatological diseases such as rheumatoid arthritis or vasculitides, it is fairly difficult to achieve complete remission in BD with current therapeutic regimens. The reluctance of the clinician to be aggressive for some manifestations with low morbidity, such as mucocutaneous lesions, might be influencing the continuous, low-disease activity state in BD patients.

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Efficacy of Quantitative Analysis of Brainstem Atrophy On Magnetic Resonance Imaging for Diagnosis of Chronic Progressive Neuro-Behçet's Disease. Hirotoshi Kikuchi[1], Maki Takayama[2], Yoshitaka Kimura[2], Kurumi Asako[2], Hajime Kono[2], Yasuo Ono[1] and Shunsei Hirohata[3]. [1]Teikyo University Shool of Medicine, Tokyo, Japan, [2]Teikyo University School of Medicine, Tokyo, Japan, [3]Kitasato University School of Medicine, Sagamihara, Japan

Background/Purpose: CNS involvement in Behçet's disease, usually called neuro-Behçet's disease (NB), can be classified into acute NB (ANB) and chronic progressive NB (CPNB) based upon the differences in clinical courses and responses to corticosteroid treatment. Previous studies demonstrated that brainstem atrophy was significantly more frequently observed in CPNB than in ANB or non-NB. Since the presence of brainstem atrophy depends on the anecdotal judgment by expert radiologists, more objective definition of brainstem atrophy is required. The present study was designed to examine whether quantitative analysis of the brainstem areas on magnetic resonance imaging (MRI) scans might be useful for early diagnosis as well as for evaluation of the disease activity of CPNB.

Methods: MRI scans recorded at the diagnosis and at various periods thereafter were evaluated in patients with ANB (n=10), CPNB (n=10), non-NB (n=8), and NPSLE (n=8). MRI scans of age- and sex- matched control patients for CPNB (non-inflammatory CNS diseases [NID]) (n=10) were also studied. The areas of midbrain tegmentum and pons were measured on mid-sagittal sections of T1-weightened images of brain MRI using image analysis software Image J (ver.1.45, National Institutes of Health: NIH, U.S. [http://imagej.nih.gov/ij/download.html]).

Results: The areas of midbrain tegmentum (ANB: 145.9 ± 20.1 mm^2 [mean $\pm$ SD], CPNB: 125.6 ± 18.0 mm^2, non-NB: 133.0 ± 16.4 mm^2, NPSLE: 133.4 ± 19.7 mm^2, NID: 151.1 ± 11.8 mm^2) as well as those of pons (ANB: 540.1 ± 87.2 mm^2, CPNB: 482.0 ± 91.3 mm^2, non-NB: 540.3 ± 40.2 mm^2, NPSLE: 517.3 ± 47.1 mm^2, NID: 574.1 ± 43.4 mm^2) were found to be lower in CPNB than those in the other 4 groups. On receiver operating characteristic (ROC) analysis, the sensitivity / specificity of the areas of midbrain tegmentum, pons and brainstem (midbrain tegmentum + pons) for diagnosis of CPNB against non-CPNB (ANB + non-NB) were 80.6% / 66.7% at cut-off value of 134.0 mm^2, 70.0% / 77.8% at cut-off value of 483.7 mm^2 and 70.0% / 94.4% at cut-off value of 614.9 mm^2 respectively (figure). The time kinetics analysis demonstrated that brainstem atrophy progressed most markedly during the first 2 years from the initial diagnosis of CPNB. Finally, brainstem atrophy progressed at significantly greater degree in CPNB patients with continuous elevation of cerebrospinal fluid (CSF) IL-6 (>20 pg/ml) compared with those in whom CSF IL-6 levels were kept bellow 20 pg/ml.

The area of brainstem for CPNB vs non-CPNB

Sensitivity 70.0%
Specificity 94.4%
at 614.9 mm^2
AUC: 0.75
p=0.03
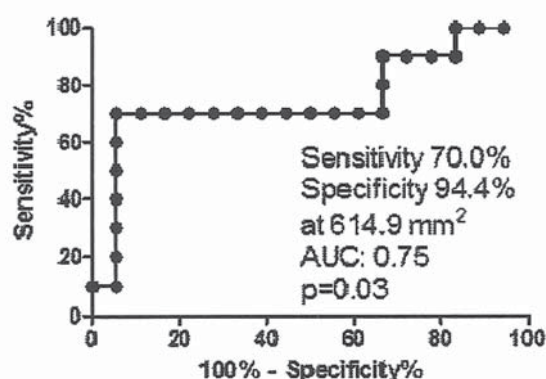
Conclusion: These results confirm that brainstem atrophy is one of the characteristic features of CPNB. Moreover, the data suggest that quantitative analysis of the brainstem areas on MRI scans might be effective for early diagnosis as well as for evaluation of the disease activity of CPNB. Finally, it is also suggested that brainstem atrophy might progress due to CNS inflammation mediated by IL-6 during the early phase of CPNB.

The Clinical Course of the Acute Deep Vein Thrombosis of the Legs in Behçet's Syndrome. Yesim Ozguler[1], Melike Melikoglu[2], Firat Cetinkaya[3], Serdal Ugurlu[4], Emire Seyahi[5], Koray Tascilar[4] and Hasan Yazici[2]. [1]Istanbul University, Cerrahpasa Medical School, Rheumatology, Istanbul, Turkey, [2]Rheumatology, Istanbul, Turkey, [3]Istanbul, Turkey, [4]Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, [5]Cerrahpasa Faculty of Medicine, Istanbul University, İstanbul, Turkey

Background/Purpose: 15-50% of patients with Behçet's syndrome have vascular involvement (BS). Deep vein thrombosis is the most common form with lower extremity deep vein thrombosis (LEDVT) making up 70% of all vascular involvement. The aim of this study was to determine the clinical course of LEDVT about which there has been little data.

Methods: Consecutive BS patients attending our multidisciplinary BS outpatient clinic were included after an acute or subacute first episode of LEDVT in one leg. They might have had a previous episode of LEDVT in the contralateral extremity. The same radiologist performed a structured and detailed lower extremity Doppler ultrasonography (US). All deep veins, VCI and major superficial veins were examined at 1, 3, 6, 18 and 24 months after the index event. Nodular lesions that evolved during the follow-up were also examined for their US structure to differentiate between the presence of superficial vein thrombosis and erythema nodosum.

Results: Within a course of 20 months 31 patients (4F, 27M) with LEDVT in a previously uninvolved leg were seen and included in the study. 10 patients had had a previous episode of LEDVT in the opposite leg. Mean age was 29.5 ± 7, mean disease duration since disease onset was 49.5 ± 34.6, and the mean follow-up duration during the study was 13.4 ± 6.2 months. Veins involved in order of frequency were popliteal vein (42%), superficial femoral vein (31%), crural veins (29%) and common femoral vein (27%). VCI was involved in 3 (5%) patients. 14 patients (45%) relapsed during follow-up. 11 patients relapsed with a superficial thrombophlebitis and 5 patients relapsed with a new deep vein thrombosis. Mean time to relapse was 2.83 ± 1.99 months when the relapse was a superficial thrombophlebitis and 6.0 ± 2.3 months when the relapse was a LEDVT (P=0.001). Only 3 out of 19 patients who had a recanalization ($\geq$50%) at month 3 follow-up had a relapse. On the other hand, a relapse was observed in 11 of the 12 patients with poor recanalization(<50%) (P=0.001). All 3 patients with VCI involvement had venous skin ulcers in the lower extremity and these 3 patients were also the only patients with skin ulcers in the whole group. 17/31 (55%) patients developed nodular lesions during the study. 13/17 had had previous episodes of nodular lesions while in 4 patients these appeared for the first time. Doppler ultrasonographic examination of these nodules revealed superficial thrombophlebitis in 12 (70%) and like lesions in 5 patients (29%).

Conclusion: The more common vascular relapse after an episode of LEDVT is superficial thrombophlebitis. Relapses of a superficial thrombophlebitis occur earlier than relapses with a LEDVT. Poor recanalization of the index LEDVT at 3 months is associated with relapses. The presence of skin ulcers seems to go along with inferior vena caval thrombosis. As expected, LEDVT in BS is associated more with superficial thrombophlebitis than with erythema nodosum lesions.

Characteristics, Treatment and Outcome of Gastrointestinal Involvement in Behçet's Syndrome: Experience in A Dedicated Center. Ibrahim Hatemi[1], Gulen Hatemi[2], Yusuf Erzin[1], Aykut Ferhat Celik[1] and Hasan Yazici[3]. [1]Istanbul University, Cerrahpasa Medical School, Gastroenterology, Istanbul, Turkey, [2]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [3]Istanbul University, Cerrahpasa Medical School, Rheumatology, Istanbul, Turkey

Background/Purpose: Gastrointestinal involvement can be a severe complication resulting in perforation and massive bleeding. Controlled data regarding treatment is lacking and long term prognosis is not well known.

Methods: We retrospectively reviewed the charts of all BS patients evaluated with a suspicion of gastrointestinal involvement. We identified those with GIBS and surveyed their demographic features, other BS manifestations, clinical, endoscopic and histologic gastrointestinal findings, and treatment modalities. Patients were evaluated either in the outpatient clinic or if not possible by phone calls to assess their outcome.

Results: Among the 8058 recorded BS patients in our multidisciplinary outpatient clinic, 69 had symptoms suggesting gastrointestinal involvement and lesions on endoscopy. Among these, 18 patients had other reasons for their gastrointestinal symptomes and endoscopic lessions. The remaining 51 patients had GIBS (Table). The presenting symptoms were acute abdomen caused by perforations in 4/51 patients, massive bleeding in 8/51 patients and abdominal pain and/or diarrhea in 39/51 patients. Surgery had to be performed in 20/51 patients, and 4 of them had to be re-operated for development of stricture, progressive disease, relapse, and corrective surgery, 1 patient each. The most commonly used drugs for initial management were azathioprine 2–2.5 mg/kg/day (n=33) and 5 ASA compounds 3–4 g/day (n=13). Remission was observed and there were no relapses during a mean follow-up of 44.3±46.9 months in 22/33 (67%) patients who had initially been prescribed azathioprine (2.5 mg/kg) and during 45.0±50.1 months in 9/13 (68%) patients who had been prescribed 5 ASA compounds. Other than the 33 patients who used azathioprine as their initial treatment, remission was also obtained with azathioprine in 3/4 patients who were resistant to 5 ASA compounds. Among the 10 patients who had relatively severe symptoms and persistent large ulcers despite at least 6 months of azathioprine treatment, endoscopic and symptomatic remission could be obtained with thalidomide in 4 patients, infliximab in 4 patients and adalimumab in 2 patients. After a mean follow-up of 7.1±4.8 years (range 0.25–17 years), 42 (84%) patients were in remission and 14 (28%) of these were off treatment. Four (8%) patients were still active, 3 (6%) patients had died due to non-GI releated reasons and 2 (4%) were lost to follow-up. The reasons for death were pulmonary artery thrombosis, infection and acute renal failure due to amyloidosis in 1 patient each.

Patients with GI involvement of BS (n)	51
Men:women	27:24
Mean age ± SD (years)	38.5 ± 9.3
Mean age at diagnosis of GIBS ± SD (years)	31.2 ± 7.1
Oral ulcers	51/51
Genital ulcers	43/51 (86%)
Positive pathergy reaction	27/51 (54%)
Papulopustular lesions	34/51 (68%)
Erythema nodosum	24/51 (48)
Arthritis	17/51 (33%)
Uveitis	10/51 (20%)
Deep vein thrombosis	4/51 (8%)
Superficial thrombophlebitis	4/51 (8%)
Pulmonary artery thrombosis	1/51 (2%)
Neurologic parenchymal involvement	3/51 (6%)
Dural sinus thrombosis	3/51 (6%)
Ileocecal region involvement	20/51 (40%)
Colonic involvement	14/51 (28%)
Terminal ileum involvement	12/51 (24%)
Iliocolonic involvement	4/51 (8%)
Duodenal bulbus involvement	1/51 (2%)

Conclusion: 84% of patients with GIBS were in remission after a mean of 7 years of follow-up. Surgery was required in 40% of patients with GIBS. 5 ASA compounds or azathioprine provided remission and prevented relapses in two thirds of the patients. The latter was also beneficial in some patients resistant to 5 ASA compounds. Resistant and relapsing cases could be managed with thalidomide or TNF-alpha antagonists.

Disclosure: **I. Hatemi**, None; **G. Hatemi**, None; **Y. Erzin**, None; **A. F. Celik**, None; **H. Yazici**, None.

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What Affects the Quality of Life in Patients with BEHCET'S Disease?
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Background/Purpose: The aim of this study was to evaluate the possible associations between quality of life (QoL) and sociodemographic features, disease characteristics and the Behcet's Disease (BD) disease activity.

Methods: One hundred and seven patients with BD were included in this study. Sociodemographic features including age, gender, education level of the patients and the disease characteristics including disease duration, disease onset age, the history BD clinical involvements were recorded. In patients with BD, the BD Current Activity Form was used for the evaluation of disease activity. The short form-36 (SF-36) QoL scale was used to evaluate the QoL in patients with BD. The Student t test, analysis of variance and Spearman's correlation matrix were used for the statistical analysis.

Results: Men showed higher mean scores of role-physical and bodily pain domains of SF-36 than women did (p <0.000 and 0.001). Patients over 41 years of age had higher mean general health scores and university graduates had higher mean mental health scores than the other groups (p <0,01). Patients with a disease duration more than 5 years and patients have a younger disease onset age showed lower general health score than the others (p<0,01). Also patients with an anamnesis of uveitis, genital ulceration, erythema nodosum, thrombophlebitis, joint and gastrointestinal system involvement showed lower QoL than the patients without these complaints (p <0,05 and p <0,01). In the analysis of disease activity physical subscores of SF-36 were found to be correlated with fatigue, oral ulceration and joint involvement (p<0, 01). Bodily pain showed a correlation with fatigue, headache and more highly with joint involvement (p<0,01 and p<0,001 respectively). General health was correlated with GIS and eye involvement and vitality was found to be correlated with fatigue, patient's and doctor's impression of disease activity (p<0,01). Mental and emotional scores were correlated with oral- genital ulceration, eye and joint involvements (p<0,01).

Conclusion: In addition to demografic features and clinical involvements, BD disease activity can affect QoL in patients with BD. These results highlight the importance of managing the symptoms and the disease activity effectively in order to improve QoL in BD.

Disclosure: **M. Melikoglu**, None; **M. A. Melikoglu**, None.

2376

Behcet's Disease: Combination of Pulse Cyclophosphamide, Azathioprine, and Prednisolone for the Treatment of Retinal Vasculitis; Longitudinal Study On 10 Years.
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Background/Purpose: Ocular lesions of Behcet's Disease (BD), need aggressive treatment to prevent severe loss of vision or blindness. Cytotoxic drugs are the main therapeutic agents and the first line treatment for it. Retinal vasculitis is the most aggressive lesion of ocular manifestations. It has the worse outcome. We present here the outcome with a combination of pulse cyclophosphamide, azathioprine, and prednisolone, on long-term usage up to 10 years on 291 patients (17286 eyes-months of follow-up).

Methods: Cyclophosphamide was used as one gram as monthly pulse for 6 months and then every 2 to 3 months as necessary. Azathioprine was used as 2 to 3 mg/kg/weight/daily. Prednisolone was associated as 0.5 mg/kg/ daily. Upon the suppression of the inflammatory reaction, prednisolone was tapered gradually. Inclusion Criteria: 1- Fulfilling the International criteria, the ICBD. 2- Having active posterior uveitis (PU) and/or retinal vasculitis (RV). Visual acuity (VA): was calculated by the Snellen chart on a scale of 10 (best vision 10/10). An activity index was calculated for PU and RV. A Total Adjusted Disease Activity Index (TADAI) was calculated for both eyes taking in account all parameters. Results were assessed at 3, 6, 9 months, then at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 10 years.

Results: The mean improvement for Visual Acuity (p value) was: 0.9 (<0.001), 0.9 (<0.001), 0.9 (<0.001), 1.0 (<0.001), 0.8 (<0.001), 0.9 (<0.001), 0.9 (<0.001), 0.9 (<0.001), 1.1 (0.005), 0.1 (0.9), −0.5 (0.3), −0.5 (0.35), +2.0 (0.2), +2.9 (0.2), +0.3 (0.9). The mean improvement for Posterior Uveitis was: 1 (<0.001), 1.2 (<0.001), 1.5 (<0.001), 1.4 (<0.001), 1.4 (<0.001), 1.6 (<0.001), 1.6 (<0.001), 1.7 (<0.001), 1.9 (<0.001), 1.9 (<0.001), 1.9 (<0.001), 2 (<0.001), 2 (0.01), 2.8 (0.08), 1 (0.9). The mean improvement for Retinal Vasculitis was: 1.1 (<0.001), 1.7 (<0.001), 1.6 (<0.001), 1.6 (<0.001), 1.8 (<0.001), 1.7 (<0.001), 1.9 (<0.001), 1.8 (<0.001), 2.1 (<0.001), 2.2 (<0.001), 2.2 (<0.001), 1.8 (0.004), 6 (0.11), 4 (0), 2 (0). The mean improvement for TADAI was: 9.1 (<0.001), 11.7 (<0.001), 12.7 (<0.001), 11.9 (<0.001), 13 (<0.001), 13.8 (<0.001), 14.2 (<0.001), 14.6 (<0.001), 13.5 (<0.001), 16.3 (<0.001), 19.6 (<0.001), 17.1 (<0.001), 16.2 (0.6), 5.4 (0.2), 4 (0.6). Overall results (from baseline to the last evaluation): The mean VA improvement was 0.8 (<001), PU 1.4 (<0.001), RV 1.6 (<0.001), and TADAI 11 (<0.001). VA improved in 45.4% of eyes, PU in 75.6% of eyes, RV in 71.5% of eyes, and TADAI in 74.9% of patients. VA aggravated in 33% of eyes, PU in 14% of eyes, RV in 16.9% of eyes, and TADAI in 18.9% of patients. The remaining kept their baseline values.

Conclusion: All parameters improved significantly. The improvement in VA was the least. It was mainly due to cataract. The non-significance of p values in the last years of follow-up was due to the low number of patients.

Combination of pulse cyclophosphamide and azathioprine is the best treatment choice for retinal vasculitis before opting for biologic agents.

2377

Impaired Endothelial Function in Patients with Takayasu's Arteritis.
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Background/Purpose: Takayasu' s arteritis (TAK) is a chronic, inflammatory, large-vessel vasculitis. In the present study we aimed to evaluate vascular endothelial function in patients with TAK compared to systemic lupus erythematosus (SLE), another inflammatory, autoimmune disorder.

Methods: We studied 33 patients with TAK, 18 patients with SLE and 20, age and sex-matched healthy controls. Brachial artery Doppler ultrasonography (USG) and bilateral carotid artery intima-media thickness (CIMT) measurements were performed.

Results: Basal diameter and nitrate- induced dilatation (NID) values of the brachial artery were similar between the three groups. However, flow-mediated dilation (FMD) was markedly reduced in patients with TAK (Table 1). Carotid artery intima-media thickness (CIMT) was also significantly increased in TAK group, compared to the controls (0.11 ± 0.03 vs to 0.07 ± 0.009 cm, respectively, p=0.0001). Presence of hypertension had no association with FMD and CIMT measurements. In the SLE group, a marked impairment in FMD % was obtained (8.85 ± 2.8, p=0.0001). % NID and CIMT measurements was observed to be similar between the patients with SLE and the healthy controls (p=0.60 and p=0.05, respectively).

Table 1. Brachial artery Doppler ultrasonography measurements in patients with Takayasu's Arteritis and SLE as compared controls

	Basal diameter (cm)	FMD (%)	NID (%)
TAK patients (N=33)	0.28 ± 0.06	**6.96 ± 4.5***	16.28 ± 9.8
SLE patients(N=18)	0.29 ± 0.04	**8.85 ± 2.8****	15.67 ± 4.5
Controls (N=20)	0.29 ± 0.02	15.6 ± 2.2	16.07 ± 2.36

*P:0.0001, **P:0.0001
TAK: Takayasu' s arteritis, FMD: Flow mediated dilatation, NID: Nitrate induced dilatation.

Conclusion: In the present study, we detected significantly decreased FMD and increased CIMT in TAK patients, suggesting a marked endothelial dysfunction. Chronic inflammation and vascular fibrosis might lead to increased atherosclerosis in TAK.

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Evaluation of the EULAR/ACR 2012 Classification Criteria for Polymyalgia Rheumatica: Comparison of the New Algorithms with and without Ultrasound to the Formerly Used Criteria. Sandra Balser[1], Wolfgang Hartung[1], Emmanuelle LeBras[1], Boris P. Ehrenstein[1], Martina Müller[2] and Martin Fleck[1]. [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [2]University Clinic Regensburg, Regensburg

Background/Purpose: The purpose of this study was to compare the sensitivity of the algorithms with and without ultrasound of the EULAR/ACR 2012 Classification Criteria for Polymyalgia rheumatica (PMR) to the former criteria in a retrospective single center study.

Methods: All patients newly diagnosed with PMR at our tertiary rheumatology center between 01/2011 to 06/2012 were included in this retrospective study and analyzed whether the EULAR/ACR 2012 Classification Criteria for PMR with and without ultrasound as well as the formerly used PMR criteria (Bird & Wood's, Chuang & Hunder's, Healey's, Jones & Hazelman's) were fulfilled. All patients with suspected PMR underwent physical examination, questionaires, laboratory analysis, ultrasound examination of joints and an organ staging to exclude other conditions mimicking PMR (mostly laboratory analysis, chest X-ray and abdominal ultrasound examination).

Results: PMR was established as a new diagnosis by a rheumatologist of our center in 35 patients between 01/2011 to 06/2012. The average age was 66.4 +/- 8.8 (mean +/- standard-deviation) years. 60.0% of those 35 patients were female. The average ESR before treatment was 43.0 +/- 24.6 mm/1h, the average CRP 43.8 +/- 31.6 mg/l, the average duration of morning stiffness 88.7 +/- 59.0 min. 82.9 % had hip pain or limited range of motion, 91.4 % had normal values for RF and ACPA and 34.3 % had no other joint involvement. We found that the sensitivity of the EULAR/ACR 2012 classification criteria for PMR without ultrasound was 88.6 %, the sensitivity of the algorithm with ultrasound was 82.9 %. We did not detect any patient fulfilling the classification criteria with ultrasound but not the criteria without ultrasound. The sensitivity of the formerly used criteria was 82.9 % for Bird & Wood's, 40.0 % for Chuang & Hunder's, 77.1 % for Healey's and 82.9 % for Jones & Hazelman's criteria.

Conclusion: The results demonstrate a higher sensitivity of the novel EULAR/ACR criteria compared to the previous PMR classification criteria. However, ultrasound findings did not contribute to the higher sensitivity observed in our cohort of recent onset PMR patients.

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Successful Treatment of Churg-Strauss Syndrome with Rituximab. Christin Dubrau[1], Fabian Arndt[2], Wolfgang L. Gross and Frank Moosig[2]. [1]University Hospital Schleswig-Holstein, Campus Luebeck and Klinikum Bad Bramstedt, Bad Bramstedt, Germany, [2]University Hospital Schleswig Holstein and Klinikum Bad Bramstedt, Bad Bramstedt, Germany

Background/Purpose: Rituximab has recently been shown to be equipotent to cyclophosphamide for induction of remission in generalized ANCA-associated vasculitis. A substantial number of observational pro- and retrospective studies also investigate the efficacy of RTX in refractory ANCA-assiciated vasculitis. However, there are only few data regarding the effectiveness of rituximab in Churg-Stauss syndrome.

Objective: To investigate the overall efficacy and safety of rituximab in Churg-Strauss syndrome at a tertiary vasculitis referral center.

Methods: This study represents a retrospective, standardized data collection from all Churg-Strauss syndrome patients treated with rituximab from 06/2007 to 06/2012. Patients were assessed in a standardized diagnostic procedure (ANCA, CRP, B cell levels, immunoglobulin levels, Eosinophil count, Birmingham Vasculitis Activity Score, glucocorticoid demand etc.) before and after receiving rituximab. After achieving complete remission or a response under rituximab, patients were switched on maintenance therapy with methotrexat or azathioprine or leflunomide.

Results: 11 patients were included in the study. Five were ANCA positive. Five were refractory tostandard cyclophophamide treatment, three were relapsers and three patients could not be treated with cyclophosphamide in order to preserve fertility (2) or because of hemorrhagic cystitis (1). Manifestations prior to rituximab were sinusitis (7), alveolitis (7), polyneuropathy/mononeuritis (4), myositis (2), glomerulonephritis (1), cardiac involvement (1), skleritis (1), gastrointestinal involvement (1), purpura (2) and arthritis (2). Eight patients had more than one manifestation before the start of RTX. The median BVAS was 7 (range 1–27).

Regarding overall efficacy eight patients had a response (1 remission, 7 response), one patient was refractory. In two patients follow-up was pending. Birmingham Vasculitis Activity Score version 3 (BVAS 3), glucocorticoid demand, Eosinophil count, CRP and immunoglobulin levels decreased in all patients (table 1). ANCA and peripheral blood lymphocyte counts became undetectable after rituximab treatment. After a median follow-up of eight months (1–54) there was no increase in disease activity. Three infections occurred during follow-up: one pneumonia, two bronchopulmonary infection.

Table 1.

	Before rituximab Median (range)	After rituximab Median (range)
BVAS 3	7 (1–27)	4 (1–8)
glucocorticoid demand (mg)	30 (5–80)	9 (4–12)
Eosinophil count (Eosinophils/μl)	300 (0–3300)	200 (0–1600)
CRP (mg/dl)	0,6 (0,1–5,5)	0,2 (0–8)
immunoglobulin G (g/l)	7,4 (0,3–11)	5,3 (5–7,7)

Conclusion: The overall response rate of Churg-Strauss syndrome to RTX was high (1 remission, 7 respond). There was no increase in disease activity in all patients until the end of follow-up.

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High Frequency of Ferritin Autoantibodies in Takayasu Arteritis.
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Background/Purpose: Takayasu arteritis (TA) may be difficult to diagnose since diagnostic biomarkers have not been established so far. In a previous study, we could show the presence of autoantibodies against the human ferritin heavy chain protein (HFC) in sera of patients with giant cell arteritis (GCA) and/or polymyalgia rheumatica (PMR). Therefore, we studied the presence of autoantibodies against HFC in TA.

Methods: We established 7 ELISAs for the detection of autoantibodies against HFC. As autoantigen we used the full recombinant HFC expressed by E. coli or one of six different peptides of the HFC: 1–18Aa (purity 98.8%), 19–45Aa (purity 98.8%), 52–78Aa purity 98.3%), 79–104Aa (purity 98.8%), 105–143Aa (purity 98.4%), 145–183Aa (purity 98.5%). We collected sera of 43 patients with TA, 36 patients with systemic lupus erythematosus (SLE), 77 patients age >65yrs, 35 patients with arteriosclerosis, 118 sera of fever patients with underlying chronic infectious and malignant diseases, which are known for having unspecific autoantibodies, and 50 blood donors' sera served as controls.

Results: The best results were obtained by using ferritin pedtides as antigens. By combining different ELISAs detecting autoantibodies against HFC peptide 19–44A, 79–104A and 105–144A, we were able to detect ferritin peptide antibodies in 27/43 (63%) TA patients. For early TA, the frequency was lower than in early GCA and PMR (previous study up to 92%). In the controls, 0/100 (0%) of the *blood donors*, 10/36 (28%) of the patients with SLE, 7/77 (9%) of the patients with age >65yrs, 4/35 (11%) of the patients with arteriosclerosis and 24/118 (20%) of the fever patients were positive.

Conclusion: Considering the lack of biomarkers for TA, autoantibodies against peptides of HFC could be helpful as a marker for TA.

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Serum Level of IL-33 and Soluble ST2 and Their Association with Disease Activity in Patients with Behcet's Disease.
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Background/Purpose: Interleukin-33 (IL-33) is a new member of the IL-1 family of cytokines which signals via receptor, ST2(IL-33R), and has an important role in Neutrophil migrations, Th2 responses and mast cell responses. This study aims to measure the serum levels of IL-33 and soluble ST2 (sST2) in patients with Behcet's disease (BD) and to examine their association with disease activity.

Methods: Fifty three BD patients were evaluated for disease activity, determined by BDCAF, IBDDAM, ESR/CRP levels. IL-33 and sST2 were measured by sandwich ELISA in the 53 BD serum samples and compared with 31 age- and sex-matched healthy controls. The cutaneous expressions of IL-33 and sST2 in BD patients with erythema nodosum(EN) or EN-like lesion was compared with normal control skin tissues by immunohistochemical stains

Results: Serum IL-33 level was significantly higher in active BD patients [594.48 pg/ml] compared with normal controls [224.23 pg/ml] (P<0.05), and soluble ST2(sST2) level was also significantly higher in active BD patients [99.01 pg/ml] compared with normal controls [23.56 pg/ml]. The tissue expressions of IL-33 and sST2, shown by immunohistochemistry, were higher in BD compared with the controls. Serum sST2 level correlated significantly with BDCAF, IBDDAM, ESR and CRP. Multiple linear regression showed that both serum CRP and serum sST2 were independent

predictive factor for IBDDAM (regression coefficient: 0.519; P = 0.000, regression coefficient: 0.300; P = 0.016, respectively).

Conclusion: These results suggest that IL-33 and sST2 area increased in Behcet's disease and The level of sST2 are correlated with Behcet's disease activity index (IBDDAM) and acute phase reactant (ESR, CRP) and also a independent predictive factor of IBDDAM, suggesting a potential role of sST2 as a surrogate marker of disease activity of BD.

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Plasma Fibrinogen is an Accurate Marker of Disease Activity in Patients with Polymyalgia Rheumatica.
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Background/Purpose: Accurate determination of disease activity in polymyalgia rheumatica(PMR) is challenging due to the subjective nature of symptoms and concurrent musculoskeletal complaints in an elderly population.Any biomarker than assists physicians in more accurately determining patients disease state, thereby enabling safe adjustment of steroid dose would be welcomed. Previously we have demonstrated the enhanced specificity of plasma fibrinogen over both ESR and CRP for the detection of response to treatment in patients with active PMR. We sought to prospectively evaluate the utility of the biomarkers ESR, CRP and Fibrinogen for identifying different disease states in patients with known PMR.

Methods: Patients with PMR were divided into high/moderate disease activity(Group 1) or low disease activity(Group 2) according to the Polymyalgia Rheumatica Activity Score(PMR-AS) as per Bird and Leeb. PMR-AS =CRP(mg/dl)+ VAS pain(0–10 scale)+ VASphysician (0–10scale)+ Morning stiffness([min]x.1)+ Upper Limb Elevation(0–3 scale). A PMR-AS > 7 indicates medium/high disease activity with a PMR-AS < 7 indicating low disease activity. Plasma fibrinogen, CRP and ESR were also assayed. An ESR value of 30mm/hr(lab normal<20mm/hr) and CRP of 6mg/L (lab normal<5mg/l) were considered the upper limit for detection of low disease activity. The upper limit of the lab normal for Fibrinogen (4g/L) was used. Sensitivity, specificity, positive predictive values and likelihood ratios were calculated for all biomarkers.

Results: Data was available from 120 patient visits. Demographic data was similar in both groups. Mean age was 71.8 years. All patients were receiving glucocorticoids with a median steroid dose of 10mg in Group 1 and 5mg in Group 2.There were significant differences in steroid dose between the two groups(p<.001). 70 patients were defined as having low disease activity as per the PMR-AS. Of these 64/70 had a normal plasma fibrinogen with 56/70 having an ESR <30mm/hr and 45/70 a CRP < 6mg/L. Table 1 shows the specificity, sensitivity, positive predictive values and likelihood ratios for the biomarkers as calculated for all 120 patient visits.

	Specificity	Sensitivity	PPV	Likelihood Ratio	Fischers Exact Test
Fibrinogen	91%	52%	.81	6.06	P<.001
CRP	80%	90%	.66	2.68	P<.001
ESR	64%	50%	.64	2.5	P<.001

Overall plasma fibrinogen was more specific than either ESR or CRP for differentiating between low disease activity and moderate/high disease activity in PMR. It also demonstrated a better positive predictive value and likelihood ratio than the standard biomarkers ESR and CRP for identifying patients with moderate/high disease activity.

Conclusion: Plasma fibrinogen can aid treating physicians in determining disease activity in PMR. An elevated plasma fibrinogen level more accurately indicates that patients are in a moderate or highly active disease state than either the ESR or CRP alone. Measurement of fibrinogen as an adjunct to ESR and CRP in patients with PMR can help treating physicians more accurately identify patients' disease status and guide decisions with regards glucocorticoid dosage.

2383

Rituximab As Induction and Maintenance Therapies for ANCA-Associated Vasculitis: A Multicenter Retrospective Study On 80 Patients.

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Background/Purpose: Rituximab has been shown to induce remission of ANCA-associated vasculitis (AAV). Our study was undertaken to 1) describe the clinical response of AAV to rituximab used for remission-induction and/or maintenance therapy, 2) assess rituximab's safety profile, and 3) evaluate French clinical practices (choice of rituximab, modalities of its use and monitoring).

Methods: This retrospective cohort study concerned AAV patients who had received at least 1 rituximab infusion, between 2002 and January 2011, and all patients had at least 12 months of follow-up.

Results: Eighty patients were included, most had refractory or relapsing AAV: 70 (88%) had granulomatosis with polyangiitis (GPA), 9 (11%) had microscopic polyangiitis (MPA), 1 (1%) had eosinophilic granulomatosis with polyangiitis (EGPA). Rituximab was first prescribed to induce remission in 73 patients. The 2 most commonly administered regimens were: 1 infusion of 375 mg/m2/week for 4 weeks (55 patients) and 1 infusion of 1 g every 2 weeks for a month (17 patients). Rituximab was first prescribed to maintain remission in 7 patients, usually at a dose of 500 mg every 6 months. Relapse-free survival rates at 1, 2 and 3 years after the first rituximab infusion were, respectively, 80% (95% CI 72–89), 63% (95% CI 51–77) and 52% (95% CI 39–70). A trend towards rituximab superiority as maintenance therapy was observed: 9/45 (20%) patients given rituximab relapsed vs 7/14 (50%) prescribed various other therapies (p = 0.13). Twenty-two (27.5%) rituximab-treated patients experienced a severe adverse event. Among them, 12 (15%) had infectious complications leading to 4 (5%) deaths. Only 15 (19%) patients had received anti-pneumococcal vaccine before the first rituximab infusion.

Conclusion: Rituximab was able to induce AAV remission in already immunodepressed patients and seems to be superior to other therapies at maintaining remission. However, caution is needed concerning its safety, especially bacterial infections, in this immunosuppressant-treated population.

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Giant Cell Arteritis and Cardiovascular Events in the French Apogee Cohort. A Population-Based Study Using the French Health Insurance System Database.

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Background/Purpose: The risk of cardiovascular events (CVE) during giant cell arteritis (GCA) has rarely been quantified in population-based studies. Our objective was to quantify the risk of CVE during GCA in a population-based GCA cohort and to compare it to controls using the French Health Insurance system reimbursement database.

Methods: The APOGEE cohort includes most incident GCA patients of the Midi-Pyrénées County, south of France from January 2005 to December 2008. GCA patients are identified in the French Health Insurance System database by their international classification of diseases code, 10th version (M31.5: "GCA with polymyalgia rheumatica (PMR)" or M31.6: "GCA without PMR"). Incident cases are defined by a continuous glucocorticosteroids (GCs) course lasting for at least 6 months, and no previous exposure to GCs during the 6 preceding months. For each case two controls matched on gender and age were randomly selected in the FIHS database. The cardiovascular risk factors (CVRF) were identified through the exposure to drugs prescribed to treat diabetes mellitus, hypertension or dyslipidaemia CVE were cerebrovascular disease (CVD), coronary disease (CD), peripheral arterial disease (PAD) congestive heart failure and atrial fibrillation. New CVE were identified by analysing comprehensive data on drugs' reimbursement, diagnostic procedures, hospital stays and new cardiovascular diseases registered in the database. Serious CVE were defined as CVE leading to hospitalization > 24 hours or death. Follow-up ended in April 2011. We compared the occurrence of the first CVE in cases and controls by a log-rank test. The analysis was then stratified on exposure to statins or anti-platelets drugs (APD). We did not perform a multivariate analysis because of the limited number of events.

Results: The cohort included 103 patients (80 women (77.7%); mean age 74.8 ($\pm$9) years; mean follow-up 48.9 ($\pm$14.8) months). The mean initial GC dosage was 54 ($\pm$ 27) mg/d. At study entry, there was no difference between cases and controls for CVRF except for diabetes mellitus, which was more prevalent in controls (p<0.01). CVE all combined as well as serious CVE occurred more frequently in GCA patients (respectively, 33% vs. 19%, RR= 1.8 [1.25–2.53], p= 0.0011 and 15.5% vs. 7.8%, RR= 2.0 [1.15–3.49], p= 0.014). The mortality rate among GCA patients was not different from matched-controls (8/103 vs. 18/206, p> 0.05).

Conclusion: In the general population, the probabilities of first non-serious and serious CVE are significantly increased among incident GCA patients. Further studies are necessary to measure the protective effects of statins and anti-platelets drugs in these patients.

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Prognostic Impact of *HLA-B* 51* and *HLA-A* 26:01* On Ocular Behcet's Disease.

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Background/Purpose: To investigate the prognostic implication of *HLA-B*51* and *HLA-A*26:01*on visual outcome in Korean Behcet's disease (BD) patients with uveitis.

Methods: Seventy-seven Korean BD patients with uveitis (F:M=29;48) who met the classification criteria by the International Study Group were enrolled. The presence of *HLA-B*51* was determined by polymerase chain reaction (PCR) using sequence specific primers. Genotyping for *HLA-A* locus was performed with PCR-Luminex typing method. Patient visual acuity (VA) was measured using Snellen chart at every visit to ophthalmology clinic. Loss of useful vision (LUV) was defined as VA worse than 20/200 for more than 6 months and near blindness (NB) was defined as VA of light perception or worse.

Results: The onset of uveitis was 36.6 $\pm$ 10.8 (mean $\pm$ standard deviation) years of age and the duration of uveitis was 10.8 $\pm$ 7.2 years. Posterior uveitis was found in 64.9% (50/77) of patients. Forty-seven (61.0%) patients were treated with one or more systemic immunosuppressants other than steroids; azathioprine (n=38), cyclosporine (n=24), methotrexate (n=7), mycophenolate mofetil (n=7), cyclophosphamide (n=6), tacrolimus (n=2), or anti-TNF-a agents (n=2). *HLA-B*51* was positive in 44.2% (34/77) while *HLA-A*26:01* in 18.2% (14/77) of patients. In multivariate analyses, LUV was associated with male gender (p=0.032), duration of uveitis (p = 0.016), and posterior uveitis (p=0.010). *HLA-A*26:01* was not directly associated with LUV but with posterior involvement (p<0.001). *HLA-B*51* did not show any significant associations with LUV or posterior involvement. NB was associated with duration of uveitis (p=0.022) and glaucoma (p=0.026) in multivariate analysis. When patients with posterior uveitis were analyzed, the single most important factor for LUV was duration of uveitis

(p=0.036) in multivariate analysis. NB in posterior uveitis patients was associated with the presence of *HLA-B[*]51* (p = 0.025 in univariate analysis, p=0.062 in multivariate analysis).

Conclusion: *HLA-A[*]26:01* was found to be associated with posterior involvement of uveitis in BD patients while *HLA-B[*]51* tended to be associated with NB in those who develop posterior uveitis.

2386

Disability and Mortality Related to Cerebrovascular Disease in Systemic Vasculitis. Jamal Mikdashi and Marcia Wozniak. University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: Despite improved therapeutic strategies, patients with systemic vasculitis (SV) continue to experience serious morbidity and mortality from persistent low grade disease activity and permanent damage, particularly cardiovascular diseases. Nonetheless, the outcome of cerebrovascular disease (CVD) in patients with SV during the first-ever stroke remains unclear when compared to patient with other causes for their first-ever stroke. Purpose: To examine the clinical outcome related to CVD in SV, and determine whether disability and mortality are related to the disease itself, or associated comorbidities.

Methods: Disability and mortality were examined in 24 SV patients (large vessel vasculitis n = 8, medium vessel vasculitis n = 10, and small vessel vasculitis n = 6; with mean age of 55.7 years, 55% men) admitted to a tertiary care stroke center with validated first-ever stroke between January 2000 and January 2012. Disability rated according with modified Rankin Scale (mRS> 3), and mortality defined as all-cause fatal event were measured the day of first-ever stroke and at 90 days of follow up. Demographics and clinical manifestations were compared between those with SV and age- and gender –matched non SV controls with their first-ever stroke (n = 24) from the same tertiary stroke center. Significant variables in these analyses and the National Institute of Health Stroke Severity Scale (NIHSS) were entered into the multivariate analyses and Cox proportional hazards analyses to determine their contribution to disability and mortality related to CVD.

Results: Patients from the SV and non SV groups had comparable ethnic distribution, socioeconomic features, smoking, and their stroke type (ischemic, hemorrhagic) and Charlson comorbidity scores were similar. Disability was more frequent among SV patients as compared to controls (odds ratio= 4.2, 95% Confidence interval: 1.2–14.4, p value = 0.04). Within the SV patients 18 were disabled (mRS > 3), and 6 were not. Intractable disease activity and cumulative damage involving the pulmonary and renal organs were higher in disabled than the non disabled SV patients, although the difference was not statistically significant. Four patients died among SV group as compared to one patient among the controls. Death due to infection was more frequent among SV patients compared to controls (odds ratio = 2.0; 95% CI: 0.2–21.4, p value = 0.50).

Table 1. Proportional Cox hazard analyses of factors associated with disability related to first-ever CVD in patients with SV

Proportional Hazard Model

Factors	Hazard Ratio (95 % Confidence interval)
BVAS2	7.2 (1.1–47.9)
VDI	10.0 (1.4–69.3)
ANCA PR 3	0.7 (0.03–12.57)
ANCA MPO	5.0 (0.5–51.7)
C Reactive Protein	1.6 (0.4–11.1)
Long -term Prednisone use	8.5(1.3–54.9)

Birmingham Vasculitis Activity Score (BVAS2), Vasculitis Damage Index (VDI)

Conclusion: SV patients are at an increased risk for disability and mortality after the first –ever CVD event. Intractable disease activity, cumulative damage and long-term prednisone use are independently associated with disability related to CVD after adjustment for stroke severity. Death due to infection is frequent.

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Takayasu's Arteritis: Features and Management of 216 Patients in China. Xia Liu[1], Tao Zhang[2], Xiaofeng Zhuang[3], Kai Yuan[1], Xiaoming Shu[1] and Guochun Wang[1]. [1]China-Japan Friendship Hospital, Beijing, China, [2]Chinese PLA General Hospital, Beijing, China, [3]FuWai Hospital and Cardiovascular Institute, Beijing, China

Background/Purpose: Takayasu's arteritis (TA) is a rare vasculitis. Although it appears to be most common in Asia countries, research on Chinese TA patients with large sample size was still deficient in recent years. This study on Chinese TA patients aimed to not only evaluate demographic, clinical, laboratory, and radiological features but also the responses to treatments.

Methods: 216 patients in China diagnosed as TA between the year 2000 and 2011 were retrospectively evaluated.

Results: The mean age of all patients was 27 years (14–65) and 84.2% were female. Vascular bruit, headache, diminished or absent pulse, malaise, hypertension, and dizziness were presented in 75%, 60.2%, 56.5%, 51.9%, 49.5%, and 48.1% of the patients, respectively. The active TA patients had more frequent involvement of the fever, claudication, hypertension, retinopathy, dyslipidemia, and heart failure than did the inactive group. According to the angiographic findings, the distribution of all patients was as follows, 45.4% Type I, 14.4% Type IIa, 5.1% Type IIb, 2.3% Type III, 6.5% Type IV, and 26.4% Type V arteritis. Most patients (61.1%) were treated with pharmacotherapy, while the others received interventional therapy (26.4%) or surgical operation (12.5%). And in those patients treated by medicine, 76.7% showed effective improvement. Especially, in patients received prednisone joint with immunosuppressive agents, 84.2% responded well.

Table 1. Characteristics of TA patients

Characteristics	All patients n=216		Inactive patients n=53		Active patients n=163		p
Sex Female no. (%)	182	(84.2)	44	(83.0)	138	(84.6)	
Age median, yrs	27		33		25		
Disease duration, median month	10		9		11		
Disease onset age, years							
≤18 no. (%)	47	(21.8)					
19–40 no. (%)	148	(68.5)					
≥41 no. (%)	21	(9.7)					
Symptoms at initial diagnosis							
Constitutional findings, no. (%)							
Fever	82	(38)	7	(13.2)	75	(46.0)	0.002#
Malaise	112	(51.9)	26	(49.1)	86	(52.8)	0.639
Myosalgia	15	(6.9)	3	(5.7)	12	(7.4)	0.672
Arthralgia	52	(24.1)	12	(22.6)	40	(24.5)	0.779
Chest pain	43	(19.9)	10	(18.9)	33	(20.2)	0.827
Weight loss	10	(4.6)	2	(3.8)	8	(4.9)	0.733
Vascular findings, no. (%)							
Vascular pain	59	(27.3)	15	(28.3)	44	(27)	0.853
Diminished or absent pulse	122	(56.5)	26	(49.1)	96	(58.9)	0.209
Vascular bruit	162	(75)	35	(66)	127	(77.9)	0.083
Claudication	47	(21.8)	5	(9.4)	42	(25.8)	0.037#
Cardiac findings, no. (%)							
Hypertension	107	(49.5)	14	(26.4)	93	(57.1)	0.019#
Cardiopalmus	25	(11.6)	6	(11.3)	19	(11.7)	0.947
Dyspnea on exertion	10	(4.6)	1	(1.9)	9	(5.5)	0.274
Eye findings, no. (%)							
Retinopathy	21	(9.7)	1	(1.9)	20	(12.3)	0.039#
Blurred vision	45	(20.8)	11	(20.8)	34	(20.9)	0.987
Sudden visual loss	13	(6.0)	3	(5.7)	10	(6.1)	0.900
Neurologic findings, no. (%)							
Dizziness	104	(48.1)	25	(47.2)	79	(48.5)	0.870
Headache	130	(60.2)	30	(56.6)	100	(61.3)	0.540
Cutaneous findings, no. (%)							
Erythema nodosum	4	(1.9)	0	(0.0)	5	(3.1)	0.197
Cutaneous ischemic ulcer	2	(0.9)	0	(0)	2	(1.2)	0.418
Co-morbidity							
Anemia, no. (%)	113	(52.3)	25	(47.2)	88	(54.0)	0.388
Dyslipidemia, no. (%)	44	(20.4)	5	(9.4)	39	(23.9)	0.038#
Heart failure, no. (%)	13	(6.0)	0	(0)	13	(8.0)	0.040#
Cerebral infarction, no. (%)	8	(3.7)	1	(1.9)	7	(4.3)	0.420
Diabetes mellitus, no. (%)	4	(1.9)	1	(1.9)	3	(1.8)	0.983
Thyroid diseases, no. (%)	25	(11.6)	5	(9.4)	20	(12.3)	0.575
Lab							
Hb, mean ± SD, g/l	117.2±19.1		120.2±20.1		113.2±23.1		0.892
PLT, mean ± SD, *10⁹/L	275.7±119.6		270.7±112.6		268.7±150.6		0.901
ESR, mean ± SD, mm/h	53.11±45.5		23.9±45.5		69.9±125.5		0.024#
CRP, median mg/dl	2.68±3.34		1.2±6.2		4.4±20.9		0.031#
IgG, median mg/dl	1230		1154		1320		0.827
IgA, median mg/dl	338		364		332		0.736
IgM, median mg/dl	139		126		140		0.534

P <0.05

Table 2. Selction of treatment strategies on diagnosis of different lesion types

Lesion type	no. (%)		Medicine no. (%)		Interventional therapy no. (%)		Operation no. (%)	
Type I	98/216	(45.4)	59/98	(60.2)	23/98	(23.5)	16/98	(16.3)
Type II a	31/216	(14.4)	14/31	(45.2)	'13/31	(41.9)	4/31	(12.9)
Type II b	11/216	(5.1)	7/11	(63.6)	3/11	(27.3)	1/11	(9.1)
Type III	5/216	(2.3)	4/5	(80.0)	1/5	(20.0)	0/5	(0)
Type IV	14/216	(6.5)	12/14	(85.7)	2/14	(14.3)	0/14	(0)
Type V	57/216	(26.4)	36/57	(63.2)	15/57	(26.3)	6/57	(10.5)
Total	216/216	(100)	132/216	(61.1)	57/216	(26.4)	27/216	(12.5)

Table 3. Features of corticosteroid and immunosuppressive therapy

Drugs	N number no. (%)		Effectiveness no. (%)	
Pred	27/132	(20.5)	16/27	(59.3)
CTX	3/132	(2.3)	1/3	(33.3)
Pred+CTX	65/132	(49.2)	58/65	(89.2)
Pred+MTX	13/132	(9.8)	11/13	(84.6)
Pred+CTX+MTX	8/132	(6.1)	5/8	(62.5)
Pred+HCQ	3/132	(2.3)	2/3	(66.7)
Pred+AZA	2/132	(1.5)	2/2	(100)
Pred+CysA	2/132	(1.5)	1/2	(50.0)
Pred+TGV	2/132	(1.5)	1/2	(50.0)
Anti-TNFα+MTX	1/132	(0.8)	1/1	(100)
Others	6/132	(4.5)	3/6	(50.0)
Total	132/132	(100)	101/132	(76.5)

Pred: prednisone, CTX:Cyclophosphamide, MTX:Methotrexate, HCQ:Hydroxychloroquine; AZA:Azathioprine, CysA:Cyclosporine-A, TGV:Thunder god vine

Conclusion: Our study indicated that TA could non-accidentally happen in people over 40 years old. It also revealed that, in all expressions, vascular symptoms occurred more frequently than systemic symptoms. Moreover, fever, claudication, hypertension, and retinopathy were more typical in active TA patients. When monitoring disease activity, erythrocyte sedimentation rate and C-reactive protein were useful. Most of our patients received medicine treatments after definite diagnosis. And the outcome revealed that glucocorticoids and immunosuppressive agents were notably effective.

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Urticarial Vasculitis: Clinical Study. Javier Loricera[1], Vanesa Calvo-Rio[1], Francisco Ortiz Sanjuan[1], Marcos Antonio Gonzalez-Lopez[1], Hector Fernandez-Llaca[1], Javier Rueda-Gotor[1], Carmen Gonzalez-Vela[1], Cristina Mata-Arnaiz[2], Jose Luis Peña-Sagredo[1], Miguel A. Gonzalez-Gay[1] and Ricardo Blanco[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Laredo, Santander, Spain

Background/Purpose: Urticarial vasculitis is an infrequent subset of vasculitis described by McDuffy et al, in 1973, characterized clinically by urticarial skin lesions of more than 24 hours duration and histologically by vasculitis. Our aim was to evaluate the frequency, clinical and pathological features and treatment of UV from a large series of patients with cutaneous vasculitis.

Methods: Retrospective study of UV from a series of 877 patients with cutaneous vasculitis of a University Hospital. For the diagnosis of UV, besides urticarial lesions persisting more than 24 hours, a skin biopsy showing necrotizing vasculitis of small vessels was required.

Results: UV was observed in 19 (2.17%) of 877 patients with cutaneous vasculitis. There were 8 men and 11women, with a mean age of 33.21 ± 26.08 years. Precipitating factors and/or possible causes identified were upper respiratory tract infections (4 cases), drugs (4 cases), malignancy (megakaryocytic leukemia, 1 case) and 1 patient had a Schnitzler syndrome. Besides urticarial lesions, other features such as palpable purpura (7 patients), arthralgias (5 patients), arthritis (7 patients), abdominal pain (2 patients), and nephropathy (2 patients) were observed. Hypocomplementemia (low C4) was observed in 2 of the 19 patients. These patients also had low C1q. Other abnormal laboratory data

observed were increase of ESR (6 cases), leukocytosis (7 cases), anemia (4 cases), positive ANA (2 cases), and positive Rheumatoid Factor (1 case). Neither of the patients with positive ANA or Rheumatoid Factor developed systemic lupus erythematosus, rheumatoid arthritis or any other connective-tissue disease. The main histological findings were vascular and perivascular infiltration, endothelial swelling and fibrinoid necrosis. The cellular infiltrate was composed mainly of neutrophils, lymphocytes and eosinophils. The most common treatments were corticosteroids (10 cases), antihistaminic drugs (6 cases), chloroquine (4 cases), colchicine (2 cases) and NSAIDs (1 case). The patient with Schnitzler syndrome needed cytotoxic agents. After a mean follow-up of 16.68 ± 27.78 months (median 4 months) recurrences were observed in 4 patients. A patient died because of an underlying malignancy while the remaining had full recovery without complications.

Conclusion: UV is a rare subtype of cutaneous vasculitis. In addition to urticarial skin lesions, joint involvement was the most common clinical manifestation. Corticosteroids and antihistaminic drugs are the drugs more commonly used. The prognosis depends on the underlying disease but is usually good.

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Cutaneous Leukocytoclastic Angiitis: Study of 173 Patients. Javier Loricera, Vanesa Calvo-Rio, Francisco Ortiz-Sanjuan, Marcos Antonio Gonzalez-Lopez, Hector Fernandez-Llaca, Javier Rueda-Gotor, Carmen Gonzalez-Vela, Miguel A. Gonzalez-Gay and Ricardo Blanco. Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain

Background/Purpose: Cutaneous leukocytoclastic angiitis (CLA) was defined by the International Consensus Conference for the Nomenclature of the Vasculitis (Chapel Hill, A&R 1994) as an isolated cutaneous vasculitis without systemic vasculitis or glomerulonephritis. Our objective was to evaluate the clinical features, treatment and outcome of patients with CLA.

Methods: From a large series of patients with cutaneous vasculitis those diagnosed as having cutaneous vasculitis in the setting of connective tissue diseases, malignancies, infections, primary systemic necrotizing vasculitis and other entities such as Henoch-Schönlein Purpura and Essential Mixed Cryoglobulinemia were excluded from this analysis. Patients with systemic involvement including gastro-intestinal or renal involvement (glomerulonephritis) were also excluded. The remaining patients were classified as having CLA.

Results: According to the above mentioned methodology, 173 patients (91 men and 82 women), with a mean age of 46.29 ± 24.37 years (range, 1 to 95 years) were diagnosed as having CLA.

Precipitating events were found in 146 (84.39%) patients. A history of drug intake before the onset of the vasculitis was found in 82 (47.40%) patients and a previous history of upper respiratory tract infection in 48 (27.74%) patients. The most frequent drugs taken shortly before the onset of the cutaneous vasculitis were Beta-lactam antibiotics (38 cases), NSAIDS (20 cases) and diuretics (8 cases). The most frequent clinical manifestations were cutaneous (100%), joint manifestations (41.51%) and fever (17.92%). The main laboratory data were elevated ESR (46.82%), leukocytosis (28.90%), anemia (10.98%), positive Rheumatoid Factor (13.87%), positive ANA (16.18%), hypocomplementemia (C3 and/or C4) (2.89%), cryoglobulins (2.31%) and positive ANCA (0.58%).

Treatment included NSAIDS (17.34%), Corticosteroids (16.18%), Colchicine (2.89%) and Azathioprine (1.73%). After a mean follow-up of 12.42 ± 30.31 months (median, 3 months), relapses were observed in 19.65% of patients.

Conclusion: CLA is usually a benign syndrome, often secondary to drugs or infections, or both. Its main clinical features are skin and joint manifestations. Its prognosis is very good.

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Color Doppler Ultrasonography an Alternative to CT/MR Angiography for Identifying Large Vessel Involvement in Giant Cell Arteritis? Andreas P. Diamantopoulos[1], Glenn Haugeberg[1] and Geirmund Myklebust[2]. [1]Hospital of Southern Norway HF, Kristiansand, Norway, [2]Hospital of Southern Norway, Kristiansand, Norway

Background/Purpose: Large vessel involvement has been reported to be present in 20–50% of patients with giant cell arteritis (GCA). Computed tomography (CT) and magnetic resonance (MR) angiography are used for assessment of large vessel involvement in patients with GCA. Our aim was to compare color Doppler ultrasonography (CDUS) to CT/ MR angiography for identifying large vessel involvement in patients with GCA at the time of initial evaluation.

Methods: Consecutive GCA patients with large vessel involvement assessed by CDUS underwent CT/MR angiography between January 2010 and May 2012. The aorta and supraaortic vessels were assessed by CT/MR angiography, while the carotid and axillary arteries were assessed by CDUS. The patients were diagnosed by CDUS with large vessel vasculitis (LVV) when intima-media complex thickness was homogenous and more than 1.5 mm in the carotid artery and more than 1 mm in the axillary artery.

Results: A total of 13 GCA patients (7 females, 6 males, mean age 70 years) were identified with LVV using CDUS. In these 13 patients aortic involvement was observed in 5 patients (38%) by CT/MR angiography. In all of these 5 patients, involvement of axillary arteries (4 patients) or carotid arteries (3 patients) were found by CDUS. In the other 8 patients axillary arteritis was visible on CDUS whereas only 2 these patients revealed large vessel vasculitis on CT/MR. Interestingly, inflammation in large vessels was retrospectively identified by CT/MR angiography in 6 of 13 patients and this after reevaluating the images after the positive CDUS examination.

Conclusion: CDUS seems to be a valuable tool for assessment of large vessel vasculitis. The data from our pilot study suggest that CDUS is comparable and even better than CT/MR angiography to detect large vessel involvement in GCA. In the future CDUS may become the gold standard for first line evaluation of large vessel involvement. However further validation of the method is warranted.

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New Disease Manifestations After Diagnosis in Six Types of Vasculitis. Peter C. Grayson[1], David Cuthbertson[2], Simon Carette[3], Gary S. Hoffman[4], Nader A. Khalidi[5], Curry L. Koening[6], Carol A. Langford[4], Kathleen Maksimowicz-McKinnon[7], Paul A. Monach[8], Philip Seo[9], Ulrich Specks[10], Steven R. Ytterberg[10] and Peter A. Merkel[11]. [1]Boston University Medical Center, Boston, MA, [2]University of South Florida, Tampa, FL, [3]UHN/MSH, Toronto, ON, [4]Cleveland Clinic, Cleveland, OH, [5]McMaster University, Hamilton, ON, [6]Salt Lake City Veterans Administration, Salt Lake City, UT, [7]University of Pittsburgh, Pittsburgh, PA, [8]Boston University, Boston, MA, [9]Johns Hopkins Vasculitis Center, Baltimore, MD, [10]Mayo Clinic, Rochester, MN, [11]University of Pennsylvania, Philadelphia, PA

Background/Purpose: The proportion of patients who experience new manifestations of vasculitis after diagnosis is unknown. Our objectives were to quantify the occurrence of new features of vasculitis after diagnosis in 6 types of vasculitis and to compare patterns of disease activity over time.

Methods: Standardized data collection on 98 disease manifestations in 6 vasculitides, including granulomatosis with polyangiitis (Wegener's, GPA), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), polyarteritis nodosa (PAN), giant cell arteritis (GCA), and Takayasu's arteritis (TAK), was performed within a set of multicenter, longitudinal cohorts. For each form of vasculitis, the frequency of disease-specific manifestations at diagnosis was compared to the cumulative frequency of each manifestation. The percentage of patients who developed new "severe" manifestations after diagnosis, defined as organ-threatening or life-threatening in the small and medium vessel vasculitides and as ischemic/vascular in the large vessel vasculitides, was described.

Results: The number of patients and median length of follow-up (years) for the vasculitides was: GPA 341, 7.2; MPA 26, 3.7; CSS 117, 5.1; PAN 55, 4.3; GCA 191, 2.8; TAK 132, 6.8. On average, patients with vasculitis experienced 1.3 new disease manifestations after diagnosis (GPA - 1.9, MPA - 1.2, CSS - 1.5, PAN - 1.2, GCA - 0.7, TAK - 1.0). Depending on the type of vasculitis, at least 1 new disease manifestation occurred after diagnosis in

44%–69% of patients **(Figure)**, most notably in GPA and CSS. A subset of patients (7–28%) with each type of vasculitis experienced ≥ 3 new manifestations after diagnosis. The 3 most frequent new manifestations after diagnosis for each type of vasculitis are listed in the **Table**. New severe manifestations occurred after diagnosis in GPA - 30%, MPA - 27%, CSS - 23%, PAN - 29%, GCA - 26%, and TAK - 45%. Mean time from diagnosis to initial flare in disease activity did not significantly differ among those who experienced a new manifestation versus a recurrence of prior disease (1.15 vs 1.18 years, p=0.8).

Frequency of New Manifestations After Diagnosis
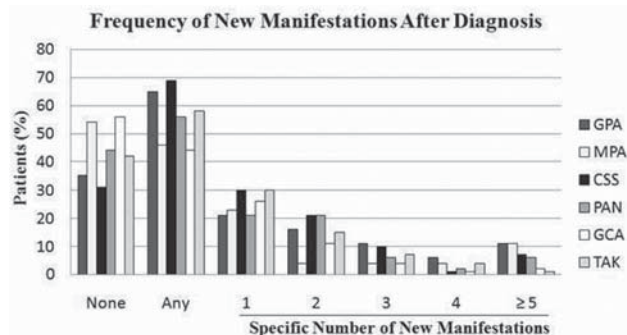
Three Most Frequent New Manifestations After Diagnosis

Type of Vasculitis	New Manifestation
Granulomatosis with polyangiitis (Wegener's)	Arthralgias (11%)
	Rhinitis (9%)
	Glomerular disease (9%)
Microscopic polyangiitis	Venous thromboembolic event (12%)
	Glomerular disease (11%)
	Arthalgias (8%)
Churg-Strauss syndrome	Nasal polyp (10%)
	Eosinophilic pulmonary infiltrate (9%)
	Purpura (8%)
Polyarteritis nodosa	Motor mononeuritis multiplex (12%)
	Arthralgias (12%)
	Venous thromboembolic event (10%)
Giant cell arteritis	Polymyalgia rheumatica (11%)
	Headache (7%)
	Arthralgias (7%)
Takayasu's arteritis	Upper extremity claudication (14%)
	Lightheadedness (8%)
	Carotidynia (7%)

Conclusion: A majority of patients with vasculitis develop new features of disease after diagnosis, including a substantial number of new, severe manifestations. New manifestations after diagnosis, although more frequent among the small-vessel vasculitides, are also common in patients with medium- or large-vessel vasculitis. Patterns of disease recurrence after diagnosis are not related to disease duration. Ongoing clinical assessment of patients with all types of established vasculitis should remain broad in scope.

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Blood Vessel Instability and Oxidative Damage in Giant Cell Arteritis. Danielle Molloy[1], Jennifer McCormick[1], Mary Connolly[1], Muhammad Haroon[1], Douglas J. Veale[1], Conor Murphy[2], Ursula Fearon[1] and Eamonn S. Molloy[1]. [1]Dublin Academic Medical Center, St. Vincent's University Hospital, Dublin, Ireland, [2]Royal Victoria Eye and Ear Hospital, Dublin, Ireland

Background/Purpose: Giant cell arteritis (GCA) is the most common form of primary vasculitis. The pathogenesis is incompletely understood, but involves neoangiogenesis and inflammatory infiltration of the arterial wall. The aim of the present study was to assess blood vessel stability and oxidative damage in patients with the condition and correlate with disease activity.

Methods: 20 patients with a clinical diagnosis of GCA were included, 16 of whom had a positive temporal artery biopsy. Temporal artery (TA) sections were assessed for blood vessel maturity (%BVM) by dual-immunofluorescent staining for Factor VIII/αSMA. Oxidative DNA damage (8-oxo-7,8-dihydro-2′-deoxyguanosine; 8-oxo-dG), lipid peroxidation (4-hydroxy-2-nonenal; 4-HNE), angiogenic growth factor Angiopoietin 2 (Ang2) and it receptor Tie-2 were assessed by immunohistochemistry. *Ex vivo* TA explant cultures were established directly from fresh biopsy specimens (n=4) and spontaneous release of pro-angiogenic factors were examined by ELISA and gelatine zymography. Patients were categorised into low disease (CRP<50) vs high disease activity (CRP>50).

Results: Strong expression of 8-oxo-dG, 4HNE, Ang2 and Tie2 were demonstrated in the adventitial and intimal regions. 8-oxo-dG and 4HNE correlated with disease activity marker ESR (r=.568, p<0.017: r=.451, p<0.05 respectively). Expression of 8-oxodG significantly correlated with Tie2 (r=0.538, p<0.017) and that of 4HNE significantly correlated with Ang2 (r=0.0529, p<0.02). A mixture of immature and mature blood vessels was demonstrated in all GCA patients, with a lower number of vessels expressing α-SMA in patients with high disease activity (41% ± 13.4) compared to low disease activity (66% ± 8.2) suggesting a more unstable vascular microenvironment is associated with high disease activity. This was further supported when we demonstrated spontaneous release of pro-inflammatory mediators Ang2, MMP-2, MMP-9, IL-6 and IL-8 from *ex vivo* TA explants in culture. Furthermore conditioned media from TA explants significantly induced angiogenic tube formation (p<0.05).

Conclusion: This is the first study directly demonstrating that vessels in the inflamed temporal arteries from patients with GCA are unstable and are associated with incomplete EC/pericyte interactions, expression of Ang2 and oxidative damage markers.

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High Mobility Group Box 1 Levels Are Not Associated with Subclinical Carotid Atherosclerosis in Patients with Granulomatosis with Polyangiitis but Are Reduced by Glucocorticoids and Statins. Alexandre Wagner S. de Souza[1], Karina de Leeuw[1], Johanna Westra[2], Andries J. Smit[1], Anne Marijn van der Graaf[2], Hans L. A. Nienhuis[1], Johan Bijzet[1], Pieter C. Limburg[2], Coen A. Stegeman[2], Marc Bijl[3] and Cees G.M. Kallenberg[2]. [1]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands, [3]Martini Hospital, Groningen, Netherlands

Background/Purpose: High mobility group box 1 (HMGB1) is a non-histone DNA binding protein that is passively released by dying cells or actively secreted by immunocompetent cells and the receptor for advanced glycation end-products (RAGE) is one of its receptors. Higher levels of HMGB1 have been found in patients with granulomatosis with polyangiitis (GPA) with active disease whereas higher HMGB1 and lower soluble (sRAGE) levels have been found in patients with acute atherosclerotic events suggesting sRAGE acts as a decoy receptor. This study aims to evaluate HMGB1 levels in relation to subclinical carotid atherosclerosis in GPA, and the impact of therapy on HMGB1 levels.

Methods: A cross-sectional study was performed on 23 GPA patients during a quiescent phase of the disease in comparison to 20 matched controls. All study participants underwent carotid ultrasound to assess atherosclerotic plaques and intima-media thickness (IMT) and were tested for traditional risk factors for atherosclerosis, serum HMGB1 levels (ELISA–Shino Test, Kanagawa, Japan), and sRAGE levels (ELISA R&D Systems, Minneapolis, Minnesota, USA).

Results: GPA patients and controls had similar mean levels of total cholesterol (4.99±0.78 vs. 4.98±0.82 mmol/L; $P = 0.978$), HDL-cholesterol (1.41 ± 0.37 vs. 1.51±0.33 mmol/L; $P = 0.359$), LDL-cholesterol (3.01±0.79 vs. 3.29±0.82 mmol/L; $P = 0.267$), and a similar frequency of smoking (8.7% vs. 5.0%; $P = 0.635$), family history of premature coronary artery disease (CAD) (39.1% vs. 40.0%; $P = 0.954$), and obesity (4.3% vs. 10.0%; $P = 0.446$). Hypertension was only found in GPA patients (39.1% vs. 0.0%; $P = 0.002$) while no study participants

had diabetes. Overt cardiovascular disease was found only in 13.0% of GPA patients. Statins were prescribed for 21.7% of GPA patients and 5.0% of controls ($P = 0.127$). Among GPA patients, prednisolone was being used by 34.8% with a median daily dose of 5.0mg (2.5–15.0) and azathioprine by 34.8%. Only two GPA patients used statins and prednisolone concomitantly. Carotid plaques were found in 30.4% of GPA patients and in 15.0% of controls ($P = 0.203$) and the overall IMT was similar in GPA patients and in controls (0.833±0.256 vs. 0.765±0.133mm; $P = 0.861$). Median serum HMGB1 levels were similar between GPA patients and controls [2.13ng/mL (1.11–7.22) vs. 2.42ng/mL (0.38–6.75); $P = 0.827$] as well as mean sRAGE levels (1256.1±559.6 vs. 1483.3±399.8pg/mL; $P = 0.155$). No correlations were found between HMGB1 and sRAGE ($\rho = 0.068$; $P = 0.681$) and between HMGB1 and maximum IMT in carotid arteries ($\rho = -0.067$; $P = 0.720$). GPA patients on prednisolone (1.77±0.76 vs. 3.53±2.06ng/mL; P = 0.017) and statins (1.39±0.28 vs. 3.34±1.94ng/mL; $P = 0.001$) presented significantly lower serum HMGB1 levels whereas no difference in mean HMGB1 levels was found regarding azathioprine use (2.89±2.28 vs. 2.93±1.75; $P = 0.970$).

Conclusion: No association was found between subclinical atherosclerosis in carotid arteries and HMGB1 levels in GPA patients. Furthermore, the use of either prednisone or statins was associated with lower HMGB1 levels in GPA patients. These findings suggest that the anti-inflammatory properties of statins include effects on serum HMGB1 levels in GPA.

2394

Fibromyalgia in Behçet's Disease Is Associated with Disease Activity. Meryem Can[1], Fatma Alibaz-Öner[2], Sibel Yılmaz-Öner[1], Birkan İlhan[1], Tülin Ergun[1], Gonca Mumcu[3] and Haner Direskeneli[1]. [1]Marmara University School of Medicine, Istanbul, Turkey, [2]Marmara University School of Medicine, Turkey, [3]Marmara University,Faculty of Health Sciences, Department of Health Informatics and Technologies, Istanbul, Turkey

Background/Purpose: Studies on the relationship between Fibromyalgia (FM), a generalized pain disorder with up to 2% prevalence and Behcet's Disease (BD), a systemic, inflammatory vasculitis, is limited. We conducted the present study to assess the prevalance of FM in BD diagnosed according to 2010 American College of Rheumatology (ACR) criteria and to evaluate the association of FM with disease activity, disability, depression, anxiety and quality of life (QoL) in BD patients.

Methods: One hundred-two patients followed as BD (F/M:56/46, mean age: 40.4 years) fullfilling the International Study Group Criteria (ISG,1990), 85 patients with systemic lupus erythematosus (SLE) (F/M:81/4, mean age: 41.4 years) and 51 healthy controls (HC) (F/M: 30/21, mean age: 40.9 years) were enrolled to the study. All patients were examined for FM tender points (according to ACR 1990 criteria for the classification of FM) by two observers (kappa=0.8) and asked to complete new ACR 2010 FM questionnaire for FM (ref1). The clinical activity score in BD was determined by Behcet's Syndrome Activity Scale (BSAS) and SLE by SLEDAI. *SF-36* and hospital anxiety and depression scales were also used to assess QoL together with health assessment questionnaire (HAQ).

Results: Twenty-four (23.5%) BD patients met the ACR 2010 criteria for FM, compared to 18 (21.2%) in SLE and 5 (9.8%) in HC (p=0.1). When we analysed according to 1990 ACR FM criteria, 13(12.7%) in BD group, 6 (7.1%) in SLE and one (2.7%) in HC were classified as FM.

BSAS score correlated with FM (r=0.5, p=0.002), whereas FM and SLEDAI had no correlation (r=0.2,p=0.1). While mean anxiety scores were similar between groups (7.1±4.3, 7.01±4.3 and 5.8±4.6 in BD, SLE and HC, respectively)(p>0.05), mean depression scores were significantly different (5.8±3.4, 6.4±4.8 and 3.9±3.5 in BD, SLE and HC respectively)(p>0.05) between the groups. When anxiety and depression scores were analyzed as possible contibuting factors for FM presence, correlation was observed between anxiety and depression scores with FM (r=0.3, p=0.002 vs r=0.3, p=0.002, respectively) in BD.

Mean SF-36 physical component scores (PCS) were observed significantly lower in BD and SLE patients [41.7(11.3), 41.6(12.2) and 49.9(8.5) in BD, SLE and HC, respectively] (p<0.01). Also, SF36-mental components (MCS) were different between BD and HC groups [42.3(9.8), 46.6(10.3) in

BD and HC, respectively] (p=0.05). There were negative correlations between SF36 –PCS and -MCS with FM (r=−0.4 and r=−0.1).

BSAS score (median) was 20 (0–79) in BD and %53.2 (n=50) of the BD group had a mucocutaneous and %46.8 (n=44) had major disease. The presence of FM did not differ significantly between the patients with mucocutenous and major organ involvement (p=0.6). No significant difference were also observed between SF36 parameters, HAQ scores, BSAS score and anxiety-depression scores between the two subsets.

Conclusion: Fibromyalgia, with new diagnostic criteria, seem to be more prevalent in BD compared to previous studies. Association of BSAS and SF-36 with FM in our study group suggests that disease activity and QoL status seems to influence FM presence in BD.

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Body Composition, Strength, and Function in Elderly Patients with Giant Cell Arteritis. Rebecca L. Manno[1], Allan C. Gelber[1], Philip Seo[2], Stuart M. Levine[1], Sharon R. Ghazarian[3], Po-Han Chen[3], Kerry J. Stewart[1], Jeffrey Metter[4], Luigi Ferrucci[4] and Kevin R. Fontaine[5]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Vasculitis Center, Baltimore, MD, [3]Baltimore, MD, [4]National Institute on Aging, Baltimore, MD, [5]The University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Loss of muscle and strength typically occur with advanced age. Chronic inflammatory diseases, such as rheumatoid arthritis, have reported similar deficits. Giant cell arteritis (GCA) is an inflammatory systemic vasculitis that occurs almost exclusively in the elderly. We sought to determine the body composition, strength, and functional disability in a cross-sectional sample of GCA patients (pts) and compare these parameters to age-matched community dwelling non-GCA controls.

Methods: Pts were recruited from a tertiary academic center. Body composition was evaluated by dual energy x-ray absorptiometry (DEXA, GE Lunar Prodigy Software V13); strength was assessed by hand grip dynamometry and lower extremity isokinetic testing (Biodex System 3 dynamometer); and functional disability by the short physical performance battery (SPPB). The SPPB includes: chair stands, semitandem, tandem, one-leg stand, and gait speed (6 meter walk). GCA pts were matched (1:2 ratio) by age (within 1 year), gender, and race to eligible controls randomly selected from the Baltimore Longitudinal Study of Aging (BLSA). The BLSA prospectively follows a cohort of healthy volunteers who undergo comprehensive evaluation every 1–2 years. Continuous and categorical variables were compared using student's t-test and chi-square analyses respectively.

Results: GCA pts (N=18) had a mean ± SD age of 74 ± 7 yrs (range 59–86). They were mostly female (83%), white (83%) and had a positive temporal artery biopsy (89%). Mean disease duration was 2.7 ± 4.1 yrs (range 0.1–16); 7 (39%) were diagnosed >2 years prior to their study visit. Most (78%) were on daily prednisone (11 ± 13 mg/d) with a mean duration of steroid exposure at the study visit of 11 ± 13 months. GCA pts were significantly weaker on all measures of strength compared to BLSA controls (Table 1). GCA pts also had marked slowness as indicated by longer time to complete chair stands and slower gait speed. Body composition was similar between the two groups without a corresponding decrease in lean mass among the GCA group despite their decreased strength.

Table 1.

	GCA N=18	BLSA N=36	p-value
Age, mean ± SD (years)	75 ± 7	74 ± 7	0.672
Gender (% women)	83	78	0.633
Race (% Caucasian)	83	83	1.000
Strength Measures			
Grip strength (kg)	21 ± 6	27 ± 9	0.015
Leg extension 180d/s peak torque (Nm)			
Left quadriceps	46 ± 17	89 ± 2 (n=23)	<0.001
Right quadriceps	49 ± 20	69 ± 16 (n=31)	0.001
Leg flexion 180d/s peak torque (Nm)			
Left hamstrings	21 ± 10	66 ± 22 (n=23)	<0.001
Right hamstrings	23 ± 10	49 ± 15 (n=31)	<0.001
Functional Measures (Short Physical Performance Battery)			
Completes 10 chair stands (%)	83	94	0.184
Time to complete (seconds)	32 ± 8	23 ± 5	<0.001
Holds semi tandem stand 30 seconds (%)	94	97	0.610
Holds tandem stand 30 seconds (%)	83	83	0.149
Holds one leg stand 30 seconds (%)	17	100	<0.001
Gait Speed (m/s)	0.86	1.06	0.005
Body Composition by DEXA			
BMI (kg/m²)	28 ± 6	25 ± 4	0.079
Bilateral arms			
Total fat mass (g)	3177 ± 1155	2559 ± 989	0.046
Total lean mass (g)	4262 ± 1070	4337 ± 1315	0.836
Bilateral legs			
Total fat mass (g)	10334 ± 4352	8965 ± 3830	0.242
Total lean mass (g)	13141 ± 2853	13600 ± 3242	0.538
Trunk			
Total fat mass (g)	16360 ± 3834	13603 ± 5915	0.079
Total lean mass (g)	19235 ± 2533	20889 ± 4311	0.140
Total Body			
Total fat mass (g)	30915 ± 8614	25942 ± 9772	0.073
Total lean mass (g)	39995 ± 6065	42216 ± 8898	0.346

Conclusion: GCA pts in this small cross-sectional study were significantly weaker and slower than age-matched controls in the absence of significant differences in body composition. Slow gait speed (<0.8 m/s) is associated with disability, morbidity, and mortality among elderly adults. The preservation of lean mass in elderly GCA pts, in the presence of clinically significant weakness, suggests that impairment/dysfunction in muscle quality rather than muscle quantity may be the culprit. Prednisone use may be a significant contributor to weakness and slowness in elderly GCA pts. However, prednisone is unavoidable in the treatment of this potentially catastrophic illness and future investigation should focus on methods to improve strength and function in GCA pts regardless of their need for steroid therapy.

2396

Higher Homocysteine Levels Are Associated with Ischemic Arterial Events Rather Than Disease Activity and the Extension of Arterial Involvement in Takayasu Arteritis. Alexandre W.S. Souza[1], Carla S. Lima[2], Ana Cecilia D. Oliveira[3], Luiz Samuel G. Machado[3], Frederico A. G. Pinheiro[3], Sonia Hix[4] and Vânia D'Almeida[5]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil, [4]Universidade Federal de São Paulo - Escola Paulista de Medicina, São Paulo, Brazil, [5]Universidade Federal de São Paulo- Escola Paulista de Medicina, São Paulo, Brazil

Background/Purpose: High plasma homocysteine is an independent risk factor for arterial ischemic events. The objective of this study is to evaluate plasma homocysteine levels in patients with Takayasu arteritis (TA) and in controls, and to analyze the association between homocysteine levels and paraoxonase 1 (PON1) activity, methotrexate and folate use, disease activity, extension of arterial involvement and with ischemic arterial events in TA.

Methods: A cross-sectional study was performed with 29 TA patients and 30 control subjects. Plasma homocysteine levels were determined by high performance liquid chromatography using fluorimetric detection and isocratic elution. PON1 activity was evaluated by spectrophotometry using paraoxon as substrate with 1M sodium chloride. Disease activity was ascertained by the National Institutes of Healthy criteria and the extension of arterial involvement by the angiographic classification of the International TA conference in Tokyo 1994.

Results: Active disease was observed in 9 (31.0%) and previous arterial ischemic events in 10 (34.5%) TA patients. Nine (31.0%) TA patients were on methotrexate therapy with a mean dose of 20.5 ± 3.9 mg/week and it was associated to folic acid in 8 cases. Median homocysteine levels were significantly higher in TA patients in comparison to control subjects [10.9 (8.5–24.7) vs. 6.9 μmol/L (2.8–15.1); $P < 0.001$]. TA patients with active

disease presented lower homocysteine (10.4 ± 2.1 vs. 13.1 ± 4.2 μmol/L; $P = 0.034$) when compared to patients in remission. Median homocysteine levels were higher in patients with previous ischemic events [13.2 (9.6–24.4) vs. 9.8 (8.5–17.9) μmol/L; $P = 0.027$]. In a multivariate model that included age, disease duration and homocysteine levels, age (OR: 1.13; 95% CI: 1.01–1.25; $P = 0.022$) and 1 μmol/L increase in homocysteine plasma levels (OR: 1.31; 95% CI: 1.01–1.71; $P = 0.041$) were independently associated with ischemic events in TA. Mean homocysteine levels were similar in TA patients on methotrexate and in those being treated with other immunosuppressive agents (12.8 ± 5.3 vs. 12.1 ± 3.2 μmol/L; $P = 0.662$) and regarding the extension of arterial involvement, no differences in homocysteine levels were found in TA patients with angiographic type V in comparison to other angiographic types (12.7 ± 4.2 vs. 11.0 ± 2.6 μmol/L; $P = 0.342$). No differences in PON1 activity were found in TA patients with active disease in than those in remission (386.7 ± 251.2 vs. 323.7 ± 264.1 U/mL; $P = 0.552$) and between TA patients with and without previous ischemic events (411.4 ± 232.3 vs. 307.4 ± 268.6 U/mL; $P = 0.310$). No correlation was found between plasma homocysteine and PON1 activity ($\rho = 0.214$; $P = 0.265$).

Conclusion: Patients with TA presented higher homocysteine levels than control subjects and homocysteine levels were independently associated with acute arterial ischemic events in TA. Higher homocysteine levels were not observed in TA patients with active disease or with extensive vascular involvement and folate use associated to methotrexate seemed to prevent higher homocysteine levels in TA. No associations were found between PON1 activity with homocysteine levels, active disease or ischemic events.

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Urinary Biomarkers in Vasculitis Associated with Anti-Neutrophil Cytoplasmic Antibodies. Jason G. Lieberthal[1], David Cuthbertson[2], Simon Carette[3], Gary S. Hoffman[4], Nader A. Khalidi[5], Curry L. Koening[6], Carol A. Langford[4], Kathleen Maksimowicz-McKinnon[7], Philip Seo[8], Ulrich Specks[9], Steven R. Ytterberg[9], Peter A. Merkel[10] and Paul A. Monach[11]. [1]Boston University School of Medicine, Boston, MA, [2]University of South Florida, Tampa, FL, [3]UHN/MSH, Toronto, ON, [4]Cleveland Clinic, Cleveland, OH, [5]McMaster University, Hamilton, ON, [6]Salt Lake City Veterans Administration, Salt Lake City, UT, [7]University of Pittsburgh, Pittsburgh, PA, [8]Johns Hopkins Vasculitis Center, Baltimore, MD, [9]Mayo Clinic, Rochester, MN, [10]University of Pennsylvania, Philadelphia, PA, [11]Boston University, Boston, MA

Background/Purpose: Glomerulonephritis is common in ANCA-associated vasculitis (AAV), but non-invasive tools for early detection of renal involvement suffer from low sensitivity (red blood cell casts) or low specificity (hematuria). We investigated four urinary proteins as potential markers of active renal AAV: alpha-1 acid glycoprotein (AGP), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), and neutrophil gelatinase-associated lipocalin (NGAL).

Methods: Patients with active renal AAV (n=20), active non-renal AAV (n=16), and AAV in long-term remission (n=14) were identified within a longitudinal cohort, in which detailed clinical assessment and urinalysis results had been recorded at every visit. Biomarker concentrations were measured by ELISA and normalized for urine creatinine. Marker levels during active AAV were compared to baseline remission levels determined from 1–4 remission visits for each patient. Areas under receiver-operating characteristic curves (AUC), sensitivities, specificities, and likelihood ratios (LR) comparing disease states were calculated. Generalized linear models were used to assess the effects of proteinuria, treatment, and other variables on marker levels.

Results: Baseline biomarker levels varied among patients. All four markers increased during renal flares (P<0.05). MCP-1 discriminated best between active renal disease and remission: a 1.3-fold increase in MCP-1 per mg creatinine had 94% sensitivity and 89% specificity for active renal disease (AUC=0.93, positive LR 8.5, negative LR 0.07; see Figure 1). However, increased MCP-1 also characterized 50% of apparently non-renal flares. Changes in non-specific proteinuria did not account for the association of MCP-1 with active renal disease, nor did changes in treatment. Change in AGP, KIM-1, or NGAL showed more modest ability to distinguish active renal disease from remission (AUC 0.71–0.75). Hematuria was noted during 63% of active renal episodes, but also during 38% of non-renal flares and 25%

of remission visits.
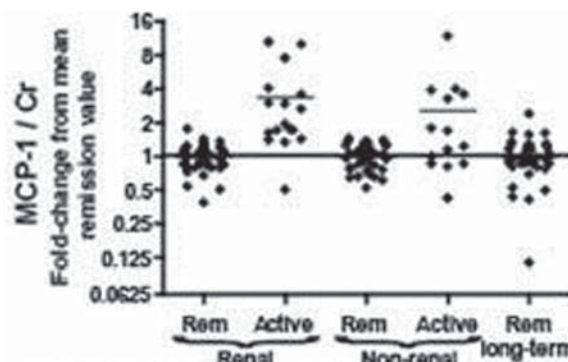
Figure 1. Fold-changes above baseline in urinary MCP-1/Cr in individual samples from patients with active renal AAV, active AAV thought to be lacking renal involvement (Non-renal), from the same patients during remission (Rem), and from other patients in long-term remission.

Conclusion: An increase in urinary MCP-1 may signal renal involvement in AAV. In contrast to a previous report, MCP-1 was imperfect in distinguishing active renal AAV from remission and was also elevated in cases in which renal involvement was thought to be absent. Either MCP-1 showed poor specificity for renal disease, or it improved sensitivity for detecting it, and urinalyses indicated that non-invasive assessment of active renal disease might be challenging in this cohort. AGP, KIM-1, and NGAL, despite being among the most promising markers in other kidney diseases, have lower prospects for clinical use in AAV.

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Pauci-Immune Glomerulonephritis in the Elderly: Disease Severity and Outcomes. Rebecca L. Manno[1], Duvuru Geetha[1], Stuart M. Levine[1], Philip Seo[2] and Allan C. Gelber[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Vasculitis Center, Baltimore, MD

Background/Purpose: Incident cases of pauci-immune glomerulonephritis affect adults at the older end of the age spectrum though relevant published data are limited. We sought to determine whether the clinical expression of disease differed in adults older than 70 years of age.

Methods: Between January 1, 1995 and June 22, 2012, a total of 55 patients (pts) $\geq$ age 60 years with histologic evidence of pauci-immune glomerulonephritis were evaluated at a single university center. The association of demographic and clinical parameters with age category was assessed using student's t and chi-square tests for continuous and categorical variables, respectively. The association of age category (vasculitis onset age 60–69 vs $\geq$70 yrs) with several outcome measures was examined using logistic regression in univariate analyses.

Results: 33 pts were age 60–69 yrs at presentation; 22 were $\geq$70 yrs. This cohort was 87% Caucasian, 44% female, and 89% ANCA-positive; the proportion pANCA and cANCA positive did not differ by age group. There were no differences in mean BVAS/WG scores at diagnosis between the 2 groups (8.2 ± 4.4 vs 9.5 ± 3.4, p=0.25). Peak serum creatinine at the time of renal biopsy was 4.6 mg/dl $\pm$ 2.4 among the older vs 3.4 ± 2.3 (p=0.085) among the younger age group with a mean GFR 15.9 ± 8.4 vs 26.8 ± 21.6 (p=0.035), respectively. Combination therapy with steroids and cyclophosphamide was the most frequently employed first vasculitis treatment regardless of age group (n=15; 68% older vs. n=26; 79% younger; p=0.53). There were 4 total deaths in the cohort, 2 in each age group. Ultimately, 5 renal transplants were performed among the younger vs. none in the older patient group (p=0.056). Further associations of key clinical features of disease differed between the two age groups, as follows:

Outcome	Univariate Odds Ratio (95%CI) (older vs younger)
Hospitalization at Presentation	5.0 (1.0,25.4)
Hemodialysis-dependent at diagnosis	3.1 (1.0,9.9)
Severe infection (hospitalization) during initial therapy	5.7 (1.3–24.9)
Leukopenia during initial therapy	1.1 (0.4–3.5)

Conclusion: There is relatively little information on the clinical features and outcomes regarding pauci-immune glomerulonephritis in the elderly. This single center experience, limited by retrospective design and small sample size, suggests that patients ≥70 years of age have worse renal outcomes associated with a higher serum creatinine and lower GFR at time of diagnosis, and an increased risk of progression to hemodialysis (borderline statistically significant) despite similar BVAS/WG scores. Elderly patients may be diagnosed later in their disease course, which may reflect a delay in initiating effective therapy. Our experience also suggests that elderly patients are more likely to experience treatment complications such as severe infection; although this did not correlate with an increased rate of leukopenia. These data imply that older pates may require a different treatment paradigm with more aggressive surveillance for both incipient renal disease and treatment complications.

Disclosure: R. L. Manno, None; D. Geetha, Genentech and Biogen IDEC Inc.,; S. M. Levine, CE Outcomes, 5, Up to Date, 7; P. Seo, None; A. C. Gelber, None.

ACR/ARHP Poster Session C
Education/Community Programs
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

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Exercise On Prescription: Barriers to Participation in Community Based Exercise Programmes. Dr Nicola E. Walsh[1] and Professor Mike Hurley[2]. [1]University of the West of England, Bristol, United Kingdom, [2]St George's University of London, London, United Kingdom

Background/Purpose: Osteoarthritis (OA) is highly prevalent, disabling and incurs considerable healthcare costs. Symptoms of pain and functional impairment can be ameliorated through participation in regular exercise, and this is encouraged as a long-term self-management strategy. Community based, instructor-led 'exercise on referral' schemes are common but infrequently assessed to determine their effectiveness; furthermore, participant and instructor views on these services are rarely reported. The aims of this study were to audit a 12-week local authority subsidised exercise programme and to report on participant and instructor views of this scheme.

Methods: Pre-existing databases were analysed to determine participation and health outcomes, an on-line survey and semi-structured interviews recorded instructor beliefs, whilst focus groups were used to collect data regarding participant views of community-based exercise. (Ethical approval references IRAS 11/SW/0084 and UREC HSC/11/02/27).

Results: In a two-year period 2101 people, age 45 and over with chronic joint pain/OA were referred for exercise. 36% of individuals completed the 12-week scheme; 22% of individuals did not start the programme; the remainder started but did not finish. Improvements were seen in BMI, blood pressure and self-reported activity levels for those that did complete all 12 sessions. Qualitative interviews (n=14) suggested people with OA were sceptical regarding the ability of gym instructors to manage their condition appropriately when exercising, and they feared their condition may worsen in this environment. Feedback from instructors (n=88) demonstrated a reduced specialist knowledge regarding the management of rheumatological conditions, and a recogntion that they required further specialist training to manage OA effectively. Instructors did however consider themselves appropriately trained to manage psychosocial issues, and to motivate individuals to exercise.

Conclusion: Community based exercise schemes are common, but there is an apparent reluctance amongst people with OA to engage with these schemes. Reasons for non-engagement include a perception that instructors are not appropriately qualified to manage their condition safely, and that symptoms may worsen. These beliefs may be vindicated as instructors reported a lack of specialised knowledge to support exercise programmes in people with rheumatological conditions. Although only 36% of individuals referred onto a 12-week exercise scheme completed the programme, these individuals demonstrated physiological improvements and an increase in self-reported activity levels. Future success of these programmes is likely to be dependant on exercise instructors gaining further qualifications in managing rheumatological conditions.

Disclosure: D. N. E. Walsh, None; P. M. Hurley, None.

2400

Hospital for Special Surgery Osteoarthritis Wellness Initiative: the Impact of a Hospital-Based Exercise Program On Osteoarthritis. Sandra Goldsmith, Dana Friedman, Linda Roberts, Dana Sperber and Laura Robbins. Hospital for Special Surgery, New York, NY

Background/Purpose: The Centers for Disease Control and Prevention (CDC) reports that about 27 million adults were affected by osteoarthritis (OA) in 2005. OA is characterized by degeneration of cartilage and bone within a joint, leading to pain and joint stiffness. Its effects are not just physical; lifestyle also declines (NIAMS). Research has shown that physical activity reduces pain, improves physical function, and delays disability in people with OA. Among older adults with knee OA, engaging in moderate physical activity at least 3 times per week can reduce the risk of arthritis related disability by 47%. However, almost 44% of adults with doctor-diagnosed arthritis report no leisure time physical activity compared with 36% of adults without arthritis (CDC). This specialty orthopedic hospital developed its Osteoarthritis Wellness Initiative, comprised of educational and exercise programs, to raise awareness, educate and reduce the impact of OA. This study attempts to support the efficacy of hospital-based exercise programs in increasing physical activity and improving quality of life (QOL) through pain reduction in the older adult community.

Methods: This prospective cohort study assesses the impact of participation in exercise classes on self-reported pain, balance, falls and level of physical activity, based on responses to a pre/post-test survey of 120 participants conducted in the Fall of 2011. The 11-point Numeric Pain Intensity Scale was used to quantify the intensity of muscle or joint pain. Pain interference on aspects of QOL (general activity, mood, walking ability, sleep, enjoyment of life etc.) was measured using items from the 10-point Brief Pain Inventory. Participants were asked to rate their balance on a 6-point rating scale, while self-reported number of falls and fall severity was assessed on a 5-point scale. Independent sample t-tests were performed to measure changes in mean pain intensity, pain interference scores, physical activity and fall severity scores from pre- to post test. Chi square tests were conducted to ascertain whether reports of pain, balance ratings and physical activity significantly changed from pre- to post test. Demographics such as age, gender and race/ethnicity were also collected.

Results: Most respondents were female (88.6%) with the majority ages 65+ (77.3%). The proportion of respondents who reported pain decreased from pre- to post test (73.4% to 56.5%). Statistically significant differences (p < 0.001) were found in mean pain intensity ratings between pre- and post test (pre-test = 5.1; post-test = 2.8). Significant differences in pain interference scores were found with regard to mood, walking ability and enjoyment of life (p < 0.05). Balance ratings improved, number and severity of falls diminished and vigorous physical activity increased.

Conclusion: Preliminary results indicate that providing low cost exercise programs to the community can play an important role in fighting OA with minimal resources. Data indicate that hospital-based exercise classes are associated with positive changes in pain, fitness and QOL, suggesting these exercise programs may play an important role in alleviating and/or minimizing symptoms of OA.

Disclosure: S. Goldsmith, None; D. Friedman, None; L. Roberts, None; D. Sperber, None; L. Robbins, None.

2401

An International Framework for Chronic Condition Self Management Support: Results from an International Electronic Consultation Process. Teresa J. Brady[1], Sue Mills[2], Peter Sargious[3] and Shabnam Ziabakhsh[4]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]University of British Columbia, Vancouver, BC, [3]Alberta Health Services, Calgary, AB, [4]BC Women's Hospital & Health Centre, Vancouver, BC

Background/Purpose: Self-management support (SMS)—a grouping of policies, programs, services, and structures that extend across health care, social sectors and communities to support and improve the way individuals manage their chronic conditions—is important in both health care delivery and population-based public health approaches, in the United States and internationally. However, SMS initiatives have evolved differently in differ-

ent professional disciplines, service systems and countries, with very limited cross-fertilization among them. The purpose of this project was to establish a framework of SMS (definitions, guiding principles, and strategic directions) to guide the development of self-management support initiatives locally, regionally, nationally and internationally. The purpose of this paper is to report on the international framework that emerged from an international electronic consultation process.

Methods: The British Columbia Center of Excellence for Women's Health hosted a three day roundtable discussion among twenty-three opinion-leaders from five English-speaking countries to explore SMS from a broad system perspective encompassing health care delivery, public health, and the social services sectors; a wide variety of funding sources supported the initiative. Roundtable participants were selected to represent a balance of policy, practice, and research perspectives across the US, Canada, Australia, the UK, and New Zealand. A preliminary draft framework was developed using a thematic analysis of the roundtable proceeding; the draft framework was refined through two rounds of a modified Delphi process among roundtable participants.

International electronic consultation was conducted using an online survey tool. A snowball sampling technique was used to gather international responses to the key elements of the draft framework. Data was collected using an on-line survey tool.

Results: A total of 204 reviewers from 16 countries responded to the electronic consultation. Representation by country ranged from 31% (Canada) to 1% (9 countries including Austria, Brazil, Denmark, Germany). 24% of respondents were researchers, 18% health care providers, 7% policy-makers, 6% consumers or patient advocates. 96% of respondents agreed or strongly agreed with the definitions of self management and self management support. The final draft framework contained eight guiding principles and seven strategic directions, with international agreement ranging from 94–96% and 98–99% respectively.

Conclusion: The international electronic consultation demonstrated strong international agreement with the definitions, guiding principles, and strategic directions that emerged from the modified Delphi process. While the original draft framework was developed by opinion-leaders in 5 English-speaking countries, the framework also resonated with respondents from 11 other countries where English is not the national language. While SMS developments need to reflect local, regional, and national needs, this international framework provides an emerging consensus on strategies to move the field forward across multiple perspectives and countries.

Disclosure: **T. J. Brady**, None; **S. Mills**, None; **P. Sargious**, None; **S. Ziabakhsh**, None.

2402

Clinical Utility of the Hospital Anxiety and Depression Scale for an Outpatient Fibromyalgia Education Program. Diane Tin[1], Lorna J. Bain[1], J. Carter Thorne[1], Seungree Nam[2] and Liane Ginsburg[2]. [1]Southlake Regional Health Centre, Newmarket, ON, [2]York University, Toronto, ON

Background/Purpose: The Arthritis Program (TAP) at Southlake Regional Health Centre has offered an inter-professional, patient centered Fibromyalgia (FM) education program for nearly two decades. This program currently consists of seven weekly group sessions covering topics such as: medications options, exercise techniques, problem solving skills to attain empowerment, self-management and increased emotional well- being. For many years, TAP has been using the Fibromyalgia Impact Questionnaire (FIQ) and Arthritis Self-Efficacy (ASE) Scale to measure patient outcomes Recently, TAP added the Hospital Anxiety and Depression Scale (HADS). The objective of this study was to examine the clinical utility of adopting HADS in measuring effectiveness of the outpatient FM education program in helping patients to manage anxiety and depression.

Methods: A retrospective chart review was performed on 232 outpatients who attended fibromyalgia education program between November 2011 and March 2012. These patients completed HADS, FIQ and ASE just prior to attending the first class. Post-program questionnaires were completed during the final class. Paired t-tests were performed on the 59 cases with complete pre and post program data. Results for the ASE and HADS scales are presented. Large sections of the FIQ were not applicable for this population.

Results: There was significant improvement in the ASE Pain subscale (mean±SD) (N=59) (35.14±15.52 vs. 45.04±17.65, p=0.00) and the ASE Other Symptoms subscale (N=57) (40.02±18.10 vs. 49.44±17.61, p=0.00). ASE Daily Activity subscale did not see significant change (N=59) (63.05±22.47 vs. 61.75±21.20, p=0.521). There was no significant differ-

ence between the overall pre and post HADS score, HADS-A (N=61) (11.97±4.04 vs. 11.90±4.16, p=0.866) and HADS-D (N=60) (9.98±3.76 vs. 9.33±3.87, p=0.074). In order to further explore our HADS data, HADS paired pretest and posttest scores were examined for two subsets of patients: (1) those taking one or more neuropathic pain reliever (SNRI, antiepileptics, TCA) and/or mood stabilizer (SSRI, Bupropion) at the beginning of program and (2) those who were not taking any of these drugs at the beginning of the program. There was a significant improvement in their HADS depression scale score and HADS anxiety scale score in the pre-post period for the group not taking any neuropathic pain reliever or mood stabilizer at baseline (HADS-A (N=19) (10.99±4.29 vs. 9.79±4.17, p=0.043) and HADS-D (N=19) (9.53±4.03 vs. 8.16±3.53, p=0.008)).

Conclusion: HADS is a sensitive outcome measure tool for detecting changes in level of anxiety and depression for certain subsets of fibromyalgia patients. Those who are not taking any neuropathic pain relievers or mood stabilizers at baseline show improvement in level of anxiety and depression measured by HADS upon completion of a seven week outpatient FM education program. Furthermore, improvement in the pain and other symptoms subscales of the ASE were demonstrated in the full sample of patients who completed the outpatient FM education program.

Disclosure: **D. Tin**, None; **L. J. Bain**, None; **J. C. Thorne**, None; **S. Nam**, not applicable, 2; **L. Ginsburg**, None.

2403

The Effect of a Rheumatoid Arthritis Peer Support Program On Clinical Outcomes. Rebecca Thrower[1], Christine K. Iannaccone[1], Hsun Tsao[2], Michael Weinblatt[3], Jing Cui[4] and Nancy A. Shadick[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [4]Brigham and Womens Hospital, Boston, MA, [5]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

Background/Purpose: To evaluate the effect of a rheumatoid arthritis (RA) peer support program on fatigue, functional status (pain, SF-12 PCS), self-efficacy, emotional health (SF-12 MCS) and medication adherence (ASK-20).

Methods: RA patients enrolled at a tertiary hospital arthritis center were recommended for peer support (mentees) by their rheumatologist. Peer support mentors received a three hour training to learn how to help other patients with concerns, coping strategies and medical decision-making. Mentors contacted mentees by phone once a week for 6 months, with optional email. Mentees were compared with controls who were not receiving peer support. They were matched on disease duration (years), age (years), and gender. Both groups filled out questionnaires at baseline and six month follow-up, assessing VAS fatigue and pain, arthritis self-efficacy, functional status (SF-12 PCS), emotional health (SF-12 MCS), and medication adherence (ASK20). A linear regression model with and without adjustment for baseline outcome differences was used to assess outcomes at 6 months.

Results: 20 mentees and 22 controls completed the baseline and 6 month questionnaires. Only 2 participants dropped out of the program. There were no differences in baseline demographics or disease duration between groups. The mean age was 49.7 years (SD, 12.3), 88.1% were female, and the mean disease duration was 8.5 years (SD, 10.2). Mentees entered the study with worse pain, fatigue, health status, and self-efficacy, but with similar medication adherence scores compared to controls. In linear regression analyses, the mentees had a significant improvement in self-efficacy (p=0.01) and physical function (p=0.007) compared to controls (see Table 1) and physical function improvement persisted after adjusting for baseline clinical outcome differences (p=0.02).

	Mentees (N=19)* Change (SD)	Controls (N=22) Change (SD)	P-Value	P-Value†
VAS Pain (0–100)	−9.7 (33.1)	1.4 (36.0)	0.31	0.86
VAS Fatigue (0–100)	−9.2 (34.3)	4.3 (27.1)	0.17	0.59
Arthritis Self-Efficacy	13.1 (21.0)	−3.6 (10.6)	0.01	0.72
SF-12 (MCS)	3.4 (9.2)	1.7 (8.8)	0.61	0.29
SF-12 (PCS)	5.8 (7.7)	−2.0 (8.2)	0.007	0.02
ASK-20 Scale (20–100)	−3.6 (11.5)	−0.5 (7.0)	0.33	0.69

*Outlier removed;
† Adjusted for baseline outcome differences

Conclusion: This pilot study suggests that RA patients who have active disease and receive peer support show improvement in self-efficacy and physical function. Peer support programs may be effective in enhancing patients' coping skills. Further analyses on a larger number of participants are needed to demonstrate the impact of the program on patient self-reported outcomes of fatigue, pain and medical adherence.

2404

Cardiovascular Disease Prevention Counseling Program for Systemic Lupus Erythematosus and/or Antiphospholipid Antibody Positive Patients: Two-Year Preliminary Analysis of Diet and Exercise Habits. Virginia Haiduc, Monica C. Richey, Sotiria Everett, Aeshita Dwivedi, Lisa Konstantellis, Hassan Ghomrawi and Doruk Erkan. Hospital for Special Surgery, New York, NY

Background/Purpose: SLE patients have high rate of cardiovascular events due to increased prevalence of traditional cardiovascular disease (CVD)- and other lupus-related thrombosis risk factors. In addition, antiphospholipid antibody (aPL)- positive patients are at increased risk for thrombosis. We have developed a free-of-charge CVD prevention counseling program (PCP) for SLE and/or aPL-positive patients that provides a basic assessment of and education about the CVD and thrombosis risk factors (Arthritis Rheum 2009;60;S743). We report two-year patient reported outcomes in our ongoing CVD-PCP.

Methods: The CVD PCP consists of two phases: "*assessment*" (blood pressure, blood glucose, cholesterol profile, waist circumference, body mass index, family history of CVD, smoking status, Framingham 10-year CVD risk calculation, aPL-profile, and medications) and "*education*" (counseling about the above mentioned risk factors). Patients are followed every 3–6 months for a maximum of 3 years; they are questioned about their diet and exercise habits during each visit. In addition, patients are offered to fill out baseline and follow-up surveys during each visit. We analyzed diet and exercise habits in a descriptive fashion (Likert Scale; 1–5, 5 is best). Repeated measures analysis was utilized to assess the change of the need for counseling on dietary and exercise habits over time. Our hypothesis was that over time there will be less need for counseling as a result of the program.

Results: Between 3/2009 and 12/2011, 115 SLE and/or aPL-positive patients received baseline counseling and 102/115 (89%) completed the baseline surveys. The mean (+ SD) scores for the baseline surveys were: a) improvement in patient's knowledge about CVD risk factors: 4.3 ± 0.9; b) likelihood of the counseling program improving patients' diet: 4.1 ± 1.1; and c) likelihood of the counseling program improving patients' exercise pattern: 4.0 ± 1.1. Patients completed surveys during 268/429 (63%) of follow-up visits (range: 3–33 months); some-to-significant improvement in the diet and exercise habits were reported during 251 (94%) and 225 (84%) of the visits, respectively. Repeated measures analysis showed that there was a significant decrease over time of the need for counseling on all dietary habits investigated (fruits, vegetables, whole-grain, fiber, fish) and 30 min/day exercise habits mostly starting at 9–12 months, continuing up to 2 years (Table).

Variable	3 or 6m Visit OR (95%CI)	9 or 12m Visit OR (95%CI)	15 or 18m Visit OR (95%CI)	21 or 24m Visit OR (95%CI)
Need for counseling on Fruits & Vegetables	0.63 (0.32–1.26)	0.44 (0.22–0.88)*	0.24 (0.1–0.54)*	0.20 (0.08–0.51)*
Need for counseling on Whole-Grain & High-fiber	0.62 (0.31–1.22)	0.4 (0.3–0.8)*	0.48 (0.23–0.99)*	0.22 (0.09–0.52)*
Need for counseling on Fish	0.51 (0.3–1.02)	0.4 (0.54–0.8)*	0.41 (0.2–0.86)*	0.33 (0.15–0.73)*
Need for counseling on Cholesterol Free Diet	0.50 (0.21–1.15)	0.70 (0.29–1.66)	0.95 (0.27–1.09)	0.72 (0.27–1.93)
Need for counseling on exercise at least 30 min/day	0.33 (0.15–0.71)*	0.23 (0.11–0.5)*	0.28 (0.13–0.63)*	0.19 (0.08–0.44)*

Conclusion: Two year preliminary analysis of our ongoing CVD prevention counseling program demonstrates our patients' belief that the program is helping them make healthful lifestyle choices in terms of diet and physical exercise. These findings are supported by the significant reported improvement in their diet and exercise. The three-year longitudinal analysis of clinical outcomes will determine the true effectiveness of the program with respect to decreasing the prevalence of cardiovascular disease risk factors.

2405

A Proof-of-Concept Study of an Animated, Web-Based Methotrexate Decision Aid for Patients with Rheumatoid Arthritis. Linda C. Li[1], Paul M. Adam[2], Catherine L. Backman[1], Sydney Brooks[3], Gwen A. Ellert[4], Allyson Jones[5], Otto Kamensek[6], Cheryl Koehn[7], Diane Lacaille[6], Colleen Maloney[6], Anne F. Townsend[6], Elaine Yacyshyn[5], Charlene Yousefi[6] and Dawn Stacey[8]. [1]University of British Columbia, Vancouver, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]The Arthritis Society, Ontario Division, Toronto, [4]Trelle Enterprises Inc, Vancouver, BC, [5]University of Alberta, Edmonton, AB, [6]Arthritis Research Centre of Canada, Vancouver, BC, [7]Vancouver, BC, [8]University of Ottawa, Ottawa, ON

Background/Purpose: Patient decision aids are designed to present the potential benefits and harm of treatment options, clarify individuals' preferences, and guide discussion at a clinic visit. The majority of decision aids on arthritis treatments are in printed formats. Although informative, they tend to be less engaging for users. We applied the concept of edutainment (i.e., education that engages through entertainment) to develop a web-based decision aid called ANSWER. Designed for patients with rheumatoid arthritis (RA), ANSWER presents information on methotrexate (MTX) in print, voice recording, and animated stories created with Adobe Photoshop. The current study aims to assess the extent to which ANSWER reduces patient's decisional conflict, and improves their medication knowledge and skills of being 'effective healthcare consumers'.

Methods: We used a pre-post study design. Participants were recruited from rheumatologists' clinics, patient groups and social networking sites (Facebook, Twitter, Craigslist, Kijiji). Eligible participants were those who: 1) had a physician diagnosis of RA, 2) had been prescribed MTX but were unsure about starting it, 3) had access to the internet. Password access to the ANSWER was provided immediately after enrollment. Participants completed a questionnaire before and within 48 hours after using the ANSWER. Outcome measures included: 1) Decisional Conflict Scale (DCS, primary outcome; 0–100, scores <25 are associated with follow-through with decisions), 2) MTX in RA Knowledge Test (MiRAK; 0–60, higher=better), and 3) Effective Consumer Scale (EC-17; 0–100, higher=better). Paired t-test was used to assess differences before and after the intervention.

Results: 30 participants were recruited between November 2010 and April 2012. The majority were women (n=23, 76.7%) with a mean age of 54.90 years (SD=14.91). 73.3% (n=22) attended/graduated from university. The median disease duration was 1 year (IRQ=0.3; 5.0), and the mean Health Assessment Questionnaire score was 1.16 (SD=0.68). The mean DCS was 49.50 (SD=23.17) pre-intervention and 21.83 (SD=24.12) post-intervention (change= -27.67, 95% CI= -15.44, -39.89; p<0.001). Before using the ANSWER, 13.3% of participants scored <25, compared to 70% after the intervention. Similar results were observed in MiRAK (pre: 30.62, SD=9.26; post: 41.67, SD=6.81; change: 11.03, 95% CI=6.73, 15.34; p<0.001), but not in EC-17 (pre: 68.24, SD=12.46; post: 72.94, SD=12.74; change: 4.71; 95% CI= -1.81, 11.22; p=0.15). After using the ANSWER, 20 participants (66.6%) were able to make a decision (14 would take MTX, 6 would decline MTX and talk to their doctor about other treatment options). 10 participants (33.3%) remained unsure about their preferred choice.

Conclusion: Patients' decisional conflict and MTX knowledge improved after using the ANSWER. Our results show similar changes to other studies evaluating decision aids in chronic diseases. The lack of a statistically significant change in the EC-17 might reflect the fact that it takes time to develop effective consumer attributes, such as how to find resources. Further research into the application of edutainment in developing patient decision aids and education programs is warranted.

Tuesday, November 13

2406

Implementation of a Pilot Nutrition Education Intervention for Culturally Diverse Teens with Lupus and Their Families in Hospital for Special Surgery's Charla De Lupus/Lupus Chat® Teen and Parent Support Group. Jillian A. Rose[1], Roberta Horton[1], Dariana M. Pichardo[2], Dana Friedman[1], Robyn Wiesel[1], Sandra Goldsmith[1], Sotiria Everett[1] and Lisa F. Imundo[3]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital For Special Surgery, New York, NY, [3]Morgan Stanely Children's Hospital of New York-Presbyterian, Columbia University Medical Center, New York, NY

Background/Purpose: Based on results of our previously reported needs assessment, the hospital's national lupus support and education program worked with our Public and Patient Education Department to adapt their existing culturally sensitive nutrition program to the needs of predominantly Hispanic teens with lupus and their families. This community service plan initiative was affiliated with an urban medical center's pediatric rheumatology department. The 5 session curriculum focused on whole grains/fiber, calcium/vit D, fruits/vegetables, protein foods, and snacks/fast foods. Portion control, food labels, sodium and culturally appropriate recipe examples were included throughout. "Lupus Links" were provided by a Registered Dietitian to address bone and cardiac health, hypertension, renal disease, and obesity. The program's goal was to provide practical strategies to initiate/sustain healthy nutrition practices in this community.

Methods: A bilingual (English/Spanish) 68 item pre-test was administered at the 1st session and a 78 item post-test at the 5th session to assess the program's impact on knowledge and behavior. True/false, multiple choice, Likert-type, and open ended questions were included. Program satisfaction was also assessed. A 3 month follow-up was conducted.

Results: Pre/post tests were completed by all 19 participants (8 teens, 11 parents), a total of 7 households. 80% of participants were female; ages ranged from 12–50; >70% were Hispanic; 66% indicated household incomes of 10,000–29,999 per year. 94% reported the program led them to include more nutritious foods in their diet. Results indicated a statistically significant increase ($p \leq 0.05$) cooking with canola oil (41% to 76%); weekly frequency of reported consumption of fish, chicken (turkey)and hot cereals increased, as did consumption of whole or rye bread($p \leq 0.05$).Positive behavioral changes occurred in most households along every nutritional item.

Although mean knowledge scores > from pre to post-test (64% to 70%), this was not statistically significant. The most knowledge gained (11%) related to whole grains/fiber. Overall, teens and their parents didn't always agree on how often they cooked or ate healthy at pre-test, but more congruent behavioral responses were reported from most households at post test.

The program was well -received by participants: 94% rated overall content as excellent; 88% rated the program excellent in terms of organization, clarity, and level of presentation; 93% rated the instructor's knowledge of the subject, and ability to keep the group engaged as excellent.

Seven participants completed the 3-month follow up survey (3 teens, 4 parents); all reported eating healthier. The use of canola oil for cooking < to 66.7% at follow-up, though still higher than baseline. There were slight reductions in several knowledge items.

Conclusion: Overall this program, limited by our small sample size, helped families implement healthy dietary changes. A consideration for future planning is building in follow-up communications (nutritional tips, facts and strategies) using texting/social media to reinforce knowledge and engage participants in sustaining healthy nutritional choices.

Disclosure: **J. A. Rose**, None; **R. Horton**, None; **D. M. Pichardo**, None; **D. Friedman**, None; **R. Wiesel**, None; **S. Goldsmith**, None; **S. Everett**, None; **L. F. Imundo**, None.

2407

Perceptions of the Chronic Disease Self-Management Program Among Low Income African American Women with Lupus. Charmayne M. Dunlop-Thomas, Terrika Barham, Natasha DeVeauuse Brown and Cristina Drenkard. Emory University, Atlanta, GA

Background/Purpose: Chronic illnesses have emerged as major health concerns of Americans in recent decades. African Americans with lupus are at high risk for poor disease outcomes and may face challenges in effectively self-managing multiple health problems, par-

ticularly among patients of low income. The Chronic Disease Self-Management Program (CDSMP) is a skill-building group-based, evidence-based intervention that improves the health of people with chronic illnesses. It is important to assess the perceptions of this program as success is regarded as dependent on its value to the targeted group. This study assessed the perceived acceptability, relevance and value of the program among a group of low-income African American (AA) female patients with lupus.

Methods: The CDSMP consisted of six weekly sessions led by two African American instructors and conducted in a small group (10–15 participants) workshop. Contents of the CDSMP are emotion and fatigue management, better communication, exercise, healthy eating, medication management, working with healthcare professionals, and cognitive techniques for relaxation and symptom management. Twenty-seven of the 45 study participants who completed the CDSMP workshops participated in 4 focus groups. A moderator led each focus group discussion using a guide. Participants' perceptions on the acceptability to general elements and settings of the program, relevance of contents and tools of the CDSMP, and beneficial value of the intervention to participants' disease experience were assessed. Semi-structured interviews were conducted with the two CDSMP instructors to supplement findings from the focus groups.

Data Analysis: Audio recordings of the focus groups and instructor semi-structured interviews were transcribed verbatim and thematically analyzed. Three research coders independently reviewed and coded each transcript to identify common themes. Two or more quotes were used to develop a theme.

Results: Participants were empowered by the group and program environment. They had a positive experience and were accepting of the program's locations and times. The program tools (CD on relaxation, textbook topics, action plan), as well as curricular contents were deemed as relevant and relatable to their disease experience. Participants felt empowered to use skills learned to make behavioral changes and manage their health. They valued the group peer interactions and relationships that were established. The instructors' perspectives were consistent with the participants' viewpoints.

Conclusion: This study suggests that the CDSMP was well received by low-income African American women with lupus. The education and social support provided as part of the program dynamics appear to be especially important for this targeted group. This overall acceptability was demonstrated through the expressed value and motivation in this sample. Further study is needed to examine long-term implications of participating in the CDSMP as an AA lupus patient, and the best community-based venues for implementation.

Disclosure: **C. M. Dunlop-Thomas**, None; **T. Barham**, None; **N. DeVeauuse Brown**, None; **C. Drenkard**, None.

ACR/ARHP Poster Session C
Epidemiology and Public Health
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

2408

Effects of Ground and Joint Reaction Force Exercise On Bone Mineral Density in Postmenopausal Women: A Meta-Analysis of Randomized Controlled Trials. George A. Kelley[1], Kristi S. Kelley[1] and Wendy M. Kohrt[2]. [1]West Virginia University, Morgantown, WV, [2]University of Colorado @ Denver, Aurora, CO

Background/Purpose: Previous randomized controlled trials have led to conflicting findings regarding the effects of ground and/or joint reaction force exercise on femoral neck (FN) and lumbar spine (LS) bone mineral density (BMD) in postmenopausal women. The purpose of this study was to use the aggregate data meta-analytic approach to resolve these discrepancies.

Methods: The *a priori* inclusion criteria were: (1) randomized controlled trials, (2) ground and/or joint reaction force exercise > 24 weeks, (3) comparative control group, (4) postmenopausal women, (5) participants not regularly active, (6) published and unpublished studies in any language since January 1, 1989, (7) BMD data available at the FN and/or LS. Studies were located by searching six electronic databases, cross-referencing, hand searching and expert review. Dual selection of studies and data abstraction were performed. Hedge's standardized effect size (g)

was calculated for each FN and LS BMD result and pooled using random-effects models. Z-score alpha values, 95% confidence intervals (CI) and number-needed-to-treat (NNT) were calculated for pooled results. Heterogeneity was examined using Q and I^2. Mixed-effects ANOVA and simple meta-regression were used to examine changes in FN and LS BMD according to selected categorical and continuous variables. Statistical significance was set at an alpha value ≤ 0.05 and a trend at >0.05 to ≤ 0.10.

Results: Statistically significant exercise minus control group improvements were found for both FN (28 g's, 1632 participants, $g = 0.288$, 95% CI = 0.102, 0.474, $p = 0.002$, Q = 90.5, $p<0.0001$, $I^2 = 70.1\%$, NNT = 6) and LS (28 g's, 1504 participants, $g = 0.179$, 95% CI = -0.003, 0.361, $p = 0.05$, Q = 77.7, $p<0.0001$, $I^2 = 65.3\%$, NNT = 6) BMD. None of the mixed-effects ANOVA analyses were statistically significant. For both FN and LS BMD, statistically significant, or a trend for statistically significant and positive associations were observed for intensity of training and compliance (joint reaction force exercise only) as well as changes in static balance. Inverse associations were observed for compliance (combined ground and joint reaction force exercise) as well as changes in body mass index, body weight and percent body fat. When limited to the LS, statistically significant, or a trend for statistically significant and positive associations were found for age, years postmenopausal and changes in lean body mass while inverse associations were observed for duration of training (minutes per session, ground reaction force exercise only), total minutes of training per week (ground reaction force exercise only), compliance (combined ground and joint reaction force exercise) and changes in aerobic fitness.

Conclusion: Exercise benefits FN and LS BMD in postmenopausal women. Several of the observed associations appear worthy of further investigation in well-designed randomized controlled trials.

Disclosure: G. A. Kelley, None; K. S. Kelley, None; W. M. Kohrt, None.

2409

Work Productivity in a Population Based Cohort of Patients with Spondyloarthritis. Emma Haglund[1], Ann B. I. Bremander[2], Stefan Bergman, Lennart TH Jacobsson[3], Britta Strömbeck[4] and Ingemar F. Petersson[4]. [1]R&D Center Spenshult, Oskarstrom, Sweden, [2]Halmstad University School of Business and Engineering,, Halmstad, Sweden, [3]Department of Rheumatology, Clinical sciences, Skane University Hospital, Malmö, Sweden, [4]Musculoskeletal Sciences, Department of Orthopedics, Clinical Sciences, Lund, Sweden

Background/Purpose: Spondyloarthritis (SpA) often causes impaired function, activity limitations, affected health related quality of life and work disability. Work disability has been shown to be affected both in terms of absenteeism and in impaired productivity while working (presenteeism). In this group with increased socioeconomic costs there is also an increase in the use of expensive pharmacotherapies. Thus, it is important to study factors related to the ability to stay productive while at work. The aim was to study factors associated with presenteeism in patients with SpA. Also to analyse possible differences in age, gender and SpA subtypes (ankylosing spondylitis, psoriatic arthritis and undifferentiated SpA).

Methods: The analysis was based on 1773 patients seeking health care for SpA aged 18–67 years from southern Sweden, identified by a health care register. A questionnaire survey in 2009 included questions concerning self-reported presenteeism, defined as the percentage of impairment due to SpA while working 0–100, (0=no impact), was answered by 1447 individuals. Patients' characteristics: disease duration, disease activity (BASDAI), physical function (BASFI), health related quality of life (EQ-5D), anxiety (HAD-a), depression (HAD-d), self-efficacy pain and symptom (ASES) and register based sick leave. The Pearson's correlation coefficient and univariate analyses with ANOVA were used to study factors associated with presenteeism and t-test was used for group comparisons.

Results: Fifty-five percent (n=802/1447) reported no impact on work presenteeism, while mean impairment was 20 (95% CI 18–21) (n=1447). Women reported higher impact on work presenteeism than men (mean impairment 23 vs. 17, p<0.001) but no statistically significant differences were found between the SpA subtype groups. Twenty-eight percent (n=504/1773) were registered for any sick leave (absenteeism > 14 days). Worse outcome in quality of life (EQ-5D), disease activity (BASDAI) and physical function (BASFI) all correlated to higher impact on work presenteeism (r >0.5, p <0.001), while sick leave (absenteeism) did not. In the univariate

analyses experiencing worse outcome in EQ-5D (β-est -9.6, p<0.001) BASDAI (β-est 7.8, p<0.001) and BASFI (β-est 7.3, p<0.001) were all associated to higher impact on presenteeism regardless of age, gender and disease subtype. Worse outcome of EQ-5D was associated to a higher degree impact on presenteeism in the younger women (18–52 yrs). Self-efficacy, anxiety, depression, disease duration and education level <12 years were all associated to higher impact on presenteeism but were not significant in all strata for age, gender and disease subtype.

Conclusion: Quality of life, disease activity and physical function all affect work presenteeism in patients with SpA, regardless of age, gender and disease subtype. The results indicate that work presenteeism is affected in patients with all types of SpA and more affected in women. We also find that presenteeism and register based sick leave (absenteeism) may be related to different dimensions of the individuals and their disease.

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2410

The Impact of Severe Hip and Knee Joint Disease On Paid and Unpaid Work Participation in Australia. Ilana N. Ackerman[1], Zanfina Ademi[1], Richard H. Osborne[2] and Danny Liew[1]. [1]The University of Melbourne, Melbourne, Australia, [2]Deakin University, Melbourne, Australia

Background/Purpose: Severe hip and knee joint disease are common and disabling conditions which represent a growing public health problem internationally. Although people of working age are commonly affected, the impact of severe hip and knee joint disease on work participation is not well understood. Using a national approach, this study aimed to evaluate participation in paid and unpaid work according to the severity of hip and knee joint disease.

Methods: A sample of 5000 people was randomly selected from the Australian electoral roll and invited to complete a questionnaire to screen for doctor-diagnosed hip arthritis, hip osteoarthritis (OA), knee arthritis and knee OA, and evaluate the severity and burden of these conditions. Joint disease severity was classified using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (range 0–100): <7=asymptomatic, 7–38=mild to moderate and $\geq$39=severe. Self-reported data were collected on paid and unpaid work status, premature exit from the workforce, and changes to work due to hip or knee arthritis or OA.

Results: Data were available for 1157 participants, with 237 (20%) reporting hip or knee joint disease. Of these, 16% (n=37) were classified as asymptomatic, 51% (n=120) as mild-moderate and 27% (n=64) were classified as severe. Neither age nor gender was associated with severity (p>0.05). Only 25% of the severe group was in paid employment, compared with 40% of the mild to moderate group and 54% of the asymptomatic group (p<0.01). Nine per cent of the severe group had stopped work due to their hip or knee, while no participant from the asymptomatic or mild to moderate groups had stopped work for this reason. After adjustment for age and gender, the severe group was over 3 times less likely to be in paid employment (adjusted odds ratio (AOR) 0.28, 95%CI 0.09–0.88), and over 4 times less likely to undertake unpaid work (AOR 0.24, 95%CI 0.10–0.62), compared with the asymptomatic group. Mild to moderate joint disease was not associated with a reduced likelihood of either being in paid employment or of undertaking unpaid work (p>0.05). Increasing severity was associated with greater difficulty in undertaking work; the proportion of participants who reported having to change the way they worked due to arthritis or OA rose with increasing disease severity (5% for asymptomatic group, 20% for mild to moderate group, and 59% for severe group; p<0.01). The proportion who reported having to change the number of hours worked due to arthritis or OA also increased with greater disease severity (3% for asymptomatic group, 15% for mild to moderate group, and 33% for severe group; p<0.01).

Conclusion: This study has generated new information on the relationship between severity of joint disease and work. Compared with those who had milder disease, individuals with severe joint disease reported markedly reduced paid and unpaid work participation, and greater difficulty in undertaking work. These data provide further evidence of the personal burden of severe joint disease and highlight the need for timely access to care.

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2411

Obesity Is Associated with Higher Levels of Fatigue in RA. Patricia P. Katz[1], Vladimir Chernitskiy[2] and Mary Margaretten[3]. [1]Univercity of California San Francisco, San Francisco, CA, [2]University of California San Francisco, San Francisco, CA, [3]UCSF, San Francisco, CA

Background/Purpose: Fatigue is recognized as a major problem for individuals with rheumatoid arthritis (RA), yet the causes of fatigue are not well defined. Obesity appears to be common in RA, and studies outside RA have linked obesity with fatigue. This analysis examined the association of obesity with fatigue in RA.

Methods: Subjects are participants in an on-going study of RA fatigue (current n=136). Home visits are made to individuals with documented RA to assess a number of factors, including the following variables used to estimate body composition: height, weight, waist circumference, and bioelectrical impedance analysis (BIA). Height and weight were used to calculate body mass index (BMI). Obesity was defined by standard definitions of BMI (≥ 30 kg/m^2) and waist circumference (women: ≥ 88cm; men: ≥ 102cm). Revised definitions of obesity from BMI (≥ 26 kg/m^2) and waist circumference (women: ≥ 83 cm; men: ≥ 96 cm)* were also examined. Total percent body fat was calculated from BIA. Fatigue was measured with the Fatigue Severity Index, and used the rating of average fatigue severity over the past week (range 0–10, no fatigue to severe fatigue). Subjects also completed questionnaires to measure RA disease activity (RA Disease Activity Index [RADAI]), sleep quality (Pittsburgh Sleep Quality Index [PSQI]), depression (PHQ), and functioning (HAQ). Multiple linear regression analyses were used to identify the association of each measure of obesity with fatigue severity. Covariates included RADAI, PHQ, HAQ, sleep quality, age, sex, and RA duration.

Results: Mean ($\pm$SD) age was 59 ($\pm$12) years, 87% were female, and 77% were white. Mean fatigue severity rating was 3.8 ($\pm$2.1; range 0–10). Proportion defined as obese ranged from 27% (BMI≥ 30) to 61% (waist circumference, revised), and mean percent fat was 35.6% ($\pm$09.0). In unadjusted analyses, all measure of obesity and body fatness were significantly associated with fatigue (Table). Adjustment for covariates attenuated the relationship of body composition measures with fatigue, but the association persisted.

Table. Associations of body composition measures with fatigue severity

	% (n) obese	Unadjusted		Adjusted[1]	
		Beta (95% CI)	p	Beta (95% CI)	p
BMI obese (30 kg/m^2)	27% (37)	1.2 (0.4, 1.9)	.003	0.5 (-0.2, 1.1)	.18
BMI obese (revised; 26 kg/m^2)	51% (70)	1.6 (1.0, 2.3)	<.0001	0.7 (0.1, 1.3)	.02
Waist obese (women $\geq$ 88cm, men $\geq$ 102 cm)	47% (63)	1.3 (0.6, 2.0)	.0002	0.5 (-0. 1, 1.1)	.11
Waist obese (revised; Women $\geq$ 83cm, Men $\geq$ 96 cm)	61% (82)	1.3 (0.6, 2.0)	.0004	0.6 (-0.02, 1.2)	.06
Total % fat (per 10% increment)		1.4 (0.7, 2.1)	.0002	0.3 (-0.06, 0.7)	.10

[1]Adjusted for RADAI, PHQ, HAQ, self-reported sleep quality, age, sex, RA duration.
* Katz, presented at ACR/ARHP, 2011.

Conclusion: Obesity appears to play a role in RA fatigue, even after controlling for important covariates such as disease activity, sleep, and depression. Associations found using the revised obesity definitions, which increased the number of individuals classified as obese by 89% (BMI) and 30% (waist circumference), were not substantially different from those found with the standard definitions. Addressing obesity in RA may be part of effective interventions for RA fatigue.

Disclosure: P. P. Katz, None; **V. Chernitskiy**, None; **M. Margaretten**, None.

2412

Valdiation of a Diagnosis of Gout in the Epiccare Electronic Medical Records. Neera Narang[1] and Eswar Krishnan[2]. [1]Stanford Univ Medical Center, Stanford, CA, [2]Stanford University, Stanford, CA

Background/Purpose: Electronic Medical Records (EMR) offer great opportunities for pharmacoepidemiologic, health outcome and health services research. However, the critical limiting factor in the widespread use of these data is the accuracy, precision and validity of diagnoses. EpicCare is a large and growing proprietary EMR software system that has been adopted by several large tertiary care facilities.The goal of this FDA funded project was to assess the validity of an ICD code of 274.* to identify patients meeting a clinical diagnosis of gout from among those who have ever been prescribed colchicine.

Methods: We identified 143 patients in the Stanford EpicCare system in the past 6 years that met our case definition for gout -at least one prescription of colchicine and one instance of ICD-9 code of 274.*. The records of these patients were individually reviewed and data on the following aspects were abstracted: physician diagnosis (notes), performance of arthrocentesis, use of urate lowering therapy, and documentation of each of the American College of Rheumatology (ACR) criteria for diagnosis/classification of gout. Data were analyzed quantitatively and qualitatively.

Results: Overall 143 case records were reviewed, of which 3 did not have any physician authored clinical documents. A physician diagnosis of gout was documented in 114 (80%). Three charts revealed a diagnosis of pseudogout and 31 did not have any physician documentation of gout. Among those records with a physician diagnosis of gout, 35 records documented intra-articular urate crystals, 36 records had documentation that met the ACR criteria, and 19 records had documentation of ACR criteria and urate crystals. The median number of ACR criteria met in the 114 charts was 4, with an interquartile range of 2 to 6. Among those records with a positive crystal identification, only 48% had documentation that met the ACR criteria. Among those records where arthrocentesis was performed and found to be negative for crystals, physician diagnosis was documented in 90%, and ACR criteria were met in 40%. In the case records that did not show documentation of arthrocentesis or any relevant laboratory evaluation, 75% had physician diagnosis and about 13% met the American College of Rheumatology criteria.

Conclusion: This study showed that in the setting of a tertiary medical center, Electronic Medical Records are an excellent resource for gout research. Documentation of the individual ACR criteria and performance of arthrocentesis is infrequent and hence these may not be useful gold standards for validation studies of gout in the EMR. From our qualitative review, documentation of physician diagnosis may be considered a useful benchmark for assessing the utility of case definitions for gout.

Disclosure: N. Narang, None; **E. Krishnan**, savient, 1, URL, takeda, metbolex-,ARDEA, 2, METABOLEX TAKEDA, 5.

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The Impact of Asymptomatic Vertebral Fractures On Quality of Life in Community-Dwelling Older Women: The Sao Paulo Ageing & Health Study (SPAH). Jaqueline B. Lopes[1], Leandro Fung[2], Carolina C. Cha[2], Camille P. Figueiredo[2], Liliam Takayama[2], Valéria Caparbo[2] and Rosa M.R. Pereira[2]. [1]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: Health-related Quality of life (HRQL) has been used as a complementary measure of bone mineral density to evaluate the burden of osteoporosis on a patient's daily life. There are few epidemiological studies evaluate HRQL and vertebral fractures in non-ambulatory or non-institutionalized elderly individuals. The aim of this study was to investigate the impact of asymptomatic vertebral fractures on quality of life in community-dwelling older women.

Methods: This cross-sectional study is nested within the larger epidemiological project of prevalence vertebral fractures in older living in Sao Paulo, Brazil. A random sample of 180 women with 65 years of age or over was evaluated. The Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) was applied to all subjects. The QUALEFFO is a specific questionnaire designed to be used by patients with vertebral fractures attributed to osteoporosis. A low domain score indicates worse health and a high score indicates better health. Anthropometric data was obtained by physical examination and body mass index (BMI) was calculated. A lateral thoracic and lumbar spine X-ray was performed to identify asymptomatic vertebral fractures using Genant semi-quantitative method. A generalized linear model (GLM) with gamma distribution and logarithmic link function was used in the final statistical analysis.

Results: Women with asymptomatic vertebral fractures had lower QUALEFFO total score [61.4(15.3) *vs.* 67.1(14.2), p=0.03] and worse QUALEFFO-physical-function domain [69.5(20.1) *vs.* 77.3(17.1), p=0.02] compared to those without fractures. QUALEFFO total score was also worse in women classified as obese, compare those classified as overweight and normal. High physical activity was related with better QUALEFFO total score (p=0.01). Likewise, lower QUALEFFO-physical-function score was observed in women with higher BMI (p<0.05) and lower physical activity (p<0.05). GLM with gamma distribution and logarithmic link function,

adjusted to age, showed that impair QUALLEFFO-total score and QUALEFFO-physical-function domain was related with high BMI, lower physical activity and vertebral fractures (p<0.05).

Conclusion: Vertebral fractures are associated to decrease QOL in community-dwelling older women regardless of age, BMI, and physical activity. Therefore, our results highlight the importance of preventing and controlling asymptomatic vertebral fractures in order to reduce their impact on QOL among older women.

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2414

Multisite Joint Pain and Fatigue: the Role of Pain Severity and Sleep Problems in Adults with Arthritis. Mayilee Canizares[1] and E.M. Badley[2]. [1]Division of Health Care and Outcomes Research. Toronto Western Research Institute, Toronto, ON, [2]Division of Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: Little is known about the severity and determinants of fatigue in adults with arthritis. We hypothesize that the number of joint sites affected is associated with fatigue through pain severity and sleep problems.

Methods: Data source: a representative sample of people reporting arthritis, the 2009 Survey on Living with Chronic Diseases in Canada—Arthritis Component (age 20+: n=4,565). Variables: frequency and severity of fatigue and of pain, sleep difficulties (a lot, a little, not at all), sites of joint pain (up to 18 joint sites), other chronic conditions, arthritis type (most frequently unknown type or osteoarthritis), and personal characteristics (age, sex, education, income, obesity). The number of joint sites affected were grouped: no pain, single site, 2–3 sites, 4–7 sites, and 8+ sites (widespread). For multivariate analysis, the frequency and severity of fatigue were combined into a continuous score (0 = no fatigue to 100 = always and as bad as it could be). A similar score was calculated for pain. Sequential multivariate linear regression models, controlling for personal and health characteristics were fitted to investigate the relationship of joint site groups, pain severity, and sleep problems with fatigue.

Results: 91.7% reported fatigue with a mean score of 50.4. The average joint site count was 5.1 (95% CI: 4.9–5.3). Over 80% reported multisite joint pain (24.3% 2–3 sites, 25.2% 4–7 sites, 30.4% 8+ sites). There was a significant gradient of higher pain severity and more sleep problems with increasing joint site count. Women, obese individuals and those with comorbidities had higher levels of fatigue. No differences were seen by arthritis type. In the model adjusting only for personal and health characteristics having 2–3 sites or more was significantly associated with higher levels of fatigue. When pain severity was added to the model the coefficients for 2–3 and 4–7 sites were no longer significant, and for the 8+ sites group was decreased by 67.4% (β=5.7, 95% CI: 0.5–9.1) suggesting that the effect of joint count on fatigue was fully mediated by pain severity for <8 joints and partially mediated for 8+ joint sites group. Adding sleep problems to the model, further decreased the coefficient for 8+ sites by 15.8% (β=4.8, 95% CI: 0.5–9.1).

Conclusion: The results underscore the high frequency of multiple joint site involvement among people with arthritis, as well as the importance of joint site count for pain severity, sleep problems, and fatigue. The findings confirm that the effect of number of joint sites on fatigue is mediated through pain severity and sleep problems, and indicate at least some direct effect of widespread joint involvement on fatigue. These findings together with the similarities for the different types of arthritis point to the need to pay attention to the number of joint sites affected for all types of arthritis in strategies aiming to reduce the impact of fatigue.

Disclosure: M. Canizares, None; **E. M. Badley**, None.

2415

Does Interleukin-6 Mediate the Relation Between Estrogen and Bone? an Epidemiologic Approach in the Framingham Osteoporosis Study. Robert R. McLean[1], Xiaochun Zhang[2], Andrea D. Coviello[3], Joao D.T. Fontes[4], L. Adrienne Cupples[5], Douglas P. Kiel[1] and Marian T. Hannan[1]. [1]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [2]Hebrew Senior Life, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]Framingham Heart Study and Boston University, Framingham, MA, [5]Boston University School of Public Health, Boston, MA

Background/Purpose: Laboratory and animal studies suggest that lower sex hormone levels promote production and activity of pro-inflammatory cytokines that trigger bone resorption. This paradigm is a hypothesized mechanism for accelerated bone loss following menopause, and may influence bone loss in men and premenopausal women as cytokine levels may vary across the range of endogenous hormones within these groups. Confirmation of these hypotheses in epidemiologic studies could inform the development of interventions to prevent bone loss. We examined whether interleukin-6 (IL-6) concentration is a mediator of the cross-sectional relation between total estradiol concentration and hip bone mineral density (BMD), separately among men, premenopausal women and postmenopausal women in the Framingham Osteoporosis Study. We hypothesized that a direct association between total estradiol and BMD would be attenuated after adjusting for IL-6, suggesting IL-6 as a potential mediator.

Methods: Fasting blood samples and BMD measures were obtained (1996–2001) from 1,230 men, 215 premenopausal and 1,300 women. Serum total estradiol (pg/mL) and IL-6 (pg/mL) concentrations were measured via LC-MS/MS and ELISA, respectively. Femoral neck BMD (g/cm²) was measured with a Lunar DPX-L. Separately for men, premenopausal and postmenopausal women, total estradiol was categorized into quartiles and analysis of covariance was used to calculate least squares-adjusted mean BMD for each quartile and test for a linear trend, adjusting for age, BMI, height, physical activity, current smoking and in postmenopausal women, use of hormone replacement therapy (HRT). To examine potential effect modification by HRT in postmenopausal women analyses were also stratified by HRT use. Models were additionally adjusted for IL-6 and if an association between total estradiol and BMD was consequently attenuated, IL-6 was considered a mediator.

Results: Mean age was 61 y (range 29–86 y). There was a statistically significant positive association between total estradiol and BMD among men and a similar, though not statistically significant, relation in postmenopausal women (Table). There was no association in premenopausal women. In postmenopausal women the relation was similar for HRT users and non-users (data not shown). Associations were nearly identical after adjusting for IL-6, suggesting no mediation by IL-6.

Least squares-adjusted mean femoral neck BMD (g/cm²) for quartiles of serum total estradiol, with and without adjustment for IL-6, among men and women in the Framingham Osteoporosis Study.

	Estradiol quartile (range, pg/mL)	N	Median IL-6 (pg/mL)	LS Mean BMD (SE) Model 1*	Model 1 + IL-6
Men	1 (1.1, 19.6)	307	2.53	0.960 (0.007)	0.960 (0.007)
	2 (19.7, 24.9)	310	2.68	0.972 (0.007)	0.972 (0.007)
	3 (25.0, 31.4)	304	3.13	0.979 (0.007)	0.979 (0.007)
	4 (31.5, 118)	309	3.19	0.985 (0.007)	0.985 (0.007)
			P for trend	0.01	
Premenopausal women	1 (3.0, 14.0)	53	1.87	0.942 (0.016)	0.943 (0.016)
	2 (15.0, 58.0)	54	2.39	0.979 (0.016)	0.981 (0.016)
	3 (60.0, 136)	54	1.64	0.994 (0.016)	0.992 (0.016)
	4 (137, 678)	54	2.10	0.948 (0.016)	0.948 (0.016)
			P for trend	0.73	
Postmenopausal women	1 (3.0, 6.0)	323	2.59	0.846 (0.007)	0.846 (0.007)
	2 (7.0, 11.0)	347	2.70	0.849 (0.006)	0.850 (0.006)
	3 (12.0, 22.0)	317	3.06	0.854 (0.007)	0.855 (0.007)
	4 (23.0, 459)	313	2.63	0.862 (0.007)	0.862 (0.007)
			P for trend	0.15	

*Adjusted for age, BMI, height, physical activity, current smoking, and, in postmenopausal women, current HRT use.

Conclusion: These cross-sectional findings suggest that while lower estrogen status was associated with lower hip BMD in men and postmenopausal women, these relations are not influenced by IL-6. Subsequent analyses should examine additional markers of estrogen status (free estradiol, estrone, sex hormone-binding globulin) and pro-inflammatory cytokines (CRP, TNF-α), the role of hormonal contraceptive use and phase of menstrual cycle in premenopausal women, and prospective changes in BMD.

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Arthritis-Attributable Interference in Routine Life Activities. Kristina A. Theis[1], Teresa J. Brady[1], Charles G. Helmick[1], Louise Murphy[2] and Kamil E. Barbour[1]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]CDC, Atlanta, GA

Background/Purpose: Arthritis-attributable interference (AAI) in routine life activities are indicators of quality-of-life (QOL) that have not often been studied in a population-based sample of U.S. adults with arthritis. The purpose of this study is to estimate, among people with arthritis, the proportion and number with AAI in four routine life activity domains (1. recreation, leisure, and hobbies; 2. household chores; 3. errands and shopping; and 4. normal social activities), as well as the proportion affected among those with select characteristics.

Methods: Data were from ACHES, a cross-sectional, random digit dialed national telephone survey of non-institutionalized U.S. adults ≥ 45 years with self-reported doctor-diagnosed arthritis conducted in 2005–06. All respondents (n=1,793) confirmed a diagnosis of arthritis from a health professional. AAI for the first 3 life activity domains was asked by: "During the past 7 days, how much did your arthritis or joint symptoms interfere with the following activities?" AAI in the fourth domain used a 30-day recall; responses for all 4 questions were: a lot, a little, or not at all. For analysis across the 4 activity domains, a composite measure of AAI was created with three mutually exclusive subgroups: substantial ("a lot" in ≥1 domain), modest ("a little" in ≥1 domain), and none (no interference in any domain). The proportion of adults in each of these subgroups was examined overall and by demographics, clinical measures, and psychological factors. Weighted proportions and 95% confidence intervals (CI) were calculated accounting for the complex sample design (SAS 9.2).

Results: AAI (a lot, a little) was reported by more than half of respondents in each of the 4 life activity domains and was highest for household chores (68%) and recreation/leisure/hobbies (65%). The proportion of U.S. adults ≥45 years with arthritis who reported any degree of composite AAI in routine life activities was 79% (29.9 million) (substantial AAI = 38% (14.3 million); modest AAI = 41% (15.6 million)). Only 21% (7.8 million) reported no AAI. Substantial AAI was significantly higher in women compared with men (42% vs. 31%) but similar by age and race/ethnicity. Substantial AAI was significantly lower among those with high confidence in ability to manage arthritis symptoms. The proportion with substantial AAI by select characteristics was > 50% for those with: severe fatigue (74%), severe joint stiffness (69%), severe joint pain (68%), anxiety (61%), depression (68%), low confidence in managing arthritis symptoms (65%), and those currently seeing a doctor or healthcare provider (51%).

Conclusion: Severe arthritis symptoms identify patients with substantial interference in routine life activities, but other characteristics (above) may identify additional patients who can benefit from interventions to preserve QOL. Controlling arthritis symptoms medically, in combination with referrals for evidence-based self-management education and physical activity programs, may reduce AAI in these important life activity domains and help address the large and growing public health problem of arthritis and its related QOL impacts.

2417

Transitioning to Adulthood: Employment Experiences of Young Adults with Lupus and Juvenile Arthritis. Arif Jetha[1], E. M. Badley[2], Dorcas Beaton[3], Paul R. Fortin[4], Natalie J. Shiff[5], Alan M. Rosenberg[6], Lori B. Tucker[7], Dianne P. Mosher[8] and M. A. Gignac[9]. [1]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [2]Division of Health Care and Outcomes Research,Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [3]Institute for Work & Health; Mobility Program, Clinical Research Unit, St. Michaels Hospital, Toronto, ON, [4]Division of Rheumatology, Centre de recherche du centre hospitalier universitaire de Québec, Faculté de médecine de L'université Laval, Quebec City, QC, [5]University of Saskatchewan, Saskatoon, SK, [6]Royal University Hospital, Saskatoon, SK, [7]BC Childrens Hospital, Vancouver, BC, [8]University of Calgary, Calgary, AB, [9]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto; Institute for Work & Health, Toronto, ON

Background/Purpose: A considerable body of evidence highlights the negative impact of rheumatic disease on employment. However, most research examines middle- and older-aged adults. We lack information on the employment experiences of young adults with rheumatic diseases who are transitioning to adulthood.

Objectives: To describe the working experiences of young adults (ages 18 to 30 years) with systemic lupus erythematosus (SLE) and juvenile arthritis (JA) in terms of: 1) employment status 2) disease-related job absenteeism and disruptions and 3) demographic, health, psychological and work factors associated with job disruptions.

Methods: 143 participants (mean age=23.3 years, SD=3.5, 80%= female) with SLE (n=78) and JA (n=65) were recruited from rheumatology clinics in four Canadian provinces (Ontario, Saskatchewan, British Columbia and Alberta). All completed an online questionnaire asking about demographic (age, gender, education), health (diagnosis, pain, fatigue, disease activity), work context (job sector, hours worked), absenteeism, job stress, and psychosocial factors (perceived independence, disclosure of disease). The number of disease-related job disruptions (work interruptions, arriving late/leaving early, missed meetings) were also asked (1=yes; 0=no). A multivariate linear regression analysis examining the association of demographic, health, work context, and psychological factors with disease-related job disruptions was conducted.

Results: 61% of the sample were employed, 26% were students and 13% were not working. Participants mostly reported a well controlled disease with low pain (mean=3.5 SD=3.0), fatigue (mean=4.2, SD=3.1) and disease activity (mean=3.1, SD=3.0). 56% had attended post-secondary school. Among those employed, half worked full-time (54%) and about a third of participants worked in sales and service jobs (36%). Over half of employed participants (53%) reported at least one disease-related job disruption (mean=1.5, SD=2.3; range: 0–7) and 56.5% reported a job absence because of their disease in the previous 6 months. The most common disease-related job disruptions in the past 6 months were work interruptions of 20 minutes or more (33%), lost time because of arriving late/leaving early (22%) and being unable to work requested schedules (20%). Greater job disruptions were significantly associated with older age, greater job stress, workplace activity limitations, and having disclosed arthritis to one's manager. Increased fatigue and perceiving that one would be able to remain employed were significantly associated with fewer job disruptions.

Conclusion: Similar to their healthy peers, the majority of young adults with SLE and JA in this sample were employed or pursuing an education. However, many experienced disease-related absenteeism or job disruptions that were associated with having discussed their disease with an employer, higher work stress and workplace limitations, signaling the need for intervention. Flextime or workplace self-management are examples of interventions, in this age group, that may improve long-term success in employment.

2418

The Everyday Challenge of Living with Lupus. Brenda L. Frie. St. Catherine University, St. Paul, MN

Background/Purpose: The purpose of this study was; 1) to assess the unmet needs of adults with lupus; 2) to explore their future interest in attending community based educational programing.

Systemic Lupus Erythematosus (SLE) is an arthritis related chronic autoimmune disease. SLE is the most common and most severe form of lupus involving multiple body systems including the blood, muscles, joints, organs and the nervous system (Wallace, 2009). It is estimated that 161,000 to 322,000 adults with SLE live in the United States (Helmick, et al., 2008). The rising costs of health care, increasing incidence and the impact of SLE on quality of life provides rationale for this study. This research can be used to support the future design of community based services.

Methods: This research proposal was reviewed and approved by the University Institutional Review Board and the Lupus Foundation of Minnesota (LFM). Adult members of LFM were invited to participate in the survey. The survey was conducted in Minneapolis and St. Paul, Minnesota. Items for the needs assessment survey were selected by the researcher in collaboration with the Lupus Foundation of Minnesota. The survey included 23 items listed

on the Systemic Lupus Erythematosus Needs Questionnaire (SNLEQ) (Moses, Wiggers, Nicholas, & Cockburn, 2007) and 25 items from categories listed on the World Health Organization Quality of Life Assessment (1995) and the Healthcare Assessment Questionnaire developed by Fries, Spitz, Kraines, & Holman (1980). Survey items were ranked on a 5 point rating scale based on level of difficulty participating in daily life tasks, managing physical symptoms and emotional concerns. Demographic information, access to services, and interest in community based programing was assessed through open ended and multiple choice questions. The data was analyzed descriptively.

Results: Ninety six participants completed the survey. The majority of the study participants were women (95%), with an average age of 49 years old. Over half of the respondents (52%) reported that they were not working at the time of the survey. Three percent of those surveyed received occupational therapy services within the past year. Most participants were Caucasian (82%). Fifty percent of participants reported moderate or higher level difficulty doing the daily tasks of sports, climbing, outdoor work, and managing the physical symptoms of pain and fatigue. Thirty percent of those surveyed reported difficulty coping with emotional concerns of depression, stress and anxiety. Management of fatigue was the most prevalent area of concern. Eighty seven percent of participants reported that they may be interested in attending a community based educational program addressing the areas of fatigue, pain, stress, strength and conditioning, coping skills and life balance.

Conclusion: This study is important in that it identifies there is a need for and interest in community based educational programing for those living with lupus. Community based services can play a key role in improving the quality of life of those with SLE through providing services to help adapt or modify their environments and manage the disease symptoms.

2419

Novel Candidate Genes for Structural Foot Disorders: A Genome-Wide Association Study in an Older Caucasian Population. Marian T. Hannan[1], Yi-Hsiang Hsu[2], Chia Ho Cheng[2], Youfang Liu[3] and Joanne M. Jordan[4]. [1]Hebrew SeniorLife & Harvard Medical School, Boston, MA, [2]Hebrew SeniorLife & Harvard Med Sch, Boston, MA, [3]University of North Carolina, Chapel Hill, NC, [4]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC

Background/Purpose: Structural foot disorders, such as hallux valgus, deformities of the lesser toes (toes 2–5) and plantar soft-tissue atrophy, commonly affect 60% of older adults at the population level and are often linked with foot pain, chronic mobility limitations, and disability. Although, body weight and other environmental factors are considered possible causes of these foot conditions, the importance of genetics is commonly suspected in clinical observations of family aggregation. Previously, we reported strong heritability (h^2) for lesser-toe deformity (61% in men; 85% in women) and moderate h^2 for hallux valgus (35%) and plantar soft-tissue atrophy (20%) in older men and women, suggesting potential genetic predisposition to structural foot disorders. To identify their genetic determinants, we have undertaken a GWAS using 2.5M imputed SNPs (HapMapII CEU reference panel) to localize susceptible genes in the population-based Framingham Foot Study.

Methods: Structural foot disorders were indicated as present or absent and were assessed based on an atlas of pictorial depictions. Plantar soft tissue atrophy was determined by palpating the plantar fat pad at the forefoot and heel during a validated foot examination. Among 2,446 Framingham participants (mean age 66 yrs; 57% women; Caucasian), we identified 753 (31%), 764 (31%) and 665 (27%) participants with deformities of the lesser-toes, hallux valgus and plantar soft-tissue atrophy, respectively. A mixed-effect regression model was performed and adjusted for age, sex, weight and principal components of ancestral genetic background. A kinship covariance matrix was used to take into account within-family correlations among siblings. We filtered out SNPs with low imputation quality (O/E variance ratio of allele frequency $<$ 0.3) and SNPs with MAF $<$ 1%. In addition, p-values were also adjusted for λGC.

Results: We found several associations achieved genome-wide significance ($p < 5 \times 10^{-8}$), i.e. SNPs on *TBC1D22A* and *OR5D13* gene for lesser-toe deformity. For hallux valgus, the most significant SNP (p=4.9×10^{-7}) is located in *GATAD2B* gene. For plantar soft-tissue atrophy, the most significant SNP (p=4.76×10–7) is located near *ADAMTS16* gene. Pathway and gene-set analyses for the genome-wide significant and suggestive genes suggested significant clustering of genes involved in

connective tissue disorders (such as oligoarticular arthritis, osteoarthritis and osteosclerosis). Of note, a few SNPs were reported to associate with longevity. These results are undergoing replication in independent samples.

Conclusion: In conclusion, our results identify novel candidate genes to further elucidate the etiology of structural foot disorders.

ACR/ARHP Poster Session C
Pediatrics
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

2420

Frequent Self-Reported Pain and Disease Symptoms in Juvenile Idiopathic Arthritis Persist Despite Advances in Medication Therapies: An Electronic Diary Study. Maggie H. Bromberg[1], Mark Connelly[2], Kelly K. Anthony[3], Karen M. Gil[1] and Laura E. Schanberg[3]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Children's Mercy Hospitals and Clinics, Kansas City, MO, [3]Duke University Medical Center, Durham, NC

Background/Purpose: Previous research has demonstrated that children with Juvenile Idiopathic Arthritis (JIA) experience frequent pain that interferes with performing tasks at home and at school. However, it is unclear whether pain and associated functional limitations persist despite recent advances in the understanding and medical treatment of the disease. The present study used electronic (e-) diaries to determine whether pain, stiffness, and fatigue continue to be common, disabling symptoms in children with JIA despite aggressive contemporary medical management.

Methods: Fifty-nine children with JIA (44 girls, 73% Caucasian, mean age 13.3 years) were recruited during routine pediatric rheumatology clinic visits. Most had mild (42%) or moderate (43%) physician-rated disease activity (minimal 11%, severe 4%). Participants provided current ratings of pain, stiffness, and fatigue intensity; number of painful locations; and functional limitations using a Smartphone e-diary three times each day for one month. Medication information was collected via parent report and checked for accuracy by chart review. Descriptive analyses were conducted to determine typical symptom intensity, frequency, and variability for the sample. Multilevel modeling was then used to analyze associations between symptoms and functional outcomes and between medication use and symptom intensity.

Results: Across 3258 completed e-diary entries, the average pain intensity rating was 26.3/100 (SD = 27.5), average stiffness intensity 24.4/100 (SD =25.2), and average fatigue intensity 42.7/100 (SD = 28.19). Children reported pain ($>$1/100) on 69% of e-diary entries. No children were entirely pain-free across the reporting period. Children endorsed high pain ($> 40/100$) on 31% of all e-diaries with 86% reporting high pain at least once in study period. The majority of children in this sample were prescribed DMARDS (chart review 79%, caregiver report 54%). Biologics were the next most commonly prescribed medication (chart review 47%, caregiver report 32%). Few children were taking opioids (chart review 1%, caregiver report 3%). Medication type did not reliably predict differences in symptom intensity. Momentary pain intensity ($t(3040) = 19.76$, $p <.01$), number of painful locations ($t(3039)= 8.44$, $p <.01$), and stiffness intensity ($t(3038)= 2.60$, $p <.01$) uniquely predicted functional limitations, but fatigue intensity did not ($t(3037)= -1.71$, $p=.09$).

Conclusion: Self-reported pain, stiffness, and fatigue continue to be common in children with JIA despite contemporary treatment advances including biologics. Prescribed medication class did not have a significant effect on reported symptoms. The findings are surprisingly consistent with previous results from paper daily diary research in the pre-biologic era. There remains a pressing ongoing need to optimize pain and symptom management in JIA.

2421

The Pediatric Rheumatology Nursing Network: An International Email MANAGED COMMUNICATION System. Norma L. Liburd. All Children's Hospital, St. Petersburg, FL

Background/Purpose: The Pediatric Rheumatology Nursing (PRN) Network is an electronic listserv linking 190 pediatric rheumatology nurses in 8 countries. Pediatric rheumatology nurses often have a sense of isolation because the closest nurse in this specialty could be 1000 miles away. However, this communication system makes consultation with another pediatric rheumatology nurse as close as one click away.

The purpose of the PRN Network is to promote communication, networking and to enhance practice knowledge, thereby improving patient care in pediatric rheumatology. The listserv goals are to exchange best pediatric rheumatology nursing practices; discuss difficult treatment issues such as patient adherence; share family educational and support products, activities, and materials; and exchange disease information, resources, school forms, treatment protocols, and procedures.

Methods: The PRN Network began in 1988 with a quarterly newsletter disseminated to pediatric rheumatology nurses in the United States (US). The nurses who initially received the newsletter were part of 11 multidisciplinary pediatric rheumatology teams from SPRANS Grant Programs (Special Programs of Regional and National Significance) through the US Division of Maternal & Child Health. The newsletter was published from 1988 to 1996. Grants totaling $3,000 were obtained from Astra USA to underwrite the newsletter. By 1997, the newsletter reached pediatric rheumatology nurses throughout the United States and Canada. The number of nurses on the mailing list increased from 20 to 60 nurses, primarily through word of mouth.

In 1998, the PRN Network listserv was initiated. Some nurses were participating on the well-established pediatric rheumatology (physician) listserv run by Peter Dent, MD, through McMaster Children's Hospital in Ontario, Canada. However, the pediatric rheumatology nurses felt that a nurse-only listserv would enable them to discuss issues relevant to their profession. This listserv was launched on a trial basis with 7 nurses. By 2002 there were 31 nurses on the listserv. By 2004 subscribers had grown to 82. In 2010, there were 146 nurses.

Lack of funding required startup from a home computer. Eventually the listserv transitioned to the server at All Children's Hospital in St. Petersburg, Florida. The listserv coordination is done from a home laptop and the database is maintained on gmail. Twice a year listserv members receive a copy of the updated member list.

Results: There are currently 190 nurses on the Listserv—from the United States, Canada, United Kingdom, Germany, Spain, Australia, New Zealand, and Singapore. Benefits of the listserv include increased knowledge of timely issues, management of medication shortages, sharing of difficult cases, promotion of patient adherence, conference planning, and sharing of educational materials.

Conclusion: There is no cost to participate on the PRN Network listserv. Once a year, an email is sent to the physicians' pediatric rheumatology listserv to recruit nurses for the PRN Network. All pediatric rheumatology nurses are welcome to join. For more information, contact Norma Liburd at norma.liburd@allkids.org.

ACR/ARHP Poster Session C
Psychology/Social Sciences
Tuesday, November 13, 2012, 9:00 AM–6:00 PM

2422

Sexual Activity and Sexual Functioning Among Women with Systemic Sclerosis Compared to Women From a Population Sample. Brooke Levis[1], Andrea Burri[2], Marie Hudson[1], Murray Baron[3] and Brett D. Thombs[1]. [1]McGill University, Montreal, QC, [2]King's College, London, United Kingdom, [3]Jewish General Hospital, Montreal, QC

Background/Purpose: Systemic sclerosis (SSc), or scleroderma, is a chronic, multi-system, connective tissue disorder characterized by thickening and fibrosis of the skin and internal organ involvement. Approximately 80% of patients are women, with highest onset rates between ages 30–60. Common problems include pain, fatigue, pruritus, body image distress, depressive symptoms, and general disability. Reduced sexual activity and impaired sexual functioning are also common among women with SSc and, in addition to age and marital status, are associated with disease severity and symptoms. To date, however, no studies have compared the rates of sexual activity and impairment of women with chronic medical disease to general population data. Thus, the objectives of this study were to 1) determine the rates of sexual activity and sexual impairment, stratified by age and marital status, for a SSc sample and a female population sample, 2) identify the odds of sexual activity and sexual impairment for women with SSc compared to the population sample, controlling for age and marital status, 3) identify the domains of sexual function (desire, arousal, lubrication, orgasm, and pain) most closely related to impairment in SSc compared to the general population, and 4) assess the association between sexual domain scores and sexual satisfaction in SSc versus the general population.

Methods: Female SSc patients from the Canadian Scleroderma Research Group Registry were compared to females from a UK population sample. SSc patients were asked whether they had engaged in sexual activities with a partner in the past 4 weeks. Sexually active patients completed a 9-item version of the Female Sexual Function Index (FSFI) and an item on sexual satisfaction. Women from the UK completed the FSFI as part of a study on female sexual dysfunction. Multivariate logistic regression analyses were used to assess the independent association of sample group with sexual activity and impairment status. Analysis of covariance was used to assess differences in sexual domain scores in both samples, controlling for total FSFI scores. Pearson's correlations were used to assess the association between sexual domain scores and sexual satisfaction.

Results: Among 730 women with SSc, 296 (41%) were sexually active, 181 (61%) of whom were sexually impaired. Among 1,498 women in the population sample, 956 (64%) were sexually active, 420 (44%) of whom were impaired. Adjusting for age and marital status, women with SSc were significantly less likely to be sexually active (OR=0.34, 95%CI=0.28–0.42) and significantly more likely to be sexually impaired (OR=1.88, 95%CI=1.42–2.49), compared to women from the general population. Adjusting for total FSFI scores, women with SSc had significantly worse lubrication and pain scores than women in the general population. All domains were substantially more highly correlated with satisfaction among women with SSc compared to population sample women.

Conclusion: This study highlights that sexual functioning is a problem for many women living with scleroderma and that it is associated with pain and poor lubrication, two known problems for women with SSc.

2423

Perceptions Regarding Cardiovascular Risk Factors and Barriers to Risk Reduction Among African American Women with Lupus. Barron Mia[1], Lynne Nemeth[1], Diane L. Kamen[2] and Youlanda C. Gibbs[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC

Background/Purpose: Cardiovascular disease (CVD) is highly prevalent among African American (AA) women diagnosed with systemic lupus erythematosus (SLE). Studies have suggested that CVD risk factors in AA women are different from that experience by other ethnic groups. However little is known regarding the perceptions or barriers and facilitators in reducing CVD risk factors among this population. The objective of this study was to assess perceptions of modifiable risk factors for CVD and to evaluate the barriers and facilitators to implementing any lifestyle changes needed to reduce CVD risk.

Methods: Eight AA women with SLE participating in a longitudinal observational registry (SLE in Gullah Health (SLEIGH) were invited to participate in this study. After informed consent was obtained, a formative, qualitative study using a focus group format was conducted, audio taped, transcribed verbatim and entered into a qualitative text management software program (NVIVO) to facilitate analysis. Transcript content was evaluated in relation to perception of CVD risk factors with a diagnosis of lupus and barriers to lifestyle changes in reducing CVD risk factors. Participants completed questionnaires on sociodemographics and CVD risk factors. Duration of SLE and disease activity was obtained as part of the SLEIGH registry.

Results: Participant characteristics are displayed in Table 1. The total prevalence of CVD risk factors among this population was 86%, 50% accounting for family history of CVD before age 55. Significant themes (Table 2) included lack of education and awareness along with ineffective patient-clinician communication. Barriers included physical and psychosocial limitations in adopting healthier behaviors.

Table 1. Patient demographics and disease characteristics

Number of participants (% female)	8 (100%)
Mean age in years	45 (range 19–65)
Highest Education (>12 years)	8 (100%)
Yearly Income (under 10,000)	4 (50%)
Family history of CVD before age 55	4 (50%)
Personal History of CVD with SLE	3 (37.5%)
Disease duration of SLE in years	20.6 (range 12–39)
Median Disease Severity (SLICC scores)	2 (range 0–4)

Table 2. Five key themes identified with examples

THEMES	QUOTES
A need for more information and awareness about CVD risk	"Yes. I think it would be real beneficial. You would have the awareness and the knowledge to know what to look for."
A desire for healthcare providers time, attention and communication regarding CVD risk factors	"Because when you get a diagnosis like lupus, you already think your life is over and I just think that they have to know how to present the information in order for the patient to really understand yes you are at risk but I mean you can do things to prevent this and as it stands right now, in my experience and I don't know what kind of experience you guys have had but like my doctor basically told me my life was over."
Physical and psychosocial limitations related to the impact of lupus	"Doing things that I used to do is limited now, very, very limited"
The need for effective prevention and disease management approaches	"Well I've never been offered screening so if it was offered to me, [crosstalk], then I would go through the process but I mean it's never been offered to me."
Adoption of healthier living habits (activity and diet)	"I can add to what she's saying. You eat more whole food. If you can pick it off a tree or pull it out of the ground eat that." "Aquatic therapy. I've been doing that for about maybe four or five years. Aquatic therapy seems to help."

Conclusion: This study provides additional data illustrating the importance of patient-clinician communication and the obstacles of effective management in reducing CVD risk. These findings suggest the need for further exploration of interventions used to eliminate barriers and foster facilitation in reducing CVD risk factors in the presence of SLE.

2424

Sleep Disturbances in Systemic Sclerosis: Evidence for the Role of Gastrointestinal Symptoms, Pain, and Pruritus. Katherine Milette[1], Marie Hudson[1], Annett Koerner[1], Murray Baron[2] and Brett D. Thombs[1]. [1]McGill University, Montreal, QC, [2]Jewish General Hospital, Montreal, QC

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune connective tissue disorder characterized by thickening and fibrosis of the skin and internal organs. There is significant mortality and morbidity in SSc, considerable functional disability, and no known cure. Therefore, appropriate symptom management is critical in improving patient quality of life. SSc patients experience numerous problems contributing to reduced quality of life, including fatigue, pain, depression, sexual dysfunction, body image distress, and itching. In SSc, as well as other rheumatic diseases, sleep disturbances also appear to be common. However, to date, there has been very little research in this area. In fact, only 3 relatively small studies have investigated sleep disturbance in SSc. This study's objective was therefore to investigate the association of factors potentially associated with sleep disturbance in the general population (gender, age, marital status, education, income, current medications, and medical diagnoses), in SSc (shortness of breath, gastrointestinal symptoms, pain, and pruritus), and across rheumatic diseases (pain) with sleep disturbance in a large Canadian sample of SSc patients.

Methods: The sample included patients enrolled in the Canadian Scleroderma Research Group's (CSRG) 15-center, pan-Canadian Registry. To be eligible for the Registry, patients must have a diagnosis of SSc, be >18 years of age, and be fluent in English or French. Pearson correlations were used to assess bivariate associations of sociodemographic and medical variables with PROMIS sleep disturbance scores (range 8–40). Multivariate linear regression was used to assess the association of factors associated with sleep disturbance in the general population, in SSc, and across rheumatic diseases with PROMIS sleep disturbance scores.

Results: There were 397 patients in the study. The mean (SD) sleep disturbance score was 22.8 (8.0). More gastrointestinal (GI) symptoms (standardized β = 0.19, p = 0.001), pain severity (standardized β = 0.21, p < 0.001), and pruritus severity (standardized β = 0.13, p = 0.024) were associated with more severe sleep disturbance in multivariate regression.

Conclusion: The number of GI symptoms, pain severity, and pruritus severity are medical factors that are associated with increased sleep disturbance in SSc. This is consistent with previous studies that identified GI involvement and pain as independent predictors of sleep disturbance in SSc. Previous studies did not include pruritus, however. This is the first study to do so and findings support the need for further research into pruritus, as well as possible interactions between the itch- and pain-processing pathways of the neuronal system. Important sociodemographic and medical factors related to sleep disturbance in the general population were also investigated. However, none of these factors were related to sleep disturbance in SSc, possibly because of the strong influence of disease-specific factors. Overall, better management of GI symptoms, pain, and pruritus, which are key medical factors in SSc, may have important ramifications for quality of life in SSc, including sleep quality.

2425

A Qualitative Study of Self-Image and Body Image in Individuals with Systemic Lupus Erythematosus. Afton L. Hassett[1], Diane C. Radvanski[2] and Elizabeth Hale[3]. [1]University of Michigan, Ann Arbor, MI, [2]Robert Wood Johnson Medical School, NJ, [3]Dudley Group NHS Foundation Trust, Dudley, United Kingdom

Background/Purpose: Symptoms and treatment related to SLE are often outwardly evident. Patients with SLE cope with such external manifestations as joint swelling, rashes, scarring, loss of skin pigmentation, alopecia, facial changes (Cushingoid appearance) and overall weight gain. Despite findings that side effects affecting appearance are associated with poor medication adherence, body-image and self-image in general have received very little attention in the SLE scientific literature. The primary objective of this qualitative study was to learn more about the role of self-image and body image in SLE.

Methods: 15 patients with SLE underwent semi-structured interviews that were approximately one hour long. Interviews were audio recorded, transcribed verbatim and analyzed using Interpretive Phenomenological Analysis (IPA). IPA is a qualitative method that takes an idiographic approach, trying to understand the experience from an individual account, then building up to commonalities and differences when looking across cases. Themes for these interviews were identified and collected under major thematic headings.

Results: Our participants included 14 females and 1 male all between the ages of 22 and 57. Patients were ethnically and racially diverse (e.g., 53.3% African American, 13.3% Caucasian) and just over half were married (53.3%). Running throughout the interviews were the themes of the changed self, the battle for normality and being attacked by an unwanted physical enemy. It also became clear that it is the outward "cosmetic" effects of SLE that can cause the most distress for participants, quite apart from the internal effects with which they were coping. We found that the concepts of body-image and self-image were inextricably linked; body-image impacts self-image and when feeling negative about one, it's hard to feel positive about the other. This was the daily challenge our participants faced. Often highlighted was how much they felt they had changed when talking about their body image, particularly in outward appearance. This was a topic that caused great distress as individuals remembered how they used to be. Sometimes this was expressed as

looking in the mirror and not recognizing the person looking back, which suggests that not only did individuals experience a distancing from other people and valued social roles, they experienced a disembodiment from their own selves as well.

Conclusion: Patients reported that self-image and body image are adversely affected by SLE and these changes in perception can impact quality of life. Weight gain, Cushingoid appearance, hair loss and rashes were the most troubling manifestations.

Disclosure: **A. L. Hassett**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Pfizer Inc, 2; **D. C. Radvanski**, None; **E. Hale**, None.

2426

Prevalence and Characteristics of Sleep Problems in Rheumatoid Arthritis: A Systematic Review of the Literature. Cassandra Coleman and Yvonne C. Lee. Brigham and Women's Hospital, Boston, MA

Background/Purpose: Rheumatoid arthritis (RA) patients commonly complain of sleep problems. Difficulties with sleep may be associated with increased fatigue, greater pain and worse quality of life. We aimed to establish the prevalence of sleep problems among RA patients and to characterize these sleep problems based on survey and polysomnographic measurements.

Methods: We conducted a systematic literature review to identify studies reporting the prevalence and characteristics of sleep problems in RA. Pubmed searches were conducted using MESH keywords for "Arthritis, Rheumatoid," "Sleep," Sleep Disorders", and "Fatigue", for studies published worldwide in English between August 1989 and April 2012. Further articles were obtained from the reference lists of these articles. Articles were selected based on title, abstract and manuscript review. Inclusion criteria included studies focusing on sleep problems in adult-onset RA patients. Review articles, case reports, and qualitative studies were excluded. One author (CC) screened titles and abstracts. Both authors independently extracted data from the articles. Data regarding the prevalence of sleep problems and specific types of sleep problems were extracted, and ranges of values and median of means are reported.

Results: The literature search identified 1410 articles of which 23 were included in the review. Of these articles, 8 had specific measures of the prevalence of sleep problems, and 18 used survey and/or polysomnograph methods to characterize these problems based on sleep duration, sleep efficiency and sleep disturbance. Only 5 articles had data comparing RA patients to controls (**Table**). Methods and scales for evaluating prevalence and characteristics of sleep disturbances varied greatly among these articles. The prevalence of sleep problems ranged from 60–97% by self-report questionnaires. The Pittsburgh Sleep Quality Index score, reflecting sleep quality, sleep latency, sleep efficiency, sleep disturbance, and sleep duration, was markedly higher, signifying poorer sleep, in RA patients compared to control patients. Polysomnograph studies also indicated lower sleep efficiency, increased number of awakenings, and longer sleep latency among RA patients compared to control subjects. However, mean hours of sleep, measured by polysomnograph, were similar among RA patients compared to controls.

Table. Median of means and ranges of reported values for survey and polysomnograph measures among RA patients and controls

Clinical Characteristics	Median of Means (Range of Values) Rheumatoid Arthritis	Controls	Number of Studies
Survey Measures			
Pittsburgh Sleep Quality Index [1]	8.5 (7.6–9.5)	2.6 (2.4–2.8)	2
Polysomnograph Measures			
Mean Hours of Sleep (hrs)	6.3 (5–7.2)	6.9 (6–7.6)	4
Sleep Efficiency (%)	80.9 (61–93.6)	90.8 (85–94)	4
Number of Awakenings	67.6 (3.1–194)	7.4 (2.6–112)	4
Sleep Latency (min)	25.1 (21.8–30.5)	13.7 (12.1–25.2)	4

[1]Range = 0–21, PSQI score < 5 = "good sleeper", PSQI > 5 = "poor sleeper"

Conclusion: Sleep disturbances, notably increased awakenings, were reported by the majority of RA patients, while sleep duration was similar among RA patients compared to controls. These results suggest that widespread sleep problems among RA patients may be a result of disturbed sleep rather than an overall lack of sleep. Future studies are needed using uniform sleep measures in large cohorts of well-characterized RA patients with appropriately selected controls.

Disclosure: **C. Coleman**, None; **Y. C. Lee**, Forest Laboratories, 2, Merck Pharmaceuticals, 1, Novartis Pharmaceutical Corporation, 1, Elan Corporation, 1.

2427

Health-Related Quality of Life in Adolescents with Rheumatic Disease. Sandra J. Watcher[1], Maggie Sepkowitz[1], Suhas M. Radhakrishna[2], Anusha Ramanathan[3], Elizabeth Morasso[3], Jennifer Chang[3] and Jeffrey I. Gold[4]. [1]Children's Hospital of LA, Los Angeles, CA, [2]Kaiser Permananete Medical Group, Oakland, CA, [3]Childrens Hospital Los Angeles, Los Angeles, CA, [4]Keck School of Medicine, University of Southern California - Children's Hospital Los Angeles, Los Angeles, CA

Background/Purpose: Adolescents with chronic health disease face a variety of physical and psychological challenges. Adolescents with rheumatologic conditions vary with regard to their physical, emotional, and functional health outcomes, such as quality of life. The purpose of this project was to evaluate health-related quality of life (HRQOL) in adolescents with rheumatic disease. In addition, an examination of agreement between adolescent and parent-report of HRQOL was completed.

Methods: Adolescents and their parents participated in concurrent rheumatology support groups focused on psychoeducation, medical management, and quality of life. The sample consists of 38 adolescent (11–20 years)/parent pairs. Prior to attending the support/education group one parent and their adolescent completed self-reports of HRQOL. Measures of interest included a demographic questionnaire and the Simple Measure of Impact of Illness or Lupus Erythematous in Youngsters© (SMI-ILY© - SMILEY©) for parents and adolescents. This tool evaluates perception of overall quality of life, current illness and four individual domains: effect on self, burden of illness, social impact, and limitations of illness. Scores are calculated into a percentile score for each domain, with a higher score indicating greater HRQOL.

Results: 65.8% were Latino/Hispanic and 34.3% reported other (Asian, Asian/pacific, Asian pacific-islander black or white/non-Latino). Mothers represented 69.4%, fathers 22.2% and other 8.3%. Gender of the adolescent was 82.4% female.

Adolescents reported functioning above average quality of life in the domains of effect on self (61.26%) and social impact (73.02%). Two domains demonstrated a moderate impact on HRQOL in the domains of burden of illness (51.73%) and limitations (54.27%). Parent-report reflected similar responses being slightly lower in all domains reflecting the effect on self (58%), social impact (66.97%), burden of illness (47.59%) and limitations (52.76%).

The Wilks' Lambda distribution was used and no significant differences were found between adolescent and parent ratings. Additionally, there was no significant corelation between the parent and adolescent-reports on all domains and total score of the SMI-ILY© - SMILEY©.

Conclusion: Adolescents and their parents enrolled in a support/education program reported moderate to moderately high levels of self and social support. Of interest is the consistent burden of illness and limitations reported by adolescent with rheumatic disease and their parents. The findings are consistent with other literature supporting the effects of pediatric chronic health disease on HRQOL. While similar trends were reported across all domains of HRQOL, measures of agreement were not statistically significant. Information regarding the effects of rheumatic disease on the four domains lend further support for interventions focused on the direct burden of illness and limitations caused by the patient's disease. Future investigations should focus on maintaining the impact of rheumatic disease on self and social support and focus on interventions for specific aspects of burden of illness and disease specific limitations.

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2428

Causal Beliefs of Disease Among Patients with Systemic Vasculitis. Peter C. Grayson[1], Naomi Amudala[1], Carol McAlear[2], Renée Leduc[3], Denise Shereff[3], Rachel Richesson[3], Liana Fraenkel[4] and Peter A. Merkel[5]. [1]Boston University Medical Center, Boston, MA, [2]Vasculitis Clinical Research Consortium, University of Pennsylvania, Philadelphia, [3]University of South Florida, Tampa, FL, [4]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [5]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Patients vary in their beliefs related to the cause of serious illness. The impact of these beliefs among patients with systemic vasculitis is not known. This study aimed to describe patient beliefs related to the cause of systemic vasculitis and to examine whether casual beliefs are associated with psychological impact of disease and functional impairment.

Methods: Participants were recruited online from a patient contact registry in vasculitis. Causal beliefs were measured using two approaches. Using an open-ended question, participants were asked to list the three most

important causal beliefs about disease-onset. Responses were categorized and weighted by rank to determine the relative frequency of beliefs. Participants also rated 18 specified causal beliefs (obtained from the well-validated revised Illness Perception Questionnaire, IPQ-R) on a 5-point scale, with higher scores indicating stronger agreement. Response scores to the specified items were summed into a *belief score* which defined strength of causal beliefs. Psychological impact was measured using a scale from the IPQ-R assessing the negative emotional impact of vasculitis. The Medical Outcomes Study General Health Survey was used to assess functional impairment (*physical*, *role*, and *social*). Pearson correlation coefficients were calculated between belief scores, psychological, and functional impairment.

Results: 692 participants with 9 forms of vasculitis were included. There was considerable variability of causal beliefs among participants and beliefs differed by type of vasculitis (**Table**). The most common beliefs listed by participants using the open-ended approach were environmental exposures (16%), stress (15%), hereditary factors (15%), and infection (15%). For the 18 specified items (scored 1–5), altered immunity (3.6 ± 1.1) and stress (3.2 ± 1.3) were the most agreed upon causal items for each type of vasculitis. Negative emotional impact of illness, role, and social function were significantly correlated with belief score (r= 0.26, 0.12, 0.12; p<0.01). Physical function was not significantly associated with belief score (r=0.07, p=0.09).

Table. Frequency (%) of Disease-Onset Causal Beliefs in Systemic Vasculitis

Causal Belief	Total n=692	BD n=48	CNS n=12	CSS n=121	GCA n=32	HSP n=12	MPA n=42	PAN n=36	TAK n=57	GPA n=332
Environmental Exposure	16	9	3	18	12	11	15	1	3	20
Stress	15	12	14	11	17	11	15	13	17	17
Hereditary	15	**29**	9	11	10	0	13	11	**19**	15
Infectious	15	23	**17**	8	6	**40**	22	18	17	15
Altered Immunity	11	11	13	16	15	13	8	7	17	10
Other Risk Factors*	7	6	11	9	**16**	7	9	**20**	7	4
Medications and Vaccines	6	3	0	11	9	18	7	8	3	3
Psychological Factors#	6	3	2	3	5	0	5	6	8	6
Chance	5	2	9	4	2	0	3	7	2	6
Past Medical Problems	4	3	14	7	5	0	2	5	5	3

The most common beliefs per column are highlighted in bold. * Other Risk Factors = diet or eating habits, poor medical care, my own behavior, ageing, alcohol, smoking, accident or injury. # Psychological Factors = my mental attitude, family problems, my emotional state, overwork, my personality. BD= Behçet's disease; CNS= central nervous system vasculitis; CSS= Churg-Strauss syndrome; GCA= giant cell arteritis; HSP= Henoch-Schönlein purpura; MPA= microscopic polyangiitis; PAN= polyarteritis nodosa; TAK= Takayasu's arteritis; GPA= granulomatosis with polyangiitis (Wegener's).

Conclusion: Patient beliefs related to the cause of systemic vasculitis are highly variable. Patients with strongly-held causal beliefs report that their illness has greater negative impact on their psychological well-being and their ability to perform role and social functions. Clinicians who care for patients with vasculitis should be mindful of these associations and consider asking patients about their causal beliefs.

2429

Balancing Work and Health: Do Younger Workers Experience More Work-Health Conflict Than Middle- and Older-Aged Workers with Rheumatic Diseases? Arif Jetha[1], Xingshan Cao[2] and Monique A. Gignac[3]. [1]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [2]Arthritis Community Research and Evaluation Unit, Toronto Western Research Institute, Toronto, ON, [3]Arthritis Community Research and Evaluation Unit, Toronto Western Research Institute, University of Toronto and Institute for Work and Health, Toronto, ON

Background/Purpose: Research on work-life balance with healthy adults finds that difficulties balancing roles is related to negative employment outcomes. Yet, little is known about work-health balance among those with rheumatic diseases, especially in different age groups or career stages.

Objective: To compare perceptions of work-health balance/conflict in younger (18 to 30 years of age) and older (greater than 30 years of age) workers, as well as demographic, health, and job context factors associated with work-health balance/conflict.

Methods: Data from two separate studies were combined: an online survey of 143 young adults (mean age=23.3, SD=3.5, range: 18–30 years) with juvenile arthritis and systemic lupus erythematosus; and a telephone survey of 350 workers (mean age =54.2, SD = 8.9; range: 26–69 years) with inflammatory arthritis and osteoarthritis. Respondents completed the Arthritis-Work Spillover Scale (AWS), a 6-item measure of perceived rheumatic disease-related work-health conflict (1 = "strongly disagree"; 5 = "strongly agree"). Participants also completed information on demographics, health (e.g. diagnosis, pain), and work context factors (e.g. work hours, work activity limitations). Descriptive analyses and separate multivariate linear regression analyses by age group (18 to 30 years of age; greater than 30 years) examined factors associated with AWS.

Results: Younger workers reported working significantly fewer hours (30.7 vs. 34.8) and were more likely to work in sales and service jobs (36% vs. 21%) than workers aged 30 years or older (p<.05). AWS was significantly lower among younger workers (mean=2.5, SD= 1.1 versus mean=2.9, SD=1.0, p <.05). Although health and work context factors were associated with AWS for all workers, R-squared values indicated that health factors explained more of the variance in younger workers and work context factors were more important for older workers. Specifically, pain was related to more AWS in younger adults and work hours, job disruptions (e.g., missed meetings), and disclosing one's disease to an employer were associated with higher AWS in workers older than 30 years of age. Workplace activity limitations was related to increased AWS for all workers.

Conclusion: Younger workers with rheumatic diseases reported less work-health conflict which can be related to differences in the type and hours of their work. In reducing work-health conflict, pain management may be particularly important for younger workers and workplace accommodations may be important for older workers. Future research needs to examine age differences in greater detail, as well as health care management and work context factors.

2430

Using the Internet in Help-Seeking As Illness Develops in Early Rheumatoid Arthritis. Anne F. Townsend[1], Jenny Leese[2], Catherine L. Backman[3], Paul M. Adam[4] and Linda C. Li[5]. [1]Arthritis Research Centre of Canada, Vancouver, BC, [2]Arthritis Research Centre, Vancouver, BC, [3]University of British Columbia, Vancouver, BC, [4]Mary Pack Arthritis Centre, Vancouver, BC, [5]Arthritis Centre of Canada and Department of Physical Therapy, University of British Columbia, Vancouver, BC

Background/Purpose: Patients' Internet use for health purposes is regarded as potentially transformational. Using on-line resources is associated with the emergence of the e-patient; broadly defined as someone who is an involved and empowered partner in care and is engaged in informed decision-making. We know little however, about how Internet use influences help seeking, the patient-clinician consultation and informed decision-making in early rheumatoid arthritis (RA). This qualitative study examines patient accounts of their Internet use during the 12 months following their diagnosis of RA, how it impacted patient help seeking and how Internet use evolved over time.

Methods: Twenty-two participants (17 women, 5 men), age range 30s–70s, were recruited, within 12 months of an RA diagnosis, from rheumatologist and family physician offices and online patient advocacy groups. A series of 3–4 in-depth interviews were conducted over twelve months to track illness experiences and behaviors over time. The interview guide is based on 3 areas: 1) Pre-diagnosis symptoms, impact and management; 2) Experiences with health professionals leading to the diagnosis; 3) Post-diagnosis experience of symptoms, management and the health care system. Analysis is informed by grounded theory. Early analysis was concurrent with data collection enabling new and salient questions to be introduced to the interview schedule. Internet use as impacting illness behaviors emerged as an early theme and was subsequently included as a topic for inquiry in all interviews.

Results: Preliminary analysis identified that online patients' experiences affected help seeking in a range of ways. Three early themes emerged: 1) Assessing trustworthiness: participants compared different sites to validate information and favored institutional sites offering factual information over personal blogs, which could heighten their anxieties; 2) Help-seeking support: the Internet provided participants with information which some discussed with their family doctor e.g. to gain a specialist referral, while others used it to gain a 'second opinion' to compare with their doctor's advice; 3) Evolving strategies: Over time participants changed the way they used the Internet; e.g. some used it less as they secured knowledge and support from their doctors, and others used it in a more targeted or selective way.

Conclusion: Our findings show how our participants used the Internet in a range of ways, which impacted their help seeking, and had the potential for both positive and negative impacts. As Internet use becomes a key feature of help seeking, it influences patients' experiences. This has implications for both the patient's and clinician's role in managing RA. More research is needed to identify the ways in which health professionals can best support patient Internet use for optimum outcome, and encourage patients to become more informed partners in care.

ARHP Concurrent Abstract Session
Physical/Occupational Therapy and Exercise in Patients with Rhematologic Disease
Tuesday, November 13, 2012, 9:00 AM–10:30 PM

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Are Occupational Therapy Interventions Included in the Most Commonly Used European Clinical-Practice Guidelines for the Management of Osteoarthritis? Michaela Stoffer[1], Doris Taurok[2], Birgit Prodinger[3], Josef S. Smolen[4], Anthony D. Woolf[5] and Tanja A. Stamm[6]. [1]Medical University of Vienna, A–1090 Vienna, Austria, [2]Orthopaedic Hospital Vienna Speising, 1130 Wien, Austria, [3]University of Western Ontario, London, ON, [4]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [5]Royal Cornwall Hospital, Truro Cornwall, United Kingdom, [6]Medical University of Vienna, Vienna, Austria

Background/Purpose: The EUMUSC.net project facilitates cooperation between EU Member States and promotes a comprehensive European strategy to optimise musculoskeletal health.

Part of the EUMUSC.net project was devoted to retrieving clinical practice guidelines (CPG) for Osteoarthritis (OA) and to appraise them critically. The purpose of this study was to identify the relevance given to occupational therapy interventions.

Methods: National rheumatological scientific societies, social leagues and health professional associations were contacted and asked to provide relevant documents. Furthermore, a systematic review of the respective literature was conducted in Medline, CINAHL and the Internet. Documents fulfilling pre-defined inclusion and exclusion criteria have been critically appraised by two independent assessors using the AGREE II Instrument. The appraised documents were examined for occupational therapy interventions/occupational therapy (OT).

Results: Six guidelines/recommendations have been included into this study and appraised using the AGREE II Instrument. All six CPGs obtained the highest scores in the domain "Scope and Purpose" followed by remarkably high scores in the domain "Rigor of Development".

Four CPGs had low scores in the domain "Stakeholder Involvement" and five in the domain "Applicability". We identified ten interventions relevant to occupational therapy: adapting the environment, assistive devices for activities of daily living, hand exercise, joint protection, comprehensive occupational therapy, patient education, self management, splinting/orthoses, thermotherapy and walking assistive devices. Only "patient education" was recommended in all CPGs. "Adapting the environment" in one.

Inclusion Criteria for the documents	Exclusion Criteria for the documents
Published after 1/2002 till 3/2011	Non-European origin
Dealing with hand, hip and knee OA	Full text not available
Denoting themselves as a guideline or as recommendations	Full text neither German nor English
Non-pharmacological approach included	Pharmacological approach only
Last Version (if the CPG was updated)	Guidelines dealing with back pain/OA of the spine

Conclusion: All six guidelines/recommendations addressed occupational therapy interventions. Two CPGs were referring to the term occupational therapy while the others did not. In all appraised documents no occupational therapist could be identified to be a member of an OA Guideline development group.

2432

Arthritis Foundation's Tai Chi Program for People with Arthritis: One Year Follow-up. My-Linh Luong[1], Rebecca J. Cleveland[1], Betsy Hackney[1] and Leigh F. Callahan[2]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina, Chapel Hill, NC

Background/Purpose: To evaluate program adherence and whether the improvements seen after completing the Arthritis Foundation's 8-week Tai Chi course remained for reduction of symptoms, increased function, and improved psychosocial status in participants with arthritis one year after program completion.

Methods: At one year after the end of the intervention, individuals who completed the 8-week follow-up (n=144) were mailed a self-report questionnaire designed to assess continuation of the Tai Chi program as well as evaluate pain, fatigue and stiffness visual analog scales (VAS), Health Assessment Questionnaire (HAQ), general health, Rheumatology Attitudes Index (RAI, helplessness), and Arthritis self-efficacy (ASE) for pain and symptoms. Participants also completed the PROMIS™ (PR) Short Form instruments for sleep disturbance and satisfaction with social roles. Regression analyses evaluated the change in scores from baseline assessment to 1-year follow-up, with adjustment for baseline score, age, gender, and BMI.

Results: The follow-up rate for the 1-year evaluation was 78% (n=113) and 31% reported that they continued participation in the Tai Chi Program (n=35) after completion of the 8-week follow up. Overall, those who participated in the Tai Chi program at baseline reported improvements in several self-reported health status measures one year after completion of the program. Modest improvements were seen for pain and stiffness VAS (effect size [ES] =0.30 and 0.25, respectively). Participants also reported statistically significant improvements for helplessness, pain impact and pain behavior (ES=0.23, 0.21, and 0.32, respectively). However, when comparing those who continued to practice Tai Chi at one year with those who did not, there were no statistically significant differences in improvements from baseline in self-reported measures for those who continued with the Tai Chi program except for helplessness (RAI, ES=0.49 vs. ES=.11, p=0.03). The most frequently cited reasons for not continuing the Tai Chi program were that participants did not feel comfortable doing Tai Chi outside of a class setting (41%) and that there were no classes convenient to them (37%). 95% of participants said they would recommend the program to others.

Conclusion: Participants in the AF Tai Chi program showed continued modest improvements in pain, and stiffness. The HAQ measure of physical function did not indicate significant change; however those who continued practicing Tai Chi saw improvements in feelings of helplessness. While we did not observe sustained effects of the Tai Chi program, those who participated enjoyed the program and many did not continue with the program due to lack of availability in their area.

2433

Integration of a Healthy Aging Program Into the Arthritis Foundation Exercise Program: Six-Month Results. Elizabeth A. Schlenk[1], Joni Vander Bilt[1], Wei-Hsuan Lo-Ciganic[1], Sarah E. Woody[1], Janice C. Zgibor[1], Molly B. Conroy[2], C. Kent Kwoh[3] and Anne B. Newman[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, PIttsburgh, PA, [3]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA

Background/Purpose: In 2001, the University of Pittsburgh Prevention Research Center (PRC) developed the "10 Keys"™ to Healthy Aging program in response to the need to promote healthy aging. The "10 Keys"™ focus on systolic blood pressure (BP), smoking cessation, cancer screenings (breast, cervical, prostate, and colon), immunizations (influenza and pneumonia), blood glucose, LDL cholesterol, physical activity, musculoskeletal health (bone density test and BMI), social contact, and combat of depression. Primary objectives of the program were collaboration and dissemination. In 2010, the PRC partnered with the Arthritis Foundation (AF) of Western Pennsylvania and targeted older adults with arthritis or joint pain for a

community-based, group-delivered intervention. We hypothesized that the integrated program would improve preventive behaviors and outcomes targeting both arthritis and clinical assessments of preventive health goals.

Methods: A quasi-experimental design was used for this pilot study ($N=51$). A 10-week curriculum that integrated the "10 Keys"™ program into the AF Exercise Program was developed, instructors were recruited and trained, and host sites and participants were recruited. Classes were held twice weekly in three sites and once weekly in one site. Data were collected at baseline, post-intervention, and six months post-intervention and included BP, BMI, cholesterol and glucose levels, questionnaires [preventive behaviors; WOMAC scales: pain (range 0–20), stiffness, and function (range 0–68); Loneliness subscale of the Perceived Isolation scale (range 0–12); and Stanford Arthritis self-efficacy scale (range 0–30)], and Short Physical Performance Battery (SPPB, range 0–12).

Results: Participants were on average 75.5 ($SD=9.3$) years of age and primarily white (92%, $n=47$) women (88%, $n=44$) who reported an arthritis diagnosis (73%, $n=37$). Thirty-eight (75%) participants attended >50% of the classes. At six months, 50% ($n=18$) performed the AF Exercise Program exercises 1–2 days/week, and 28% ($n=10$) did so 3–7 days/week. Baseline to six-month results demonstrated significant improvements in WOMAC function in worst knee/hip (Ms 23.0 to 17.7, $p=.01$), loneliness (Ms 4.3 to 3.6, $p=.002$), self-efficacy for communication with physician ($Mdns$ 28.5 to 30.0, $p=.006$), and SPPB ($Mdns$ 10.0 to 11.0, $p=.02$). Trends in improvements from baseline to six months were seen in diastolic BP (Ms 72.4 to 69.3 mm HG, $p=.07$), influenza vaccinations (Ms 54% to 69%, $p=.06$), and WOMAC pain in worst knee/hip (Ms 7.4 to 6.2, $p=.09$). Participants (92%, $n=34$) rated the program overall as excellent or very good.

Conclusion: Our results indicate that this pilot program was feasible, was successful in engaging community partners, and improved participant behaviors and outcomes six months post-intervention. A clustered randomized trial comparing the integrated community program to the AF Exercise Program is underway.

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2434

Effects of Interventions That Aim to Increase Exercise Adherence in People with Arthritis: A Best Evidence Synthesis. Katie, E. MacPherson[1], Allison M. Ezzat[2], Jenny Leese[3] and Linda C. Li[2]. [1]New Westminster, BC, [2]University of British Columbia, Vancouver, BC, [3]Arthritis Research Centre, Vancouver, BC

Background/Purpose: Exercise is a central component in treatment and rehabilitation for chronic musculoskeletal conditions. Current literature supports the use of therapeutic exercise to reduce pain, improve function, and enhance quality of life in people with arthritis. Due to an estimated 30–60% of patients not following prescribed exercises, studies have investigated barriers and predictors of exercise adherence, as well as interventions that aim to increase it. The objective of this best evidence synthesis was to determine the effectiveness of interventions aiming to increase exercise adherence to prescribed exercise programs in adults living with arthritis.

Methods: This study is part of a larger systematic review on the effectiveness of exericse adherence in people with a variety of chronic diseases. A literature search was conducted from 1947 to December 2010 using MEDLINE, EMBASE, PubMed, CINAHL, Academic Search Complete, IS Web of Science, PSYCInfo, SPORTDiscus, and Cochrane Database of Systematic Reviews using search terms related to chronic diseases and exercise adherence. Eligible studies for the current review included: participants 18 years and older with a diagnosis of arthritis; intervention(s) that aimed to improve adherence to a prescribed exercise regimen; a control or comparison group; and, measured exercise adherence as an outcome. Four independent assessors scanned titles and abstracts, performed data extraction and assessed study quality using the Pedro scale. The relative difference of exercise adherence was calculated for each study.

Results: The search strategy revealed 12,085 articles. Of the 68 eligible articles on exercise adherence interventions in chronic diseases, 13 articles from 12 studies involved patients with arthritis. Interventions varied from knowledge-based programs (ie. educational brochure) to motivational-based strategies (ie. social cognitive model). Of the 12 studies, 7 had a Pedro score >6, indicating high quality. Of the 4 studies in rheumatoid arthritis (RA), 3 were of high quality reporting a statistically significant difference in exercise adherence between the intervention and control groups (relative difference = 20.9%–66.7%). Six studies involved patients with osteoarthritis (OA), 4 of which were rated high quality,

with only 1 reporting a statistically significant difference between groups (relative difference = 32.2%–106.3%). Two low quality studies included a mix of patients with OA and inflammatory arthritis; one reported a statistically significant result while the other did not provide sufficient data to determine statistical significance (relative difference = 42.1%–104.8%).

Conclusion: Based on three high quality studies in RA, there is strong evidence supporting the effectiveness of exercise adherence interventions in this population. The evidence for OA neither supports nor disproves the effectiveness of interventions for this population as results among 4 high quality studies were mixed. The evidence was also unclear in mixed types of arthritis due to poor quality of the studies. Our results suggest that future research efforts on exercise adherence interventions should target those with OA.

Disclosure: K. E. MacPherson, None; **A. M. Ezzat**, None; **J. Leese**, None; **L. C. Li**, None.

2435

Lumbrical Splinting and Stretching Versus Standard Treatment On Grip, Pinch, and Dexterity in People with Carpal Tunnel Syndrome. Nancy A. Baker[1], Krissy Moehling[2], Elaine Rubinstein[3], Norman Gustafson[1] and Mark Baratz[4]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, [4]Alleghancy General Hospital, Pittsburgh, PA

Background/Purpose: Carpal tunnel syndrome (CTS) is a prevalent peripheral upper extremity neuropathy. Splinting and exercise is often recommended for those with mild to moderate symptoms. Lumbrical muscles of the hand appear to affect carpal tunnel canal pressure and CTS symptoms. We hypothesized that a lumbrical intensive treatment of nocturnal splinting and stretching exercises would provide greater improvements in impairments than less lumbrical intensive treatments.

Methods: A randomized controlled 2×2 factorial design study was conducted with four groups: Lumbrical splint/Lumbrical stretch (Lsp/Lst); General splint/Lumbrical stretch (Gsp/Lst); Lumbrical splint/General stretch (Lsp/Gst); General splint/General stretch (Gsp/Gst). Appropriate patients with mild/moderate CTS were recruited by 2 hand surgeons.

Assessments were obtained at baseline and 4 weeks after completion of an at-home regimen of splinting and exercise. Grip strength and lateral and palmar pinch were measured using standardized assessment tools. Fine motor dexterity was evaluated using the Purdue Pegboard.

Results: The average age of this cohort (N=103) was 53.3 ± 11.8 years. The majority were female (71.8%), with chronic carpal tunnel symptoms ≥ 3 months (85.7%). As CTS was most prevalent for the right (43.7%) or bilateral hand (38.8%) and the majority were right handed (91.3%), only right-sided results are provided for strength measurements (Table 1). There were no significant differences in demographics between groups.

Table 1. Results of 2-way ANOVA between Baseline and 4 week follow-up

Variable	Time	LspLst[a] N=26 M±SD (d score)	GspLst[b] N=30 M±SD (d score)	LspGst[c] N=24 M±SD (d score)	GspGst[d] N=23 M±SD (d score)
*Right Grasp (kg)	Base	22.8 ± 12.5	25.2 ± 11.1	24.0 ± 11.3	24.9 ± 12.7
	4 wk	25.8 ± 13.2 (0.24)	27.6 ± 10.6 (0.22)	27.6 ± 12.5 (0.32)	28.2 ± 12.9 (0.26)
*Right Palmar	Base	6.0 ± 2.4	7.3 ± 1.4	6.5 ± 2.5	6.8 ± 2.5
Pinch (kg)	4 wk	6.5 ± 2.4 (0.21)	7.4 ± 1.7 (0.07)	6.7 ± 2.5 (0.08)	7.5 ± 2.3 (0.28)
*Right Lateral	Base	7.3 ± 2.3	8.4 ± 2.0	7.0 ± 2.2	7.8 ± 2.5
Pinch (kg)	4 wk	7.5 ± 2.5 (0.09)	8.5 ± 2.1 (0.05)	7.3 ± 2.2 (0.14)	8.6 ± 2.1† (0.32)
*Purdue Right (n)	Base	11.6 ± 3.1	12.3 ± 2.1	11.6 ± 2.5	12.5 ± 2.1
	4 wk	12.6 ± 3.2 (0.32)	13.5 ± 2.9 (0.57)	12.3 ± 2.8 (0.28)	13.2 ± 1.9 (0.33)
*Purdue Left (n)	Base	11.3 ± 2.5	12.2 ± 2.6	12.0 ± 2.9	12.3 ± 1.8
	4 wk	12.5 ± 2.5† (0.48)	12.6 ± 2.5 (0.15)	12.0 ± 3.3 (0)	13.3 ± 2.0 (0.56)
Purdue Both (n)	Base	18.5 ± 5.4	19.5 ± 4.4	18.2 ± 5.2	20.3 ± 3.4
	4 wk	19.5 ± 5.4 (0.19)	19.9 ± 4.6 (0.09)	19.0 ± 5.1 (0.15)	19.7 ± 2.8 (-0.18)
*Purdue Assembly	Base	26.5 ± 8.3	28.3 ± 8.5	25.2 ± 9.2	29.8 ± 7.3
(n)	4 wk	29.9 ± 8.9 (0.52)	28.8 ± 7.2 (0.06)	26.8 ± 9.7 (0.17)	31.5 ± 8.7 (0.23)

[a](lumbrical splint, lumbrical stretch); [b](general splint, lumbrical stretch); [c](lumbrical splint, general stretch);
[d](General splint, general stretch)
* effect of time significant; †effect of group×time significant

2-way ANOVAs were performed using SPSS 18 with group as the between-subjects factor and time as the within-subjects factor. Post hoc analyses used pairwise comparisons on difference scores for significant between-group outcomes with alpha set at.05. We calculated a Cohen's D to identify the clinical effect of the intervention.

The main effect of time was significant for all but Purdue - both hands. When analyzing group by time interactions the only outcomes with significant changes were right lateral pinch (p=.03) with greatest improvement in the Gsp/Gst group, and Purdue - left hand only (p=.03) with greatest improvement in the Lsp/Lst group. Overall the group using the GSP/GST demonstrated the greatest clinical improvements (small to moderate D).

Conclusion: All groups showed significant improvements over time regardless of treatment. Intensive lumbrical treatment was significantly better only for Purdue left hand, however, dexterity tasks such as Purdue both hands and Purdue assembly also showed greater improvement for this group (D scores were small to moderate). It appears that a more intensive lumbrical treatment may affect dexterity more than strength at 4 weeks follow-up. Future CTS research should examine the effects of more intensive lumbrical treatments on impairments over a longer follow-up period.

Disclosure: **N. A. Baker**, None; **K. Moehling**, None; **E. Rubinstein**, None; **N. Gustafson**, None; **M. Baratz**, None.

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Clinical Effectiveness and Costs of an Integrated Rehabilitation Programme Compared with Outpatient Physiotherapy for Chronic Knee Pain. Mike Hurley[1], Dr Nicola E. Walsh[2] and Sally Jessep[3]. [1]St George's University of London, London, United Kingdom, [2]University of the West of England Bristol, Bristol, United Kingdom, [3]Kent, United Kingdom

Background/Purpose: Chronic knee pain is a major cause of disability. Management guidelines recommend exercise and self-management interventions. We previously described a rehabilitation programme that integrates exercise and self-management *(Enabling Self-Management and Coping with Arthritic Knee Pain through Exercise, ESCAPE-knee pain)* that produced short term improvements in pain and physical function. Sustaining these improvements is problematic. In addition, the programme is untried in the community where it is most likely to be delivered. This study evaluated the feasibility of delivering *ESCAPE-knee pain* in a community setting, and compared its clinical effectiveness and costs with Out-Patient Physiotherapy.

Methods: This was a pragmatic, randomised controlled trial. 64 people with chronic knee pain were randomised to receive Out-Patient Physiotherapy or the *ESCAPE-knee pain* programme in a Local Adult Education Community Centre. Primary outcome was physical function assessed using the Western Ontario and McMaster Universities Osteoarthritis Index. Secondary outcomes included pain, objective functional performance, anxiety, depression, exercise-related health beliefs, exercise self-efficacy and healthcare utilisation. All outcomes were assessed at baseline and 12 months after completing the interventions (primary endpoint). ANCOVA investigated between-group differences.

Results: Both groups demonstrated similar improvements in clinical outcomes, except health beliefs and self-efficacy where imporvements were greater in *ESCAPE-knee pain* participants. Out-Patient Physiotherapy cost £130 per person and its participants had healthcare utilisation costs over one year of £583, the *ESCAPE-knee pain* programme cost £64 per person and participant's healthcare utilisation was £320.

Conclusion: *ESCAPE-knee pain* and Out-Patient Physiotherapy produced sustained physical and psychosocial benefits, but *ESCAPE-knee pain* cost less and was more cost-effective. Greater improvements in beliefs about the role of exercise in the management of knee pain, and their confidence in their abilty to perform exercise that will help their knee pain (exercise self-efficacy), may make *ESCAPE-knee pain* participants more self-reliant and utilise less healthcare resources, thereby accounting for the better cost-effectiveness of *ESCAPE-knee pain*.

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ARHP Concurrent Abstract Session
Programs and Literacy in Patients with Rheumatolgic Diseases
Tuesday, November 13, 2012, 9:00 AM–10:30 AM

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Initiating an Innovative Training Programme to Improve Access to Musculoskeletal Health Care in Kenya. Anthony D. Woolf[1], Jo Erwin[2], Omondi G. Oyoo[3], Lillian Mwaniki[4], Ingrid Cederlund[5], Paul Etau[6] and Katie Edwards[7]. [1]Royal Cornwall Hospital, Truro Cornwall, United Kingdom, [2]Royal Cornwall Hospital, Teliske, United Kingdom, [3]University of Nairobi, Nairobi, Kenya, [4]Association for Arthritis & Rheumatic Diseases of Kenya, Nairobi, Kenya, [5]Reumatikerforbundet, Stockholm, Sweden, [6]University of Nairobi, Nairobi, Kuwait, [7]Royal Cornwall Hospital, Truro, United Kingdom

Background/Purpose: Musculoskeletal conditions (MSC) are common in Kenya yet the training of primary care physicians in MSC is minimal and there are only 2 full time rheumatologists for a population of 41 million. The aim of this project, supported by ILAR, is to enable early access to appropriate health care for MSC in Kenyan communities. In a collaboration between colleagues in Kenya, UK and Sweden an innovative sustainable training programme has been developed to raise the knowledge and skills of health professionals working in the community in the early detection, diagnosis and management of MSC.

Methods: A programme was developed to train a cohort of mid-grade physicians and patients as trainers in musculoskeletal health. These trainers teach health providers that are the first point of contact for patients in the community e.g. clinical officers. The training emphasises history and examination to identify the musculoskeletal syndrome; the use of basic investigations, diagnosis, management and referral. The trainers work as a physician/patient team with the patients playing a key role in teaching history taking and examination skills and in making health providers aware of the impact of MSC on patient's lives.

Results: A train the trainer session was held in March 2012. 10 physicians and 9 patients were trained to become trainers in a 2.5 day session followed by a one-day demonstration training session which was videoed as a resource for the trainers. The trainers have gone on to deliver training to 150 first contact providers in 4 regions across Kenya. The content and delivery of the trainer and health provider courses were rated by participants as very good or excellent. After the first round of health provider training 75% of participants felt they were well prepared to use the skills in MSC diagnosis and 68% felt they were well prepared to use the skills in MSC management in their daily work. A 6 month post training evaluation is to be completed.

Training patients to be educators has started empowering them in advocacy and self-management. The project recognises the need to work with patients to develop an appropriate self management programme for Kenya and plans to address this in the future.

Conclusion: This sustainable programme has developed a system and resources for delivering effective and appropriate musculoskeletal health care training to first contact health providers across Kenya. It has also raised the level of knowledge and competency of mid-grade physicians so they can fill the gap between first contact providers and hospital specialists. Should the project evaluation show it to be effective in changing practice and improving care for MSC this may provide a template for a programme of MSC training which could be implemented in other low income countries globally.

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2438

The Effect of a Systematic, Personalized Computer Workstation Redesign On Musculoskeletal Symptoms. Nancy A. Baker and Krissy Moehling. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Musculoskeletal symptoms (MSS), such as pain, numbness or cold, are common and distressing occurrences during computer use. One commonly used method to reduce MSS is workstation redesign which aims to "fit the workstation to the worker" and thereby reduce awkward postures. However, recent systematic reviews have reported that this method may not be effective [1]. This pilot study tested if a systematic method of workstation redesign which focused on 19 areas where mismatch could occur combined with active involvement of the worker in the development of the workstation redesign intervention plan (personalized ergonomics) would reduce or eliminate MSS one month after intervention.

Methods: This was a single group pretest/posttest study that examined 26 computer operators with self-reported computer related MSS of at least 2 in one body area (neck/shoulder, arm/wrist, hand) on a scale of 0 to 10 (with 0 being no pain and 10 the worst possible). Workers completed an MSS survey, as well as a self-assessment of their workstation set-up, the Computer Ergonomic Survey (CES), and were photographed in their computer workstations. An expert in workstation redesign used the results of the CES and photographs to identify in which of the 19 areas mismatch occurred. The expert and the computer operator then developed an intervention plan to rectify these mismatches. Workers implemented this plan over a one month period. Workers then completed the MSS survey again. They also rated their satisfaction with the workstation redesign process.

Results: The 26 computer operators mean age was 46.4 ($\pm$10.5). They were primarily female (92%) and used a computer, on average, 6.0 ($\pm$1.2)

hours per day. There were significant reductions in MSS for all body areas on both the left and right sides. Reductions in MSS achieved clinically important levels of at least 1 point for the neck/shoulder (left -1.23; right - 1.08), and right hand (1.01). Many subjects reported complete elimination of MSS at follow-up: neck/shoulder – left 35%, right 31%; arm/wrist – left 27%, right 46%; hand – left 27%, right 35%. This change was significant for the left arm/wrist and both hands. The changes reported to have the greatest effect on MSS were: adjusting the chair height to ensure that the feet were well supported (29%), adjusting the monitor height to reduce head tilt (18%), and adjusting the arm support height to support the arm during computer use (18%). Ninety-five percent of subjects reported that they were satisfied with the recommended changes, and 100% reported that they found the process to be helpful and they felt empowered to be able to continue to adjust their workstation to continue reducing MSS.

Conclusion: This study suggests that a systematic method of computer workstation redesign combined with worker involvement lead to significant improvements in computer-related MSS.

Reference
1. Kennedy CA, Amick BC, Dennerlein JT, *et al.* Systematic review of the role of occupational health and safety interventions in the prevention of upper extremity musculoskeletal symptoms, signs, disorders, injuries, claims and lost time. Journal of Occupational Rehabilitation 2010;20:127–62.

Disclosure: N. A. Baker, None; **K. Moehling**, None.

2439

A Brief Exercise and Self Management Programme Improves Upper Limb Disability in People with Early Rheumatoid Arthritis.
Lindsay M. Bearne[1], Victoria L. Manning[1], David L. Scott[2], Ernest Choy[3] and Michael V. Hurley[4]. [1]Kings College London, London, United Kingdom, [2]King's College London, London, United Kingdom, [3]Cardiff University School of Medicine, Cardiff, United Kingdom, [4]St George's University of London, London, United Kingdom

Background/Purpose: Upper limb dysfunction occurs early in people with rheumatoid arthritis (RA) and deteriorates as the disease progresses, impacting on independence and work capacity. Exercise is a important component in the management of upper limb disability, however, studies focus on the hand in isolation and do not address potential proximal motor deficits. Individually tailored, home exercise regimens are required to address global upper limb dysfunction which, if completed in the long term, could encourage self management. This study evaluated the efficacy of a gobal, upper limb home exercise programme supplemented with a brief supervised exercise, education and self management (Education and eXercise Training in early Rheumatoid Arthritis (EXTRA)) programme.

Methods: 108 adults with RA of less than 5 years duration (26 males, age mean (SD) 55 (15) years, disease duration 20 (19) months) were randomized to receive either Usual Care (n= 52) or the EXTRA programme (n=56). This progamme is a tailored home exercise regimen, focused on improving upper limb function, which is supplemented with 4 group supervised exercise, education and self management sessions, aimed at improving self efficacy and disease self management (2 sessions per week for the first 2 weeks, each session lasting approximately 1 hour, with 4–6 participants per group). Upper limb disability (Disability of Arm, Shoulder, Hand questionnaire (DASH)), grip strength, function (Grip Ability Test (GAT)), self efficacy (Arthritis Self Efficacy Scale - pain subscale (PSE)) and disease activity (Disease Activity Score (DAS 28)) were assessed at baseline, 3 months (primary end point) and 9 months. Intention to treat analysis using full factorial mixed Analysis of Variance (ANOVA) (treatment, time and treatment × time interaction) adjusted for baseline disease duration, disease activity and disability, and corrected for multiple comparisons, were used to determine between group differences,. Significance was accepted at $P<0.05$.

Results: Compared to a usual care control group, participants who completed the EXTRA programme demonstrated improved disability, function, non dominant grip strength and self efficacy with no adverse effects on disease activity (Table).

Table. Changes in disability, grip strength, function, self efficacy and disease activity following the EXTRA programme or Usual Care

Mean (95% Confidence intervals)	EXTRA programme	Usual Care	Between Group Differences	Effect size (95% CI)(P value)
Disability (DASH)				
Baseline	44.6 (37.2,52.0)	40.8 (33.6,48.0)	3.8 (-6.6,14.1)	
change at 3 months	-5.3 (-10.4,-0.2)†	1.5 (-3.5, 6.5)	-6.8 (-12.6,-1.0)†	0.5 (-2.3,3.3) **(0.022)**†
change at 6 months	-2.7 (-9.5,4.2)	-1.4 (-8.0,5.3)	-1.3 (-9.1,6.5)	0.1 (-3.7,3.9) **(0.730)**
Dominant Grip Strength (N)				
Baseline	183.3 (150.2,216.5)	220.5 (188.5,252.4)	-37.2 (-83.2,8.9)	
change at 3 months	23.1 (0.8,45.4)	0.3 (-21.2,21.8)	22.9 (-2.4,48.1)	0.35 (-12.0,12.7) **(0.140)**
change at 6 months	16.0 (-14.3,46.2)	-3.0 (-32.1,26.2)	18.9 (-15.3,53.2)	0.21 (-16.5,17.0) **(0.480)**
Non Dominant Grip strength (N)				
Baseline	171.7 (139.9,203.6)	214.2 (183.5,244.9)	-42.5 (-86.7,1.8)	
change at 3 months	17.5 (-1.9,36.9)†	-6.8 (-25.5,11.9)	24.3 (2.3,46.3)†	0.43 (-10.3,11.2) **(0.037)**†
change at 6 months	6.1 (-22.7,34.9)	-8.4 (-36.1,19.4)	14.5 (-18.2,47.1)	0.17 (-15.8, 16.1) **(0.648)**
Function (GAT seconds)				
Baseline	23.1 (19.3,26.8)	21.9 (18.3,25.5)	1.1 (-4.0,6.3)	
change at 3 months	-1.8 (-5.1,1.5)‡	1.5 (-1.6,4.7)	-3.3 (-7.0,0.4)†	0.4 (-1.4,2.2) **(0.010)**†
change at 6 months	-0.8 (-4.7,3.0)‡	-0.5 (-4.2,3.2)	-0.4 (-4.7,4.0)	0.0 (-2.1,2.1) **(0.130)**
Self efficacy (PSE)				
Baseline	57.5 (50.7,64.2)	59.2 (52.9,65.6)	-1.7 (-11.0,7.5)	
Change at 3 months	4.8 (-3.1,12.8)	-5.7 (-13.2,1.8)	10.5 (1.6,19.5)†	0.53 (-3.8,4.9) **(0.020)**†
Change at 6 months	6.6 (-0.8,14.0)	-1.8 (-8.8,5.2)	8.4 (0.1,16.7)†	0.45 (-3.6,4.5) **(0.047)**†
Disease Activity (DAS28)				
Baseline	5.3 (4.7,5.9)	4.9 (4.4,5.5)	0.4 (-0.4,1.2)	
change at 3months	-0.8 (-1.4,-0.2)‡	-0.1 (-0.7,0.4)	-0.7 (-1.4,0.0)†	0.55 (0.2,0.9) **(0.048)**†
change at 6 months	-0.8 (-1.4,-0.1)†	-0.2 (-0.8,0.4)	-0.5 (-1.2,0.1)	0.43 (0.1,0.8) **(0.120)**

‡ $P<0.01$
† $P0.05$

Conclusion: The EXTRA programme improves upper limb disability, grip strength, self efficacy and function in people with early RA, with no detrimental effects on disease activity. This brief intervention may be easily implemented into clinical practice.

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Decisional Conflict Among Vulnerable Patient Populations with Rheumatoid Arthritis Is Associated with Limited Health Literacy and Non-English Language.
Laura Trupin, Jennifer Barton, Gina Evans-Young, John B. Imboden, Andrew J. Gross. Dean Schillinger and Edward H. Yelin, UCSF, San Francisco, CA

Background/Purpose: Suboptimal communication in shared decision-making among vulnerable populations has been reported in rheumatoid arthritis (RA). National and international recommendations for quality health care highlight the importance of patient-centered care and involvement of patients in decision-making. The concept of decisional conflict captures the extent to which patients lack adequate information and support to make an informed health care decision. The objective of this study was to identify patient-level factors associated with high decisional conflict in RA treatment decisions among vulnerable populations who are at highest risk for poor health outcomes.

Methods: Data derive from a subset of participants in the RA Cohort Study, which enrolls adult RA patients from university-affiliated rheumatology clinics at an urban county hospital and a tertiary care facility. Enrollment for the present study occurred from September 2011 to May 2012; eligibility included having moderate to high disease activity, defined as a RAPID-3 score >6, and being a member of a vulnerable population based on the following criteria: immigrant, ethnic/racial minority, non-English speaker, age >65, or limited health literacy. Eligible patients completed a questionnaire in English, Spanish, or Chinese immediately after their clinic appointment. The questionnaire included a screening measure of health literacy, a series of true-false questions about RA and its treatments, and a low-literacy version of the 10-item Decisional Conflict Scale (DCS), given to patients who reported discussing a medication change with their doctor. DCS scores were compared by gender, race/ethnicity, age, and language using non-parametric ANOVA (Kruskal-Wallis) tests. Correlations among DCS, RA knowledge, and health literacy were assessed with Spearman correlation coefficients.

Results: Of 163 cohort members screened, 97 had active disease according to their RAPID-3 score and were enrolled in the study; 48 of those patients reported receiving a new prescription or discussing a medication change and were included in this analysis. Mean age was 59 (±12), 75% were women, 58% immigrants, 82% ethnic minorities, 35% Spanish or Chinese speakers, 61% had limited health literacy. DCS scores ranged from 0 to 80 (higher scores indicate more decisional conflict). Scores were significantly higher ($p<0.01$) among Chinese (45 ± 7) and Spanish speakers (23 ± 6) compared with African Americans (14 ± 7) and Whites (12 ± 8), but did not

differ by age or gender. Higher decisional conflict was associated with lower levels of health literacy (Spearman's r=-0.35, p=0.01) and poorer RA knowledge (Spearman's r=-0.36, p=0.01).

Conclusion: Limited health literacy and non-English language were associated with greater levels of decisional conflict about a real-time RA treatment decision. Providing low literacy decision aid tools to reduce decisional conflict and promote shared decision-making may lead to more patient-centered care, treatment decisions that align with patient preferences, and ultimately, improved health outcomes among vulnerable populations with RA.

Disclosure: L. Trupin, None; **J. Barton**, None; **G. Evans-Young**, None; **J. B. Imboden**, None; **A. J. Gross**, None; **D. Schillinger**, None; **E. H. Yelin**, None.

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Readability and Suitability Assessment of Patient Education Materials in Rheumatic Diseases. Rennie L. Rhee[1], Joan Marie Von Feldt[2], H. Ralph Schumacher[3] and Peter A. Merkel[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA

Background/Purpose: Comprehension of health resources may be challenging for patients particularly those with limited health literacy. The objective of this study was to examine the readability and suitability of commonly used patient education materials for systemic lupus erythematosus (SLE), vasculitis, rheumatoid arthritis (RA), and osteoarthritis (OA) and to determine whether readability and suitability vary among diseases of different complexities.

Methods: Several highly popular web-based patient resources were chosen for evaluation: American College of Rheumatology (ACR), Arthritis Foundation (AF), Mayo Clinic Health Information, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), UpToDate Basics, UpToDate Beyond the Basics, Vasculitis Clinical Research Consortium (VCRC), and Vasculitis Foundation. Readability was measured using the Flesch-Kincaid Reading Ease and Grade Level and computed after the removal of illustrations, tables, captions, disease and medication names, all forms of "rheumatology," and defined terms. Suitability was determined by the Suitability Assessment of Materials (SAM), a score that considers characteristics such as content, graphics, layout/topography, and cultural appropriateness. Three different reviewers rated the SAM score and means were used in the analysis. Scores were then converted into a percentage by dividing the given score by the total possible score. A score of 0–39% was considered not suitable, 40–69% adequate, 70–100% superior.

Results: The education material for all four diseases studied had readability above the 8th grade level and readability did not differ among the diseases. The mean grade level for each resource ranged from 4.8 to 12.5 with a median grade level of 9.6. Only 5 of the 23 resources received superior suitability scores (ACR for SLE, ACR for OA, AF for RA, AF for OA, UpToDate Basics for OA). Suitability scores among the four diseases were similar and again did not differ based on disease complexity.

Readability by Grade Level

Resource	SLE	Vasculitis	RA	OA	Mean
ACR	10.0	10.5	7.3	8.8	**9.2**
AF	9.0	—	9.7	8.4	**9.0**
Mayo Clinic	8.0	7.8	7.6	7.0	**7.6**
NIAMS	11.4	—	11.6	9.8	**10.9**
UpToDate Basics	5.1	—	4.5	4.8	**4.8**
UpToDate Beyond Basics	9.9	8.5	11.1	10.3	**10.0**
VCRC	—	10.6	—	—	**10.6**
Vasculitis Foundation	—	12.5	—	—	**12.5**
Mean	**8.9**	**10.0**	**8.6**	**8.2**	

Suitability by mean SAM score (in percentage)

	SLE	Vasculitis	RA	OA	Mean
ACR	76%*	48%	56%	79%*	**65%**
AF	67%	—	71%*	78%*	**72%**
Mayo Clinic	61%	61%	63%	69%	**64%**
NIAMS	26%	—	40%	47%	**38%**
UpToDate Basics	58%	—	60%	76%*	**65%**
UpToDate Beyond Basics	52%	52%	46%	57%	**52%**
VCRC	—	32%	—	—	**32%**
Vasculitis Foundation	—	33%	—	—	**33%**
Mean	**57%**	**45%**	**56%**	**68%**	

*SAM score considered superior

Conclusion: Patient education materials for rheumatic diseases other than UpToDate Basics are written at readability levels above the recommended sixth-grade reading level for the general public. Most resources were considered to have only adequate suitability. Scores were similar among the four diseases which suggest that disease complexity does not explain poor readability and suitability indices. Most educational resources for patients with rheumatic diseases should be revised to more appropriately communicate information about these diseases.

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Screening of Osteoporosis in Men Age 70 and Older: A Need for Increased Awareness. Sian Yik Lim, Kenneth Nugent, Joon Hee Lim, Hoda Mojazi Amiri, Rie Okamura and Dan Nguyen. Texas Tech University Health Sciences Center, Lubbock, TX

Background/Purpose: The National Osteoporosis Foundation (NOF) currently recommends osteoporosis screening with bone mineral density (BMD) testing in men age 70 and older, regardless of clinical risk factors. Despite these recommendations being published initially in 2008, data regarding BMD testing rates in men age 70 and older in a primary care setting in the United States are lacking. We hypothesize that BMD testing rates using Dual-energy X-ray absorptiometry (DEXA) scan in men age 70 and older remains low despite recommendations by the NOF.

Methods: We performed a retrospective chart review of male patients age 70 and older who were seen at the Internal Medicine Clinic at Texas Tech University Health Science Center, a major primary care setting in West Texas. We reviewed charts of patients seen between January 1st, 2011 and January 1st, 2012. We identified patients who had established the Internal Medicine Clinic as their primary care provider. We included patients who had been seen at least twice over a 3 year period. We excluded patients who were one time hospital discharge follow-ups and those who visited the internal medicine clinic for preoperative evaluations. Demographic information and BMD testing status were determined from electronic medical records. 10-year osteoporotic and hip fracture probabilities of individual patients were calculated using the World Health Organization Fracture Risk Assessment Tool. Analysis of the effect of increasing age on BMD testing was performed using chi square test for trend with patients divided into age groups of 70–74, 75–79, 80–84, 85–89, 90–94 and 95–99. The Pearson's correlation was used to analyze correlation of age with 10-year osteoporotic and hip fracture probabilities.

Results: The median age of our patients was 76 years (range 70–98 years). There were 341 male patients age 70 and older who were seen at the clinic during the study period. 310 patients were included in the study. 35 patients, which is 11.4% (95%CI [7.9–15.7]) of the study population received BMD testing using DEXA scans. BMD testing indicated that 8 patients (22.9%) were osteoporotic, 22 patients (62.9%) were osteopenic, and 5 patients (14.3%) had normal BMD. No significant association was found between increasing age and BMD testing (p=0.299). The medians of the 10-year osteoporotic and hip fracture probabilities in the 70–74 age group were 5.6% (range 2.0–14.0%) and 1.4% (range 0.2–5.3%). The medians of the 10-year osteoporotic and hip fracture probabilities peaked in the 90–94 age group at 9.4% (range 5.7–10.0%) and 6.1% (range 3.0–7.9%) respectively. Age was positively correlated with 10-year hip fracture probability (r=0.68, p<0.0001) and 10-year osteoporotic fracture probability (r= 0.53, p<0.0001).

Conclusion: Osteoporosis in men age 70 and older is still underscreened and underrecognized. Despite recommendations by the NOF for BMD testing using DEXA scan in men age 70 and older since 2008, BMD testing rates remain low. Although there was an increase in both the 10-year osteoporotic and hip fracture probabilities with age, no association was found between increased age and BMD testing. In view of the aging society in the United States, more has to be done to increase awareness of this major public health problem.

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Pain and Function Outcomes in Systemic Lupus Erythematosus Hip and Knee Arthroplasty. Ummara Shah[1], Lisa A. Mandl[2], Mark P. Figgie[2], Michael Alexiades[2] and Susan M. Goodman[2]. [1]New York University School of Medicine, NYC, NY, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: There is little information on Systemic Lupus Erythematosus (SLE) patients undergoing total joint arthroplasty (TJA). The purposes of this study were to determine the patterns of TJA in a contemporary SLE cohort and to determine if SLE is a risk factor for worse outcomes compared with similar osteoarthritis (OA) patients.

Methods: Patients with SLE who underwent hip or knee arthroplasty between May 2007 and June 2011 and enrolled in our institution's arthroplasty registry were eligible for this study. SLE cases were identified by ICD-9 code 710 and confirmed if they met 3/14 ACR criteria, were on immunosuppressant therapy, or had the diagnosis confirmed by a rheumatologist. Validated SLE cases were matched to two OA controls by age ($+/- 2.5$ years), gender, procedure, and presence of osteonecrosis (ON). ON was confirmed in cases and controls by pathology or radiology review. Pain and function were measured by WOMAC and the validated Lower Extremity Activity Scale (LEAS). Administrative and self-report data were collected at baseline and 2 years. Standard univariate comparisons were performed to compare SLE with matched OA cases at baseline and at two years post-op. Multivariate regressions were performed to analyze the relationship between diagnosis, presence of ON, and WOMAC pain and function at 2 years. TKA patients' pre-operative expectations were measured with the validated TKR Expectations Survey.

Results: 101 SLE cases were identified, 56 hip (THR) and 45 knee (TKR). 5 cases could only be matched to 1 control. Pre-operatively, SLE THR cases had statistically and clinically significantly worse WOMAC pain, stiffness, and function than matched OA hips, (see Table). Renal failure, hypertension, pulmonary, and valvular disease were also more common in SLE THA patients. Both SLE THA and TKA has statistically significantly worse SF-36 PCS pre-operatively, and, despite significant improvements, they remained statistically significantly worse compared to matched OA controls post-operatively. Two-years post-operatively, there were no differences in pain and function scores between SLE and OA controls. In multivariate regressions controlling for type of surgery, disease type, and ON, neither SLE nor ON predicted worse pain or function at 2 years. There were no differences in expectations of surgery between SLE TKA and OA TKA.

Table.

	SLE THA +/− SD n= 56	OA THA +/− SD n=108	p-value	SLE TKA +/− SD n= 45	OA TKA +/− SD n=89	p-value
Age	54.4+/−14.4	54.8+/−14.2	0.89	62.4+/−10.1	62.6+/−9.4	0.9
Female	50 (89.3%)	95 (88.8%)	0.9	40 (90.9)	83 (93.3)	0.6
ON*	18 (32.1%)	29 (26.9%)	0.5	0 (0.0%)	2 (2.2%)	0.55
WOMAC Baseline pain	42.9+/−19.7	53+/−17.8	0.011	42.6+/−17.3	49.4+/−15.0	0.073
WOMAC pain2 yr	90.0+/−13.2	92.4+/−13.8	0.5	81.8+/−15.7	90.7+/−13.4	0.06
WOMAC Baseline function	39.1+/−20.7	48.5+/−20	0.04	42.1+/−17	47.5+/−17.3	0.21
WOMAC function p2 yr	87.1+/−17	91.5+/−15.1	0.33	79.7+/−17.7	87.0+/−16.0	0.2
ED-5Q scale Baseline	59.8+/−17.0	67.9+/−20.6	0.06	69.7+/−18.8	73.7+/−15.0	0.3
ED-5Q 2 yrs	69.9+/−16.8	84.0+/−12.9	0.002	82.2+/−9.7	81.5+/−17.0	0.88
SF-36 PCS Baseline	24.5+/−6.5	31.9+/−8.8	0.0001	27.3+/−6.7	33.7+/−8.1	0.0006
SF-36 PCS p2 yr	39.0+/−12.4	50.1+/−10.6	0.001	38.0+/−5.5	48.4+/−9.8	0.0007
LEAS Baseline	8.1+/−3.1	9.4+/−3.1	0.034	8.4+/−2.3	9.6+/−3.1	0.09
LEAS 2 yr	10.4+/−3.9	12.2+/−2.9	0.06	9.9+/−2.5	11.6+/−2.9	0.05
Elix-hauser Co-morbidities						
Valvular disease	10 (17.9%)	2 (1.9%)	0.0004	4(8.9%)	3 (3.4%)	0.22
Renal failure	8(14.3%)	1 (0.9%)	0.0009	5(11.1%)	2 (2.2%)	0.04
Hypertension	29 (51.8%)	32 (29.6%)	0.007	25 (55.6%)	53 (59.6%)	0.7
Pulmonary circulation disease	3 (5.4%)	0 (0.0%)	0.04	0 (0.0%)	0 (0.0%)	—
corticosteroids	9 (16.1%)	0 (0.0%)	—	3 (6.7%)	0 (0.0%)	—
immunosuppressants	40 (71.4%)	0 (0.0%)	—	34 (75.6%)	0 (0.0%)	—

* 5 patients have no controls so prevalence of ON is different between SLE and OA; this imbalance was addressed by including ON in the multivariate regressions

Conclusion: SLE THA and TKA patients have similar pain and functional outcomes at 2 years compared with matched OA controls. Although PCS scores improved after arthroplasty, they remained lower in SLE patients than OA

controls. To our knowledge, this is the first study to demonstrate that neither SLE nor ON should be considered risk factors for poor post-operative outcomes.

2444

Restricting Back Pain Is Associated with Disability in Community-Living Older Persons. Una E. Makris[1], Liana Fraenkel[2], Ling Han[3], Linda Leo-Summers[3] and Thomas M. Gill[4]. [1]UT Southwestern Medical Center, Dallas, TX, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [3]Department of Medicine, New Haven, CT, [4]Yale University, New Haven

Background/Purpose: Although back pain is common and costly, few longitudinal studies have evaluated the association between back pain, severe enough to restrict activity (hereafter referred to as restricting back pain), and the development of disability in mobility. Older persons who lose independent mobility have higher rates of morbidity and mortality, and experience a poorer quality of life. We hypothesized that restricting back pain would be strongly associated with mobility disability over the $13+$ years of follow-up.

Methods: We evaluated the 555 participants (mean age 77.5 years, 56% women) of the Precipitating Events Project, a prospective study of community-living persons, aged 70+ years, all non-disabled at baseline, who completed monthly telephone assessments of restricting back pain and who were at risk for developing mobility disability for up to 159 months. Restricting back pain was defined as staying in bed for at least half a day and/or cutting down on one's usual activities due to back pain. Mobility disability (hereafter referred to as disability) was defined as needing help with or inability to complete any of the following four tasks in any given month: walking a 1/4 mile, climbing a flight of stairs, lifting or carrying 10 pounds, or driving a car. The event rate for disability was estimated using a Generalized Estimation Equation Poisson model. A recurrent events Cox model was used to evaluate the associations between the occurrence of restricting back pain (yes/no) and subsequent (within one month) disability. The model was adjusted for fixed-in-time (sex, education, ethnicity) and time-varying covariates (age, chronic conditions, BMI, depressive symptoms, cognitive impairment, and physical frailty defined by slow gait speed) that were updated every 18 months. We tested potential interactions of restricting back pain with sex, BMI, depressive symptoms, and physical frailty.

Results: The event rate for disability was 8.47 per 100-person months (95% CI 8.08,8.88) with a median duration of 2 (interquartile range: 1–5) months. The frequency of each of the four disability items at baseline was 13.2% for walking a 1/4 mile, 3.6% for climbing stairs, 10.5% for lifting/carrying 10 pounds, and 11.2% for driving a car. After adjusting for covariates, restricting back pain was strongly associated with subsequent disability, with a hazard ratio (95% CI, p-value) of 3.35 (2.91,3.86, <0.001). Only the interaction with physical frailty was statistically significant (p = <0.001). Subgroup analyses suggest that restricting back pain is associated with disability among participants with and without physical frailty at baseline assessment 2.10 (1.67,2.63) and 4.06 (3.42,4.81), respectively.

Conclusion: In this longitudinal study, restricting back pain was independently associated with disability among older persons. It is possible that individuals who are not physically frail may be more active and therefore at higher risk for developing subsequent disability. Calculating absolute risk differences may help to clarify the results of our subgroup analysis. Interventions implemented to decrease or prevent restricting back pain are likely to decrease disability.

2445

Ipsilateral Lower Extremity Joint Involvement Increases the Risk of Poor Pain and Function Outcomes After Hip or Knee Arthroplasty. Jasvinder A. Singh[1] and David Lewallen[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Mayo Clinic college of medicine, Rochester

Background/Purpose: Persistent pain and functional limitation are unfavorable outcomes after knee and hip replacement, which are getting increasing attention due to a dramatic increase in rates of knee and hip replacements. Our objective was to assess the association of ipsilateral knee/hip pain on short- and mid-term pain and function outcomes after total hip or knee arthroplasty (THA/TKA).

Methods: We used the prospectively collected data from the Mayo Clinic Total Joint Registry to assess the association of ipsilateral knee or hip joint

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involvement with moderate-severe pain and moderate-severe functional limitation at 2- and 5-year follow-up after primary and revision THA and TKA using multivariable-adjusted logistic regression analyses. Analyses were adjusted for patient characteristics (unmodifiable—age and gender; and modifiable—BMI, comorbidity, depression and anxiety), implant fixation (cemented/hybrid versus not cemented) and health care access as assessed by the distance from medical center.

Results: At 2-year, 3,823 primary THA, 4,701 primary TKA, 1,218 revision THA and 725 revision TKA were studied. After adjusting for multiple covariates, ipsilateral knee pain was significantly associated with outcomes after primary THA (all p-values <0.01): (1) moderate-severe pain: at 2-years, odds ratio (OR), 2.3 [95% confidence interval (CI), 1.5, 3.6]; at 5-years, OR 1.8 [95% CI:1.1, 2.7]; (2) moderate-severe functional limitation: at 2-years, OR 3.1 [95% CI:2.3, 4.3]; at 5-years, OR 3.6 [95% CI:2.6, 5.0]. Ipsilateral hip pain was significantly associated with outcomes after primary TKA (all p-values <0.01): (1) moderate-severe pain: at 2-years, OR 3.3 [95% CI:2.3, 4.7]]; at 5-years, OR 1.8 [95% CI:1.1, 2.7]; (2) moderate-severe functional limitation: at 2-years, OR 3.6 [95% CI:2.6, 4.9]; at 5-years, OR 2.2 [95% CI:1.6, 3.2]. Similar associations were noted for revision THA and TKA patients.

Conclusion: Presence of ipsilateral joint involvement after primary and revision THA and TKA is a poor prognostic factor for pain and function outcomes. A potential way to improve outcomes may be to address ipsilateral lower extremity joint involvement.

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2446

Activity Limitations Experienced by People with Rheumatoid Arthritis On Biologic Medications and Their Use of Ergonomic Methods. Alison Hammond[1] and Sarah Tyson[2]. [1]University of Salford, Salford, United Kingdom, [2]University of Salford, Manchester, United Kingdom

Background/Purpose: People with rheumatoid arthritis (RA) commonly have daily activity difficulties. Whilst biologics significantly improve ability, ergonomic methods (e.g. altered working methods, ergonomic equipment, activity and environment modification) may still improve ability further. The aim of this study was to investigate activity limitations of people with RA on biologics and their use of ergonomic methods.

Methods: Participants on biologics completed the Evaluation of Daily Activity Questionnaire (EDAQ): measuring ability performing 138 activities (grouped in 14 domains: Table 1). Activities are scored as 0 (no difficulty) to 3 (unable to do). Each is scored twice: Section A = ability without ergonomic methods or help; Section B (completed if difficulty) =ability with ergonomic methods (if used). Percentages of participants experiencing difficulties per activity (Section A) were calculated. Score differences between sections A and B were analysed using paired t-tests.

Results: Participants were recruited from 14 Rheumatology units (n=198: 156 women; 42 men). Mean age = 59.16 (SD 10.46) years; RA duration 13.83 (SD 9.24) years. Biologics prescribed were: etanercept (n=75); adalimumab (57); rituximab (44), infliximab (16), golimumab (3), certolizumab (1) and abatacept (1). Average pain was 4.69 (SD2.57) and fatigue 5.47 (SD2.47). Average HAQ score was 1.21 (SD 0.83).Participants rated their health as: very good (9%); good (29%); fair (42%); poor (16%) and very poor (4%). Average EDAQ scores without ergonomic methods were at or below the lower tertile in all domains (Table 1). Common difficulties included: opening jars (88%); carrying pans (82%); preparing vegetables (76%); using a kettle (68%); vacuuming (67%); turning taps (56%); preparing meals (49%). Average ability using ergonomic methods (section B) was significantly better for all domains, except Caring (as many had few childcare responsibilities due to their age). Ergonomic methods were used more by those rating health as fair, poor or very poor.

Table 1. EDAQ domain scores for people with RA on biologic drugs (n=198)

EDAQ Domain score	Domain score range	n	Section A Mean (SD)	Section B Mean (SD)	p
1. Eating/Drinking	0–30	187	10.47 (6.70)	8.21 (6.12)	<0.001
2. Bathroom	0–36	184	5.83 (5.80)	5.24 (5.49)	<0.001
3. Dressing	0–33	190	8.65 (7.30)	8.25 (7.10)	<0.001
4. Bathing	0–33	192	9.85 (8.36)	8.95 (7.86)	<0.001
5. Cooking	0–42	182	12.26 (9.69)	11.26 (9.63)	<0.001
6. Moving Indoors	0–36	180	10.38 (7.78)	9.81 (7.62)	<0.001
7. Cleaning	0–27	194	9.66 (7.15)	9.43 (7.19)	<0.001
8. Laundry	0–27	191	8.41 (7.31)	7.92 (7.17)	<0.001
9. Transfers	0–18	196	4.68 (3.71)	4.44 (3.64)	<0.001
10. Communication	0–18	192	3.15 (3.13)	2.83 (2.98)	<0.001
11. Moving Outdoors	0–39	182	11.86 (9.32)	11.12 (9.14)	<0.001
12. House/Garden maintenance	0–21	194	10.30 (7.08)	10.21 (7.08)	<0.001
13. Caring	0–27	189	3.99 (7.16)	3.97 (7.12)	0.1
14. Leisure	0–27	184	6.43 (6.26)	6.24 (6.29)	<0.001

Conclusion: People with RA on biologics continued using ergonomic methods, reporting significantly better ability as a result. Section B scores indicated scope for greater use of ergonomic methods to further reduce limitations. Many on biologics might benefit from occupational therapy assessment and ergonomic advice to help further reduce limitations.

Disclosure: **A. Hammond**, None; **S. Tyson**, None.

2447

Accuracy of Sensewear Mini[TM] and Actigraph GT3X[TM] Accelerometers for Differentiating Sedentary and Light Physical Activities in a Controlled Laboratory Setting. April Y. F. Leung[1], Lynne M. Feehan[2], Cynthia Macdonald[1], Jenny Leese[3], Erin Carruthers[3] and Linda C. Li[1]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada and University of British Columbia, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC

Background/Purpose: People living with inflammatory arthritis are likely to be less physically active due to pain and fatigue. To understand the relationship between physical inactivity and poor health outcomes in inflammatory arthritis, it is necessary to accurately identify and quantify lower levels of physical activity. Accelerometers are small activity monitors used to measure moderate and higher levels of physical activity. However, it is unclear how accurately different monitors capture sedentary and light physical activities. The purpose of this study was to compare the accuracy of the SenseWear Mini™ (SW) and Actigraph GT3X™ (AG) accelerometers for differentiating between sedentary and non-sedentary/light physical activities in a controlled laboratory setting.

Methods: 22 adults (F=15, M=7, mean age 35.7, range 19 to 72) volunteered to participate. Both monitors were synchronized with Greenwich Mean Time and were set to collect data at 1-minute intervals. Participants were randomly assigned to perform 9 activities for 5 minutes each. All activities were observed and timed. The activities were performed in: 1) standing (**slow treadmill, **wash dishes, *text messaging), 2) sitting (**slow cycling, *watch television, **computer typing), and 3) lying down (*rest with music, *read book, *knee ROM exercise in lying). According to the 2011 Compendium of Physical Activities (CPA), 5 activities were defined as *sedentary (<1.6 METs) and 4 were defined as **non-sedentary/light (1.6 to 3 METs). The middle 3-minute interval from each 5-minute time period was analyzed. Each SW activity was categorized as sedentary (< 1.6 METs) or non-sedentary (≥ 1.6 METs) based on the SW proprietary MET data. Each AG activity was categorized as sedentary or non-sedentary, based on 2 different sedentary cut-points (< 100 and < 589 activity counts/minute) for the AG vertical axis data.

Percentage of activities correctly identified as sedentary (sensitivity) and non-sedentary (specificity), proportion of all activities identified as sedentary or non-sedentary that were in fact sedentary (positive predictive value – PPV) or non-sedentary (negative predictive value – NPV), as well as, the positive (LR+) and negative (LR-) likelihood ratios were calculated for both accelerometers.

Results: Compared against derived values from the 2011 Compendium of Physical Activities, SW performed notably better than AG in differentiating between sedentary and non-sedentary/light physical activities under controlled laboratory settings (Table 1). Accuracy of AG was not affected by the cut-point chosen.

Table 1. Summary of measurement accuracy of SenseWear Mini and Actigraph GTX3 compared with the Compendium of Physical Activities

	SenseWear Mini	Actigraph GTX3 (<100 activity counts/minute)	Actigraph GTX3 (<589 activity counts/minute)
Sensitivity (Sedentary)	0.98	1.00	1.00
Specificity (Non-Sedentary)	0.70	0.27	0.11
PPV (Sedentary)	0.81	0.63	0.59
NPV (Non-Sedentary)	0.97	1.00	1.00
LR+ (Sedentary)	3.32	1.38	1.13
LR− (Non-Sedentary)	0.03	0.00	0.00

Conclusion: Our results suggest that SenseWear Mini may be a better accelerometer for objective measurements of low physical activity in people

with inflammatory arthritis. Further studies are needed to examine the accuracy of SenseWear Mini for measuring physical activity under free-living conditions.

Disclosure: **A. Y. F. Leung**, None; **L. M. Feehan**, None; **C. Macdonald**, None; **J. Leese**, None; **E. Carruthers**, None; **L. C. Li**, None.

2448

Sustained Improvement Physical Function Following an Integrated Rehabilitation Programme for Chronic Knee Pain. Mike Hurley[1] and Dr Nicola E. Walsh[2]. [1]St George's University of London, London, United Kingdom, [2]University of the West of England Bristol, Bristol, United Kingdom

Background/Purpose: Chronic knee pain causes personal suffering and impairs physical function and quality of life. Usual primary care involves prolonged drug therapy in spite of growing concerns about effectiveness and side-effects. Exercise and self-management interventions can have good short-medium term (up to 6 months) benefits, but whether short term benefits are sustained is largely unknown. Since chronic knee pain is a long term problem establishing long term outcome is important. We devised a rehabilitation programme that integrates exercise and self-management (*Enabling Self-management and Coping with Arthritic knee Pain through Exercise, ESCAPE-knee pain*), that produced short-medium term (6-months) improvements in physical functioning. To measure long term effects of the programme we continued to follow participants for 30 months after completing the programme.

Methods: 418 people from 54 primary care surgeries were (cluster) randomised to receive i) usual care, or *ESCAPE-knee pain* delivered to ii) individual or iii) groups of 8 participants. As there no differences in the baseline or post-rehabilitation data between participants who received the programme individually or in groups these data were combined. Subjective physical function was measured by the Western Ontario and McMasters University Osteoarthritis Index function sub-scale (WOMAC-func) was assessed at baseline, immediately post-rehabilitation, 6-months, 18-months and 30-months after completing the *ESCAPE-knee pain* programme. Multilevel Modelling was performed to adjust for clustering, baseline WOMAC-func and missing data.

Results: At baseline physical function in both groups were similar. Immediately after the intervention, participants who undertook *ESCAPE-knee pain* reported better physical function than participants who remained on usual primary care. In the following 30 months, physical function of participants who remained on usual care remained unchanged. Physical function of participants who undertook the *ESCAPE-knee pain* programme improved at each assessment compared to baseline value, i.e. mean WOMAC-func decreased, (post-rehabilitation WOMAC-func -5.49 (95%CI -7.78, -3.19; p<0.0001); 6-month WOMAC-func -4.44 (-6.54, -2.33; p<0.0001); 18-month WOMAC-func -3.10 (-5.44, -0.76; p<0.0095) 30-month WOMAC-func -2.78 (-5.32, -0.23; p<0.0323)), but declined over time becoming more similar to the usual care values.

Conclusion: *ESCAPE-knee pain* is an exercise-based rehabilitation programme for chronic knee pain that has sustained improvement in physical function for up to 2½ years after completing the programme. Models of care should be developed that will sustain for longer the large initial improvement in physical functioning.

Disclosure: **M. Hurley**, None; **D. N. E. Walsh**, None.

ACR Plenary Session III:
Discovery 2012
Tuesday, November 13, 2012, 11:00 AM–12:30 PM

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Head to Head Comparison of Subcutaneous Abatacept Versus Adalimumab in the Treatment of Rheumatoid Arthritis: Key Efficacy and Safety Results From the Ample (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) Trial. Michael E. Weinblatt[1], Michael H. Schiff[2], Roy Fleischmann[3], Robert Valente[4], Désirée van der Heijde[5], Gustavo Citera[6], Cathy Zhao[7] and Michael A. Maldonado[7]. [1]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [2]University of Colorado, Denver, CO, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Arthritis Center of Nebraska, Lincoln, NE, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [7]Bristol-Myers Squibb, Princeton, NJ

Background/Purpose: The availability of multiple biologic agents to treat rheumatoid arthritis (RA) has created a need for comparative assessment. AMPLE (**A**batacept Versus Adali**m**umab Com**p**arison in Bio**l**ogic-Naiv**e** RA Subjects with Background Methotrexate) is the first head-to-head study powered to compare SC abatacept (ABA) and adalimumab (ADA) on a background of methotrexate (MTX). Here, we report key 1 year data from AMPLE including ACR core component data.

Methods: AMPLE is an ongoing, phase IIIb, randomized, investigator-blinded study of 24 months duration with a 12 month primary efficacy endpoint. Biologic-naïve RA patients with an inadequate response to MTX were randomized to 125 mg ABA weekly or 40 mg ADA bi-weekly, in combination with MTX. The primary end point was non-inferiority (NI) of ABA to ADA based on ACR 20 at 12 months; key secondary endpoints were rates of radiographic non-progression, safety, injection site reactions and retention. ACR core component data were also analyzed.

Results: A total of 646 patients were randomized and treated; 86.2% of ABA patients and 82.0% of ADA patients completed 12 months. Baseline characteristics were balanced across both arms (mean DAS28-CRP of 5.5 and disease duration 1.8 yrs). At 1 year, 64.8% of ABA patients and 63.4% of ADA patients achieved an ACR 20 response, with an estimated difference between the two arms (95% CI) of 1.8 (-5.6, 9.2) supporting NI of ABA to ADA. The kinetics of response across ACR scores were comparable overall, with an ACR50 of 46.2% and 46% and ACR70 of 29.2% and 26.2% for ABA and ADA, respectively, at 1 year. Similar responses over time were seen in some ACR core components (Figure). At 1 year, the rates of radiographic non-progression were comparable, as were mean changes in van der Heijde-modified total Sharp scores (0.58 vs. 0.38, for ABA vs. ADA respectively). The rates of AEs, SAEs, serious infections and malignancies were comparable. There were more patients with autoimmune AEs (3.1% vs. 0.9%) in the ABA arm; however, none were serious. One patient discontinued in each arm due to an autoimmune event. There were fewer discontinuations with ABA due to AEs (3.5% vs. 6.1%) and due to serious infections (0% vs. 1.5%). Injection site reactions occurred in significantly fewer ABA-treated patients (3.8% vs. 9.1% [p=0.006]).
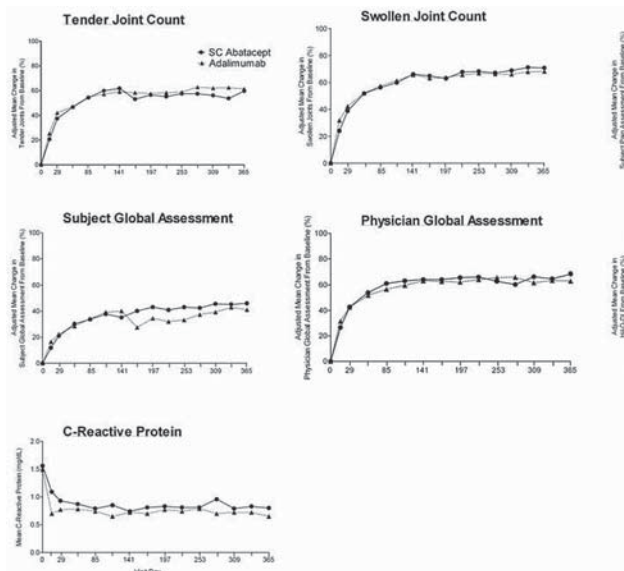
Conclusion: This first head-to-head study in RA patients comparing biologic agents on background MTX demonstrated that subcutaneous abatacept is comparable to adalimumab by most efficacy measures, including radiographic progression. Safety was generally similar with fewer discontinuations and injection site reactions observed with abatacept.

Disclosure: **M. E. Weinblatt**, Bristol-Myers Squibb, Abbott, 2, Bristol-Myers Squibb, Abbott, 5; **M. H. Schiff**, Bristol-Myers Squibb, 5, Abbott Laboratories, 8; **R. Fleischmann**, Genentech Inc,, Roche, Abbott, Amgen, UCB, Pfizer, BMS, Lilly, Sanofi Aventis, Lexicon, MSD, Novartis, BiogenIdec, Astellas, Astra-Zeneca, Jansen, 2, Roche, Abbott, Amgen, UCB, Pfizer, BMS, Lilly, Sanofi Aventis, Lexicon, Novartis, Astellas, Astra-Zeneca, Jansen, HGS, 5; **R. Valente**, UCB, Pfizer, Novartis,Eli Lilly,Takeda, Centocor, 2; **D. van der Heijde**, Abbott, Amgen, AstraZeneca, BMS, Centocor, Chugai, Eli-Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth, 5, Owner of Imaging Rheumatology bv, 4; **G. Citera**, Pfizer Inc, 2, Pfizer, Bristol-Myers Squib, Astra Zeneca, 5; **C. Zhao**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **M. A. Maldonado**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1.

2450

Evoked Pain Brain Response Is Associated with Reduced μ-Opioid Receptor Binding in Fibromyalgia. Heng Wang[1], Daniel J. Clauw[2], Jon-Kar Zubieta[1] and Richard E. Harris[2]. [1]University of Michigan, Ann Arbor, [2]University of Michigan, Ann Arbor, MI

Background/Purpose: Previous studies indicate that fibromyalgia (FM) patients have augmented clinical and brain responses to painful stimuli (i.e. hyperalgesia/allodynia), as well as increased production of endogenous opioids, and reduced μ-opioid receptor (MOR) binding. However, it is not known if these factors co-occur within the same individual or if these factors act independently. We performed a longitudinal investigation using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) in chronic pain patients diagnosed with FM to address this question. If these factors operate in the same individual, we expected an inverse correlation between changes in fMRI evoked pain activity and MOR binding potential (BP).

Methods: fMRI and PET imaging sessions were performed on 18 female opioid-naïve FM patients (age $45.4+/- 13.0$). Each participant underwent 4 weeks of non-pharmacological treatment. Before and after treatment, each patient underwent an fMRI scan with varying levels of pressure pain applied to the thumb as well as a 90-minute [11C]carfentanil PET scan under resting conditions. After quantification of the PET data with Logan plots, fMRI images and preprocessing of PET data were performed with statistical parametric mapping (SPM5). fMRI and PET scans were normalized to the same template. Difference images before and after treatment were calculated for both the fMRI contrast and PET images. A whole-brain voxel-by-voxel correlation analysis between the fMRI and PET difference images were carried out using the Biological Parametric Mapping toolbox. Activation clusters were defined based on a correlation coefficient, with $R >= 0.6$ uncorrected. Clinical pain was assessed with Short Form McGill Pain Questionnaire (SFMPQ).

Results: Negative correlations between the change in the fMRI blood oxygenation level dependent (BOLD) signal and MOR BP were observed in multiple regions involved in pain processing and modulation: right posterior insula $R=-0.82, P=0.0004$; left medial insula $R=-0.82$, $P=0.0003$; left orbital frontal cortex $R=-0.75$, $P=0.0004$; right amygdala $R=-0.68$, $P=0.002$; brainstem $R=-0.71$, $P=0.0009$. Positive correlations were observed in right DLPFC $R=0.66$, $P=0.003$; posterior cingulate $R=0.62$, $P=0.006$; right putamen $R=0.72$, $P=0.0008$. Changes in both functional imaging outcomes were negatively associated with changes in clinical pain: BOLD in right DLPFC and clinical pain SFMPQ $R=-0.52$, $P=0.03$; MOR BP in left medial insula and SFMPQ present pain $R=-0.51$, $P=0.03$.

Conclusion: We find strong longitudinal associations between evoked pain activations suggestive of hyperalgesia, and μ-opioid receptor availability (binding potential, BP) within the same brain regions, in individual FM patients. Positive associations were also observed between BOLD responses, and μ-opioid receptor BP (in opposite directions) with respect to clinical pain. These data suggest that the μ-opioid system is somehow involved in the pathogenesis of FM, and may even help explain why these patients are generally not felt to respond to narcotic analgesics, and may even be made worse when these drugs are used therapeutically.

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Laquinimod (LAQ) Is Equivalent to Mycophenolate Mofetil (MMF) in Preventing and Suppressing Murine Lupus Nephritis and Has Greater Effects On Myeloid/Monocyte/Macrophage Cells. Bevra H. Hahn, Maida Wong, Elaine Lourenco and Brian Skaggs. UCLA David Geffen School of Medicine, Los Angeles, CA

Background/Purpose: Lupus nephritis (LN) depends on autoAb deposition and activation of multiple cell types that infiltrate kidneys and promote inflammation—monocytes/macrophages (MM), DCs, T and B cells. Laquinimod (LAQ) administered to humans downregulates Ag presentation, decreases chemokine production, decreases MHC expression on MM, and induces apoptotic pathways in PBMC (Gurevich M et al 2010). LAQ reduces progression of relapsing remitting multiple sclerosis (Comi G et al NEJM 2012); it is currently in clinical trials in SLE. MMF targets primarily lymphocytes; it is effective in many LN patients.

Methods: We compared clinical and immune cell changes in groups of 10–12 BWF1 female mice treated orally 3 times a week for 24 weeks with a)

water; b) LAQ 1 mg/kg; c) LAQ 25 mg/kg; d) MMF 30 mg/kg; e) MMF100 mg/kg.

Results: Survival was better in both LAQ groups and the MMF100 group vs controls ($p=0.028$). LAQ at both doses was equivalent to MMF100 in preventing proteinuria in mice treated before disease appeared. At 32 wks of age 50% of mice on water had proteinuria vs zero in LAQ and MMF100 groups ($p<0.0001$) Renal histology mirrored proteinuria: mean total histologic scores were 7.8 on water, 1.0 on LAQ and 0.9 on MMF100 ($p<0.01$ both treatment groups compared to controls). Glomerular deposition of Ig and C3 were in the normal range in LAQ and MMF, but significantly increased in the water group ($p<0.001$).

Mice treated after clinical nephritis appeared ($\geq 3+$ proteinuria) improved on LAQ: after 3 wks of treatment proteinuria was present in 100% on water vs 25% on LAQ ($p<0.001$). Survival was also better in mice treated with LAQ ($p<0.0001$).

Effects on splenic PBMC differed between LAQ and MMF. Neither treatment changed total numbers of B cells. MMF decreased CD4+ and CD8+ T cell percents; LAQ did not. LAQ compared to MMF increased numbers of two putative regulatory cells, CD4+CD25+Foxp3+ Treg and CD11b+Ly6^{int}GR-1+ myeloid MM. Most interesting was the observation that LAQ, but not MMF, significantly reduced numbers of MM.

Conclusion: LAQ was highly effective in preventing and suppressing proteinuria and glomerular immune disease in BWF1 mice. Responses to MMF in high dose were similarly good. However, LAQ reduced numbers of MM, and MMF did not. In addition, LAQ induced different types of regulatory cells, distinguishing it from MMF. Since suppression of MM is likely to reduce renal inflammation and damage, future development of LAQ as a therapeutic for lupus nephritis is especially promising.

2452

Rheumatoid Arthritis-Associated PTPN22 Modulates Toll-Like Receptor-Mediated, Type 1 Interferon-Dependent Innate Immunoregulation. Yaya Wang[1], Stephanie Stanford[2], Wenbo Zhou[1], Jennifer L. Auger[1], Genhong Cheng[3], Amanda Campbell[2], Fernanda M. Shoyama[1], Henry H. Balfour Jr.[4], Andrew C. Chan[5], Bryce A. Binstadt[1], Nunzio Bottini[2] and Erik J. Peterson[1]. [1]University of Minnesota, Minneapolis, MN, [2]La Jolla Institute for Allergy and Immunology, La Jolla, CA, [3]University of California, Los Angeles, Los Angeles, CA, [4]University of Minnesota, Minneapolis, [5]Genentech Inc, South San Francisco, CA

Background/Purpose: A coding polymorphism (C1858T) in *PTPN22* is strongly associated with risk of Rheumatoid Arthritis (RA) and other autoimmune diseases. *PTPN22* encodes Lymphoid Phosphatase (Lyp); the Lyp disease variant bears an R620W substitution ("LypW"). The mechanism by which LypW increases disease susceptibility remains unclear. *PTPN22*-expressing dendritic cells (DC) and macrophages have been implicated in RA pathology. Such myeloid cells produce type 1 interferons (IFN) and proinflammatory cytokines in response to Toll-like receptor (TLR) engagement. We hypothesized that *PTPN22* might modulate TLR signaling and attendant innate immune responses.

Methods: We studied TLR signaling and type 1 IFN-mediated antiviral responses and immunoregulation in *Ptpn22*-deficient myeloid cells and mice, in transgenic mice harboring human LypW or LypR (major allele protein product), and in human LypW carrier peripheral blood mononuclear cells (PBMC).

Results: We found markedly decreased induction of type 1 IFN after TLR3/4/7/9 activation in *Ptpn22*$^{-/-}$ macrophages, DC, and plasmacytoid DC. Interestingly, *Ptpn22* was dispensable for induction of proinflammatory cytokines, including TNFα, IL-6, and IL-1β, after TLR2/3/4/7/9 stimulation. The selective TLR signalling defect in *Ptpn22*$^{-/-}$ cells was associated with impaired type 1 IFN-dependent immunity, manifested by reduced serum type 1 IFN, impaired dendritic cell activation, and diminished T cell responses after lymphocytic choriomeningitis virus (LCMV) infection of *Ptpn22*$^{-/-}$ mice. In the K/BxN serum transfer model of rheumatoid arthritis, treatment with type 1 IFN-inducing TLR ligands suppresses disease. However, we observed significantly decreased TLR ligand-mediated suppression of inflammatory arthritis in *Ptpn22*$^{-/-}$ mice. RA-associated LypW carrier human PBMC and myeloid cells derived from LypW transgenic mice displayed defective induction of type 1 IFN after TLR stimulation. LypR directly associated with TNF receptor-associated factor 3 (TRAF3), a key TLR signaling mediator upstream of type 1 IFN induction. LypR, but not LypW promoted TRAF3 K63-linked polyubiquitinylation, which is required for TLR-induced type 1 IFN production.

Conclusion: *PTPN22* is a key positive regulator of TLR-driven upregulation of type 1 IFN. LypW, product of the RA-associated *PTPN22* allele, exhibits "loss of function" in type 1 IFN dependent processes, including antiviral host defense and amelioration of inflammatory arthritis. Our findings strongly suggest that *PTPN22* could regulate severity of joint inflammation in RA through modulation of TLR signaling in innate immune cells.

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The Role of Bob1 in Rheumatoid Arthritis: Potential Implications for Autoimmunity. Nataliya Yeremenko[1], Tineke Cantaert[1], Melissa N. van Tok[1], Ioana Gofita[1], Juan D. Canete[2], Paul P. Tak[1], Hergen Spits[3] and Dominique L. Baeten[1]. [1]Division of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Rheumatology Department, Hospital Clinic, Barcelona, Spain, [3]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a prototypic autoimmune disease characterized by a prominent humoral autoimmunity. Of particular relevance is the local production of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies in the inflamed synovial tissue. The mechanisms underlying break of B cell tolerance and local autoantibody production remains poorly understood. This study was conducted in order to identify cellular and molecular pathways implicated in RA-specific humoral autoimmunity.

Methods: Synovial tissue samples were obtained by arthroscopy from untreated individuals with RA (n=33) and inflammation matched SpA controls (n=58). Gene expression profiling was performed on tissue samples of patients with established arthritis using 44K Whole Genome Human microarrays (Agilent). Top differentially expressed genes were validated on three independent cohorts by Taqman based RT-qPCR and immunohistochemistry. Collagen-induced arthritis (CIA) and Experimental autoimmune encephalomyelitis (EAE) experiments were conducted using Bob1 knockout mice and their littermate controls.

Results: Microarray screening for genes differentially expressed in the inflamed synovium, the key target of the disease process in RA, revealed a prominent and disease-specific B cell/plasma cell signature with the B cell-specific transcriptional co-activator Bob1 and its transcriptional target BCMA among the most upregulated genes. Validation by RT-qPCR on two independent cohorts representing early and established arthritis confirmed microarray data and demonstrated elevated expression of Bob1 and BCMA not only in established RA, but also at the early phase of the disease. Quantitative evaluation of immunohistochemical stainings of synovial tissue with monoclonal antibody for Bob1 revealed significant increase in Bob1 positive cells in RA synovium (p<0.01). Next we determined whether lack of functional Bob1 modifies disease onset or severity in CIA. Interestingly, the results showed that Bob1$^{-/-}$ mice were fully resistant to CIA induction compared to their wild-type littermates. This remarkable protection from CIA is explained by failure to produce pathogenic anti-collagen autoantibodies in the absence of Bob1. In contrast, Bob1$^{-/-}$ mice were susceptible to MOG protein induced EAE and incidence and severity of clinical disease were not altered in these mice comparing to wild-type littermates, suggesting that absence of Bob1 does not impact on antigen-presentation/costimulatory capacity of B cells.

Conclusion: The specific increase in Bob1 expressing cells in RA synovitis and the resistance of Bob1-defecient mice to development of CIA indicate that Bob1/BCMA axis may contribute to humoral autoimmunity in RA. The relationship between an aberrant Bob1 expression and the break of peripheral tolerance in RA is currently under investigation.

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Expression of TLR5 Strongly Correlates with Levels of TNF-a and DAS28 in RA Monocytes and Ligation of TLR5 Induces Angiogenesis in RA. Nathan D. Chamberlain[1], Michael Volin[2], Olga M. Vila[1], Shiva Arami[1], Suncica Volkov[1] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL

Background/Purpose: This study was performed to determine whether expression of TLR5 is associated with Rheumatoid Arthritis (RA) disease activity as well as to examine the role of TLR5 ligation in the pathogenesis of RA.

Methods: Expression of TLR5 was determined in RA and normal (NL) PB monocytes and *in vitro* differentiated macrophages by real-time RT-PCR and/or flow cytometry. Next, linear regression analysis was employed to correlate expression of TLR5 with levels of TNF-a and DAS28 score in RA monocytes from 43–48 patients. Finally, the mechanism by which TLR5 ligation mediates RA pathogenesis was determined by endothelial chemotaxis and tube formation.

Results: We performed microarray studies to identify differentially regulated genes in RA synovial fluid macrophages from active patients and identified Toll like receptor (TLR)5 as one of the most highly upregulated genes in RA synovial fluid macrophages compared to normal macrophages. Using real-time RT-PCR and FACS analysis we confirmed that expression of TLR5 is significantly elevated in RA synovial fluid macrophages (35 fold) and RA monocytes (7 fold) compared to normal counterpart cells. Interestingly, we found that blockade of TLR5 on RA peripheral blood (PB) monocytes greatly reduces RA synovial fluid mediated TNF-a transcription by 80% suggesting that there are endogenous TLR5 ligands expressed in the RA synovial fluid that are crucial for joint TNF-a modulation. Since TNF-a stimulation is also capable of upregulating TLR5 levels there is a positive feedback modulation in RA monocytes between TNF-a and TLR5 ligation and expression. We found that patients with higher expression of TNF-a expressed elevated levels of TLR5 (R^2=0.79, p=3.6×10^{-7}) in RA monocytes and the concentrations of TLR5 and TNF-a strongly correlated with increased disease activity as determined by examination of 28 defined joints (DAS28) (correlation of TLR5 with DAS28; R^2=0.75) (correlation of TNF-a with DAS28; R^2=0.58). Since our previous studies demonstrated that TLR5 expression is elevated on RA synovial tissue endothelial cells compared to control tissue we asked whether ligation of this receptor induces angiogenesis and if TLR5 endogenous ligands present in RA synovial fluid play a role in this process. We found that when endothelial cells were exposed to a dose response of flagellin, a TLR5 agonist, migration of endothelial cells was induced at concentrations ranging from 0.1 to 100 ng/ml (p<0.05). Further, incubation of endothelial cells with neutralizing antibody to TLR5 significantly suppressed RA synovial fluid endothelial migration and tube formation suggesting that the RA synovial fluid contains TLR5 endogenous ligands that are chemotactic for TLR5+ endothelial cells.

Conclusion: Our observations highlight that there is a strong correlation between TNF-a and TLR5 expression with disease activity in RA monocytes suggesting that TLR5 may be a TNF-a responsive gene that is linked to RA progression through induction of angiogenesis.

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ACR Concurrent Abstract Session
Antiphospholipid Syndrome
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

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Establishment of Standardized International Units for IgG Anti-$\beta_2$glycoprotein Antibody Measurement. Rohan Willis[1], Claudia Grossi[2], Gabriella Lakos[3], Pier Luigi Meroni[4], Maria Borghi[2], Luis R. Lopez[5], Corina Dima[6], Marius C. Teodorescu[7], Nicholas Ozarka[7], Matthias Kast[8], Nina Olschowka[8], Alfredo Villarreal[9], Maria Crisostomo[10], Mike Watkins[9], Wendy Vandam[11], Tony Prestigiacomo[10], Josep Puig[12], Kerrie Jaskal[13], Roger Walker[10], Sarah Paul[9], T. Buckner[14], Fernando S. Cavalcanti[12] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Lab of immunology, IRCCS Istituto Auxologico Italiano, Milano, Italy, [3]INOVA Diagnostics, Inc., San Diego, CA, [4]Division of Rheumatology - Istituto G. Pini, University of Milan, Milano, Italy, [5]Corgenix Inc, Broomfield, CO, [6]Theratest Laboratories Inc, Lombard, IL, [7]TheraTest Laboratories Inc, Lombard, IL, [8]Phadia Thermofisher, Freiburg, Germany, [9]Bio-Rad Laboratories, Benicia, CA, [10]Bio-Rad Laboratories, Hercules, CA, [11]Bio-Rad Laboratories, Hercules, [12]Biokit, Barcelona, Spain, [13]Instrumentation Laboratories, Bedford, MA, [14]Corgenix, Broomfield, CO

Background/Purpose: Despite numerous efforts aimed at the standardization of assays for detection of anti-β_2Glycoprotein I (aβ_2GPI) antibodies, there are still concerns, including the type and source of properly validated calibrant and reference material and the lack of universal units of measurement. Based on recommendations of an international task force at the 13th Congress on Antiphospholipid Antibodies, a project was started with the goals of establishing a

reference preparation (RP) and international consensus units (IU) for the measurement for IgG aβ_2GPI antibodies.

Methods: Whole IgG fractions were affinity-purified (AP) from sera of 2 primary Antiphospholipid syndrome patients with high IgG ab$_2$GPI levels using a Protein G Sepharose column. Pooled IgG fractions were further AP using an affinity column coupled to β_2-GPI, and the protein concentration of the AP material was determined using two methods, and a value based on the definition that 1 IU/ml equates to 1 μg/ml of AP aβ_2GPI, was assigned. A reference preparation (RP) serum created from sera taken from the 2 original PAPS patients was then assigned an IU value based on repeated testing using original AP material as a calibrator. RP was sent to six commercial companies for testing in their respective kits (eight total) according to an approved protocol to enable evaluation of linearity and unit equivalency, along with a set of 30 samples (APS samples and healthy controls) to allow for commutability studies to be done. Companies (and kits) included INOVA Diagnostics (QUANTA Lite® β_2GPI IgG ELISA, QUANTA Flash® β_2GPI IgG chemiluminescent assay), Bio-Rad Laboratories (BioPlex® 2200 APLS IgG Kit, Anti-β_2Glycoprotein I IgG EIA Test Kit) TheraTest (EL-b$_2$GPI IgG kit), Corgenix (IgG Anti-Beta 2 Glycoprotein I Test Kit), Phadia (EliA β2-Glycoprotein I IgG on Phadia® 250) and Instrumentation Laboratory (HemosIL® AcuStar anti-β_2Glycoprotein-I IgG).

Results: The pooled AP material had a protein concentration of 103.1 μg/ml (OD280nm) and 108.8 μg/ml (Bradford) and was assigned a value of 100 IgG aβ_2GPI IU/ml. RP had a value of 270 IgG aβ_2GPI IU/ml. The R^2 values of the regression lines of the RP for all kits were >0.95. The value of the RP in the various kit units ranged from 115 to 9993.1. Results of correlations between kits with commutability samples are shown in Table 1 (kit units and international units).

Table 1. Correlation of commutability sample values among various ab$_2$GPI assays

		IL AcuStar	INOVA BIO-FLASH	INOVA ELISA	Bio-Rad ELISA	Bio-Rad BioPlex	Theratest	Corgenix	Phadia	
	IL AcuStar		.996	.961	.940	.990	.978	.966	.950	
	INOVA BIO-FLASH	0.996		.959	.935	.988	.971	.961	.939	
CORRELATIONS OF COMMUTABILTY SAMPLES IN INTERNATIONAL UNITS	INOVA ELISA	0.938	0.933		.896	.942	.987	.925	.956	CORRELATIONS OF COMMUTABILITY SAMPLES IN KIT UNITS
	BioRad ELISA	0.972	0.963	0.897		.929	.914	.915	.846	
	Bio-Rad BioPlex	0.948	0.945	0.810	0.920		.960	.963	.933	
	Theratest	0.964	0.958	0.978	0.936	0.891		.949	.958	
	Corgenix	0.974	0.968	0.911	0.993	0.907	0.939		.905	
	Phadia	0.953	0.944	0.944	0.898	0.878	0.958	0.903		

For values in table: p<0.001

Conclusion: Establishment of equivalency between kit units and IU value of RP was successful. The RP demonstrated excellent linearity and was commutable in the various aβ_2GPI IgG assays and is therefore adequate to be used as a reference material. Expressing results in the new IU instead of arbitrary kit units illustrated the comparability of the results obtained in the different kits. These studies contribute significantly to the much-needed standardization of aβ_2GPI immunoassays.

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Pro-Inflammatory and Pro-Thrombotic Markers in Persistently Antiphospholipid Antibody-Positive Patients with/without Systemic Lupus Erythematosus. Gurjot Basra[1], Doruk Erkan[2], Rohan Willis[1], JoAnn Vega[2], Ana Laura Carrera Marin[1], Patricia Ruiz Limon[1], Vijaya L. Murthy[1], Shraddha Jatwani[1], Neha Dang[1], Emilio B. Gonzalez[1] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: Pro-inflammatory/thrombotic biomarkers (BMR), which are associated with aPL-mediated pathogenic effects in vitro/vivo, are also increased in aPL-positive patients. Here we examined whether those BMR are differentially upregulated in persistently aPL-positive patients with or without systemic lupus erythematosus (SLE).

Methods: In this cross-sectional study, persistently aPL-positive patients (aCL IgG/M≥40 GPL/MPL, aβ_2GPI≥20U IgG/M, and/or positive lupus anticoagulant [LA] test on 2 occasions at least 12w apart) were identified from our open-label prospective mechanistic pilot study of fluvastatin (selected exclusion criteria for this trial were pregnancy, prior statin use, prednisone

>10 mg/day, and immunosuppressive use [except hydroxychloroquine]). Control samples (age/sex matched) were identified from our databank of healthy people. Interferon (IFN)-α, Interleukin (IL)1b, IL6, IL8, inducible protein (IP)10, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), and soluble CD40 ligand (sCD40L) levels were determined by the MILLIPLEXMAP human cytokine/chemokine assay (Millipore, Billerica, MA) in the serum of patients and controls. Plasma samples were used to detect sTF using a chromogenic assay. aCL (IgG, IgM and IgA), aβ_2GPI (IgG, IgM and IgA), soluble intercellular cell adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin (E-sel) were evaluated by ELISA. Mann-Whitney Rank Sum test was used to analyze the data for differences between patient subgroups and controls; Kruskal-Walllis One Way Analysis of Variance was used to compare medians of BMR among groups.

Results: 41 persistently aPL-positive patients (mean age: 44.6±13.6 y; female: 70%; primary APS; 18, SLE/APS: 7; Primary aPL [no history of thrombosis or pregnancy morbidity]: 9; and SLE/aPL: 7) and 30 healthy controls were included in this analysis. All APS patients had history of thrombosis except two SLE/APS patients who had only obstetric APS. Median levels of: a) all BMR except IL-8, sVCAM-1, and sE-sel was significantly higher in all groups combined when compared to the controls; b) IL-8, TNF-α, and IP-10, were significantly higher in Primary APS, SLE/APS and SLE/aPL when compared to primary aPL; c) VEGF, sICAM-1, and sVCAM-1 were significantly higher in Primary APS when compared to the other groups; and d) sTF was elevated in all subgroups (Table). There was no difference in aCL/aβ_2GPI titers among the groups.

Biomarkers (median)	Controls n: 30	Combined n:41	Primary APS n:18	SLE/APS n:7	Primary aPL n:9	SLE/aPL n:7
IL-6 (pg/ml)	0.7	38.0*	31.2*	12.2*	0.4	2.7*
IL-1b (pg/ml)	0.3	4.7*	3.0*	11.4*	0.3	0.5
IL-8 (pg/ml)	27.4	42.6	24.5	27.4	7.2	21.6
VEGF (pg/ml)	88.3	225.1*	242.2	109.1	74.6	67.2
TNF-α (pg/ml)	0.5	29.9*	21.5*	11.6*	8.9*	53.9
IFN-α (pg/ml)	0.1	12.9*	10.1	0.3	0.3	13.2
IP-10 (pg/ml)	96.2	584.4*	427.2*	656.2*	249.7	472.5*
sCD40L (pg/ml)	16.4	230.1*	276.5*	145.6*	149.7*	76.9*
sTF pM	13.0	134*	153.6*	329.2*	190.4*	102.1*
sICAM-1 (pg/ml)	9.5	151.3*	281.6*	55.1*	163.5	2.8
sVCAM-1 (pg/ml)	33.7	41.9	1128.4*	156.4	321.3	41.1
sE-sel (pg/ml)	10.1	14.1	27.7*	14.7	10.9	4.1
# of BMR elevated		9/12	9/12	7/12	3/12	4/12

* significantly different from the median of controls (p<0.05)

Conclusion: Our study suggests that the pro-inflammatory and prothrombotic markers are differentially upregulated in persistently aPL-positive patients with or without vascular events and/or SLE. These findings have implications in the pathophysiology of APS and the risk-stratification of aPL-positive patients.

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An Open-Label Prospective Pilot Mechanistic Study of Fluvastatin in Persistently Antiphospholipid Antibody-Positive Patients. Doruk Erkan[1], Rohan Willis[2], JoAnn Vega[1], Vijaya L. Murthy[2], Ana Laura Carrera Marin[2], Gurjot Basra[2], Patricia Ruiz Limon[2], Emilio B. Gonzalez[2] and Silvia S. Pierangeli[2]. [1]Hospital for Special Surgery, New York, NY, [2]University of Texas Medical Branch, Galveston, TX

Background/Purpose: Antiphospholipid antibodies (aPL) induce a pro-inflammatory and pro-thrombotic state by upregulating various cytokines, chemokines, and tissue factor (TF). Fluvastatin reduces TF expression and decrease thrombogenic effects of aPL in vitro and in mice. The purpose of this prospective pilot study was to examine the effects of fluvastatin on pro-inflammatory and pro-thrombotic biomarkers (BMR) in persistently aPL-positive patients.

Methods: Persistently aPL-positive patients (IgG/M aCL≥40 GPL/MPL, IgG/M aβ_2GPI≥20U, and/or positive lupus anticoagulant (LA) test on 2 occasions at least 12w apart) received fluvastatin 40 mg daily for at least 3 months. At 3 months, patients were instructed to stop fluvastatin and they were followed for another 3 months. Serum samples were collected at baseline and monthly thereafter for 6 months. Selected exclusion criteria were pregnancy, statin use, prednisone >10 mg/day, and immunosuppressive use (except hydroxychloroquine [HCQ]). Interferon (IFN)-α, Interleukin (IL)1b,

IL6, IL8, inducible protein (IP)10, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), and soluble CD40 ligand (sCD40L) levels were determined by the MILLIPLEXMAP human cytokine/chemokine assay (Millipore, Billerica,MA) in serum of patients and controls. Plasma samples were used to detect sTF using a chromogenic assay. aCL IgG/M/A, aβ_2GPI IgG/M/A, soluble intercellular cell adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin (E-sel) were evaluated by ELISA. We used Spearman test to analyze the significance of monthly changes in BMR levels.

Results: Of 41 patients recruited, 24 completed the study (mean age: 44.6 + 13.6y; female: 70%; Primary APS: 8, SLE/APS: 7, Primary aPL: 5; SLE/aPL: 4; HCQ: 61%; and Anticoagulation: 43%). The early withdrawal reasons for 15/41 patients were: 6 lost to follow-up or refused further treatment without adverse events; 4 stopped treatment due to myalgia (normal muscle/liver enzymes); 3 wanted to continue fluvastatin after 3 months; 1 screen failure after the baseline visit; and i stopped treatment due to insomnia. The table shows the number of patients with elevated BMR (above the assay cut-off) at baseline as well as follow-up BMR levels during and after fluvastatin. The levels of 6/12 (50%) BMR (IL-6, IL-1b, VEGF, TNF-α, IP-10, sCD40L, and sTF) significantly decreased with fluvastatin, followed by significant increases after stopping the treatment. Of note, aCL/aβ_2GPI and LA tests remained unchanged throughout the study.

Biomarker (BMR)	# of Patients with Elevated BMR at BL	# of Patients with Decreased BMR after Fluvastatin	Mean+SD Maximum BMR reduction with fluvastatin	# of Patients with Increased BMR After Stopping Fluvastatin	Mean+SD maximum BMR Increase After Stopping Fluvastatin
IL-6	17/24 (71%)	12/17 (71%)	80.5 ± 25.3*	9/12 (75%)	56.7 ± 34.5
IL-1b	11/24 (45%)	6/11 (54%)	67.5 ± 24.5*	5/6 (83%)	89.0 ± 23.5*
IL-8	6/24 (25%)	5/6 (83%)	33.9 ± 11.0	3/5 (60%)	45.6 ± 34.1
VEGF	13/24 (54%)	10/13 (77%)	87.8 ± 13.0*	5/10 (50%)	57.8 ± 28.5*
TNF-α	23/24 (96%)	9/23 (39%)	87.3 ± 45.8*	6/9 (67%)	90.3 ± 4.5*
IFN-α	9/24 (37%)	8/9 (89%)	71.8 ± 15.4*	6/8 (75%)	56.7 ± 21.0
IP-10	19/24 (79%)	12/19 (63%)	65.4 ± 13.9*	8/12 (67%)	87.5 ± 14.5*
sCD40L	22/24 (92%)	10/22 (45%)	68.0 ± 21.0*	9/10 (90%)	90.6 ± 4.3*
sTF	24/24 (100)	20/24 (83)	57.0 ± 29.9*	13/20 (65%)	80.4 ± 10.3*
sICAM-1	9/24 (37)	7/9 (77)	45.6 ± 35.9	1/7 (14%)	23.4 ± 12.0
sVCAM-1	15/24 (62)	4/15 (27)	38.7 ± 34.6	3/4 (75%)	47.6 ± 10.4
sE-sel	8/24 (33)	2/8 (25)	43.8 ± 36.1	0/2 (0)	N/A

* p<0.05

Conclusion: Our pilot study demonstrating that fluvastatin can reversibly reduce the pro-inflammatory and prothrombotic biomarkers in persistently aPL-positive patients with or without SLE provide the basis for future larger randomized-control trials to examine the effects of the statins on the aPL-induced biomarkers as well as on the aPL-related clinical manifestations.

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The Estimated Prevalence of Antiphospholipid Antibodies in General Population Patients with Pregnancy Loss, Stroke, Myocardial Infarction, and Deep Vein Thrombosis. Laura Andreoli[1], Alessandra Banzato[2], Cecilia B. Chighizola[3], Guillermo J. Pons-Estel[4], Guilherme Ramires de Jesus[5], Michael D. Lockshin[6], Doruk Erkan[6] and On Behalf of APS Action[7]. [1]Rheumatology and Clinical Immunology, University of Brescia, Brescia, Italy, [2]Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua, Italy, [3]Istituto Auxologico Italiano, University of Milan, Milan, Italy, [4]Department of Autoimmune Diseases, Institut Clìnic de Medicina i Dermatologia, Hospital Clìnic, Barcelona, Spain, [5]Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [6]Hospital for Special Surgery, New York, NY[7].

Background/Purpose: Anti**P**hospholipid **S**yndrome **A**lliance For **C**linical **T**rials and Internati**O**nal **N**etworking (APS ACTION) is an international research network that has been created specifically to design and conduct well-designed, large-scale, multi-center clinical trials in persistently antiphospholipid antibody (aPL)-positive patients. One of the first needs of APS ACTION was to know the true prevalence of aPL in the general population with pregnancy loss (PrL), stroke (ST), myocardial infarction (MI) and deep venous thrombosis (DVT).

Methods: The search for "aPL" and multiple keywords regarding the outcomes of interest was completed in PubMed; additionally, review articles were searched. A total of 108 full-text papers were collected and analyzed for the type of outcome, the aPL tests used (criteria tests *vs.* non criteria), the definition of "positive aPL" (low, medium, high, other), the confirmation of aPL (at least 6–12w apart), and the prevalence of positive aPL in the study population (defined by sex and age range). The mean, median, and range of the aPL prevalence were calculated separately for papers with and without aPL confirmation. The incidence of PrL, ST, MI and DVT in the general US population was retrieved from official sources.

Results: Of 108 papers, the outcome of interest was early/late PrL in 32, ST in 31, MI in 24, and DVT in 21. Despite the limitations of the literature, the table demonstrates the estimated prevalence and incidence of aPL-related events. These limitations were: a) approximately 60% of the papers were published between 1984 and 2000; b) the number of aPL criteria tests used was single test in 45 (36.6%), two tests in 65 (52.8%), and 3 tests in 13 (10.6%); c) anticardiolipin and/or anti-β2glycoprotein-I ELISA cut-off was not available in 10% of the papers and "low titer" (<20U) was used in 36% of the papers; d) the method of reporting the cut-off for anti-β2GPI was quite heterogeneous, reflecting the lack of international reference units; e) the confirmation of aPL was performed only in 24 papers (19.5%); and f) half of the studies were not designed to answer our research question (case-control:30%; retrospective cohort/case series:20%).

	Estimated aPL Prevalence (%) (Literature Review) Mean, Median (Range)			US Incidence/y*	Estimated US Incidence/y
	aPL Confirmation (−)	aPL Confirmation (+)	Average (median)	All Events	aPL-associated Events
PrL	12, 9 (0–48)	14, 14 (0–25)	12%	526,000	~ 60,000
ST	23, 21 (0–49)	10, 6 (0–53)	14%	795,000	~ 120,000
MI	14, 8 (3–39)	17, 17 (14–21)	13%	935,000	~ 120,000
DVT	14, 11 (0–35)	10, 9 (5–19)	10%	300,000	~ 30,000

* Source: **PrL:** Macklon N, Hum Reprod Update 2002;8:333; Stephenson MD. Fertil Steril 1996;66:24; National Vital Statistics for the year 2009. **ST, MI, DVT:** "Heart Disease and Stroke Statistics -2012 Update", Circulation 2012;125:e12; White RH. Circulation 2003;107:I4; 2010 US Census.

Conclusion: It is difficult to determine the prevalence of a "clinically significant aPL profile" in the general population patients with pregnancy loss and thrombosis due to the lack of robust data. Pending more rigorous data collection, our best estimates of the incidence of aPL-associated events should be confirmed with appropriately sampled and designed population studies. One of the goals of APS ACTION is to improve upon existing aPL prevalence studies.

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Efficacy of Aspirin for the Prevention of the First Thrombo-Embolic Events in Patients with Antiphospholipid Antibodies: A Meta-nalysis of Literature Data. Laurent Arnaud[1], Alexis Mathian[1], Amelia Ruffatti[2], Maria Tecktonidou[3], Ricard Cervera[4], Ricardo Forastiero[5], Vittorio Pengo[6], Marc Lambert[7], Stephane Zuily[8], Denis Wahl[8] and Zahir Amoura[1]. [1]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [2]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy, [3]First Department of Internal Medicine, School of Medicine, National University of Athens, Athens, Greece, [4]Hospital Clínic of Barcelona, Barcelona, Spain, [5]Favaloro University, Argentina, [6]Clinical Cardiology, Department of Cardiac Thoracic and Vascular Sciences, University of Padova, Padova, Italy, [7]Internal Medicine Department, Universitary hospital, Lille, France, [8]Nancy University Hospital, Université de Lorraine & INSERM U961, Vandoeuvre-Les-Nancy, France

Background/Purpose: Whether aspirin is needed in patients with antiphospholipid antibodies (aPL+) for prevention of a first thrombotic event is controversial. The aim of this metaanalysis was to determine whether aspirin had a protective effect in aPL+ patients with no history of thrombosis.

Methods: Both observational (either prospective or retrospective) and interventional studies were selected if they assessed the incidence of the

first thrombosis in patients with aPL, either treated with aspirin or not, were included. Data sources were MEDLINE, Embase, Cochrane Library, hand search, contact with investigators, and reference lists of studies, without language restrictions. Data on study and patient characteristics, risk estimates, and study quality were independently extracted by 2 investigators. Pooled effect estimates were obtained by using random-effect models according to the DerSimonian and Laird method.

Results: Of 342 identified abstracts, 9 primary studies (8 observational and 1 interventional) met inclusion criteria, including 1136 aPL patients and 133 thrombotic events. Compared with aPL+ patients without aspirin (n=556), the overall pooled odds ratio for the risk of first thrombosis in aPL+ patients treated with aspirin (n=580) was 0.48 (95%CI: 0.24 to 0.93), with significant heterogeneity across studies (I^2=53%, p=0.03). Subgroup analysis according to the type of study suggested a protective effect of aspirin when considering only retrospective (OR: 0.25 [0.15–0.43]) but not prospective (OR: 0.84 [0.46–1.54]) studies. Subgroup analysis according to the type of thrombotic event suggested a protective effect of aspirin when considering only arterial (OR: 0.48 [0.28–0.83]) but not venous (OR: 0.52 [0.24–1.14]) thrombosis.

Conclusion: This metaanalysis suggests that aspirin has a protective effect for the risk of first thrombosis among aPL+ patients. Significant heterogeneity was found across included studies, with subgroup analyses showing a protective effect in retrospective but not in prospective studies, as well as for arterial but not venous first thrombotic events. A collaborative metaanalysis of individual patient data is currently underway to clarify these findings at patient level by taking into account the various pathogenic backgrounds as well as potential confounding factors.

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2460

Dual Antiplatelet Therapy As Prophylaxis of Recurrent Arterial Thrombosis in Patients with antiphospholipid Syndrome. Yuichiro Fujieda, Olga Amengual, Toshiyuki Watanabe, Michihito Kono, Yusaku Kanetsuka, Takashi Kurita, Toshio Odani, Kotaro Otomo, Toshiyuki Bohgaki, Tetsuya Horita, Shinsuke Yasuda and Tatsuya Atsumi. Hokkaido University, Sapporo, Japan

Background/Purpose: Arterial thrombosis (AT) is a major clinicalmanifestation of the antiphospholipid syndrome (APS). A number of studies have evaluated the rate of recurrent thromboembolism, including arterial and venous thrombosis, after an initial event in patients with APS. Regardless of the presence of warfarin therapy, recurrent events were seen in >11% of APS patients-year. Therefore, the optimal treatment for recurrent AT in patients with APS remains unclear. The purpose of this study is to clarify the efficacy of prophylaxis for recurrent AT in patients with APS.

Methods: This study comprised 82 unselected consecutive APS patients with AT recruited at one single center. Patients were included in this observation study at the initial arterial thrombotic event and followed up. We retrospectively assessed the efficacy and safety of several therapies for the secondary prevention of AT in those patients.The recurrence rate of AT was analyzed as the efficacy outcome and the occurrence of major bleeding event and overall mortality as the safety outcome. The evaluated therapies include warfarin monotherapy (Group1), antiplatelet monotherapy (Group2), combination therapy with warfarin and antiplatelet agent (Group3), and dual antiplatelet therapy (Group4).

Results: Among all the patients, 67 (76%) were females, the mean age was 44 years (range 15–74 years) and 51 (62%) were diagnosed as systemic lupus erythematosus. The mean follow up period was 8.5 years (range 2–22 years). Thirteen (16%) patients were in Group1, 35 (43%) in Group2, 21 (26%) in Group3, and 13 (16%) in Group4. Antiplatlet therapy consisted on aspirin, ticlopidine, clopidogrel, cilostazol, or others such as dipyridamole, beraprost and sarpogrelate hydrochloride. Distribution of antiplatelet agents in each group is shown in Table. Dual antiplatelet treatment comprised 7 (54%) patients on aspirin and ticlopidine/clopidogrel, 3 (23%) on aspirin and others, 2 (15%) on aspirin and cilostazol, 1 (8%) on cilostazol andticlopidine.

Thrombotic events recurred in 25 patients (3.4 100 patient-year). No recurrences were observed in the Group 4. However, a high incidence of recurrences rate observed in Groups 1, 2, 3 (Log-rank p=0.01) (Fig).There was no statistically significant difference in the bleeding events nor in the mortality rate between the study groups.

Table. Distribution of anti-platelet agents in each treatment groups

	Total N = 82	Warfarin monotherapy N = 13	Antiplatelet monotherapy N = 35	Warfarin Antiplatelet combination N = 21	Dual antiplatelet N = 13
aspirin	55 (67%)	-	26 (74%)	17 (81%)	12 (92%)
ticlopridin/clopidogrel	12 (15%)	-	3 (9%)	1 (5%)	8 (62%)
cilostazol	8 (10%)	-	3 (9%)	2 (10%)	3 (23%)
others*	7 (9%)	-	3 (9%)	1 (5%)	3 (23%)

others*: dipyridamole, beraprost and sarpogrelate hydrochloride.
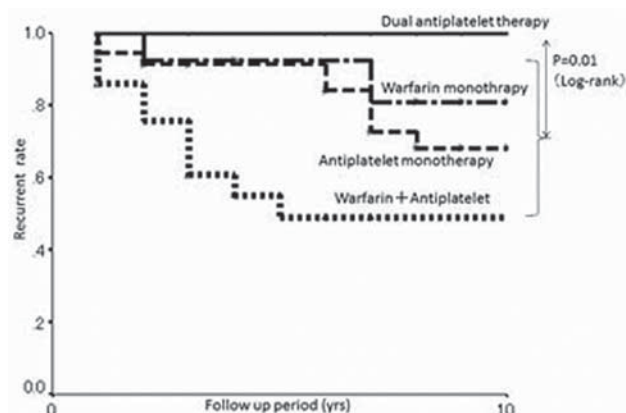
Fig. Kaplan-Meier analysis shows that the treatment with dual antiplatelet therapy was more effective for the prevention of thrombotic recurrences than other therapies (Log-rank p=0.01).

Conclusion: Dual antiplatelet therapy may be an effective therapy for prevention of recurrent arterial thrombosis in patients with APS.

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ACR Concurrent Abstract Session
Epidemiology and Health Services Research IV:
Outcomes and Costs in Rheumatic Disease
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

2461

Cost-Effectiveness of Systemic Therapies for Acute Gouty Arthritis. Kimberly Reiter[1], Jeremy Goldhaber-Fiebert[2] and Eswar Krishnan[3]. [1]Stanford University School of Medicine, Palo Alto, CA, [2]Stanford, Stanford, CA, [3]Stanford University, Stanford, CA

Background/Purpose: Rising prevalence has led to increased demand for newer and potentially costly treatments for acute gouty arthritis, but few studies comparing effectiveness and costs of both older and novel treatments exist to guide best clinical practice. We aimed to assess the effectiveness and cost-effectiveness of currently available drug classes (non-selective and COX-2 selective non-steroidal anti-inflammatory drugs, colchicine, and systemic corticosteroids), as well as a long-acting biologic agent for the treatment of acute gout flare.

Methods: We modeled acute gout flare in 50 year old adult men with definite gout and no contraindications to considered therapies. Our decision analytic model incorporated quality of life impact of the flare, and costs and health effects of drugs and drug-related adverse events. The perspective was that of a third party payer, with an 8 week time horizon. Probabilities of response to therapies and adverse events, health state utilities, and costs in 2010 U.S. dollars were informed by published literature, U.S. hospital statistics, and payment algorithms that may be employed by a third party payer. We utilized published data for canakinumab (Ilaris®, Novartis) as representative of a long-acting biologic drug, although this drug is not approved for use in gout. Outcomes were measured in quality-adjusted-life-days (QALDs) and quality-adjusted-life-years (QALYs).

Results: Literature review revealed relatively small differences in overall effectiveness between treatments, in spite of a wide range of costs. Steroids provided 47.17 QALDs, colchicine 47.39 QALDs, and biologic 47.57

QALDs. After accounting for toxicities and for the cost of COX-2 selective NSAIDs, both NSAID sub-classes were more expensive and less effective than other non-biologics. Intramuscular steroid cost $11,935 per QALY over no treatment, and branded colchicine cost $18,234 per QALY compared to steroid. The biologic drug cost over $22 million per QALY gained. Results were sensitive to untreated flare duration, probability of first-day drug response, and drug costs. When priced as an unbranded product, colchicine offered greater benefits at a lower cost than all other non-biologic drugs. A scenario analysis assuming equivalent efficacy of oral prednisone to intramuscular steroid showed prednisone to cost less than $3,000 per QALY, in which case branded colchicine exceeded a traditional willingness-to-pay threshold of $50,000 per QALY.

Conclusion: Compared to moderate dose intramuscular corticosteroid, colchicine provides reasonable value for money in the treatment of acute gout flare. When priced as an unbranded product, it is more effective and less expensive than all other options. If oral prednisone is similar in effectiveness to intramuscular steroid, then it is most cost-effective and branded colchicine costs much more for its incremental benefits. At current prices, biologic therapy does not provide additional benefits commensurate with its higher cost.

Limitations: These results apply only to uncomplicated gout among men in outpatient settings. Non-canakinumab biologics may have a different cost-effectiveness profile.

2462

Projecting the Direct Cost Burden of Osteoarthritis in Canada Using a Population-Based Microsimulation Model From [2010–2031]. Behnam Sharif[1], Jacek A. Kopec[1], Mushfiqur Rahman[1], Nick Bansback[2], Eric C. Sayre[1], Philippe Finès[3], Hubert Wong[2] and Aslam H. Anis[2]. [1]Arthritis Research Centre of Canada, Vancouver, BC, [2]St Paul's Hospital, University of British Columbia, Vancouver, V6Z 1Y6, Canada, Vancouver, BC, [3]Statistics Canada, 150 Tunney's Pasture Driveway, Ottawa, ON, Canada, Ottawa, ON

Background/Purpose: POHEM-OA (Population Health Model-Osteoarthritis) is a population-based microsimulation model that uses Canadian Community Health Survey-2001 to generate the initial population and models every individual's life history in terms of osteoarthritis (OA) diagnosis and treatment for the entire Canadian population. The objective of this study was to incorporate treatment and other costs of OA into POHEM-OA to project the future direct cost burden of OA in Canada for the years 2010 to 2031.

Methods: Average healthcare treatment costs were estimated from the British Columbia (BC) linked health administrative database spanning 1986/87–2003/03 that included physician visits, surgical procedures, medication, and all hospital admissions covered by the Medical Services Plan (MSP) of BC. Surgical procedures related to OA were micro-costed based on unit costs available from the fully allocated St. Paul's hospital (Vancouver) cost model. Since the number of hip and knee replacements almost doubled in the last 10 years, replacement rates were recalibrated and a time trend was introduced based on the Canadian Joint Registry database from 1997–2007. Average drug costs (both over-the-counter and prescription drugs) were estimated from the PharmaNet (BC) database in 2003 and the National Population Health Survey for four main types of OA-related drugs (acetaminophen, NSAID, coxibs and opioids). Each patient was assigned a cost variable based on sex, age category, OA stage (defined by OA diagnosis, orthopedic surgeon visit, primary replacement surgery, and revision), and time in each stage. All costs were implemented in POHEM according to two categories: "ongoing costs" as they accumulated based on the person-years of each individual staying in a given OA stage and "event-based costs" for hip and knee replacement surgeries. A 5% annual discount rate was applied.

Results: The total direct costs of OA in Canada were estimated to rise from $1.8 billion dollars in 2010 ($0.7 and $1.1 billion dollars for males and females, respectively) to $8.1 billion dollars in 2031 ($3.3 and $4.8 billion dollars for males and females, respectively) (Figure 1). This rise is in part attributable to an increase in the number of persons living with OA, due to increasing OA incidence and general longevity. OA prevalence is projected to increase from 3 million (14%) in 2010 to 5.8 million (18%) in 2031 (Figure 1). Other contributing factors are the increasing number of total knee/hip replacements, greater use of services by patients treated surgically, and the aging of the OA population.

Figure 1. Sex-specific direct costs and prevalence of OA in [2010,2031]
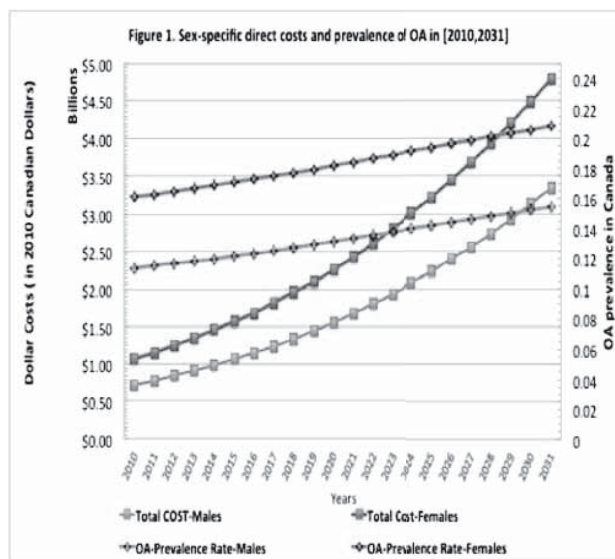
Conclusion: This population simulation model predicts a 350% increase in the total costs of OA over the next 20 years. The model will be helpful in the estimation of the economic consequences of potential changes in the prevailing model of care for persons with OA.

2463

Cost-Effectiveness of Tocilizumab Monotherapy Vs. Adalimumab Monotherapy in the Treatment of Severe Active Rheumatoid Arthritis. Josh J. Carlson[1], Sarika Ogale[2], Fred Dejonckheere[3] and Sean Sullivan[1]. [1]University of Washington, Seattle, WA, [2]Genentech, South San Francisco, CA, [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background/Purpose: The ADACTA trial found that biologic naïve patients with severe active RA who are methotrexate (MTX) intolerant or in whom continued MTX treatment is inappropriate, achieved a significant benefit after 24 weeks on tocilizumab (TCZ) 8mg/kg IV every 4 weeks monotherapy vs. 40mg adalimumab (ADA) every 2 weeks monotherapy. The objective of our study was to estimate the cost-effectiveness of TCZ vs. ADA used as monotherapy (mono) for RA from the U.S. payer perspective.

Methods: We compared treatment initiation with TCZ (8mg/kg every 4 weeks) mono vs. two different dose regimens of ADA mono: 1) 40mg weekly, 2) 40mg every 2 weeks. Efficacy for TCZ and ADA every 2 weeks was obtained from ADACTA. Efficacy for ADA weekly was estimated by adjusting upward the ADA response in ADACTA, using a ratio of response rates for ADA weekly:ADA every 2 weeks derived from the 2004 van de Putte et al. study, which evaluated both doses of ADA mono. For the 6-month trial period, we calculated the incremental cost per additional ACR20, 50, 70 responder, and low disease activity score (LDAS) achieved for TCZ vs. ADA ("6-month model"). We also used a patient-level simulation model (10,000 patients, 2,000 simulations) to estimate the lifetime incremental cost per quality-adjusted life year (QALY) of initiating treatment with TCZ vs. ADA mono ("life-time model"). In this model, both drugs are followed by an etanercept-certolizumab-palliative care sequence. Non-responders discontinue at 6 months; responders experience a constant probability of discontinuation thereafter. Discontinued patients go to the next treatment in the sequence. Trial-based ACR responses are linked to changes in HAQ scores at 6 months. HAQ remains constant while on biologics and is mapped to utility to estimate QALYs using pooled data from TCZ trials (Diamantopoulos 2012). Costs are derived from published sources and include drug treatment, monitoring, and direct medical resource utilization (derived from HAQ score; Kobelt 1999). Costs and QALYs were discounted at 3%. Sensitivity analyses were performed to test the robustness of the model results.

Results: In the 6-month and lifetime models, TCZ 8mg/kg mono had higher ACR response rates and QALYs, respectively, and lower costs

compared with ADA mono 40mg weekly (Table). Compared with ADA 40mg every 2 weeks, the 6-month incremental cost for TCZ ranged from $2,077 per additional LDAS achiever to $4,509 per additional ACR70 responder; in the lifetime model the incremental cost-effectiveness ratio was $49,195/QALY. Based on one-way sensitivity analyses, model results were most sensitive to changes in drug costs and ACR response rates.

	TCZ Monotherapy	ADA Monotherapy	Difference: TCZ Mono-ADA mono	Incremental Cost-effectiveness Ratio (ICER)
Comparison 1: Life-time Cost/QALY for TCZ Mono 8mg/kg every 4 weeks vs. ADA Mono 40mg every week				
Costs	$202,707	$270,779	($68,072)	
Life-years	16.13	16.09	0.04	
QALYs	7.49	7.35	0.14	**TCZ Dominates ADA weekly (more effective, less costly)**
Comparison 1a: 24-week ICERs for clinical outcomes- TCZ Mono 8mg/kg every 4 weeks vs. ADA Mono 40mg every week				
Costs	$13,758	$25,512	($11,754)	
ACR20	65%	57%	8%	**TCZ Dominates ADA weekly (more effective, less costly)**
ACR50	47%	44%	3%	
ACR70	33%	27%	6%	
Comparison 2: Life-time Cost/QALY for TCZ Mono 8mg/kg every 4 weeks vs. ADA Mono 40mg every 2 weeks				
Costs	$202,707	$186,064	$16,643	
Life-years	16.13	16.05	0.08	
QALYs	7.49	7.15	0.34	**$49,195/QALY**
Comparison 2a: 24-week ICERs for clinical outcomes- TCZ Mono 8mg/kg every 4 weeks vs. ADA Mono 40mg every 2 weeks				
Costs	$13,758	$13,100	$658	
ACR20	65%	49%	16%	**$4,220/ACR20 resp**
ACR50	47%	28%	19%	**$3,393/ACR50 resp**
ACR70	33%	18%	15%	**$4,509/ACR70 resp**
LDAS	52%	20%	32%	**$2,077/LDAS**

Conclusion: TCZ (8mg/kg every 4 weeks) mono dominates (more effective and less costly) ADA (40mg weekly) mono and is cost-effective compared to ADA (40mg every 2 weeks) mono, from a US payer perspective, in patients with severe RA for whom methotrexate treatment is not appropriate.

2464

Cost-Sharing and Utilization of Biologic and Non-Biologic Dmards Among U.S. Medicare Beneficiaries with Rheumatoid Arthritis. Chris Tonner, Gabriela Schmajuk and Jinoos Yazdany. University of California, San Francisco, San Francisco, CA

Background/Purpose: While Medicare's Part D prescription drug benefit expanded access to drugs for many patients, it also includes a controversial provision called the "coverage gap" during which beneficiaries are fully responsible for drug costs. As an initial step in understanding the potential impact of cost-sharing for beneficiaries with rheumatoid arthritis (RA), we compared drug utilization and out-of-pocket (OOP) costs for biologic and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) for two groups of patients: those with a coverage gap and those who were not subject to cost-sharing because they were fully eligible for the low-income subsidy program.

Methods: Data derive from Medicare fee-for-service claims files for 2009 for a 5% random sample of beneficiaries linked to the Medicare Part D prescription drug event file. We included 5,808 individuals age ≥ 65 years with ≥ 2 face-to-face encounters for RA who were continuously enrolled in a Part D drug plan and had at least one prescription DMARD event. We compared patients who had no, partial or full coverage during the gap phase to those who were fully eligible for the low-income subsidy program, which is intended to reduce OOP costs for those with low socioeconomic status. We calculated mean annual RA drug OOP costs per patient for the deductible, initial, gap, and catastrophic phases of Part D coverage in two mutually exclusive groups: 1) those using biologic DMARDs (with or without non-biologic DMARDs) and 2) those using only non-biologic DMARDs.

Results: Among the 5,808 RA beneficiaries with Part D drug events for DMARDs in 2009, 679 (12%) were classified as biologic DMARD users, 5,129 (88%) as non-biologic DMARD users and 1,414 (24%) received a low-income subsidy. 44% of biologic DMARD users received a low-income subsidy compared to 22% of non-biologic users. For the low-income subsidy group, OOP annual costs for biologic and non-biologics were low as expected ($26, $11, respectively) and varied little over the benefit phases (range $2–13; see **Figure**). The non-subsidized group's annual OOP costs for biologics and non-biologics were $3,009 and $85, respectively; larger variations in OOP

cost existed for biologics ($21 to $1,805) compared to non-biologics ($21 to $75) across the benefit phases (**Figure**) with the highest costs incurred during the gap phase.

Figure 1. Medicare FFS Beneficiaries Out-of-pocket Costs, by DMARD Type and Part D Benefit Phase
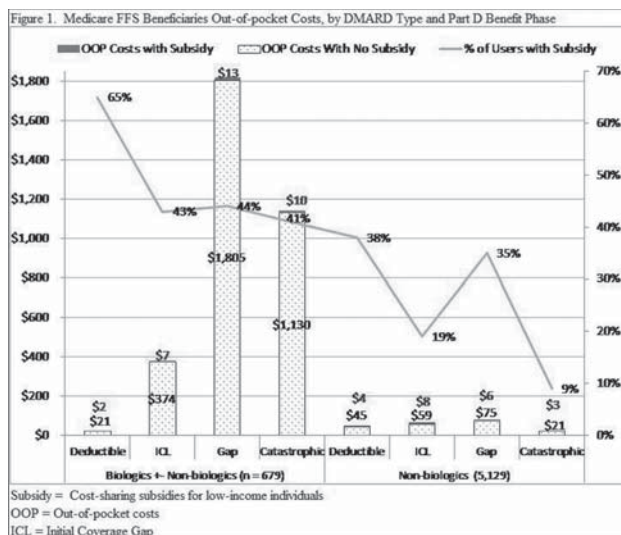
Conclusion: We found that a significantly larger proportion of biologic DMARD users were enrolled in the low-income subsidy program compared to non-biologic DMARD users. Whether the low rates of biologic DMARD use among Medicare beneficiaries who are not eligible for financial subsidies is a consequence of substantial cost-sharing warrants further investigation.

2465

Seroresponse Rates After Influenza Vaccination in Rheumatoid Arthritis Patients Treated with Biological Agents During the 2011–2012 Flu Season. Masatoshi Hayashi[1], Toshihisa Kojima[2], Naoki Ishiguro[3], Tomonori Kobayakawa[1] and Toshihisa Kanamono[1]. [1]Nagano Red Cross Hospital, Nagano, Japan, [2]Nagoya Univeristy, School of Medicine, Nagoya, Japan, [3]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan

Background/Purpose: At present, annual vaccination against influenza is recommended for rheumatoid arthritis (RA) patients. However, whether humoral responses to influenza vaccine are impaired in RA patients treated with biological agents remains controversial. This study aimed to compare seroresponse rates after influenza vaccination in RA patients treated with five biological agents.

Methods: Trivalent influenza subunit vaccines containing A/H1N1, A/H3N2, and B-1 were administered subcutaneously once to 64 RA patients treated with methotrexate (MTX, control, n = 15), infliximab (IFX, n = 12), etanercept (ETN, n = 11), adalimumab (ADA, n = 3), tocilizumab (TCZ, n = 12), or abatacept (ABT, n = 11). We measured antibody titers using hemagglutination inhibition (HI) test at baseline and 4–8 weeks after vaccination. The immunogenicity end points were the proportion of patients with antibody titers of 1:40 or more on HT test and the proportion of patients with either seroconversion or a significant increase in antibody titer.

Results: Table 1 shows baseline characteristics of all the 64 RA patients. Seroconversion and seropositive rates (%) after subcutaneous vaccination were 54.3 and 64.4, respectively, in MTX; 46.2 and 61.1, respectively, in IFX; 73.3 and 87.9, respectively, in ETN; 62.5 and 66.7, respectively, in ADA; 48.3 and 58.3, respectively, in TCZ; and 21.4 and 33.3, respectively, in ABT. Seronegative rates (%) were 45.7 in MTX, 53.8 in IFX, 26.7 in ETN, 37.5 in ADA, 51.7 in TCZ, and 78.6 in ABT (Table 2). Both the decrease in the seroresponse rate after influenza vaccination in the ABT group and increase in the seropositive rate in the ETN group were significant compared with those in the MTX control group ($P < 0.01$) (Table 2). Of the 64 RA patients, only one patient in the MTX group was infected by influenza during this season.

Table 1. Baseline characteristics of 64 RA patients

Agents	Number of patients	Males (%)	Mean age ± SD (years)	PSL rate (%)	Mean usage of PSL ± SD (mg/day)
MTX	15	6.7	68.3 ± 9.8	33.3	4.1 ± 2.2
IFX	12	16.7	61.6 ± 10.8	66.7	3.9 ± 2.1
ETN	11	9.1	58.6 ± 15.6	54.5	3.5 ± 2.4
ADA	3	33.3	69.3 ± 7.0	33.3	5.0 ± 0.0
TCZ	12	25.0	67.7 ± 12.8	58.3	3.6 ± 1.7
ABT	11	27.3	62.0 ± 9.8	81.8	3.8 ± 2.8

RA, rheumatoid arthritis; *SD*, standard deviation; *PSL*, prednisolone; *MTX*, methotrexate; *IFX*, infliximab; *ETN*, etanercept; *ADA*, adalimumab; *TCZ*, tocilizumab; *ABT*, abatacept

Table 2. Seroresponse rates to influenza vaccination in 64 RA patients treated with MTX or five biological agents (192 vaccines)

Agents	Number of vaccinations	Seroconversion (%)	Seropositive (%)	Seronegative (%)
MTX	45	54.3	64.4	45.7
IFX	36	46.2	61.1	53.8
ETN	33	73.3	87.9**	26.7
ADA	9	62.5	66.7	37.5
TCZ	36	48.3	58.3	51.7
ABT	33	21.4**	33.3**	78.6**

**significant difference from MTX (control). **: $P < 0.01$.
RA, rheumatoid arthritis; *MTX*, methotrexate; *IFX*, infliximab; *ETN*, etanercept; *ADA*, adalimumab; *TCZ*, tocilizumab; *ABT*, abatacept

Conclusion: RA patients treated with ABT exhibited compromised immune responses to influenza vaccine compared with those treated with MTX or other biological agents. Therefore, RA patients treated with ABT would benefit from repeated influenza vaccinations.

2466

Pregnancy Outcome in Women Treated with Adalimumab for the Treatment of Rheumatoid Arthritis: The OTIS Autoimmune Diseases in Pregnancy Project. Christina D. Chambers[1], Diana L. Johnson[1], Yunjun Luo[1], Janina L. Jimenez[1], Nicole Mirrasoul[1], Elizabeth Salas[1], Kenneth Lyons Jones[1] and OTIS Research Group[2]. [1]University of California, San Diego, La Jolla, CA, [2]La Jolla

Background/Purpose: The fully human, anti-tumor necrosis factor monoclonal antibody, adalimumab (ADA), is approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease and psoriasis in the United States and elsewhere. The effect of ADA during human pregnancy is unknown. Outcome data collected by the Organization of Teratology Information Specialists (OTIS) provides some information on the safety of ADA when used by pregnant patients with RA.

Methods: In this ongoing, prospective cohort study, women with RA in the U.S. or Canada exposed to ADA during the first trimester of pregnancy were enrolled, followed for 1-year postpartum, and medical records are obtained. Additionally, live born infants receive a dysmorphology exam for both major and minor structural anomalies. Outcomes in the ADA-exposed group are primarily compared with those in a disease-matched group of women without ADA exposure during pregnancy, and secondarily compared to those in a group of pregnant women who neither have autoimmune disease nor have been treated with ADA, all followed in the same manner.

Results: Between November 2004 and May 2012, pregnancy outcomes were collected on 312 women in the ADA RA cohort study. Of these, 69 were in the ADA-exposed cohort, 80 in the disease-matched comparison group, and 163 in the healthy comparison group (Table 1). Spontaneous abortion (SAB) occurred in 10.1% of ADA-exposed, compared to 7.5% and 2.5% of the disease-matched and healthy comparison women respectively. After adjustment for gestational age at enrollment, the relative risk (RR) for SAB in the ADA-exposed group compared to the disease-matched group was not statistically significant (RR 1.33, 95% CI, 0.42, 4.28, p = 0.62). Among all births with known outcome, major birth defects were reported in 4.5% of the ADA-exposed pregnancies, 5.2% of the disease-matched pregnancies, and 6.6% of the healthy comparison pregnancies (p = 1.0 for ADA-exposed vs. disease-matched group). There was no evidence of a pattern of either major or minor structural defects in the ADA-exposed group, nor were

there any statistically significant differences between the ADA-exposed group and the disease-matched comparison group for preterm delivery (p = 0.49), birth weight in full-term infants (p = 0.59) or serious infections (p = 1.0) (Table 1).

Table 1.

Outcome	ADA-Exposed n=69	RA Comparison n=80	p – value ADA-Exposed vs. RA Comparison	Healthy Comparison n=163
Live born - n (%)	60 (87.0)	71 (88.8)	0.80	148 (90.8)
Spontaneous Abortion - n (%)	7 (10.1)	6 (7.5)	0.62**	4 (2.5)
Therapeutic Termination – n (%)	0	0	—	0
Stillbirth - n (%)	0	0	—	0
Lost to follow-up - n (%)	2 (2.9)	3 (3.8)	1.0	11 (6.7)
Preterm live born infants – n (%)	8/59 (13.6)	13/71 (18.3)	0.49	8/148 (5.4)
Birth Weight full term infants – gm (SD)	3292 (489)	3342 (460)	0.59	3468 (503)
Number of infants with major birth defects among live born infants – n/N (%)	3/60 (5.0)	3/71 (4.2)	1.0	10/148 (6.8)
Number of infants with major birth defects among all pregnancies – n/N (%)	3/67 (4.5)	4/77 (5.2)	1.0	10/152 (6.6)
Serious infections in live born infants up to 1 yr of age – n (%)	2 (3.3)	2 (2.8)	1.0	3 (2.0)

* Excludes lost-to follow-up, **After adjustment for gestational age at enrollment

Conclusion: Based on these findings, there are no significant differences for any adverse pregnancy outcome studied in the ADA-exposed group vs. the primary comparison group of women with RA and no ADA exposure. Additionally, there is no evidence of a specific pattern of major or minor malformations in infants born to women with ADA-exposure.

ACR Concurrent Abstract Session
Osteoarthritis - Clinical Aspects II: Structural Risks for Osteoarthritis End-points and Potential Treatments
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

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Tissue Lesions in Osteoarthritis Initiative Participants with Normal X-Rays and Risk Factors for Incident Cartilage Damage. Leena Sharma[1], Ali Guermazi[2], Orit Almagor[1], Michel Crema[3], Dorothy D. Dunlop[1], Frank Roemer[4], Marc C. Hochberg[5], Charles Eaton[6], Joan M. Bathon[7], Rebecca D. Jackson[8], W.J. Mysiw[8], C. Kent Kwoh[9], Michael C. Nevitt[10] and Joan S. Chmiel[1]. [1]Northwestern University, Chicago, IL, [2]Boston University School of Medicine, Boston, MA, [3]Boston University, Boston, MA, [4]Klinikum Augsburg, Augsburg, Germany, [5]University of Maryland, Baltimore, MD, [6]Warren Alpert Medical School at Brown University, RI, [7]Columbia University Medical Center, New York, NY, [8]Ohio State University, Columbus, OH, [9]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [10]University of California-San Francisco, San Francisco, CA

Background/Purpose: Understanding factors underlying initial development of knee OA is crucial to effective prevention strategy design. Our goals were to: 1) determine extent of tissue damage on MRI in knees of persons at higher risk for knee OA and in whom both knee x-rays were normal (KL 0); and 2) evaluate whether presence of any bone marrow lesions (BML), meniscal tears (MT), meniscal extrusion (ME), or hand OA is associated with risk of incident cartilage damage.

Methods: The Osteoarthritis Initiative (OAI) is a cohort study of men

and women, 45–79 years, all with or at increased risk to develop knee OA. 850 participants had had bilateral KL 0 at 12 months (baseline for this study) by centralized reading. On their right knee MRIs, we undertook assessment of cartilage morphology, BML, MT, and ME using a modified MOAKS scoring system. Readers were blinded to hypotheses, clinical data, and KL grade. The definition of hand OA relied upon number of bony enlargements. 12 and 48 month image assessments occurred within an ancillary study; in addition, OAI clinical data V6.2.1 and BU x-ray reading data V1.5 were used. Mulitiple logistic regression models were used to evaluate associations between baseline data and incident cartilage damage by 3 year follow-up; results are reported as adjusted odds ratios (aORs) with 95% CIs.

Results: 850 persons met criteria for inclusion [mean age 59.6 years (8.8, SD), mean BMI 26.7 kg/m^2(4.2), 475 (56%) women]. Among the 850 KL 0 knees, the number with abnormal tissue in one or more subregions at baseline was: 483 (57%) with cartilage damage (full-thickness in 67); 353 (42%) with BML; 180 (21%) with MT; and 117 (14%) with ME. In only 56 (7%) knees were all of these tissues normal. 367 persons [age 58.5 (8.8), BMI 26.4 (4.2), 226 (62%) women] contributed 367 knees with normal cartilage morphology in all regions at baseline. Of the 367, 80 had BML, 45 had MT (32 horizontal, 9 vertical, 4 partial maceration), and 25 had ME. Lesions coexisted in some knees (11 with BML+MT, 7 with BML+ME, and 10 with MT+ME). In separate models, each adjusting for age, gender, BMI, and hand OA, BML [aOR 2.24, 95% CI (1.15, 4.34)] and ME [aOR 2.83, 95% CI (1.03, 7.79)] were each associated with incident cartilage damage. In a model including all covariates, BML continued to be significant [aOR 2.19, 95% CI (1.12, 4.28)], while ME was not quite significant [aOR 2.71, 95% CI (0.97, 7.58)]. Of note, hand OA presence was consistently associated with incident cartilage damage, e.g., in the fully adjusted model, aOR 2.30, 95% CI (1.15, 4.60) for this variable.

Conclusion: Cartilage damage was already present in 57% of right knees from persons without OA in either knee by protocolized x-ray, but at higher risk, suggesting that radiographic studies of incident OA in this population, even restricted to KL 0, are frequently evaluating not incidence but early progression. Among knees with normal cartilage morphology, hand OA, BML, and ME were each associated with an increased risk of incident cartilage damage. While MRI is superior to x-ray, the optimal window for cohort studies to capture the onset of knee OA by MRI may fall earlier in the lifetime of individuals at higher risk than is being evaluated in many current studies. Prevention strategies may be most powerful at this time point.

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Incident Symptomatic Hip Osteoarthritis Is Associated with Differences in Hip Shape by Active Shape Modeling: The Johnston County Osteoarthritis Project. Amanda E. Nelson[1], Felix Liu[2], John A. Lynch[2], Jordan B. Renner[3], Todd A. Schwartz[4], Nancy E. Lane[5] and Joanne M. Jordan[1]. [1]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [2]University of California at San Francisco, San Francisco, CA, [3]University of North Carolina at Chapel Hill Dept of Radiology, Chapel Hill, NC, [4]University of North Carolina Gillings School of Global Public Health, Dept of Biostatistics, Chapel Hill, NC, [5]UC Davis School of Medicine, Sacramento, CA

Background/Purpose: We investigated hip shape by active shape modeling (ASM) as a potential predictor of incident radiographic and symptomatic hip OA (rHOA and srHOA) in a community-based study that includes African American and Caucasian men and women.

Methods: All hips developing rHOA from baseline (Kellgren-Lawrence grade [KLG] 0 or 1, 1991–7) to follow up (KLG >=2, 1999–2004, mean 6 years follow up, 190 hips), and 1:1 control hips (KLG 0 or 1 at both timepoints, 192 hips) were selected in approximately equal numbers from 4 race-by-gender strata. The shape of the proximal femur was defined on a baseline AP pelvis radiograph for all hips by a trained reader (AEN), and 60 landmark points were input into an ASM. The ASM produced a mean shape, plus continuous variables representing independent modes of variation in that shape. The scores for modes which together explained 95% of shape variance (n=14) were simultaneously included in logistic regression models as

independent predictors, with incident 1) rHOA and 2) srHOA (defined as rHOA plus symptoms in the case hip at follow up) as the dependent variables, and adjusted for intra-person correlations. Analyses were adjusted for sex, race, body mass index (BMI), and baseline KLG and/or symptoms. Stratified analyses for sex, baseline KLG and symptoms were performed.

Results: We evaluated 382 hips (Figure) from 342 individuals: 61% women, 83% Caucasians, with a mean age of 62 years and BMI of 29 kg/m^2. No ASM modes were associated with incident rHOA in the sample, or in stratified analyses among women. However, among men only, modes 1 and 2 (53% of total shape variance) were significantly associated (for a 1-SD *decrease* in mode 1 score, OR 1.7 [95% CI 1.1, 2.5], and for a 1-SD *increase* in mode 2 score, OR 1.5 [95% CI 1.0, 2.2]) with incident rHOA (Figure, left).

Figure. Numbers of hips by demographic group and selected modes associated with incident rHOA and srHOA [± 2 SD]
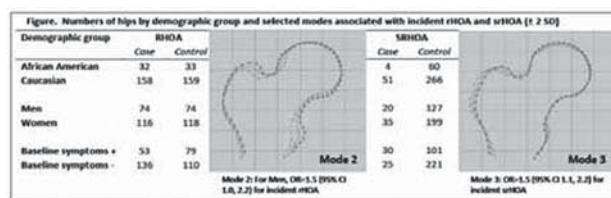
For incident srHOA, modes 2 and 3 (representing 16 and 13% of total shape variance, respectively) were significantly associated, with a 1-SD *decrease* in either of these modes increasing the odds of srHOA by 50% (mode 2: OR 1.5 [95% CI 1.0, 2.1], mode 3: figure, right). The presence of baseline hip symptoms increased the odds (OR 3.2 [95% CI 1.7, 5.9]) of incident srHOA, while African Americans compared to Caucasians had 70% lower odds of incident srHOA (OR 0.3, [95% CI 0.1, 0.8]); no other covariates were associated. Analyses stratified by the presence of baseline symptoms showed a consistent association between mode 3 and srHOA. However, among those *without* baseline symptoms, an *increase* in mode 6 (3% of variance) was associated with srHOA (OR 1.9 [95% CI 1.2, 3.1]), while among those *with* symptoms the association was with a *decrease* in mode 6 (OR 2.1 [95% CI 1.3, 3.5]).

Conclusion: Variations in shape modes 1 and 2, derived from the ASM, were associated with incident rHOA in men only. Shape modes 2 and 3 were associated with srHOA overall, and mode 6 with srHOA depending upon baseline symptom presence. Such shape variations may contribute to hip OA risk.

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A Virtual Knee Joint Replacement Clinical Endpoint Based On Longitudinal Trends and Thresholds in Koos Knee Pain and Function in Osteoarthritis Initiative Participants. Robert M. Boudreau[1], David J. Hunter[2], Zhijie Wang[3], Frank Roemer[4], Felix Eckstein[5], Michael J. Hannon[3], Ali Guermazi[4] and C. Kent Kwoh[6]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Sydney, Sydney, Australia, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]Boston University School of Medicine, Boston, MA, [5]Paracelsus Medical University, Salzburg, Austria, [6]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA

Background/Purpose: Knee joint replacement (KR) is a cost-effective procedure with good long-term outcomes, but has limitations as an endpoint in OA intervention trials. A definition of virtual total joint replacement (vTKR) based on clinical measures may be a more useful, efficient and practical outcome measure. The aim of this study was therefore to develop and evaluate a potential vTKR definition based on clinical measures in the OAI.

Methods: The sample included 8204 knees from 4143 individuals (42% male, age 61.6 ± 9.2) in the Progression, Incident and Control cohorts. A total of 187 individuals underwent KR (216 knees) over the five years after baseline. Individuals with continuous health care coverage during the five years were included, except for individuals who underwent KR. Clinical measures individually predictive of KR, thus considered for inclusion in the model, were: WOMAC Knee Pain, Stiffness, Disability and Total scores; KOOS Knee Pain (KOOSKP), Symptoms, ADL, Quality of Life (QOL) and Total scores; Knee pain severity in past 30 days and PASE. Several other clinical measures were excluded as not predictive. At each annual visit, logistic regression models were developed predicting actual KR during the following year. Baseline, the two timepoints prior to KR (and changes between them) entered models with up to three clinical measures. Sensitivity, specificity, ROCs and AUCs were evaluated. Adapting a propensity-score approach, the 5% of non-KR knees with the highest predicted probability of being a KR were eligible vTKR knees. We then further

required that clinical measures at the incident vTKR timepoint be as poor or worse than baseline and also did not improve through year 5.

Results: A combination of KOOS Knee Pain and QOL scores was identified as the best KR-predicting vTKR model. vTKR criterion was based on three factors that increased the predicted odds of KR: crossing a threshold of severe knee pain (KOOS), a threshold of sufficiently poor quality of life, a weighted combination of these two, and/or a marked increase in knee pain over the year prior. Cross-validated AUCs, distinguishing between KR and non-KR knees across annual visits ranged from 0.867 to 0.921. A parity-inducing probability cutpoint correctly separated KR from non-KR knees with sensitivity and specificity of 0.85. A total of 399 knees maintained or got worse after their vTKR. Of these, 143 were as bad or worse than baseline.

Final clinical variable vTKR prediction model Odds-ratios* (95% C.I.'s) for KOOSKP and KOOSQOL (during preceding two periods) Predicting Actual KR

vTKR month	KOOSKP Threshold (OR per 1 unit lower)	KOOSQOL Threshold (OR per 1 unit lower)	Additional effect if KOOSKP got worse during preceding two periods (OR per 1 unit worsening)
24†	1.047 (1.028,1.065)	1.032 (1.013,1.051)	1.018 (0.997,1.039)**
36	1.043 (1.025,1.062)	1.028 (1.011,1.044)	1.054 (1.035,1.073)
48	1.053 (1.035,1.072)	1.027 (1.010,1.044)	1.060 (1.041,1.079)
60	1.048 (1.030,1.066)	1.023 (1.008,1.039)	1.048 (1.029,1.067)

† vTKR month 24: Model predicting KRs during year following 12 month OAI contact * All OR's were statistically significant at p < 0.003, except KOOSKP worsening at 24m ** KOOSKP worsening at 24m: p=0.0903

Conclusion: We have developed a promising vTKR criterion based on a combination of threshold KOOS Knee Pain and QOL scores, and/or worsening KOOS Knee Pain. This vTKR criterion may be a useful outcome measure for OA intervention trials.

Disclosure: R. M. Boudreau, None; **D. J. Hunter**, None; **Z. Wang**, None; **F. Roemer**, None; **F. Eckstein**, None; **M. J. Hannon**, None; **A. Guermazi**, None; **C. K. Kwoh**, None.

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Does Structural Progression of Knee Osteoarthritis Measured with Magnetic Resonance Imaging or Radiography Predict Knee Replacement?—Data From the Osteoarthritis Initiative. Felix Eckstein[1], C. Kent Kwoh[2], Robert M. Boudreau[3], Zhijie Wang[4], Michael J. Hannon[4], Wolfgang Wirth[1], Ali Guermazi[5], Frank Roemer[6], Michael C. Nevitt[7], Markus R. John[8], Leena Sharma[9], Jeffrey W. Duryea[10], David J. Hunter[11] and Osteoarthritis Initiative Investigators[12]. [1]Paracelsus Medical University, Salzburg, Austria, [2]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh School of Medicine, Pittsburgh, PA, [5]Boston University, Boston, MA, [6]Klinikum Augsburg, Augsburg, Germany, [7]University of California-San Francisco, San Francisco, CA, [8]Novartis Pharma AG, Basel, Switzerland, [9]Northwestern University, Chicago, IL, [10]Brigham & Women, Boston, MA, [11]University of Sydney, Sydney, Australia, [12]San Francisco

Background/Purpose: Imaging biomarkers that predict relevant clinical endpoints, such as knee replacement (KR), are valuable tools for knee osteoarthritis prognosis. Currently, measurement of minimum radiographic joint space width (mJSW) is the accepted standard for testing the efficacy of disease modifying drugs (DMOADs) in clinical trials. The purpose of this study was to compare the predictive power of magnetic resonance imaging (MRI)-based longitudinal measures of cartilage loss and mJSW for KR.

Methods: We studied knees from Osteoarthritis Initiative (OAI) participants who received a KR between 24 and 60 month (M) follow-up (confirmed by radiography and/or review of hospital records). A matched control knee that did not receive a KR during this period was selected for each case, with the same sex, similar age (within 5 years), and the same baseline Kellgren Lawrence (KL) grade (central X-ray readings; strata 0–1, 2, 3, 4). Knees were not discordant for medial vs. lateral semi-quantitative joint space narrowing (JSN). Medial femorotibial compartment (MFTC) cartilage thickness change was determined from a sagittal 3 Tesla double echo steady state water excitation (DESSwe) MRI sequence, and, mJSW from fixed flexion radiography. The time points prior to KR (T0) and that 12 months earlier (T-1) were analyzed in case knees (i.e. in a knee with KR between 24M and 36M: 24M=T0;12M=T-1), and the same time points in control knees, with blinding to acquisition order. P-values for differences in longitudinal change between case/control pairs were assessed using the Wilcoxon signed rank test, and the area (AUC) under the receiver operation curve (ROC).

Results: 261 knees of 225 OAI participants received a KR (between 24M and 60M). Of these, 93 had central X-ray readings, JSW, and MRI readings available

at both T0 and T-1, and a matched control based on the above criteria (38 men, 55 women, age 63.4±9.3, BMI 30.2±4.9). Medial (MFTC) cartilage loss (over a 12 month period prior to KR), measured with MRI, was significantly greater in KR case than in control knees (-0.13±0.29 vs. -0.04±0.15mm; p=0.038, AUC=0.57). The differences in longitudinal change was borderline significant for the central MFTC (-0.24±0.57 vs. -0.07±0.23 mm; p=0.079, AUC=0.57) and was not significant for the change in radiographic mJSW (-0.19±0.91 vs. 0.01±0.58mm; p=0.397, AUC=0.55). The difference in cartilage loss (MRI) between KR case and control knees was particularly strong in knees with early radiographic OA (KLG2: n=22; MFTC p=0.008; AUC=0.72), whereas no difference in mJSW change was detectable in KLG2 case/control pairs (p=0.126; AUC=0.58).

Conclusion: Medial compartment longitudinal cartilage thickness loss, measured with MRI, predicts knee replacement as a clinical endpoint. In contrast, no significant difference in the 12 month change of radiographic mJSW was detected between case and control knees in the above sample. Given the relationship with an important clinical endpoint (i.e. knee replacement), MRI-based measures of cartilage thickness change are useful imaging biomarkers for clinical trials, for instance to demonstrate the efficacy of a DMOAD. The current findings also support the concept that treatments that slow cartilage loss may delay or prevent KR.

Disclosure: F. Eckstein, Chondrometrics GmbH, 3, Chondrometrics GmbH, 4, Novartis AG, 2, Novartis, MerckSeronoSanofi Aventis, Abbot, Perceptive, Bioclinica, 5; **C. K. Kwoh**, None; **R. M. Boudreau**, None; **Z. Wang**, None; **M. J. Hannon**, None; **W. Wirth**, Chondrometrics GmbH, 3, Chondrometrics GmbH, 4, MerckSerono, 5; **A. Guermazi**, BICL, LLC, 4, AstraZeneca, Genzyme, Novartis, and MerckSerono, 5; **F. Roemer**, Boston Imaging Core Lab, 1, National Institute of Health, 5, Merck Serono, 5; **M. C. Nevitt**, None; **M. R. John**, Novartis Pharma AG, 1, Novartis Pharma AG, 3; **L. Sharma**, None; **J. W. Duryea**, None; **D. J. Hunter**, None;

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Oral Glucosamine Sulphate for the Prevention of Knee Osteoarthritis in Overweight Females; The First Ever Preventive Randomized Controlled Trial. Jos Runhaar[1], Marienke van Middelkoop[1], Max Reijman[1], Edwin Oei[1], Dammis Vroegindeweij[2], Gerjo van Osch[1], Bart Koes[1] and Sita Bierma-Zeinstra[1]. [1]Erasmus MC, Rotterdam, Netherlands, [2]Maasstad Hospital, Rotterdam, Netherlands

Background/Purpose: Previous studies showed the largest effects of glucosamine on osteoarthritis (OA) symptoms of the knee joint and when used in an early phase of the disease. The present study evaluates the effect of a tailor made diet and exercise program (DEP) and of oral glucosamine sulphate, in a 2×2 factorial design, on the incidence of knee OA over 2.5 years in a high risk group of overweight, middle-aged females; free of clinical knee OA at baseline (ISRCTN 42823086; financed by The Netherlands Organisation for Health Research and Development). Worldwide, this is the first large RCT on prevention of knee OA. Here we present the results of the glucosamine intervention and the interaction with DEP.

Methods: 50 general practitioners contacted all registered women between 50 and 60 years. In total, 407 women met all inclusion criteria (BMI ≥ 27, no clinical knee OA (ACR criteria), no contraindications to MRI, no rheumatic diseases, no recent glucosamine usage), were invited for baseline measurements and were randomised. All subjects were instructed to dissolve and consume 1500 mg of the distributed study drug (crystalline glucosamine sulphate and placebo) each day, for 2.5 years. Pre-specified primary outcome was incidence of knee OA, defined by incidence of either K&L ≥ 2, joint space narrowing of ≥ 1.0 mm or incident clinical knee OA (ACR criteria).

Results: After 2.5 years of follow-up, forty-three women (11%) were lost to follow-up. Twenty-nine percent of all subjects reported one or more adverse events throughout the study; without difference in frequency between groups (p = 0.23). The interaction term between both interventions on the primary outcome proved to be significant (p = 0.04). Adjusted Generalized Estimated Equations showed no significant effect of glucosamine sulphate within the DEP control group (OR 0.59; 95%CI 0.31–1.12) or within the DEP intervention group (OR 1.44; 95%CI 0.83–2.48), for the Intention To Treat population (see table). The difference in direction of the association, however, is notable. Within subjects compliant to the study drug (≥75% of study drug, N = 250), also no significant effects of glucosamine sulphate over placebo were found (OR 0.69, 95%CI 0.32–1.52 and OR 1.32, 95%CI 0.70–2.51 respectively). Interestingly, among subjects compliant to DEP the interaction effect became stronger (p = 0.01) and, hence, the contrast

of the effects in the placebo and glucosamine group more distinct (see table).

Baseline characteristics and incident OA figures for Intention To Treat and Per Protocol analyses

| | Diet & Exercise Program | | | |
| | Control group | | Intervention group | |
	Placebo	Glucosamine	Placebo	Glucosamine
Baseline characteristics				
N - subjects	102	102	101	102
Age (yr)	55.7 ± 3.3	55.7 ± 3.1	55.7 ± 3.2	55.7 ± 3.1
BMI (kg/m2)	32.6 ± 4.3	32.4 ± 4.6	32.3 ± 4.5	32.1 ± 3.7
Heberden nodes				
uni-lateral	15%	16%	12%	12%
bi-lateral	10%	14%	20%	9%
Postmenopausal status	70%	68%	66%	67%
N - knees	204	204	202	204
K&L				
grade 0	53%	47%	53%	50%
grade ≥ 1	46%	53%	46%	50%
Varus	46%	38%	38%	37%
Mild symptoms	17%	20%	27%	19%
Past injury	14%	12%	10%	13%
Incident knee OA (after 2.5 years)				
ITT	19%	13%	15%	20%
PP glucosamine	21%	17%	18%	24%
PP DEP	19%	13%	9%	23%
PP glucosamine and DEP	21%	17%	7%	24%

ITT: Intention To Treat population (all randomized subjects). PP: Per Protocol population (compliant to intervention). DEP: diet and exercise program

Conclusion: Although safe compared to placebo, crystalline glucosamine sulphate was ineffective for the prevention of knee OA in overweight females over 2.5 years of follow-up.

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A Randomized, Multicentre, Double Blind, Placebo-Controlled Trial of Anti TNF Alpha (adalimumab) in Refractory Hand Osteoarthritis: The Dora Study. Xavier Chevalier[1], Philippe Ravaud[2], Emmanuel Maheu[3], Gabriel Baron[4], Amandine Rialland[5], Philippe Vergnaud[6], Christian Roux[7], Yves Maugars[8], Denis Mulleman[9], Bernard Combe[10], Daniel Wendling[11], Pierre Laforgue[12], Damien Loeuille[13], Violaine Foltz[14] and Pascal Richette[15]. [1]Department of Rheumatology Hopital Henri Mondor, Créteil, France, [2]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [3]AP-HP, St Antoine Hospital, Paris, France, [4]Epidemiology, Paris, France, [5]Unité de recherche clinique Henri Mondor, Créteil, France, [6]CCRB Synarc Lyon, Lyon, France, [7]CHU L' Archet University Nice, Nice, France, [8]CHU Nantes, Nantes, France, [9]CHU Trousseau Tours, Tours, France, [10]Lapeyronie Hospital, Montpellier, France, [11]Minjoz University Hospital, Besancon, France, [12]CHU la conception Marseille, Marseille, France, [13]CHU Brabois, Vandoeuvre les Nancy, France, [14]Pitié Salpétrière Hospital, Paris, France, [15]Lariboisière Hospital, Paris, France

Background/Purpose: Hand osteoarthritis (HOA) is a frequent painful polyarticular disease which often does not respond to any classical therapeutics. TNF a is involved in the osteoarthritic process both in disease progression and in pain perception.

Objective: To evaluate TNF blockers in patients with painful OA refractory to analgesics and NSAIDs.

Methods: The digital osteoarthritis in refractory hand OA study (DORA), is a phase 3 randomized superiority, double-blind (patients and assessors of outcomes), parallel, placebo controlled, 26 weeks, multicenter trial (conducted in 16 French clinical sites), using TNF blocker adalimumab (2 sub cutaneous injections at week 0 and week 2). Patients meeting the American College of Rheumatology criteria for hand OA with pain above 40 mm on a 100 mm visual analogue scale (VAS), involving at least 3 painful interphalangeal joints and at least 3 OA joints at Kellgren Lawrence (KL) grade > 2 on a recent radiograph, who did not respond to analgesics and NSAIDs, were recruited. Randomization and allocation to trial group were carried out by a central computer system. The primary endpoint was change in pain score after 6 weeks. Secondary outcomes at 6 weeks were change in the number of spontaneous painful joints, in number of painful joints on pressure, in number of swollen joints, in morning stiffness, in patient' and practitioner' global assessments, in functional index for hand OA (FIHOA) and Cochin hand functional index. Consumption of analgesics was recorded (acetaminophen up to 3g/D was the only rescue medication allowed until week 6). Serum markers (COMP, PIIANP, HA, usCRP, cytokines level of TNF a, IL-6, IL-1) and urine level of CTX-II (corrected by creatinine) were measured at W0 and W6.

Results: On the 99 patients selected, 85 were randomized (42 in the placebo group, 41 in the adalimumab group). 35 patients in the placebo group and 38 in the adalimumab group received the two injections. 78 patients with at least one injection were analyzed (37 placebo and 41 adalimumab) (mITT). Mean (SD) age was 62.5 (6.9), 85 % of women, mean (SD) level of pain was 65.4 (12.9) mm; mean (SD) number of painful IP joints: 11 (6), mean number of joints with clinical synovitis was 5.9(4.4), mean FIHOA score 15.6 (6.3). The difference in the mean change in pain score on VAS (0–100 mm) over 6 weeks between adalimumab and placebo (primary end point) was: -2.5 mm (95% CI, -14.0 to 9.0), p: 0.67, non significant. No statistically significant differences were found for any of the secondary outcomes, except for a decrease in the number of swollen joints between week 0 and week 26 which favoured adalimumab group: mean difference: -1.9 (95% CI, -3.2 to - 0.6), p: 0.006. Analgesics use was similar between groups. There were no safety concerns. There was none variations of any biological markers between the 2 groups. TNF alpha serum level was not correlated with clinical outcome in the group of patients treated with adalimumab.

Conclusion: In a group of patients with refractory hand OA, TNFa blockers (adalimumab, 2 sc injections) failed to demonstrate any clinical improvement.

ACR Concurrent Abstract Session
Pediatric Rheumatology: Clinical and Therapeutic Disease III:
Childhood Systemic Lupus Erythematosus and Other Vasculidities
Tuesday, November 13, 2012, 2:30 PM– 4:00 PM

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A Randomized Trial in New Onset Juvenile Dermatomyositis: Prednisone Versus Prednisone Plus Cyclosporine Versus Prednisone Plus Methotrexate. Nicolino Ruperto, Angela Pistorio, Sheila Oliveira, Rubén J. Cuttica, Angelo Ravelli, Michel Fischbach, Stefan Hagelberg, Tadej Avcin, Emanuel Cheuret, Fabrizia Corona, Gerard Couillault, Frank Dressler, Valeria Gerloni, Gary Sterba, Francesco Zulian, Maria Teresa Apaz, Adriana Cespedes-Cruz, Rolando Cimaz, Fabrizio De Benedetti, Pierre Quartier, Ricardo Russo, Nico Wulffraat, Simona Angioloni and Alberto Martini. Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Data regarding the safety and efficacy of treatment regimens for juvenile dermatomyositis(JDM) tends to be from anecdotal, small, uncontrolled, non-randomized case series. This randomized trial was aimed to find out the treatment regimen associated with the lowest occurrence of flare and the lowest drug related toxicity.

Methods: Children with newly diagnosed JDM were randomized in an open fashion to receive one of 3 different therapeutic approaches: prednisone (PDN) versus PDN plus methotrexate (MTX) versus PDN plus Cyclosporine A. The overall hypothesis to be tested in this trial was that the early introduction of combination therapy of corticosteroids and either MTX or CsA will prove more effective and safe than corticosteroids alone in the treatment of JDM.

Primary outcome measures after 6 months of treatment: response rate according to the PRINTO provisional definition of improvement in the 3 arms (20% improvement in at least 3 core set variables with no more than 1 of the remaining variables, (muscle strength excluded), worsened by > 30%). The PRINTO JDM core set variables are: 1) muscle strength by the mean of the Childhood Myositis Assessment Scale (CMAS); 2) physician's global assessment of disease activity on a 10 cm VAS; 3) global

disease activity assessment by the mean of the Disease Activity Index (DAS); 4) parent's/patient's global assessment of overall well-being on a 10 cm VAS; 5) functional ability assessment by the mean of the Childhood Health Assessment Questionnaire (CHAQ); 6) health-related quality of life assessment.

Primary outcome measures after 24 months of treatment: a) time to inactive disease; b) time to major therapeutic changes because of inefficacy/flare/adverse events.

Results: 138/139 randomized patients were included in the efficacy dataset. There were 81/138 females (59%) with a median age at onset of 7.4 years (1st–3rd quartiles 1.1–15.4) and a median disease duration of 2.8 months (1.4–5.3). Frequency of response at 6 months was for 24/46 (52.2%) for PDN, 31/46 (67.4%) for PDN+CSA and 34/46 (73.9%) for PDN+MTX (p 0.082). Time to inactive disease (Figure) in the combination group (PDN+CSA or PDN+MTX) was significantly shorter than that of PDN alone (p 0.031). Time to major therapeutic changes in the combination group (PDN+CSA or PDN+MTX) was significantly longer than that of PDN alone (p 0.006). Total number of adverse events were 57/276 (20.7%) in the PDN group, 141/276 (51.1%) in PDN+CSA and 78//276 (28.3%) in PDN+MTX (p < 0.0001). Skin and subcutaneous tissue disorders, and nervous system disorders were statistically more frequent in PDN+CSA (p 0.0015, p 0.039 respectively).

Time to inactive disease in the 3 randomized groups

Log-Rank test; P=0.031
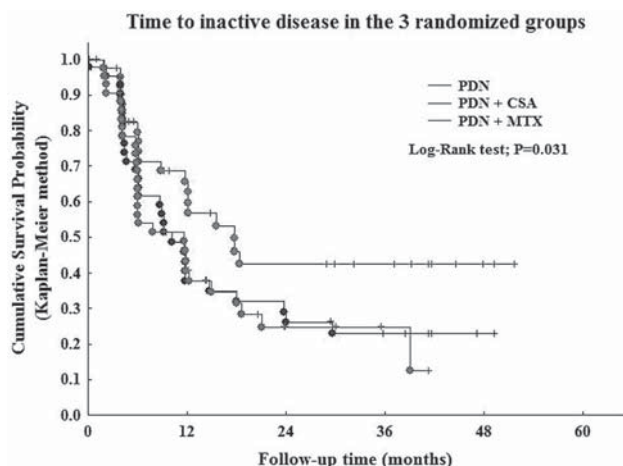
Conclusion: combined therapy with PDN and either CSA or MTX was more effective than with PDN alone. However the safety profile favour the combination with MTX toward that with CSA.

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Urine Biomarkers Distinguish Between Proliferative and Membranous Lupus Nephritis in Childhood Onset Systemic Lupus Erythematosus.
Rina Mina[1], Michael Bennett[2], Lining Qi[3], Shannen Nelson[4], Jessica Hummel[5], Pavel Shiyanov[3], John Schlager[3], Prasad Devarajan[2] and Hermine I. Brunner[4]. [1]Cincinnati Children's Hospital Medical Center/University of Cincinnati, Cincinnati, OH, [2]Cincinnati Children's Med Ctr, Cincinnati, OH, [3]US Air Force Research Lab, Wright-Patterson Air Force Base, OH, [4]Cincinnati Children's Hospital, Cincinnati, OH, [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: The ISN/RPS Morphologic Classification of Lupus Nephritis (LN) reports on histological features that differentiate among various forms of LN, most notably between proliferative and membranous classes which have different renal outcomes. There is a lack of non-invasive biomarkers that can discriminate among LN subtypes which are important so that appropriate therapies can be planned. We aim to investigate candidate urine biomarkers that will distinguish between proliferative and membranous LN in childhood onset systemic lupus erythematosus (cSLE).

Methods: Using liquid chromatography tandem mass spectrometry proteomics, we isolated Vitamin-D Binding Protein (VDBP) and Prostaglandin D synthase (PGDS) from urine collected from 53 patients with LN. Levels of VDBP were measured using a commercially available ELISA assay and these were standardized to urine creatinine (UCr). Differences in the levels of VDBP between proliferative and membranous LN were analyzed using Mann-Whitney rank sum analysis. For PGDS, we performed spectral counting through ProteoIQ and validated the results with western blot.

Results: There were 27 renal biopsies classified as proliferative LN and 26 were classified as membranous LN. Median levels in ng/ml (range) of urinary VDBP levels were significantly higher in proliferative LN compared to membranous LN [90.9 (IQR 28.9–948.4) versus 33.5 (IQR 21.3–124.1), p-value=0.046]. The results remained significant when VDBP levels were corrected for UCr [median in ng/mg (range) = 22.2 (29.0–1822.9) versus 44.1 (14.8–139.5), p-value=0.045]. PGDS was overexpressed in the urine of patients with membranous LN compared to proliferative LN with an average spectral count of 13 versus 4, respectively, and a ratio of 3.25 (p-value < 0.05). This difference was confirmed by western blot.

Conclusion: We isolated two candidate urine biomarkers, Vitamin-D Binding Protein and Prostaglandin D synthase, and thereafter validated our proteomic finding that these can distinguish between proliferative LN and membranous LN. The discovery of these non-invasive biomarkers and its application in a clinically usable platform could lead to a substantial impact on management strategies for LN in cSLE.

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2475

Cancer in Pediatric-Onset Systemic Lupus: What Is the Role of Disease Duration and Other Factors on Risk?
Sasha Bernatsky[1], Ann E. Clarke[1], Jeremy Labrecque[2], Emily von Scheven[3], Laura E. Schanberg[4], Earl D. Silverman[5], Hermine I. Brunner[6], Kathleen A. Haines[7], Randy Q. Cron[8], Kathleen M. O'Neil[9], Kiem Oen[10], Alan M. Rosenberg[11], Ciaran M. Duffy[12], Jennifer LF Lee[13], Mruganka Kale[13], Elizabeth M. Turnbull[2] and Rosalind Ramsey-Goldman[14]. [1]McGill University, Montreal, QC, [2]Research Institute of the McGill Univ. Health Ctre, Montreal, QC, [3]UC San Francisco, San Francisco, CA, [4]Duke University Medical Center, Durham, NC, [5]PRSCG, Cincinnati, OH, [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]Hackensack Univ Med Ctr, Hackensack, NJ, [8]Univ of Alabama-Birmingham, Birmingham, AL, [9]Okla Univ Health Science Ctr, Oklahoma City, OK, [10]University of Manitoba, Winnipeg, MB, [11]Royal University Hospital, Saskatoon, SK, [12]Children's Hospital of Eastern Ontario, Ottawa, ON, [13]RI McGill Univ Health Ctr, Montreal, QC, [14]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: Compared to adults with SLE, relatively little is known about cancer risk in pediatric-onset SLE. We assessed cancer incidence in a multi-centre pediatric-onset SLE cohort, compared to general population cancer rates.

Methods: We ascertained cancers within SLE clinic registries at 10 pediatric centers, located in Birmingham AL; Cincinnati OH, Durham NC; Hackensack NJ; Oklahoma OK; San Francisco CA; Montreal QC; Toronto ON; Saskatoon SK; and Winnipeg MB. Subjects were linked to state or provincial cancer registries for the observational interval, spanning 1974–2009. In-situ cancers were excluded. Follow-up was calculated from the date first seen at the clinic, and the first of 3 possible events: death, cancer, or end of study interval (Dec. 2009). We pooled observed cancers and person-years of observation. The cancers expected to occur were calculated by multiplying the person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates. The ratio of observed to expected cancers represents the SIR, or relative cancer risk in pediatric SLE, versus the general population. We provided estimates for total cancer and for hematological cancers, and also results stratified on sex, age group, and SLE duration.

Results: There were 999 patients aged <18 at cohort entry. Most (82%) were female; mean age at cohort entry was 12.9 years (SD=3.6).The majority were Caucasian. Subjects were observed for a total of 7,986 patient-years (average 8.0 years). Within this interval, only 3.0 invasive cancers were expected, however, 14 invasive cancers occurred, for an SIR of 4.7, 95%

confidence interval, CI 2.6, 7.8. Three hematologic cancers were found (2 non-Hodgkin's lymphoma, 1 leukemia), for an SIR of 5.2 (95% CI 1.1, 15.2). The non-hematologic cancers included one cancer each of bladder, brain, breast, and thyroid, 3 head and neck cancers, and 4 unspecified cancers. At time of cancer diagnosis, mean SLE duration was 12.3 years (range 0.1, 25.2 years). Excluding cancers that occurred within the first year of cohort entry, the over-all cancer SIR was 3.0 (95% CI 2.3, 7.8). The SIRs stratified by age group and sex, were similar across strata (though more precise for females than males, due to relatively small numbers of males). Though not definitive, there was a trend for heightened relative risk in the period 10–19 years after SLE diagnosis. However, in absolute terms, this stratum experienced only 8 cancers.

Conclusion: These up-dated results suggest an increased cancer risk in pediatric onset SLE versus the general population. However, in absolute terms, this still translates into few events, which is somewhat re-assuring. A limitation is that some patients may have developed a cancer after relocating to another state or province, thus under-representing the true cancer incidence. Of note, risk may be highest in the period 10–19 years after SLE diagnosis, at a time when patients will have transferred to an adult provider. Further work will assess other potential factors of interest, such as race/ethnicity and calendar effects. Our work highlights the importance of continuity as adolescents transition to adult care, and a need for collaborations to allow longitudinal assessment of long-term risks.

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Role of Whole-Body Magnetic Resonance Imaging in the Assessment of Disease Activity in Juvenile Dermatomyositis. A Pilot Study. Clara Malattia[1], Annalisa Madeo[1], Silvia Pederzoli[1], Anna Providenti[2], Marta Mazzoni[1], Agnese Beltramo[1], Alessandro Consolaro[1], Stefania Viola[1], Antonella Buoncompagni[1] and A. Martini[1]. [1]Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [2]Istituto G Gaslini, Genova, UO Fisioterapia, Genova, Italy

Background/Purpose: Musculoskeletal MRI represents a valuable non-invasive technique for dectecting muscle inflammation in idiopathic inflammatory myopathies (IIM). So far, all MRI studies in juvenile dermatomyosis (JDM) have focused on the thighs muscles. Whole-body MRI (WB-MRI) is a new technique which allows to screen the entire muscular-skeletal system and gives a complete assessment of the total inflammatory burden in patients with IIM. However, its potential in children with JDM has never been explored so far.

Purpose: to evaluate the contribution of WB-MRI examination in the clinical assessment of JDM patients and to investigate its feasibility and validity in the assessment of disease activity.

Methods: WB-MR images were obtained from 30 JDM patients (12M;18F, median age 8.6 years) and from 30 children (13M; 17F, median age 10.4 years) without inflammatory myopathies (control group), using a 1.5 Tesla and Short Tau Inversion Recovery (STIR) sequences. Signal intensity was scored using a 0–2 point scale in 42 muscular groups; myofascial and subcutaneous tissue inflammation were assessed on the upper and lower extremities using a 0–1 point scale. Validation procedures included the analysis of reliability, construct validity, discriminant validity and sensitivity to change.

Results: in addition to a symptomatic proximal distribution of inflammation, WB-MRI revealed asymptomatic distal legs muscle inflammation in 19 out of 30 patients (70%) and asymptomatic forearms inflammation in 15 out of 30 patients (50%). Twenty-three patients showed a typical patchy and heterogeneous distribution of muscular inflammation. In 3 patients the abnormal hyperintense areas tended to be diffusely and homogeneously distributed within the muscles. WB-MRI showed inactive disease in 4 patients. Fascial and subcutaneous tissue inflammation were detected in 9 out of 30 (30%) and 18 out of 30 (60%) patients, respectively. WB-MRI scores were significantly increased in active JDM when compared with the inactive JDM group (p=0.02) and the control group (p<0.0001), indicating an excellent discriminant validity of the WB-MRI. The inter- and intra-reader agreement for the muscular,

subcutaneous and fascial WB-MRI scores were excellent (intra-class correlation coefficient >0.8). The muscular WB-MRI score showed moderate to excellent correlations with indicators of disease activity such as the Manual Muscle Test (MMT; rs=0.86), the Childhood Myositis Assessment Scale (CMAS; rs=0.85) and physician's assessment of disease activity (VAS Phys; rs=0.75). WB-MRI score showed a higher responsiveness to change (standardized response mean=0.86) compared to MMT (SRM=0.51), CMAS (SRM=0.28), VAS Phys (SRM=0.63) and CPK (SRM=0.17).

Conclusion: WB-MRI provides additional information to the clinical assessment by revealing a wider involvement of muscle groups and different patterns of distribution of muscle inflammation. WB-MRI score allows to reliably visualize the extent of the inflammatory process and therefore it represents a promising non-invasive tool to estimate the total disease burden, to adjust treatment to disease severity and to monitor treatment efficacy in JDM.

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The Comparison of Childhood Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa and a New Set of Diagnostic Criteria for Cut-Polyarteritis Nodosa. Erkan Demirkaya, Seza Ozen, Turker Turker, Rubén J. Cuttica, Paul Brogan, Pierre Quartier, Jordi Anton, Nuray Aktay Ayaz, Stella Maris Garay, Graciela Espada, Raju Khubchandani. Francesco Zulian, Arvind Bagga, Alexandre Belot, Clovis Artur Silva, Sulaiman Al-Mayouf, Amparo Ibanez Estrella, Sheila Oliveira, Cengizhan Acikel, Claudia Saad-Magalhães, Alberto Martini and Nicolino Ruperto, Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Systemic polyarteritis nodosa (PAN) is a predominantly medium size vasculitis characterized by non granulomatous necrotizing vasculitis. We aimed to evaluate clinical, laboratory and imaging features of cutaneous (cut-) PAN and the PAN form and to develop a new set of diagnostic criteria for cut-PAN in a large international pediatric vasculitis registry available on the PRINTO database.

Methods: We extracted from the PRINTO database all the patients who fulfilled the Ankara 2008-EULAR/PRES/PRINTO criteria for PAN. The cut-PAN patients as per the treating physician diagnosis were also extracted. To define clinical and laboratory characteristics who could help to differentiate cut-PAN from PAN and univariate logistic regression analysis was performed.

Developing a new set of diagnostic criteria for cut-PAN: Principle component analysis were performed to detect best representative factors of cutaneous symptoms in cut-PAN patients. The one with the highest sensitivity and specificity in the generated models were accepted as diagnostic criteria in our study.

Results: There were 109 and 45 patients classified as PAN, and cut-PAN respectively with a mean age at diagnosis of 9.47±3.59 years; and 9.12±3.83 years; respectively. The female/male ratio and ethnicity did not differ in the 2 subtypes. The cutaneous group had significantly less constitutional features and less acute phase reactant levels, as expected. The median values (IQR 25–75%) for the ESR and CRP for PAN were 78 (48–108) mm/h and 7.36 (2.76–15.03) mg/dL. Musculoskeletal features such as myalgia was present in 82 (75.2 %) patients with PAN and 18 (40.9%) patients with cut-PAN (p<0.001) both groups. As differentiating features skin infarcts were observed in PAN only and constitutional features, angiographic abnormalities, and organ involvement was not seen in any of the cut-PAN patients. Malaise, fever, severe headache, motor mononeuritis multiplex, sensory peripheral neuropathy, abdominal pain, and hematuria were the most statistically significant clinical characteristics able to differentiate these two entities.

New set of diagnostic criteria for cut-PAN is the absence of any organ involvement (constitutional and musculo skeletal symptoms are acceptable) and presence of any of 4 cutaneous findings (Livedo reticularis, skin nodules, polymorphous exanthema, panniculitis). Sensitivity of proposed diagnostic criteria obtained from the existing database for cut-PAN was calculated as 88.8%, specificity 97.8%, positive predictive value 83.3% and negative predictive value 98.6%.
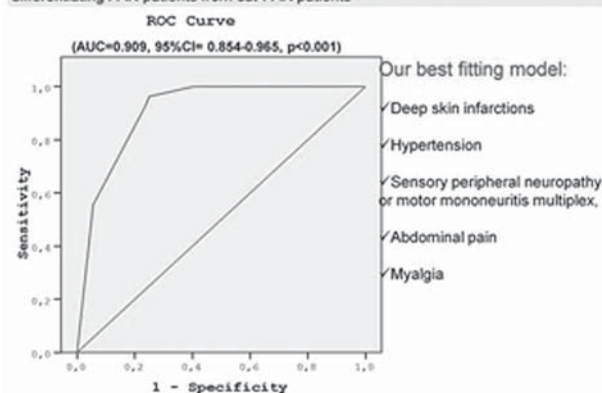
Conclusion: The large number of patients with other vasculitides and cutaneous PAN has enabled us to have a significant specificity and sensitivity for the suggested criteria. Furhter biological studies are needed to effectively differentiate the two entities.

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Identification of Disease-Specific Neuroimaging Phenotypes in Childhood Inflammatory Brain Diseases. Tania Cellucci, Pascal N. Tyrrell, Shehla Sheikh, Suzanne Laughlin and Susanne M. Benseler. The Hospital for Sick Children, Toronto, ON

Background/Purpose: Magnetic resonance imaging (MRI) is a key diagnostic modality of childhood inflammatory brain diseases (IBrainD). While overlapping clinical features contribute to significant diagnostic uncertainty, neuroimaging characteristics may provide guidance for a targeted diagnostic approach. The aim of this study was to identify specific MRI patterns at diagnosis of distinct childhood IBrainD.

Methods: This single centre cohort study included children less than 18 years old who were diagnosed with an IBrainD between June 1989 and December 2010 and were enrolled in the BrainWorks cohort at SickKids Hospital. All patients also had a high-quality brain MRI based on institutional protocol at diagnosis. Demographic, clinical, laboratory, neuroimaging and histologic data at diagnosis were collected. Correspondence analysis was performed to obtain a multidimensional representation of the relationship between MRI findings and IBrainD diagnoses. Pearson residuals (PR) were calculated to estimate the strength of associations.

Results: A total of 142 children (51% females, median age 8.8 years) with IBrainD were identified: 104 primary angiitis of the CNS (cPACNS), 11 secondary CNS vasculitis, 8 neuronal antibody syndromes, 6 post-infectious IBrainD and 13 unclassified IBrainD. Children with angiography-positive non-progressive cPACNS were likely to have unilateral, unifocal and ischemic lesions (PR 4.2, 3.4, and 3.0, respectively). Common sites for lesions were the basal ganglia (PR 3.5), middle cerebral artery territory (PR 1.8), and internal capsule (PR 1.3). Angiography-negative cPACNS was grouped together with multifocal lesions (PR 1.64) and involvement of the leptomeninges (PR 2.3), parietal or temporal lobes (PR 1.5, 2.8), and subcortical or deep white matter (PR 2.8, 1.5). Optic neuritis (PR 2.9), volume loss (PR 1.8) and frontal lobe lesions (PR 1.5) were more likely in neuronal antibody syndromes. Frontal lobe involvement was also seen in post-infectious IBrainD (PR 1.6). Symmetric lesions were grouped with secondary CNS vasculitis (PR 2.0) and unclassified IBrainD (PR 2.7).

Conclusion: Childhood inflammatory brain diseases are characterized by distinct patterns of neuroimaging findings with respect to location and type of lesion. Identifying these patterns requires a standardized approach involving high-quality MRI for any child with suspected IBrainD. The neuroimaging phenotype may guide further diagnostic work-up and should be incorporated into diagnostic algorithms for childhood IBrainD in the future.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects IV:
Non-biologic Drugs for Rheumatoid Arthritis:
New Insights on Comorbidities and Adverse Events
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

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Rheumatoid Arthritis Does Not Increase Risk of Short Term Total Knee Replacement (TKR) Adverse Events (AE). Zachary J. LoVerde[1], Lisa A. Mandl[2], Beverly K. Johnson[2], Mark P. Figgie[2], Friedrich Boettner[2] and Susan M. Goodman[2]. [1]New York Medical College, Valhalla, NY, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: TKR is commonly performed for rheumatoid arthritis (RA) and osteoarthritis (OA). Historically, RA patients were at higher risk of post-operative AEs. The purpose of this study was to evaluate whether this is true in the era of widespread DMARD and biologic use.

Methods: Patients participating in the institution's TKR registry between 2007 and 2010 were screened for RA by ICD-9 code or self report, and the diagnosis confirmed by chart review. AEs were identified by 6 month questionnaire, and review of office and hospital notes. Self-reported AEs were validated by chart review or phone call. Infection was defined as any surgical site infection as well as systemic infections. Each RA patient was matched to 2 controls by age ($+/-$ 5 years), gender, and primary vs. revision surgery. Baseline characteristics of RA and OA patients were compared by standard statistics and bivariate relationships to AE calculated.

Results: 159 RA TKA patients were identified, and matched to 318 OA controls. Mean age: 63 years (range 22–93), 88% female. 20% of RA were on corticosteroids, and 67% were on DMARDS. Assessment of co-morbidities using Charlson co-morbidity scores did not reveal a significant difference between groups. RA had significantly worse baseline WOMAC pain (47.1 vs. 53.7; p-value < 0.01) and function scores (43.8 vs. 54.2; p-value < 0.01), and lower perceived health status on the EQ-5D (0.59 vs. 0.65; p-value < 0.01), and SF-36 PCS (29.3 vs. 33.3; p-value < 0.01). Operative time (144 minutes RA vs. 146 minutes OA; p-value = 0.66) and length of stay (5 days for both) were no different between groups. There were no deep joint infections in either group, and there was no significant difference between OA and RA rates of superficial infection, i.e. cellulitis or stitch abscesses (9.4% RA vs. 10.1%; p-value = 0.82) or thromboembolism (1.3% RA vs. 0.6%; p-value = 0.60). Re-operation was more common in OA (2.5% vs. 8.8% p-value =.015), largely due to manipulations.

Adverse Events	RA cases (N=159)	OA controls (N=318)	P-Value
In hospital (post-op, prior to discharge)			
Surgical Site Infection (SSI), N (%)	2 (1.3%)	3 (0.9%)	0.99
Other infection, N (%)	2 (1.3%)	7 (2.2%)	0.72
DVT, N (%)	1 (0.6%)	4 (1.3%)	0.67
PE, N (%)	0	1 (0.3%)	0.99
Pneumonia, N (%)	1 (0.6%)	1 (0.3%)	0.99
In office (post-op, within 6 months)			
SSI, N (%)	6 (3.8%)	19 (6.0%)	0.39
Other infection, N (%)	3 (1.9%)	4 (1.3%)	0.69
DVT, N (%)	0	1 (0.3%)	0.99
PE, N (%)	1 (0.6%)	1 (0.3%)	0.99
Pneumonia, N (%)	0	0	—
REOP, N (%)	4 (2.5%)	28 (8.8%)	**0.02**
REOP manipulation	2 (1.3%)	25 (7.9%)	**<0.01**
REOP revision	1 (0.6%)	3 (0.9%)	0.99
REOP other	1 (0.6%)	0	0.33
Self-report (at 6 months)			
Infection, N (%)	1 (0.72%)	6 (2.0%)	0.44
DVT, N (%)	0	8 (2.6%)	0.06
PE, N (%)	1 (0.72%)	1 (0.3%)	0.52
Pneumonia, N (%)	2 (1.5%)	1 (0.3%)	0.23
6-month Totals*			
Infection (SSI and other Infection), N (%)	15 (9.4%)	32 (10.1%)	0.83
DVT, N (%)	1 (0.6%)	10 (3.1%)	0.11
PE, N (%)	2 (1.3%)	2 (0.6%)	0.60
Pneumonia, N (%)	3 (1.9%)	2 (0.6%)	0.34
REOP (manipulation, revision, and other), N (%)	4 (2.5%)	28 (8.8%)	**0.02**

The same AE identified by multiple sources was counted only once

Conclusion: The belief that RA increases post-operative AEs may be outdated. In spite of worse pre-operative function, and high steroid and DMARD use, infection and wound healing complications were not increased in RA in a high volume orthopedic hospital. RA patients additionally had

lower rates of re-operation. These data are reassuring, but further study is needed to see if these trends continue and are generalizable.

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Disease-Modifying Antirheumatic Drug Use and Toxicities Among Elderly Patients with Rheumatoid Arthritis.
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Background/Purpose: The aging population has resulted in large numbers of *older* individuals requiring treatment for rheumatoid arthritis (RA). We sought to describe the clinical characteristics of elderly (≥70 yrs) RA pts in a large prospective cohort and determine the frequency of DMARD use and factors associated with drug toxicities among elderly RA pts.

Methods: Data were obtained from the Consortium of Rheumatology Researchers of North America (CORRONA) registry; an independent prospective observational cohort with >30,000 RA patients from over 100 US academic and private practices. We evaluated RA pts aged ≥ 70 yrs with ≥1 post-enrollment follow up (f/u) visit after age 70 [the 'index visit' (IV)]. Pts were classified as either aging with RA (RA onset <70) or older-age onset RA (RA onset ≥70). A subset of older RA patients with > 12 mo f/u beyond the IV was also identified. Demographic, clinical, and DMARD data were obtained. Unadjusted ORs were calculated to determine characteristics associated with DMARD or biologic exposure and drug-associated toxicities at IV and 12 mo f/u.

Results: 5801 RA pts age ≥70 yrs were identified with the following clinical features: 44% erosive, 30.8% joint deformities, mHAQ 0.7 ± 0.6. 4017 elderly RA patients were aging with RA (RA onset 56 ± 10.9 yrs) and 1784 had older-age onset RA (RA onset 75 ± 4.6 yrs). Mean age at IV was 74.9 ± 5.1 yrs with disease duration 13 ±11.6 yrs. 88.6% were on DMARD treatment (68.8% MTX, 34.8% biologic). Among those with 12 mo f/u (n=4077), 93.8% were on DMARD therapy (73.6% MTX, 42.8% biologic) with 16.1% adding a DMARD during f/u. Drug toxicity with non-biologic (1.6%) and biologic DMARDs (0.4%) was overall low. Among those with 12 mo f/u, 3.9% reported toxicity associated with non-biologic DMARD and 0.9% with biologic DMARD. The most commonly reported infection was URI (9%). Factors associated with DMARD, biologic use, or adverse events at the IV or 12 mo f/u are reported in *Table 1*.

Table 1.

Outcome	Parameter	OR (95% CI) at index visit	OR (95% CI) at 12 mo follow up
DMARD use	N (%)	5141 (88.6%)	3825 (93.8%)
	RA onset ≥70 yo	0.961 (0.807, 1.144)	1.140 (0.857, 1.517)
	Duration of RA	0.996 (0.989, 1.003)	0.990 (0.979, 1.000)
	Age	0.990 (0.975, 1.005)	0.994 (0.970, 1.020)
	Patient global assessment	0.997 (0.994, 1.001)	0.999 (0.993, 1.004)
	Physician global assessment	0.991 (0.987, 0.996)*	0.998 (0.991, 1.006)
	Swollen joint count	0.983 (0.968, 0.997)*	1.010 (0.984, 1.036)
	Tender joint count	0.977 (0.962, 0.993)*	1.018 (0.985, 1.051)
	Modified HAQ	0.862 (0.724, 1.027)	0.815 (0.611, 1.087)
	DAS28	0.870 (0.791, 0.957)*	0.995 (0.846, 1.170)
Biologic use	N (%)	2021 (34.8%)	1744 (42.8%)
	RA onset ≥70 yo	0.551 (0.487, 0.623)*	0.576 (0.501, 0.662)*
	Duration of RA	1.022 (1.017, 1.026)*	1.019 (1.013, 1.025)*
	Age	0.970 (0.960, 0.981)*	0.966 (0.954, 0.978)*
	Patient global assessment	1.004 (1.002, 1.006)*	1.005 (1.003, 1.008)*
	Physician global assessment	1.004 (1.001, 1.007)*	1.011 (1.008, 1.015)*
	Swollen joint count	1.001 (0.991, 1.012)	1.028 (1.016, 1.041)*
	Tender joint count	1.014 (1.002, 1.026)*	1.041 (1.026, 1.056)*
	Modified HAQ	1.476 (1.311, 1.662)*	1.708 (1.468, 1.988)*
	DAS28	1.006 (1.004, 1.133)*	1.177 (1.095, 1.265)*
Infection requiring hospitalization	N (%)	34 (0.6%)	41 (1%)
	RA onset ≥70 yo	0.481 (0.199, 1.163)	0.323 (0.126, 0.825)*
	Duration of RA	1.026 (1.001, 1.051)*	1.038 (1.016, 1.061)*
	Age	0.900 (0.824, 0.984)*	0.946 (0.881, 1.015)
	Patient global assessment	1.019 (1.007, 1.031)*	1.011 (0.999, 1.023)
	Physician global assessment	1.027 (1.013, 1.042)*	1.007 (0.990, 1.024)
	Swollen joint count	1.062 (1.010, 1.115)*	1.001 (0.942, 1.063)
	Tender joint count	1.092 (1.046, 1.141)*	1.073 (1.025, 1.063)*
	Modified HAQ	2.763 (1.658, 4.604)*	2.933 (1.753, 4.905)*
	DAS28	1.458 (1.012, 2.100)*	1.010 (0.719, 1.417)
	h/o MTX	1.876 (0.572, 6.150)	2.321 (0.714, 7.544)
	h/o biologic	4.381 (1.980, 9.696)*	2.631 (1.375, 5.034)*
Toxicity associated with biologic use	N (%)	23 (0.4%)	35 (0.9%)
	RA onset ≥70 yo	0.794 (0.312, 2.018)	0.937 (0.449, 1.958)
	Duration of RA	1.024 (0.464, 2.591)	1.013 (0.692, 2.694)
	Age	0.963 (0.882, 1.052)	0.966 (0.899, 1.039)
	Patient global assessment	1.011 (0.996, 1.027)	1.006 (0.992, 1.020)
	Physician global assessment	1.002 (0.980, 1.025)	1.016 (1.000, 1.033)
	Swollen joint count	0.995 (0.918, 1.080)	1.042 (0.989, 1.099)
	Tender joint count	0.968 (0.867, 1.080)	1.013 (0.944, 1.086)
	Modified HAQ	1.560 (0.721, 3.377)	1.419 (0.705, 2.854)
	DAS28	0.551 (0.257, 1.180)	1.107 (0.742, 1.651)
	h/o MTX	0.650 (0.241, 1.756)	0.726 (0.316, 1.670)

* p <0.05

Conclusion: Most elderly (≥70) RA pts in this large cohort received DMARD therapy, but DMARD and biologic toxicities were very low (<5%). Age of RA onset and age at f/u were not associated with increased biologic side effects. Greater RA severity and longer RA duration influenced if elderly RA patients were on DMARD or biologic therapy. Disability was strongly associated with risk of serious infection in this older age group. Limitations of this study include limited data on co-morbid conditions and precise medication timing. These data confirm that elderly RA patients tolerate DMARD and biologic therapy well with low rates of side effects and emphasize that treatment decisions for RA should never be based on age alone. However, disabled elderly RA patients are at high risk for serious infections. This vulnerable population should be the focus of future studies to determine strategies to improve outcomes beyond measures of RA activity alone.

2481

Time Trends in Corticosteroid Use in Rheumatoid Arthritis: Results From a Population Based Inception Cohort 1980–1994 Vs. 1995–2007.
Ashima Makol, John M. Davis III, Cynthia S. Crowson, Terry M. Therneau, Sherine E. Gabriel and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Corticosteroids (CS) are a double edged sword in rheumatoid arthritis (RA) treatment. Low doses may have disease modifying effects but long-term use risks detrimental side-effects. Treat-to-target strategies with intense use of disease-modifying anti-rheumatic drugs (DMARDs) and biologic response modifiers as steroid-sparing agents have impacted RA management in recent years, but it is unknown whether this has actually resulted in less CS use. The purpose of this study was to examine trends in CS use among patients diagnosed with RA in 1995–2007 compared to 1980–1994.

Methods: A population-based inception cohort of patients with RA who fulfilled 1987 ACR criteria for RA in 1980–2007 was assembled. All subjects were followed longitudinally through their complete medical records until death, migration or 12/31/2008. RA disease characteristics, DMARD use, and CS doses were ascertained by medical record review, including the use of oral, intravenous and intramuscular CS, their start date, stop date and number of weeks to taper. Cumulative incidence of CS initiation and discontinuation was computed with adjustment for competing risk of death. The current prevalence of CS use was estimated as the fraction of subjects on CS from among those under observation during each month of RA duration.

Results: The study population comprised 349 (68% female) diagnosed in 1980–1994 and 464 (69% female) diagnosed in 1995–2007, with mean followup of 15.3 and 5.7 years, respectively. Mean age was 55 years and 66% were rheumatoid factor positive in both cohorts. Those in 1995–2007 had a higher BMI (28.6 vs 26.8, p<0.001) and lower mean ESR at diagnosis (23.0 vs 27.2 mm/hr, p<0.001) than in 1980–1994. More patients started DMARDs in the 1st year of disease in 1995–2007 than in 1980–1994 (83% vs. 52%, p<0.001). A higher proportion of patients started CS in their 1st year of disease in 1995–2007 (68% vs 36%, p<0.001), but the starting dose (mean 8.7 vs 10.3 mg, p=0.08) and cumulative dose in the 1st year of use (mean 1.8 g vs 2.1 g, p=0.48) were not different than in 1980–1994. Differences in CS initiation in 1995–2007 vs 1980–1994 persisted throughout followup (81% vs 50% at 5y, 89% vs 62% at 10y; p<0.001). Discontinuing CS for at least 90 days was also more common in the 1995–2007 cohort than in the 1980–1994 cohort (41% vs 31% at 1 year after CS start, 78% vs 51% at 5y, 94% vs 69% at 10y; p<0.001). Current prevalence of CS use according to RA duration is displayed in the figure.
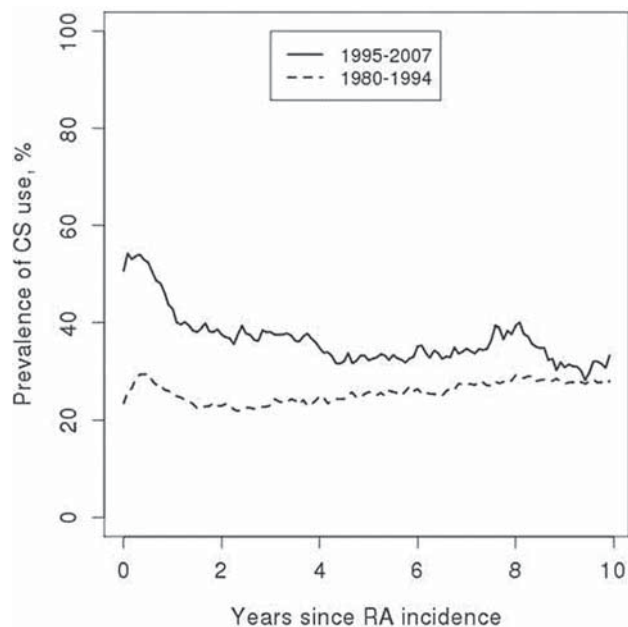
Conclusion: A higher proportion of patients are starting CS early in their disease course now compared to previously. Although more patients are also discontinuing CS now compared to previously, the proportion of patients on CS at any given time point of disease duration is higher now than previously.

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2482

Hydroxychloroquine Has Lipid-Lowering Effects in US Veterans with Rheumatoid Arthritis. Nicole A. Kieffer[1], Gail S. Kerr[2], J. Steuart Richards[3], Lisa A. Davis[4], Liron Caplan[5], Jeffrey Huang[6], Grant W. Cannon[7], Harlan Sayles[8] and Kaleb Michaud[9]. [1]Georgetown University, Washington, DC, [2]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [3]Washington DC VA and Georgetown University, Washington, DC, [4]Denver VA and Univ of Colorado School of Med, Aurora, CO, [5]Denver VA and Univ of Colorado School of Medicine, Aurora, CO, [6]Washington DC VA and Howard University Hospital, Washington, DC, [7]George E. Wahlen VA Medical Center, Salt Lake City, UT, [8]University of Nebraska Medical School, Omaha, NE, [9]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Recent data report significant decreases in low-density lipoprotein (LDL) and total cholesterol (TC) levels in predominantly female Caucasian rheumatoid arthritis (RA) patients treated with hydroxy-chloroquine (HCQ). We evaluated the association of HCQ use with lipid profiles in Veterans Affairs registry (VARA) patients; a predominantly male cohort with multiple comorbidities.

Methods: VARA patients that had post-enrollment lipid profiles available were evaluated. [LDL, TC, high-density lipoprotein (HDL), triglycerides (TG)] values and HCQ status were extracted through links to national VA administrative and pharmacy databases. HCQ user was defined as at least 3 consecutive months of prescription prior to the index lipid value. Patient data included socio-demographics, MDHAQ, RA disease activity measures (TJC, SJC, ESR, CRP, 3vDAS28), treatment [DMARD (excluding HCQ), anti-TNF], statin and prednisone use, and presence of diabetes mellitus (DM). HCQ users and HCQ non-users were compared using chi-square tests for categorical variables and t-tests for continuous variables. Multivariate analysis was performed, controlling for age, gender, race, 3vDAS28, prednisone, DMARD, statin use and DM.

Results: A total of 1012 VARA patients had at least one lipid profile following enrollment; 208 were excluded (< 3 consecutive months of HCQ use). Of 804 patients, the mean age was 62.5 yrs, predominantly male (91.7%) and Caucasian (79.6%), with established disease (10.6 yrs, SD12.2). Seventy-five percent received DMARDS, 24.6% biologic therapy. One hundred and sixty-six patients (20.7%) were HCQ users and 638 (79.3%) were HCQ non-users. Significant differences in HCQ-users versus non-users were age

(64.4 vs 62.1 yrs, p<0.009), disease duration (13.0 vs 10.0 yrs, p=0.003), TJC (3.9 vs. 5.8, p < 0.001), SJC (3.5 vs. 5.0, p =0.001), 3vDAS28 (3.4 vs 3.8, p=0.001), and DMARD use (94.6 vs 70.5%, p<0.001).

HCQ users had statistically significant lower levels of TC, TC/HDL and LDL compared to HCQ non-users that persisted after multivariate analyses (Table). Despite no ethnic differences in HCQ use vs non-user status, prednisone, DMARD, and statin use or 3vDAS28 scores, multivariate analyses found significantly better lipid profiles in Caucasian but not African-American HCQ users versus non-users.

Table. Univariate and Multivariate Associations of Lipid values in HCQ Users vs Non-Users in RA patients

	HCQ Usage				Multivariate Analysis Model Coefficients (p value)			
	Total n = 804 mean (mg/dl) (SD)	Current n = 166 mean (mg/dl) (SD)	Never n = 638 mean (mg/dl) (SD)	Univariate Analysis (p value)	Total Cohort (n=643)	Men[a] (n=595)	Caucasian[b] (n=547)	African American[c] (n=96)
TC	180.2 (37.7)	170.3 (31.4)	182.7 (38.8)	<0.001	−9.3 (0.004)	−9.1 (0.007)	−11.0 (<0.002)	−1.0 (0.898)
LDL	106.4 (33.4)	97.9 (30.1)	108.6 (33.9)	<0.001	−8.1 (0.007)	−7.9 (0.011)	−9.8 (0.003)	−0.5 (0.947)
HDL	46.0 (15.6)	47.7 (16.6)	45.5 (15.4)	0.128	1.5 (0.301)	1.6 (0.279)	1.7 (0.291)	0.6 (0.874)
TC/HDL	4.3 (1.6)	3.9 (1.2)	4.4 (1.6)	<0.001	−0.40 (0.001)	−0.402 (<0.002)	−0.45 (<0.001)	−0.18 (0.488)

[a] Controlling for Age, Race, Gender, Prednisone Use, Statin Use, 3vDAS28, and Diabetes
[b] Controlling for Age, Race, Prednisone Use, Statin Use, 3vDAS28, and Diabetes
[c] Controlling for Age, Gender, Prednisone Use, Statin Use, 3vDAS28, and Diabetes

Conclusion: In a cohort of US Veterans, RA patients taking HCQ had more optimal lipid profiles than those not using the drug. However, African Americans on HCQ did not demonstrate similar benefits as Caucasian patients. For a relatively inexpensive, low-risk drug, there may be a potential lipid lowering role for HCQ in some RA patients.

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2483

Folic Acid Pathway Single Neucelotide Polymorphisms Associated with Methotrexate-Related Significant Adverse Events. Lisa A. Davis[1], Brooke Ivan Polk[2], Alyse D. Mann[3], Roger K. Wolff[4], Gail S. Kerr[5], Andreas M. Reimold[6], Grant W. Cannon[7], Ted R. Mikuls[8] and Liron Caplan[9]. [1]Univ of Colorado School of Med, Aurora, CO, [2]University of Colorado Medical School, Aurora, CO, [3]Denver VA Medical Center, Denver, CO, [4]University of Utah, Salt Lake City, UT, [5]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [6]Dallas VA and University of Texas Southwestern, Dallas, TX, [7]George E. Wahlen VA Medical Center, Salt Lake City, UT, [8]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [9]Denver VA and University of Colorado School of Medicine, Aurora, CO

Background/Purpose: Methotrexate (MTX) is the cornerstone medication in the treatment of rheumatoid arthritis (RA). While MTX has been associated with a number of adverse events (AE), most are insignificant, and do not result in cessation of MTX. We examined whether single nucleotide polymorphisms (SNPs) in enzymes that participate in the folic acid pathway (folypoly-gamma-glutamate synthetase [FPGS], gamma-glutamyl hydrolase [GGH], and methylenetetrahydrofolate reductase [MTHFR]) are associated with significant adverse events (SigAE) complicating MTX treatment.

Methods: Patients (n=319) enrolled in the prospective Veterans Affairs RA (VARA) registry and who were taking MTX were genotyped for multiple SNPs with DNA samples derived from whole blood. Genes and associated SNPs included: FPGS (rs7033913, rs10760503, rs10106), GGH (12548933, rs7010484, rs4617146, rs719235, rs11988534), MTHFR (rs1801131, rs1801133). Patients were also genotyped for HLA-DRB1 polymorphisms. Covariates included: age, gender, Charlson-Deyo comorbidity index at VARA enrollment, glucocorticoid use concomitant with MTX, and mean 4-variable disease activity score. SigAE was defined as an AE leading to MTX discontinuation (operationalized as an AE occurring within 120 days prior to MTX cessation). Multivariate backward stepwise logistic and Cox regression were performed to determine factors associated with the presence of SigAE and time to SigAE, respectively. SNPs were modeled as a categorical variable comparing no minor alleles (homozygous major allele) and ≥ 1 copy of minor allele. A p-value <0.005 was deemed significant in the final model.

Results: The SNP associated with an increased odds of SigAE by logistic regression was the minor allele of GGH rs12548933 (OR 3.43, 95% CI 1.58–7.48) (see Table). This same variable was also associated with an increased hazard ratio (HR) of SigAE (HR 2.42, 95% CI 1.32–4.41) (see Figure).

Table. Final Regression results for logistic and Cox models

		Logistic				Cox		
	OR	95% CI		p-value	HR	95% CI		p-value
GGH, rs12548933, ≥1 copy of minor allele	3.43	1.58	7.43	0.002	2.42	1.32	4.41	0.004
GGH, rs7010484, ≥ 1 copy of minor allele	2.86	1.31	6.27	0.009				
MTHFR, rs1801131, ≥ 1 copy of minor allele					2.67	1.33	5.36	0.006

Figure: Significant MTX AE, by rs12548933 status
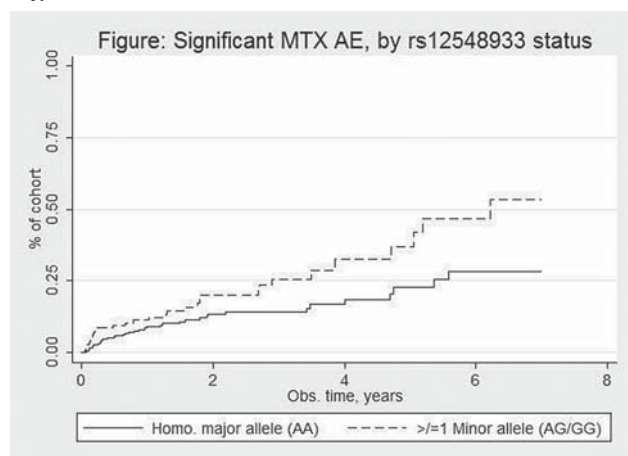
Conclusion: RA subjects on MTX may be at increased risk of AE leading to cessation of MTX if they have ≥ 1 copy of the minor allele in GGH rs12548933. Further investigation is warranted, as this SNP may indicate a susceptibility to MTX toxicity.

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2484

Hepatic Steatosis in Rheumatoid Arthritis: Associations with Disease Characteristics, Pharmacotherapies, and Atherosclerosis. Jon T. Giles and Joan M. Bathon. Columbia University Medical Center, New York, NY

Background/Purpose: Ectopic deposition of liver fat (steatosis) is associated with insulin resistance (IR), cardiovascular disease (CVD), and is a potent risk factor for cirrhosis. RA patients are at risk for IR and CVD, and cirrhosis risk is a concern with several RA pharmacotherapies.

Methods: RA patients underwent abdominal computed tomography (CT). Liver images were analyzed using Slice-o-Matic software, with the average radiographic attenuation [in Hounsfield units (HU)] for five (250 pixels each) sites of liver parenchyma, selected away from hepatic vasculature. Attenuation was corrected using a tissue phantom of known density. Steatosis was defined as average hepatic attenuation <48 HU (a standard definition that correlates histologically to ≥30% fatty deposition).

Results: A total of 113 RA patients were studied [mean age 64 ± 8 years, 70% female, median RA duration=13 years, median DAS28=3.1]. Mean hepatic attenuation was 54 ± 9 HU and steatosis was detected in 20 (18%). Steatosis was unrelated to age, gender, or ethnicity. Those with steatosis reported fewer minutes of exercise and more minutes of daily television watching, had significantly higher IR and serum triglyceride levels, and lower HDL levels. All measures of adiposity were higher among those with steatosis. Current alcohol use, and average and maximum number of alcoholic drinks consumed were not significantly associated with steatosis. Among RA patients, liver HU was, on average, 5 HU lower for those seropositive for RF vs. negative (p=0.003). CRP was strongly inversely correlated with liver HU, but DAS28 was unassociated. Current prednisone use>5 mg/day was associated with, on average, 7 HU lower liver density compared to no prednisone use, an association that was maintained after adjustment (Fig A). Among non-biologics, leflunomide was associated with a higher adjusted liver HU (Fig B), an association not modified by concomitant methotrexate use. Methotrexate use was only significantly associated with lower liver HU among the group with trunk fat above the median (14.7 kg). Likewise, the magnitude of the associations of RF, prednisone, CRP, leflunomide, and lean mass with liver HU was greater in the group with higher trunk fat. Biologics

were not associated with liver density in any analysis. Liver HU was not associated with coronary calcium score, ultrasound measures of carotid atherosclerosis, or ankle brachial index.

Figure: Adjusted Average Radiographic Hepatic Attenuation [in Hounsfield Units (HU)] According to Medication Use
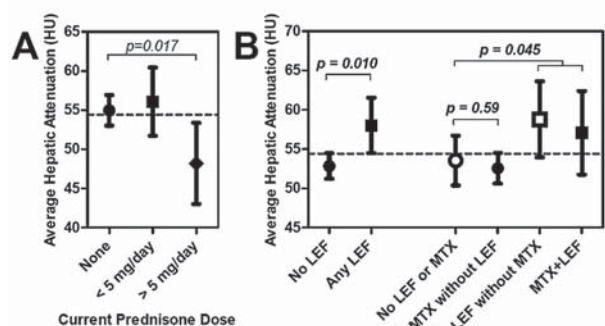
Adjusted for age, exercise, rheumatoid factor, leflunomide use (A), current prednisone dose (B), trunk fat, and fat free mass index (FFMI). Adjusted means and 95% confidence intervals are depicted. The dotted horizontal line is at the population mean HU for liver attenuation (54.4 HU).

Conclusion: No prior studies have explored hepatic attenuation in RA. The findings of this cross-sectional investigation link body composition, systemic inflammation, immunologic characteristics, and pharmacotherapies to the degree of steatosis. For most associations, the effects were accentuated in the setting of increased adiposity, suggesting a biologic interaction. Although strongly associated with insulin resistance, steatosis was unassociated with measures of atherosclerosis.

Disclosure: J. T. Giles, Roche/Genentech, 5; J. M. Bathon, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety & Efficacy of Janus Activated-Kinase (JAK) Inhibitors
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

2485

Tofacitinib, an Oral Janus Kinase Inhibitor: Analyses of Efficacy and Safety of 10 versus 5mg Twice Daily in a Pooled Phase 3 and Long-Term Extension Rheumatoid Arthritis Population. S. Cohen[1], S. Krishnaswami[2], B. Benda[3], R. Riese[2], M.G. Boy[2], D. Gruben[2], G. Wallenstein[2], C. A. Mebus[2], S. H. Zwillich[2] and J. D. Bradley[2]. [1]Metroplex Clinical Research Centre, Dallas, TX, [2]Pfizer Inc., Groton, CT, [3]Pfizer Inc., Collegeville, PA

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. Phase (P) 3 studies demonstrated tofacitinib is effective and has a manageable safety profile at both 5 and 10 mg twice daily (BID) doses. These post-hoc analyses of pooled P3 and long-term extension (LTE) data assessed whether there are relative differences in efficacy or safety between the two doses.

Methods: Data from patients (pts) receiving tofacitinib 5 or 10 mg BID were pooled from five randomized P3 and two open-label LTE studies. Pooling was justified by similarity of demographic and baseline (BL) disease characteristics of pts across the studies. For efficacy comparisons, pooled P3 data were assessed for signs and symptoms (rates of ACR response, rates of DAS28-4[ESR] (DAS) ≤3.2 and <2.6), physical function (rates of HAQ-DI improvement ≥0.3), and fatigue (rates of FACIT improvement ≥4) (all at Month 3). For safety comparisons, pooled P3 and LTE incidence rates (IR) (events/100 pt-y) were assessed for all-cause mortality, serious infection events (SIE), malignancies (excluding non-melanoma skin cancer), lung cancers, major adverse cardiovascular events, GI perforations and herpes zoster. Results were expressed as probability (proportion of responders for efficacy) or risk (IR for safety) ratios, respectively, for 10 mg BID divided by that of 5 mg BID, with 95% confidence intervals (CIs).

Results: In the efficacy analysis, the robust group sizes (approximately 1100 pts each) allowed demonstration of statistical separation (95% CIs excluding 1) of 10 mg BID from 5 mg BID for each of the efficacy

endpoints except fatigue. Point estimates for the 10 mg BID/5 mg BID ratios were between 1.11 and 1.15 for ACR20 responses, ACR50 responses and HAQ-DI improvement ≥0.3, and between 1.30 and 1.43 for ACR70 responses and rates of DAS28 ≤3.2 and <2.6, indicating a greater likelihood of achieving the more stringent outcomes with the 10 mg BID dose compared with 5 mg BID. In the safety analyses, all the CIs for important safety events included 1, indicating similar rates between doses, with the exception of increases in SIEs for 10 mg BID in LTE (risk ratio 1.74 [95% CI 1.24, 2.45]). In contrast to LTE, SIE risk ratio was 0.92 (95% CI 0.55, 1.56) in P3. Malignancy risk ratios were 1.59 (95% CI 0.52, 4.86) in P3 and 1.17 (95% CI 0.67, 2.05) in LTE. As patients from P2 received 5 mg BID in LTE, and pts from P3 received 10 mg BID in LTE, there were more pts receiving 10 (N=2415) compared with 5 mg BID (N=1370) in LTE but the exposure was greater for 5 than 10 mg BID (2700 vs 1700 pt-y).

Conclusion: Both doses of tofacitinib, 5 and 10 mg BID, are efficacious across multiple domains of efficacy. Pooled analyses show statistical separation of 10 mg BID vs 5 mg BID on most efficacy parameters except fatigue. Event rates for safety are generally similar between the two doses but differences were noted in SIE rates in LTE, favoring 5 mg BID. Importantly, event rates for the tofacitinib 5 and 10 mg BID dose groups in both the P3 and LTE studies are well within the ranges observed with biologic therapies approved for treatment of RA.

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2486

Radiographic, Clinical and Functional Comparison of Tofacitinib Monotherapy Versus Methotrexate in Methotrexate-Naïve Patients with Rheumatoid Arthritis. Eun Bong Lee[1], Roy M. Fleischmann[2], Stephen Hall[3], Ronald F. van Vollenhoven[4], John Bradley[5], David Gruben[5], Tamas Koncz[6], Sriram Krishnaswami[5], Gene Wallenstein[5], Samuel H. Zwillich[5], Bethanie E. Wilkinson[5] and the ORAL Start Investigators[7]. [1]Seoul National University, Seoul, South Korea, [2]Metroplex Clinical Research Center, Dallas, TX, [3]Cabrini Health and Monash University, Melbourne, Australia, [4]Karolinska Institute, Stockholm, Sweden, [5]Pfizer Inc., Groton, CT, [6]Pfizer Inc., New York, NY, [7]Groton, CT

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. This Phase 3, 24-mo study (ORAL Start; NCT01039688) compared efficacy, inhibition of structural damage, and safety of tofacitinib vs methotrexate (MTX, 10–20 mg/wk) in MTX-naïve patients (pts) with active RA.

Methods: Pts were randomized 2:2:1 (double-dummy, double-blind) to: tofacitinib 5 mg twice daily (BID); tofacitinib 10 mg BID; or MTX 10 mg/wk with 5 mg/wk increments every 4 wks to 20 mg/wk. Predetermined primary endpoints (Mo 6) compared tofacitinib vs MTX for: 1) mean changes from baseline (BL) in van der Heijde modified Total Sharp Score (mTSS); 2) ACR70 response. Evaluation of safety and tolerability was also a primary objective. **Results** are from planned 12-mo interim analyses.

Results: Overall, 952 pts were randomized and treated with tofacitinib 5 mg BID (N=371), 10 mg BID (N=395), and MTX (N=186). Demographic and BL RA disease characteristics, including radiographic scores (mTSS: 20.30, 18.85, and 16.51 for 5 mg BID, 10 mg BID, and MTX, respectively), were similar across groups. Mean changes from BL in mTSS and ACR70 rates at Mo 6 were statistically superior for both doses of tofacitinib vs MTX (Table). There was a statistically significant difference in ACR70 response for both doses of tofacitinib vs MTX by Mo 1 (first post-BL visit) with increasing efficacy over time. Secondary radiographic endpoints were also significantly different for tofacitinib vs MTX: smaller changes in erosion and joint space narrowing scores and greater proportions of pts with no progression from BL (mTSS change ≤0.5) at Mo 6. Other secondary endpoints, including ACR20 and ACR50 responses, mean change in DAS28-4(ESR), DAS28-4(ESR) <2.6 rates, and mean change in HAQ-DI, were significantly better with tofacitinib vs MTX at all timepoints.

The incidence of adverse events (AEs) and serious AEs was similar across groups (Table). Most AEs were mild or moderate; the most frequently reported AEs in all groups were infections. Herpes zoster occurred in 2.2%, 2.5%, and 1.1% of tofacitinib 5 mg BID, 10 mg BID, and MTX pts, respectively; 1 pt had bone tuberculosis (10 mg BID) and 1 had cytomega-

lovirus infection (MTX); 2 tofacitinib pts died later in the same trial. Decreases in mean neutrophil counts and small increases in mean serum creatinine were seen in all groups. Increases were seen in mean LDL- and HDL-cholesterol levels with tofacitinib. The incidence of aspartate and alanine aminotransferase elevations ≥3x the upper limit of normal was low.

Table. Primary and selected secondary efficacy endpoints and safety data

	Tofacitinib 5 mg BID (N = 371)	Tofacitinib 10 mg BID (N = 395)	Methotrexate (N = 186)
Efficacy (Month 6)			
LS mean change from BL in mTSS[a,b]	0.18**	0.04***	0.84
Pts with no radiographic progression (mTSS change from BL ≤0.5) (%)[b]	83.5*	89.7***	70.5
ACR20 (%)[c]	71.0***	75.8***	50.5
ACR50 (%)[c]	46.6***	56.2***	27.2
ACR70 (%)[a,c]	25.5***	37.7***	12.0
LS mean change from BL in HAQ-DI[d]	−0.82***	−0.93***	−0.57
DAS28-4(ESR) <2.6 (%)[c]	14.6*	21.6***	7.6
Safety (Months 0–12)			
Discontinuations due to lack of efficacy (%)	4.0	1.8	9.7
Discontinuations due to AEs (%)	3.5	4.3	5.9
AEs (%)	70.1	74.4	69.9
Serious AEs (%)	6.5	6.1	7.0
Infections and infestations (%)	31.8	38.7	27.4
Gastrointestinal disorders (%)	21.0	25.1	34.3

***p < 0.0001; **p < 0.001; *p ≤ 0.05 vs MTX
[a]For mTSS and ACR70 co-primary endpoints, type 1 error rate is protected at 0.05 through a step- down procedure. [b]Full analysis set, linear extrapolation. [c]Full analysis set, non-responder imputation.
[d]Longitudinal model, no imputation
ACR, American College of Rheumatology criteria; AE, adverse event; BL, baseline; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire- Disability Index; LS, least squares; mTSS, modified Total Sharp Score.

Conclusion: In this Phase 3 study tofacitinib monotherapy significantly inhibited progression of structural damage and improved RA signs and symptoms and physical functioning vs MTX in MTX-naïve pts. The safety of tofacitinib was similar to that reported in other Phase 3 trials reported previously.

Disclosure: E. B. Lee, Pfizer Inc., 5; **R. M. Fleischmann**, Pfizer Inc., 2, Pfizer Inc., 5; **S. Hall**, None; **R. F. van Vollenhoven**, Abbott, BMS, GSK, HGS, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, GSK, HGS, MSD, Pfizer, Roche, UCB, 5; **J. Bradley**, Pfizer Inc., 1, Pfizer Inc., 3; **D. Gruben**, Pfizer Inc., 1, Pfizer Inc., 3; **T. Koncz**, Pfizer Inc., 1, Pfizer Inc., 3; **S. Krishnaswami**, Pfizer Inc., 1, Pfizer Inc., 3; **G. Wallenstein**, Pfizer Inc., 1, Pfizer Inc., 3; **S. H. Zwillich**, Pfizer Inc., 1, Pfizer Inc., 3; **B. E. Wilkinson**, Pfizer Inc., 1, Pfizer Inc., 3;

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24-Week Results of a Blinded Phase 2b Dose-Ranging Study of Baricitinib, an Oral Janus Kinase 1/Januse Kinase 2 Inhibitor, in Combination with Traditional Disease Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis. Mark C. Genovese[1], Edward Keystone[2], Peter Taylor[3], Edit Drescher[4], Pierre-Yves Berclaz[5], Chin H. Lee[5], Douglas E. Schlichting[5], Scott D. Beattie[5], Rosanne K. Fidelus-Gort[6], Monica E. Luchi[6] and William Macias[5]. [1]Stanford University Medical Center, Palo Alto, CA, [2]University of Toronto, Toronto, ON, [3]University of Oxford, Oxford, United Kingdom, [4]Veszprém Csolnoky Ferenc County Hospital, Department of Rheumatology and Physical Rehabilitation, Veszprém, Hungary, [5]Eli Lilly and Company, Indianapolis, IN, [6]Incyte Corporation, Wilmington, DE

Background/Purpose: Baricitinib (formerly LY3009104/INCB028050), a novel, oral inhibitor of JAK1 and JAK2 in the JAK-STAT signaling pathway, has been evaluated in a 24 week blinded phase 2b study in patients (pts) with moderate to severe RA with inadequate response to methotrexate (MTX).The primary endpoint after 12 weeks of treatment was met[1]. The 24 week safety and efficacy findings are reported here.

Methods: Pts with active RA (defined as at least 8 swollen and 8 tender joints based on the 66/68 joint assessment) on stable MTX were randomized 2:1:1:1:1 to receive placebo (PBO) or 1of 4 once-daily baricitinib doses (1, 2, 4, or 8 mg) for 12 wks. Pts assigned to 2 mg, 4 mg or 8 mg continued blinded treatment for an additional 12 weeks. Patients assigned to placebo or 1 mg were reassigned to an exploratory 4 mg daily or 2 mg twice daily group between weeks 12–24 and were excluded from the primary 24-week analysis.

Results: Three hundred one pts entered the study. After 12 weeks of treatment, significant differences versus placebo (p<0.05) were observed in the proportion of patients achieving ACR20, ACR50 and ACR70, DAS28CRP<2.6 and CDAI≤2.8, and for DAS28CRP, HAQ-DI and CDAI (Table1). At week 24, patients receiving 2 mg, 4 mg or 8 mg baricitinib

maintained or improved in all measures. Over 12 weeks in the PBO and combined baricitinib groups, there were similar incidence rates of TEAEs (44% vs 41%), infections (12% vs 14%) and SAEs (2% vs 2%, respectively) over 12 weeks. Over 24 weeks in the combined 2 mg, 4 mg and 8 mg groups, the rate of TEAEs was 64% (36% mild, 23% moderate, 5% severe), the rate of infections was 27% (16% mild, 9% moderate, 1% severe), and the rate of SAEs was 5%. There were no opportunistic infections and no deaths. Decreases in hemoglobin and small increases in serum creatinine were seen. Increases were seen in LDL and HDL (Table 2).

Table 1. Primary and Selected Secondary Efficacy Endpoints at 12-and 24 weeks

	PBO (N=98)	1 mg QD (N=49)	2mg QD (N=52)	4 mg QD (N=52)	8 mg QD (N=50)
12 weeks					
% ACR20[†]	41	57*	54	75*	78*
% ACR50[†]	10	31*	17	35*	40*
% ACR70[†]	2	12*	8	23*	20*
% DAS28CRP<2.6[†]	4	14*	15*	37*	22*
%CDAI ≤2.8[†]	1	2	6	21*	12*
DAS28-CRP[§]	4.5	4.0*	4.0*	3.2*	3.6*
CDAI[§]	23.7	20.8	20.7	13.7*	16.3*
HAQ-DI Δ from baseline[§]	−0.10	−0.35*	−0.18	−0.33*	−0.39*
24 weeks					
% ACR20[†]	—	—	63	78	73
% ACR50[†]	—	—	20	48	55
% ACR70[†]	—	—	10	28	24
% DAS28CRP<2.6[†]	—	—	16	34	37
%CDAI ≤2.8[†]	—	—	8	23	22
DAS28-CRP	—	—	3.9	3.0	3.3
CDAI	—	—	19.4	11.1	12.9
HAQ-DI Δ from baseline	—	—	−0.19	−0.33	−0.45

[†]non-responder imputation and 1-sided p-value from Fisher's exact test; [§]2-sided p-value from LY dose vs. PBO contrast from ANCOVA with treatment as fixed factor and baseline (Week 0) value as covariate (Mean, LOCF); *p<0.05 vs. PBO

Table 2. Summary of Laboratory Data at Week 24: Change from Baseline

Mean (SD)	2 mg QD	4 mg QD	8 mg QD
Hemoglobin (g/dL)	−0.28 (1.1)	−0.24 (0.9)	−0.44 (1.0)
Neutrophil count (10^3/mm^3)	−0.25 (2.2)	−0.21 (2.0)	−1.37 (2.3)
Creatinine (mg/dL)	0.04 (0.10)	0.05 (0.08)	0.07 (0.13)
HDL cholesterol (mg/dL)	5.63 (12.21)	5.40 (10.62)	8.24 (13.05)
LDL cholesterol (mg/dL)	11.52 (22.80)	8.75 (32.60)	13.98 (30.87)

Conclusion: Significant improvements in the signs and symptoms of RA versus placebo were observed over 12 weeks. These responses were maintained or improved for an additional 12 weeks of blinded treatment with 2 mg, 4 mg and 8 mg. In addition, safety signals observed over 12 and 24 weeks were consistent with previously conducted studies of baricitinib.

Reference

1. Keystone et al. Ann Rheum Dis 2012;71(Suppl3):152

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Magnetic Resonance Imaging Substudy in a Phase 2b Dose-Ranging Study of Baricitinib, an Oral Janus Kinase 1/Janus Kinase 2 Inhibitor, in Combination with Traditional Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis. Charles G. Peterfy[1], Paul Emery[2], Mark C. Genovese[3], Edward Keystone[4], Peter Taylor[5], Pierre-Yves Berclaz[6], Julie C. DiCarlo[1], Chin H. Lee[6], Douglas E. Schlichting[6], Scott D. Beattie[6], Monica E. Luchi[7] and William Macias[6]. [1]Spire Sciences LLC, Kentfield, CA, [2]University of Leeds, Leeds, United Kingdom, [3]Stanford University Medical Center, Palo Alto, CA, [4]University of Toronto, Toronto, ON, [5]University of Oxford, Oxford, United Kingdom, [6]Eli Lilly and Company, Indianapolis, IN, [7]Incyte Corporation, Wilmington, DE

Background/Purpose: Baricitinib (formerly, LY3009104/INCB028050) is a novel, oral inhibitor of JAK1 and JAK2 in the JAK-STAT pathway. Primary results of this phase 2b study have already been reported and show that baricitinib reduces signs and symptoms of rheumatoid arthritis (RA) with no unexpected safety signals[1]. MRI was used in this study to examine dose dependency of baricitinib on joint changes in a subgroup of patients (pts) with erosive RA and inadequate response to methotrexate (MTX).

Methods: In this phase 2b randomized, double-blind, placebo-controlled trial, 301 pts with active, established RA (≥ 8 swollen and 8 tender joints) on stable MTX were randomized 2:1:1:1:1 to placebo or 1 of 4 once-daily LY doses (1, 2, 4 or 8 mg) for up to 24 weeks. 208 pts (placebo [n=68], 1 mg [n=34], 2 mg [n=40], 4 mg [n=33], 8 mg [n=33]) with definitive radiographic erosion had MRI of the dominant hand/wrist at baseline, week 12 and week 24. Pts assigned to placebo or 1 mg were reassigned to an exploratory 4 mg or 2 mg twice daily group at week 12 and excluded from the 24-week analysis. Fat-suppressed, T1-weighted 3D gradient-echo and STIR images were obtained with and without gadolinium contrast using 1.5T MRI and a hand frame to ensure reproducible positioning. MR images were read independently by 2 expert radiologists blinded to treatment and visit order. Images were scored using RAMRIS and a validated 9-point cartilage loss scale. Total inflammation (osteitis + 3x synovitis) and total joint damage (erosion + 2.5x cartilage loss) scores were calculated. ANCOVA adjusting for baseline score and dose group was used for analysis. Due to the exploratory nature of the substudy, 1-sided p-values less than 0.1 were considered indicative of possible MRI difference (trends) vs placebo.

Results: There was a significant (≥ smallest detectable change) decrease in osteitis over 12 weeks in 15% of pts on placebo vs 29% and 29% on baricitinib 4 and 8 mg, respectively. Similarly, synovitis decreased in 18% of pts on placebo vs 33% and 29% of pts on 4 or 8 mg baricitinib. Significant decreases in bone erosion did not progress in 80% of placebo vs 96% and 88% of pts on 4 or 8 mg baricitinib. Significant decreases in adjusted mean synovitis, osteitis and total inflammation scores were observed in the 4 mg and 8 mg groups compared to placebo at week 12 that persisted to week 24 (table 1). A trend in improvement in total joint damage was also observed for the 4 mg group. These MRI improvements correlated with significant improvements in tender and swollen joints in the 4 mg and 8 mg groups and with numeric decreases in median CRP.

Table 1. MRI and Clinical Changes Over 12 and 24 weeks

MRI and Clinical Parameters	Placebo	1-mg	2-mg	4-mg	8-mg
			Baricitinib Treatment Groups		
Synovitis					
12-week LS Mean change	−0.6	−1.2	−0.6	−1.6	−1.5
p-value[a]	−	NS	NS	0.036	0.047
24-week mean change	−	−	−0.8	−1.7	−2.1
Osteitis					
12-week LS Mean change	−0.4	−1.3	−0.8	−3.6	−2.2
p-value[a]	−	NS	NS	<.001	0.037
24-week mean change	−	−	−1	−3.7	−2.1
Total Inflammation					
12-week LS Mean change	−2.1	−4.9	−2.7	−8.6	−6.6
p-value[a]	−	NS	NS	0.003	0.027
24-week mean change	−	−	−3.5	−8.7	−8.3
Bone Erosion					
12-week LS Mean change	0.8	0.1	0.1	0.3	0.5
p-value[a]	−	0.071	0.051	NS	NS
24-week mean change	−	−	0.5	−0.5	0.2
Cartilage Loss					
12-week LS Mean change	−0.2	0	−0.2	−0.4	−0.2
p-value[a]	−	NS	NS	NS	NS
24-week mean change	−	−	0.2	−0.3	−0.1
Total Joint Damage					
12-week LS Mean change	0.4	0.1	−0.3	−0.8	−0.1
p-value[a]	−	NS	NS	0.068	NS
24-week mean change	−	−	0.9	−1.3	0
CRP (mg/L)					
12-week median	4.6	3.1	2.4	2.3	2.6
24-week median	−	−	3.4	2.5	2.5
Tender joints (of 68)					
12-week LS Mean change	−7.5	−8.8	−10.8	−13.7	−13.4
p-value[b]	−	NS	0.064	<.001	0.001
24-week mean change	−	−	−12.4	−14	−17.5
Swollen joints (of 66)					
12-week LS Mean change	−6.7	−8.4	−8	−10.5	−10.1
p-value[b]	−	NS	NS	<.001	0.002
24-week mean change	−	−	−10	−10.5	−12.2

a 1-sided comparison vs Placebo; b 2-sided comparison vs Placebo; NS=non-significant

Conclusion: MRI findings in this subgroup of pts with active erosive RA suggest dose-dependent suppression of synovitis, osteitis and total inflammation by baricitinib for the 4-mg and 8-mg groups at 12 and 24 weeks. These findings corroborate previously demonstrated clinical efficacy of bariticinib.

1 Keystone et al. Ann Rheum Dis 2012;71(Suppl3):152

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Selective JAK1 Inhibition in the Treatment of Rheumatoid Arthritis: Proof of Concept with GLPG0634. Frédéric Vanhoutte[1], Minodora Mazur[2], Annegret Van der Aa[1], Piet Wigerinck[1] and Gerben van 't Klooster[1]. [1]Galapagos NV, Mechelen, Belgium, [2]State Medical and Pharmaceutical University "Nicolae Testemitanu", Chisinau, Moldova

Background/Purpose: Janus kinases (JAKs) are critical components in signaling pathways for a number of cytokines and growth factors, including those involved in the disease process of rheumatoid arthritis (RA). Non-selective JAK inhibitors have shown long-term efficacy in RA trials with an early onset of action, but doses and thereby efficacy are limited by side effects. By specifically targeting JAK1, we hypothesize that selective inhibition of JAK1 will result in a cleaner safety profile while maintaining high levels of clinical efficacy and a rapid onset of action. We have therefore developed GLPG0634, an orally-available, selective inhibitor of JAK1.

Objectives: Evaluate the short-term efficacy and safety of GLPG0634 in RA patients with insufficient response to methotrexate (MTX) alone.

Methods: A double-blind, placebo-controlled Proof-of-Concept trial in patients with active RA, showing an insufficient response to MTX, was conducted. Twenty-four patients with moderate to severe disease received GLPG0634 200 mg daily, half as once-daily regimen (200 mg QD) and half as twice-daily regimen (100 mg BID), and 12 patients received a matching placebo for a period of four weeks, while continuing to take their stable background therapy of MTX.

Results: Patient and disease characteristics were comparable for all three dose groups, with DAS28 (CRP) disease activity scores between 6.3 and 6.6. In each dose group, 11 out of 12 patients were female. Across the groups the mean background MTX dose was 11 mg/week.

GLPG0634 was found to be well tolerated and safe with a rapid onset and high level of efficacy. Considering the small sample size, no clinically relevant differences were observed among the 100 mg BID and the 200 mg QD dose regimens. GLPG0634 met the primary endpoint of significant improvement in ACR20 response rate. Overall ACR20 responses were observed in 83% of patients receiving GLPG0634 vs. 33% of patients receiving placebo (p<0.01). GLPG0634 showed impressive results in secondary efficacy endpoints, such as the DAS28 (-2.5), and in reductions of serum C-reactive protein levels (-24.4 mg/L), both significant changes vs. placebo (p<0.0001). All patients completed the trial, and no treatment-emergent safety signals were reported. No severe adverse events were reported in patients receiving GLPG0634. Instead of anemia, a modest improvement in hemoglobin was observed. In contrast to observations with JAK inhibitors with other selectivity profiles, no increases in LDL/cholesterol, no liver effects (ALT/AST) and no effect on creatinine were observed in this trial.

Conclusion: These early clinical results are the first to demonstrate that selective inhibition of JAK1 is efficacious and safe for the treatment of RA. Consistent with the lack of inhibition of JAK2, no anemia was observed. Encouraging results include the high level of response within 4 weeks and the absence of effects on LDL/lipid. An extended GLPG0634 dose-range finding trial is now being conducted to further define the optimal doses for efficacy and safety for longer term studies.

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Herpes Zoster and Tofacitinib Therapy in Patients with Rheumatoid Arthritis. K. L. Winthrop[1], H. Valdez[2], E. Mortensen[3], R. Chew[4], S. Krishnaswami[4], T. Kawabata[4] and R. Riese[4]. [1]Division of Infectious Diseases, Oregon Health and Science University, Portland, OR, [2]Pfizer Inc., New York, NY, [3]Pfizer Inc., Collegeville, PA, [4]Pfizer Inc., Groton, CT

Background/Purpose: Patients (pts) with RA are at increased risk for herpes zoster (HZ) i.e. 'shingles'. Tofacitinib, a novel oral Janus kinase inhibitor investigated as a targeted immunomodulator and disease-modifying therapy for RA, down-regulates cytokine-induced signalling that is potentially important to HZ immunity. It has been reported previously that HZ incidence rates (IRs) in the tofacitinib RA program are higher than those reported with biologic and non-biologic DMARDs,[1–4] however the reasons are unknown.

Methods: Adverse events of HZ were identified in the randomized controlled Phase 2, 3, and open-label long-term extension (LTE) tofacitinib RA studies (data cut March 29, 2011). HZ IRs (per 100 pt-years [pt-yrs] [95% CI]) were calculated and logistic regression was used to evaluate potential risk factors for HZ.

Results: In the tofacitinib RA program Phase 2, 3, and LTE studies (4789 pts with 5651 pt-yrs of tofacitinib treatment), 239 tofacitinib-treated pts experienced HZ. One case (0.4%) was multidermatomal, and none involved visceral dissemination or death. Twenty-five pts with HZ (10.5%) permanently discontinued tofacitinib and 16 (6.7%) were hospitalized or received intravenous antiviral drugs. In Phase 3 studies the number of HZ cases and IRs per 100 pt-yrs (95% CI) for each treatment were: tofacitinib 90 cases, IR 4.4 (3.5, 5.4); placebo 3 cases, IR 1.5 (0.5, 4.6); and adalimumab (included as active control in one study) 5 cases, IR 2.8 (1.2, 6.8). In LTE studies, 134 HZ cases were identified in tofacitinib recipients, with an IR of 4.5 (3.8, 5.3). Tofacitinib-associated HZ IRs varied widely across countries of enrollment and were significantly higher among Asians (7.6 [6.3, 9.2]) vs whites (3.3 [2.8, 4.0]), blacks (2.3 [0.7, 7.1]), and others (3.0 [1.8, 4.9]). For tofacitinib-treated pts, those aged ≥65 years (odds ratio [OR] 1.26 [95% CI 0.91, 1.75]), females (OR 1.31 [95% CI 0.89, 1.92]), those using glucocorticoids (OR 1.24 [95% CI 0.95, 1.61]), and those with a longer disease duration (OR 1.02 for each extra year of RA [95% CI 1.00, 1.03]) were more likely to develop HZ. There was no association between HZ risk and background non-biologic DMARD use (i.e. tofacitinib monotherapy or in combination with DMARD), neutrophil or lymphocyte count, or baseline RA severity. In Phase 3 studies, patients treated with tofacitinib 5 mg BID were no more likely to develop HZ than those treated with 10 mg BID (OR 0.96 [95% CI 0.62, 1.51]).

Conclusion: In the tofacitinib RA program, rates of HZ observed among placebo, adalimumab, and tofacitinib-treated pts (particularly in pts of Asian race) were higher than those reported in the literature for patients with RA treated with biologic and non-biologic DMARDs (IRs 0.56–1.32 events per 100 pt-yrs).[2–4] HZ was more common among tofacitinib-treated pts compared with placebo-treated subjects, although confidence intervals were overlapping, with similar rates between tofacitinib 5 mg and 10 mg BID dose groups. Complicated HZ was rare in tofacitinib-treated pts.

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IL-17 Expression Is Low in Psoriatic Arthritis Synovium Compared to Expression in Matched Skin Lesions. Jennifer Belasco[1], Hiroshi Mitsui[1], Mayte Suarez-Farinas[1], James S. Louie[2], Nathan Wei[3], Nicholas Gulati[1] and James G. Krueger[1]. [1]The Rockefeller University, New York, NY, [2]UCLA School of Medicine, Los Angeles, CA, [3]Arthritis Treatment Center, Frederick, MD

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. It is known that treatment modalities are not equally effective for both skin and joint disease, indicating that there are different pathomechanisms driving each component. For example, TNF antagonists are relatively effective treatments for both psoriasis vulgaris and skin/joint manifestations of PsA. However, results from the set of emerging IL-17 antagonists for psoriasis show marked psoriatic lesional skin improvement, but less robust results for PsA joint symptoms. The purpose of this study was to determine differential gene expression between matched lesional skin and affected synovial tissue in patients with psoriatic arthritis to better define the inflammatory pathways of PsA in both skin and joint pathogenesis.

Methods: Matched lesional psoriatic skin samples and synovial samples from inflamed joints were obtained from subjects with PsA (n=13). Gene expression analysis was conducted using Affymetrix HGU133 2.0 plus arrays. The gene expression profile of each diseased tissue was then compared to that of corresponding normal tissue. We considered differentially expressed genes (DEGs) with a cut-off of fold change >2.0 and false discovery rate <0.01. Results were confirmed using RT-PCR with coupled directed pre-amplification. Ingenuity Pathway Analysis (IPA) was utilized to identify canonical pathways among differentially expressed genes.

Results: Principal components analysis demonstrates that there is a clear difference between gene expression patterns of skin and synovium from psoriatic arthritis patients even when adjusted for tissue specificity. The total number of DEGs after adjustment for tissue specificity in both skin and synovium was 2532. The number of genes shared by both was 518. The number of genes unique to the skin was 686 and to synovium was 1328. IPA revealed that the role of IL17A in psoriasis was significant in lesional skin but not in synovial tissue. RT-PCR confirmed the marked expression of IL17A, IL17F, and IL22 in lesional skin compared to inflamed synovium (p<0.05). TNF was present in both tissues without any significant difference between the two. There was no correlation at the messenger level of IL17A, IL17F, IL22 and TNF between pairs of skin and synovium from the same subject.

Conclusion: These results demonstrate that gene expression differs greatly between matched pairs of lesional psoriatic skin and synovium from inflamed joints in patients with PsA. Our results support clinical trial data that indicate psoriatic arthritis skin and joint disease are both responsive to TNF antagonists whereas skin shows better results when compared to joints with IL17 antagonists. Genes selectively expressed in PsA synovium might direct future therapies for this condition.

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Protective and Pathogenic Effects of the IL-23 Family of Cytokines in Spondyloarthropathy in SKG Mice. Helen Benham[1], Linda Rehaume[1], Merja Ruutu[1], Jared Velasco[1], Kristine Kikly[2], Geoffrey Strutton[3], Michael McGuckin[4] and Ranjeny Thomas[1]. [1]Diamantina Institute University of Queensland, Brisbane, Australia, [2]Biotechnology Discovery Research, Eli Lilly and Co., Indianapolis, [3]Department of Pathology, Princess Alexandra Hospital, Brisbane, Australia, [4]Mater Medical Research Institute, Brisbane, Australia

Background/Purpose: IL-23 is required for the expansion and maintenance of T cells and innate cells secreting IL-17 and IL-22. These cytokines are important for control of fungal infections. Genetic studies implicate IL-23 receptor signalling in the pathogenesis of spondyloarthropathies. Spondyloarthritis and Crohn's-like ileitis develop in an IL-23-dependent fashion in ZAP70-mutant SKG mice, which have deficient T cell receptor signalling. Our aim was to determine the role of IL-23, IL-17 and IL-22 in pathogenesis of spondyloarthritis and ileitis in this model.

Methods: SKG mice or IL-17A deficient SKG mice were injected intraperitoneally with curdlan (1,3-D β-glucan) to induce disease. Anti-mouse IL-22, anti-IL-23 or isotype control antibodies were given i.p one day before curdlan, and weekly until sacrifice and anti-mouse IL-23 and IL-17A or isotype control antibodies were given in weekly doses commencing three weeks after i.p curdlan in a treatment regime. Outcomes were measured by clinical and histological scoring. Cytokines were measured by quantitative RT-PCR and in supernatants of cultured tissue explants.

Results: Curdlan induced spondyloarthritis in 100% and ileitis in 60% of SKG mice. Weekly anti-IL-23 treatment of SKG mice from induction suppressed development of spondyloarthritis and decreased the severity of ileitis. In curdlan-treated IL-17A deficient SKG mice, or SKG mice treated with anti-IL-17 from induction, spondyloarthritis and ileitis were less severe than control treated mice. In absence of IL-17A, peripheral enthesitis was particularly spared. Treatment with anti-IL-23 or anti-IL-17 three weeks after induction improved spondyloarthritis and ileitis, and anti-IL-23 was significantly more beneficial than anti-IL17. In contrast, anti-IL-22 modestly suppressed arthritis, increased anti-proteoglycan auto antibodies, and exacerbated ileitis. IL-23 mRNA and protein were expressed within days of induction, and increased over time in the ileum, but not in serum, lymph nodes or joint.

Conclusion: In curdlan-treated SKG mice, initiation and perpetuation of spondyloarthritis is dependent on IL-23, likely derived from the gut. IL-17A is particularly associated with enthesitis. Ileal inflammation is dependent on IL-23 and IL-17A and protected by IL-22. The data suggest that beta-glucan promotes IL-23 secretion, with protective and pathogenic consequences in different tissues through T cell cytokines downstream. Defective T cell signalling in SKG mice not only hinders negative selection of self-reactive T cells but also microbial defence, potentially enhancing the requirement for innate immune mechanisms, including IL-23, IL-17 and IL-22 for host protection.

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The Presence of HLA-B27 Shapes Gut Microbiome Composition in Rats. Mary H. Bach[1], Russell N. Van Gelder[1], Joel D. Taurog[2] and James T. Rosenbaum[3]. [1]University of Washington Medical Center, Seattle, WA, [2]UT Southwestern Medical Center, Dallas, TX, [3]Oregon Health & Science University, Portland, OR

Background/Purpose: The association of spondyloarthropathies (SpA) with HLA-B27 was first described in 1973. However, the mechanism remains unknown. The HLA-B27-human beta2 microglobulin (B27/hβ2m) transgenic (TG) rat model has been used to study SpAs. It is known that the gut microbiome affects the immune response. Previous studies characterized the gut microbiome of TG and wild type (WT) animals using standard culture media or limited 16S rRNA sequencing from denaturing gradient electrophoresis gels. In this study we tested the hypothesis that B27 shapes the cecal microbiome by utilizing a deep DNA sequencing technique called biome representational in silico karyotyping (BRiSK). This technique has the potential for more complete microbiome analysis.

Methods: We studied (21–3×283–2)F1 B27/hβ2m TG rats on the LEW background, which develop arthritis but not colitis (*A&R* 54:1317, 2006), and WT LEW controls. Sixteen rat cecum and content samples (7 TG co-housed with WT, 6 WT co-housed with TG, 3 WT housed separately) underwent DNA digestion and were subjected to BRiSK for high throughput DNA sequencing. Quantitative PCR (qPCR) normalized to 16S was used to confirm the BRiSK results. Statistical analysis was done with Graphpad Prism.

Results: Over 900 bacterial and bacteriophage species were identified using BRiSK. Heat map analysis indicated quantitative differences of 4 bacteria between separately housed WT and TG rats. Two differences were identified by BRiSK and confirmed independently by qPCR (p<0.05 for comparison of non-cohoused wild type to other groups) for the microorganisms *Akkermansia muciniphila* and *Bacteroides vulgatus*. Consistent with other recent reports, co-housing tended to obscure differences in microbiota.

A muciniphila BRiSK
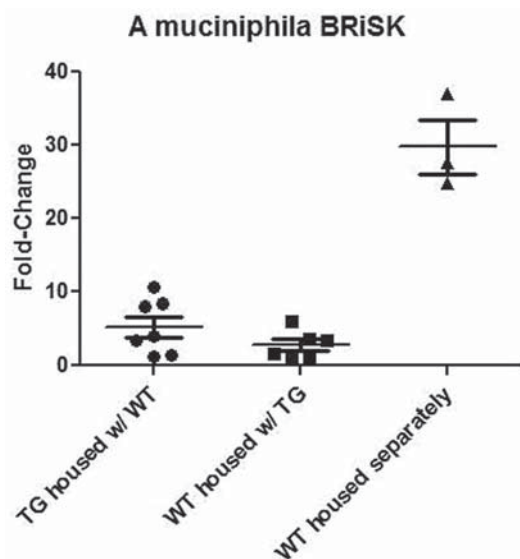
Relative Expression of A muciniphila with Normalization to 16S (qPCR)

B vulgatus BRiSK
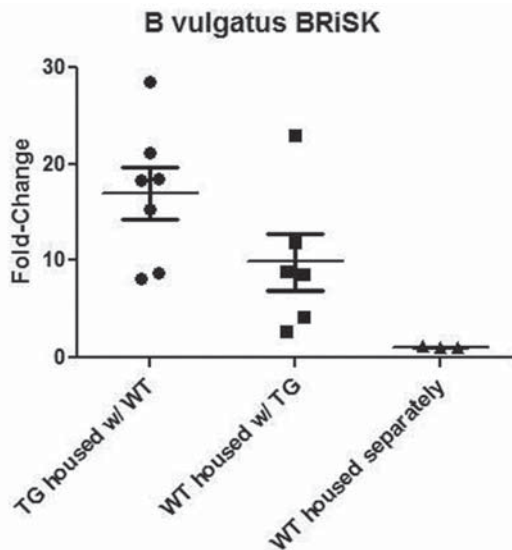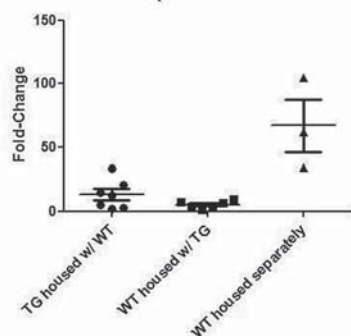
Conclusion: B27/hβ2m TG rats showed altered abundance of certain bacteria in the cecum, compared with WT rats housed apart. Differences were also seen in WT rats housed with the TG rats. *B. vulgatus* has been implicated in the pathogenesis of colitis (*J Clin Invest* 1996;98:945),and *A. muciniphila* is reduced in inflammatory bowel disease (*Am J Gastroenterol* 2010;105:2420). This study suggests that the increase in *B. vulgatus* and reduction of *A. muciniphila* in the TG rats are effects of B27 that may be related to the pathogenesis of SpA.

Disclosure: M. H. Bach, None; **R. N. Van Gelder**, Novartis Institute for Biomedical Research and Alcon Research Laboratories, 2; **J. D. Taurog**, None; **J. T. Rosenbaum**, None.

2494

Incidence and Severity of Spondyloarthritis and Crohn's Ileitis Are Determined by Interaction Between the Microbiota and Genetic Susceptibility in Beta-Glucan-Treated SKG Mice.

Ranjeny Thomas[1], Linda Rehaume[1], Daniel Aguirre de Cárcer[2], Stan Mondot[2], Jared Velasco[1], Helen Benham[1], Merja Ruutu[1], Mark Morrison[2] and Michael McGuckin[3]. [1]University of Queensland Diamantina Institute, Brisbane, Australia, [2]CSIRO Livestock Industries, Brisbane, Australia, [3]Mater Medical Research Institute, Brisbane, Australia

Background/Purpose: Spondyloarthritis and inflammatory bowel disease (IBD) or microscopic gut inflammation co-exist in many patients. These conditions share genetic associations in the *IL23R* signaling pathway. Rodent models of spondyloarthritis or IBD typically improve in germ free (GF) conditions and intestinal microbial diversity is reduced in Crohn's disease, with enrichment in Gram negative rods. Thus resident microbiota are implicated in pathogenesis. We hypothesized that microbiota directly affect incidence and severity of spondyloarthritis and ileitis in SKG mice, where the ZAP-70[W163C] mutation of the BALB/c strain reduces T cell receptor signaling.

Methods: SKG and BALB/c mice were housed in SPF or rederived to GF conditions then injected i.p. with 1,3-D beta-glucan (curdlan). Paw width was scored for 8 weeks. Joint, tail and small intestinal histological sections were scored at sacrifice. The fecal microbiota of BALB/c and SKG mice was assessed by 454 pyrosequencing 0, 3, 7, 10 and 14 days after curdlan treatment. Double principal components analysis (DPCA) and other methods were used to compare phylogenetic groups across samples.

Results: In SPF conditions, i.p. curdlan triggered IL-23-dependent severe spondyloarthritis and Crohn's-like ileitis in 100% and 70% of female SKG mice respectively. BALB/c control mice developed mild peripheral arthritis without ileitis. In GF conditions, the incidence of spondyloarthritis in SKG mice was 10% and ileitis 0%. No priming of anti-proteoglycan autoantibodies occurred without spondyloarthritis. Spondyloarthritis and ileitis incidence and severity, and anti-proteoglycan antibodies were restored when GF mice were reconstituted with a limited bacterial consortium. Within days after curdlan under SPF but not GF conditions, IL-23 and Grp-78 mRNA increased in the ileum, and activated dendritic cells (DC) were recruited to the mesenteric lymph nodes, where IL-17 mRNA expression increased. By DPCA of fecal and cecal microbiota, a large shift in community structure occurred in SKG but not BALB/c mice 3 days after curdlan, related to increased *Bacteroides*-affiliated sequences. Segmented filamentous bacteria were absent. When BALB/c and SKG mice were cohoused after weaning and injected with curdlan at 6 weeks of age, arthritis and ileitis severity was similar in BALB/c and SKG mice cohoused in each cage.

Conclusion: Microbiota are necessary and sufficient for priming spondyloarthritis and Crohn's-like ileitis by DC in gut draining lymph nodes in SKG mice. The SKG mutation predisposes to lack of control of particular transmissable microbial species triggered by systemic delivery of curdlan, which enhance susceptibility to spondyloarthritis and Crohn's-like ileitis.

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2495

Dense Genotyping of Candidate Genes Identifies 16 New Susceptibility Loci in Ankylosing Spondylitis.

Adrian Cortes[1], Philip Robinson[1], International Spondyloarthritis Genetics Consortium[2] and Matthew A. Brown[1]. [1]The University of Queensland Diamantina Insititute, Brisbane, Australia, [2]Brisbane, Australia

Background/Purpose: Ankylosing spondylitis (AS) is a highly heritable inflammatory arthritis common in both Asian and European populations. Thus far genes identified include the HLA-B*27 allele, and 13 non-MHC loci identified in European populations. In this study we aimed to better characterize the genetic architecture of AS and to fine-map known susceptibility loci.

Methods: We successfully genotyped 129,030 polymorphic SNPs in 10,624 AS affected and 15,174 healthy individuals of European and Asian descent using the Illumina Immunochip microarray, which designed for immunogenetic studies.

Results: In this study we identified 16 new AS risk loci reaching genome-wide significance ($P < 5 \times 10^{-8}$), bringing the number of known non-MHC loci to 27. All attempted genome-wide significant loci reported in European populations were replicated. We found multiple independent association signals in 8 of these loci, caused by both common and low frequency variants, suggesting that multiple genetic variants within a gene can affect disease susceptibility. Three AS-loci encoding four aminopeptidases were identified which are involved in peptide handling prior to MHC Class I presentation; protective variants at two of these are associated with both reduced aminopeptidase function and MHC Class I cell surface expression. European and Asian specific signals were observed in *IL23R* and *PTGER4*. Identified loci implicate microbial sensing (*NOS2, NKX2–3, SH2B3* and *ICOSLG*), intracellular antigenic peptide handling (*ERAP1, ERAP2, LNPEP, NPEPPS*) and CD8+ T cells (*EOMES* and *IL7R*) pathways as important in AS etiology as well as increase the number of susceptibility genes in the TH17 pathway (*TYK2* and *IL6R*). A second MHC association with the classical HLA-A*0201 was observed in both HLA-B*27 positive and negative disease (OR=1.2; P= 4.5×10^{-9}).

Conclusion: This increased characterization of the genetic architecture of AS aids greatly in explaining the currently poorly understood high observed heritability and familiality in AS. This data also guides functional studies towards uncovering how these genes cause disease and in the development of new therapeutics**.**

Disclosure: **A. Cortes**, None; **P. Robinson**, None; **M. A. Brown**, None.

2496

Elevated Serum Level of the Vascular Endothelial Growth Factor Is Highly Predictive for New Syndesmophytes Formation in Patients with Ankylosing Spondylitis. Denis Poddubnyy[1], Kristina Conrad[1], Uta Syrbe[1], Hildrun Haibel[1], Heiner Appel[1], Martin Rudwaleit[2] and Joachim Sieper[3]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Endokrinologikum Berlin, Berlin, Germany, [3]Charité Universitätesmedizin Berlin, Berlin, Germany

Background/Purpose: In the recent years several predictors of radiographic spinal progression/syndesmophyte formation in ankylosing spondylitis (AS) were identified: syndesmophytes at baseline (the strongest predictor so far), smoking, elevated level of the C-reactive protein [1]. Furthermore, a number of predictive biomarkers (such as matrix metalloproteinase 3, procollagen II N-terminal propeptide, Wnt-antagonists) were identified, all, however, with a rather modest predictive value. Vascular endothelial growth factor (VEGF) is an essential mediator of the enchondral ossification and, therefore, might play a role in the process of syndesmophyte formation in AS.

The aim of the study was to investigate the predictive role of serum VEGF regarding radiographic spinal progression (new syndesmophytes formation) in patients with AS.

Methods: Altogether 54 patients with AS from the German Spondyloarthritis Inception Cohort (GESPIC) were included in this analysis. Radiographs of the lumbar (lateral and anteroposterior views) and cervical spine (lateral view) performed at baseline and after 2 years of follow-up were centrally collected, digitized, and subsequently scored independently by two trained readers. Syndesmophytes were considered to be present if both readers agreed on it. Serum VEGF levels were detected at baseline.

Results: At baseline, syndesmophytes were present in 25 patients (46%), after 2 years of follow-up new syndesmophytes developed in 6 patients (11%). Mean baseline VEGF value was significantly higher in patients who developed new syndesmophytes in comparison to those without radiographic progression: 544±167 vs 296±159 pg/ml, p=0.004. Receiver operating characteristic (ROC) analysis demonstrated a good performance of VEGF as a predictor of radiographic progression: area under the curve (AUC) = 0.851, p=0.005—figure. A threshold of 494 (rounded for further analysis to 500) pg/ml demonstrated both high sensitivity (83%) and specificity (92%). Elevated VEGF had a positive predictive value of 56%, negative predictive value of 98%, positive likelihood ratio (LR) = 10, negative LR = 0.18, and an odds ratio (OR) = 55.0 (95% CI 5.1–593.4), p=0.001, as a predictor of new syndesmophytes development. This association remained statistically significant also after adjustment for the baseline level of CRP, presence of syndesmophytes at baseline (or mSASSS at baseline), and smoking status.
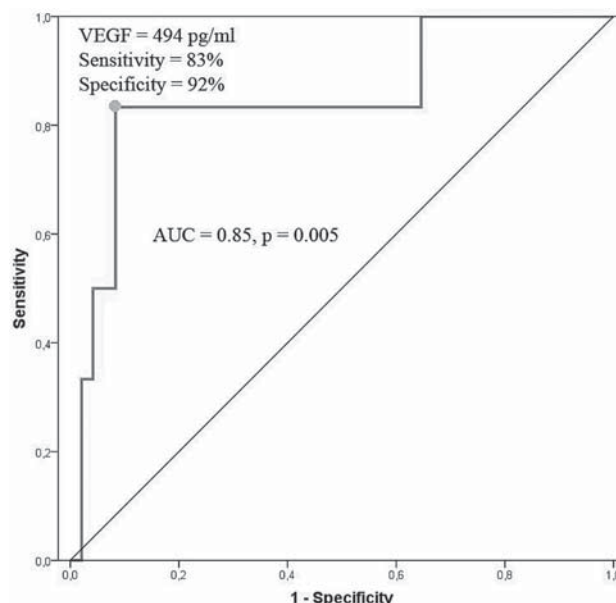
Figure. ROC analysis of the association between VEGF serum level at baseline and development of new syndesmophytes after 2 years in AS.

Conclusion: High serum level of VEGF (>500 pg/ml) seems to be highly predictive for development of new syndesmophytes in patients with AS.

References
1. Poddubnyy D, et al. Arthritis Rheum 2012;64:1388–98.
2. Patil AS, et al. J Cell Physiol 2012;227:1298–308.

Disclosure: **D. Poddubnyy**, None; **K. Conrad**, None; **U. Syrbe**, None; **H. Haibel**, None; **H. Appel**, None; **M. Rudwaleit**, None; **J. Sieper**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

2497

Altered Circulating Follicular Helper T Cell Phenotype and Subset Composition Are Associated with Disease Activity in Patients with Systemic Lupus Erythematosus. Hsi-en Ho[1], Jin Young Choi[2], Viviane M. Bunin[2], Sandra G. Pasoto[3], Solange Carrasco[3], Eduardo F. Borba[3], Celio R. Goncalves[3], Priscila R. Costa[4], Esper G. Kallas[4], Eloisa Bonfa[3] and Joseph E. Craft[2]. [1]Yale University School of Medicine, New Haven, CT, [2]Yale University School of Medicine, Internal Medicine, Section of Rheumatology, New Haven, CT, [3]Universidade de São Paulo, Division of Rheumatology, Faculdade de Medicina, Sao Paulo, Brazil, [4]Universidade de São Paulo, Division of Immunology, Faculdade de Medicina, Sao Paulo, Brazil

Background/Purpose: Autoreactive B cells in SLE undergo autoantigen selection, suggesting a requirement for germinal center follicular helper T (Tfh) cells in their maturation. However, evidence for dysregulation of Tfh cells in SLE and their potential contribution to disease remains unclear. Recently, blood CXCR5+ CD4 T cells, a heterogeneous pool consisting of functionally distinct Th1-, Th2-, and Th17-like subsets, have been proposed to be the circulating counterpart of Tfh (cTfh) cells. We now ask if changes in cTfh markers or subset composition within blood CXCR5+ cells are found in SLE patients, and the extent to which such alterations are associated with B cell and disease activity.

Methods: Blood samples from 49 clinically well-characterized SLE patients, 28 Behçet's disease (BD) patients, and 16 healthy controls were included. Expression of Tfh surface markers (CXCR5; ICOS, inducible T-cell costimulator; PD-1, programmed cell death protein-1), composition of blood CXCR5+ subsets, and frequency of plasmablasts were enumerated by flow cytometry. The phenotype of blood CXCR5+ subsets was

correlated with disease activity, clinical history, and plasmablast expansion.

Results: SLE patients had significant expansion of CXCR5+ ICOS+PD-1+ CD4 T cells compared to controls (p < 0.001). PD-1, but not ICOS or CXCR5, expression was markedly elevated in CD4 T cells of SLE patients compared to BD patients and healthy controls (p < 0.001). PD-1 MFI in CXCR5+ cells correlated with SLE disease activity index (SLEDAI; Spearman r = 0.43, p = 0.03). PD-1 MFI also correlated with expansion of plasmablasts (Spearman r = 0.34, p = 0.02). In SLE patients with high anti-dsDNA antibody titers, PD-1 expression in CXCR5+ cells was also significantly elevated compared to patients with no detectable titers (p = 0.004). Enhanced PD-1 expression was neither a function of disease duration nor past activity; rather, it reflected current disease activity. Compared to BD patients, SLE patients also had an increase in the CXCR5+ Th2 (p < 0.05) and a decrease in the Th17 (p < 0.001) subsets. Concurrently, PD-1 expression in SLE patients was significantly higher in CXCR5+ Th2 cells compared to Th17 cells (p < 0.01). The expansion of the CXCR5+ Th2 subset was also positively associated with SLEDAI scores.

Conclusion: Our results demonstrate that dysregulation of cTfh cells is strongly correlated with disease activity in SLE, supporting a potential causal relationship. The altered composition of blood CXCR5+ cells also appeared to be a fundamental cellular defect in SLE, with our results revealing a novel dimension of Tfh dysregulation that may be central to disease pathogenesis.

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2498

Biomarkers of Mitochondrial Dysfunction Correlate with Disease Activity in SLE. Zhi-Wei Lai[1], Tiffany Telarico[2], Robert Hanczko[1], Adam Bartos[1], Lisa Francis[3], Hajra I. Tily[4], Ricardo Garcia[1], Maha M. Dawood[5], Jianghong Yu[2], Ashwini Shadakshari[2], Paul E. Phillips[6] and Andras Perl[7]. [1]SUNY, Syracuse, NY, [2]SUNY Upstate Medical University, Syracuse, NY, [3]SUNY upstate medical university, Syracuse, NY, [4]SUNY, NY, [5]SUNY Upstate, Syracuse, NY, [6]SUNY-Upstate Medical Univ, Syracuse, NY, [7]Upstate Medical University, Syracuse, NY

Background/Purpose: Systemic lupus erythematosus (SLE) patients' T cells exhibit mitochondrial dysfunction, characterized by the persistent elevation of the mitochondrial transmembrane potential ($\Delta\Psi_m$) or mitochondrial hyperpolarization (MHP), that predisposes to oxidative stress, activation of the mammalian target of rapamycin (mTOR), and pro-inflammatory death via necrosis. Here, we evaluated metabolic checkpoints of mitochondrial dysfunction as biomarkers of disease activity in patients with SLE.

Methods: 49 female SLE patients and 41 female healthy controls were matched for 209 independent study visits. SLE disease activity was assessed by using the British Isles Lupus Assessment Group (BILAG), SLE Disease Activity Index (SLEDAI), and Fatigue Assessment Scale (FAS). Peripheral blood lymphocytes (PBL) and untouched T cells (using Dynal negative T-cell isolation kit) were freshly isolated on the same morning from patients and controls matched for ethnicity and age within 10 years and investigated in parallel for $\Delta\Psi_m$, mitochondrial mass, glutathione, NO and ROI production, cytosolic ($[Ca^{2+}]_c$) and mitochondrial calcium levels ($[Ca^{2+}]_m$), T and B cell subset distribution, and mTOR activity by flow cytometry with or without CD3/CD28 co-stimulation.

Results: The SLEDAI (9.8 ± 0.5), BILAG (25.0 ±0.7) and FAS (26.3 ±0.4) scores showed significant correlations (SLEDAI and BILAG scores: r = 0.5138; p = 0.0014;. FAS and SLEDAI: r = 0.3570; p = 0.0326; FAS and BILAG, r = 0.4341; p = 0.0082). SLEDAI positively correlated with necrotic T cells (r = 0.383; p=0.007), necrotic CD4+ T cells (r = 0.418; p=0.003), and necrotic CD4-/CD8- double negative (DN) T cells (r = 0.347; p=0.016). SLEDAI negatively correlated with Foxp3+/CD25+/CD4+ Tregs (r = -0.293; p=0.043) and CD3/CD28-induced mTOR activation in CD4+ (r = -0.310; p=0.032) and CD8+ T cells (r = -0.410; p=0.004). Among the immunological biomarkers of SLEDAI, C3 negatively correlated with viable CD8+ T cells (r = -0.388; p=0.008) and positively correlated with viable CD4+ T cells (r = 0.405; p=0.005). C4 negatively correlated with MHP of T cells (r = -0.370; p=0.011) and DN T cells by TMRM fluorescence (r = -0.428; p=0.003). C4 positively correlated with viable CD4+ T cells (r = 0.302; p=0.041) and necrotic CD8+ T cells (r = 0.307; p=0.038). Anti-DNA positively correlated with the increased mitochondrial mass in DN T cells (r = 0.438; p=0.002), increased H_2O_2 levels in

CD8+ T cells (r = 0.447; p=0.002), and increased $[Ca^{2+}]_c$ in T cells (r = 0.480; p=0.001), CD4+ T cells (r = 0.467; p=0.001), CD8+ T cells (r = 0.487; p=0.001), DN T cells (r = 0.456; p=0.001), and CD19+ B cells (r = 0.432; p=0.003).

Conclusion: MHP, necrosis rate, and $[Ca^{2+}]_c$, particularly in DN T cells, represent biomarkers of disease activity in patients with SLE.

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2499

The Peroxisome-Proliferator Activated Receptor-γ Agonist Pioglitazone Modulates Aberrant T-Cell Responses in Systemic Lupus Erythematosus. Wenpu Zhao[1], Celine C. Berthier[1], Matthias Kretzler[2] and Mariana J. Kaplan[1]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan, MI

Background/Purpose: Previous studies indicate that PPAR-γ agonists, including pioglitazone (PIO), down-regulate autoimmune responses and renal inflammation in murine SLE. However, the mechanisms implicated in this process remain unclear. We tested the effect of PIO in human SLE and control PBMCs with regards to gene regulation and various functional assays.

Methods: RNA from PIO-treated or untreated SLE and control PBMCs (4–5/group) was extracted and processed on microarrays (Affymetrix Human U133 Plus 2.0). Confirmation of modulation of specific genes was performed by real-time PCR in lupus and control CD3+, CD4+ or CD8+ T cells isolated by magnetic beads.

T cell proliferation was quantified by flow cytometry with CFSE. Numbers and function of peripheral blood T regulatory cells were quantified by flow cytometry, IL10 synthesis and by suppression assays of effector T cells.

Results: Several T cell-related pathways were highlighted in the analysis of the 1362 transcripts altered by PIO-treated vs. unteated SLE PBMCs. In contrast, only 215 mRNAs were modified in the PIO-treated vs. untreated controls. Resulting network analysis showed Interferon-γ as a major regulatory node, with PIO treatment downregulating various genes implicated in T-cell responses. These suppressive effects of PIO were confirmed in in purified CD4+ and CD8+ T cells by real-time PCR, with significative induction of downregulation of *IFN-gamma, CCL4, CCR5, CXCL10* and *HES1*, among others. PIO downregulated lupus CD4+ T cell proliferation, while it significantly increased numbers and function of lupus T regulatory cells, as assessed by IL-10 synthesis and suppression assays of T effector cells. These effects of PIO were not observed in control T cells.

Conclusion: These results indicate that PPAR-γ agonists selectively modulate T cell function in SLE. Given their beneficial effect in murine lupus, these results support the concept that PIO and related-agents should be further explored as potential therapies in this disease.

Disclosure: **W. Zhao**, None; **C. C. Berthier**, None; **M. Kretzler**, None; **M. J. Kaplan**, Takeda, 9.

2500

Podocyte Injury in Membranous and Proliferative Lupus Nephritis: Distinct Underlying Mechanisms? Gabriela M. Rezende[1], Vilma S. T. Viana[1], Denise M. Malheiros[2], Elaine P. Leon[3], Eduardo F. Borba[1], Neila AS Silva[2], Irene L. Noronha[4], Cleonice Silva[4] and Eloisa Bonfá[5]. [1]Division of Rheumatology - Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Division of AnatomoPathology - Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Division of Nephrology - Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [5]University of Sao Paulo, São Paulo, Brazil

Background/Purpose: Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) with proteinuria being the predominant common manifestation and may therefore reflect podocyte injury. Podocytes are highly specialized cells that have a relevant role in the glomerular filtration barrier and alteration in the expression of their biomarkers has been shown to be associated with podocyte dysfunction in some glomerulopathies.

A systematic analysis of podocyte-associated molecules encom-

passing different subcellular compartments was performed in a large series of LN biopsies. Expression of Wilms′ tumor protein (WT1), Synaptopodin (Synpo) and glomerular epithelial protein 1 (GLEPP1) with nuclear, cytoplasmic and membrane distribution respectively, were evaluated attempting to identify if podocyte phenotype is distinct in proliferative and membranous nephritis. Possible association of molecular expression alterations with long term proteinuria severity and outcome in lupus was also investigated.

Methods: Immunohistochemistry analysis was performed using monoclonal antibodies to WT1, Synpo and GLEPP1 proteins in 52 biopsies from patients with lupus nephritis fulfilling the revised ACR criteria for SLE. Demographic, clinical and laboratorial data at the time of biopsy were analyzed.

Results: Thirty-nine (75%) biopsies were classified as proliferative LN and thirteen (25%) as pure membranous class V. Immunohistochemistry analysis in normal kidney revealed preserved staining of WT1, Synpo and GLEPP1 podocyte biomarkers along the capillary walls. Preserved and concomitant WT1 and Synpo staining was observed in a significant higher frequency in pure class V biopsies than in proliferative LN (69.23 *vs*. 2.56%, *p*<0.0001). Likewise, preserved GLEPP1 expression was also more frequent in pure class V LN (53.85 vs. 2.86%, *p*=0.0002). Proteinuria and serum albumin levels at the time of biopsy did not statistically differ in the two groups (*p*=0.87 and *p*=0.41) whereas in the mean long-term follow-up of four years a tendency of lower proteinuria (*p*=0.050) was observed in those patients with biopsies expressing preserved WT1/Synpo staining.

Conclusion: This is the first study comparing proliferative and membranous lupus nephritis which evaluated simultaneously the expression of proteins in different subcellular podocyte compartments and provided novel evidence of preserved podocyte structural architecture predominantly in membranous lesions which may account for a better long term outcome of patients with this LN histological class. These findings suggest possible different underlying mechanisms for proteinuria in both conditions.

Disclosure: G. M. Rezende, None; **V. S. T. Viana**, None; **D. M. Malheiros**, None; **E. P. Leon**, None; **E. F. Borba**, None; **N. A. Silva**, None; **I. L. Noronha**, None; **C. Silva**, None; **E. Bonfá**, None.

2501

Mirorna Mir-150 Contributes to Chronic Kidney Injury in Lupus Nephritis by Increasing the Synthesis of Fibrotic Proteins Via Down-regulation of SOCS1. Hua Zhou[1], Sarfaraz A. Hasni[2], Mayank Tandon[1], Shyh-Ing Jang[1], Howard A. Austin[3], James E. Balow[3], Ilias Alevizos[1] and Gabor G. Illei[1]. [1]NIDCR/NIH, Bethesda, MD, [2]NIAMS/NIH, Bethesda, MD, [3]NIDDK/NIH, Bethesda, MD

Background/Purpose: We have previously shown that renal expression of miR-150 correlates with chronicity index (CI) in lupus nephritis. Since fibrosis is a major histologic feature of the CI we explored the potential role of miR-150 in renal fibrosis. Our data showed a positive correlation between fibrosis and miR-150 expression, therefore we assumed that miR-150 increases the production of pro-fibrotic molecules by downregulating a regulator of fibrotic proteins. The European Bioinformatic Institute (EBI) database identified SOCS-1 (suppressor of cytokine signaling-1) as such a target of miR-150. SOCS-1 has previously been shown to decrease fibronectin in mesangial cells as well as reduce fibronectin and collagen 1 in renal tubular fibroblast. SOCS1−/− mice developed lupus nephritis-like disease. We hypothesized that miR-150 increases the synthesis of profibrotic molecules by down regulating SOCS1.

Methods: The localization of miR-150 in kidney was identified by in situ hybridization in 6 kidney needle biopsies from patients with lupus nephritis (3 from patients with high renal miR-150 and 3 from patients with low renal miR150) and 2 kidneys from autopsies without known kidney diseases. Renal collagen 1(COL1) immunofluorescent staining was performed on the same samples. Primary human renal proximal tubular epithelial cells (RPTEC) and primary human mesangial cells (MC) were used for transfection with miR-150. To confirm SOCS1 as a mir-150 target a luciferase gene linked with the 3'UTR of SOCS1 was cotransfected with miR-150 in RPTEC cells and the luciferase activity was measured 48hrs after the cotransfection. Protein expression of SOCS1 and fibrotic proteins, COL1, collagen 3 (COL3) and fibronectin (FN) were analyzed by western blot in these cultured cells 48hr after miR-150 transfection.

Results: miR-150 predominantly localized in renal cortical proximal tubular cells. Moderate staining was seen in podocytes in kidney biopsies

with high but not in those with low renal miR-150 expression. Immunofluorescent staining showed significantly increased COL1 in kidney biopsies with high renal miR-150 and high CI compared to the kidneys with low renal miR-150 and low CI. Luciferase activity linked to the 3'UTR of SOCS1 was downregulated to 68.5% (p<0.01) of control cells by miR-150 in RPTEC, confirming SOCS1 as a direct target of miR-150. miR-150 transfection significantly decreased SOCS1 signal and increased expression of FN in both RPTEC and MC whereas it led to increased levels of COL3 in RPTEC and COL1 levels in mesangial cells.

Conclusion: miR-150 transfection increased the synthesis of pro-fibrotic molecules in two primary human renal cells by downregulating the expression of SOCS1, a negative regulator of fibrosis. These data together with the previously described observavtion that miR-150 expression in lupus nephritis correlates with chronicity index suggest that miR-150 plays an important role in chronic kidney injury in lupus nephritis.

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2502

Neutrophil Extracellular Trap-Associated Protein Activation of the Inflammasome Is Enhanced in Lupus M1 Macrophages. J. Michelle Kahlenberg, Carolyne K. Smith, Carmelo Carmona-Rivera and Mariana J. Kaplan. University of Michigan, Ann Arbor, MI

Background/Purpose: Neutrophil extracellular traps (NETs) contain numerous bactericidal proteins and are an important defense mechanism against microorganisms. Clearance of NETs is impaired in a subset of patients with systemic lupus erythematosus (SLE), which may contribute to disease pathogenesis. Additionally, we recently described that NETs are vigorously and spontaneously released from low density granulocytes (LDGs) isolated from lupus patients and that these lattices are toxic to the endothelium, expose immunostimulatory molecules and may participate in organ damage through incompletely characterized pathways. We propose that in antigen presenting cells, NETs may act as strong activators of inflammatory pathways, such as the inflammasome, contributing to organ damage. We have examined the role of NETs in inflammasome activation and have specifically characterized the ability of one NET-associated antibacterial peptide, LL37, in stimulating this process.

Methods: Primary human macrophages were derived from monocytes isolated from control and lupus patients. Murine macrophages were cultured from bone marrow. M1 and M2 differentiation were promoted by growth in GM-CSF or M-CSF, respectively, and confirmed by FACs. Spontaneously-induced NETs from LDGs were isolated by micrococcal nuclease incubation to allow their release into the supernatant. Macrophages were primed for 4 hours with 100 ng/ml LPS, prior to stimulation with LL37 peptide or NETs for 2 hours. Active IL-1beta and IL-18 release was determined by ELISA. Quantification of caspase-1 activation was determined by incubating macrophages with a specific fluorogenic marker, followed by fluorescent microscopy.

Results: Stimulation of human macrophages with NETs resulted in activation of caspase-1 and in IL-1beta and IL-18 activation and secretion. Incubation of macrophages with the NET-associated peptide LL37 resulted in robust activation of caspase-1 and release of IL-1beta and IL-18; this activation was enhanced in M1 versus M2 macrophages. Caspase-1 activation required the NLRP3 inflammasome, as murine macrophages deficient in NLRP3, ASC or caspase-1 did not respond to the murine LL37 analog mCRAMP, whereas wild-type macrophages demonstrated caspase-1 activation and IL-1beta release. Comparison of control versus lupus macrophage dose responses to LL37 revealed a lower threshold for inflammasome activation in lupus macrophages, suggesting that exposure to this molecule in vivo may trigger enhanced inflammatory responses. Exposure of lupus macrophages to NETs also led to a significant increase in caspase-1 activation when compared to control macrophages.

Conclusion: Macrophages isolated from lupus patients have enhanced activation of the inflammasome in response to NETs or to the NET-associated peptide LL37. As NETs are increased in SLE, these results suggest that these structures could be an important trigger for inflammasome activation and the resultant downstream inflammatory pathways in SLE patients.

Disclosure: J. M. Kahlenberg, None; **C. K. Smith**, None; **C. Carmona-Rivera**, None; **M. J. Kaplan**, None.

2503

CD8+Foxp3-CD103+ Regulatory T Cells Generated Ex Vivo with TGF-β Suppress Autoimmunity Through IL-10-Dependet Mechanism. Ya Liu[1], An-Ping Xu[2], David A. Horwitz[3] and Song G. Zheng[3]. [1]USC Keck School of Medicine, Los Angeles, CA, [2]2nd Affiliated Hospital of Sun Yat-sen University, [3]Keck School of Medicine of USC, Los Angeles, CA

Background/Purpose: TGF-β is crucial for induction of CD4+Foxp3+ Tregs and maintenance of immunologic tolerance. It is, however, unclear if TGF-β also induces the similar CD8+ Tregs.

Methods: CD8+Foxp3- cells isolated from Foxp3-GFP knock-in mice were stimulated with anti-CD3/28 antibodies and IL-2 with (Tregs) or without TGF-β (Tcon cells). After 3–4 days, Granzyme A/B, Perforin and other Tregs related markers were examined by FACS staining. GFP+, GFP-, GFP+CD103+, GFP+CD103-, and GFP-CD103- were sorted. Suppressive activity in vitro was examined by adding various ratios of CD8+ subsets to responder T cells. Anti-TGF-β, anti-IL-10R, or the TGF-β receptor I (ALK5) inhibitor was added to some cultures. The effect of CD8+ Tregs in vivo was tested following iv injection with 5×10^5 C57BL/6 CD4+CD45RB^{high} cells to Rag2-/- mice. CD8+ iTregs were also injected to Experimental Allergic Encephalomyelitis (EAE) model and lupus-like chronic Graft-versus-host disease (GVHD) model.

Results: While CD8+ iTregs displayed much low Foxp3 expression compared with compartment CD4+ cells, their suppression activity in vitro and in vivo was equivalent or even better. These cells did not express Granzyme A, B or Perforin A and lacked cytotoxic activity on T response cells. CD8+ iTregs generated from Granzyme B and Perforn A KO mice still suppressed autoimmunity. Transwell experiments revealed that cell-contact is required for their suppression. CD8+ iTregs infusion markedly suppressed experimental colitis, EAE and cGVHD. Both Foxp3- and Foxp3+ subsets from TGF-primed CD8+ cells had suppressive activities. Among CD8+Foxp3- cells, CD103 is crucial for their generation and function since CD8+ but not CD4+ iTreg production decreased on CD103 KO mice. CD4+CD103+Foxp3- subset suppressed colitis through IL-10 signal.

Results: While CD8+ cells primed with TGF-β (CD8+ iTregs) displayed much low Foxp3 expression compared with compartment CD4+ cells, their suppression activity in vitro and in vivo was equivalent or even better than CD4+ Tregs. These cells did not express Granzyme A, Granzyme B or Perforin A and lacked cytotoxic activity on T response cells. Additionally, CD8+ iTregs generated from Granzyme B and Perforn A KO mice still suppressed autoimmunity. Transwell experiments revealed that cell-contact is required for their suppressive activity. Adoptive transfer of the CD8+ iTregs markedly suppressed experimental colitis, EAE and cGVHD. We further found both Foxp3- and Foxp3+ subsets from TGF-primed CD8+ cells had suppressive activities. Among CD8+Foxp3- cells, we identified CD103 expression is crucial for their generation and function since CD8+ but not CD4+ iTreg production decreased on CD103 KO mice. Adoptive transfer of CD4+CD103+Foxp3- subset suppressed colitis and EAE and IL-10 signal seems to be crucial for this therapeutic effect.

Conclusion: TGF-β can induce CD8+Foxp3- and CD8+Foxp3+ iTreg subsets that displayed suppressive activity in cell contact-dependent, non-cytotoxic manner and have protective effects on autoimmune diseases. Generation of CD8+ iTregs may have considerable therapeutic potential on patients with autoimmune diseases.

Disclosure: Y. Liu, None; **A. P. Xu**, None; **D. A. Horwitz**, None; **S. G. Zheng**, None.

2504

SOCS1 Is One of the Key Molecules to Prevent the Plasticity of Regulatory T Cells and the Development of Autoimmunity. Reiko Takahashi[1], Kenji Itoh[1], Fumihiko Kimura[1] and Akihiko Yoshimura[2]. [1]National Defense Medical College, Tokorozawa, Japan, [2]Keio University School of Medicine, Tokyo, Japan

Background/Purpose: Suppression of autoimmunity or inflamation by regulatory T cells (Tregs) is now well established, recently, natural Foxp3+ T cells have been shown to be a heterogeneous population consisting of a committed Treg lineage and an uncommitted subpopulation with develop-

mental plasticity. Tregs have been reported to convert into Th1- or Th17-like cells (exFoxp3 cells) under lymphopenic or inflammatory conditions, which might be one of causes of autoimmunity. SOCS1 is defined as an important mechanism for the negative regulation of the cytokine-JAK-STAT pathway. SOCS1-deletion specifically in T cells (LckCre-SOCS1-flox mice) or Tregs (Foxp3Cre-SOCS1-flox mice) induced lupus-like phenomenon such as dermatitis, splenomegaly and lymphoadenopathy, suggesting a defective Treg function in these mice.

We examined the role of SOCS1 to maintain the Foxp3 expression or suppressive functions in natural Tregs.

Methods: Natural Tregs (CD3$^+$CD4$^+$CD25$^+$Foxp3^{GFP}) from LN of wild type (WT), LckCre-SOCS1-flox, or Foxp3Cre-SOCS1-flox mice sorted by flowcytometry

Transfer of Treg cells with naïve T cells into $Rag2^{-/-}$ mice

Single transfer of Tregs into $Rag2^{-/-}$ mice

Tregs cultured with CD3/CD28 or antigen presenting cells in vitro

Results: 1) SOCS1$^{+/+}$Tregs from WT mice efficiently suppressed colitis induced by naive CD4$^+$ T cell transfer into $Rag2^{-/-}$ mice, however, SOCS1$^{-/-}$ Tregs from LckCre-SOCS1-flox mice could not prevent it (n=3). Only SOCS1$^{-/-}$ Tregs transferred into $Rag2^{-/-}$ mice caused colitis, lost Foxp3 expression more rapidly, and converted into IFNγ-producing cells accompanying with hyperactivation of STAT1 (n=3). Foxp3 was stable in IFN$\gamma^{-/-}$ SOCS1$^{-/-}$Tregs (n=3).

2) Because Tregs from LckCre-SOCS1-flox mice were constantly exposed to inflammatory cytokines from non-Treg cells in vivo, we then analyzed Treg specific SOCS1 deficient mice (Foxp3Cre-SOCS1-flox). Tregs from Foxp3Cre-SOCS1-flox mice maintained Foxp3 expression transferred into $Rag2^{-/-}$ mice, on the contrary, those from LckCre-SOCS1-flox mice (n=3).

3) Tregs from LckCre-SOCS1-flox mice produced IFNγ after culture with CD3/CD28 in vitro, however, Tregs from Foxp3Cre-SOCS1-flox mice did not (n=3). When Tregs from Foxp3Cre-SOCS1-flox mice were cultured with antigen presenting cells (APCs) from LckCre-SOCS1-flox mice, they produced IFNγ, which was blocked by anti-IL-12 antibodies (n=3).

Conclusion: SOCS1 plays important roles in maintaining Foxp3 expression and is necessary for suppression activity of Tregs by regulating STAT1 under inflammatory conditions in which APCs are highly activated.

Disclosure: R. Takahashi, None; **K. Itoh**, None; **F. Kimura**, None; **A. Yoshimura**, None.

2505

Involvment of CD4$^+$ FoxP3$^+$ Regulatory T Cells in Interleukin-6 Receptor Targeted Treatment in Murine Arthritis and Rheumatoid Arthritis. Allan Thiolat[1], Jerome Biton[1], Luca Semerano[1], Yves-Marie Pers[2], Pierre Portales[2], Delphine Lemeiter[1], Patrice Decker[1], Christian Jorgensen[2], Pascale Louis-Plence[2], Natacha Bessis[1] and Marie-Christophe Boissier[1]. [1]EA4222, Li2P, University Paris 13, Sorbonne Paris Cité and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, 93009, France, Bobigny, France, [2]Inserm U844, CHU saint-Eloi, Université Montpellier 1, CHU Lapeyronie, Montpellier, France

Background/Purpose: Studies have demonstrated the clinical efficacy of tocilizumab, a humanized anti-IL-6 receptor (R) antibody (Ab), in patients with rheumatoid arthritis (RA). The rational for blocking IL-6 in this disease mainly lays on the pro-inflammatory role of this cytokine in the disease. However, only few works have studied the consequences of anti-IL-6R treatment on Tregs cells and mainly focuses on their frequency. Our objective was thus to elucidate anti-IL-6R mode of action, by studying the consequences of this treatment on Tregs phenotype and biological activity. in RA patients treated with tocilizumab and in a RA model, namely collagen-induced arthritis (CIA).

Methods: Mice with CIA were treated at day 0 by MR16-1 (a rat anti-mouse IL-6 receptor monoclonal Ab provided by Chugai Pharmaceutical Co. LTD, Japan) and the evolution of Tregs (defined as CD4$^+$ FoxP3$^+$) during arthritis course was assessed at key time points (day 8–18–28 and 42 after CIA induction) by studying their number, frequency and phenotype (expression of GITR, ICOS, Helios, CD62L, CTLA-4 and CD39) in lymph nodes (LN), thymus and spleen by flow cytometry. The immunosuppressive activity of the Treg cells on CFSE-labeled CD4+ CD25- T effector (Teff) cells proliferation was also studied. Numerical analysis of Th17 and Th1 cells was also performed at the same times by flow cytometry.

Twenty patients with severe and active RA, refractory to methotrexate or anti-TNF therapies were recruited and treated with 8mg/kg of tocili-

zumab monthly. Peripheral blood was recovered for each patient at day 0, as well as 1 and 3 month, and Th17and Tregs were analyzed by flow cytometry.

Results: In mice, clinical and histological evaluation of arthritides in mice treated with anti-mouse IL-6R mAb showed, as expected, a less severe disease as compared to control Ig treated mice. Th17 frequency was unchanged, but Tregs frequency was enhanced in the LN of MR16-1 treated mice. In the thymus, we observed an enhanced frequency of Tregs $CD4^+CD8^-FoxP3^+$. Tregs phenotype was also modified in treated mice, with an increased frequency of $CD39^+$ Tregs (LN and spleen), suggesting an enhanced ATP hydrolysis immunosuppressive activity of Tregs. In contrast, the immunosuppressive activity of the Treg cells on Teff cells proliferation was not modified.

In RA patients, we also shown that tocilizumab did not changed Th17 frequency but rather acted on Tregs. Indeed, in responder patients to tocilizumab, $CD4^+CD25^+FoxP3^+$ staining was confined to $CD127^{low}$, suggesting the induction of induced Tregs following treatment.

Conclusion: Tregs, but not Th17, are modified by anti-IL-6R treatment in RA, that could result in an enhanced central and peripheral generation of Tregs. These results highlight the benefit of therapeutic approaches based on Treg promotion in RA, and stress the relevance of the monitoring of cell populations in arthritis following cytokine blockade.

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2506

Expression of Helios Facilitates Distinction Between FoxP3$^+$ Treg and FoxP3$^+$ Activated T Conventional Cells in Patients with Systemic Lupus Erythematosus. Amit Golding[1], Sarfaraz A. Hasni[2], Gabor G. Illei[3] and Ethan M. Shevach[4]. [1]NIAID/National Institutes of Health, Bethesda, MD, [2]National Institutes of Health, Bethesda, MD, [3]NIDCR/NIH, Bethesda, MD, [4]NIAID/NIH, Bethesda, MD

Background/Purpose: FoxP3 is not a reliable marker for distinguishing regulatory T (Treg) cells in humans due to the fact that FoxP3 may be up-regulated in activated, conventional T (Tconv) cells. Recently, the marker CD45RA has been added to distinguish RA^+, "resting" FoxP3$^+$ Tregs from RA^- "activated" FoxP3^{hi} Tregs (Miyara et al, 2009). This scheme has also included a third "non-Treg" group that is RA^- and expresses lower levels of FoxP3 similar to that seen in RA^+ Tregs. Previous data demonstrated that in normal individuals as well as in patients with systemic lupus erythematosus (SLE), the largest subset of FoxP3$^+$cells is, in fact, the "non-Treg" group. The transcription factor Helios has recently been defined as a marker of thymus-derived Tregs in both mouse and man (J. Immunol. 2010). The goal of this study was to determine if expression of Helios could reliably indicate what fraction of FoxP3$^+$cells are true Tregs in healthy controls and in SLE patients.

Methods: Samples included 35 healthy donors and 52 SLE patients (23 SLEDAI 0; 19 SLEDAI 2–4; 10 SLEDAI 6–20). Ficoll-purified PBMCs were surface stained followed by fixation/pemeabilization and intracellular staining prior to FACS analysis. When appropriate, cells were pre-stimulated for 4–5 hours with PMA/ionomycin/golgistop. CpG methylation analysis of sorted cells was performed using the Qiagen EpiTect platform.

Results: We found that $CD4^+$ T cells in SLE patients contain both resting (RA^+) and activated (RA^-/FoxP3^{hi}) Tregs and that the majority of cells in each group were Helios$^+$, (3/4 and 4/5, respectively). Surprisingly, even within the sub-group defined as "non-Tregs", the majority of the cells in both healthy controls (2/3) and SLE patients (3/4) were Helios$^+$. All FoxP3$^+$ Helios$^+$ cells, including those within the "non-Treg" RA^- subset, were found to be demethylated at the FoxP3 locus (a gold standard epigenetic mark of the Treg lineage), as compared to Helios$^-$cells. In pre-stimulated cells, FoxP3$^+$ Helios$^-$ cells consistently produced significantly high amounts of cytokines (IFN-gamma and IL-2), whereas FoxP3$^+$Helios$^+$ cells produced essentially no cytokines, which is characteristic of Tregs. In SLE patients with mild and highly active disease, there was a significant increase in both the % Foxp3$^+$Helios$^+$ and % FoxP3$^+$Helios$^-$ relative to both healthy controls and inactive patients (p<0.05, Mann-Whitney test). There was not a significant difference for *absolute* numbers of either Helios$^+$ or Helios$^-$ cells, likely due to the significant reduction in total CD4 counts in more active patients (p<0.05, Mann-Whitney test).

Conclusion: Expression of Helios is a highly useful tool for distinguishing true Tregs from FoxP3$^+$ cells that include activated Tconvs. The use of Helios has allowed us to de-convolute the largest subset of CD45RA-based grouping of FoxP3 cells. Furthermore, we have also shown that active SLE patients *do* have a higher frequency of FoxP3$^+$Helios$^+$ Tregs, but that in active SLE patients these are counter-balanced with a higher frequency of Foxp3$^+$Helios$^-$ cells that contain cytokine-producing Tconvs. Future studies may make use of Helios to reliably monitor both true Tregs and activated Tconvs in SLE and other autoimmune diseases.

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2507

Activated Cullin-Ring Ubiquitin Ligases (CRLs) Dampen T Cell Signaling and Inactivation of Crls Arrests the Progression of Inflammatory Arthritis. Leonard L. Dragone[1], Lisa K. Peterson[1], Allison Berger[2] and Samantha F. Friend[1]. [1]National Jewish Health, Denver, CO, [2]Millennium Pharmaceuticals, Inc, Cambridge, MA

Background/Purpose: The role of Cullin-Ring ubiquitin ligase (CRL) activity in regulating T cell function is largely unexplored. Thus, we sought to determine if cullin neddylation and CRL activity regulates signaling initiated through the T-cell receptor (TCR) complex to modulate T cell activation and effector functions.

Methods: To determine if TCR complex signaling affects CRL activity, we treated T cells *in vitro*, with a specific neddylation inhibitor (MLN4924), a drug currently undergoing clinical trials for several malignancies, that prevents CRL activation in combination with CD3 activation and measured IL-2 production. We then assessed CRL activity during TCR complex signaling by examining the neddylation status of the cullin subunit of the CRL. In addition, we knocked down the cullin subunit of the CRLs in T cell lines and examined T cell function. Further we treated arthritis prone mice that have a TCR signaling defect with MLN4924 *in vivo* to assess the impact of CRL inactivation on T cell activation and effector function.

Results: Treating T cells with MLN4924 lowers the threshold for TCR signaling, as evidenced by enhanced IL-2 production and regulatory T cell (Treg) development upon suboptimal TCR stimulation. Moreover, MLN4924 treatment of the arthritis-prone SKG mouse, arrests arthritis progression and decreases the numbers of IL-17 producing T cell effectors *in vivo*. We found that strong TCR complex signaling results in cullin deneddylation, which renders the CRL inactive. After knocking down cullins in T cell lines, we found that IL-2 production is increased compared to the parental cell line, but some individual cullin knockdowns do not achieve the same enhancement of IL-2 production as MLN4924 treatment, suggesting that multiple CRLs contribute to regulating TCR complex signaling and IL-2 production.

Conclusion: Thus, we propose that strong TCR complex signaling normally triggers cullin deneddylation to shut off CRL activity and the otherwise tonic ubiquitination and degradation of proteins essential for TCR complex signaling and IL-2 production. Ongoing studies are elucidating the specific CRL targets that contribute to the phenotype seen.

Significance: These findings represent the first step in understanding the interplay between neddylation, CRL-mediated ubiquitination and TCR complex signaling. Expanding our knowledge of how CRLs neddylation regulates TCR complex signaling and T cell function will create opportunities for developing drugs to modulate T cell function to treat immune-mediated diseases.

Disclosure: **L. L. Dragone**, None; **L. K. Peterson**, None; **A. Berger**, Millenium Pharmaceuticals, 3; **S. F. Friend**, None.

2508

miR142-3p Interfers with T Cell Proliferation by Targeting the Expression of Garp in Patients with Rheumatoid Arthritis. Qihui Zhou, Sonja Haupt, Johannes Thomas Kreuzer, Hendrik Schulze-Koops and Alla Skapenko. University of Munich, Munich, Germany

Background/Purpose: Rheumatoid arthritis (RA) is a systematic chronic inflammatory disorder, characterized by severe joint destruction. Regulatory T cells (Tregs) have been implicated to be important for maintaining peripheral tolerance and controlling disease development. A novel surface protein, Glycoprotein A repetitions predominant (GARP), was recently identified to be specifically expressed on human Tregs and important for the suppressive capacity of Tregs. Several studies suggest that GARP expression in Tregs is post-transcriptionally regulated. In this study, we investigated in detail miRNA regulation of GARP expression, and dissected

the functional outcome of miRNA:GARP-mRNA interaction and its resulting effects in patients with RA.

Methods: *In silico* analysis was performed to predict putative miRNA binding sites (MRE) in the 3'UTR of the GARP mRNA. Luciferase reporter vectors were used to identify specific GARP 3'UTR-recognizing MREs. Ribonucleoprotein immunoprecipitation (RNP-IP) was performed using antibodies against the Ago1- or Ago2-asscociated RISC complex. For cell proliferation and GARP expression, CD25+ and CD25- CD4 T cells were isolated from the peripheral blood. Cells were transfected with miRNA mimics or antagomirs and labeled with CFSE. The proliferating capacity was accessed by FACS. For Treg function assays, CD25+ T cells were transfected with miRNA mimics and co-cultured with CFSE-labeled CD25- T cells. Eight patients with early treatment naive RA (disease duration 3.0±2.4 months, DAS28 5.2±1.2) and 20 age and gender-matched healthy individuals were analyzed for GARP surface expression as accessed by FACS, or GARP mRNA and miRNA expression as measured by RT-PCR.

Results: The distal part of the GARP 3'UTR was capable to down-modulate reporter protein expression. Within this region, one MRE was recognized by its miRNA, miR142-3p. Mutation of this site abrogated the respective miRNA recognition confirming the specificity of the binding to the GARP 3'UTR. GARP mRNAs and miR142-3p were both immunoprecipitated in the Ago2-associated RISC complex by RNP-IP using an antibody against Ago2. Co-transfection with the antagomir of miR142-3p prevented GARP mRNA loading into the Ago2-associated RNP complex. CD25+ CD4 T cells treated with the antagomir showed a higher proliferating capacity upon stimulation. Complementary, treatment of cells with miRNA mimics lead to reduction of proliferation. CD25+ CD4 T cells treated with miRNA mimics showed a reduced suppressive capacity. The up-regulation of miR-142-3p was more prominent in RA patients than in healthy individuals resulting in consequentially diminished up-regulation of GARP.

Conclusion: We identified and characterized miR-142-3p regulation of GARP expression in Tregs. miR142-3p is critical for high GARP expression on Tregs and therefore for Treg function. Delineation of miR-142-3p expression and the linked GARP expression in RA provides an important hint for the reduced Treg function in RA.

Disclosure: **Q. Zhou**, None; **S. Haupt**, None; **J. T. Kreuzer**, None; **H. Schulze-Koops**, None; **A. Skapenko**, None.

ACR/ARHP Combined Abstract Session
ACR/ARHP Combined Epidemiology Abstract Session
Tuesday, November 13, 2012, 2:30 PM–4:00 PM

2509

Cost-Effectiveness of Training Rural Providers to Perform Joint Injections. Michael J. Battistone, Richard E. Nelson, William D. Ashworth, Andrea Barker. Marissa Grotzke, Timothy A. Huhtala, Robert Z. Tashjian and Grant W. Cannon, Salt Lake City VA and University of Utah, Salt Lake City, UT

Background/Purpose: Community based outpatient clinics (CBOCs) have been established by the Department of Veteran Affairs (VA) to provide primary care services to veterans living in remote and rural regions. While CBOCs provide excellent primary care services, the current model does not allow providers in CBOCs to develop and deliver specialty services. The objective of this study was to evaluate the cost-effectiveness of training rural primary care providers to perform knee injections in CBOCs, rather than referring the patient to an urban medical center with rheumatology and orthopaedic specialists. Referral often involves significant travel for patients in rural areas.

Methods: We developed a decision analytic model to compare costs and outcomes between rural providers who are trained to perform knee injections and those who are not trained. In the model, each type of provider is presented with a hypothetical patient who has knee pain and should receive an injection. Costs included in the model (including medical management for patients who do not receive an injection, training of the rural provider to perform injections, travel reimbursement for patients who are sent to an urban medical center) were from the perspective of the VHA. The effectiveness outcome was quality-adjusted life years (QALYs). In our primary analysis, a range of values were used for 2 key inputs: the number of patients with knee pain presenting to the rural clinic in 1 year period (range:10–100) and the average distance from the patients' home address to the urban medical center (range:50–500). Probabilistic sensitivity analyses were performed using

1,000 2nd order Monte Carlo simulations and the benefits of knee injection were assumed to last 90 days.
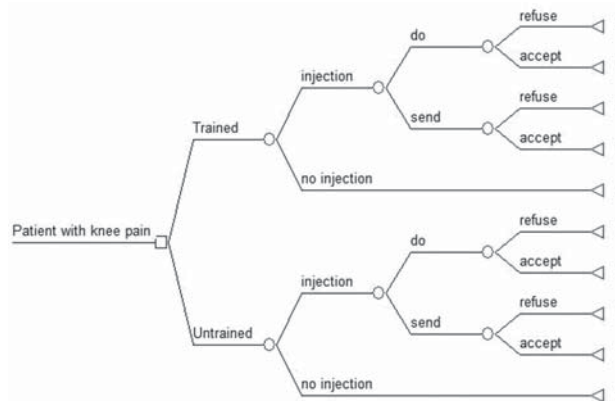
Results: In our base case analyses (which assumed 30 patients per year presenting with knee pain that could benefit from an injection and an average distance of 100 miles from the patient's home adders to the urban medical center), the incremental cost-effectiveness ratio (ICER) for trained rural providers was $27,692/QALY. ICERs were more sensitive to the number of patients than to distance Table 1. Training rural providers was cost-effective in 68.6% of 1,000 Monte Carlo simulations at a willingness to pay threshold of $50,000/QALY.

Incremental cost effectiveness ratios for range of values for average distance and number of patients per year (US dollars/QALY)

	Number of patients			
Distance	10	30	50	100
50	$70,732	$27,888	$19,319	$12,893
100	$70,536	$27,692	$19,124	$12,697
200	$70,145	$27,301	$18,732	$12,305
500	$68,970	$26,126	$17,557	$11,130

Conclusion: Training rural providers to perform knee injections for patients with knee pain appears cost-effective at the commonly used threshold of $50,000/QALY if sufficient numbers of such patients are seen at rural primary care clinics. We are currently implementing such a training program to test the validity of these projections.

Disclosure: **M. J. Battistone**, None; **R. E. Nelson**, None; **W. D. Ashworth**, None; **A. Barker**, None; **M. Grotzke**, None; **T. A. Huhtala**, None; **R. Z. Tashjian**, None; **G. W. Cannon**, None.

2510

Patient and Provider Factors Associated with Compliance with Rheumatoid Arthritis Treatment Recommendations. Leslie R. Harrold[1], George W. Reed[2], Katherine C. Saunders[3], Ying Shan[1], Tanya Spruill[4] and Jeffrey D. Greenberg[5]. [1]UMass Medical School, Worcester, MA, [2]University of Massachusetts Medical School, Worcester, MA, [3]CORRONA, Inc., Southborough, MA, [4]NYU School of Medicine, New York, NY, [5]New York University School of Medicine, New York, NY

Background/Purpose: Only approximately 50% of rheumatoid arthritis (RA) patient with active disease receive care consistent with the American College of Rheumatology (ACR) recommendations for the use of biologic and nonbiologic disease modifying anti-rheumatic drugs (DMARDs). Therefore we examined patient and provider factors associated with receipt of the recommended care using data from a multi-center observational registry within the United States (the Consortium of Rheumatology Researchers of North America: CORRONA).

Methods: We identified biologic naïve RA patients cared for within the CORRONA network between 12/08 and 12/11. Initiation or dose escalation of biologic and nonbiologic DMARDs in response to active disease (using the Clinical Disease Activity Index) was assessed in comparison to the ACR recommendations. The population was divided into two mutually exclusive cohorts: 1) methotrexate (MTX) only users; and 2) multiple non-biologic DMARD users. We compared the characteristics of patients (age, gender, race/ethnicity, working status, insurance

and RA disease characteristics) who received care consistent with the ACR recommendations and their treating providers (gender, years since medical school graduation, academic vs. private practice and region of the country [Northeast, South, Midwest and West]) to those who did not in the two cohorts with active disease using logistic regression adjusting for clustering of physicians and patients.

Results: There were 5,196 patients who met inclusion criteria cared for by 191 providers at 86 practice sites. Of the 991 MTX only users with active disease (moderate disease activity with a poor prognosis or high disease activity), 44% received care consistent with the treatment recommendations. In adjusted analyses, patient characteristics including age 65 and older (OR 0.70; 95% CI 0.54–0.91), female gender (OR 1.47, 95% CI 1.10–1.98) and prednisone dose (OR 1.37, 95%CI 1.05–1.79) were associated with care practices while physician characteristics were not. Among the 1209 multiple nonbiologic DMARD users with moderate or high disease activity, 48% received care consistent with the recommendations. Patient age 65 and older (OR 0.73, 95% 0.57–0.94), residence in the South (OR 0.69, 95% CI 0.50–0.94) or Midwest (OR 0.73, 95% CI 0.54–0.99) and care by a private practice rheumatologist (OR 0.56, 95% CI 0.37–0.83) were associated with a reduced likelihood of receiving care consistent with the recommendations.

Conclusion: Compliance with the ACR treatment recommendations is influenced by both patient and provider characteristics. Identification of these characteristics will help us identify which patients and providers to target for interventions to improve care.

2511

Potential Barriers That Limit Access to Rheumatologists Among Patients with Early Rheumatoid Arthritis in a Universal Access Health Care System. Jessica Widdifield[1], J. Michael Paterson[2], Sasha Bernatsky[3], Karen Tu[2], Nadia Gunraj[2], Noah Ivers[1], Debra Butt[2], R. Liisa Jaakkimainen[1], J. Carter Thorne[4], Vandana Ahluwalia[5] and Claire Bombardier[1]. [1]University of Toronto, Toronto, ON, [2]Institute for Clinical Evaluative Sciences, Toronto, ON, [3]Research Institute of the McGill University Health Ctre, Montreal, QC, [4]Southlake Regional Health Centre, Newmarket, ON, [5]William Osler Health Center, Mississauga, ON

Background/Purpose: Current guidelines for the optimal care of rheumatoid arthritis (RA) recommend prompt referral to a rheumatologist. In the province of Ontario, Canada all 13 million residents are covered by universal public health insurance. However, almost 2 million residents do no have a regular family physician. Previous research has shown that sustained continuity of primary care plays a positive role in patient health outcomes for other chronic diseases. However, the impact of sustained continuity of primary care on access to rheumatologists remains unstudied. This is particularly concerning since family physicians function as gatekeepers for access to rheumatologists. Our objective was to estimate the percent of incident RA patients who see a rheumatologist within 1 year of diagnosis, and to identify determinants of contact with a rheumatologist within 1 year of RA diagnosis.

Methods: We assembled an incident RA cohort aged >65 years from Ontario health administrative data across 1997–2008. We used a validated algorithm to identify 27,127 seniors with early RA. We followed patients for 1 year, assessing if they had a visit to a rheumatologist. We assessed secular trends and differences for patients who saw a rheumatologist versus those who had not. We performed multilevel logistic regression analyses to determine whether receipt of rheumatology care was associated with: patient characteristics, primary care physician characteristics and provider continuity, and geographic characteristics.

Results: Overall, 17830 (66%) seniors with early RA identified over 1997–2008 saw a rheumatologist within 1 year of diagnosis. This increased from 50% in 1997 to 78% in 2008. The majority of patients (67%) were female. Few patients (16%) resided in rural areas. Factors associated with a rheumatologist encounter included increasing continuity of primary care, [adjusted Odds Ratio (aOR)=1.30 95% CI 1.11, 1.53], patients of highest socioeconomic status (SES) [aOR=1.24 95% CI 1.13–1.36], and having more rheumatologists in the area (Rheumatology supply per 100,000 adults aOR=1.20 95% CI 1.16, 1.24). Less contact with rheumatologists occurred among patients with increasing age (aOR= 0.97 95% CI 0.97, 0.98), patients

who had male primary care physicians (aOR=0.73 95% CI 0.66, 0.80), residing in a rural area (aOR=0.74 95% CI 0.68, 0.81) and at a remote distance (≥100 km) to the closest rheumatologist (aOR=0.37 95% CI 0.31, 0.44).

Conclusion: Improvements in access to rheumatologists for RA care have occurred over time but more efforts are needed. Potential barriers that limit timely access to rheumatologists include increasing age, lower SES, and having a male primary care physician. Measures of poor access (poor continuity of primary care, density and proximity to rheumatologists) negatively impacted rates of encounters with a rheumatologist. Proactive, tailored approaches are needed to provide rheumatology care to such populations.

2512

Changes in Bone Marrow Lesion Volume Relate to Changes in Knee Pain. Data From the Osteoarthritis Initiative. Jeffrey B. Driban[1], Lori Lyn Price[1], Grace H. Lo[2], Jincheng Pang[3], Eric Miller[3], Charles Eaton[4], John A. Lynch[5] and Timothy E. McAlindon[1]. [1]Tufts Medical Center, Boston, MA, [2]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, [3]Tufts University, Medford, MA, [4]Warren Alpert Medical School at Brown University, RI, [5]University of California at San Francisco, San Francisco, CA

Background/Purpose: Changes in bone marrow lesions (BMLs), common magnetic resonance (MR) imaging findings in osteoarthritis (OA), are predictive of OA progression. However, it is unclear if quantitative measurements of BML volume change are related to knee pain. Therefore, the purpose of this study was to determine whether quantitative measures of BML volume change are positively associated with knee pain change.

Methods: The sample comprised 404 participants in the Osteoarthritis Initiative (OAI) progression cohort who had sagittal intermediate-weighted, turbo spin echo, fat-suppressed MR images at the 24- and 48-month OAI visits. The right knee was assessed unless contraindicated. BML volume was determined on the sagittal fat-suppressed MR images by one rater using a semi-automated segmentation method (ICC [3,1 model] = 0.95). BML volumes were calculated for each knee region and then summed to form a total knee BML volume (cm^3). Knee pain was defined based on WOMAC pain score at the 24- and 48-month OAI visits. Multiple linear regressions were used to evaluate the association between the WOMAC pain, as an outcome, and BML volume while controlling for sex, weight, height, and age. To further explore these associations we assessed the associations stratified among tertiles based on baseline BML volume. Based on diagnostic tests (e.g., DFFITs, Cook's D) for the linear regression models among tertiles we opted to perform robust regression models. WOMAC scores and participant characteristics are available at http://oai.epi-ucsf.org.

Results: The cohort included 199 (49%) females and were 64.9 ± 9.2 years old, 85.3 ± 16.2 kg, and 1.7 ± 0.1 m. The average baseline total knee BML volume was 2.6 ± 2.7 cm^3(range =0.1 to 10.2 cm^3). Total knee BML volume change was -0.2 ± 2.1 cm^3(range =-12.7 to 10.2 cm^3; see Figure). Larger BML volumes are associated with greater knee pain and larger BML volume changes are associated with worsening knee pain (see Table). Stratified analyses by baseline BML volume (tertiles) indicated that only in the first tertile (no BMLs or BMLs < 1.0 cm^3) was BML volume change and WOMAC pain change significantly related (estimate = 0.65, standard error =0.25, p = 0.009).

Table. Cross-sectional and Longitudinal Association between BML Volume and WOMAC Pain

Outcome Variable Stratified by Baseline BML Volume Tertile	Descriptives Mean ± SD	Models* with Baseline BML Volume B (p-value)	Models* with BML Volume Change B (p-value)
Full Cohort (n = 404)			
WOMAC pain (baseline)	3.3 ± 3.4	0.16 (0.01)	n/a
WOMAC pain (change)	0.0 ± 3.0	−0.01 (0.87)	0.21 (0.004)

* All models adjusted for sex, weight, height, and age. SD = standard deviation, BML = bone marrow lesion, B = parameter estimate, n/a = not assessed.
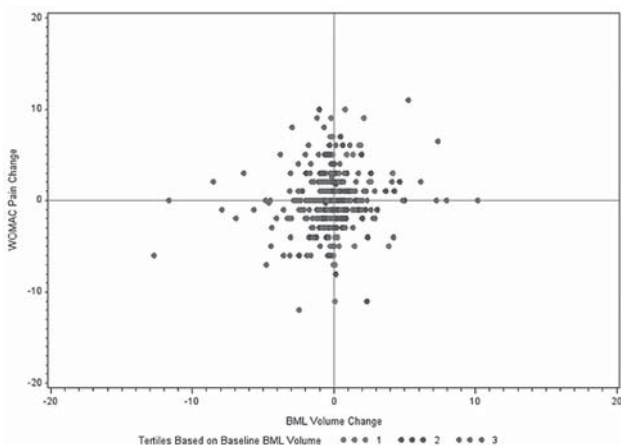
Figure. Scatter plot of WOMAC Pain Change by BML Volume Change Stratified by Tertiles (colors). Tertiles, based on baseline BML volume, had average baseline total knee BML volumes of 0.6 ± 0.2 cm^3, 1.6 ± 0.5 cm^3, and 5.5 ± 2.9 cm^3; respectively.

Conclusion: Change in BML volume is associated with change in knee pain severity. This association may primarily be driven by knees that are progressing from no or small BML volumes to larger BML volumes.

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Association of Arthritis and Joint Pain with Accelerometer-Measured Physical Activity in Adults Aged 50 and Older in the United States: Findings From the National Health and Nutrition Examination Survey (2003–2004). Kathryn Remmes Martin[1], Dane Van Domelen[1], Matthew Pantell[1], Ming-yang Hung[1], Tamara B. Harris[1] and Kushang Patel[2]. [1]NIA/NIH, Bethesda, MD, [2]University of Washington, Seattle, WA

Background/Purpose: To compare the prevalence of meeting current public health physical activity (PA) guidelines by arthritis and knee/hip joint pain status, and to examine the relationship between arthritis, joint pain and accelerometer-measured PA in US older adults.

Methods: Data are a sample of 1680 men and women from the 2003–2004 NHANES aged $\geq$50 years who had 4+ valid days ($\geq$ 10 hrs $\cdot$ d^{-1}) of hip-worn accelerometer wear-time. PA was examined 2 ways: 1) adherence to PA guidelines of accumulated 10-minute bouts of moderate/vigorous physical activity (MVPA) (inactive: no bouts; insufficient <150 min $\cdot$ wk^{-1}; recommended: $\geq$150 min $\cdot$ wk^{-1}) using average daily minutes; and 2) average counts per minute (CPM) during wear-time and min $\cdot$ d^{-1}spent in sedentary, light, lifestyle, and MVPA. Participants self-reported doctor-diagnosed arthritis and knee and/or hip joint pain, and were categorized as follows: 1) no arthritis or joint pain (NEITHER); 2) arthritis only (ARTH); 3) joint pain only (JP); and 4) arthritis and joint pain (BOTH). Regression analyses adjusted for age, education, race, occupation, BMI, smoking status, self-rated health, self-reported functional limitations, arthritis-attributable limitations, and current pain medication use. All analyses were stratified by gender and accounted for NHANES PA monitor sampling weights.

Results: Age-adjusted prevalence of arthritis and joint pain (knee and/or hip) was 44% and 47%, respectively. These conditions co-occurred in 33% of participants (BOTH); 42% had NEITHER condition, 11% had ARTH only, and 14% had JP only. Having BOTH was more common among women (40%) than in men (24%).

The proportions of women meeting PA guidelines in the NEITHER (5%) and JP (6%) groups were similar. Women with ARTH and BOTH had the lowest proportion of recommended PA (<1%; 2%). Only 7% of men without either condition (NEITHER) achieved recommended PA, which was similar to men with ARTH (7%); however, the proportion meeting recommended PA was substantially lower in men with JP or BOTH (2%; 3%).

Regression models adjusted for demographics showed that women with ARTH, JP, or BOTH had lower CPM and lower levels of PA by various measures, which remained significant, though attenuated, after further adjustment for health conditions and functional limitations. Rela-

tive to the NEITHER group, women with ARTH had fewer CPM (B=-23.6, p=0.027) and fewer min $\cdot$ d^{-1} of MVPA (B=-3.2, p$\leq$0.001), and women with BOTH had 2.4 fewer min $\cdot$ d^{-1}of MVPA (p=0.013). Among men, only those with BOTH had fewer min $\cdot$ d^{-1}of MVPA compared to men in the NEITHER group (B=-12.2, p=0.004); however further adjustment for health conditions and functional limitations yielded unexpectedly higher CPM, fewer sedentary min $\cdot$ d^{-1}, and greater time in lifestyle-intensity activity in men with ARTH and BOTH compared to men in the NEITHER group.

Conclusion: Adherence to PA guidelines was low across all groups. Our data suggests gender differences in the relationship between arthritis, joint pain and PA. Women with ARTH and BOTH were generally less active, whereas men with ARTH and BOTH were more active than those with NEITHER. Continued PA promotion and pain management should be intensively targeted to US older adults with arthritis and joint pain.

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2514

Racial/Ethnic Trends in Incidence and Prevalence of Rheumatoid Arthritis in a Large Multi-Ethnic Managed Care Population. Aniket A. Kawatkar[1], Cecilia Portugal[1], Li-Hao Chu[2] and Rajan Iyer[1]. [1]Kaiser Permanente Southern California, Pasadena, CA, [2]Kaiser Permanente Southern California, Pasadena

Background/Purpose: As epidemiologic studies throughout the world have shown significant variations, we sought to characterize racial differences in longitudinal epidemiologic trends of adult rheumatoid arthritis (RA) in a large, racially diverse, managed care organization. The study objective was to estimate racial/ethnic differences in incidence density (ID) and prevalence rates (PR) of RA over time, while adjusting for age, and gender.

Methods: This was a retrospective population based study using active members from a large managed care health plan, during 01/01/2002 and 12/31/2010. RA patients were identified using a diagnosis code for RA in combination with the use of a disease modifying antirheumatic treatment within a year of the diagnosis code date. Subjects were required to be between the ages of 18 years and 100 years at the time of diagnosis. Non-RA adult health plan members informed the denominator for the ID and PR rates which were calculated on an annual basis. The longitudinal trend of ID and PR across 2002 to 2010, was further stratified by race/ethnic groups (Caucasian; Hispanic; African American; Asian and Other race); age (18–34; 35–44; 45–54; 55–64; and >= 65), and gender. Negative binomial regression models were used to estimate age, gender and race, adjusted rate ratios, for incidence density (aIDr) and prevalence (aPRr). The negative binomial models also included yearly dummy indicators to evaluate the statistical significance (alpha 0.05) in changes of these rates overtime.

Results: During the study period, a total of 8,108 incident cases and 58,644 prevalent cases of RA were identified. The majority of incident (76.9%) and prevalent (77.8%) cases were females. The major race/ethnic group was Caucasians, in the incident (55.8%) as well as the prevalent (64.2%) cases. Due to the predominance of females, the negative binomial models were stratified by gender. For females, the aIDr (mean (95% CI) with Caucasians as reference category) was as follows: Asian 0.7 (0.51–0.89); African Americans 1.0 (0.77–1.35); Hispanics 0.6 (0.45–0.78) and other race 0.9 (0.72–1.25). The aPRr in females (with Caucasians as reference category) was as follows: Asian 0.69 (0.56–0.83); African Americans 1.02 (0.84–1.24); Hispanics 0.45 (0.37–0.55) and other race 0.88 (0.73–1.07). Additionally, as compared to the 18–34 year age group, all other age groups had significantly higher aIDr and aPRr in both genders. Lastly, as compared to reference year 2002, the time trend for aPRr confirmed a statistically significant increase in prevalence rates in both genders.

Conclusion: We find evidence of racial differences in epidemiologic trends in RA with Asians and Hispanics having significantly lower incidence density and prevalence rates as compared to Caucasians. We also find evidence on increase in incidence and prevalence of RA with increasing age and also increase in prevalence rates over time.

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2515

Low Density Lipoprotein Receptor Deficiency Results in Osteophyte Formation During Experimental Osteoarthritis Which Is Enhanced Under High Cholesterol Conditions. Wouter de Munter, Birgitte Walgreen, Monique M. Helsen, Annet W. Sloëtjes, Wim B. van den Berg and Peter L.E.M. van Lent. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Synovial macrophages are involved in osteophyte formation during experimental collagenase-induced osteoarthritis (OA). Accumulated LDL can be oxidized in an inflammatory environment such as OA and be taken up by scavenger receptors of macrophages, changing the macrophage fenotype. The effect of LDLr deficiency and cholesterol accumulation on OA pathology was investigated using an experimental OA model.

Methods: LDLr deficient (LDLr$^{-/-}$) mice and their wild type (WT) controls received either a high cholesterol or control diet for 120 days. Experimental OA was induced by intra-articular injection of collagenase on day 84 and 86. Paraffin sections of total knee joints were stained with safranin O – fast green or haematoxylin – eosin to determine OA development. Thickening of the synovial lining layer was measured using an arbitrary scale (0 to 3). Cartilage destruction was determined in four cartilage surfaces of the knee joint (lateral and media femur and tibia) using the OA score developed by Pritzker *et al.*(2006), adapted by us for mice (0 to 30). Size of osteophyte formation was determined using image analysis by measuring osteophyte surface areas at the margins of the tibial plateau and femoral condyles. Data are depicted as mean ± SD.

Results: WT mice receiving a normal diet developed moderate cartilage destruction (6.1 ± 2.6), synovial thickening (1.4 ± 0.6), and osteophyte formation (56.5 μm^2 ± 94.6). Both LDLr$^{-/-}$ groups showed comparable cartilage destruction and showed no change in bodyweight (23.99 g ± 1.85). WT mice receiving a cholesterol-rich diet showed increased bodyweight compared to the other three groups (28.82 g ± 4.81; p<0.0001), however, no significantly increased cartilage destruction was observed. No differences between the four groups were found regarding synovial thickening. LDL levels were significantly higher in LDLr$^{-/-}$ mice compared to WT mice (7.33 mmol/L ± 1.44 and 0.54 mmol/L ± 0.11 respectively; p<0.0001), which was additionally increased by a cholesterol-rich diet (38.73 mmol/L ± 9.84; p<0.0001). At the tibial plateau, LDL$^{-/-}$ mice showed almost a 4 times increase of osteophyte formation compared to WT mice (206.3 μm^2 ± 196.3; p<0.05). When receiving a cholesterol-rich diet, osteophyte formation at the lateral side of the tibial plateau in LDLr$^{-/-}$ mice further increased from 107.0 μm^2 ± 156.0 to 309.4 μm^2± 132.0 (p<0.05).

Conclusion: Enhanced LDL levels correlate with increased osteophyte formation in LDLr$^{-/-}$ mice, suggesting a pathologic role of LDL accumulation during OA.

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Adenosine Receptors Stimulate Bone Regeneration by Targeting Osteoclasts. Aranzazu Mediero[1], Tuere Wilder[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY

Background/Purpose: Various types of orthopedic procedures, including spinal fusion and repair of bone defects due to trauma, infection or metastatic disease, require formation of new bone. Adenosine, generated from the catabolism of adenine nucleotides, modulates cell function by interacting with specific cell-surface receptors (A$_1$R, A$_{2A}$R, A$_{2B}$R, A$_3$R). We have previously reported that A$_1$R receptor blockade and A$_{2A}$R stimulation inhibit osteoclast (OC) differentiation but only A$_{2B}$R stimulation affects osteoblast (OB) differentiation or function. We determined whether A$_1$R blockade, A$_{2A}$R stimulation or enhancing adenosine concentrations via blockade of purine transport into cells via ent1 with dipyridamole regulates bone formation in a murine calvarial model.

Methods: Male C57Bl/6 mice were anesthetized, a 3mm trephine defect

was formed and covered with a collagen scaffold soaked in saline or 1mM adenosine receptor agonists/antagonists. Animals received appropriate treatment daily until sacrifice. At 0, 2, 4, 6 and 8 weeks calvarias were harvested and prepared for microCT and histology. XenoLight Rediject Bone Probe 680 was injected intravenously at different time points.

Results: 8 weeks after surgery microCT examination of mouse calvaria demonstrate that an A$_1$R antagonist (DPCPX), A$_{2A}$R agonist (CGS21680M) or dipyridamole markedly enhances bone regeneration (77±0.2%, 60±2% and 79±2% bone regeneration, respectively, vs. 32±4% in control, p<0.001, n=5 mice per condition) whereas an A$_3$R agonist (IB-MECA) had no effect (32±3% regeneration, n=5). In DPCPX-, CGS21680- and dipyridamole-treated mice there is increased immunostaining for osteoblast or bone formation markers (Alkaline Phosphatase, Osteocalcin and Osteonectin) in the bony defects (Alkaline Phosphatase positive cells/hpf increased from 15±1 for control to 22±1 for DPCPX, 21±1 for CGS21680 and 24±1 for Dipyridamole, p<0.001), and diminished inmunostaining for macrophages (CD163, TNfa) and osteoclasts (RANKL, RANK) in treated defects when compared to control. TRAP staining revealed fewer OCs in DPCPX-, CGS21680- and Dipyridamole-treated defects (14±1, 17±1 and 16±1 OC/hpf respectively vs. 24±1 Osteoclast/hpf for control, p<0.001) 8 weeks after defect formation. In vivo imaging with XenoLight Rediject Bone Probe 680 (a marker of bone formation) reveals a strong fluorescent signal in treated animals (DPCPX, CGS21680 and Dipyridamole) compared to control as soon as one week after bone defect formation and lasting for at least 7 weeks.

Conclusion: Inhibition of OC formation via A$_{2A}$R stimulation, A$_1$R blockade or increasing local adenosine concentration stimulates new bone formation and represents a novel approach to stimulating bone regeneration.

Disclosure: A. Mediero, None; **T. Wilder**, None; **B. N. Cronstein**, Canfite BioPharma, 1, NIH, URL Pharma, OSI, 2, Bristol-Myers Squibb, Novartis, URL, Regeneron, Gismo Therapeutics, 5, Arthritis Foundation, SLE Foundation, 6, Patents on use of adenosine receptor antagonists to treat or prevent fibrosis. Multiple other patents.

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Inhibition of Notch Signaling Increases the Severity of Experimental Osteoarthritis. Neng-Yu Lin[1], Alfiya Distler[2], Christian Beyer[2], Clara Dees[2], Jingang Huang[3], Francesco Dell'Accio[4], Oliver Distler[5], Georg A. Schett[1] and Joerg HW Distler[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]William Harvey Research Institute, Barts and the London Queen Mary's School of Medicine and Dentistry, Centre for Experimental Medicine and Rheumatology, London, United Kingdom, [5]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Notch signaling is triggered by binding of ligands such as Jagged-1 (Jag-1) to Notch receptors, which results in cleavage of Notch receptors by the γ-secretase complex and subsequent release of the active Notch intracellular domain (NICD). The NICD is the central regulator of the pathway, which translocation to nucleus where it interacts with the DNA binding factor RBP-J. Aberrant Notch signaling has been implicated into the pathogenesis of various diseases including cancer, Alzheimer's disease and fibrosis. Of note, increased expression of Notch signaling pathway has recently been observed in OA chondrocytes. However, the implications of the findings for the pathogenesis of OA and potential therapeutic implications have not been investigated so far.

Here, we aimed to further elucidate the role of Notch signaling pathway in OA using genetic and pharmacological inhibition of Notch signaling in the mouse model of destabilization of the medial meniscus (DMM) induced OA.

Methods: To analyze the activation status of the Notch cascade, we quantified the mRNA expression of Notch receptor family by real-time PCR and also analyzed the expression of NICD and Jag-1 protein by immunohistochemistry. To characterize the effects of Notch inhibition on osteoarthritis development *in vivo*, we evaluated the outcome of Notch anti-sense transgenic mice or mice treated with the γ-secretase inhibitor DAPT in the DMM (destabilization of the medial meniscus) model of OA. We used a modified Mankin score to analyze the histological changes. Hypertrophic differentiation of chondrocytes was analyzed by staining for Collagen X. We also analyzed the mRNA level of Epas1 and Aggrecanase-1 by real-time PCR.

Results: We demonstrated that the mRNA levels of Notch1 are increased by 200 ± 79 % in human OA cartilage (p<0.05). Moreover, the protein levels of Jag-1 and of the NICD are upregulated in human OA cartilage. Similar results were also obtained in murine OA induced by DMM.

However, genetic or pharmacologic inhibition of Notch signaling exacerbated the osteoarthritic changes in the DMM model. The modified Mankin score upon surgical DMM was significantly increased in mice expressing a Notch-1 anti-sense construct or upon treatment with DAPT ($56 \pm 6\%$ increase in Notch as tg and $60\% \pm 5$ increase in DAPT treated mice compared to non-transgenic or sham-treated DMM controls, respectively, p<0.01 for both). Immunostaining for Col X was also strongly increased upon inhibition of Notch signaling indicating increased differentiation into hypertrophic chondrocytes. Genetic or pharmacologic inactivation of Notch signaling also enhanced the mRNA expression of OA markers, such as Epas1 (increases by up to $94 \pm 10\%$ (p<0.05)), Aggrecanase-1 (increases by up to $150 \pm 20\%$ (p<0.01)).

Conclusion: We demonstrate that Notch signaling is hyperactivated in chondrocytes of OA patients. However, inhibition of Notch signaling pathway enhances chondrocyte hypertrophy and exacerbates osteoarthritis in the DMM model, indicating that the activation of Notch signaling in OA is a counter-regulatory mechanism to ameliorate chondrocyte dedifferentiation and cartilage damage.

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The Sphingosine-1-Phosphate Pathway Is a Key Regulator of Bone Substrate-Mediated Osteoclast Differentiation in Inflammatory Arthritis. P. Edward Purdue[1], Jon Hill[2], Steven R. Goldring[3], Nikolaus B. Binder[3], Jennifer L. Swantek[4], Zhenxin Shen[5], Tania N. Crotti[5], Gerald H. Nabozny[4] and Kevin P. McHugh[5]. [1]Hospital for Special Surgery, Weill Cornell Medical Center, New York, NY, [2]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, [3]Hospital for Special Surgery, New York, NY, [4]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [5]Center for Advanced Orthopedic Studies, Beth Israel Deaconess Medical Center, Boston, MA

Background/Purpose: Multiple lines of evidence have established that osteoclasts are required for physiologic bone resorption and pathological bone loss in inflammatory disorders. Isolation of differentiated osteoclasts from bone is technically challenging, but with the discovery that M-CSF and RANKL are sufficient for osteoclast differentiation came the ability to generate multinucleated osteoclasts from myeloid precursor cells *in vitro* with high efficiency. *In vivo,* analysis of osteoclasts at sites of bone resorption reveals that functionally activated osteoclasts are almost exclusively localized to the immediate bone surface, indicating that cell-substrate interactions contribute to terminal osteoclast differentiation. In this study, we have employed a unique *in vitro* osteoclastogenesis system using authentic bone substrates and expression profiling and pathway analysis to identify critical bone substrate-mediated pathways of osteoclast formation and activation. We have further validated the sphingosine-1-phosphate (S1P) generation, transport and signaling pathway as a key component of the bone-substrate regulated osteoclast differentiation program *in vitro* and *in vivo*.

Methods: Murine bone marrow derived macrophages were cultured in the presence or absence of RANKL on plastic, hydroxyapatite, or calvarial bone discs. RNA was isolated at different stages of osteoclast generation and subjected to microarray analysis. Pathway analysis was performed using GSEA and Ingenuity pathway analysis. SphK inhibitors were used to validate involvement of S1P signaling in osteoclastogenesis *in vitro*. Immunohistochemical analysis of the RA bone-pannus interface was used assess activation of this pathway in osteoclasts *in vivo*.

Results: Microarray analysis revealed unique clusters of RANKL induced and bone substrate-modulated osteoclast genes. Of 1490 genes upregulated by RANKL in differentiated osteoclasts, 5.4% were further upregulated by culture on the bone substrate; an additional 8.5% were downregulated. Pathway analysis identified the S1P pathway as significantly regulated by both RANKL and bone substrate, and that this regulation was dependent upon the presence of integrin beta 3, a key mediator of osteoclast attachment to bone. SphK inhibitors dose-dependently blocked RANKL-induced human and mouse osteoclastogenesis *in vitro*. Furthermore, SphK1 was highly induced in osteoclasts at sites of RA bone erosions.

Conclusion: Interaction of osteoclasts with the bone surface regulates multiple critical pathways of osteoclast formation and activation. Pathway analysis and *in vitro/in vivo* validation identifies the S1P pathway as a critical regulator of RANKL-bone-dependent osteoclastogenesis. This pathway represents a novel therapeutic target for preventing osteoclast-mediated bone destruction in inflammatory bone loss disorders.

Disclosure: **P. E. Purdue**, Boehringer Ingelheim, 2; **J. Hill**, Boehringer Ingelheim, 3; **S. R. Goldring**, Boehringer Ingelheim, 2; **N. B. Binder**, Boehringer Ingelheim, 2; **J. L. Swantek**, Boehringer Ingelheim, 3; **Z. Shen**, Boehringer Ingelheim, 2; **T. N. Crotti**, Boehringer Ingelheim, 2; **G. H. Nabozny**, Boehringer Ingelheim, 3; **K. P. McHugh**, Boehringer Ingelheim, 2.

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IL-1β and TNF-α Regulate the Global and Locus-Specific hydroxymethylation of Genomic DNA by Modulating the Expression and Activity of Tet-1 in Human OA Chondrocytes. Abdul Haseeb[1] and Tariq M. Haqqi[2]. [1]Case Western Reserve University, Cleveland, OH, [2]Metro Health Medical Center, Cleveland, OH

Background/Purpose: 5-hydroxymethylcytosine (5-hmC), which is formed by the oxidation of 5-methylcytosine (5-mC), is a recently discovered epigenetic mark and is highest in brain and in embryonic stem cells. There have been reports supporting the notion that generation of 5-hmC may be a mechanism of DNA demethylation and thus important in the regulation of gene expression. In the present study we investigated the global and locus-specific 5-hmC content in the promoter region of MMP-3 gene and its expression in human OA chondrocytes. We also investigated the effect of IL-1β and TNF-α on the level of 5-hmC, expression and activity of the enzymes responsible for hydroxylation of 5-mC to generate 5-hmC and MMP-3 in human chondrocytes.

Methods: Primary human chondrocytes were isolated from the deep zone of the cartilage obtained from OA patients who underwent total joint replacement (n=8) and were treated with IL-1β and TNF-α for 48 hr. Global 5-hmC content in genomic DNA was quantified using a 5-hmC-specific ELISA (Epigentek, Farmingdale, NY). Total TET methylcytosine dioxygenase (Tet) activity was determined by an ELISA based activity assay kit (Epigentek). Tet-1, Tet-2 and Tet-3 and MMP-3 mRNA levels were quantitated by using the TaqMan assays (Applied Biosystems, Carlsbad, CA). Locus specific 5-mC and 5-hmC content in the MMP-3 promoter was examined by using EpiMark 5-mC and 5-hmC analysis kit (NEB, Ipswich, MA), which uses methylation sensitive HpaII and glucosylation sensitive enzyme MspI following the treatment of genomic DNA with T4-β-glucosyl transferase, and PCR using specific primers. Data were derived using Origin 6.1 software and $P<0.05$ was considered significant.

Results: The global content of 5-hmC in human chondrocytes was found to be 0.1–0.2% of the total genome. There was approximately 70% decrease (P<0.05) in the 5-hmC content upon treatment with IL-1β in combination with TNF-α for 48 hrs. This correlated with the reduction of Tet enzyme activity in chondrocytes after treatment with IL-1β and IL-1β + TNF-α. There was a significant (upto 20 fold) reduction in the level of Tet-1 mRNA expression while expression of Tet-3 mRNA was increased slightly (2–3 fold). The level of Tet-2 mRNA expression did not change upon treatment with the cytokines. MMP-3 promoter contained a high percentage (70%) of 5-hmC at HpaII locus in deep zone chondrocytes and these chondrocytes showed a dramatic (40 fold) increase in the expression level of MMP-3 upon treatment with IL-1β and TNF-α.

Conclusion: Our results demonstrate for the first time the presence of a significant amount of 5-hmC in human chondrocyte DNA. We also for the first time show that the 5-hmC content of the genomic DNA can be modulated by treatment with proinflammatory cytokines IL-1β and TNF-α in a short span of 48 hrs. The changes in 5-hmC levels correlated with the Tet-1 gene expression level and Tet enzyme activity in chondrocytes stimulated with IL-1β + TNF-α. Our data also demonstrate that the expression of MMP-3 was significantly (P<0.005) increased in chondrocytes with high content of 5-hmC in its promoter region. Taken together our novel data identify an important role for DNA hydroxymethylation in cartilage and may be important in understanding the mechanism and pathogenesis of OA.

Disclosure: **A. Haseeb**, None; **T. M. Haqqi**, None.

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Suppressor of Cytokine Signaling 3 Is Reduced in Obese Patients with Osteoarthritis and Regulates Leptin Responses in Chondrocytes. Anna Koskinen[1], Katriina Vuolteenaho[1], Riku Korhonen[1], Teemu Moilanen[2] and Eeva Moilanen[1]. [1]The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland, [2]Coxa Hospital for Joint Replacement, Tampere, Finland

Background/Purpose: Leptin is an adipokine whose concentrations in circulation are proportional to body fat stores and body mass index (BMI). Initially leptin was discovered to regulate energy metabolism and body weight. More recently it has been recognized as effector and regulator in inflammation and arthritis. Leptin has been shown to have detrimental effects on cartilage metabolism including upregulation of proinflammatory and catabolic factors.

Suppressor of cytokine signaling 3 (SOCS-3) is an intracellular regulator of inflammatory response and a negative regulator of leptin's effects in hypothalamus. It has also been shown to be expressed in chondrocytes and overexpression of SOCS-3 has been reported to reduce severity of arthritis in mice models.

The aim of the present study was to explore how SOCS-3 expression in osteoarthritic (OA) cartilage is related to obesity and synovial fluid levels of matrix metalloproteinases (MMPs) 1 and 3 and leptin in OA patients. We also studied the role of SOCS-3 in regulating leptin-induced inflammatory responses in chondrocyte cultures.

Methods: We collected synovial fluid and cartilage samples from 91 OA patients [age 70.2 (9.6) years, BMI 30.8 (5.8) kg/m^2; mean (sd); females 66%] undergoing knee replacement surgery. Leptin, MMP-1 and MMP-3 in synovial fluid were measured by immunoassay. SOCS-3 expression in cartilage (from a subgroup of the patients, n = 28) was determined by Western blotting. The results were analyzed in the whole group and in two subroups divided by BMI (non-obese, BMI < 30 kg/m^2, n = 45; obese, BMI > 30 kg/m^2, n = 46). In addition, H4 chondrocytes and OA cartilage were used in the cell culture experiments. Interleukin-6 (IL-6), MMP-1 and MMP-3 were measured in the culture media by ELISA, and inducible nitric oxide synthase (iNOS) expression was determined by RT-PCR and Western blotting.

Results: Leptin concentrations in synovial fluid were higher (p < 0.001) and SOCS-3 expression in cartilage samples was lower (p = 0.032) in obese than in non-obese patients. Leptin correlated positively with MMP-1 and MMP-3 levels in synovial fluid from obese (r = 0.49, p = 0.001; r = 0.48, p = 0.001, respectively) but not from non-obese patients. SOCS-3 levels in the cartilage correlated negatively with synovial fluid MMP-1 and MMP-3 (r=-0.49, p=0.013; r=-0.44, p=0.024, respectively). Leptin enhanced MMP-1, MMP-3, IL-6 and iNOS expression in chondrocyte cultures. Interestingly, when SOCS-3 was down-regulated by small interfering RNA, chondrocytes' response to leptin was enhanced.

Conclusion: The results show, for the first time, that SOCS-3 is associated with and regulates leptin-induced responses in cartilage; When SOCS-3 expression was down-regulated, leptin-induced effects were enhanced. In OA patients high leptin levels and low SOCS-3 levels were associated with cartilage degradation (high MMP levels) and obesity. Assuming that SOCS-3 is a factor that inhibits the effects of leptin in cartilage, obese patients are possibly more susceptible to detrimental effects of leptin not only because of its elevated levels in joint, but also because of the disturbed regulation mechanism.

ACR Concurrent Abstract Session
Innate Immunity and Rheumatic Disease
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Immunoglobulin G Fc Receptor Activity *in Vivo* Is Under Complement Control. Eveline Y. Wu, Haixiang Jiang, C. Garren Hester and Michael M. Frank. Duke Univ Med Ctr, Durham, NC

Background/Purpose: Immunoglobulin G receptors (FcγR) are critical in the development of autoimmunity and pathogenesis of immune complex (IC) diseases. Although ICs activate complement, contributing to tissue damage, it is reported complement does not affect IC interaction with FcγR. We have re-explored this issue and find complement has a major impact on IC interaction with FcγR. Specifically, the classical pathway (CP) down-regulates and the alternative pathway (AP) promotes IC binding to FcγR. We performed reverse passive Arthus reactions, a model of IC-mediated cutaneous vasculitis, in normal C57Bl/6 mice and mice genetically deficient in complement proteins C1q, C4 and Factor B. It is also reported that complement does not contribute to Arthus reactions in mice, unlike in other animals. We hypothesized the CP, rather than contributing to vasculitis, down-regulates tissue injury caused by IC interaction with activating FcγR; therefore, its absence (C1q−/− and C4−/−) would enhance cutaneous vasculitis, while absence of the AP (Factor B−/−) would diminish cutaneous vasculitis.

Methods: Sedated and shaved mice (normal, C1q−/−, C4−/−, and Factor B−/−) were injected intradermally with 20 μl of PBS alone on one side and affinity purified rabbit anti-bovine serum albumin (BSA) IgG 5 μg in PBS on the opposite side. Immediately following, BSA 100 μg and ^{125}Iodine-labeled BSA 1.25 μg in PBS containing 1% Evans blue was injected intravenously. After 4 hours, mice were sacrificed and the extravasated blue spot and control injection spot were dissected and weighed. Radioactivity per specimen weight (cpm/gm) of treated skin was divided by that of control skin to determine an Arthus index (AI) for each mouse. Arthus indices were first analyzed by Kruskal-Wallis ranked test, followed by Mann-Whitney U test to evaluate for significant differences in median AI. P values less than 0.05 were considered significant.

Results: Complement activation strongly influenced the degree of cutaneous vasculitis in mice (Fig. 1, p=0.0013). C1q−/− (mean AI 3.8±0.7, p=0.0125) and C4−/− (mean AI 4.7±2.3, p=0.0504) mice exhibited more extensive vasculitis than normal animals (mean AI 2.6±1.2). Conversely, Factor B deficient (mean AI 1.4±0.5, p=0.0553) mice trended towards significantly reduced vasculitis compared to normal animals.
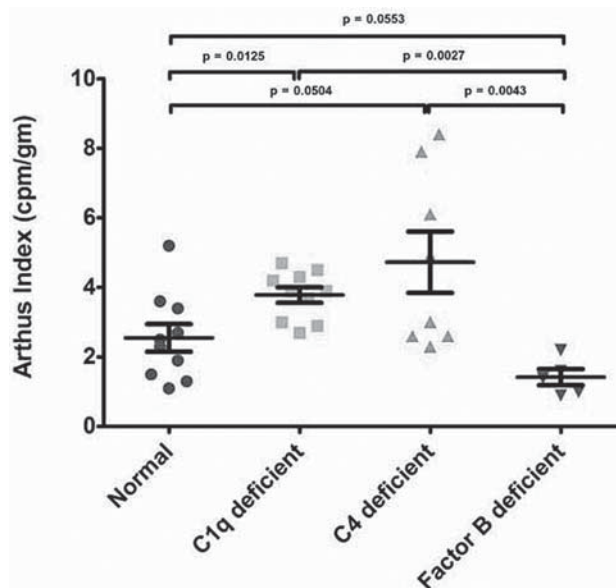
Fig 1. Reverse Passive Arthus Reactions

Conclusion: Cutaneous vasculitis is significantly greater in mice deficient in CP complement proteins and appeared reduced in mice deficient in AP complement proteins. Our results are the first to provide physiologic evidence *in vivo* that complement critically influences IC and FcγR mediated inflammation. They also refute previous data suggesting complement possesses no role in Arthus-induced vasculitis in mice. They may further our understanding of why individuals with CP defects are noted to have frequent signs of autoimmune pathology.

2522

M-Ficolin, an Activator of the Complement System, Is the Strongest Predictor of Both DAS28 Remission and Low Disease Activity in a Cohort of 180 Early DMARD Naïve Rheumatoid Arthritis Patients Followed in the Opera-Study. Christian G. Ammitzbøll[1], Jens Christian Jensenius[2], Torkell Ellingsen[3], Steffen Thiel[2], Kim Hørslev-Petersen[4], Merete L. Hetland[5], Peter Junker[6], Julia Johansen[7], Mikkel Østergaard[8], Jan Pødenphant[9] and Kristian Stengaard-Pedersen[1]. [1]Arhus University Hospital, Aarhus, Denmark, [2]Aarhus University, Aarhus, Denmark, [3]Silkeborg Regional Hospital, Silkeborg, Denmark, [4]University of Southern Denmark, Graasten, Denmark, [5]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark, [6]Odense University Hospital, Odense, Denmark, [7]Glostrup Hospital, Glostrup, Denmark, [8]Copenhagen University Hospital Glostrup, Glostrup, Denmark, [9]Gentofte Hospital

Background/Purpose: M-ficolin is a soluble pattern recognition molecule that activates the complement system. We recently reported a factor 300 difference in the synovial fluid M-ficolin concentration between rheumatoid arthritis (RA) and osteoarthritis, suggesting a pathogenic role of M-ficolin (1). We assessed M-ficolin in DMARD naïve early RA patients, investigated correlations between M-ficolin and disease activity markers, and analyzed the predictive value of M-ficolin.

Methods: 180 DMARD naïve RA patients with disease duration <6 months were included in a randomized double blind placebo-controlled trial (OPERA) of methotrexate, intraarticular glucucorticoids + either adalimumab(ADA)orplacebo(PLA).Asandwich-typetime-resolvedimmunofluorometric assay using monoclonal antibodies was used for quantification of M-ficolin in the OPERA cohort, 101 healthy adults and 51 chronic RA patients in remission. Concentrations are reported as medians. Spearman test, Students T-test and one-way analysis of variance were used. Logistic regression analyses were performed and adjusted for CRP, treatment group (ADA/PLA), x-ray erosions, anti-CCP, IgM-RF, neutrophils and monocytes.

Results: The highest M-ficolin levels were measured in the OPERA cohort at baseline ($2.84\mu g/ml$, CI 2.63–3.09), and during treatment the level decreased 24% (CI 18–31%, $p<0.001$) at year one ($2.31\mu g/ml$, CI 2.14–2.50). The healthy adults had significantly lower concentrations ($1.88\mu g/ml$, CI 1.72–2.06) than the OPERA cohort at baseline ($p<0.001$) and year one ($p<0.001$), and the chronic RA patients ($2.17\mu g/ml$, CI 1.94–2.42) ($p=0.03$). At baseline M-ficolin correlated to DAS28 (rho=0.29, $p<0.001$) and the four variables constituting DAS28 ($0.001< p \leq 0.04$). At year one M-ficolin correlated to DAS28 (rho=0.36, $p<0.001$) and 3 of the 4 variables constituting DAS28 ($0.001< p \leq 0.05$), except tender joint count 28 ($p=0.23$). Furthermore M-ficolin correlated to HAQ at debut (rho=0.25, $p=0.003$) and year one (rho=0.23, $p<0.001$).

Logistic regression analysis determined M-ficolin as the strongest predictor of DAS28<2.6 at year one (coefficient=1.42, $p=0.0001$) followed by treatment group (PLA/ADA) (coefficient=1.23, $p=0.001$) and erosions on baseline x-ray (coefficient=1.19, $p=0.02$), but M-ficolin was the only variable able to predict DAS28<3.2 at year one (coefficient=0.89, $p=0.02$). Low baseline M-ficolin level was the only variable associated with low disease activity at year one, and this was further analyzed by comparing the group with the 25% lowest baseline M-ficolin levels with the remaining 75% of patients (cutoff 2.00 $\mu g/ml$). This resulted in a sensitivity of 29%, a specificity of 96%, and a positive predictive value of 98% in determining a DAS28 score <3.2 at year one.

Conclusion: The elevated baseline M-ficolin levels in early RA correlated consistently to disease activity markers, most notably DAS28 and HAQ, thus reflecting essential parts of the disease activity. Low M-ficolin level at baseline was the strongest predictor of a favorable DAS28 level after one year, and has a positive predictive value of 98% of a DAS28<3.2 after one year irrespective of treatment and well-known prognostic factors.

Reference

(1) Ammitzbøll CG, et al. Rheumatol Int 2011

2523

Periodontal Pathogens Directly Promote Autoimmune Experimental Arthritis by Inducing a Toll-Like Receptor 2 and Interleukin-1 Driven Th17 Response. Shahla Abdollahi-Roodsaz[1], Sabrina Garcia de Aquino[2], Marije I. Koenders[1], Fons A. van de Loo[1], Ger J. Pruijn[3], Mario J. Avila Campos[4], Fernando Q. Cunha[5], Joni A. Cirelli[2] and Wim B. van den Berg[1]. [1]Rheumatology Research and Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Department of Diagnosis and Oral Surgery, Periodontic Division, Araraquara Dental School, Sao Paolo, Brazil, [3]Radboud University Nijmegen, Nijmegen, Netherlands, [4]Department of Microbiology, Institute of Biomedical Sciences—ICB/USP, Sao Paulo, Brazil, [5]Department of Pharmacology, School of Medicine of Ribeirao Preto, Sao Paolo, Brazil

Background/Purpose: The periodontal pathogen *Porphyromonas gingivalis* has been associated with the pathogenesis of rheumatoid arthritis (RA) because of its ability to citrullinate mammalian proteins and to induce disease-specific anti-citrullinated peptide antibodies (ACPA). The aim of this study was to investigate the influence of periodontal pathogens on the development of experimental arthritis and the T helper cell balance as a possible underlying mechanism for disease modulation.

Methods: The effect of *P. gingivalis* and *Prevotella nigrescens,* the latter lacking citrullinating enzymes, on T cell differentiation and the involvement of Toll-like receptors (TLRs) was studied *in vitro* using either wild-type or TLR deficient antigen-presenting cells (APCs) and CD4^{+} T cells in co-culture. *In vivo*, mice with collagen-induced arthritis received five oral inoculations of either *P. gingivalis* or *P. nigrescens*every other day starting from day 14 after immunization. Joint histopathology, synovial gene expression, collagen-specific T cell phenotype and presence of ACPA were analyzed on day 30.

Results: *P. gingivalis*strongly induced an interleukin-1 driven Th17 differentiation in the co-culture of APCs with CD4^{+} T cells, as measured by FACS and IL-17 production. This Th17 induction strongly depended on TLR2 expression on APCs and was substantially increased in the absence of IL-1 receptor antagonist. Remarkably, the Th17 inducing capacity was shared by another major periodontal pathogen, *Prevotella nigrescens*, lacking citrullination capability. In addition, both bacteria were weak inducers of Th1 and interferon γ production, which was dependent on TLR2 expression directly on T cells.

When applied in collagen-induced arthritis model through repeated oral inoculations, both *P. gingivalis* and *P. nigrescens* promoted antigen-specific Th17 response *in vivo* and aggravated the severity of arthritis. This occurred under conditions where ACPA against major citrullinated peptide candidates such as α-enolase and vimentin were undetectable. Instead, the levels of IL-17 induced by periodontal pathogens directly correlated with the intensity of arthritic bone erosions. In addition, while *P. gingivalis* induced local joint-destructive factors such as cathepsin K and matrix metalloproteinase 9 in synovial tissue, *P. nigrescens* suppressed the anti-inflammatory IL-4 production by T cells.

Conclusion: Our data reveal a novel mechanism, besides citrullination capability, by which periodontal pathogens influence autoimmune arthritis through direct modulation of the T cell phenotype, with a remarkable impact on bone erosion. This study further supports the relevance of periodontal pathogens in the pathogenesis of RA.

2524

Snapin Is Critical for the Maturation of Autophagosome and Phagosome in Macrophages. Bo Shi, Qiquan Huang, Robert Birkett, Renee E. Koessler, Andrea Dorfleutner, Christian Stehlik and Richard M. Pope, Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: We found that Snapin, a SNARE complex protein required for synaptic vesicle docking and fusion, was significantly increased in rheumatoid arthritis (RA) synovial tissue compared to control synovial tissues. Snapin was highly expressed in CD68 positive macrophages (MΦs) in the sublining, which correlated with inflammation. Snapin expression in MΦs co-localized with Rab7, a marker of late endosomes. Therefore, studies were performed to determine the role of Snapin in the formation of autophagosomes and their fusion with lysosomes.

Methods: The forced reduction of Snapin in primary human MΦs was performed using siRNA. Snapin, Lamp1, 2 and LC3 protein levels were determined by Western blot analysis. MΦ phagocytosis of living bacteria was performed by infection of *Staphylococcus aureus* and intracellular bacteria number was determined by counting the bacterial colonies on LB-agar plates with MΦ lysates. Forced reduction of Snapin in Raw 264.7 macrophage cell line was performed by infection with a lentiviral vector expressing Snapin shRNA, followed by puromycin selection. Phagocytosis of fluorescent pHrodo-labeled dead *S. aureus* by Raw stable cell lines was performed and the amount of intracellular bacteria was determined either by mean fluorescence with flow cytometry or by cell fluorescence microscopy.

Results: The expression of Snapin progressively increased during human monocyte to MΦ differentiation. The forced reduction of Snapin in MΦs (documented by immunoblot analysis) resulted in elevated levels of LC3-II, a marker for autophagosomes, and Lamp-1, Lamp-2, two lysosomal markers. Snapin siRNA combined with cell starvation by FBS deprivation to promote autophagy, further increased LC3-II. However, the reduction of Snapin in MΦs co-treated with chloroquine, an autophagy efflux blocker, did not affect LC3-II levels, suggesting that the reduction of Snapin does not affect autophagy formation but leads to accumulation of autophagosomes by impaired autolysosome formation.

Phagocytosis of pHrodo fluorescent labeled dead *S. aureus* by Raw 264.7 stably expressing Snapin shRNA demonstrated a 25% increase in mean fluorescence intensity (MFI) by flow cytometry compared to control shRNA infected Raw cells. Following the forced reduction of Snapin in primary human MΦs, phagocytized *S.aureus* numbers at 1 hour after infection did not show differences, compared to non-targeting siRNA transfected MΦs. However, after 5 hours of infection, there were significantly increased numbers of *S aureus* remaining intracellularly in Snapin siRNA transfected MΦs compared to control siRNA treated MΦs (2.6 verses 1.7 colony formation units per cell, p<0.05). These data suggested Snapin is important for phagosomal fusion with lysosomes and the clearance of bacteria in MΦs.

Conclusion: Reduction of Snapin in MΦs resulted in the blockage of the fusion of autophagosmes and phagosomes with lysosomes. By promoting autophagy, the increased expression of Snapin in the RA joint may contribute to the long term survival of MΦs which contribute to the disease pathogenesis and joint destruction.

Disclosure: B. Shi, None; **Q. Huang**, None; **R. Birkett**, None; **R. E. Koessler**, None; **A. Dorfleutner**, None; **C. Stehlik**, None; **R. M. Pope**, None.

2525

Bruton's Tyrosine Kinase Inhibition Suppresses Inflammatory Cytokine Production and Affects Gene Expression in Human Macrophages and RA Synovial Tissue Explants. Linda M. Hartkamp[1], Inge E. van Es[1], Jay S. Fine[2], Michael Smith[2], John Woods[2], Satwant Narula[2], Julie DeMartino[2], Paul P. Tak[3] and Kris A. Reedquist[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Hoffmann-La Roche, Nutley, NJ, [3]Academic Medical Center/University of Amsterdam and GlaxoSmithKline, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a chronic and progressive autoinflammatory disorder characterized by the infiltration of inflammatory cells, including B-cells, T-cells and macrophages, in the synovial membrane ultimately leading to cartilage destruction and bone erosion. Clinical disease activity in RA correlates strongly with macrophage numbers in synovial tissue and expression of macrophage-derived cytokines. Bruton's tyrosine kinase (Btk), a downstream target of phosphatidylinositol 3-kinase, is important not only in B cell activation, but also mediates immune complex-dependent activation of monocytes. Pharmacological inhibition of Btk effectively suppresses pathology in murine models of arthritis, but potential roles for Btk in the pathology of RA have not been examined.

Methods: Expression of Btk was detected by immunohistochemistry combined with digital image analysis in synovial tissue from 19 RA and 15 PsA patients, naïve to treatment with biologicals. Immunofluorescent double labelling confocal microscopy was performed to identify which cell types express Btk in RA synovial tissue, and validating qRT-PCR and immunoblotting experiments were performed on isolated relevant cell populations. Effects of a specific Btk inhibitor, RN486, on activation-dependent IL-6 production by human macrophages (n=8) and RA synovial tissue explant cultures (n=6) were assessed by ELISA. The influence of RN486 on macrophage expression of genes related to angiogenesis, cellular adhesion, tissue remodelling and innate immune responses was determined using low density qPCR arrays.

Results: Btk was expressed at equivalent levels in patients with RA and PsA, and no relationship was observed between expression levels and patient clinical characteristics (CRP, ESR, DAS28, RF-positivity). In RA, but not PsA, there was a significant relationship between Btk expression and numbers of synovial macrophages (R= 0.57, p< 0.01), T cells (R= 0.64, p< 0.005) and fibroblast-like synoviocytes (FLS) (R= 0.56, p< 0.05) but not B cells, plasma cells, or endothelial cells. qPCR and immunoblotting experiments confirmed that Btk was expressed in B cells, monocytes, and macrophages, but not T cells or RA FLS. RN486 (1μM) inhibited macrophage IL-6 production in response to Fc receptor stimulation (40% inhibition, p< 0.01) and anti-CD40 antibodies (50%, p< 0.05), but not TNFα or LPS stimulation. qPCR analysis of human macrophages demonstrated that RN486 inhibited by more than 2-fold 12 of 21 genes induced by IgG, 11 of 52 genes induced by CD40 stimulation, and 6 of 25 genes induced by RA SF in 3 independent experiments. RN486 also inhibited spontaneous IL-6 production by cultured RA synovial explants (65%, p< 0.01).

Conclusion: Our data demonstrate that Btk is expressed in RA synovial tissue and suggest that macrophages would be the prominent synovial targets of strategies aimed at inhibiting Btk in RA. As Btk activity is needed to drive macrophage activation in response to multiple stimuli relevant to RA, and drives IL-6 production in RA synovial tissue, pharmacological targeting of Btk may be of therapeutic benefit in the treatment of RA.

Disclosure: L. M. Hartkamp, None; **I. E. van Es**, None; **J. S. Fine**, Hoffmann-La Roche, Inc., 3, Hoffmann-La Roche, Inc., 1; **M. Smith**, Hoffmann-La Roche, Inc., 3, Hoffmann-La Roche, Inc., 1; **J. Woods**, Hoffmann-La Roche, Inc., 3, Hoffmann-La Roche, Inc., 1; **S. Narula**, Hoffmann-La Roche, Inc., 3, Hoffmann-La Roche, Inc., 1; **J. DeMartino**, Hoffmann-La Roche, Inc., 3, Hoffmann-La Roche, Inc., 1; **P. P. Tak**, GlaxoSmithKline, 3; **K. A. Reedquist**, Hoffmann-La Roche, Inc., 2.

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Bruton's Tyrosine Kinase and Calreticulin: A Novel Interaction with Implications for Inflammatory and Autoimmune Disease. Jennifer C. Byrne[1], Joan Ní Gabhann[1], Kevin Stacey[1], Barbara M. Coffey[1], Eoghan M. McCarthy[2], Warren Thomas[3], Eamonn S. Molloy[4], Grainne M. Kearns[2] and Caroline Jefferies[1]. [1]Royal College of Surgeons in Ireland, Dublin, Ireland, [2]Beaumont Hospital, Dublin 9, Ireland, [3]Royal College of Surgeons in Ireland, Dublin 9, Ireland, [4]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: Bruton's Tyrosine Kinase (Btk) regulates innate immune responses downstream of multiple Toll-like receptors (TLRs), including TLR7. Given the role of TLR7 in driving type I interferon and inflammatory cytokine production in the autoimmune condition systemic lupus erythematosus (SLE), pharmacological inhibition of the tyrosine kinase Btk has been proposed as a potential therapeutic. Given this interest it is essential that the role of Btk downstream of TLR7 activation be thoroughly explored.

Methods: Primary WT and Btk deficient murine macrophage were used to carry out a 2D proteomic study to identify differences downstream of TLR7 stimulation. Immunoprecipitation studies were carried out in macrophages and the human monocytic cell line THP-1. Confocal analysis was used to investigate localisation of proteins as well as uptake of apoptotic cells by primary macrophages.

Results: Our data describes a novel role for Btk as a regulator of the molecular chaperone calreticulin (CRT). Studies in primary macrophages demonstrate that CRT undergoes TLR7-induced tyrosine phosphorylation in a Btk-dependent manner. In addition Btk can directly interact with and phosphorylate CRT. Given the key role CRT in apoptotic cell uptake, we observe that in the absence of Btk, CRT fails to localise to the cell membrane or interact with the transmembrane receptor CD91, also known to be required for apoptotic cell uptake. Also, Btk-deficient macrophages show an impaired uptake of human apoptotic neutrophils in a phagocytosis assay as well as reduced staining for CRT within the phagocytic cup. In a preliminary study, pharmacological inhibition of Btk in monocytes derived from healthy controls demonstrated a reduction in apoptotic cell uptake following Btk inhibition, an effect that was exacerbated in monocytes derived from SLE patients.

Conclusion: Overall our data has revealed a novel regulatory role for the tyrosine kinase Btk with regard to CRT. Loss of Btk results in an alteration in the cellular trafficking of CRT downstream of TLR7 stimulation in myeloid cells as well as a reduction in their ability clear apoptotic cells. Given the interest in the use of pharmacological inhibitors of Btk for the treatment of

SLE, our data indicates that further investigation into the effect of Btk inhibition with regard to myeloid cell function is warranted.

Disclosure: J. C. Byrne, None; J. Ní Gabhann, None; K. Stacey, None; B. M. Coffey, None; E. M. McCarthy, None; W. Thomas, None; E. S. Molloy, None; G. M. Kearns, None; C. Jefferies, None.

ACR Concurrent Abstract Session
Miscellaneous Rheumatic and Inflammatory I
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Prozone Phenomenon Leads to Low IgG4 Concentrations in IgG4-Related Disease. Arezou Khosroshahi[1], Lynn A. Cheryk[2], Mollie Carruthers[1], Judith A. Edwards[2], Donald B. Bloch[1] and John H. Stone[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Mayo Medical Laboratories, Andover

Background/Purpose: IgG4-related disease (IgG4-RD) is frequently associated with elevations in serum IgG4 concentration. However, the frequency of serum IgG4 elevation varies in published series from 44%–100%. The prozone effect, also known as the "hook" effect, occurs when antigen excess interferes with antibody-based assay methods that require immune complex formation for detection, and can lead to spuriously low results. Additional sample dilutions are the solution to the prozone effect. After identifying the prozone effect in one patient with IgG4-RD whose serum IgG4 corrected following appropriate dilutions from 17 to 1850 mg/dL (nl: 2.4–121 mg/dL), we examined additional samples to determine the frequency of this problem.

Methods: We re-tested 38 serum samples from patients with the diagnosis of IgG4-RD whose original serum IgG4 results had been reported earlier. The IgG subclasses were measured by nephelometry in dilutions up to 1:160,000, using two different commercially-available reagents (Siemens; The Binding Site). The testing laboratory was blinded to the patients' clinical history and previous values. The serum IgG4 concentrations from these assays were compared to the original results.

Results: Falsely low IgG4 values were reported in 10/38 patients (26%) using The Binding Site assay (Table). The prozone effect was identified as the cause of 8 incorrect values (21% of all samples tested). Correction of the prozone effect by sample dilution until the concentration reported was stable, led to a revision of the mean IgG4 result from 21.6 to 2440. In contrast, samples measured by the Siemens reagent were checked automatically for antigen excess as part of the testing method; the appropriate numbers of dilutions were performed either automatically by the instrument or manually as the result of a flag associated with the value, thereby avoiding the prozone effect. The Binding Site assay gave no indication that antigen excess might be present.

Table. Characteristics of patients with IgG4-RD with significant differences in their retested IgG4 results

Case #	* Original reported IgG4 values (mg/dL)	** Retested IgG4 values (mg/dL)	X-fold increase after dilution	Number of affected organs	Active disease	Presence of prozone effect
1	10.3	2470	247	1	Yes	Yes
2	28.4	941	33	3	Yes	Yes
3	29.3	219	7.5	1	Yes	No
4	59.8	337	5.6	1	Yes	No
5	12.7	5340	420	3	Yes	Yes
6	17.6	1850	105	4	Yes	Yes
7	8.0	5160	645	7	Yes	Yes
8	43.9	1030	23	4	Yes	Yes
9	14.4	1910	132	7	Yes	Yes
10	37.5	819	22	1	Yes	Yes

* The Binding Site reagent was used for the assay
** Siemens reagent was used for the assay

All 8 patients whose samples were affected by the prozone effect had active IgG4-RD, and 6 had multi-organ disease. Medical record review indicated that the original clinical decision regarding further evaluation (e.g.,

tissue biopsy) or treatment might have been different had the correct value been known to the clinician.

Conclusion: We have identified a major issue in the serological measurement of IgG4 concentrations. The prozone effect which led to substantial underestimations of IgG4 concentrations in 21% of the samples, offers potential explanations for the poor correlation observed between disease activity and serum IgG4 level in some patients. This phenomenon should be considered when the serum IgG4 measurement appears discordant with the clinician's assessment of disease activity.

Disclosure: A. Khosroshahi, None; L. A. Cheryk, None; M. Carruthers, None; J. A. Edwards, None; D. B. Bloch, None; J. H. Stone, None.

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Hypertrophic Pachymeningitis: IgG4-Related Disease Is A Common Etiology. Zachary S. Wallace, Mollie Carruthers, Arezou Khosroshahi, Robert Carruthers, Shweta Shinagare, Anat Stemmer-Rachamimov, Vikram Deshpande and John H. Stone. Massachusetts General Hospital, Boston, MA

Background/Purpose: Hypertrophic pachymeningitis (HP) is an inflammatory condition in which the dura mater of the cranium or spine becomes thickened, leading to symptoms that result from mass effect, nerve compression, or vascular compromise. The differential diagnosis of HP includes immune-mediated conditions such as rheumatoid arthritis and vasculitis, malignancies, and infections. Many times, no diagnosis is reached; in such cases, the disease has been described as idiopathic HP. IgG4-related disease (IgG4-RD) is a recently described inflammatory condition known to cause tumefactive lesions at myriad anatomical locations. Both IgG4-RD and idiopathic HP share similar demographics, histopathology, and natural history. We hypothesized that IgG4-RD is a common cause of idiopathic HP.

Methods: To investigate this hypothesis, we identified all pathology specimens diagnosed as HP in a 25-year time span at our institution. Fourteen cases had extant stained slides and cell blocks to permit review of the original hematoxylin and eosin (H&E) stained slides was well as immunostaining of cell blocks. Recently published consensus guidelines describing characteristic histopathology and the necessary quantity of IgG4+ plasma cell infiltrate were used to diagnose IgG4-RD.

Results: Four cases (29%) that had been regarded previously as representing idiopathic HP were diagnosed as IgG4-RD (Table 1). Of the remaining cases, there were three cases associated with granulomatosis with polyangiitis (GPA), two with lymphoma, and one each with rheumatoid arthritis, giant cell arteritis, and sarcoidosis. Two of the cases could not be diagnosed more precisely and were classified as undifferentiated HP.

Table 1.

Case	Diagnosis	Site	Age	Gender	Symptoms	Lympho-plasmacytic Infiltrate	Storiform Fibrosis	Phlebitis	Eos	Granulomas	Giant Cells
1	IgG4-Related Disease	Intracranial dura	50	Female	Seizures	Y	Y	N	N	N	Y
2	IgG4-related Disease	Intracranial dura	52	Female	Headache	Y	Y	Y	Y	Y (few)	N
3	IgG4-related Disease	Intracranial dura	39	Male	Headache & arm numbness	Y	Y	N	N	N	N
4	IgG4-related Disease	L5 nerve root dura	32	Male	Weakness	Y	Y	Y	Y	N	N
5	Granulomatosis with Polyangiitis	T2-T8 dura	59	Female	Sensory abnormalities & urinary retention	Y	N	N	Y	Y	Y
6	Granulomatosis with Polyangiitis	Intracranial dura	75	Female	Gait instability	N	Y	N	N	N	Y
7	Granulomatosis with Polyangiitis	Intracranial dura	55	Male	Painful diplopia	Y	Y	N	N	Y	Y
8	Rheumatoid Arthritis	Intracranial dura	58	Female	Ataxia, numbness & visual loss	Y	N	N	N	Y	Y
9	Giant Cell Arteritis	Intracranial dura	59	Male	Central DI	N	N	N	N	N	N
10	Sarcoidosis	Intracranial dura	67	Male	Nausea, vomiting & ataxia	Y	N	N	N	Y	N
11	Lymphoma	Intracranial dura	52	Male	Headache & dizziness	Y	N	N	N	N	N
12	Lymphoma	Intracranial dura	61	Female	CN III Palsy	Y	N	N	N	N	N
13	Undifferentiated	Intracranial dura	44	Female	Headaches & thrombosis	Y	N	N	N	N	Y
14	Undifferentiated	Intracranial dura	75	Male	FUO, gait instability & eye pain	N	N	N	N	N	N

Conclusion: This case series demonstrates that IgG4-RD may be the most common etiology of non-infectious HP and highlights the necessity of biopsy for accurate diagnosis. Clinical history, serologic tests, cerebrospinal fluid studies, and radiology alone could not identify the cause of HP. Rather, biopsy with histopathology and immunostaining was necessary to reach an accurate diagnosis. Significant IgG4+ plasma cell infiltrates were observed in rheumatoid arthritis, granulomatosis with polyangiitis, and lymphoma, underscoring the importance of histopathology in making the diagnosis of IgG4-RD.

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Molecular Mechanism of IgG4 Class Switch Recombination in IgG4-Related Disease. Hiroto Tsuboi[1], Mana Iizuka[1], Hiromitsu Asashima[1], Sayaka Tsuzuki[1], Yuya Kondo[1], Akihiko Tanaka[2], Masafumi Moriyama[2], Isao Matsumoto[1], Seiji Nakamura[2] and Takayuki Sumida[1]. [1]University of Tsukuba, Tsukuba, Japan, [2]Kyushu University, Fukuoka, Japan

Background/Purpose: IgG4-related disease (IgG4-RD) is a new disease entity characterized by high serum IgG4 levels, IgG4-positive plasmacytic infiltration and fibrosis in various organs. Although the clinical features including serum abnormalities, organ involvement, diagnosis, and the therapeutic approach have been reported recently, the molecular mechanism of this disease remains unclear. The purpose of this study was to determine the mechanism of up-regulation of IgG4 class switch recombination in IgG4-RD.

Methods: 1) We extracted RNA from PBMC of patients with IgG4-RD (n=6), Sjögren's syndrome (SS) (n=6), and healthy control (HC) (n=8), from CD3 positive T cells and CD20 positive B cell sorted from PBMC of patients with IgG4-RD (n=3), SS (n=4), and HC (n=4). The RNAs were also prepared from labial salivary glands (LSG) of patients with IgG4-RD (n=11), SS (n=13), and HC (n=3).

2) The mRNA expression levels of IgG4-specific class switch-related molecules such as Th2 cytokines (IL-4 and IL-13), Treg cytokines (IL-10 and TGFβ), transcriptional factors (GATA3 and Foxp3) were examined by quantitative PCR assay.

3) IgG4-non-specific class switch related molecules such as CD40, CD154, BAFF, APRIL, IRF4, and AID were also examined by quantitative PCR assay.

Results: 1) IgG4-specific class switch-related molecules. The mRNA expression level of IL-4 was significantly higher in LSG of IgG4-RD than HC (P<0.05). Treg cytokines (IL-10 and TGFβ) were significantly higher in LSG of IgG4-RD than SS and HC (P<0.05, each). There were no significant differences in the PBMC expression levels of various cytokines, among the three groups. In LSG, the expression of GATA3 was significantly lower in IgG4-RD than in SS, Foxp3 was significantly higher in IgG4-RD and SS than in HC (P<0.05, each).

2) IgG4-non-specific class switch-related molecules. The mRNA expression levels of CD40 and CD154 were significantly lower in PBMC of IgG4-RD than SS (P<0.05, each). However, the expression of CD40 in CD20 positive B cells and that of CD154 in CD3 positive T cells were comparable in the three groups. The expression of BAFF was significantly higher in LSG of IgG4-RD than HC (P<0.05). The expression of APRIL was significantly lower in PBMC of IgG4-RD than HC (P<0.05). The expression of AID was significantly higher in LSG of IgG4-RD than SS and HC (P<0.05, each).

Conclusion: In LSG of IgG4-RD, increased Treg cytokines (IL-10 and TGFβ) might play important roles in IgG4-specific class switch recombination and fibrosis, which are characteristic features of IgG4-RD. High expression of AID could also contribute to up-regulation of IgG4-specific class switch recombination along with IL-10 in LSG of IgG4-RD. Thus overexpression of IL-10, TGFβ, and AID in LSG might play important pathogenic roles in IgG4-RD. This study showed different expression levels of IgG4 class switch-related molecules in LSG than in PBMC of IgG4-RD, which suggested that IgG4 class switch recombination seem be mainly up-regulated in affected organs.

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Anti-Ribosomal P Antibodies in a Large Cohort of Autoimmune Hepatitis with No Evidence of Lupus: A Common Underlying Mechanism Targeting Liver? Ana Luisa Calich[1], Vilma S. T. Viana[1], Eduardo L. Cançado[1], Débora R. Terrabuio[1], Francisco Tustumi[1], Elaine P. Leon[1], Clovis Artur Silva[2], Eduardo F. Borba Neto[1] and Eloisa Bonfa[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Anti-ribosomal P proteins antibody (anti-rib P) is a highly specific marker for systemic lupus erythematosus (SLE) and it is associated with liver involvement in this disease. Similarities between autoimmune hepatitis (AIH) and SLE-associated hepatitis raised the possibility that anti-rib P antibodies may also have relevance in AIH. This study was therefore undertaken to evaluate the frequency and clinical significance of anti-rib P antibodies in a large AIH cohort before treatment.

Methods: Ninety-six patients with AIH diagnosed according to the Revised Original Pretreatment Scoring System of the International Autoimmune Hepatitis Group were studied. Charts were reviewed for demographic, clinical, treatment and laboratorial parameters. 82 healthy individuals were included as control. Available frozen sera samples from AIH patients obtained at diagnosis were tested for IgG anti-rib P by ELISA using a commercial kit employing synthetic 22 amino acid C-terminal peptide as antigen and reactivity was confirmed by immunoblotting using rat liver ribosomal fraction. All sera were screened for other lupus specific autoantibodies, anti-dsDNA and anti-Sm. Three patients positive for anti-dsDNA (n=1) and anti-Sm (n=2) were excluded.

Results: Moderate to high titers (>40U) of anti-rib P antibody were found in 9.7% (9/93) AIH patients and in none of the controls (p=0.003).Mean antibody titer was 93.6 ± 33.1 units. Positive results by ELISA were confirmed by immunoblotting. Patients with positive results for anti-rib P were referred to the Rheumatology Outpatient Clinic for a more detailed clinical evaluation. No sign of lupus was found in all of them. At presentation, AIH patients with and without anti-rib P antibodies had similar demographic/clinical features, including the frequency of cirrhosis (44% vs. 28%, p=0.44), hepatic laboratorial findings (p>0.05), corticosteroid and azathioprine therapy frequencies (100% vs. 99%, p=0.17 and 78% vs. 92%, p=0.17, respectively). The long follow up period was also comparable in those with and without anti-rib P antibodies (10.7± 5.1 vs. 10.3 ± 5.2 years, p=0.68). Importantly, at the final observation AIH patients with anti-rib P had a significantly higher frequency of cirrhosis compared to negative group (100% vs. 60%, p=0.04) despite no difference in the frequency of drugs at the last visit (p>0.05).

Conclusion: The novel demonstration of anti-rib P in AIH patients without clinical and laboratorial evidence of SLE suggests a common underlying mechanism targeting liver in these two diseases. In addition, this antibody seems to predict a group of patients with worse AIH prognosis.

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The Relapsing Polychondritis Disease Activity Index: International Development and Initial Validation of the First Disease Activity Score for Relapsing Polychondritis. Laurent Arnaud[1], Hervé Devilliers[2], Stanford L. Peng[3], Zahir Amoura[4] and the RPDAI study group[5]. [1]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [2]CHU Dijon, Dijon, France, [3]Virginia Mason Medical Center, Seattle, WA, [4]CHU Pitié-Salpêtrière, Paris, France, [5]Paris

Background/Purpose: Relapsing polychondritis (RP) is a rare multisystemic disorder characterized by recurrent, destructive, inflammatory lesions of the auricular, nasal, and laryngo-tracheo-bronchial cartilages. Additional clinical features include ocular inflammation, audio-vestibular impairment, vasculitis, skin involvement, valvular insufficiency, and non-erosive arthritis. The rarity of the disease makes it difficult to provide a standardized approach for treatment and follow-up of RP patients, and there is no consensus agreement on any outcome measures in this dis-

ease. Here, we describe the development of a score for assessing disease activity in RP, the Relapsing Polychondritis Disease Activity Index (RPDAI).

Methods: This study reflects a multi-center, international and inter-disciplinary collaboration of experts involved in the management of RP. Selection and definition of items for disease activity were established by consensus between 27 experts during a 4-round internet-based Delphi survey. Then, twenty-six experts assessed the Physician's Global Assessment (PGA) of disease activity of 43 test cases on a 0–100 scale. The weight of each item was estimated by multivariate regression models with generalized estimating equation, using PGA as the dependent variable.

Results: Experts decided in consensus that the RPDAI should consider the 28-day period before each scoring. Twenty-seven items were selected using the Delphi survey and a glossary defining each item was derived by consensus. Then, item weighting was performed by 26 experts, who assessed the Physician's Global Assessment (PGA) of disease activity of 43 test cases on a 0–100 scale. Inter-rater reliability assessed by the intra-class correlation coefficient for these PGA ratings was 0.51 (CI95%: 0.41–0.64). Multivariate analysis revealed that the individual weigh of items ranged from 1 to 24. The final RPDAI score therefore comprised 27 items with a maximum theoretical score of 265. Correlation between the RPDAI scores calculated for all test cases based on the weights derived from the final multivariate model, and the PGA of these cases was good (r=0.56, p<0.0001).

Conclusion: We have developed a consensus scoring system to measure disease activity in relapsing polychondritis (see www.RPDAI.org for online scoring). We believe this tool will be valuable for improving the care of patients with this rare disease.

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Whole Transcriptome Analysis in Relapsing Polychondritis: A Single-Center Analysis of 35 Patients. Laurent Arnaud[1], Alexis Mathian[1], Bruno Faivre[2], Karim Dorgham[2], Julien Haroche[1], Nathalie Costedoat-Chalumeau[1], Jean-Charles Piette[1], Guy Gorochov[2] and Zahir Amoura[1]. [1]Hôpital Pitié-Salpêtrière, AP-HP & UPMC Univ Paris 06, Paris, France, [2]Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S 945, Paris, France

Background/Purpose: Relapsing polychondritis (RP) is a severe and episodic inflammatory condition involving cartilaginous structures, predom-inantly those of the ears, nose, and laryngotracheobronchial tree. Other affected structures may include the eyes, cardiovascular system, peripheral joints, skin, middle and inner ear, and CNS. To date, gene expression profiling has not been performed in RP. The aim of this study was to analyze the transcriptome of RP compared to healthy individuals, as a manner to identify new pathways involved in the pathogenesis of the disease as well as new therapeutic targets.

Methods: Total RNA was extracted from peripheral blood mononuclear cell (PBMC) obtained in 35 patients with RP (according to Michet criteria) and 36 healthy individuals. Complementary DNA (cDNA) was hybridized in Illumina Human HT-12® v4 Expression Bead Chips. Statistical analysis of Microarray (SAM) algorithm with Benjamini and Hochberg multiple testing correction was used to determine the statistical significance of the differences in gene expression while controlling the false-discovery rate. Cluster analysis was also performed with JMP8 software. Differentially expressed genes were analyzed to identify potential functional pathways using Ingenuity®Pathway Analysis (IPA).

Results: Gene expression analysis using SAM showed 165 significantly down- or up-regulated transcripts between RP patients and controls. Cluster analysis of these transcripts by similarity on gene expression patterns identified several clusters containing only RP patients, healthy individuals, or both, underlining the strong heterogeneity of the disease. The set of genes statistically different between RP and healthy individuals was further ana-lyzed with IPA Analysis, which revealed a role for genes related to growth factor and cytokine activities, control of the cell-cycle, and kinase-phosphorylation.

Conclusion: This transcriptome analysis of 35 patients with relapsing polychondritis reveals that complex gene expression patterns are involved in the pathogenesis of the disease. This may be seen as a significant advance in this under researched disease with complex clinical presentation and non-formally codified therapeutic management.

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ACR Concurrent Abstract Session
Osteoarthritis - Clinical Aspects I:
Weight, Activity, and Metabolic Effects on Osteoarthritis
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Weight Loss Is Associated with Structure Modification in Subjects with Radiographic Osteoarthritis of the Knee: Data From the Osteo-arthritis Initiative. Marc C. Hochberg[1], Danuta I. Bujak[1], Jeffrey W. Duryea[2], Knachelle Favors[3] and John D. Sorkin[4]. [1]University of Mary-land, Baltimore, MD, [2]Brigham & Women, Boston, MA, [3]VA Maryland Health Care System, Baltimore, [4]VA Maryland Health Care System, Baltimore, MD

Background/Purpose: Obesity is a risk factor for the development and progression of knee osteoarthritis (OA) and weight loss is recom-mended as part of the management of patients with knee OA. We tested the hypothesis that weight loss is associated with structural progression, as measured by the rate of decline in joint space width (JSW), in subjects with radiographic knee OA.

Methods: Data for this analysis were obtained from the Osteoarthritis Initiative (OAI) public access database (http://www.oai.ucsf.edu). At each visit, subjects completed an extensive battery of questionnaires; weight was measured with a balance beam scale; and fixed flexion, weight-bearing PA radiographs of both knees were obtained using a standard protocol and the Synaflexer platform. We examined data from the baseline, 12-, 24-, 36- and 48-month follow-up visits for subjects with radiographic knee OA. Medial compartment JSW was determined using digitized images and a software tool; all images from a subject were analyzed together blinded to time sequence (see http://oai.epi-ucsf.org/datarelease/SASDocs/kXR_QJSW_Duryea_descrip.pdf for documenta-tion). Mean change in both minimum (mJSW) and JSW0.25 were examined using multiple variable random effects (random slope and random intercept) models including weight, age, WOMAC pain score and use of analgesic and/or anti-inflammatory medications at each visit along with sex, race/ethnicity, and study site from baseline.

Results: Data from 2683 subjects with radiographic OA in one or both knees (Kellgren-Lawrence grade >=2 on baseline radiograph), with measurement of mJSW and JSW0.25 at one or more time points (median = 3) were included in the analysis. If both knees were affected by radiographic OA, data for the right knee were arbitrarily used in the analysis. Mean (SD) age was 62.1 (9.1) years, weight was 83.9 (16.0) kg, mJSW was 3.97 (1.46) mm and JSW0.25 was 5.36 (1.54) mm at baseline. The mean rate of decline in JSW was more rapid for JSW0.25 than mJSW (0.110 [0.0055] mm vs. 0.088 [0.0055] mm; difference = 0.021 mm/year [95% CI 0.006, 0.037], P = 0.006). Heavier weight was significantly associated with narrower joint space at both mJSW and JSW0.25 at all visits (P < 0.0001). There was a significant inverse association between change in weight and change in both mJSW and JSW0,25 in the multiple variable adjusted models such that subjects with a decline in weight over time had a smaller adjusted rate of decline in both mJSW and JSW0.25 that those who had an increase in weight. The rate of decline in JSW per unit change in weight did not differ, however, for JSW0.25 and mJSW. Sensitivity analyses performed after ex-cluding subjects with isolated lateral compartment disease (OARSI medial compartment JSN grade = 0 and lateral compartment JSN grade >=1) did not alter the results. Finally, higher WOMAC pain scores and use of analgesic and/or anti-inflammatory medications were both inde-pendently associated with the rate of decline in JSW in multiple variable models.

Conclusion: These data demonstrate an association between weight loss and a reduction in the rate of decline in both mJSW and JSW0.25 in subjects with radiographic knee OA. Weight loss should be recommended as an approach for both symptom and structure modification in knee OA.

Disclosure: **M. C. Hochberg**, Abbott Laboratories, Astra-Zeneca, Bioiberica S.A., Eli Lilly Inc., Genentech/Roche, Merck Inc., Novartis Pharma A.G., Pfizer Inc., Stryker LLC, Xoma., 5; **D. I. Bujak**, None; **J. W. Duryea**, None; **K. Favors**, None; **J. D. Sorkin**, None.

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The Intensive Diet and Exercise for Arthritis Trial (IDEA): 18-Month Radiographic and MRI Outcomes. David J. Hunter[1], D. Beavers[2], Felix Eckstein[3], Ali Guermazi[4], Richard F. Loeser[5], Barbara J. Nicklas[6], Shannon Mihalko[7], Gary D. Miller[7], Mary Lyles[8], Paul DeVita[9], Claudine Legault[8], J. Jeffery Carr[8], Jeff D. Williamson[8] and Stephen P. Messier[7]. [1]University of Sydney, Sydney, Australia, [2]Winston Salem, NC, [3]Paracelsus Medical University, Salzburg, Austria, [4]Boston University, Boston, MA, [5]Wake Forest School of Medicine, Winston-Salem, NC, [6]Winston-Salem, NC, [7]Wake Forest University, Winston-Salem, NC, [8]Wake Forest University School of Medicine, Winston-Salem, NC, [9]East Carolina University, Greenville, NC

Background/Purpose: Dietary induced weight loss is a proven non-pharmacologic intervention for osteoarthritis. Based upon current literature it is unclear if weight loss modifies structural progression. We report the radiographic and MRI structural outcomes of an 18 month study of intensive weight loss, with or without exercise compared to exercise alone in older, overweight and obese adults with symptomatic knee osteoarthritis.

Methods: The Intensive Diet and Exercise for Arthritis trial (IDEA) was a prospective, single-blind, randomized controlled trial that enrolled 454 overweight and obese (BMI = 27–42 kg/m2) older (age ≥ 55 yrs) adults with pain and radiographic evidence of tibiofemoral osteoarthritis (KL = 2–3). Participants were randomized to one of three 18-month interventions: intensive dietary weight loss-only (D); intensive dietary weight loss-plus-exercise (D+E); or exercise-only control (E). X-rays and MRIs were acquired at baseline and 18 months of follow-up. Standardized weight bearing x-rays (N = 325) were acquired and joint space width (JSW) was measured (blinded to time point) using an automated algorithm for minimum JSW and JSW at 4 fixed locations in the medial compartment. MRIs were obtained on a subsample of study participants (N = 105) and tibiofemoral cartilage thickness measured and semi-quantitative (SQ) MRI scoring performed using BLOKS. We used an intention to treat analysis to compare change between groups at 18 month follow-up. X-ray and MRI results were analyzed using ANCOVA adjusted for baseline values, BMI, and gender. X-ray was also adjusted for inter-rim distance. Ordinal logistic regression was used for the ordinal SQ analyses, adjusting for baseline values, BMI and gender.

Results: Mean baseline descriptive characteristics of the cohort included: age, 65.6 yrs.; BMI 33.6 kg/m^{2}; 72% female; 81% white. A total of 399 (88%) participants completed the study and returned for FU18mth testing. Mean weight loss was: D, -9.5%; D+E, -11.4%; E, -2.2%. There were no baseline differences between groups in JSWx (0.225) 4.5 (1.9)mm or for cartilage thickness of the medial tibia and central medial femur combined 2.90 (0.08)mm. All 3 groups demonstrated continued progression of JSW loss with no significant difference between groups D -0.07(0.22)mm, D+E -0.27(0.22)mm and E -0.16(0.24)mm (p=0.79). All 3 groups demonstrated continued progression of MRI cartilage loss with no significant difference between groups D -0.10(0.05) mm, D+E -0.13(0.04)mm and E -0.05(0.04)mm (p=0.42). Maximal bone marrow lesion (BML) size showed a trend to improvement for the D+E OR 0.70 (0.25–1.95) and D OR 0.44 (0.16 – 1.23) groups.

Conclusion: Despite the potent effects of weight loss on symptoms, there does not appear to be any amelioration in the rate of structural progression either on x-ray or MRI cartilage measurement. The evidence of a trend towards improvements in BML suggests that this may be one mechanism for the symptom improvements related to weight loss.

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Childhood Physical Fitness Predicts Adulthood Knee Cartilage Volume and Bone Area: A 25-Year Cohort Study. Benny Samuel Eathakkattu Antony[1], Graeme Jones[1], Alison Venn[1], Leigh Blizzard[2], Flavia Cicuttini[3], L. March[4], Terry Dwyer[5] and Changhai Ding[6]. [1]Menzies Research Institute Tasmania, Hobart, Australia, [2]Hobart, Australia, [3]Monash University, Central and Eastern Clinical School, Melbourne, Australia, [4]University of Sydney, Insitute of Bone and Joint Research, Royal North Shore Hospital, St Leonards - Sydney, Australia, [5]Murdoch Children's Research Institute, Melbourne, Australia, [6]Menzies research institute & Monash University, Hobart, Australia

Background/Purpose: Physical activity interventions are often advised for management of osteoarthritis patients, despite contradictory findings regarding its effect on knee structure. In particular, there is little evidence relating childhood physical performance measures to adult joint structure. The aim of this cohort study was to determine the associations between childhood physical performance measures and knee cartilage volume and tibial bone area in adults 25 years later.

Methods: Subjects broadly representative of the Australian population (n=298, aged 31–41 years, female 48.7%) were selected from the Childhood Determinants of Adult Health study. They underwent T1-weighted fat-suppressed magnetic resonance imaging of their dominant knee and cartilage volume and tibial bone area were measured. Childhood measures including physical work capacity at 170 beats per minute (PWC_{170}), leg and hand muscle strength, sit-ups, long-run, and short-run were measured by standard protocols 25 years prior.

Results: There were consistent and significant associations of all childhood measures including PWC_{170}(β: 0.48 cm[2]per 100 mW, 95% CI: 0.22, 0.73), hand muscle strength (β: 1.49 cm[2]per 100g, 95% CI: 0.79, 2.19), leg muscle strength (β: 0.29 cm[2]per 100g, 95% CI: 0.09, 0.50), short-run (β: -0.71 cm[2]per second, 95% CI: -1.21, -0.21) and sit-ups (β: 0.28 cm[2]per count/10, 95% CI: 0.13, 0.43) with adult tibial bone area in multivariable linear regression, after adjustment for sex, childhood age, duration of follow-up and childhood and adulthood measures (body mass index and knee injury). In addition, these associations were independent of the corresponding adulthood fitness measures and tibial cartilage volume.

Similarly, there was a significant positive association between childhood PWC_{170} and adult medial tibial cartilage volume (β: 0.1 mm[3]per 100 mW, 95% CI: 0.03, 0.17) after adjustment for covariates including adult PWC_{170}. The magnitude of the association decreased by 33% but remained significant after further adjustment for tibial bone area. Other childhood measures such as hand muscle strength (β: 0.21 mm[3]per 100g, 95% CI: 0.04, 0.37) and sit-ups (β: 0.04 mm[3]per count/10, 95% CI: 0.01, 0.08) were significantly associated with medial tibial cartilage volume, but these became non-significant after further adjustment for medial tibial bone area.

Conclusion: A number of childhood physical performance measures are significantly associated with knee bone area and cartilage volume in adulthood. The associations with cartilage volume appear to be mediated by tibial bone area. This suggests physical activity in childhood can independently influence adult knee joint health possibly through adaptive mechanisms during growth.

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The Effects of Intensive Diet and Exercise On Bone Density in Older Adults with Knee Osteoarthritis: The Intensive Diet and Exercise for Arthritis (IDEA) Trial. Nicole R. Walton[1], Richard F. Loeser[2], Daniel Beavers[3], Barbara J. Nicklas[4], Mary Lyles[3] and Stephen P. Messier[5]. [1]Wake Forest University School of Medicine, Winston Salem, NC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Wake Forest University School of Medicine, Winston-Salem, NC, [4]Winston-Salem, NC, [5]Wake Forest University, Winston-Salem, NC

Background/Purpose: Previous studies on the effects of weight loss and exercise on bone mass show conflicting results and there are no studies of older adults with knee OA. We examined change in bone mineral density (BMD) in response to weight loss, with and without exercise, and to exercise alone in older adults enrolled in the IDEA trial and determined whether BMD changes were related to the magnitude of fat mass loss and to changes in leptin.

Methods: 454 overweight and obese (avg BMI 34) adults (avg age 66yrs, 72% female) with symptomatic knee OA were randomized to 18 months of intensive dietary induced weight loss (D); intensive weight loss plus exercise (D+E); or exercise control (E). The weight loss goal for the two diet groups was ≥ 10% of baseline body weight. The exercise intervention consisted of low to moderate intensity walking and resistance training 3 d/wk for 1 hr/d. A total of 399 (88%) participants completed the study. BMD at the hip (total hip=thip and femoral neck=FN) and spine, as well as total body fat mass, were measured by DXA and vitamin D levels (baseline only) were assessed in 392 subjects. Osteoporosis (OP) and osteopenia (OPE) were defined as location-specific t-scores <-2.5 and between -2.5 and -1, respectively. A subset of 162 subjects had serum leptin levels measured. Treatment group means were compared using ANCOVA, adjusted for baseline dependent variable values, BMI, and gender. Corrections for multiple comparisons used

Tukey's method. Linear associations of change measures used a general model, adjusted for baseline values, BMI, gender, and treatment arm.

Results: Mean weight loss was: D+E, 11.4%; D, 9.5%; E, 2.2%. BMD declined at the hip but not the spine in both weight loss groups (D= -0.024g/cm^2 thip; -.013 FN; both p<.0001 and D+E =-0.020 thip; -.012 FN; both p<.0001) but not the E group (-0.002;p=0.54 thip; -0.001; p=0.8 FN). At baseline 10 subjects (2.5%) had OP (4 hip and 6 spine) and 45% had OPE in at least 1 site. Following intervention, 9 subjects had OP and no subjects with OPE became OP. The mean serum vitamin D level at baseline was 29 ng/mL and baseline BMD values were not related to vitamin D levels. The D and D+E groups but not the E group had significant declines in fat mass and leptin. Changes in hip (but not spine) BMD correlated positively with changes in fat mass (b=.003 g/cm^2/kg, p<.0001) (Fig 1) and changes in leptin (b=.001ng/ml/kg, p<.0001).
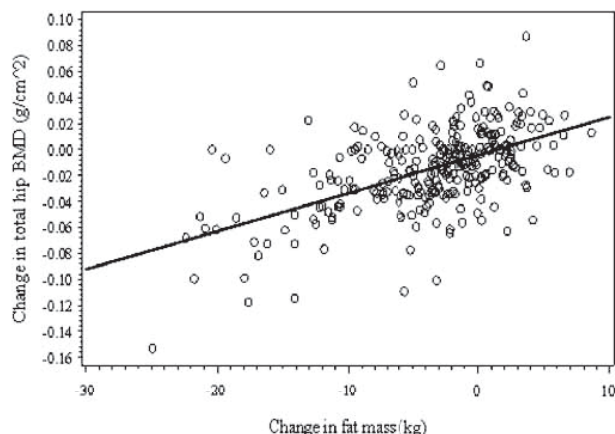
Conclusion: To our knowledge, this is the longest study to date that analyzed change in BMD with intentional weight loss and the first in older adults with knee OA. Weight loss and the associated reduction in fat mass resulted in a decrease in total hip and femoral neck, but not spine, BMD. The addition of exercise did not prevent these declines. The bone loss was not severe enough to result in osteoporosis but the findings suggest patients with low BMD should be monitored when starting a weight loss interevention.

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Cross-Sectional and Longitudinal Associations Between Circulating Leptin and Knee Cartilage Thickness in Older Adults. Oliver Stannus[1], Yuelong Cao[2], Benny Samuel Eathakkattu Antony[1], Graeme Jones[3] and Changhai Ding[4]. [1]Menzies Research Institute Tasmania, Hobart, Australia, [2]Menzies Research Institute Tasmania, Research Institute of Orthopaedics, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine,, Hobart, Australia, [3]Menzies Research institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [4]Menzies research institute & Monash University, Hobart, Australia

Background/Purpose: To investigate cross-sectional and longitudinal associations between serum leptin levels and knee cartilage thickness in older adults.

Methods: A prospective cohort of 163 randomly selected subjects (mean 63 years, range 52–78, 46% female) were studied. Knee cartilage thickness at medial tibial, lateral tibial, femoral and patellar sites was determined using T1-weighted fat suppressed magnetic resonance imaging (MRI) using custom semi-automated segmentation software written in MAT-LAB. Serum leptin levels were measured by radioimmunoassay. Radiographic osteoarthritic changes including joint space narrowing and osteophytes were assessed according to Osteoarthritis Research Society International (OARSI) atlas. Fat mass and lean mass (kg) were measured using a Hologic dual energy x-ray absorptiometry (DXA) scanner. Weight and height were measured, and body mass index (BMI) was calculated.

Results: Knee cartilage thickness was negatively and significantly associated with age, female sex and BMI in multivariable analyses. It was also associated with joint space narrowing at medial tibial, lateral tibial and patellar sites (β: -0.08 to -0.12 mm per grade, all P<0.05) and osteophytes.

Cross-sectionally, serum levels of leptin were negatively associated with femoral (β: -0.012 mm per pg/ml, 95% CI: -0.021, -0.003), medial tibial (β: -0.008 mm per pg/ml, 95% CI: -0.016, 0.001), lateral tibial (β: -0.010 mm per pg/ml, 95% CI: -0.019, -0.001) and patellar (β: -0.015 mm per pg/ml, 95% CI: -0.026, -0.003) cartilage thickness after adjustment for covariates including BMI and radiographic OA. Moreover, BMI, trunk fat and total fat were negatively associated with cartilage thickness at various sites, and the significant associations disappeared after further adjustment for leptin.

Longitudinally, both baseline leptin and change in leptin were associated with greater deleterious changes in medial tibial cartilage thickness (β; -0.004 mm per pg/ml, 95% CI: -0.007, -0.001 and β: -0.009 mm per pg/ml, 95% CI: -0.018, -0.001, respectively) in multivariable analyses.

Conclusion: This is the first study to examine the cross-sectional and longitudinal associations between serum levels of leptin and cartilage thickness in older adults. Serum levels of leptin are independently and consistently associated with reduced cartilage thickness cross-sectionally and over time. In addition, the associations between adiposity measures and cartilage thickness are mediated by leptin suggesting leptin may play a key role in cartilage loss.

Disclosure: O. Stannus, None; **Y. Cao**, None; **B. S. Eathakkattu Antony**, None; **G. Jones**, None; **C. Ding**, None.

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The Association of Fat Mass and Skeletal Muscle Mass with Clinical and Structural Knee Osteoarthritis: The Netherlands Epidemiology of Obesity Study. A. Willemien Visser, Marieke Loef, Martin den Heijer, Monique Reijnierse, Frits R. Rosendaal and Margreet Kloppenburg. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Body mass index (BMI) is an important risk factor for knee osteoarthritis (OA), but BMI depends only upon height and weight and gives no insight in underlying causal pathways. The objective of this study was to investigate whether the association of BMI with clinical and structural OA can be explained by the amount of fat mass (FM) and/or skeletal muscle mass (SMM).

Methods: Participants of the NEO (Netherlands Epidemiology of Obesity) study, a population-based cohort of individuals aged 45–65 years with a BMI ≥ 27 kg/m^2 and a control group with a BMI < 27 kg/m^2, were used. BMI was assessed by measured weight and length. FM and SMM were assessed using bioelectrical impedance analysis. Clinical OA was defined according to the ACR criteria; based on self-reported knee complaints and physical examination of the knees. Structural OA was defined based on MR imaging of the right knee, performed on 1.5T (Philips, Best, The Netherlands) using a standard knee protocol. Osteophytes were scored according to the Knee Osteoarthritis Score System in nine compartments. Osteophytes were graded from 0 (absent) to 3 (severe). A total score was calculated for each individual, a score of ≥ 6 was considered as structural OA. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to associate BMI, FM, SMM and the FM/SMM ratio with OA using logistic regression analyses, stratified for sex and adjusted for age.

Results: In 4562 participants (mean age 56 years, 52% women) median (IQR) BMI was 30.3 kg/m^2 (28.4–33.1), FM 33.5 kg (27.5–40.8) kg and SMM 28.3 (23.0–33.8) kg. Clinical OA was present in 24% of women and 12% of men. MRI data were available in 1134 participants; structural OA was present in 34% of women and 35% of men. In women and men, BMI was associated with clinical and structural OA. Both FM and SMM were associated with clinical OA, in women ORs were 1.02 (1.01–1.03) and OR 1.05 (1.02–1.08) respectively, and in men; ORs 1.02 (1.01–1.04) and 1.04 (1.01–1.07), respectively. Comparable associations were found with structural OA. Remarkably, in clinical OA the FM/SMM ratio was positively associated with OA (ORs 1.48 (1.13–1.94) and 1.92 (1.20–3.06) in women and men respectively), meaning that a higher FM relative to SMM is unfavorable. In structural OA we found that in multivariate analysis including BMI and FM, the association between BMI and OA disappeared, but the association between FM and OA was unchanged, suggesting that FM is mediating the association of BMI with OA. In multivariate analysis including BMI and SMM, the association of both BMI and SMM with structural OA decreased, suggesting that SMM acts as a partial mediator.

Conclusion: BMI, FM and SMM were associated with structural and clinical OA in both women and men. Further analyses suggest that both FM and SMM are involved in the underlying mechanisms of developing knee OA and associated complaints.

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Fine-Specificity of Anti-Citrullinated Peptide Auto-Antibodies: Associations with Cardiac Structure and Function in Rheumatoid Arthritis.

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Background/Purpose: Despite advancements in rheumatoid arthritis (RA) treatment, standardized mortality rates remain up to 3 times higher than in the general population. Cardiovascular disease (CVD) is the leading cause of excess deaths in RA. Our group has recently found lower left ventricular (LV) mass in RA patients which was associated with anti-CCP antibody levels. Although anti-CCP Abs have been associated with increased CVD and mortality in RA, little is known about the underlying pathophysiology and whether specific anti-citrullinated peptide antibodies (ACPAs) play a role in altering cardiac function or structure. Our objective was to test the association of autoreactivity of a selected panel of ACPAs with myocardial function and structure parameters in RA patients.

Methods: This study was nested in an RA cohort without known CVD. A cross-sectional analysis was performed using clinical data and collected serum from a subset of participants who underwent cardiac magnetic resonance (CMR) imaging at baseline. With a custom multiplex bead based antigen array using the BioPlex platform and ran on the Luminex 200 instrument, the autoreactivity against a panel of 17 ACPAs was tested. The association of each ACPA with CMR-derived cardiac measures was tested by linear regression analyses, adjusting for potential confounders.

Results: A total of 76 RA patients underwent CMR [mean age 59 ± 9 years, 49% male, mean disease duration 12 ± 11 years, mean DAS28$=3.5 \pm 1.1$]. At an established level of significance of <0.05, categories of anti-citrullinated vimentin (epitopes 58–77), anti-citrullinated histone2b (epitopes 62–81) and anti-citrullinated enolase antibodies were associated with a decrease in LV end diastolic mass. A decrease in LV mass index was associated with categories of anti-citrullinated histone2b, anti-citrullinated histone2b (epitopes 62–81), anti-citrullinated fibrinogen (epitopes 211–230, 556–575), anti-citrullinated histone2a (epitopes 1–20) and anti-citrullinated enolase antibodies. These and additional associations with other tested cardiac parameters are shown in table 1.

Table 1. Summary of Linear Regression Analysis of the Associations between Specific ACPAs and statistically significant directional changes in each individual left ventricular measure

ACPA categories-per quartile	EDM	MI	EDVI	HR	ESV	EF	SV	CO	ESVI
Anti-cit-vimentin			↓						
Anti-cit-fibrinogen									
Anti-cit-histone2b*		↓							
Anti-citfibrinogen (616–635)				↑					
Anti-cit-vimentin (58–77)	↓			↑					
Anti-cit-fibrinogen (41–60)									↓
Anti-cit-fillagrin (48–65)									
Anti-cit-biglycan (247–266)				↑	↓				↓
Anti-cit-clusterin (231–250)				↑					↓
Anti-cit-histone2b (62–81)	↓	↓	↓	↑	↓		↓		
Anti-cit-fibrinogen (211–230)		↓	↓	↑	↓				↓
Anti-cit-fibrinogen (556–575)		↓	↓	↑	↓				
Anti-cit-histone2a (1–20)		↓	↓	↑					
Anti-cit-apo E (277–296)									
Anti-cit-apo A				↑			↑		
Anti-cit-apo E				↑			↑		
Anti-cit-enolase	↓	↓	↓	↑	↓				↓

EDM=LV end diastolic mass, MI= LV mass index, EDVI= LV end diastolic volume index, HR= heart rate, ESV= end systolic volume, EF=ejection fraction, SV=stroke volume, CO=cardiac output, ESVI= end systolic volume index. ↑ =increase, ↓ =decrease. *Adjusted for Framingham score. Statistical significance: p-value <0.05.

Conclusion: Our results suggest that categories of specific ACPAs are associated with alterations in cardiac parameters in RA patients. Identifying the specific peptide(s) against which the anti-CCP reactivity is directed represents an indirect, but important, advance in understanding the pathophysiology of accelerated CVD in RA.

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Prescription of Tumour Necrosis Factor α Antagonists Is Strongly Associated with a Reduction in Hospital Admissions and in Musculoskeletal Surgical Procedures for Rheumatoid Arthritis Based On a 16 Year Analysis of Nationwide Data.

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Background/Purpose: Comorbidities, joint destruction leading to orthopaedic intervention and physical disability are predictable outcomes of uncontrolled Rheumatoid Arthritis (RA). Synthetic DMARDS have a slow mechanism of action and used as monotherapy induce remission in <20% of RA patients. Tumour Necrosis Factor inhibitors (TNFi) were first prescribed in 1999, have a faster mechanism of action and in combination with methotrexate in early RA induce remission in up to 50%. It is argued that the clinical, functional and quality of life benefits of TNFi may not be sufficient to justify their significant economic cost (National expense, >€100 million/year in 2010). We thus sought to evaluate the number of hospital inpatient days and of musculoskeletal surgical procedures (MSKSPs) in RA patients from 1995 to 2010 and to assess whether there is any association with TNFi usage.

Methods: The Hospital In-Patient Enquiry system (HIPE), which is a national system recording information on hospital bed utilization, was evaluated from 57 hospitals from 1995–2010 for patients admitted with a diagnosis of RA. Age group, number of inpatient days, gender and reason for admission (ICD codes) were also recorded. Annual prescription data for TNFi usage nationally was separately analysed from 2000 to 2010. Descriptive analyses are presented as totals, mean (standard deviation (SD)) and mean % change. Correlations were examined by Spearman's rho; p<0.05 was considered statistically significant.

Results: 57,774 inpatient records in RA patients were reviewed from 1995–2010; F: M 2:1, mean age 66 (16). Annual TNFi prescribing has increased by 156% per annum (pa) from 2389 units in 2000 to 116,747 in 2010. An increase in TNFi prescribing coincided with a decrease in RA inpatient days for any reason: 49,000 (4880) pa pre-2002, reducing by 13% pa thereafter to 31000 pa in 2010 (r= -0.78, p=0.0055), likely contributing significantly to savings of approximately €16,000,000 pa based on current inpatient hospital costing. 550 (51) pa MSKSPs were recorded on RA in-patients pre-2002 with a subsequent reduction of 10% pa to 291 in 2010 (overall 47% decrease) and correlating significantly but negatively with number of TNFi prescriptions (r= -0.96, p<0.0001). 71 (27) pa elective hip procedures (64 replacements) were recorded pre-2002 with a subsequent reduction of 8% pa to 40 in 2010 (r= -0.88, p=0.0007), a 44% decrease on pre 2002. 79 (12) pa elective knee procedures (64 replacements) were recorded pre-2004 with a subsequent 7% pa reduction to 37 in 2010 (r= -0.96, p=0.003), a 53% decrease on pre-2004.

Conclusion: Increased prescription of TNFi drugs for RA patients negatively correlates with reduction in RA hospital inpatient bed days and likely contributed significantly to estimated €16,000,000 pa savings. TNFi usage also correlates negatively with a reduction in all MSKSPs and specifically with both elective hip and knee procedures. It is recognised that factors other than TNFi usage, such as improved use of non-biologic disease-modifying treatments and prevention of comorbidities, may also have contributed to these improved patient outcomes. Further analysis of these data including the economic impact is underway.

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High Risk of Intensive Care Unit Admission in Rheumatoid Arthritis Patients: A Population Based Study. Christine Peschken, Carol A. Hitchon, Allan Garland, Charles N. Bernstein, Randy Fransoo and Ruth Ann Marrie. University of Manitoba, Winnipeg, MB

Background/Purpose: Comorbidity in Rheumatoid arthritis (RA) has been a focus of intensive research in recent years, but little is known about the incidence of critical illness in RA, as defined by admissions to Intensive Care Units (ICU). While hospital care is the largest component of health resource use in Canada, admissions to ICU consume a disproportionate share of costs. Using a large, population-based dataset we determined the incidence of ICU admissions in RA patients.

Methods: In a stable population of over 900,000 adults, we used hospital claims from a large administrative database linked to a population based ICU database to determine the incidence of ICU admissions from 2000–2010. RA patients were compared to a cohort from the general population, matched on sex, year of birth and region of residence, with up to 5 controls for each case. Individuals with any diagnostic codes (ICD-9/10) for autoimmune inflammatory disease were excluded from the general population cohort. We estimated the annual incidence rates by age group, sex, and geographic region by stratification; (number of persons in each cohort who had at least one ICU admission/number of persons alive in that cohort at year-end). The results were age and sex standardized to the general Canadian population. The incidence of ICU admission between the RA cohorts and matched cohorts were compared using incidence rate ratios (RR). We compared the 10 year cumulative incidence of ICU admission for the period 2000–2010: (number of persons with disease who had at least one episode of critical illness/person-years at risk).

Results: The age and sex standardized annual incidence of ICU admission was relatively stable over the 10 year period, at 0.82–1.18% for RA patients compared to 0.32–0.59% for the matched cohort, RR 1.53–3.14. The risk of ICU admission increased with age (age 18–39, 0.38% for RA vs. 0.10% for controls; age 40–59, 0.81% vs. 0.31%; age 60+ 1.74% vs. 1.09%) in a similar pattern to that seen in the general population. The 10 year cumulative incidence rate for RA patients was7.68% compared to 4.73% in the general population, with a RR of 1.62 (95% CI 1.46–1.80).
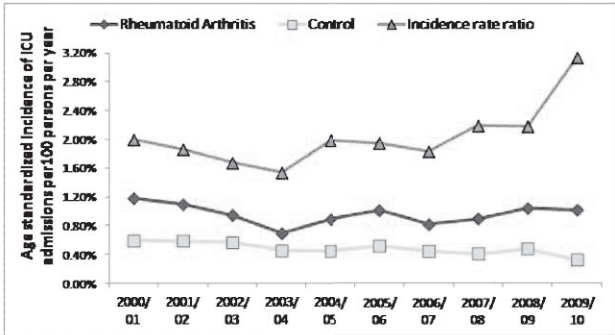
Conclusion: The risk of ICU admission is significantly increased in RA patients compared to the general population, with more than 1% of adults with RA developing critical illness each year, and a 10 year risk near 8%. This represents a substantial disease burden and cost to the healthcare system. Further work is ongoing to determine causes and predictors of ICU admission.

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The Association Between Inflammatory Markers and Hyperlipidemia and the Risk of Myocardial Infarction in Patients with Rheumatoid Arthritis. Jie Zhang[1], Lang Chen[1], Elizabeth S. Delzell[1], Paul M. Muntner[1], William B. Hillegass[2], Monika M. Safford[1], Iris E. Navarro[1] and Jeffrey R. Curtis[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Birmingham, AL, [3]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of developing myocardial infarction (MI) which is not explained by Framingham CHD risk factors. We examined the association between RA-related inflammatory markers, hyperlipidemia and the risk of MI in RA patients.

Methods: We conducted a retrospective cohort study of RA patients using administrative claims data from a large U.S. commercial health plan from 2005 to 2010. Eligible patients were required to have two or more RA diagnoses from physician visits that were between 7 and 365 days apart, a baseline period of 6 months with continuous enrollment with medical and pharmacy benefits, and have results for at least one of the three lab tests occurring either during baseline or follow-up. Labs of interest included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and low density lipoprotein cholesterol (LDL-C) and were available for a subset of RA patients from electronic records of tests performed by a national laboratory chain ordered during routine clinical care. We identified the first hospitalized MI event by inpatient primary ICD9 diagnosis codes '41001', '41011', '41021', '41031', '41041', '41051', '41061', '41071', '41081', or '41091' with at least a 3 day length of stay (or expired as the discharge status of the hospitalization). We examined the association between ESR, CRP and LDL-C quartiles (to avoid assumptions of linearity) and hospitalized MI, controlling for age and sex; and stratified by sex, controlling for age, using proportional hazard regression to estimate hazard ratios (HRs).

Results: We identified 116,181 RA patients, 74.8% of whom were women. Mean age was 48.2 ± 15.2 SD years and 74.8% were female. Depending on lab tests of interest, the numbers patients who had MI during follow-up ranged from 85 to 110 (table). The overall and sex-specific crude incidence rates of MI were 2.7 cases per 1,000 person-years, 2.1 among women, and 4.8 among men. After controlling for age and sex, higher CRP (highest compared to the lowest CRP quartile) was associated with a 3.0 (95% CI: 1.5–5.9) and higher ESR (highest compared to the lowest quartile of ESR) had an HR = 2.5 (95% CI: 1.5–4.3) for MI, but higher LDL-C was not significantly associated with increased MI risk (table). The observed association between CRP and MI appeared greater for women.

Table. Hazard Ratios (95% CI) for Factors Associated with Myocardial Infarction

	Overall[a]			Men[b]			Women[b]		
C-Reactive Protein quartile (mg/dL)									
Events, N	85			42			43		
1st (<=1.2) [referent]	1.00			1.00					
2nd (>1.2 and <=3.1)	1.09	(0.48	2.48)	0.88	(0.32	2.44)	1.64	(0.39	6.89)
3rd (>3.1 and <=8.1)	2.56	(1.28	5.15)	2.02	(0.85	4.82)	4.06	(1.16	14.19)
4th (>8.1)	2.97	(1.49	5.93)	1.51	(0.61	3.77)	6.76	(2.00	22.89)
Erythrocyte sedimentation rate quartile (mm/hr)									
Events, N	95			40			55		
1st (<=4) [referent]	1.00			1.00			1.00		
2nd (>4 and <=9)	0.85	(0.40	1.77)	0.95	(0.34	2.72)	0.81	(0.29	2.27)
3rd (>9 and <=20)	1.52	(0.81	2.83)	2.00	(0.82	4.88)	1.30	(0.55	3.11)
4th (>20)	2.52	(1.46	4.34)	2.77	(1.24	6.19)	2.40	(1.12	5.11)
Low density lipoprotein cholesterol quartile (mg/dL)									
Events, N	110			59			51		
1st (<=83) [referent]	1.00			1.00			1.00		
2nd (>83 and <=105)	1.09	(0.66	1.81)	0.97	(0.50	1.90)	1.29	(0.59	2.86)
3rd (>105 and <=130)	0.81	(0.46	1.40)	0.72	(0.34	1.52)	0.94	(0.40	2.18)
4th (>130)	1.03	(0.60	1.78)	0.97	(0.46	2.04)	1.15	(0.50	2.64)

a. Adjusting for age and gender; b. Adjusting for age.

Conclusion: Among this large national sample of RA patients, inflammatory markers (both CRP and ESR) were significantly associated with increased MI risk but LDL-C was not.

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Hospitalized Bacterial Infections Among U.S. Veterans with Rheumatoid Arthritis Initiating TNF Antagonist and Newer Biologic Agents. Jeffrey Curtis[1], Shuo Yang[1], Nivedita M. Patkar[2], Lang Chen[1], Jasvinder A. Singh[1], Grant W. Cannon[3], Ted R. Mikuls[4], Elizabeth S. Delzell[1], Kenneth G. Saag[2], Monika M. Safford[1], Scott DuVall[5], Kimberly Alexander[6], Pavel Napalkov[6], Aaron Kamauu[7] and John Baddley[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]George E. Wahlen VA Medical Center, Salt Lake City, UT, [4]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [5]VA Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [6]Genentech, Inc., South San Francisco, CA, [7]Anolinx, Bountiful, UT

Background/Purpose: Risks of hospitalized infections for newer biologic agents have not been well characterized compared to risks for anti-TNF therapy. **Purpose:** To compare the risk of hospitalized bacterial infections among RA patients starting rituximab (RTX), abatacept (ABA) or a new anti-TNF after failure of at least one previous anti-TNF

Methods: Using data from 1998–2011 from the U.S. Veteran's Health Administration, we identified 3872 patients who started RTX, ABA, or anti-TNF therapy after prior exposure to another anti-TNF agent. *To minimize confounding from channeling of cancer patients to certain biologics, the 720 patients with a history of cancer between 1998 and 2011 were excluded, leaving a final sample of 3152 patients. Baseline characteristics were defined in the year prior to treatment initiation. For each subject, exposure episodes were defined based upon days supply (injections) or usual dosing intervals (infusions), with 9 months assumed for RTX exposure. Current exposure was extended by 90 days for all biologics. The outcome was hospitalization with a primary diagnosis of bacterial infection. The hazard ratio (HR, 95% CI) for hospitalized infection for RTX and ABA vs. anti-TNFs was calculated, adjusting for confounders as in the Table.*

Table 1. Multivariable Adjusted* Hazard Ratios for Risks of Hospitalized infections Among RA Patients Switching to Abatacept or Rituximab Compared to Patients Switching to Another Anti-TNF (Analysis Restricted to Patients Without Prior Cancer)

Infection-Related Risk Factor	Hazard Ratio (95% CI)
Medication Exposure (referent to anti-TNF therapy)	
Abatacept	0.72 (0.41–1.26)
Rituximab	1.14 (0.70–1.87)
Age Group (years) (referent to <50)	
50–60	1.82 (0.86–3.86)
60–70	1.78 (0.82–3.86)
70–80	2.11 (0.92–4.80)
≥ 80	2.40 (0.80–7.15)
Comorbidities	
COPD	1.77 (1.20–2.59)
Diabetes	1.06 (0.75–1.51)
Prednisone-equivalent steroid dose (referent to no use)	
1 – 7 mg/day	1.33 (0.88–2.02)
7 – 10mg/day	1.31 (0.83–2.08)
> 10mg/day	1.71 (1.10–2.68)

* adjusted for variables included in the table and additionally for heart failure, recent biologic switch in last 90 days, number of biologic switches and calendar year; none were significantly associated with the outcome

Results: A total of 596 RTX, 451 ABA and 3111 anti-TNF (61% adalimumab) switcher treatment episodes (first initiation of the biologic),were identified among the eligible patients. Mean age was 60.2 +10.6 years, 87% were male; 25% had diabetes, 14% had COPD, and 44% used oral glucocorticoids. Two-thirds of anti-TNF exposure episodes were adalimumab. The mean ± SD follow-up time for each treatment episode was 11±12 months. The most common types of hospitalized infections were pneumonia (37%), skin/soft tissue infections (22%), urinary tract infections (9%), and bacteremia/sepsis (7%).

Crude hospitalized infection rates/100 person years (95% CI) were: RTX=4.4 (3.1, 6.4), ABA=2.8 (1.7, 4.7), anti-TNF=3.0 (2.8, 3.9). Results were similar for a less restrictive cohort of RA patients excluding only hematologic cancer in the prior 12 months (4927 episodes, 3727 RA patients).

Conclusion: In older, predominantly male US veterans with RA and a high comorbidity burden, risk of hospitalized bacterial infections for patients treated with RTX or ABA were comparable to patients switching to a different anti-TNF therapy (mostly adalimumab).

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Widening Gap Between Cardiovascular Specific Mortality in Patients with Inflammatory Polyarthritis Compared to the General Population? Alexander J. Warner[1], Jh Humphreys[2], Mark Lunt[3], Tarnya Marshall[4], Deborah P. M. Symmons[1] and Suzanne Verstappen[5]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit,, Manchester, United Kingdom, [3]University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [4]Norfolk and Norwich University Hospitals Trust, Norwich, United Kingdom, [5]University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

Background/Purpose: Cardiovascular (CVD) mortality rates are raised in patients with inflammatory polyarthritis (IP) but have been shown to be falling in the general population. This study aims to examine CVD mortality over time in a cohort of recent onset IP patients compared to the general population in Norfolk, UK.

Methods: Between 1990–2004, patients >16 years with ≥2 swollen joints for >4 weeks were registered to an inception cohort, the Norfolk Arthritis Register (NOAR), in Norfolk, UK. Three cohorts (limited to symptom onset <2 years before baseline assessment) were defined by year of baseline assessment: cohort 1 (1990–1994); cohort 2 (1995–1999); cohort 3 (2000–2004). Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) status (+/−) were determined from blood samples obtained at baseline assessment. The 1987 ACR criteria for RA were also applied. Patients were tracked via Office for National Statistics (ONS) for notification of death. CVD as underlying cause of death was defined according to ICD-10 (Chapter "I"). ONS also provided CVD death rates for the Norfolk general population. For all cohorts, standardised mortality ratios (SMRs) for CVD were calculated over 5 years from baseline as well as for subgroups who fulfilled the 1987 ACR criteria for RA; those RF+ or ACPA+ at baseline. To ensure adequate statistical power, analyses were performed only for sub-groups with at least 10 observed CVD deaths over the 5 year follow up.

Results: Cohort 1 comprised 1006 patients, cohort 2: 880 patients and cohort 3: 638 patients. Approximately two-thirds were women in each cohort and median age at symptom onset was 54 (IQR 42–67); 55 (IQR 44–67); 58 (IQR 47–70) years in each respective cohort. The percentages RF+ were 28% (249/877), 29% (225/788) and 36% (203/559) and ACPA+ were 23% (174/745), 26% (191/730) and 31% (160/517) in each respective cohort.

By 5 years from baseline there were 96 (3.8% of the total cohort) CVD deaths: 36 (3.6%); 34 (3.9%); 26 (4.1%) in each respective cohort. The overall crude CVD death rate in adults >16 years in Norfolk decreased over time: 3.3% (1990–1994); 3.0% (1990–1994) and 2.7% (2000–2004). Five year CVD SMRs were raised in all cohorts but only significant statistically in cohort 3: cohort 1: 1.13 [95% CI 0.82–1.57]; cohort 2: 1.29 [95% CI 0.92–1.81] and cohort 3: 1.51 [95% CI 1.03–2.22]. RF+ patients had significantly raised 5 year CVD SMRs (1.74 [95%CI 1.05–2.88]) as did ACPA+ patients (2.17 [95%CI 1.23–3.80]) in cohort 1; more recent cohorts were excluded as <10 CVD deaths were observed. CVD SMRs were not statistically significantly increased in the subgroup of patients who met the ACR 1987 criteria for RA at baseline. No consistent differences in CVD SMRs between men and women were observed across the cohorts.

Conclusion: Raised SMRs for IP patients in advancing cohort years may be due to the declining CVD deaths observed in the general population over the same time period. The status of RF+ and ACPA+ may also contribute to excess early CVD mortality in IP patients.

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A Randomized, Double-Blind, Parallel Group Study of the Safety and Efficacy of Tocilizumab SC Versus Tocilizumab IV, in Combination with Traditional Dmards in Patients with Moderate to Severe RA. G. R. Burmester[1], Andrea Rubbert-Roth[2], Alain G. Cantagrel[3], Stephen Hall[4], Piotr Leszczynski[5], Daniel Feldman[6], Madura J. Rangaraj[7], Georgia Roane[8], Charles L. Ludivico[9], Francesco Ramirez[10] and Min Bao[11]. [1]Charité-Universitätsmedizin Berlin, Berlin, Germany, [2]Klinikum der Universität zu Köln, Köln, Germany, [3]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [4]Cabrini Medical Centre, Malvern, Australia, [5]Hospital J. Strusia, Poznan, Poland, [6]Universidade Federal de de São Paulo, Sao Paulo, Brazil, [7]Arthritis & Diabetes Clinic, Monroe, LA, [8]Rheumatology Associates, P.A., Charleston, SC, [9]East Penn Rheumatology Assoc, Bethlehem, PA, [10]Roche Products Limited, Welwyn, United Kingdom, [11]Genentech, South San Francisco, CA

Background/Purpose: The objective of this study was to compare the efficacy and safety of tocilizumab (TCZ) subcutaneous (SC) and TCZ intravenous (IV) regimen in patients with adult rheumatoid arthritis (RA) who had an inadequate response to DMARDs (up to 20% may have failed one or more anti-TNF agents).

Methods: This 2-year Phase 3 trial is a randomized, active controlled, parallel group, study including a 24-week double-blind (DB) period, followed by a 72-week open-label phase. TCZ SC dose was based on previous pharmacological studies. During the DB period, patients (pts) received TCZ SC 162 mg qw + placebo IV q4w or TCZ IV 8mg/kg q4w + placebo SC qw, in combination with traditional DMARDs. The primary end point to demonstrate the non-inferiority of TCZ SC to TCZ IV was the proportion of patients in each group meeting the ACR20 improvement criteria at Week 24. Additional clinical efficacy, immunogenicity and safety assessments were evaluated as secondary outcomes. Pts were stratified by body weight and regions at baseline. The hypothesis of non-inferiority of TCZ SC with respect to TCZ IV regarding ACR20 response was tested by means of 95% confidence interval (CI) and with a 12% non-inferiority margin (NIM).

Results: A total of 1262 pts were enrolled globally. Mean baseline characteristics were similar between TCZ SC and TCZ IV groups: age 53 years; RA duration 9 years; DAS28-ESR 6.6 and 6.7, respectively. At Week 24, 69.4% (95% CI: 65.5, 73.2) of TCZ SC-treated pts versus 73.4% (95% CI: 69.6, 77.1) of TCZ IV-treated pts achieved an ACR20 response (weighted difference between groups 4.0% [95% CI: -9.2, 1.2]); a 12% NIM was met. ACR50/70 responses, disease activity and physical function improvements were also comparable between TCZ SC and TCZ IV groups. Up to Week 24, the proportions of pts with at least one adverse event (AE) and serious AE were 76.2% and 4.6%, respectively in the TCZ SC group compared with 77.0% and 5.2%, respectively in the TCZ IV group. The most common AEs in both groups were infections. Injection site reactions occurred more frequently in the TCZ SC (placebo IV) group than the TCZ IV (placebo SC) group (10.1% vs 2.3%, respectively); most were grade 1 severity. No anaphylaxis was reported over the 24-week period.

Conclusion: TCZ SC 162mg qw demonstrated comparable efficacy and safety to TCZ IV 8mg/kg q4w. No new clinically meaningful safety signals were identified in TCZ SC-treated pts.

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Tofacitinib Inhibits Radiographic Progression in Patients with Rheumatoid Arthritis Prone to Develop Structural Damage: A Post-Hoc Analysis of a Phase 3 Trial. Désirée van der Heijde[1], Robert B. M. Landewé[2] and David Gruben[3]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Academic Medical Center/University of Amsterdam & Atrium Medical Center, Amsterdam, Netherlands, [3]Pfizer Inc., Groton, CT

Background/Purpose: Tofacitinib is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy for RA. In the ORAL Scan trial [NCT00847613] progression in radiographic scores (mean change from baseline [BL] in modified Total Sharp Scores [mTSS] at Month 6) was a primary analysis using an Analysis of Covariance (ANCOVA). ANCOVA demonstrated statistically significant inhibition of structural damage progression for tofacitinib 10 mg but not 5 mg twice daily (BID) doses, versus placebo (PBO).[1] Rank analysis of change from BL values performed as a sensitivity analysis demonstrated borderline evidence of inhibition by both doses. Mean change from BL in mTSS with PBO was <0.50 at Month 6 and also 77.7% of PBO patients showed no progression (mTSS change from BL ≤0.5). There is a trend towards less PBO progression in recent radiographic studies[2] driven, in part, by the early rescue of PBO patients. In ORAL Scan, PBO treatment was only 3 months for non-responders (<20% improvement from baseline in swollen/tender joint counts, approximately 50% of patients receiving PBO) and 6 months for all others. Thus analyses focusing on prognostically-relevant characteristics of patients at particular risk of damage progression may be informative.

Methods: Literature was reviewed for factors identified as predicting higher risk of structural progression.[3,4] BL data were used to subset the patients by these high-risk factors, regardless of treatment group assignment. ANCOVA was then applied to each high-risk subset.

Results: Factors reported to predict increased risk of damage progression included: anti-CCP+; BL DAS28-4(ESR) ≥5.1; both seropositive (either RF+ or anti-CCP+) and BL erosion score ≥3; and >median BL mTSS (Figure). The primary analysis of the whole data set is displayed for reference. Each of these high-risk subsets showed maintained or increased differentiation between tofacitinib and PBO treatments. We further evaluated the predictive power of BL mTSS by tertiles, ie across three evenly divided groups irrespective of treatment assignment. In the first tertile, inhibition could not be demonstrated because of lack of progression in the PBO group. In the 2nd and 3rd tertiles, PBO progression led to large mean differences between both tofacitinib doses and PBO (Figure).
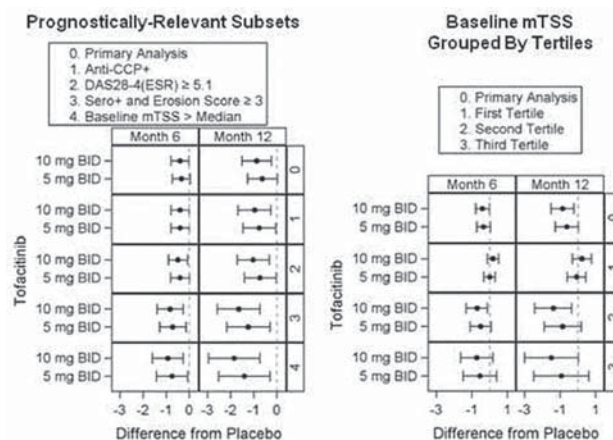
Figure. Dots = means; Bars = confidence intervals

Conclusion: In prognostically relevant subsets of patients with RA, especially in patients at increased risk of radiographic progression, both tofacitinib 5 and 10 mg BID demonstrated inhibition of damage progression compared to PBO. These analyses support the conclusion of the primary analysis that tofacitinib inhibits progression of structural damage.

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Weekly Subcutaneous Abatacept Confers Comparable Onset of Treatment Response and Magnitude of Efficacy Improvement Over 6 Months When Administered with or without an Intravenous Abatacept Loading Dose. M. Schiff[1], R. Alten[2], M. Weinblatt[3], P. Nash[4], R. Fleischmann[5], P. Durez[6], J. Kaine[7], I. Delaet[8], S. Kelly[8], M. Maldonado[8], S. Patel[8] and M. C. Genovese[9]. [1]University of Colorado, Denver, CO, [2]Schlosspark-Klinik, University Medicine, Berlin, Germany, [3]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [4]University of Queensland, Brisbane, Australia, [5]University of Texas Southwestern Medical Center, Dallas, TX, [6]Université Catholique de Louvain, Brussels, Belgium, [7]Sarasota Arthritis Research Center, Sarasota, FL, [8]Bristol-Myers Squibb, Princeton, NJ, [9]Stanford University, Palo Alto, CA

Background/Purpose: To compare clinical and functional responses with SC abatacept administered with or without an IV loading dose, in pts with active RA and inadequate response to methotrexate (MTX).

Methods: Pts from the intent-to-treat (ITT) populations of the ACQUIRE[1] and AMPLE[2] studies randomized to SC abatacept plus MTX were included in this analysis. All pts received fixed-dose SC abatacept 125 mg/week; in ACQUIRE, pts also received an IV loading dose (10 mg/kg based on weight range) on Day 1; no IV loading dose was administered in AMPLE. For this *post-hoc* analysis, assessments included ACR 20 and Health Assessment Questionnaire-Disability Index (HAQ-DI) response (improvement of ≥0.3) over 6 months, with pts who discontinued considered non-responders. Mean changes from baseline over 6 months in Disease Activity Score (DAS) 28 (C-reactive protein; CRP) were assessed in pts with DAS28 >5.1 at baseline (last observation carried forward), to account for differences in baseline disease activity between the two studies.

Results: A total of 736 pts from ACQUIRE (IV loading dose) and 318 pts from AMPLE (no IV loading dose) were included. All pts were biologic-naïve at baseline, with mean disease duration of 7.6 and 1.8 years, DAS28 (CRP) 6.2 and 5.5, and HAQ-DI 1.72 and 1.5 in ACQUIRE and AMPLE, respectively. Efficacy was compared at Days 15, 29, 57, 85, 113, 141 and 169. For pts treated with SC abatacept with an IV loading dose, ACR 20 response rates were 24.6, 44.5, 58.0, 66.6, 69.3, 72.4 and 74.8%, respectively. For pts treated without an IV loading dose, ACR 20 response rates were similar: 27.4, 42.5, 58.5, 60.1, 66.0, 70.1 and 66.0%, respectively. HAQ-DI response rates were also similar: 31.7, 45.1, 53.5, 59.5, 63.2, 64.4 and 68.3%, respectively, with the IV loading dose, and 31.8, 42.8, 54.4, 58.5, 60.1, 61.9 and 61.0%, respectively, without. For the overall populations, mean (SD) changes from baseline to Day 169 in DAS28 were –2.57 (1.30) and –2.09 (1.38) in ACQUIRE and AMPLE, respectively. For pts with baseline DAS28 >5.1, mean changes in DAS28 over time were also comparable for both studies (Figure).

DAS28 (CRP) mean change from baseline in patients with baseline DAS28 >5.1
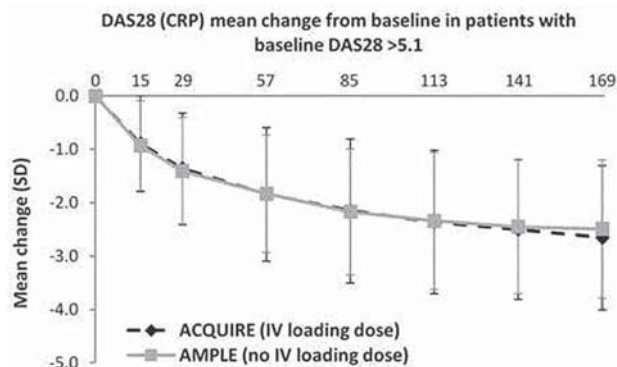
Patients, N	15	29	57	85	113	141	169
ACQUIRE (IV loading)	644	655	655	655	655	655	655
AMPLE (no IV loading)	193	197	199	199	199	199	199

Conclusion: Time to onset and magnitude of ACR 20 and HAQ-DI responses and DAS28 improvements were similar for pts treated with SC abatacept with or without IV loading in patients with RA and an inadequate response to MTX. Previous pharmacokinetic data show that in the absence of IV loading, target therapeutic concentrations are achieved in the majority of pts by Week 2 of SC abatacept treatment.[3] The findings from this post-hoc analysis suggest that SC abatacept can be given effectively without an IV abatacept loading dose.

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Global Molecular Effects of Tocilizumab Therapy in Synovial Biopsies of Early Rheumatoid Arthritis Patients. Julie Ducreux, Adrien Nzeusseu Toukap, Frédéric A. Houssiau, Patrick Durez and Bernard Lauwerys. Université catholique de Louvain, Brussels, Belgium

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that is characterized by the presence of inflammatory cytokines, including interleukin-6 (IL-6). Here, we investigated the global molecular effects of Tocilizumab, an approved humanized anti-IL6 Receptor antibody, versus Methotrexate therapy, in synovial biopsy samples collected prospectively in early RA before and 12 weeks after administration of the drug. The results were compared with our previous data, generated in prospective cohorts of Adalimumab- and Rituximab-treated (Methotrexate- and anti-TNF-resistant, respectively) RA patients.

Methods: Paired synovial biopsy samples were obtained from the affected knee of early RA patients before and 12 weeks after initiation of Tocilizumab (n=12) or Methotrexate (n=8) therapy. SDAI remission criteria were computed prospectively before, 3 months and 6 months after administration of the drugs and patients' responses were defined according to their SDAI remission status at 6 months. Gene expression studies were performed using GeneChip Human Genome U133 Plus 2.0 arrays. Quantitative real-time reverse transcriptase-polymerase chain reaction (qPCR) experiments were performed to confirm the differential expression of selected transcripts.

Results: We found that Tocilizumab induces a significant down-regulation of genes included in specific pathways: cytokines & chemokines (e.g. IL-6, IL-7, IL-22, CCL8, CCL11, CCL13, CCL19, CCL20), and T cell activation. By contrast, Tocilizumab induces a significant up-regulation of genes associated with healing processes. These effects are significantly more pronounced as compared to Methotrexate, Rituximab, or Adalimumab therapies. By opposition to the effects of Adalimumab, Tocilizumab therapy does not induce a decreased expression of genes involved in cell proliferation. Real-time qPCR experiments confirmed the differential expression of several transcripts belonging to these pathways.

Gene expression studies further identified genes differentially expressed at baseline according to SDAI remission status at 6 months. In Methotrexate-treated patients, genes involved in myeloid cell function predict remission, whereas the presence of a mesenchymal cell development signature predicts absence of remission. By opposition, in Tocilizumab-treated patients, genes involved in myeloid cell differentiation predict absence of remission, whereas genes involved in ras-dependent cell proliferation predict remission at 6 months.

Conclusion: Tocilizumab displays distinct molecular effects on synovial biopsies of RA patients. These results open perspectives for the individualization of therapeutic decisions, based on the identification of specific molecular profiles in individual patients.

Induction of Remission in Patients with up to 12 Months of Moderate-to-Severe Rheumatoid Arthritis Symptoms Treated with Etanercept Plus Methotrexate Over 52 Weeks.

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Background/Purpose: In the COMET study, etanercept (ETN) plus methotrexate (MTX) therapy in patients with early rheumatoid arthritis (RA) yielded high clinical remission rates,[1] but whether remission can be maintained after dose reduction or withdrawal (biologic-free) is unknown. The PRIZE trial is an ongoing, prospective,121-wk, 3-period study to evaluate the efficacy of ETN/MTX as first-line therapy in patients with early, active moderate-to-severe RA and to assess whether efficacy can be maintained with reduced-dose or biologic-free therapy (Period 2) or drug free (Period 3). The main objective of Period 1, reported here, was to achieve DAS28 remission at wks 39 and 52 in patients treated with ETN 50 mg QW plus MTX (ETN50/MTX); responders (DAS28 ≤3.2 at wk 39 + DAS28 <2.6 at wk 52) qualified for Period 2 enrollment.

Methods: MTX- and biologic-naïve RA patients (symptom onset ≤12 mo from enrollment; DAS28 >3.2) received ETN50/MTX for 52 wks. At the discretion of the investigator, the initial 10 mg/wk MTX dose was titrated up to a maximum of 25 mg/wk to achieve remission. Patients not achieving low disease activity (LDA; DAS28 ≤3.2) received corticosteroid boosts at wks 13 and/or 26; those not achieving LDA at wk 39 (non-responders) were withdrawn from the study. In addition to DAS28 and SDAI remission and LDA, other standard clinical outcomes were assessed. Efficacy and safety analyses were conducted in all patients who received ≥1 ETN/MTX dose (mITT).

Results: A total of 306 patients (female, 70%; Caucasian, 94%; mean age, 50 y; disease duration from symptom onset, 6.5 mo) were enrolled; 222 (72.6%) completed Period 1 (reasons for not completing Period 1 are listed in the table). No patient was excluded from the mITT population. Efficacy results are summarized in the table. Significant changes from baseline were observed in all clinical assessments and endpoints (P<0.0001). LDA was achieved in >75% of patients and DAS28 and SDAI remission in >60% of patients. Twenty-nine percent of patients achieved DAS28 <2.6 + HAQ ≤0.5 + no radiographic progression. The most common treatment-emergent AEs were nausea and nasopharyngitis (13%, each). No unexpected safety or tolerability findings were reported.

Table. Summary of ETN50/MTX efficacy in Period 1 of the PRIZE trial (N = 306)[a]

Efficacy Assessment[b]	Baseline Mean (SD)	Final on Therapy Visit Mean (SD)	Δ from Baseline Mean (SD)
DAS28	6.0 (1.1)	2.6* (1.5)	−3.5 (1.5)
SDAI	38.3 (14.0)	7.2* (11.9)	−31.1 (14.8)
Patient global assessment	58.9 (23.6)	16.3* (21.9)	−42.8 (28.4)
Tender/swollen joint count (28 joints)	14.1 (7.1)/11.1 (5.9)	2.5* (5.4)/1.4* (3.7)	−11.6 (7.6)/−9.7 (5.7)
HAQ DI	1.3 (0.7)	0.5* (0.6)	−0.8 (0.7)

Efficacy Endpoint[c]	% Patients (95% CI), Final on Therapy Visit
DAS28 LDA (≤3.2)/remission (<2.6)	78.0* (73.0, 82.6)/70.5* (65.0, 75.6)
SDAI LDA (≤11)/remission (≤3.3)	81.3* (76.4, 85.5)/60.9* (55.1, 66.4)
ACR Boolean remission	51.5* (45.7, 57.2)
ACR 20/50/70/90 responses	85.7* (81.2, 89.5)/ 76.1* (70.9, 80.8)/ 65.8* (60.1, 71.1)/ 34.9* (29.5, 40.6)
Complete response†	29.1* (24.1, 34.5)

[a]A total of 84 (27.4%) patients did not complete Period 1; due to non-response (30 patients); adverse events (20 patients); patient request (13 patients); protocol violation (10 patients); unsatisfactory response per investigator assessment (7 patients); sponsor's decision and lost to follow-up (2 patients each).
[b]Paired *t*-test.
[c]binomial test-value tests the null hypothesis that % = significantly different from 0; mITT population.
*P < 0.0001 vs baseline.
†Patients who discontinued treatment prior to week 52 were not included in this analysis.
DAS28 = Disease Activity Score based on a 28-joint count; SDAI = Simplified Disease Activity Index; HAQ DI = Health Assessment Questionnaire disability index; ACR = American College of Rheumatology; Complete response = patients achieving DAS28 <2.6, HAQ ≤0.5 at 39 and 52 wks, and no radiographic progression (mTSS ≤0.5) over 52 wks.

Conclusion: In Period 1 of the PRIZE trial, the majority of patients with early, moderate-to-severe RA who received ETN50/MTX for 52 wks achieved remission. ETN/MTX was well tolerated, with no unexpected safety issues. Forthcoming results from Periods 2 and 3 will address whether this initial response to combination therapy will be maintained with ETN dose reduction, biologic-free, or drug-free.

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Clinical, Radiographic, and Immunogenic Effects After 1 Year of Tocilizumab-Based Treatment Strategy with and without Methotrexate in Rheumatoid Arthritis: The ACT-RAY Study.

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Background/Purpose: 24-week data from ACT-RAY comparing an add-on strategy (tocilizumab [TCZ] + methotrexate [MTX]) with a switch strategy (TCZ + placebo [PBO]) in MTX-IR patients have been previously reported, demonstrating relevant clinical and radiographic benefit without a statistically significant difference between the 2 groups for most endpoints. Longer-term data are needed to assess the switch and add-on strategies over time and the effect of the protocol-specified treat-to-target strategy in patients who started on TCZ monotherapy or combination with MTX after Week 24. Therefore, the objective here is to assess the 52 week efficacy and safety of a TCZ-based treat-to-target strategy in patients who started treatment with and without MTX in adult patients with moderate to severe RA and an inadequate response to MTX.

Methods: ACT-RAY is a phase 3b clinical trial. Patients on stable doses of MTX were randomized to either add TCZ 8 mg/kg IV every 4 weeks to their existing MTX (add-on group) or switch to TCZ 8 mg/kg IV every 4 weeks with oral PBO (switch group). The protocol instituted the addition of open-label conventional DMARDs other than MTX at Week 24 or later in patients with DAS28 > 3.2, maintaining the blinding of MTX/PBO.

Results: 556 patients were randomized, with 85% completing 52 weeks of treatment. Baseline data were similar between the 2 groups (disease duration 8.2 yrs, DAS28-ESR 6.3, HAQ-DI 1.47 [all mean values]) except for Genant-modified Sharp Score (GSS), which was higher in the switch group. Efficacy results are shown in the table. Between Weeks 24 and 52, the proportion of patients receiving DMARD intensification was comparable in the add-on and switch arms (29% vs 33%). Clinical improvements at Week 24 in both groups were maintained or further improved up to Week 52 with a trend in favor of the add-on strategy for some endpoints. While the vast majority of patients did not experience a change from baseline, significantly more switch patients experienced radiographic progression (14.5% versus 7.6% in the add-on group). In a preliminary analysis in patients with samples available, 3.7% of patients developed antidrug antibodies (ADAs) up to week 52: 10/272 in the add-on group and 11/271 in the switch group. Neutralizing ADAs were developed by 3.3% of patients (9/272) in the add-on group and 4.1% (11/271) in the switch group. Rates of SAEs and serious infections per 100 PY were 14.2 and 4.9 in the add-on group and 17.7 and 6.3 in the switch group, respectively. In patients with normal baseline values, ALT elevations >3x the upper limit of normal were observed in 11% of add-on and 3% of switch patients.

Table. Week 24 and 52 Efficacy Results (ITT Population)

Clinical Parameter	Week 24 Add-on n = 277	Week 24 Switch n = 276	P value	Week 52 Add-on n = 277	Week 52 Switch n = 276	P value
DAS28, mean change from baseline	−3.43	−3.21	0.06[a]	−3.74	−3.66	0.67[a]
DAS28 remission (DAS28 <2.6), %	40.4	34.8	0.21	45.5	36.6	0.03
Low disease activity (DAS28 ≤3.2),%	61.7	51.4	0.031	62.5	57.2	0.12
ACR20/50/70/90,%	71.5/45.5/24.5/5.8	70.3/40.2/25.4/5.1	0.87/0.30/0.68/0.84	70.8/50.2/31.4/12.6	69.2/55.4/31.2/11.2	0.62/0.22/0.99/0.65
SJC (66)/TJC (68), mean change from baseline	−11.3/−17.3	−11.8/−17.0	0.8/0.9	−12.3/−19.4	−12.2/−18.9	0.9/0.7
GSS, mean change from baseline	0.27	0.40	0.33[b]	0.40	0.63	0.44[b]
Patients w/o radiographic progression,[c] %	90.6	87.3	0.18	92.4	85.5	0.007

[a] P values adjusted for baseline DAS28 and region.
[b] Estimates and Pvalues adjusted for baseline DAS28 and baseline GSS.
[c] No progression defined as GSS of ≤ 1.5 (SDC) (patients with missing observations classified as progressors). Not adjusted by GSS at baseline.

Conclusion: This one year analysis suggests that TCZ monotherapy might be an acceptable therapeutic strategy in patients with a contraindication for or intolerance to MTX.

ACR Concurrent Abstract Session
Sjögren's Syndrome II - Clinical
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Validation of EULAR Primary Sjögren's Syndrome Disease Activity and Patient Indexes. Raphaèle Seror[1], Elke Theander[2], Johan G. Brun[3], Manel Ramos-Casals[4], Valeria Valim[5], T. Dorner[6], Xavier Mariette[7], Hendrika Bootsma[8], Athanasios G. Tzioufas[9], Roser Solans-Laqué[10], Jacques-Eric Gottenberg[11], Eric Hachulla[12], Wan-Fai NG[13], Stefano Bombardieri[14], Roberto Gerli[15], Takayuki Sumida[16], Alain Saraux[17], Matija Tomsic[18], Roberto Caporali[19], Roberta Priori[20], Kathy Moser Sivils[21], A.A. Kruize[22], Cristina F. Vollenweider[23], Claudio Vitali[24] and Simon J. Bowman[25]. [1]Bicetre university hospital, LE Kremlin-Bicetre, France, [2]Skane University Hospital, Lund University, Malmö, Sweden, [3]Haukeland University Hospital, Bergen, Norway, [4]Hospital Clínic, Barcelona, Spain, [5]Universidade Federal do Espírito Santo, Vitória, Brazil, [6]Charité University Medicine Berlin, Berlin, Germany, [7]Université Paris-Sud, Le Kremlin Bicetre, France, [8]University Medical Center Groningen, Groningen, Netherlands, [9]School of Medicine, National University of Athens, Athens, Greece, [10]Senior Consultant, Barcelona, Spain, [11]Strasbourg University Hospital, Strasbourg, France, [12]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [13]Departement of rheumatology, New-Castle University Hospital, UK, Newcastle, England, [14]Rheumatology Unit, University of Pisa, Pisa, Italy, [15]Rheumatology Unit, University of Perugia, Perugia, Italy, [16]University of Tsukuba, Tsukuba City, Japan, [17]Université Brest Occidentale, Brest, France, [18]University Medical Centre Ljubljana, Ljubljana, Slovenia, [19]Division of Rheumatology, IRCCSPoliclinico S. Matteo Foundation, Pavia, Italy, [20]Rheumatology Unit, Sapienza University of Rome, Rome, Italy, [21]Oklahoma Medical Research Foundation, Oklahoma City, OK, [22]University Medical Center Utrecht, Utrecht, Netherlands, [23]German Hospital, Buenos Aires, Argentina, [24]Casa di Cura di Lecco, Lecco, Italy, [25]Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom

Background/Purpose: To validate the EULAR scores for assessment of primary Sjögren's Syndrome (SS): the EULAR SS Disease Activity Index (ESSDAI), the EULAR SS Patient Reported Index (ESSPRI).

Methods: Prospective international validation study with 2 visits: baseline and 6 months. At each physicians completed ESSDAI, SS disease activity index (SSDAI), Sjögren's Systemic Clinical Activity Index (SCAI) and physician global assessment (PhGA); and patients completed ESSPRI, Sicca

Symptoms Inventory (SSI), Profile of Fatigue and Discomfort (PROFAD) and patient global assessment (PGA). Construct validity (using correlations with gold standard), responsiveness (using standardized response mean [SRM]) and reliability (intraclass correlation coefficient [ICC]) were evaluated and compared between each scores.

Results: 395 patients (96% women, mean age 55.4 ± 13.7 years, 79% with anti-SSA and/or anti-SSB antibodies) from 15 countries have been included. At enrollment, 145 (37%) and 251 (64%) had, respectively, current or either current or past systemic manifestations. EULAR scores had higher correlation with gold standard than other scores (ESSDAI with PhGA: rho=0.59; ESSRPI with PGA: rho=0.70). Correlations between patient and systemic scores were very low (rho ranging from 0.07 to 0.29). All systemic scores had similar large responsiveness in improved patients. Responsiveness of patients scores was low in patient experiencing improvement of their symptoms but was significantly higher for ESSPRI compared to SSI and PROFAD (p=0.006 and 0.049 for SRM comparisons) Reliability was assessed in a subgroup of 47 and 62 patients, for systemic and patients scores, respectively. Reliability was very good for all scores.

	Construct validity Correlation with PhGA or PGA	Reliability ICC [95% IC]	Responsiveness SRM for improved patients	Responsiveness SRM for stable patients	Responsiveness SRM for worsened patients
Physician outcome measures		N = 62	N = 62	N = 198	N = 50
ESSDAI	0.59	0.96	−0.72	−0.17	+0.26
SSDAI	0.34	0.83	−0.82	−0.26	+0.43
SCAI	0.32	0.95	−0.69	−0.22	+0.37
Patient-centered measures		N = 62	N = 95	N = 151	N = 72
ESSPRI	0.70	0.94	−0.37	+0.08	+0.37
SSI	0.55	0.86	−0.04	+0.07	+0.34
PROFAD	0.58	0.92	−0.16	+0.15	+0.32

Conclusion: ESSDAI and ESSPRI had good construct validity, better than other scores. All scores were reliable. Systemic scores were sensitive to change in patient whose disease activity improves. Patient scores had a small sensitivity to change. However, ESSPRI was significantly better than SSI and PROFAD. The poor correlation between systemic and patients scores confirms that these 2 components are different and should be evaluated separately.

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Clinically Significant and Biopsy-Documented Renal Involvement in Primary Sjögren's Syndrome: Clinical Presentation and Outcome. Andreas V. Goules[1], Ioanna P. Tatouli[1], Alexandros A. Drosos[2], Fotini N. Skopouli[3], Haralampos M. Moutsopoulos[4] and Athanasios G. Tzioufas[5]. [1]National University of Athens, Athens, Greece, [2]Professor of Medicine/Rheumatology, Ioannina, Greece, [3]Harokopion University, Athens, Greece, [4]School of Medicine, University of Athens, Athens, Greece, [5]School of Medicine, National University of Athens, Athens, Greece

Background/Purpose: Primary Sjögren's syndrome (pSS) may affect kidneys, causing either interstitial nephritis (IN) or glomerulonephritis (GMN). However, overt renal disease in pSS is rare and does not exceed 5% of patients. The aim of this study was to estimate the prevalence and investigate the clinical features and the outcome of clinically significant and biopsy documented renal involvement in a large cohort of pSS patients.

Methods: From a cohort of 715 patients who met the American-European criteria for pSS, those with clinically significant and biopsy documented renal involvement were identified and their clinical features were recorded. The primary outcomes included death, hemodialysis, lymphoma and chronic renal failure (CRF). Statistical analysis was performed to estimate the primary outcomes per 100 person-years.

Results: Thirty five (4.9 %) pSS patients had biopsy documented renal involvement, representing a total follow up time after renal diagnosis of 271.8 person-years. Twelve patients (34.3%) had IN, 18 (51.4%) had GMN and 5 (14.2%) developed both entities. Nine patients (25.7%) presented chronic renal failure (including 4 requiring chronic hemodialysis) and 9 (25.7%) developed malignant lymphoma. Seven out of 11 (63.6%) patients with CRF had IN while the remaining 4 patients (36.4%) had GMN. The corresponding rates for lymphoma, chronic renal failure and hemodialysis were estimated at 3.30

(95%CI, 1.72–6.35), 4.04 (95%CI, 2.24–7.29), and 1.47 (95%CI, 0.55–3.91) per 100 person-years, respectively.

Overall 5-year survival was 0.82 (0.62–0.92) with median not reached. Interestingly, eight out of nine (89%) reported deaths and eight out of nine malignant lymhomas (89%) were among the GMN group. After adjusting for age, type of renal involvement (IN vs GMN), lymphoma, CRF and hemodialysis, lymphoma remained the sole significant adverse predictor for survival (adjusted Hazard Ratio, 5.96, 95% CI 1.14–21.5) for survival. Causes of death included lymphoma (33.3%), cardiac arrest (22.2%) related to hemodialysis or CRF, infection (11.1%) related to CRF, stroke (11.1%) and cerebral haemorrhage (11.1%).

Conclusion: The long term prognosis of clinically significant and biopsy documented renal involvement in pSS varies. Patients with IN display a favorable prognosis while patients with GMN are in high risk to develop lymphoma and have poor survival.

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Histological, Serological and Clinical Changes in Response to Abatacept Treatment of Sjögren's Syndrome. Sabine Adler[1], Meike Koerner[1], Frauke Foerger[2], Marco-Domenico Caversaccio[3] and Peter M. Villiger[4]. [1]University Hospital Bern, Bern, Switzerland, [2]Inselspital-University Hospital, Bern, Switzerland, [3]University Hospital Bern, Inselspital, Bern, Switzerland, [4]Inselspital-University Hospital of Bern, Bern, Switzerland

Background/Purpose: To prospectively evaluate histopathologic, blood and clinical responses to abatacept treatment in patients with primary Sjögren's syndrome (pSS).

Methods: Blood, saliva and minor salivary gland biopsies were obtained prior to and after the last of 8 doses of abatacept in 11 pSS patients. Histology evaluated the number of lymphocytic foci and of B- and T-cell subtypes ($CD20^+$, $CD3^+$, $CD4^+$, $CD8^+$). The numbers of $FoxP3^+$ regulatory T-cells and the FoxP3/CD 3 ratio was calculated. The histologic data were compared with results from peripheral blood and with changes in saliva secretion.

Results: The numbers of lymphocytic foci decreased (p=0.09) with a corresponding reduction of $CD20^+$, $CD3^+$, $CD4^+$ and $CD8^+$ T-cells. Numbers of local $FoxP3^+$ T-cells decreased in 9 of 10 samples (p=0.022). In peripheral blood $CD3^+$ cells did not change in numbers while $CD20^+$ B cells increased (p=0.038). This increase was due to an expansion of the naïve B cell pool (p=0.012). The slight decrease in gamma globulins and IgG did not reach significance (P=0.09 and 0.169, respectively). Overall, saliva secretion did not change, however 7 of 11 patients showed an increase in saliva secretion (p=0.018 for the 7 responders).

Conclusion: Inhibition of T cell co-stimulation using CTLA4-Ig leads to a reduced inflammation in glandular tissue with a 50% decrease in $FoxP3^+$ cells, to an expansion of peripheral naïve B cells and to an increase in saliva secretion in 70% of pSS patients. In conclusion, abatacept bears the potential of a disease-modifying biologic agent in pSS.

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Tolerance and Efficacy of Rituximab in Primary Sjogren Syndrome: Final Results of a Randomized Controlled Trial. Valerie Devauchelle-Pensec[1], Xavier Mariette[2], Sandrine Jousse-Joulin[3], Jean-Marie Berthelot[4], Aleth Perdriger[5], Eric Hachulla[6], Xavier Puechal[7], Véronique Le Guern[8], Jean Sibilia[9], Jacques-Eric Gottenberg[10], Laurent Chiche Sr.[11], Vincent Goeb[12], Gilles Hayem[13], Jacques Morel[14], Charles Zarnitsky[15], JJ Dubost[16], Jacques-Olivier Pers[17], Emmanuel Nowak[18] and Alain Saraux[19]. [1]Brest Occidentale university, Brest, France, [2]Université Paris-Sud, Le Kremlin Bicetre, France, [3]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche, Brest, France, [4]Nantes University Hospital, Nantes, France, [5]Hôpital Sud, Rennes, France, [6]Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille CEDEX, France, [7]Hôpital Cochin, Paris, France, [8]Cochin Hospital, Paris, France, [9]EA4438 Laboratoire Physiopathologie des Arthrites, Illkirch-Strasbourg, France, [10]Strasbourg University Hospital, Strasbourg, France, [11]Internal Medicine, CHU Marseille, Marseille, France, [12]Rouen University Hospital, Rouen, France, [13]Bichat Hospital, Paris, France, [14]Hopital Lapeyronie, Montpellier, France, [15]CH du Havre, Le Havre, France, [16]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [17]Brest Occidentale University, Brest, France, [18]CHU Brest, Brest, France, [19]Université Brest Occidentale, Brest, France

Background/Purpose: There is evidence for a critical role of B cells in the pathogenesis of pSS. Both open labelled and small controlled studies suggested the efficacy of Rituximab (RTX) in specific subgroups of pSS (early or systemic).We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of RTX in a large group of patients with active recent and/or systemic pSS.

Methods: 122 Patients were assigned to receive either RTX infusions (1g) or placebo (P) at weeks 0 and 2. They were followed up for 24 weeks. All patients fulfilled the new American-European Consensus Group criteria for pSS, had an active disease as assessed by mean values of the 2 highest visual analog scales (VAS) '50 evaluating dryness, pain, fatigue and global, and had either a recent (less than 10 years since first clinical sign) and a biologically active pSS [Auto antibodies (SSA or RF) or cryoglobulinaemia, or hypergammaglobulinaemia, or high level of beta 2-microglobulinemia or hypo-complementaemia] or at least one extra-glandular manifestation. The primary end point was an improvement of at least a 30 mm on 2 of 4 VAS between weeks 0 and 24. Secondary end points included delta of improvement of all VAS separately, the ESSDAI score, the number of swollen joints, the basal salivary flow rate, results of the Schirmer test, the schirmer score, biological and extra glandular improvement, evaluated from week 0 to week 24.

Results: 24 of 122 patients (19.5%) had a recent pSS, 31 (25.4%) had systemic pSS and 67 (54.9%) had both. 33 (28%) had pulmonary manifestations, 63 (53%) an articular involvement and 33 (28%) a parotidomegaly. 113 patients were evaluated at week 24. For primary end point, 11/53 (20.7%) patients receiving placebo and 13/60 (21.7%) treated with RTX had a favourable overall response (P = 0.9). Similarly, the 30 points improvement for each VAS separately did not reach significance, although the delta of improvement of sicca and fatigue VAS were statistically improved in RTX group (P<0.05). Delta improvement between W24 and W0 was significant for the salivary flow rate (p:0.009) but not for other objectives variables (Schirmer, focus score, Chisholm score). Concerning systemic manifestations, the ESSDAI score (total and each domain) was not significantly improved in the RTX group. For synovitis, only 2/24 patients of the P group and 4/25 of the RTX group were improved. The difference between RTX and P group at W24 did not differ in terms of primary end point or ESSDAI in the recent and systemic subgroups evaluated separately. Tolerance was similar in both groups excepted for reaction to infusion, more frequent in the RTX group.

Conclusion: In this randomized, double blind, placebo controlled study, the efficacy of RTX, was not sufficient enough to allow its prescription in both recent and systemic pSS. Studies in specific unfrequent manifestations (thrombopenia, neurological disorders) or using more specific measurement tools (parotid ultrasound) are warranted.

Disclosure: V. Devauchelle-Pensec, Roche Pharmaceuticals, 5; **X. Mariette**, Roche Pharmaceuticals, 5; **S. Jousse-Joulin**, None; **J. M. Berthelot**, None; **A. Perdriger**, None; **E. Hachulla**, Roche Pharmaceuticals, 5; **X. Puechal**, None; **V. Le Guern**, None; **J. Sibilia**,; **J. E. Gottenberg**, None; **L. Chiche Sr.**, None; **V. Goeb**, None; **G. Hayem**, None; **J. Morel**, Roche Pharmaceuticals, 5; **C. Zarnitsky**, None; **J. Dubost**, None; **J. O. Pers**, None; **E. Nowak**, None; **A. Saraux**, Roche Pharmaceuticals, 5.

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Results of the Beliss Study, the First Open Phase 2 Study of Belimumab in Primary Sjogren's Syndrome. Xavier Mariette[1], Luca Quartuccio[2], Raphaèle Seror[3], Sara Salvin[2], Frederic Desmoulins[1], Martina Fabris[4], Sara Villeneuve[5], Philippe Ravaud[6] and Salvatore De Vita[7]. [1]Université Paris-Sud, Le Kremlin Bicetre, France, [2]Rheumatology Clinic, DSMB, University of Udine, Italy, Udine, Italy, [3]Bicetre university hospital, LE Kremlin-Bicetre, France, [4]Institute of Clinical Pathology, Udine, Italy, [5]Hospital Hotel dieu, Paris, France, [6]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [7]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy

Background/Purpose: The BAFF (or BLyS) cytokine plays a key role in pathogenesis of primary Sjogren's syndrome (pSS). Belimumab, the first biological treatment inhibiting soluble BAFF, has proved its effectiveness and has been recently approved in systemic lupus. Lupus and pSS share a lot of pathogenic mechanism including interferon signature and BAFF involvement. Thus we run the first open label study of belimumab in pSS patients.

Methods: Patients were included in 2 simultaneous and identical studies in 2 European Centres. Patients had to fulfill AECG criteria, to be anti-SSA/SSB positive and had to have at the time of inclusion either systemic complications, early disease ($\leq$ 5 years), or the presence of at least one other biomarker of B-cell activation (increase in IgG, free light chains or of beta2-microglobulin, decrease of C4, presence of cryoglobulinemia or monoclonal component).The patients were treated with belimumab 10 mg/kg W0, W2, W4 and then every four weeks until W24.

The primary end-point was evaluated at W28 and consisted of improvement

of 2 of the 5 following items: 1- ≥ 30% reduction of patient's dryness VAS, 2- ≥ 30% reduction of patient's fatigue VAS, 3- ≥ 30% reduction of patient's musculoskeletal pain VAS, 4- ≥ 30% reduction of physician's systemic activity VAS, 5- ≥ 25% reduction of any of the following B cell activation biomarkers (free light chains of immunogobulins, beta2-microglobulin, monoclonal component, cryoglobulinemia, IgG) or ≥ 25% C4 increase.

Results: Thirty patients were included, 15 in each center (all female, mean age = 49.5 yrs ±16.5, mean disease duration = 5.7 yrs ± 5.6). 15 patients had systemic complications, 11 had early disease and 20 had at least one other biomarker of B-cell activation. 19/30 (63%) reached the primary end-point. For each individual component the response was as follows: VAS dryness: 10 (33%), VAS fatigue: 7 (23%), VAS pain: 7 (23%), VAS physician's systemic activity: 12 (40%), biological component: 18 (60%). The percentage of responders was 8/11 (73%) in early disease and 7/15 (47%) in systemic disease.

The ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index) score decreased from 8.8±7.39 to 5.59±5.49 (p<0.0001). The ESSPRI (EULAR Sjögren's Syndrome Patients Reported Index) score decreased from 6.44 ±1.11 to 5.56 (p=0.01). There was no significant change of salivary flow (0.62±1.23 to 0.75±1.23;p=0.43) and Schirmer test (4.09±7.23 to 4.72±8.08; p=0.17).

The treatment induced significant changes of some biological data: serum IgG from 20.92±10.25 to 18.53 ±7.21 (p<0.0001); serum IgA from 4.08 ±3.02 to 3.23 ±1.87 (p=0.001), kappa free light chain from 33.15±24.65 to 25.59 ±23.42 (p<0.0001), lambda free light chain from 28.31 ±16.59 to 20.85 ±12.24 (p<0.0001), rheumatoid factor from 146 ±174 to 97 ±91 (p<0.0001).

Concerning safety, we observed 1 severe adverse event which was a pneumococcus meningitis after 6 infusions of the drug. This patient, who was responder to belimumab, recovered completely without any sequellae.

Conclusion: Results of this first open phase 2 study of belimumab in pSS patients are very encouraging and justify the realization of randomized control trials with the drug in selected populations of patients with pSS.

Disclosure: **X. Mariette**, Human Genome Sciences, Inc., 2, GlaxoSmithKline, 5; **L. Quartuccio**, None; **R. Seror**, Human Genome Sciences, Inc., 2, GlaxoSmithKline, 5; **S. Salvin**, None; **F. Desmoulins**, None; **M. Fabris**, None; **S. Villeneuve**, None; **P. Ravaud**, None; **S. De Vita**, Human Genome Sciences, Inc., 2.

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Allogenic Mesenchymal Stem Cells Transplantation Alleviates Clinical Sjögren's Syndrome. Lingyun Sun[1], Dandan Wang[1], Junji Xu[2] and Songlin Wang[2]. [1]Department of Rheumatology and Immunology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Salivary Gland Disease Center and Molecular Laboratory for Gene Therapy & Tooth Regeneration, Beijing Key Laboratory of Tooth Regeneration and Function Reconstruction, Capital Medical University School of Stomatology, Beijing, China

Background/Purpose: Sjögren's syndrome (SS) is a systemic autoimmune disease that is characterized by dry mouth and dry eyes. Currently, treatment of SS is difficult and challenging. This study is undertaken to determine the safety and efficacy of allogenic mesenchymal stem cells (MSCs) transplantation in SS patients.

Methods: Twenty-four patients with primary SS (23 females and 1 male; age from 27 to 68 years old, mean 45 years old) refractory to standard treatments were enrolled. Fresh umbilical cords (UC) were obtained from informed healthy mothers after normal deliveries. UC MSCs were expanded and infused intravenously (one million cells per kilogram of bodyweight per infusion). The clinical manifestations and laboratory parameters were compared pre- and post- MSCs transplantation (MSCT), with all patients completed 12 months follow up. Side effects were monitored during and post-MSCT.

Results: All patients tolerated well with allogenic UCMSCT, and no adverse events occurred during or after MSCs infusion. Mean SS disease activity index (SSDAI) scores for all 24 patients decreased from 5.63 ± 1.44 (baseline) to 4.33 ± 1.79 at 1 month, 4.08 ± 1.44 at 3 months, 3.46±1.18 at 6 months, and 3.08 ± 1.21 at 12 months (all *P*<0.05). Global assessment by visual analog scale (VAS) also improved at 1 month, and showed further ameliorations at 3, 6, and 12 months after UCMSCT. Unstimulated salivary flow rate increased significantly 2 weeks after UCMSCT (1.00 ± 0.78 ml/10 min at 2 weeks *vs.* 0.63 ± 0.73 ml/10min at baseline, *P*<0.001, n=11) and showed a 2-fold increase at 1 month (1.26 ± 1.02, *P*<0.001 *vs.*baseline, n=11). This flow rate continued to increase on subsequent follow-up visits. Stimulated salivary flow rate also significantly increased after MSCT (*P*=0.008 at 2 weeks, *P* = 0.043 at 1 month, *P* = 0.016 at 3 months, *P*=0.017 at 6 months and *P* = 0.016 at 12 months *vs.*

baseline, n=11). The determination of modified treatment emergent symptom scale (TESS) score decreased at 2 weeks visit, and was maintained at this low level on subsequent visits. Furthermore, punctate sialectasias in the parotid gland declined, dilation of main duct was improved 1 year after UCMSCT, and excretory function was also partially restored. Serum levels of anti-SSA/Ro and anti-SSB/La decreased 1 month post-MSCT (*P*<0.001, n = 5). The mechanism studies showed that the frequency of Th17 cells decreased while Treg cells increased (*P*<0.05) after MSCT. Serum levels TGF-β increased and IL-17 decreased 1 month post-MSCT (*P*<0.05).

Conclusion: Allogenic UC MSCT is safe and results in amelioration of disease activity. These data provide a foundation for conducting allogenic UC MSCT for SS patients.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Psoriatic Arthritis
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Ustekinumab in Active Psoriatic Arthritis Including Patients Previously Treated with Anti-TNF Agents: Results of a Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study. Christopher T. Ritchlin[1], Alice B. Gottlieb[2], Iain B. McInnes[3], Lluis Puig[4], Proton Rahman[5], Shu Li[6], Yuhua Wang[6], Mittie K. Doyle[7], Alan Mendelsohn[8] and Arthur Kavanaugh[9]. [1]University of Rochester Medical Center, Rochester, NY, [2]Tufts Medical Center, Boston, MA, [3]University of Glasgow, Glasgow, United Kingdom, [4]Universitat Autònoma de Barcelona, [5]Memorial University, St. Johns, NF, [6]Janssen Research and Development, LLC, PA, [7]Janssen Research and Development, LLC/U of Penn, Spring House/Phila, PA, [8]Janssen Research & Development, LLC, Spring House, PA, [9]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Assess efficacy & safety of UST in reducing signs & symptoms of active PsA, including pts with & without previous anti-TNF experience, in PSUMMIT 2.

Methods: Adult PsA pts (n=312) with active disease (≥5 SJC & ≥5 TJC;CRP≥0.3mg/dL) despite DMARD &/or NSAID &/or exposure to anti-TNF's (≥8 wks of exposure to etanercept, golimumab, adalimumab or certolizumab pegol, or 14 wks exposure to infliximab, &/or documented evidence of anti-TNF intolerance/toxicity with exposure <8–14wks;n=180/312) were randomized to UST45mg, UST90mg, or PBO at wks 0, 4, & q12wks. At wk16, pts with <5% improvement in TJC & SJC entered blinded EE (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). Stable MTX was permitted but not mandated. Primary endpt was ACR20 at wk24. Secondary endpts at wk24 included: ACR 50/70 & DAS28-CRP responses, change from BL in HAQ-DI, PASI75 (in pts with ≥3% BSA psoriatic involvement at BL), & % change from BL in enthesitis & dactylitis scores. Stat testing adjusted for BL MTX status. AEs reported through PBO-controlled period (wk16) & wk24.

Results: BL disease characteristics were generally comparable across grps. Median BL disease characteristics among all pts were: PsA duration 5.08 yrs, CRP 9.32mg/L, SJC/TJC 11/22, pain VAS 6.8, pt global assessment VAS 6.2, PGA 7.1, HAQ-DI 1.3. BL disease characteristics among anti-TNF experienced pts: PsA duration 6.7 yrs, CRP 10.6 mg/L, SJC/TJC 12/24, pain VAS 7.2, pt global assessment VAS 6.4, PGA 7.4, HAQ-DI 1.4. Sig greater prop of UST vs PBO pts had ACR20 response at wk24. Sig improvements were also observed in DAS28-CRP response at wk12 & wk24 for both UST grps vs PBO. Clinically meaningful change from BL in HAQ-DI (≥0.3) was observed in 34.0%, 38.1%, & 16.3% of UST45mg, 90mg, & PBO pts, resp (p=0.003, p<0.001). Nearly half used MTX; ACR responses were greater with UST vs PBO regardless of MTX. Among pts with enthesitis (n=221), median % improvements in the enthesitis score (MASES) were 33.3%, 48.3%, & 0.0% for the UST45mg (p=0.098), 90mg (p=0.008), & PBO grps, resp. Among pts with dactylitis at BL (n=117), median % improvements in dactylitis scores were 0.0%, 65.0%, & 0.0% of pts in the UST 45mg, 90mg, & PBO grps (not stat sig).Through wk16, pts with ≥1 AE were 63.1%, 60.6% & 54.8% for the UST 45mg, UST 90mg, & PBO grps, resp, with infections being most common AE (28.2%, 26.0%, & 23.1%). Serious AEs were reported in 0.0%, 1.0%, & 4.8%, resp. Through wk24, no deaths, opportunistic infections, TB, or major adverse CV events were reported. 1 serious infection (interstitial lung disease, PBO) & 1 malignancy [squamous cell Ca in situ of skin (uncovered from cleared PsO plaque), UST90mg] were reported.

Patients Achieving Endpoint at Week 24 (n/N [%] or Median [Min, Max]): Overall randomized population and Sub-groups (anti-TNF-naïve [no prior anti-TNF use] and previous anti-TNF use)

	PBO	UST 45mg	UST 90mg
Week 24 Response			
ACR 20			
Overall (N=312)	21/104 (20.2%)	45/103 (43.7%)	46/105 (43.8%)
		p<0.001	p<0.001
Previous anti TNF (N=180)	9/62 (14.5%)	22/60 (36.7%)	20/58 (34.5%)
		p=0.006	p=0.011
Anti-TNF-naïve (N=132)	12/42 (28.6%)	23/43 (53.5%)	26/47 (55.3%)
		p=0.021	p=0.011
ACR 50			
Overall	7/104 (6.7%)	18/103 (17.5%)	24/105 (22.9%)
		p=0.018	p=0.001
Previous anti TNF	4/62 (6.5%)	9/60 (15.0%)	9/58 (15.5%)
		p=0.138	p=0.111
Anti-TNF-naïve	3/42 (7.1%)	9/43 (20.9%)	15/47 (31.9%)
		p=0.084	p=0.004
ACR 70			
Overall	3/104 (2.9%)	7/103 (6.8%)	9/105 (8.6%)
p-value		p=0.190	p=0.078
Previous anti TNF	1/62 (1.6%)	3/60 (5.0%)	3/58 (5.2%)
		p=0.322	p=0.286
Anti-TNF-naïve	2/42 (4.8%)	4/43 (9.3%)	6/47 (12.8%)
		p=0.473	p=0.215
PASI 75*			
Overall	4/80 (5.0%)	41/80 (51.3%)	45/81 (55.6%)
		p<0.001	p<0.001
Previous anti TNF	1/50 (2.0%)	20/44 (45.5%)	20/41 (48.8%)
		p<0.001	p<0.001
Anti-TNF-naïve	3/30 (10.0%)	21/36 (58.3%)	25/40 (62.5%)
		p<0.001	p<0.001
Median HAQ-DI change from baseline			
Overall	0.00 (−0.13, 1.0)	−0.13 (−1.8, 1.0)	−0.25 (−1.9, 1.5)
		p=0.001	p<0.001
Previous	0.00 (−1.0, 0.9)	−0.13 (−1.8, 1.0)	−0.19 (−1.9, 1.5)
		p=0.018	p=0.012
Anti-TNF-naïve	0.00 (−1.3, 1.0)	−0.25 (−1.5, 0.8)	−0.25 (−1.4, 0.6)
		p=0.034	p=0.018

*Among patients with ≥3% BSA psoriasis involvement at baseline

Conclusion: UST reduced signs & symptoms, improved physical fxn, enthesitis & improved plaque PsO. Safety profiles were similar between UST & PBO.

Disclosure: C. T. Ritchlin, Janssen Research and Development, LLC,; **A. B. Gottlieb**, Janssen Research and Development, LLC, 9; **I. B. McInnes**, Janssen Research and Development, LLC,; **L. Puig**, Janssen Research and Development, LLC,; **P. Rahman**, Janssen Research and Development, LLC,; **S. Li**, Janssen Research and Development, LLC, 3; **Y. Wang**, Janssen Research and Development, LLC, 3; **M. K. Doyle**, Janssen Research and Development, LLC, 3; **A. Mendelsohn**, Janssen Research & Development, LLC, 3; **A. Kavanaugh**, Janssen Research and Development, LLC.

2558

Clinical Response, Drug Survival and Predictors Thereof Among 548 Switchers of Tumor Necrosis Factor Alpha Inhibitor Therapy in Psoriatic Arthritis. Results From the Danish Nationwide Danbio Registry. Bente Glintborg[1], Mikkel Østergaard[2], Niels Steen Krogh[3], Martin Dehn Andersen[4], Ulrik Tarp[4], Anne Gitte Loft[4], Hanne M. Lindegaard[4], Mette Holland-Fischer[4], Henrik Nordin[4], Dorte Vendelbo Jensen[4] and Merete L. Hetland[5]. [1]Copenhagen University Hospital Gentofte, Copenhagen, Denmark, [2]Glostrup Hospital, Copenhagen, Denmark, [3]ZiteLab ApS, Copenhagen, Denmark, [4]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Copenhagen, Denmark, [5]Copenhagen University and Glostrup Hospital, Copenhagen, Denmark

Background/Purpose: Treatment with tumor-necrosis-factor-alpha inhibitors (TNFi) has improved the outcome in patients with psoriatic arthritis (PsA) who have failed treatment with synthetic disease modifying antirheumatic drugs (DMARDs). Failure may be due to insufficient effect or adverse events. However, knowledge on the effect of switching is scarce. We aimed to investigate frequencies and reasons for switching, treatment responses, drug survivals and predictors in patients with PsA who switched TNFi treatment in routine clinical care.

Methods: PsA patients were identified in the Danish nationwide DANBIO registry. Disease activity, treatment responses (ACR20/50/70 and EULAR good response at 3 and 6 months), drug survival and predictors thereof were studied in patients receiving ≥2 different biological drugs.

Results: Of 1,422 PsA patients starting TNFi treatment, 548 patients (39%) switched to a second and 189 (13%) to a third biological drug during up to 10

years of follow-up. Compared to non-switchers, switchers were more frequently women (56%/45%), had shorter disease duration (3 years/4 years), higher Health Assessment Questionnaire (HAQ) (1.1 (0.6–1.6)/0.9 (0.5–1.4) (median (interquartile-range))), higher 28-joint Disease Activity Score (DAS28) (4.8 (4.0–5.7)/4.4 (3.6–5.2)) and higher visual-analogue-scale (VAS) pain (65 (46–77)/62 (40–75) mm) and fatigue scores (67 (50–83)/64 (42–80) mm) when they started the first TNFi (all p<0.05). Main reason for switching was lack of response (57%). During the first, second and third treatment course HAQ, DAS28, CRP and VAS scores had decreased after 6 months' treatment (all p<0.05). Median drug survivals were 2.2, 1.3 and 1.1 years respectively (Figure, p<0.001). Drug survivals were similar regardless of the reason for switching to the second TNFi. All response rates were lower during the second treatment course (all p<0.01 compared to the first treatment) and the proportion of patients achieving sustained ACR20, ACR50, ACR70 and EULAR good response between 3–6 months treatment was 22% (number needed to treat, NNT 4.5), 13%(7.9), 5%(20) and 19%(5.3), respectively. Male gender, fewer tender joints and lower VAS fatigue increased drug survival of the second TNFi.
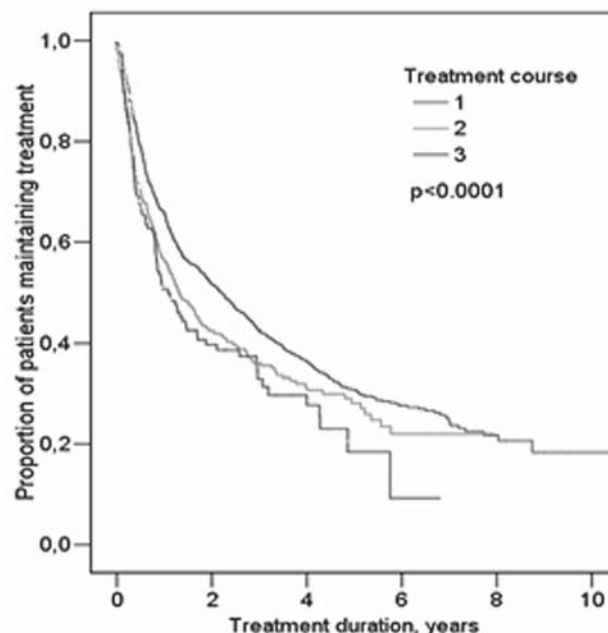
Figure. Drug adherences by treatment course number. Kaplan Meyer drug survival curves.

Conclusion: Nearly 40% of PsA patients in clinical practice switched biological treatment. Response rates and drug survivals decreased after switching and only one fifth of patients achieved ACR20 or EULAR good response within 6 months after switching to a second biological.

Disclosure: B. Glintborg, None; **M. Østergaard**, Abbott Immunology Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 8, Centocor, Inc., 5, Merck Pharmaceuticals, 5, Merck Pharmaceuticals, 8, Mundipharma, 8, Novo, 8, Pfizer Inc, 5, Pfizer Inc, 8, Roche Pharmaceuticals, 5, UCB, 5, UCB, 8; **N. S. Krogh**, None; **M. D. Andersen**, None; **U. Tarp**, None; **A. G. Loft**, MSD, UCB, Abbott, 8; **H. M. Lindegaard**, MSD, 8, Roche Pharmaceuticals, 8; **M. Holland-Fischer**, MSD, 8, UCB, 8; **H. Nordin**, None; **D. V. Jensen**, None; **M. L. Hetland**, Roche Pharmaceuticals, 5, Pfizer Inc, 8, MSD, 8, BMS, 8, Abbott Laboratories, 8, UCB, 8.

2559

Mortality in Patients with Psoriatic Arthritis Compared to Patients with Rheumatoid Arthritis, Psoriasis Alone, and the General Population. Alexis Ogdie[1], Kevin Haynes[2], Andrea Troxel[2], Thorvardur Love[3], Hyon K. Choi[4] and Joel Gelfand[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania., Philadelphia, PA, [3]Labspitali University Hospital, Reykjavik, Iceland, [4]Boston University School of Medicine, University of British Columbia, Arthritis Research Centre of Canada, Boston, MA

Background/Purpose: Conflicting reports of the mortality risk among patients with psoriatic arthritis (PsA) exist in the literature, however excess mortality has been presumed given the elevated mortality rates in rheumatoid arthritis and psoriasis. Previous studies have been small, lacked internal compar-

ison groups, and were mostly performed in rheumatology clinics rather than the general population. The objective of this study was to examine the risk of mortality in patients with PsA as compared to matched controls as well as patients with psoriasis and rheumatoid arthritis (RA).

Methods: A longitudinal cohort study was performed. Patients aged 18–89 were selected from The Health Improvement Network (THIN), a large primary care medical record database in the United Kingdom, if they had a diagnosis of PsA, RA, or psoriasis. PsA and psoriasis diagnoses have been validated in THIN (positive predictive value 85% and 90% respectively). Up to 10 unexposed controls were matched on practice and start date within the practice for each patient with PsA. Data from 1994–2010 were included. Hazard ratios (HRs) were calculated using Cox proportional hazards models. A priori we hypothesized an interaction between disease status and Disease Modifying Antirheumatic Drug (DMARD) use. We used a purposeful selection modeling approach, including in the final model only confounders which changed the main effects by >15% and had a p-value of <0.1.

Results: Patients with PsA (N=8,706), RA (N=41,752), psoriasis (N=138,424) and controls (N=82,258) had mean age 50.7, 61.4, 47.6, and 49.9 years respectively. The average follow up time was 5.3 years, and 1,442,357 person-years were observed during which 21,825 deaths occurred. There was a significant interaction between disease and DMARD use and thus, stratified results are presented. Compared with population controls, patients with PsA did not have an increased risk of mortality after adjusting for age and sex and did not significantly differ by DMARD use (DMARD users: HR 0.94, 95%CI: 0.80–1.10, DMARD non-users: HR 1.06, 95%CI: 0.94–1.19). RA patients had increased mortality when compared to population controls (DMARD users HR 1.59, 95%CI: 1.52–1.66, DMARD non-users HR 1.54, 95%CI: 1.47–1.60). Similarly, patients with psoriasis who have not been prescribed a DMARD had a small increased risk of mortality compared to population controls (HR 1.08, 95%CI: 1.04–1.12) while those who had been prescribed a DMARD had greater risk (HR 1.75, 95%CI: 1.56–1.95). These findings were unchanged after adjustment for baseline comorbidities including Charlson comorbidity index, cardiovascular disease, renal disease, diabetes, body mass index, depression and smoking status. Adjusting for start year in the cohort did not change the results.

Conclusion: Patients with RA and psoriasis had increased mortality compared to the general population, a finding corroborated by previous studies. Despite increased mortality in these related conditions, however, patients with PsA did not have a statistically significant increased risk of mortality in this study.

2560

Response and Drug Survival of 1st TNF-Inhibitor in 440 Patients with Psoriatic Arthritis - What Is the Role of Co-Medication with Methotrexate?

Karen M. Fagerli[1], Elisabeth Lie[1], Désirée van der Heijde[2], Marte S. Heiberg[3], Erik Rødevand[4], Åse S. Lexberg[5], Synnøve Kalstad[6], Knut Mikkelsen[7] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Diakonhjemmet hospital, Oslo, Norway, [4]St. Olavs Hospital, Trondheim, Norway, [5]Drammen Hospital, Drammen, Norway, [6]Tromsø, Norway, [7]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway

Background/Purpose: It is well established that methotrexate (MTX) co-medication improves efficacy of TNF-inhibitors (TNFi) in rheumatoid arthritis, while in ankylosing spondylitis it is widely accepted that it does not. The role of MTX co-medication in psoriatic arthritis (PsA) is still unclear. Our objective was to investigate if patients receiving concomitant MTX have better responses and drug survival to their 1st TNFi.

Methods: Data are from NOR-DMARD, an observational study of adult patients with inflammatory arthropathies starting DMARD-treatment. Patients with PsA receiving their 1st TNFi, either combined with MTX or in monotherapy, were selected. Due to heterogeneity in clinical presentation, the selected outcome measures were patient and physician global assessments, MHAQ and SF-6D. Baseline characteristics and state and change at 3, 6 and 12 months were compared by two-sample t-test and Chi^2 test, as appropriate. Drug survival at 1, 2 and 3 years was compared using Kaplan-Meier analysis with log-rank test, and sub-analyses were done for patients receiving Infliximab (IFX), Etanercept (ETN) and Adalimumab (ADA).

Results: 440 patients were included. We found significant baseline group differences in no. of swollen joints, physician global and SF6D scores (table 1). Three-month states and responses were similar between the groups, with signif-

icant differences only for physician global (table 1). Similar results were seen at 6 and 12 months. We did, however, find improved drug survival in the combination group (fig. 1) reaching statistical significance at 1 and 2 years. This was most prominent for IFX (p=0.01) and negligible for ETN (p= 0.79), with a trend for ADA (p=0.12).

Table 1.

	Overall	No co-medication	MTX co-medication	P-value
	Baseline characteristics			
	N=440	N=170	N=270	
Age (years)	46.5 (11.6)	47.0 (11.4)	46.1 (11.7)	0.46
Females (%)	46.4	47.6	45.6	0.70
Disease duration (yrs)*	5.2 (1.5–12.5)	5.1 (1.1–11.7)	5.5 (1.6–12.7)	0.44
No of prev. DMARDs	1.49 (1.09)	1.49 (1.20)	1.48 (1.02)	0.30
Swollen joints *	3 (1–6)	2 (0–5)	3 (1–7)	0.004
CRP mg/l *	9 (5–20)	7 (5–22)	9 (5–20)	0.44
Physician global (0–100)	37.4 (17.9)	39.6 (19.2)	36.0 (16.9)	0.04
Patient global (0–100)	54.6 (23.7)	56.5 (22.8)	53.4 (22.5)	0.17
MHAQ score (0–3)	0.70 (0.46)	0.72 (0.47)	0.69 (0.46)	0.41
SF6D score (0–1)	0.59 (0.12)	0.57 (0.12)	0.60 (0.12)	0.01
	3-month responses			
	N=328	N=123	N=205	
Physician global (0–100)	15.9 (15.0)	18.5 (17.1)	14.4 (13.5)	0.02
Δ Physician global	−21.7 (22.1)	−20.0 (23.0)	−22.6 (21.7)	0.32
Patient global (0–100)	29.2 (23.9)	32.4 (26.1)	27.3 (22.3)	0.07
Δ Patient global	−24.8 (26.4)	−22.0 (29.1)	−26.3 (24.7)	0.17
MHAQ score (0–3)	0.39 (0.41)	0.42 (0.43)	0.37 (0.40)	0.30
Δ MHAQ score	−0.31 (0.44)	−0.30 (0.50)	−0.32 (0.39)	0.67
SF-6D (0–1)	0.70 (0.15)	0.68 (0.15)	0.70 (0.14)	0.15
Δ SF-6D	0.10 (0.13)	0.10 (0.14)	0.10 (0.13)	0.92

Values are expressed as mean (SD) unless otherwise stated
MHAQ = Modified health assessment questionnaire
SF-6D = Short form – 6 dimensions
* Median(IQR)

N in figure = patients still observed at the end of the interval
•P-value by log-rank test
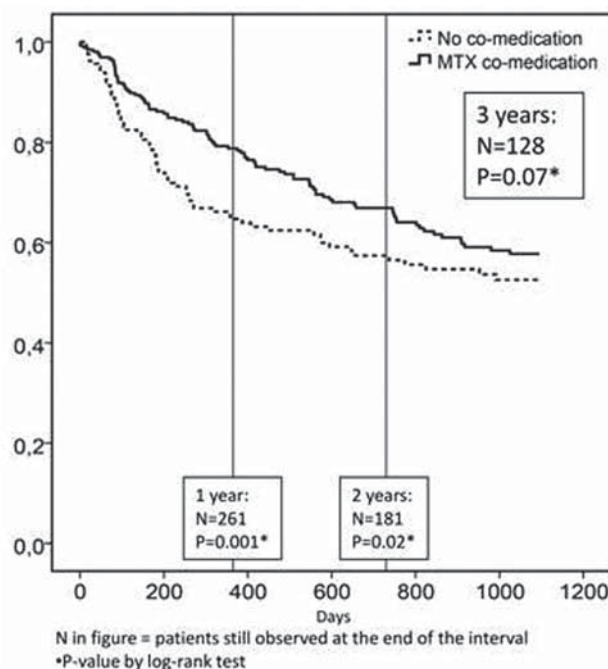
Conclusion: We found similar responses at 3 months in PsA patients receiving their first TNFi with and without MTX co-medication. However, drug survival was better in patients receiving concomitant MTX, and this was most prominent in patients receiving IFX.

2561

Switching Between TNF-Inhibitors in Psoriatic Arthritis: Data From the NOR-DMARD Study.

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Background/Purpose: Although TNF-inhibitors (TNFi) have proven efficacy in psoriatic arthritis (PsA), some patients do not respond to or do not tolerate their first TNFi. The efficacy of a second TNFi in this group is not well established. Our objective was to investigate the efficacy of switching to a second TNFi in PsA patients.

Methods: Patients were selected from NOR-DMARD – a longitudinal observational study (LOS) in which patients with inflammatory arthropathies are included when starting a new disease-modifying anti-rheumatic drug (DMARD). Patients with PsA receiving their 1st TNFi were selected, and among these patients a subgroup who later switched to a 2nd TNFi was identified (switchers). Three-month response and one year drug-survival were assessed for non-switchers and for the 1st and 2nd TNFi of the switchers. Selected outcome measures were ACR20/50/70 and EULAR responses, DAS28 remission and low disease activity rates, patient and physician global, MHAQ and SF6D. Both state and change from baseline were assessed, and compared statistically between switchers and non-switchers using Chi^2 and independent t-tests. Drug survival was compared by log-rank test. The overall response and drug survival to the first TNFi (switchers + non-switchers) was also assessed.

Results: Baseline characteristics are shown in table 1. There were no significant differences between switchers and non-switchers at baseline. There were significant differences in response between non-switchers and switchers receiving their 1st TNFi for several outcome measures, and these differences were more pronounced for the 2nd TNFi of the switchers with highly significant p-values for most outcome measures (table 2).One-year drug survival for the 2nd TNFi in switchers and non-switchers was 0.56 vs. 0.83 (p-value<0.001).

Table 1. Baseline characteristics

	Non-switchers N=344	Switchers 1st TNFi (N=95)	2nd TNFi (N=95)
Age	46.8 (11.7)	46.1 (11.6)	47.7 (11.5)
Males sex(%)	55.2	48.4	48.4
Type of TNFi(%)			
Etanercept	49.4	52.6	32.6
Infliximab	10.5	13.7	16.8
Adalimumab	29.1	29.5	36.8
Golimumab	10.5	4.2	11.6
Certolizumab	0.6	0	2.1
Co-Medication (%)	62.3	54.8	51.7
Disease duration(yrs)	6.0 (1.5–12.4)	4.7 (1.3–13.8)	6.5 (2.7–14.2)
Current smoker(%)	29.9	30.9	32.6
Previous DMARDs	1.5 (1.1)	1.7 (1.1)	1.7 (1.1)
CRP(median(IQR))	9 (5–20)	8 (4.27)	5 (2–19)
Swollen joints (median (IQR))	3 (1–6)	3 (1–6)	2 (0–4)
DAS28	4.1 (1.3)	4.4 (1.3)	4.2 (1.5)
Physician global	36.5 (17.5)	39.5 (18.4)	34.7 (18.6)
Patient global	53.2 (22.9)	57.4 (21.2)	55.3 (22.7)
MHAQ score	0.68 (0.45)	0.77 (0.47)	0.74 (0.48)
SF6D	0.59 (0.12)	0.58 (0.11)	0.59 (0.13)

Mean (SD) unless otherwise indicated. VAS (0–100), MHAQ = Modified health assessment questionnaire (0–3), SF-6D = Short form -6 dimensions (0–1).

Table 2. 3-month response

	Non-switchers N=259	Switchers 1st TNFi N=74	2nd TNFi N=63	P-value Non-switcher vs. 1st TNFi (switchers)	Non-switchers vs. 2nd TNFi (switchers)
ACR20 (%)	63.0	49.3	40.7	0.05	0.003
ACR50 (%)	40.0	30.4	24.1	0.16	0.03
ACR70 (%)	31.5	23.2	13.0	0.23	0.007
EULAR response (%)	53.4	49.0	19.5	0.63	<0.001
DAS28 <2.6 (%)	61.6	39.0	31.1	0.003	<0.001
DAS28 ≤3.2 (%)	74.7	57.6	37.8	0.014	<0.001
DAS28	2.4 (1.3)	3.2 (1.6)	3.5 (1.6)	<0.001	<0.001
DAS28 Δ	-1.7 (1.3)	-1.4 (1.5)	-0.6 (1.4)	0.17	<0.001
Physician global(0–100)	13.8 (12.9)	23.5 (18.9)	22.0 (17.3)	<0.001	<0.001
Physician global Δ	-22.7 (19.9)	-16.9 (27.3)	-14.3 (23.6)	0.05	0.01
Patient global (0–100)	27.8 (23.7)	34.2 (22.9)	38.2 (23.9)	0.04	0.003
Patient global Δ	-25.5 (25.5)	-20.8 (28.5)	-14.9 (27.6)	0.19	0.006
MHAQ (0–3)	0.36 (0.39)	0.50 (0.44)	0.50 (0.45)	0.01	0.017
MHAQ Δ	-0.32 (0.42)	-0.27 (0.45)	-0.23 (0.42)	0.40	0.15
SF6D (0–1)	0.71 (0.15)	0.66 (0.13)	0.65 (0.12)	0.01	0.002
SF6D Δ	0.11 (0.14)	0.07 (0.12)	0.06 (0.13)	0.02	0.003

Mean (SD) unless otherwise indicated. MHAQ = Modified health assessment questionnaire SF-6D = Short form -6 dimensions.

The overall ACR 20/50/70 responses for the 1st TNFi (n=439) were 59.9/37.8/29.6%, and the estimated 1-year drug survival was 0.74 – hence clearly superior to the 2nd TNFi (table 2).

There was no difference in response to second TNFi when comparing those who discontinued due to lack of efficacy (n=45) to those who discontinued due to adverse events (n=33).

Conclusion: Among patients with PsA who switched to a second TNFi after having failed their first TNFi, less than half achieved a clinical response at 3 months in this LOS. This observation highlights the need for treatments for PsA with other mechanisms of action.

Disclosure: K. M. Fagerli, Abbott Immunology Pharmaceuticals, 8, Pfizer Inc, 8, Merck Pharmaceuticals, 8, Roche Pharmaceuticals, 8; **E. Lie**, None; **D. van der Heijde**, Abbott Laboratories; Amgen; AstraZeneca; BMS; Centocor: Chugai; Eli-Lilly; GSK; Merck; Novartis; Pfizer; Roche; Sanofi-Aventis; Schering-Plough; UCB; Wyeth, 5, Imaging Rheumatology, 4; **M. S. Heiberg**, None; **S. Lexberg**, Abbott Immunology Pharmaceuticals, 8, Pfizer Inc, 8, Roche Pharmaceuticals, 8, Merck Pharmaceuticals, 8; **K. Mikkelsen**, None; **E. Rødevand**, None; **S. Kalstad**, None; **T. K. Kvien**, Abbott Immunology Pharmaceuticals, 8, AstraZeneca, 8, Merck Pharmaceuticals, 8, NiCox, S.A., 8, Pfizer Inc, 8, Roche Pharmaceuticals, 8, UCB, 8, BMS, 5, Abbott Immunology Pharmaceuticals, 5, Merck Pharmaceuticals, 5, NiCox, S.A., 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB, 5.

2562

Ustekinumab in Patients with Active Psoriatic Arthritis: Results of the Phase 3, Multicenter, Double-Blind, Placebo-Controlled Psummit I Study.

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Background/Purpose: To assess efficacy and safety of ustekinumab (UST) in reducing signs and symptoms of active psoriatic arthritis (PsA) in a large, multicenter, double-blind, placebo (PBO)-controlled, Phase 3 trial.

Methods: Adult PsA pts (n=615) with active disease (≥5 SJC and ≥5 TJC; CRP≥0.3mg/dL) despite DMARD and/or NSAID therapy were randomized to receive UST45mg, 90mg, or PBO at wks 0, 4, and q12wks, thereafter. At wk16, pts with <5% improvement in TJC & SJC entered blinded early escape (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). Stable concomitant MTX use was permitted but not mandated. Pts treated with prior anti-TNF agents were excluded. Primary endpoint was ACR20 response at wk24. Secondary endpoints at wk24 included: ACR 50/70, DAS28-CRP response, change from baseline (BL) in HAQ-DI, PASI75 response (in pts w/≥3% BSA involvement), and percent change from baseline in enthesitis and dactylitis scores (in pts affected at baseline). Adverse events (AE) are reported through the PBO-controlled period (wk16) and through wk24.

Results: Significantly greater proportions of UST-treated vs PBO–treated pts had ACR20 response at wk24 (Table). Significant improvements were also observed with UST45mg and 90mg for ACR50/70 responses and DAS28-CRP responses at wk24 vs PBO. The changes from baseline in HAQ-DI at wk24 were significantly greater in the UST than PBO grp, and significantly greater proportions of UST-treated pts had a clinically meaningful change from baseline in HAQ-DI (≥0.3). Nearly half used concomitant MTX at baseline; this did not alter the likelihood of benefit of UST vs PBO. While ACR responses were greater with UST than PBO regardless of MTX use, differences were numerically larger among pts not taking MTX. Of 440pts with ≥3% BSA involvement at baseline, significantly larger proportion of UST pts achieved PASI 75 at wk24. Among pts affected with enthesitis (n=425) or dactylitis (n=286) at baseline, significantly greater improvements in enthesitis and dactylitis were observed at wk24 in the UST grp than PBO. Through wk16, the proportion of pts with ≥1 AE was similar between pts receiving UST(41.8%) and PBO (42.0%), with infections being the most common AE; 1.7% (UST) and 2.0% (PBO) had ≥1 serious AE. No

malignancies, serious infections, TB, opportunistic infections, or deaths occurred through wk24.

Table. PSUMMIT efficacy results at Wk 24

	PBO (n=206)	UST 45mg (n=205)	UST 90mg (n=204)
ACR20, %	22.8	42.4	49.5
ACR50, %	8.7	24.9	27.9
ACR70, %	2.4	12.2	14.2
DAS28-CRP response, %	34.5	65.9	67.6
Median HAQ-DI change from baseline	0	-0.3	-0.3
Pts with ≥0.3 reduction, %	28.2	47.8	47.5
PASI75*, %	11	57.2	62.4
Median % change in enthesitis score*	0	-42.9	-50
Median % change in dactylitis score*	0	-75	-70.8

* Among pts affected at baseline.; p<0.001 for all parameters vs PBO

Conclusion: In pts with active PsA, UST significantly reduced the signs and symptoms of arthritis, improved physical function, enthesitis and dactylitis, and improved plaque psoriasis vs PBO-treated pts at wk24. Safety profiles were similar between UST-and PBO-treated pts.

ACR Concurrent Abstract Session
Vasculitis: Clinical Aspects
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Factors Associated with Major Cardiovascular Events in Patients with Primary Systemic Necrotizing Vasculitides: Results of a Longitudinal Long-Term Follow-up Study. Benjamin Terrier Sr.[1], Christian Pagnoux[2], Gilles Chironi[3], Alain Simon[3], Luc Mouthon Sr.[4], Loic Guillevin[5] and French Vasculitis Study Group (FVSG)[6]. [1]Cochin Hospital, Paris, France, [2]Mount Sinai Hospital, Toronto, ON, [3]HEGP, Paris, France, [4]Hopital Cochin, Paris, France, [5]Division of Internal Medicine, Hôpital Cochin, University Paris Descartes, Paris, France, [6]Paris

Background/Purpose: Primary systemic necrotizing vasculitides (SNV) were shown to be associated with more frequent subclinical atherosclerosis, independently of cardiovascular (CV) risk factors and C-reactive protein (CRP) level, suggesting that SNV might be associated with a higher risk of major CV events (MCVE).
Objective: To identify factors predictive of MCVE in SNV patients.
Methods: Consecutive patients in SNV remission were assessed for CV risk factors, body mass index (BMI), CRP levels and subclinical atherosclerosis [ultrasound detection of plaque in peripheral vessels and measurement of carotid intima–media thickness (IMT)], and prospectively followed in the same center. High-risk status, defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III), was a known history of CV disease, diabetes or 10-yr Framingham Risk Score ≥20%. MCVE, defined as myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina and/or death from CV causes, were recorded. Kaplan–Meier MCVE-free survival curves were plotted and compared with the log-rank test.
Results: Thirty-seven patients (24 males, age 54 ± 15 yr) were followed for 7.0 ± 2.6 yr. SNV diagnoses were: granulomatosis with polyangiitis, 19; eosinophilic granulomatosis with polyangiitis, 8; microscopic polyangiitis, 7; and polyarteritis nodosa, 3. Seven (18.9%) patients suffered MCVE, including myocardial infarction or hospitalization for unstable angina (n=4), arterial revascularization (n=2), and CV cause of death (n=1). The respective 5- and 10-yr MCVE rates were 10.8% and 25.7%.
Univariate analysis selected NCEP/ATP III-defined high-risk status [hazard ratio (HR) 5.02 (95% CI 1.17–27.4), P=0.03], BMI >30 kg/m^2 [HR 4.84 (95% CI 1.46–116), P=0.02] and plaque detection in the abdominal aorta (P=0.01) as being significantly associated with MCVE. In contrast,

SNV characteristics, corticosteroid maintenance therapy, CRP >5 mg/L, and plaque detection in the carotid and femoral arteries were not associated with MCVE. Plaque in the aorta was significantly (χ^2 test) associated with high-risk status (P<0.001), while BMI and high-risk status were independent variables (P=0.64). Thus, a BMI >30 kg/m^2 and/or a high-risk status were strongly associated with MCVE (P=0.003).
Finally, although IMT was not associated with MCVE, it distinguished between patients with early or late MCVE: 30% of patients with IMT >0.60 mm (vs none of those with IMT ≤0.60 mm) experienced MCVE within the first 3 yr of follow-up, while 23% of patients with IMT ≤0.60 mm (vs none of those with IMT >0.60 mm) experienced a 1st MCVE after 7–10 yr of follow-up. IMT was correlated with the time to MCVE (r^2=0.78, P=0.008).
Conclusion: These results suggest that factors associated with a higher MCVE risk in SNV patients are NCEP/ATP III-defined high-risk status and BMI >30 kg/m^2. Carotid IMT measurement in SNV patients could help identify those at risk of early MCVE.

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A Risk Score for Predicting Short-Term Incidence of Death or Relapse in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis. Carla Maldini[1], Matthieu Resche-Rigon[1], David Jayne[2], Kerstin Westman[3] and Alfred Mahr[1]. [1]Hospital Saint-Louis, Paris, France, [2]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [3]Skåne University Hospital Malmö, Lund University, Malmö, Sweden

Background/Purpose: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), combining granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), is associated with a substantial risk of relapse or death. Particularly, the first year after diagnosis is characterized by a marked excess of vasculitis-related deaths. The factors determining risk of death or relapse in the long term have been widely investigated, but those determining short-term outcome are not well known. Accurate prediction of short-term prognosis is crucial to identify patients at highest risk of an adverse event. We aimed to develop a risk score to predict the 1-year risk of death or relapse in newly diagnosed AAV.
Methods: We studied patients with incident AAV enrolled in 4 international, randomized, multicenter clinical trials focusing on various subgroups with AAV. An initial set of 22 candidate variables, including the main demographic, clinical and laboratory data, all assessed at diagnosis, and GPA or MPA diagnoses, were considered for predicting 1-year survival or relapse risk. A stepwise approach using univariate and multivariate logistic regression models in 2,000 bootstrap samples was used to identify variables that consistently predicted death or relapse at 1 year. The regression coefficients computed in the final multivariate model were used to derive weights for each of the identified predictors of the composite outcome. The discriminative ability of the final score was evaluated by analysis of the area under the receiver operating characteristic curve (AUC). A sensitivity analysis was performed with multiple imputation methods to account for missing data and calculate an AUC for the complete dataset.
Results: Among the 535 subjects, we had complete data for all 22 analyzed variables for 441 subjects (244 GPA, 197 MPA). At 1-year follow-up, we recorded 44 deaths (10.0%) and 12 relapses (3.3%). We retained 9 variables, assigned weights of 1 to 3, for the final risk score model: age > 60 yr (1 point); female sex (1); ear, nose and throat involvement (1); serum creatinine level > 300 μmol/l (3); ANCAs directed against proteinase 3 (PR3-ANCA) (1) and myeloperoxidase (MPO-ANCA) (3); peripheral neutrophil count > 7,000/mm^3(2); hemoglobin level < 10 g/dl (1) and C-reactive protein level > 10 mg/l (2). Each patient was assigned a risk score between 0 and 15. Accordingly, the 1-year risk for death or relapse was low (<5%) for 32% of patients, medium (5–20%) for 50%, and high (>20%) for 18%. The AUC for the prediction model was 0.79 (95% confidence interval 0.73–0.85) and 0.78 for the whole dataset of 535 subjects after missing-data imputation.
Conclusion: This integrative AAV-risk prediction score may be useful in predicting a patient's risk of death or relapse on short-term follow-up and may contribute to better risk-stratified characterization and management of AAV. Further validation in other AAV populations is required.

2565

Prevalence of Anti-Neutrophil Cytoplasmic Antibodies in Infective Endocarditis: An Analysis of 109 Cases. Alfred Mahr[1], Frédéric Batteux[2], Sarah Tubiana[3], Michel Wolff[3], Claire Goulvestre[2], Thomas Papo[3], François Vrtovsnik[3], Isabelle Klein[3], Bernard Iung[3] and Xavier Duval[3]. [1]Hospital Saint-Louis, Paris, France, [2]Hospital Cochin, Paris, France, [3]Hospital Bichat, Paris, France

Background/Purpose: Anti-neutrophil cytoplasmic antibodies (ANCAs), particularly those directed against proteinase 3 (anti-PR3) or myeloperoxidase (anti-MPO), are considered a highly specific hallmark of ANCA-associated vasculitis. Thus, false-positive ANCA tests have been reported in the context of drug exposure or infection, and several small case studies suggested that ANCAs can be detected in infective endocarditis (IE). This situation, combined with the multisystem protean presentation of IE, may lead to inappropriate diagnosis and therapy. Because the frequency of ANCAs in IE is unknown, we assessed the prevalence of ANCAs in a relatively large number of cases with IE.

Methods: The study was conducted in the framework of a prospective cohort study of consecutive cases with IE launched in 2005 in a single university hospital. Data on the principal demographic, clinical, laboratory (including serum creatinin and hematuria) and microbiological features were collected by a standardized questionnaire. Sera were stored for all patients who gave informed consent for blood sampling. Among the patients for whom sera were stored, we selected those with blood sampled not later than 30 days after the initiation of antibiotic therapy. All selected sera were tested for ANCAs in a central laboratory using indirect immunofluorescence (IIF) assays, and positive results were confirmed by ELISA. IIF involved ethanol-fixed neutrophils and categorized positive tests for C-ANCA (cytoplasmic pattern) or P-ANCA (perinuclear pattern). ELISA for anti-PR3 and anti-MPO specificities involved use of commercially available kits. In addition, we tested all sera for antinuclear antibodies by use of a commercially available indirect immunofluorescence test.

Results: Sera from 109 patients (81 [74%] men, mean age: 57.4 yrs [SD: 15.3]) were tested. All patients fulfilled Duke's criteria for definite or probable endocarditis, and 33 (30%) had prosthetic valves. The major causative pathogens were *Staphylococcus aureus* (n = 30), Streptococci (n = 23), *Streptococcus bovis* (n = 10) and Enterococci (n = 7). C-ANCAs were found in 13 patients (12%), P-ANCAs in 11 (10%) and 1 case (1%) showed both patterns. ELISA revealed anti-PR3 in 4 cases (3%) and anti-MPO in 4 (3%), some with very high titers. The 8 anti-PR3/anti-MPO–positive IE cases involved various pathogens and both native and prosthetic valves. Testing for antinuclear antibodies was positive (titer > 1:160) in 17 (16%) cases.

Conclusion: This study is the first to assess the prevalence of ANCAs in IE and suggests that ANCAs, including those with anti-PR3 or anti-MPO specificities, occur in a significant subset of cases. These observations considerably substantiate the consideration of IE as a potential cause of false ANCA positivity.

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Aβ-Related Angiitis: Comparison with Patients with Amyloid Cerebral Angiopathy without Inflammation. Carlo Salvarani[1], Caterina Giannini[2], Robert D. Brown Jr.[2], Teresa J. H. Christianson[2] and Gene G. Hunder[2]. [1]Arcispedale S Maria Nuova. IRCCS, Reggio Emilia, Italy, [2]Mayo Clinic, Rochester, MN

Background/Purpose: Coexistence of sporadic cerebral amyloid angiopathy (CAA) and primary central nervous system vasculitis (PCNSV) has been reported, particularly in patients with granulomatous vasculitis. This condition was termed Aβ–related angiitis (ABRA). We analyzed the clinical, radiographic, and pathological findings in a series of consecutive patients with pathologically diagnosed CAA. We describe the clinical characteristics of the patients with ABRA and compare them with the characteristics of patients with CAA without inflammation. Furthermore, we compare the features of patients with ABRA with those of PCNSV.

Methods: We reviewed all patients seen at the Mayo Clinic, Rochester, MN over the 25 year period of 1987 to 2011, who were diagnosed pathologically with CAA. Biopsy specimens were reviewed by one pathologist (CG) without knowledge of clinical information. Patients with changes of Alzheimer's disease were excluded. Of 74 identified patients, 46 did not show inflammation, 23 had ABRA, and 5 CAA-related inflammation (perivascular only). We also utilized our updated cohort of 131 consecutive patients with

PCNSV seen over a 25 year period of 1983 to 2007 at Mayo Clinic, Rochester, MN. The diagnosis of PCNSV was based on brain/spinal cord biopsy or cerebral angiography, or both. 14/131 patients had ABRA. 9 additional patients with ABRA were identified between 2008 and 2011.

Results: The 23 patients with ABRA were compared with the 46 cases with CAA without inflammation. The presence of altered cognition (15/23 or 65.2% vs 41/46 or 89.1%. p = 0.017), hemiparesis (3/23 or 13% vs 18/46 or 39.1%, p = 0.026), persistent neurologic deficit or stroke (5/23 or 21.7% vs 25/46 or 54.3%, p = 0.010), and intracranial hemorrhage (2/23 or 8.7% vs 31/46 or 67.4%, p < 0.001) at presentation were significantly less frequent in patients with ABRA than in the others. More patients with ABRA showed meningeal gadolinium enhancing lesions at MRI (13/23 or 56.5% vs 7/26 or 26.9%, p = 0.035). No differences in the demographics and cerebrospinal fluid (CSF) findings were observed in the two groups. Survival of the patients with CAA without inflammation was significantly lower compared to that of those with ABRA. The 23 patients with ABRA were compared to the other 117 patients with PCNSV (excluding the 14 patients with ABRA). The median age of patients with ABRA was significantly higher at diagnosis (67 years vs 47 years, p < 0.001). In ABRA patients, hemiparesis occurred less frequently at presentation (3/23 or 13% vs 51/117 or 43.6%, p =0.006), while gadolinium enhanced meningeal lesions occurred more frequently (13/23 or 56.5% vs 12/104 or 11.5%, p < 0.001). CSF abnormalities (a protein level > 700 mg/L) were observed more frequently in patients with ABRA (15/20 or 75% vs 40/90 or 47.1%, p = 0.024). The median protein CSF levels were higher in patients with ABRA (995 mg/L vs 660 mg/L, p = 0.009). No differences in the survival were observed between these 2 groups.

Conclusion: ABRA appears to represent a condition clinically distinct from CAA and PCNSV. However, the vasculitis seems to influence the clinical findings to a greater degree than the presence of amyloid deposits in the vessels.

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Predictive Value of Selected Markers of Inflammation and Platelet Activation for Complete Remission in ANCA–Associated Vasculitis. Gunnar Tomasson[1], Paul A. Monach[2], Kahraman Tanriverdi[3], Ulrich Specks[4], John H. Stone[5], Linna Ding[6], Fernando Fervenza[4], Gary S. Hoffman[7], Cees G.M. Kallenberg[8], Carol A. Langford[7], Deborah J. Phippard[9], Philip Seo[10], Robert F. Spiera[11], E. William St. Clair[12], Nadia Tchao[9], Jane E. Freedman[3] and Peter A. Merkel[13]. [1]University of Iceland, Reykjavik, Iceland, [2]Boston University, Boston, MA, [3]University of Massachusetts, Wochester, [4]Mayo Clinic, Rochester, MN, [5]Massachusetts General Hospital, Boston, MA, [6]NIAID, Bethesda, MD, [7]Cleveland Clinic, Cleveland, OH, [8]University Medical Center Groningen, Groningen, Netherlands, [9]Immune Tolerance Network, Bethesda, MD, [10]Johns Hopkins Vasculitis Center, Baltimore, MD, [11]Hospital for Special Surgery, New York, NY, [12]Duke University Medical Center, Durham, NC, [13]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Most subjects with ANCA –associated vasculitis (AAV) respond to treatment for remission induction, but predictors for complete disease remission are lacking. We have previously demonstrated that selected markers of inflammation and platelet activation (C-reactive protein (CRP), CD40 ligand (CD40L) interleukins (IL) 6 and 8, monocyte chemoattractant protein 1 (MCP-1), P-selectin and vascular endothelial growth factor (VEGF) are associated with disease activity in AAV. The aim of this study was to explore if levels of marker predict future complete remission in AAV.

Methods: Subjects were participants in the Rituximab versus cyclophosphamide for AAV clinical trial (RAVE). Subjects with active disease were randomized to either rituximab or cyclophosphamide in addition to treatment with glucocorticoids. Data from the baseline, 2-month, 4-month, and 6-month study visits were used for this analysis. Disease activity was assessed with Birmingham Vasculitis Score for Wegener's Granulomatosis (BVAS/WG). Complete remission was defined as BVAS=0 at the 6-month visit on no prednisone and without preceding severe flare or treatment failure since enrollment. CRP, CD40L, IL-6, IL-8, MCP-1, P-selectin, and VEGF were measured by ELISA. To explore if marker levels at baseline, 2 months and 4 months predicted complete remission at 6 months, logistic regression was used with complete remission as the outcome variable and marker-tertiles as independent variables. In additional analyses, the raw marker levels and log-transformed marker levels were used as independent variables in the models. The associations of the change in marker levels at the 2 4-month visits (compared to the baseline visit), with complete remission at the 6-month visit were tested with logistic regression. All analyses were adjusted for the BVAS/WG score at the baseline, 2-month, or 4-month visits, as appropriate.

Results: 197 subjects participated in the RAVE trial. The mean BVAS/WG score at baseline was 8.37 (sd 3.13). At the 6-month visit, 115 subjects achieved complete remission. Subjects with CRP levels in the third tertile at the 2-month and 4-month visits had lower odds of achieving complete remission at 6 months and subjects with IL-8 levels in the third tertile at the baseline, 2-month, and 4-month visits had lower odds of achieving complete remission at the 6-month visit compared to subjects in the lowest tertile (**Table**). In analyses using the raw or log-transformed marker levels, no marker was significantly associated with future remission, nor were changes in marker levels from the baseline visit associated with future complete remission.

Odds ratios and 95% confidence interval for achieving complete remission at 6 months, according to marker level

	Baseline (n=197)	Month 2 (n=184)	Month 4 (n=180)
CRP			
lowest tertile	reference	reference	reference
middle tertile	0.67 (0.31–1.44)	0.81 (0.36–1.81)	0.52 (0.21–1.29)
highest tertile	0.79 (0.36–1.71)	0.43 (0.20–0.95)	0.37 (0.15–0.91)
CD40L			
lowest tertile	reference	reference	reference
middle tertile	1.74 (0.83–3.66)	0.30 (0.13–0.68)	0.61 (0.26–1.43)
highest tertile	1.02 (0.49–2.12)	0.53 (0.23–1.22)	1.07 (0.44–2.6)
IL-6			
lowest tertile	reference	reference	reference
middle tertile	0.83 (0.4–1.73)	0.63 (0.29–1.36)	0.64 (0.26–1.6)
highest tertile	0.78 (0.38–1.62)	0.75 (0.34–1.63)	0.31 (0.13–0.76)
IL-8			
lowest tertile	reference	reference	reference
middle tertile	0.39 (0.17–0.86)	0.89 (0.40–2.00)	0.59 (0.23–1.47)
highest tertile	0.43 (0.19–0.96)	0.41 (0.19–0.89)	0.41 (0.16–1.01)
MCP-1			
lowest tertile	reference	reference	reference
middle tertile	1.55 (0.75–3.2)	1.58 (0.74–3.4)	0.74 (0.31–1.74)
highest tertile	1.45 (0.7–2.98)	1.16 (0.54–2.46)	0.61 (0.25–1.45)
P-selectin			
lowest tertile	reference	reference	reference
middle tertile	0.86 (0.41–1.81)	1.41 (0.63–3.16)	1.46 (0.58–3.63)
highest tertile	0.81 (0.39–1.68)	0.60 (0.28–1.28)	0.46 (0.2–1.07)
VEGF			
lowest tertile	reference	reference	reference
middle tertile	2.08 (0.97–4.47)	1.28 (0.58–2.84)	0.88 (0.35–2.22)
highest tertile	1.14 (0.55–2.36)	0.89 (0.41–1.93)	0.53 (0.22–1.27)

Conclusion: High CRP and IL-8 levels measured during treatment for remission induction of AAV are inversely associated with achieving future complete remission. These markers may be of prognostic value AAV.

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The Risk of Pulmonary Embolism and Deep Vein Thrombosis in Giant Cell Arteritis: A Population-Based Cohort Study. J. Antonio Avina-Zubieta[1], Diane Lacaille[1], Eric C. Sayre[1], Jacek A. Kopec[1] and Hyon K. Choi[2]. [1]Arthritis Research Centre of Canada/University of British Columbia, Richmond, BC, [2]Boston University School of Medicine, Arthritis Research Centre of Canada/University of British Columbia, Boston, MA

Background/Purpose: A recent hospital-based study has suggested an 8 fold increased risk of pulmonary embolism (PE) in individuals with polymyalgia rheumatica in the year following admission. It is unknown whether a similar risk exists among individuals with giant cell arteritis (GCA). We estimated the risk of incident PE and deep venous thrombosis (DVT) events, and associated time trend among incident cases with GCA compared to controls from the general population using physician billing and hospitalization databases that cover the entire province ($\sim$ million).

Methods: Our data included all visits to health professionals and hospital admissions covered by the comprehensive provincial medical services plan from January 1, 1990 until December 31, 2007 for all individuals > 18 years of age. We conducted a matched cohort study among patients meeting the following criteria: **a)** ≥ 40 years of age; **b)** new diagnosis of GCA on at least 2 visits within a two-year period between January 1996 and December 2007; and **c)**use of oral glucocorticoids between 1 month before and 6 months after the second GCA visit (or first if hospital or rheumatologist). Ten controls were matched by birth year, sex and calendar year of exposure from the general population for each case. A patient was considered to be a PE or DVT case

when he or she had a recorded code of PE (hospitalization) or DVT (outpatient or hospitalization). We estimated relative risks (RRs) of PE and DVT compared with a matched non-RA comparison cohort, adjusting for age, sex, comorbidities, trauma, fracture, surgery, and hospitalizations.

Results: Among 1,175 individuals with GCA (74% female, mean age of 75 years), 22 developed PE and 24 developed DVT. Compared with non-GCA individuals, the age-, sex-, and entry-time-matched RRs were 3.6 (95% CI, 2.1–5.8) for PE and 2.7 (95 % CI 1.74–4.32) for DVT (Table). These RRs were attenuated slightly after adjusting for covariates, but remained significant. The time-specific, age-, sex-, and entry-time-matched RRs during the first year were 15.1 (95%CI, 6.6–36.2) for PE and 5.9 (2.9–11.4) for DVT.

Table. Relative Risk of Incident PE and DVT According to GCA Status

	GCA	Non-GCA
PE Cases, N	22	65
Incidence Rate/1000 Person-Years	5.2	1.5
Age-, Sex-, Entry time Matched RR (95% CI)	3.6 (2.1–5.8)	1.0
Multivariable RR (95% CI)	3.1 (1.9–5.1)	1.0
DVT		
Cases, N	24	93
Incidence Rate/1000 Person-Years	5.8	2.1
Age-, Sex-, Entry time Matched RR (95% CI)	2.7 (1.7–4.3)	1.0
Multivariable RR (95% CI)	2.4 (1.5–3.9)	1.0
PE or DVT		
Cases, N	36	142
Incidence Rate/1000 Person-Years	8.8	3.3
Age-, Sex-, Entry time Matched RR (95% CI)	2.7 (1.8–3.9)	1.0
Multivariable RR (95% CI)	2.4 (1.6–3.5)	1

Conclusion: This large population-based study provides the first evidence for a substantially increased risk of PE and DVT in GCA and shed light on corresponding risk trends over the duration of GCA among primarily outpatients. These findings support increased monitoring of venous-thromboembolic complications and risk factors in GCA at the population level.

Rheumatology Research Foundation Special Session
Edmond L. Dubois, MD Memorial Lectureship:
Hydroxychloroquine Reduces Thrombosis in Systemic Lupus Erythematosus, Particularly in Antiphospholipid Positive Patients
Tuesday, November 13, 2012, 4:30 PM–6:00 PM

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Hydroxychloroquine Reduces Thrombosis (BOTH ARTERIAL AND VENOUS) in Systemic LUPUS Erythematosus, Particularly in Antiphospholipid Positive Patients. Genevieve Law[1], Laurence S. Magder[2], Hong Fang[3] and Michelle Petri[3]. [1]University of British Columbia, Vancouver, BC, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Past studies, mostly cross-sectional, have found a reduction in thrombosis in systemic lupus erythematosus (SLE) patients taking hydroxychloroquine (HCQ). We examined the relationship between hydroxychloroquine and other medications with thrombosis in a large prospective SLE cohort.

Methods: We studied 1795 SLE patients (56% Caucasian, 37% African American, 93.3% female, mean age 37.0 ± 12.5) with no previous thrombosis prior to entry in the cohort. The primary outcome was first thrombotic event (arterial or venous). Univariate analysis and multivariable modeling were used to examine associations between prednisone, hydroxycholoquine, and NSAID use with the risk of thrombosis.

Results: A total of 193 thrombotic events were observed over 10,508 person-years of follow-up (rate 18.4/1000 person-years). In the multivariable model controlling for age, traditional cardiovascular risk factors, and SLE disease activity, significant predictors for thrombosis included current prednisone dose (>20 mg/day, HR 4.4, p$<$0.0001) and Aspirin use (HR 1.8, p$=$0.0026). Hydroxychloroquine use remained protective for thrombosis (HR 0.6, p$=$0.0075). Subgroup analysis revealed that the protective effect of hydroxychloroquine was stronger in antiphospholipid antibody positive patients (HR 0.6, p$=$0.0090) than among antiphospholipid antibody negative patients (HR 0.8, p$=$0.57).

Subgroup		Thrombotic events	Rate of events/ 1000 person-yrs	Rate Ratios (95% CI)	P-value
Current Prednisone	None	52	10.6	1.0 (Ref. Gp)	
	1-9 mg/d	40	16.4	1.6 (1.1-2.4)	0.025
	10-19 mg/d	49	34.3	3.3 (2.2-4.8)	<0.0001
	20+ mg/d	43	71.8	6.5(4.3-9.8)	<0.0001
Cummulative Prednisone dose	None	29	13.1	1.0 (Ref. Gp)	
	<1 yr (10 mg/d)	37	23.8	1.6 (1.0-2.6)	0.075
	1-3 yrs (10 mg/d)	30	19.0	1.8 (1.1-3.1)	0.026
	3-10 yrs (10 mg/d)	45	25.5	3.0 (1.8-5.2)	<0.0001
	>10 yrs (10 mg/d)	9	24.3	3.7 (1.5-9.4)	0.0056
Current HCQ	No	95	29.0	1.0 (Ref. Gp)	
	Yes	90	14.6	0.5 (0.4-0.7)	<0.0001
HCQ use	Never	57	32.2	1.0 (Ref. Gp)	
	Past (not current)	27	27.6	0.9 (0.6-1.5)	0.81
	<6 consecutive mo	16	20.0	0.6 (0.3-1.0)	0.056
	>6 consecutive mo	64	13.8	0.5 (0.3-0.7)	0.0003
NSAID use	No	146	21.6	1.0 (Ref. Gp)	
	Yes	37	13.9	0.6 (0.4-0.9)	0.017
Aspirin use	No	137	17.9	1.0 (Ref. Gp)	
	Yes	49	28.0	1.6 (1.2-2.3)	0.0038

Conclusion: Current prednisone dose was found to be a significant independant predictor of thrombosis in SLE, after adjustment for disease activity. Current hydroxychloroquine use decreased the risk of thrombosis in this prospective cohort, particularly in those with positive antiphospholipid antibodies. Aspirin use was not protective, likely due to the bias of indication.

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Lymphoma Risk in Systemic Lupus: Effects of Disease Activity Versus Treatment.
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Background/Purpose: In systemic lupus (SLE), concern exists about immunosuppressive drugs and lymphoma risk, Yet, the relative influence of disease activity vs treatment, is unknown. Our objective was to determine, in SLE, the relative importance of disease activity vs drugs.

Methods: We performed case-cohort analyses within a multi-site SLE cohort. Cancers were ascertained by cancer registry linkage. Adjusted hazard ratios (HRs) for lymphoma were generated in multivariate regression models, for time-dependent exposures to immunomodulators (cyclophosphamide, azathioprine, methotrexate, mycophenolate, anti-malarials, glucocorticoids) demographics, calendar year, Sjogren's syndrome, SLE duration, and disease activity(mean adjusted SLEDAI-2k). Partially adjusted models were also performed, using only covariates whose HR confidence interval excluded the null value. Sensitivity analyses were performed, lagging cyclophosphamide exposures by 5 years. We used average mean SLE disease activity scores over

time, and medications were treated both categorically (ever/never) and as cumulative doses.

Results: We studied 64 lymphomas (61 non-Hodgkin's, 3 Hodgkin's) and 4,739 cancer-free controls. As is seen in the general population, lymphoma risk in SLE was higher in males versus females, and increased with age. Lymphoma cases occurred a mean of 13.1 years (standard deviation 9.8, median 12.3) after SLE diagnosis. Univariate analyses suggested a decreased lymphoma risk within the highest tertile of disease activity (relative to those with the lowest activity) but in fully adjusted models (using all variables listed above), the confidence interval widened to include the null value. Sensitivity analyses, lagging cyclophosphamide exposures, showed similar results to that portrayed in the table below. In a partially adjusted model (retaining age and highest tertile of disease activity), the HR suggested a two-fold lymphoma risk after cyclophosphamide. Despite a trend towards greater cyclophosphamide use in cases versus cancer-free controls, in fully adjusted models, no drug exposure was estimated to be an independent risk factor. Still, due to correlation, it remains difficult to differentiate the effects of medications from disease activity.

Results of the univariate and multivariate models to assess the hazard ratio (HR) of exposures on lymphoma development in patients with SLE

Variable	Univariate HR (95% CI)*	Partially adjusted model (95% CI)	Multivarate HR (95% CI)
Outside North America	1.04 (0.53, 2.05)	-	1.06 (0.45, 2.50)
Calendar year	1.01 (0.98, 1.05)	-	0.98 (0.94, 1.02)
Male	2.47 (1.24, 4.92)	-	2.21 (1.05, 4.66)
Age	1.05 (1.03, 1.07)	1.04 (1.03, 1.06)	1.05 (1.03, 1.07)
White race/ethnicity	0.97 (0.55, 1.71)	-	0.86 (0.46, 1.59)
Sjogren's syndrome	1.29 (0.66, 2.54)	-	1.21 (0.53, 2.78)
Glucocorticosteroids (GC) ever	1.39 (0.75, 2.56)	-	1.03 (0.40, 2.64)
Cumulative GC**> 3.5 gm	1.27 (0.75, 2.17)	-	1.59 (0.69, 3.67)
Cyclophosphamide (CY) ever	1.73 (0.90, 3.33)	1.99 (1.00, 3.96)	1.95 (0.61, 6.22)
Cumulative CY > 6 gm	1.51 (0.63, 3.62)	-	0.79 (0.18, 3.54)
Azathioprine (AZA) ever	0.82 (0.45, 1.52)	-	1.28 (0.53, 3.07)
Cumulative AZA > 36.5 gm	0.49 (0.19, 1.25)	-	0.46 (0.14, 1.54)
Methotrexate ever used	0.99 (0.45, 2.16)	-	0.79 (0.30, 2.05)
Mycophenolate ever used	1.38 (0.58, 3.29)	-	1.74 (0.70 4.34)
Antimalarials ever used	1.47 (0.80, 2.69)	-	1.39 (0.69, 2.78)
Disease activity (2nd tertile)***	1.00 (0.55, 1.82)	-	1.10 (0.56, 2.14)
Disease activity (3rd tertile)	0.43 (0.22, 0.84)	0.49 (0.27, 0.90)	0.52 (0.24, 1.12)

* CI=confidence interval**Systemic glucocorticosteroids, considered in prednisone equivalent doses.***Mean adjusted SLE Disease Activity-2K (SLEDAI-2k)

Conclusion: We did not definitively demonstrate an increased risk for any medications, despite a trend to greater cyclophosphamide use in the lymphoma cases. If anything, we noted a protective effect for very high SLE disease activity. Further work will focus on genetic profiles that might interact with medication exposures to influence lymphoma risk in SLE.

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Lack of Control of Hypertension in Systemic Lupus Erythematosus.
Hong Fang[1], Raheel Ahmad[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Hypertension is an independent risk factor for both actual cardiovascular events and also subclinical atherosclerosis (coronary calcium, carotid IMT) in SLE. We examined the factors that predict poorly controlled hypertension in SLE.

Methods: There were 2,182 patients with SLE (92% female, 56% Caucasian, and 37% African-American). Ninety-five percent met revised American College of Rheumatology criteria for SLE. Patients were diagnosed

as having hypertension if they had systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or if receiving any anti-hypertensive medications. Patients who had ever had hypertensive episodes during cohort follow-up were compared with patients who had never had hypertension with respect to clinical and demographic characteristics. Multivariate regression modeling using generalized estimating equations was used to assess of the association between various factors and mean systolic blood pressure over cohort follow-up among patients with hypertension.

Results: There were a total 1630 (74%) patients with hypertension (91% female, 53% Caucasian, 42% African-American). Compared to non-hypertensive patients, those with hypertension were more likely to be African-American (p<0.0001), male (p=0.0004), smokers (p<0.0001), alcoholic (p<0.0001), older (p<0.0001), lower education (p<0.0001), lower household income (p<0.0001), higher disease activity (p<0.0001), higher body mass index (p<0.0001), higher prednisone dose (p<0.0001),higher urine protein to creatinine ratio (p<0.0001) and higher serum creatinine (p<0.0001).

We next examined, in just the patients with hypertension, the association between clinical variables and systolic blood pressure over followup. In the table, a negative number indicates better control of hypertension.

Variable	Effect on Mean Systolic Blood Pressure	p-value
Age at assessment (per year)	0.22 ± 0.03	<0.0001
Gender (female)	-4.56 ± 1.14	<0.0001
Ethnicity		
African-American vs Caucasian	3.24 ± 0.91	0.0004
Other ethnicity vs Caucasian	-3.64 ± 1.45	0.012
Years of education (per year)	-0.11 ± 0.14	0.45
Family income (per $1,000)	0.002 ± 0.004	0.63
Smoking	1.19 ± 0.86	0.17
Body mass index (per kg/m^2)	0.56 ± 0.05	<0.0001
Number of anti-hypertensives	-3.08 ± 0.35	<0.0001
Prednisone (per mg/d)	0.13 ± 0.02	<0.0001
SELENA-SLEDAI	0.15 ± 0.06	0.017
Urine dipstick protein	0.85 ± 0.40	0.033
Urine protein/cr ratio	2.62 ± 0.41	<0.0001
Serum creatinine	-1.94 ± 0.79	0.014

In the multivariate model, age, male sex, African-American, BMI, prednisone, disease activity, and measures of renal lupus remained independent prediction of poor blood pressure control.

Conclusion: Hypertension remains an independent risk factor for cardiovascular events in SLE. As in the general population, older age, male gender, and African-American ethnicity are associated with both hypertension and poor control of hypertension. In SLE, body mass index, prednisone, disease activity, and urine protein to creatinine ratio remain independent predictors of poor blood pressure control. These modifiable risk factors are potential "treat to target" goals. In SLE, use of more than one anti-hypertensive was superior in blood pressure control.

Disclosure: **H. Fang**, None; **R. Ahmad**, None; **L. S. Magder**, None; **M. Petri**, None.

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Molecular Signatures in SLE: Flare Vs. Infection. Meggan Mackay[1], Michaela Oswald[1], Jorge Sanchez-Guerrero[2], Juan J. Lichuaco[3], Cynthia Aranow[1], Sean Kotkin[1], Peter K. Gregersen[1] and Betty Diamond[1]. [1]The Feinstein Institute for Medical Research, Manhasset, NY, [2]Mount Sinai Hospital, University Health Network, Toronto, ON, [3]St. Luke's Medical Center, Quezon City, Philippines

Background/Purpose: Inability to distinguish between infection and the inflammatory response related to SLE disease activity using clinical judgment often compromises timely and effective treatment. Gene expression profiling of circulating leukocytes has been used to differentiate between malignancy subtypes and between sepsis and sterile inflammation. The "IFN signature" in SLE has been linked to disease pathogenesis and disease activity. A biomarker that precisely and rapidly distinguishes between active disease and infection would allow for more directed therapy, resulting in improved outcomes. RNA microarray analysis of peripheral blood leukocytes in acutely ill SLE patients was used to identify gene expression profiles that distinguish the host response to infection from inflammation related to active disease.

Methods: 37 SLE patients with suspected infection or active SLE were recruited from 3 centers in New York, Mexico and the Philippines. Subjects

were excluded for pregnancy, a history of infection with Hepatitis B, C, HIV or if treatment had been initiated for the current illness. Whole blood was collected in Tempus™ Blood RNA Tubes and disease activity (SELENA SLEDAI) was measured at the time of enrollment. Infection determination was based on results of cultures, viral antibodies or PCR analyses. Microarray analyses were performed on the Illumina HT12v4 platform. Gene expression data were grouped using a modular analysis framework for blood genomics that has been applied to SLE previously (Immunity.2008; 29:150). Clinical characteristics were summarized using appropriate descriptive statistics with correction for multiple comparisons. Statistical significance for microarray modules was determined using a hypergeometric test.

Results: 31 subjects had adequate RNA for analysis; 19 met criteria for infection and subjects were grouped as either infection or flare as the cause of acute illness. There were no significant group differences in age, disease duration, ethnicity, co-morbid states, history of prior CNS or renal disease or current medication use. Presence of low serum complement or high anti-dsDNA antibody titers did not distinguish between groups, however, SLE-DAI scores were significantly higher with disease activity (p=0.002). Flare subjects exhibited significant over expression of genes encoding immunoglobulin chains and CD38 (plasma cell module; p=0.001) and IFN inducible genes (p<.000). Subjects with infection demonstrated significant over expression of genes encoding molecules expressed by cells of myeloid lineage (p=0.018) and molecules inducible by or inducing inflammation (inflammation II module; p=.012).

Conclusion: We have identified gene expression signatures that associate significantly with either infection or disease activity. Not surprisingly, genes over expressed in flare are those associated with plasma cells or are IFN inducible. Genes expressed in response to infection encode molecules such as FcγRIIA, CD86, CD163 and others associated with pattern recognition such as CD14, TLR2, MYD88, TNFR2 and BAFF. While SLEDAI scores correlate with disease activity, identification of a "sepsis signature" provides a more objective and reliable premise for treatment.

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Arthoplasty Rates Increased Among US Patients with Systemic Lupus Erythematosus: 1991–2005. Christina Mertelsmann-Voss[1], Ting Jung Pan[2], Huong Do[2], Mark P. Figgie[2] and Lisa A. Mandl[2]. [1]Hospital for Special Surgery, Cornell University, New York, NY, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: There is little data regarding patterns of arthroplasty use in patients with Systemic Lupus Erythematosus (SLE). This study evaluates trends in total joint replacement (TJR) for SLE from 1991–2005. Comparisons are made to patients with non-inflammatory conditions.

Methods: Administrative hospital discharge databases from 10 states (AZ, CA, CO, FL, IA, MA, NJ, NY, WA, WI) and census data annual population estimates were used to compute annual rates per 100,000 population of knee arthroplasty, total and partial hip arthroplasty, and total and partial shoulder arthroplasty for the years 1991 to 2005 in patients with SLE and those with no inflammatory or autoimmune diseases. ICD-9-CM codes were used to identify specific diseases.

Results: During the 15 year study period, 4253 TJR were performed for patients with SLE and 2,762,660 TJR for patients with no inflammatory or autoimmune disease. SLE patients were younger (54 +/− 16 years vs 70.5 +/− 12.1 years) and much more likely to be female (90.2% vs 63.5%). Hip arthroplasty was the most frequent procedure in SLE patients (50.1% vs. 31.1%), whereas knee arthroplasty was most common in the non-inflammatory group (33.7% for SLE patients vs. 47.4%); TJR rates for patients with non-inflammatory conditions almost doubled from 1991 to 2005 (124.5/100,000 in 1991 vs. 247.5/100,000 in 2005, p-value <0.001). A similar trend was observed for SLE; (0.17/100,000 vs. 0.38/100,000, p<0.001). In particular, the proportion of total knee replacements among SLE patients increased from 15% in 1991 to 45% in 2005. The mean age of patients undergoing TJR with non- inflammatory conditions decreased (71.5±11.8 yrs in 1991, 69.0±12.0 yrs in 2005, p-value <0.001). In contrast, the mean age of SLE TJR increased (47.3+/−17.0 vs 56.8+/−16.0, p-value<0.001). When stratified by age and gender, TJRs in SLE patients increased in all groups except for women with SLE <44 years of age. In this group rates decreased from 0.073/100000 to 0.067/100000 (p-value=0.009).

Conclusion: To our knowledge this is the first evaluation of TJR rates in SLE patients. From 1991–2005 arthroplasty rates increased in patients with SLE in similar proportions to overall TJR rates. This was surprising, as we had expected a decrease in TJR mirroring improved SLE mortality rates and decreases in end stage renal disease. However, the decrease in TJR among women < 44 years suggests treatment may be preventing early damage from severe active disease. In addition, while the mean age of non-inflammatory TJR fell, the age at time of SLE TJR increased. We speculate that improvements in SLE therapy may allow patients to live long enough to suffer both the osteonecrotic effects of steroids, possibly develop degenerative changes and also be healthy enough to receive an elective TJR. Increases in knee arthroplasty among SLE patients may also reflect lower SLE morbidity, and mortality, with SLE patients living long enough to develop age/obesity related knee OA. Further study is needed to see if these trends continue with ongoing improvements in SLE clinical care.

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Smoking, Autoantibodies and Vascular Events in Systemic Lupus Erythematosus. Johanna Gustafsson[1], Iva Gunnarsson[2], Susanne Pettersson[3], Agneta Zickert[1], Anna Vikerfors[4], Erik Hellbacher[4], Sonia Möller[3], Kerstin Elvin[4], Henrik Källberg[4], Julia F. Simard[5] and Elisabet Svenungsson[1]. [1]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Department of Medicine, Rheumatology Unit, Karolinska Institute, Stockholm, Sweden, [3]Karolinska University Hospital, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Smoking is a risk factor for several autoimmune diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Smoking is also a major risk factor for cardiovascular disease (CVD), both in the general population and in SLE. Smoking has furthermore been specifically associated with the occurrence of autoantibodies in RA, SLE and also in animal studies of autoimmune diseases.

We investigated the associations between patients smoking history and a set of autoantibodies in SLE. We also studied the potential interaction between smoking and autoantibodies for the occurrence of previous vascular events.

Methods: 367 prevalent SLE patients from a single center were included. Clinical evaluation, history of previous vascular events and data on smoking habits and estimated number of smoked cigarettes were recorded at inclusion. Autoantibodies: anti(a)dsDNA, aSm, aRo52, a Ro60, aSSB and antiphospholipid (aPL) antibodies (anticardiolipin antibodies (aCL) IgG/IgM/IgA, anti-b_2 glycoprotein-1 (ab$_2$GP1) IgG/IgM/IgA) and the lupus anticoagulant (LAC) were measured using ELISA and multiplex methods. Association analyses between smoking status (ever, former, current) at inclusion and antibody status were performed through logistic regression. These variables were also investigated in relation to history of CVD through interaction analysis. Never smokers were used as reference.

Results: In a first screening we noted that ever smoking was positively associated with aCL IgG (p=0.007), ab$_2$GP1 (p=0.002) and a positive LAC test (p=0.001) while the other investigated antibodies were not associated. Further analyses of the observed associations between aPL and smoking in multivariable models (including age, sex, age at disease onset, current smoking and former smoking) demonstrated that specifically former smoking was associated with LAC positivity OR 3.1(95% CI 1.6–5.9), ab$_2$GP1 IgG OR 3.1(95% CI 1.6–6.1) and aCL IgG OR 2.9(95% CI 1.6–5.8). The amount of cigarettes smoked did not affect aPL status. Interaction analysis demonstrated an interaction between occurrence of any aPL and ever smoking for the risk of venous thromboembolism (VTE), OR 2.8 (95% CI 1.3 – 5.9), attributable proportion due to interaction (AP)=0.66, p<0.05.

Conclusion: We demonstrate that among SLE patients ever smoking, and in particular former smoking, is associated with pro-thrombotic aPL. Furthermore, the combination of smoking and aPL positivity seems to interact and enhance the risk of vascular events. Our results demonstrate associations between smoking, an environmental exposure, humoral immunity and vascular events in SLE. Further studies are needed to investigate the directions and mechanisms behind these associations. Our results further underscore the importance of advocating a smoke free lifestyle among SLE patients.

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Inhibition of Pathogenic Autoantibodies by Accelerating the Exit of Germinal Center B Cells Via Manipulation of Regulator of G-Protein Signaling. John D. Mountz[1], John H. Wang[2], James S. New[3], PingAr Yang[3], Qi Wu[3], Bao Luo[3], Jun Li[3], Kirk M. Druey[4] and Hui-Chen Hsu[3]. [1]Univ of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, AL, [2]Cedars Sinai Medical Center, Los Angeles, CA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD

Background/Purpose: Regulator of G-protein Signaling (RGS) plays a key role in inhibiting chemokine signaling by desensitizing G-protein coupled receptor signals. RGS13 and RGS16 are two major regulators of B cell migration and regulate responses to CXCL12 and CXCL13 during development of germinal centers (GCs). We previously showed that IL-17 increased *Rgs13* and *Rgs16* in GC B cells, leading to high levels of activation-induced cytidine deaminase (AICDA), somatic hypermutation (SHM) and enabled development of pathogenic autoantibodies that cause immune complex nephritis and erosive arthritis. The objective of this work is to use BXD2-*Rgs13*^{−/−} and BXD2-*Rgs16*^{−/−} mice to determine if loss of RGS regulation suppressed the development of pathogenic autoantibodies.

Methods: BXD2-*Rgs13*^{−/−} and BXD2-*Rgs16*^{−/−} mice were produced by backcrossing BXD2 with B6-*Rgs13*^{−/−} and B6-*Rgs16*^{−/−} mice for > 7 generations. Confocal imaging was used to determine the location of RGS13, RGS16, AID, and GC B cells in the spleen. Immunohistochemistry staining of spleen and kidney was used to determine the presence of plasmablasts and immune complex deposition. ELISA was used to determine serum levels of autoantibodies. The levels of GC B cell (*Aicda*, *Pax5* and *Bach2*) and plasma cell (*Irf4*, *Blimp1* and *Xbp1*) program transcripts in FACS purified GC B cells were determined by quantitative real-time PCR. T-B conjugates were analyzed by sorting CD19^{+}/CD4^{+} doublets followed by EDTA dissociation and FACS identification of B-cell subsets.

Results: In spleens of wild-type (WT) BXD2 mice, RGS13 was mainly expressed by GC B cells with light zone (LZ) B cells expressed slightly higher levels of *Rgs13* compared to dark zone (DZ) B cells. RGS16 was expressed by LZ GC and marginal zone precursor (MZP) B cells in the LZ border. BXD2-*Rgs13*^{−/−} mice exhibited higher IgM antibody titers at early age compared to WT mice; though smaller GCs, lower GC B-CD4 conjugates, and lower AID levels suggested a lesser extent of SHM and affinity maturation. RGS16 deficiency led to reduced aggregation of CD86^{hi} MZP B cells in GC LZ vicinity, reduced MZP-T conjugates, and significantly fewer GCs, suggesting its role in MZP stabilization in GC LZ. Despite smaller GCs, there was increased IgM[bright] plasmablasts, upregulation of *Irf4*, *Blimp1* and *Xbp1* and down regulation of *Aicda*, *Pax5* and *Bach2* in GC B cells of BXD2-*Rgs13*^{−/−} and BXD2-*Rgs16*^{−/−} mice. At older ages, BXD2-*Rgs13*^{−/−} and BXD2-*Rgs16*^{−/−} mice showed lower titers of IgG autoantibodies and IgG deposits in the glomeruli, suggesting reduced autoantibody pathogenicity.

Conclusion: Lack of either RGS13 or RGS16 signal is associated with reduction in GC program genes and premature exit of less pathogenic IgM plasmablasts. Our results suggest that, in autoimmune mice, prolonged B-T interactions in the GC light zone, mediated by upregulation RGS13 or RGS16, enhanced the selection and generation of high affinity pathogenic autoantibody producing B cells. Redirection of B cell migration within different GC compartments via regulation of RGS13 and RGS16 and their associated signaling pathways may be a novel strategy to abrogate development of autoreactive B cells that produce pathogenic autoantibodies.

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Production of Citrullinated Filaggrin-Specific IgG in Rheumatoid Arthritis Patients Is Associated with an Expansion of Citrullinated Filaggrin Tetramer-Binding Switched Memory Blood B Cells. Philip Titcombe, Laura O. Barsness, Lauren Giacobbe, Emily Baechler Gillespie, Erik J. Peterson and Daniel L. Mueller. University of Minnesota Medical School, Minneapolis, MN

Background/Purpose: Rheumatoid Arthritis (RA) is highly associated with the production of autoantibodies, including rheumatoid factors and anti-citrullinated protein antibodies (ACPA). It remains uncertain whether production of autoantibodies in RA results from a failure of peripheral B cell deletion or anergy, or from augmented T helper cell-induced differentiation. Unfortunately, our ability to directly study pathogenic B cells in RA has been hampered by their relatively low numbers in peripheral blood and our inability to directly monitor their antigen specificity.

Methods: We now report the development of a B cell "antigen tetramer" system for use with multiparameter flow cytometry that can accurately detect and phenotype self antigen-specific B cells in RA patients. Arginine-312 —> Citrulline substituted filaggrin cyclic peptide 306–324 (Cfc1) was biotinylated and multimerized using streptavidin (SA)-phycoerythrin (PE) conjugates. A "decoy tetramer" was also created using SA-PE-Alexa Fluor 647 (AF647) conjugates and biotinylated native filaggrin cyclic peptide (Cf0) to facilitate exclusion gating of B cells that bind native filaggrin, biotin, SA, or PE.

Results: 46% of tested subjects in our University of Minnesota ACPA+ RA cohort demonstrated IgG anti-Cfc1 antibodies by ELISA (>95% specificity threshold). Using a combination of the Cfc1 and Cf0 antigen tetramers and flow cytometry, we observed in RA patients that lack Cfc1 Ab (n=22) a low number of Cfc1-specific PBMC B cells (49±31 per million) that was similar to healthy controls (HC) (51±29, n=9). Nevertheless, Cfc1-binding B cells in anti-Cfc1 Ab- RA subjects more frequently demonstrated a CD19+CD20+IgD-CD27+ phenotype consistent with isotype switching and memory cell differentiation (35±15%) as compared to either randomly selected PBMC B cells from the same patient (18±8%; p<0.01) or Cfc1-binding B cells in HC (16±11%; p=0.02). Anti-Cfc1 Ab+ RA subjects (n=21) demonstrated both an increased frequency of Cfc1-binding B cells (125±85 per million; p=0.02 vs. HC, p=0.01 vs. anti-Cfc1 Ab- RA) and increased proportion having a switched memory phenotype (55±18%; p<0.01 vs. both HC and anti-Cfc1 Ab- RA). Among all ACPA+ RA subjects tested, the level of anti-Cfc1 Ab predicted the frequency of switched memory Cfc1-binding B cells in PBMC ($r^2=0.38$).
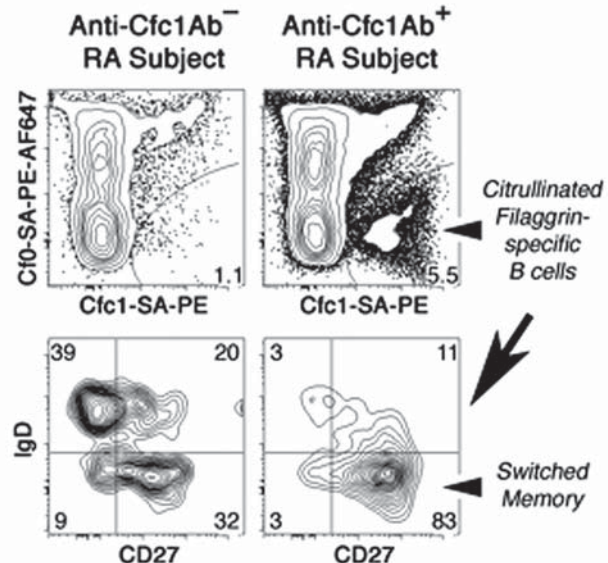
Conclusion: The loss of B cell tolerance to citrullinated filaggrin and production of anti-Cfc1 autoantibodies in RA is associated with an expanded population of Cfc1 tetramer-binding switched memory B cells in the PBMC. Use of antigen tetramers to positively identify and characterize antigen-specific B cells will accelerate the investigation of pathogenic B cells in autoimmune disease and holds promise as a valuable biomarker system for use in human therapeutic trials.

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Characterization of Circulating Human B Cells That Bind Cyclic Citrullinated Peptide Antigens in Clinically Active Rheumatoid Arthritis. Gregg J. Silverman[1], John Jung[2], Jeffrey D. Greenberg[3], Adam J. Pelzek[1], Caroline Gronwall[1] and Jaya Vas[1]. [1]NYU School of Medicine, New York, NY, [2]NYU, New York, NY, [3]New York University School of Medicine, New York, NY

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) were first identified based on their high specificity for RA and now are commonly used

as a diagnostic tool. Yet, despite the success of B cell targeted therapy, and evidence that ACPA may arise long before overt inflammatory arthritis, the roles of human B cells autoreactive for citrullinated protein antigens have been little explored.

Methods: For comprehensive B cell profiling, we developed a 12-color flow cytometry panel that assesses diverse B-cell subset specific markers, with live/dead discrimination and myeloid/T-cell exclusions. Fluorochrome-labeled tetrameric forms were made with cyclic citrullinated peptide (CCP) used in clinical testing, as well as a panel of self-protein derived peptides implicated in RA, and control peptides with a single amino acid type substitution. ACPA labeled beads were included for internal calibration. Multivariate methods were used to identify natural divisions within B cell data sets, and Spearman coefficients to assess for correlations between cytometric data and clinical/laboratory data.

Results: During panel development, we performed cross-sectional studies of a total of 30 RA and 16 healthy adults. Pilot surveys demonstrated only a low background levels of CD19+ B-cell binding to control CQP tetramer in RA and healthy adults (< 0.3% mean). While levels of B cell binding to CCP were overlapping between the groups, as some RA were indistinguishable from healthy controls, B cells from RA pts displayed significantly higher binding to CCP (7.46%+/−6.8, mean +/− SD) compared to binding of a control tetramer (p<0.0001, 2-tailed Mann-Whitney test). In RA, we found expansions of CCP-reactive B cells in diverse cellular subsets, which varied between subjects, and which included naïve mature B cells (IgD+ CD27−) and both CD27+IgD− and CD27− IgD− memory subsets. In each sample, CCP-binding by B-cell subsets was independent of relative BCR levels, as assessed by MFI. There were no significant relationships between levels of CCP-binding B cells and IgG, IgA or IgM anti-CCP or IgG to panel of peptide-specific ACPAs. Importantly, our surveys demonstrated a significant correlation between levels of CCP-binding by naïve mature (CD27− IgD+) B cells and DAS28 score (n=18, p=0.04, r=0.48). We also found correlations between CD95 expression (an activation marker) on CCP-binding B cells and DAS28 score (p=0.03, r=0.56) that was improved by exclusion of pts on biologic agents (n=7, p=0.01, r=0.89).

Conclusion: These studies have provided the first direct measurements of trafficking disease-specific B cells to citrullinated self-antigens. Our initial surveys found no relationship between levels of circulating CCP-reactive B cells with levels of serum ACPA, which therefore may reflect the contribution of sources no longer linked to synovial disease. However, we did find evidence of an association between levels of CCP-reactive B cells, and especially activated B cells, and overall disease activity by DAS28 score. Our investigative approach may therefore help to better stratify patients and identify those in whom autoantigen-specific lymphocytes are direct drivers of pathogenesis.

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Monoclonal IgG Antibodies (ACPAs) From Synovial Fluid B Cells of Rheumatoid Arthritis Patients – Antigen-Driven Affinity Maturation and Cross Reactivity.

Khaled Amara[1], Johanna Steen[1], Fiona Murray[1], Henner Morbach[2], Blanca Fernandez-Rodriguez[3], Vijay Balasingh[1], Marianne Engström[1], Omri Snir[1], Lena Israelsson[1], Anca. I. Catrina[1], Hedda Wardemann[4], Davide Corti[3], Eric Meffre Sr.[2], Lars Klareskog[1] and Vivianne Malmström[1]. [1]Rheumatology unit, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [2]Yale University School of Medicine, New Haven, CT, [3]Institute for Research in Biomedicine, Bellinzona, Switzerland, [4]Max Planck Institute for Infection Biology, Berlin, Germany

Background/Purpose: Antibodies targeting citrullinated proteins (ACPA) are commonly found in patients with Rheumatoid Arthritis (RA), strongly associate with distinct HLA-DR alleles and predict a more aggressive disease course as compared to seronegative patients. Still, many features of these antibodies, including their site of production and the extent of MHC class II driven T-cell help remain unclarified. In this study we have assessed the specificity and the immunoglobulin gene characteristics of B cells derived from RA synovial fluid of RA by utilizing a method that allows in vitro production of monoclonal antibodies derived from single human memory B cells.

Methods: Recombinant monoclonal antibodies (n=204) were generated from single flow cytometry purified synovial CD19+IgG+ B cells from active RA patients (n=5). Antigen specificity and affinity were determined by ELISA and Biacore respectively. Frozen tissue sections from active RA synovial inflammation were evaluated by immunohistochemistry for presence of citrullinated antigens using the generated recombinant antibodies.

Results: Our results demonstrate that approximately 25% of synovial IgG-expressing B-cells are specific for citrullinated autoantigens in ACPA-positive RA patients, while such antibodies were not found in seronegative patients. These citrulline-reactive antibodies did not react with the unmodified arginine peptides. Surprisingly, several antibodies displayed cross reactivity to several citrullinated antigens but with variable binding affinities. Overall, KD values ranged from $1.35 \times 10^{-06} - 5.94 \times 10^{-10}$ for CEP-1, from $3.84 \times 10^{-05} - 3.1 \times 10^{-09}$ for cit-fib, and from $2.8 \times 10^{-06} - 1.05 \times 10^{-10}$ for cit-vim. Positive staining has been observed in biopsies of two RA patients. On the molecular level, striking differences were found between the monoclonal recognizing citrullinated antigens and those that did not. Based on DNA sequences, we could demonstrate that the citrulline-specific antibodies displayed fewer overall mutations but, yet displayed more replacement mutations in their CDRs regions as compared to the citrulline-negative clones. Interestingly, the reversion of citrulline-specific antibodies to their germline sequences led to a loss of reactivity to all the autoantigens.

Conclusion: A role for active antigen selection of the citrulline-reactive synovial B-cells was supported by the strong bias towards amino acid replacement mutations in ACPA+ antibodies and by their loss of reactivity to citrullinated autoantigens when somatic mutations were reverted to the corresponding germline sequences. The observed cross reactivity suggests that multiple antigens could participate in driving these clones.

Disclosure: K. Amara, None; **J. Steen**, None; **F. Murray**, None; **H. Morbach**, None; **B. Fernandez-Rodriguez**, None; **V. Balasingh**, None; **M. Engström**, None; **O. Snir**, None; **L. Israelsson**, None; **A. I. Catrina**, None; **H. Wardemann**, None; **D. Corti**, None; **E. Meffre Sr.**, None; **L. Klareskog**, None; **V. Malmström**, None.

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Novel Autoantibodies to 14-3-3 Eta Are Highly Specific for Rheumatoid Arthritis.

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Background/Purpose: Serum 14-3-3 eta, a protein biomarker that is differentially expressed in rheumatoid arthritis (RA), has been reported to add incrementally to rheumatoid factor (RF) and anti-cyclic citrullinated protein (anti-CCP) in diagnosing both early and established RA. We recently reported that extracellular 14-3-3 eta behaves as a novel mediator of RA pathogenesis, inducing factors involved in driving both inflammation (TNFα) and joint re-modeling (MMP-9) and that serum 14-3-3 eta is an independent predictor of damage in patients with RA and psoriatic arthritis (PsA). Since 14-3-3 eta is normally an intracellular chaperone that is externalized through an exosomal-mediated process by a disease-specific trigger, we investigated whether its extracellular presence elicits an autoantibody response that may be measured for clinical utility.

Methods: Detection of 14-3-3 eta autoantibodies was evaluated by examining immunoreactivity towards human recombinant 14-3-3 eta by immunoblot analysis using serum from healthy subjects and those with RA. Epitope mapping and *in silico* modeling was performed to identify putative epitopes of which 11 peptide regions were selected. To further specify high-priority regions, the serum expression levels of 14-3-3 eta autoantibodies were evaluated in 30 healthy individuals and 58 RA patients. Individual sequences were selected based on their absolute specificity for RA, of which 4 of 11 met this criteria with sensitivities ranging from 34–62%. A composite score was generated by combining the fluorescence intensity (FI) measurements for these 4 peptides, each of which were equally weighted and expressed in units (U). T-tests and Mann-Whitney U-tests were used to determine group differences. The area under the ROC curve (AUC) was generated for diagnostic utility estimates and likelihood ratios (LR) for various 14-3-3 eta autoantibody composite cut-offs.

Results: Immunoblot analysis reveals that patients with RA possess autoantibodies directed towards 14-3-3 eta. This prototype 14-3-3 eta autoantibody assay exhibits high specificity for RA versus healthy controls with means (SD) and medians (min-max) of 828U (1292U) and 681U (340U–10386U) for RA and 385U (74U) and 371U (289U-568U) for healthy controls, p-value <0.0001. The ROC AUC was 0.93 (95% CI 0.88–0.98; p<0.0001). At the best cut-off of 476U, the specificity and sensitivity were 90% and 80%, respectively with a likelihood ratio positive of 7.9 increasing to 18 at 580U. These prioritized sequences will be further specified based on their differential expression in RA versus disease controls to develop an anti-14-3-3 eta ELISA for clinical diagnosis.

Conclusion: 14-3-3 eta is an RA biomarker whose extracellular expression elicits an autoantibody response that is highly specific for RA compared to healthy individuals.

Disclosure: W. P. Maksymowych, Augurex Life Sciences Corp., 7, 9; **D. van der Heijde**, Augurex Life Sciences Corp., 5; **R. Landewe**, Augurex Life Sciences Corp., 5; **V. P. Bykerk**, Augurex Life Sciences Corp., 5; **A. Marotta**, Augurex Life Sciences Corp, 3.

Marginal Zone Defects in Wiskott-Aldrich Syndrome Are Dependent On B Cell Intrinsic Toll-Like Receptor Signals. Shaun W. Jackson[1], Nikita Kolhatkar[2], Marc A. Schwartz[2], Socheath Khim[3] and David J. Rawlings[4]. [1]Seattle Children's Hospital, Seattle, WA, [2]Department of Immunology, University of Washington, Seattle, WA, [3]Seattle Children's Research Institute, Seattle, WA, [4]Washington, Seattle, WA

Background/Purpose: Patients with the primary immunodeficiency Wiskott-Aldrich syndrome (WAS) have severe abnormalities in splenic marginal zone (MZ) anatomy and function. Consistent with this, WAS patients fail to develop T-independent antibody responses to polysaccharide antigens and are susceptible to *Streptococcus pneumoniae* infections. We previously showed that B cell entry into the MZ is unperturbed in WAS−/− mice, but that retention within the MZ is defective. However, the factors promoting WAS−/− B cell exit from the MZ have not been determined.

Methods: Proliferation of sorted wild-type (WT) and WAS−/− MZ B cells was quantified after stimulation with LPS (TLR4 agonist), CL294 (TLR7 agonist) or CPG (TLR9 agonist) for 72 hours. To study the impact of B cell intrinsic TLR signaling on WAS MZ homeostasis, mixed bone marrow chimeras were generated in which deficiency of WAS, WAS × Myd88, WAS × TLR7 or WAS × TLR9 was limited to the B cell lineage. Splenic MZ reconstitution was then analyzed by flow-cytometry and immunohistochemistry. *In vivo* labeling of MZ cells at the vascular interface was performed by PE-labeled anti-CD19 antibody injection 5 minutes prior to sacrifice.

Results: In addition to markedly decreased MZ size, we demonstrate by *in vivo* labeling that WAS−/− MZ B cells are not normally positioned at the MZ vascular interface. Unmanipulated WAS−/− mice also exhibit increased peripheral blood MZ B cells consistent with the idea that WAS−/− B cells are not appropriately retained within the MZ. Further, we show that sorted WAS−/− MZ B cells are hyper-responsive to multiple Toll-like receptor (TLR) ligands, including TLR4, TLR7 and TLR9. These combined findings suggested that TLR-mediated activation might directly promote WAS−/− B cell exit from the MZ.

To test this idea, we generated chimeras with B cells deficient in both WAS protein and the key TLR signaling adaptor, MyD88. Strikingly, the MZ B cell compartment was restored to WT levels in WAS−/− × MyD88−/− chimeras. WAS−/− × MyD88−/− B cells were also appropriately positioned within the MZ both by *in vivo* labeling and immunohistochemistry. To address the impact of individual TLRs, we generated WAS−/− × TLR7−/− and WAS−/− × TLR9−/− chimeras. Although increased compared with WAS−/− controls, WAS−/− × TLR7−/− MZ size was reduced 50% compared with WT chimeras, suggesting a partial role for endogenous TLR7 ligands in driving WAS−/− B cells out of the MZ. In contrast, no rescue of MZ B cell numbers was noted in WAS−/− × TLR9−/− chimeras, implicating TLR9 in negatively regulating B cell activation and MZ retention, perhaps via downregulation of TLR7 signaling.

Conclusion: Our data demonstrate that activation by endogenous TLR ligands is sufficient to drive WAS−/− MZ B cells from the MZ and that B cell-intrinsic TLR7 and TLR9 signals have opposing impacts on MZ homeostasis. These data imply a previously unappreciated role for B cell intrinsic TLR signals in MZ B cell function; and have important implications regarding altered immune responses to blood-borne pathogens in WAS patients and for development of autoimmune disease in WAS and other clinical settings.

Disclosure: S. W. Jackson, None; **N. Kolhatkar**, None; **M. A. Schwartz**, None; **S. Khim**, None; **D. J. Rawlings**, None.

ACR Concurrent Abstract Session
Imaging of Rheumatic Diseases III: Computed Tomography
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

Anti-Citrullinated Protein Antibodies but Not Rheumatoid Factor Are Associated with Larger Bone Erosions in rheumatoid arthritis patients— a Cross-Sectional Micro Computed Tomography Study. Carolin Hecht[1], Stephanie Finzel[1], Matthias Englbrecht[1], Sarah Schmidt[1], Juergen Rech[1], Elizabeth Araujo[1] and Georg Schett[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Anti- citrullinated protein antibodies (ACPA) are known to be associated with joint destruction and a more severe disease course in

rheumatoid arthritis (RA) patients. Recently, ACPA have been identified to directly induce bone loss (1). No study, however, has yet compared ACPA-positive and ACPA-negative RA patients with respect to their periarticular bone structure using high-resolution imaging of bone.

Methods: Cross-sectional analysis of 234 RA-patients fulfilling the new ACR/EULAR criteria. All patients received micro-computed tomography (2) of the MCP II, II and IV joints of the dominantly affected hand. Age, gender, disease activity (DAS28), disease duration, rheumatoid factor, ACPA (by anti-CCP2 ELISA) and anti-rheumatic therapy were recorded.

Number, width, depth and volume of bone erosion were assessed by 2 independent readers, one of them reading the images twice to test for intrareader-reliability. For calculation of volumes, a semi-ellipsoid formula was used (3).

Results: 137 patients were ACPA positive (RF+: N =108, RF-: N =29), 97 patients ACPA negative (RF+. N =28, RF-: N =69). All 4 groups were comparable for age, gender, disease activity, disease duration and anti-rheumatic therapy (Tab. 1). 15 patients were excluded from further evaluation due to movement artefacts. RF+/ACPA+ RA patients had significantly more severe erosions (width: 2.00mm; depth: 2.25mm; volume: 13.86mm^3) as compared to RF−/ACPA− RA patients (1.25mm; 2.02mm; 4.60mm^3; all p<0.0001). Furthermore, when comparing only those patients without RF, we observed that bone erosions in RF−/ACPA+ RA patients were significantly larger in dimension than bone erosions in RF−/ACPA− RA patients (w−+/+−: p=0,0012; w−+/−−: p<0.0001; d: −+/+− p=0,0095 and d: −+/−− p=0,0347; vol−+/+−: p= 0,0133; vol−+/−−: p=0,0055). Intra-observer reproducibility (CH) for erosion counts, width, depth and volumes was high (Spearman's rho between 0.93–0.99; p < 0.001). Interobserver reproducibility (SF; CH) was also very high (cts: 0.99, p < 0.001; w/d: 0.98, p < 0.001; vol.: 0.996, p < 0.001).

Table 1. Details of erosions and demographic data

Group	Age	no/female/ total	disease duration	DAS28	no/erosions (total)	no/erosions (mean)	width (mm)	depth (mm)	Volume (mm3)
RF+/CCP+	55,57	77/108	6,50 ± 7,06	3,67 ± 1,70	345	4,54 ± 8,55	2,00 ± 1,18	2,25 ± 1,51	13,86 ± 69,78
RF+/CCP−	53,00	24/29	4,14 ± 5,51	4,54 ± 1,45	41	1,80 ± 1,80	1,48 ± 0,71	1,70 ± 1,06	2,40 ± 3,30
RF−/CCP+	54,38	25/29	4,52 ± 5,63	3,19 ± 1,24	40	1,74 ± 3,02	2,06 ± 1,37	3,04 ± 2,99	13,81 ± 28,15
RF/−CCP−	56,28	54/69	4,0 ± 6,06	4,03 ± 1,81	79	1,55 ± 1,90	1,25 ± 0,56	2,03 ± 1,64	3,50 ± 8,17

Means +/− standard deviation are shown if not highlighted otherwise

Conclusion: These data show that ACPA-positivity is associated with larger bone erosions in patients with RA. They also support the notion that ACPA essentially contribute to bone loss in RA by enhancing osteoclast activity, which is the key prerequisite for bone erosion. Moreover, ACPA impact bone erosion independent from the presence or absence of RF.

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2. Stach CM et al. Periarticular bone structure in rheumatoid arthritis patients and healthy individuals assessed by high-resolution computed tomography. Arthritis Rheum. 2010 Feb;62(2):330–9.
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Disclosure: C. Hecht, None; **S. Finzel**, None; **M. Englbrecht**, None; **S. Schmidt**, None; **J. Rech**, None; **E. Araujo**, None; **G. Schett**, None.

Bone Anabolic Changes Progress in Psa Patients Despite Treatment with Methotrexate or Tumour Necrosis Factor Inhibitors. Stephanie Finzel[1], Sebastian Kraus[1], Sarah Schmidt[1], Axel J. Hueber[1], Juergen Rech[1], Klaus Engelke[1], Matthias Englbrecht[1] and Georg Schett[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: To investigate whether methotrexate (MTX) or tumour necrosis factor inhibition (TNFi) affect osteophyte formation in patients with psoriatic arthritis (PsA).

Methods: 41 patients with PsA were examined for the presence of osteophytes and erosions at the metacarpophalangeal joints by high-resolution μCT imaging. The size of each individual lesion was quantified at baseline and 1-year follow-up in PsA patients treated with TNFi (N=28) or methotrexate (N=13). Groups were comparable for age, sex, disease duration and activity and baseline burden of osteophytes.

Results: In total, 415 osteophytes (TNFi: N= 284, MTX: N= 131) were detected. Osteophyte size increased significantly from baseline to follow-up in the TNFi group (mean ± SEM change: +0.23 ± 0.02 mm; p<0.0001) and the MTX group (+0.27 ± 0.03 mm, p<0.0001). In both treatment groups, the majority of osteophytes showed progression (TNFi: 54.3% MTX: 61.1%), whereas regression of lesions was rare (less than 10%). In contrast to osteophytes, clinical disease

activity decreased in both groups of PsA patients and erosions showed an arrest of progression in both groups.

Conclusion: Osteophytes progress in PsA patients treated with either MTX or TNFi. These data provide first evidence that pathologic bone formation in the appendicular skeleton of patients with PsA is not affected by current anti-rheumatic treatment strategies.

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Bone Structure and Perfusion Quantification of Bone Marrow Edema and Pannus Tissue Areas in the Wrist of Patients with RA. Jose R. Teruel Antolin, Andrew J. Burghardt, Julien Rivoire, Waraporn Srikhum, Susan M. Noworolski, Thomas M. Link, John B. Imboden and Xiaojuan Li. University of California, San Francisco, San Francisco, CA

Background/Purpose: Bone marrow edema (BME) has been suggested as a strong predictor for erosive progression in RA joints, however, no previous studies examined the bone structure within BME. This study aimed to quantify bone structure and perfusion properties of BME, normal bone marrow (NBM) and pannus tissue areas in wrists affected by RA using 3T MRI and high resolution peripheral quantitative CT (HR-pQCT).

Methods: Sixteen patients (52.9 ± 12.7 years) fulfilling ACR classification were imaged in a HR-pQCT system (82μm isotropic voxel) and in a 3T MRI scanner using an 8-channel wrist coil. Coronal T2-weighted fast spin-echo IDEAL and 3D dynamic contrast enhanced (Gd-DTPA injection, temporal resolution 12 s, 32 time points) images were acquired. BME and pannus tissue areas were segmented semi-automatically in T2-w images. NBM areas were placed 1 to 3 mm far from BME regions and with similar distance to joint space. T2-w images were register to reformatted HR-pQCT and registration was applied to the segmented ROIs that were placed on original HR-pQCT images after upsampling (Fig 1). Perfusion parameters were calculated based on the signal-time curve obtained from DCE-MRI.
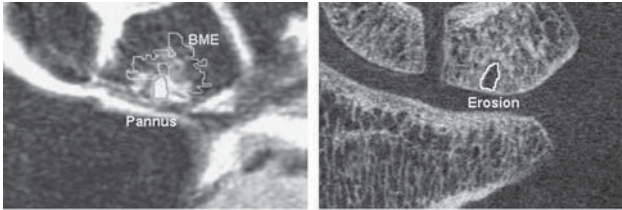
Figure 1. a: BME and pannus in T2w IDEAL image. b: HR-pQCT showing erosion and BME ROI superimposed.

Results: Eleven out of 16 RA patients presented at least one BME region. Eighteen BME areas were segmented, 13 of them were presented around areas evidently affected by pannus tissue. The regions with pannus tissue in MRI always correspond to regions with erosion in HR-pQCT images (Fig 1). Two BME areas were presented next to early stage of pannus tissue (very small quantity of pannus penetrating the bone). For 3 of the BME regions, no pannus tissue were observed. Significant increases in bone density and trabecular thickness were evidenced in all BME regions (Fig 2).
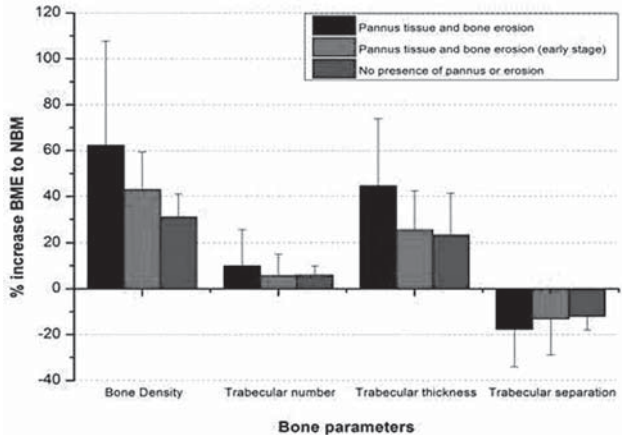
Figure 2. Percentage increase of bone parameters in regions presenting BME with regard to NBM areas (P < 0.05).

BME and pannus tissue areas show significantly increased perfusion. The maximum signal enhancement in BME was 20.33 ± 14.33 (% over NBM) within the carpal bones and 21.32 ± 10.52 within the distal radius/ulna. In pannus tissue areas was 16.48 ± 11.34 (% over NBM) within the carpal bones and 32.93 ± 16.71 within the radius/ulna.

Conclusion: BME regions show a thickening in the trabecular structure that suggests a bone regeneration before pannus tissue produces erosion. Trabecular thickening within BME is higher when pannus tissue is already presented in the patient. This higher thickening suggests sclerosis occurring to protect the bone structure from pannus tissue and kinematic re-adaptation. Combining MRI and HR-pQCT provides a powerful multi-modality approach for better understanding BME and erosion, and potentially identifying novel imaging markers for disease progression in RA.

Disclosure: **J. R. Teruel Antolin**, None; **A. J. Burghardt**, None; **J. Rivoire**, None; **W. Srikhum**, None; **S. M. Noworolski**, None; **T. M. Link**, None; **J. B. Imboden**, None; **X. Li**, None.

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Quantitative and Semi-Quantitative Bone Erosion Assessment On High-Resolution Peripheral Quantitative Computed Tomography in Rheumatoid Arthritis. Waraporn Srikhum, Warapat Virayavanich, Andrew J. Burghardt, Andrew Yu, Thomas M. Link, John B. Imboden and Xiaojuan Li. University of California, San Francisco, San Francisco, CA

Background/Purpose: The goals of this project were (i) to develop novel quantitative and semiquantitative measures of bone erosions at the metacarpophalangeal (MCP) and wrist joints in patients with rheumatoid arthritis (RA) using high-resolution peripheral quantitative computed tomography (HR-pQCT), and (ii) to correlate these measurements with disease duration and bone marrow edema (BME) pattern from MRI.

Methods: 16 RA patients (54.1±12.7 years, 13 females) underwent hand and wrist HR-pQCT and 3 Tesla MRI. Bone erosions of the 2nd and 3rd MCPs and distal radius were evaluated by measuring maximal erosion dimension on axial slices by two radiologists. Measurements were performed twice. Intraclass correlation coefficient (ICC) values were calculated for the inter- and intra-reader reliability. Bone erosions in each MCP and distal radius were graded (grades 0–3) based on the maximal dimension and number of erosions (Figure1A). The volume of bone marrow edema (BME) pattern was quantified on coronal T2-weighted fast spin-echo (FSE) MRI images using in-house software. Spearman correlation coefficients were calculated between 1) sum maximal dimensions, highest grades and sum grades of bone erosions; 2) erosion measures and the clinical evaluation (duration of disease, DAS28, ESR, and CRP); 3) erosion measures and BME pattern volume in distal radius.

Results: The mean maximal dimension of erosions at MCP2, MCP3 and distal radius were 0.39±0.21 cm, 0.32±0.21 cm and 0.46±0.31 cm, respectively. The inter- and intra-reader agreements of maximal erosion dimensions were excellent (ICC 0.89 and 0.99, respectively). Correlations between highest grades and sum grades, vs. sum maximal dimensions of all erosions were r=0.96 and 0.94 (p<0.01), respectively. Number of erosions, sum maximal erosion dimensions, highest grades and sum grades significantly correlated with duration of the disease (p<0.01), but not with DAS28, ESR and CRP, which reflected accumulation of the structural damage during the course of RA. Number of erosions, sum

maximal dimensions and erosion grading of the distal radius also correlated significantly with BME volume (p<0.01) (Figure 1B and C).
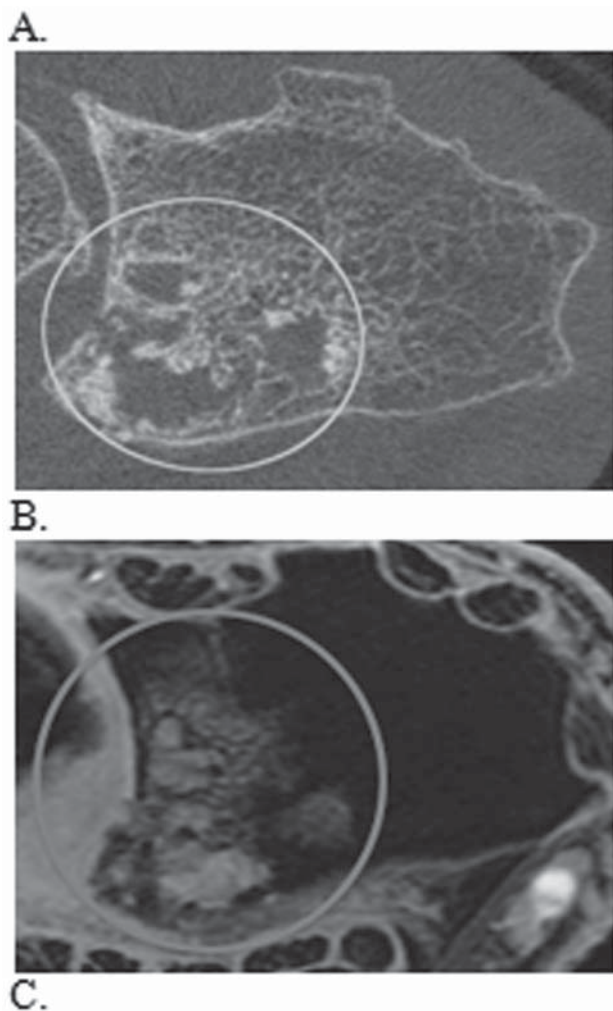
Figure 1. A, Axial HR-pQCT images (82μm isotropic resolution) of the metacarpal heads and distal radius of rheumatoid arthritis patients with different stage of erosions and definitions of the semi-quantitative grades for evaluating bone erosions at each region. B and C, Comparative axial HR-pQCT (B) and axial T2-weighted fast-spin echo (FSE) MRI using interative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequences (C) of the distal radius from a rheumatoid arthritis patient show extensive erosive change at medial aspect, which is seen as a clearly demarcated zone of hyperintense signal within normal hypointense marrow on MR image. Axial T2-weighted IDEAL FSE MR image (C) also demonstrates significant patchy hyperintense signal intensity of bone marrow edema.

Conclusion: HR-pQCT provides sensitive and highly reproducible evaluation of structural bone damage in RA. The good correlation between erosion measures with duration of the disease as well as BME volume suggests that they could become feasible measures of erosions in RA, if very detailed disease course evaluation are required.

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Magnetic Resonance Imaging Versus Dual Energy Computed Tomography for Detection of Joint Pathology in Gout.
Fiona M. McQueen[1], Anthony Doyle[1], Quentin Reeves[2], Angela Gao[2], Amy Tsai[2], Gregory Gamble[1], Barbara Curteis[1], Megan Williams[2] and Nicola Dalbeth[1]. [1]University of Auckland, Auckland, New Zealand, [2]Auckland District Health Board, Auckland, New Zealand

Background/Purpose: Magnetic resonance imaging (MRI) captures joint inflammation and damage in gouty arthropathy and can also reveal tophi. We have investigated reader reliability for scoring the MRI features of gout and have explored the association between erosions and tophi. We have also compared MRI with Dual Energy Computed Tomography (DECT) scans of the same region, to define sensitivity and specificity of MRI for tophi.

Methods: 3T MRI scans of the dominant wrist were obtained in 40 patients with severe, longstanding gout. The median/range patient age was 55.5 years (29–70), disease duration 17 years (1–42), serum urate 0.39mmol/L (0.2–0.69), 70% were of Polynesian/Maori ethnicity, and 85% had a history of tophi. All scans were scored separately (blinded) by 2 radiologist readers, for synovitis, bone oedema, erosions and tophi at 15 carpal sites including the bases of 1–5 metacarpals using RAMRIS criteria. Inter-reader reliability for scoring all features was determined. In a subgroup of 10 patients, DECT scans were obtained of the same region and scored by a separate reader for tophi at the same sites (or in adjacent soft tissue).

Results: Reliability was high between MRI readers for bone erosion and tophus size (ICCs 0.77 [95%CI: 0.71–0.87] and 0.71 [0.52, 0.83] respectively); and was moderate for synovitis and bone oedema (ICCs 0.62 [95%CI: 0.34–0.80] and 0.60 [0.36, 0.77] respectively). Concordance between readers for erosions was 82%, for all tophi was 85% and for tophi > 5mm was 93%. When a stringent analysis was performed (features were only counted if scored by both observers = "2-reader MRI"), 63% of patients were positive for bone erosions, 30% for bone oedema, 28% for tophi, 25% for tophi > 5mm and 61% for synovitis. The Odds ratio (OR) for tophus coexisting with erosion on MRI was 13.0 [95% CI: 1.5–113] when all sites were treated as independent and 2.9 [95% CI: 1.6–4.2] when the patient effect was factored in. When MRI and DECT scans from a subgroup of 10 patients were compared, using DECT as a gold standard, 2-reader MRI had a specificity of 0.98 [95% CI: 0.93–0.99], sensitivity of 0.63 [95% CI: 0.48–0.76], positive predictive value (PPV) of 94% and negative predictive value (NPV) of 84% for detecting tophi. There were only 2 instances in one patient where both MRI readers separately recorded tophus at a bone site where it was negative on DECT.
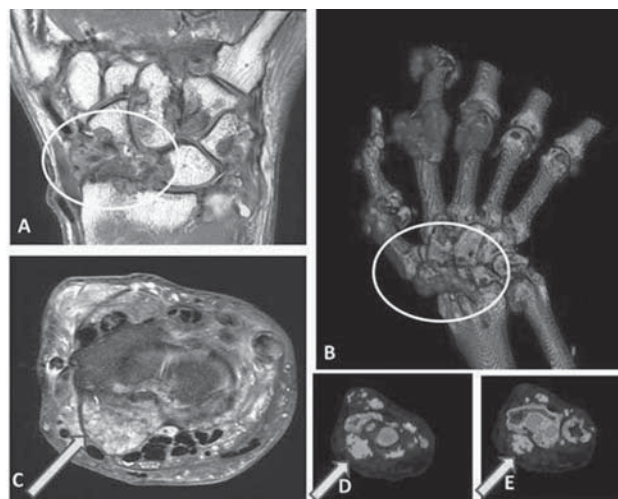
Figure. A) Coronal T1w MRI scan revealing extensive tophi dorsally at the radioscaphoid joint (circle). B) volume rendered DECT scan shows same tophus (circle) C) axial T1w MRI - tophus extends ventrally (arrow) D) axial DECT image shows same tophus (arrow) at level of the scaphoid and E) adjacent to the radius.

Conclusion: MRI has moderate to high reproducibility for assessment of gouty arthropathy and strong construct validity for detecting tophi when compared with DECT.

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Tendon and Ligament Involvement in Gout: A Dual Energy Computed Tomography Study. Nicola Dalbeth[1], Ramanamma Kalluru[2], Opetaia Aati[1], Fiona M. McQueen[1] and Anthony Doyle[1]. [1]University of Auckland, Auckland, New Zealand, [2]Department of Rheumatology, Auckland District Health Board, Auckland, New Zealand

Background/Purpose: The involvement of bone and joints is widely recognized in gout. However, soft tissue involvement is less well defined. Dual energy computed tomography (DECT) is a recently developed technology that enables detection of urate deposits. The aim of this study was to examine the frequency and patterns of tendon and ligament involvement in patients with gout using DECT.

Methods: Ninety-two patients with tophaceous gout had a study visit including DECT scan of both feet. Two readers scored the DECT scans for urate deposition at 20 tendon/ligament sites and 42 bone sites (total 1,840 tendon/ligament sites and 3,864 bone sites). For affected tendons and ligaments, involvement was recorded as entheseal and/or non-entheseal (entheseal involvement was defined as urate deposition at the point of tendon/ligament insertion into bone). Inter-reader agreement for involvement at tendon/ligament sites was 88.0% and Cohen's kappa was 0.58, and at bone sites was 94.7% and Cohen's kappa was 0.77. For a stringent analysis, urate deposition was considered present at each site only if reported by both readers.

Results: Urate deposition was observed in 199/1840 (10.8%) tendon/ligament sites and in 399/3864 (10.3%) bone sites (p=0.60). The Achilles tendon was the most frequently involved tendon/ligament site (39.1% all Achilles tendons), followed by the peroneal tendons (18.1%) (Figure). Tibialis anterior and the extensor tendons were involved less frequently (7.6–10.3%), and the flexor tendons, plantar fascia and deltoid ligaments were involved infrequently (<5%) (p<0.0001 between sites). In those 72 Achilles tendons with urate deposition, 27 (38%) had only non-entheseal involvement, 29 (40%) had both entheseal and non-entheseal involvement, and 16 (22%) had only entheseal involvement. In contrast, entheseal involvement was less frequent at the other 127 affected tendon/ligament sites; 102 (80.3%) had only non-entheseal involvement, 25 (19.9%) had both entheseal and non-entheseal involvement, and 0 (0%) had only entheseal involvement (p<0.0001 compared with Achilles tendon site).
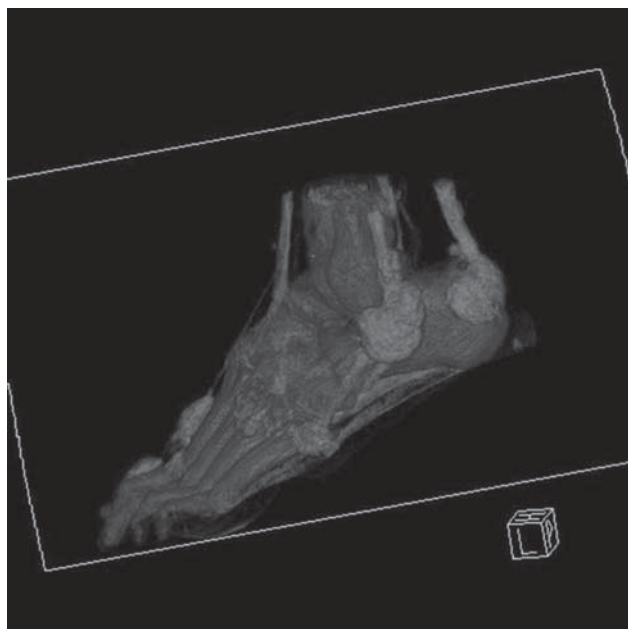
Figure. Volume rendered DECT image demonstrating urate deposition in the Achilles and peroneal tendons. Large adjacent tophi are present. Note normal tibialis anterior tendon.

Conclusion: Urate deposition is observed in tendon and ligament sites in patients with gout using DECT. The Achilles tendon and enthesis are major sites of involvement in gout. The patterns of urate deposition at certain tendon/ligament sites suggest that biomechanical strain or other local factors may contribute to formation of urate crystals.

2587

Practice Makes Perfect: Assessment of Proficiency of Rheumatology Fellows in Specific Joint Procedural Skills. Tara J. Rizvi, Min Xu and Nancy Searle. Baylor College of Medicine, Houston, TX

Background/Purpose: Rheumatology training programs require fellows to be proficient in joint procedural skills as a requirement for graduation. However, specific procedures required to attain proficiency in are not clearly defined. A minimum number required for performance of specific procedures to attain proficiency is also not established.

The purpose of our study is two-fold:

1. To gather rheumatology fellow's opinions about the number of times a joint procedure needs to be performed to attain proficiency.

2. To assess whether proficiency is attained by graduating fellows in 25 specific procedures generally performed by practicing rheumatologists.

Methods: An online survey was sent to junior and senior fellows enrolled in adult rheumatology programs in the United States. The survey was sent in April and May 2011, in order to obtain data from fellows near completion of their first or final year or fellowship. The survey included questions pertaining to: year of fellowship training, fellow's opinion of "average number of times a joint or soft tissue procedure should be performed in order to attain proficiency," and reported number of times fellows had performed 25 specific procedures during the course of fellowship training.

Results: Data was collected from senior fellows (n=76) near completion of fellowship training. 57/76 (75%) of graduating fellows felt individual joint procedures be performed 5 or more times to attain proficiency; 14/76 (18%) reported "3 times"; 5/76 (7%) answered "other" and felt it depended on the joint.

Based on the majority of fellow's views, we used "5" as the minimum number needed to attain proficiency. We identified that 6/25 procedures were performed 5 or more times by greater than 50% of graduating fellows (Table 1):): knee joint (98%), glenohumeral joint (57%), wrist joint (62%), ankle joint (60%), subacromial / subdeltoid bursa (74%) and trochanteric bursa (72%).

Table 1. Graduating rheumatology fellows having performed individual joint or soft tissue procedure 5 or more times

INDIVIDUAL JOINT PROCEDURE	PERFORMED >5 TIMES (n = 76)
Knee joint	74 (97%)*
Shoulder glenohumeral joint	43 (56%)*
Elbow joint	28 (37%)
Wrist joint	47 (62%)*
Ankle joint	46 (61%)*
Subtalar joint	7 (9%)
First MTP joint	24 (31%)
First carpometacarpal joint	16 (21%)
Finger Joint: DIP/PIP/MCP	15 (20%)
Hip joint	2 (3%)
Sacroiliac joint	0
Acromioclavicular joint	11 (14%)
Bicipital tendon	10 (13%)
Subacromial/ subdeltoid bursa	56 (73%)*
Trochanteric bursa	54 (71%)*
Ischigluteal bursa	2 (3%)
Olecranon bursa	26 (34%)
Pesanserine bursa	22 (29%)
Prepatellar bursa	13 (17%)
Lateral epicondylitis	17 (22%)
Medial epicondylitis	13 (17%)
Trigger finger	28 (37%)
DeQuervan's tenosynovitis	9 (12%)
Carpal tunnel	10 (13%)
Plantar fasciitis	3 (4%)

Conclusion: A substantial number of graduating fellows have not achieved the number needed to perform that most fellows themselves consider necessary to attain proficiency, in procedures commonly performed by practicing rheumatologists. The inadequacy of procedural exposure, and hence proficiency, can be circumvented by training authorities establishing specific, standardized criteria for rheumatology fellowship programs nationwide.

2588

Standardized Patient Simulation Improves Internal Medicine Resident Musculoskeletal Examination Skills. Floranne C. Ernste[1], Uma Thanarajasingam[1], Courtney Shourt[2], Andrew Halvorsen[3] and Furman S. McDonald[3]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic Rochester, Rochester, [3]Mayo Clinic, Rochester

Background/Purpose: Few studies have addressed use of simulation-based education (SBE) to teach musculoskeletal (MSK) medicine to Internal Medicine (IM) residents. Our purpose was to obtain IM resident confidence levels in ability to diagnose MSK disorders and observe MSK performance skills with use of SBE at a single, large academic center.

Methods: Participants were 68 first and third-year IM residents. Surveys were completed before and after SBE using a 9-point Likert scale, ranging from $1 =$ poor, $5 =$ average, and $9 =$ very good, to assess ability to confidently perform MSK exams and diagnose shoulder, hand/wrist, hip, and knee disorders. Baseline exams were performed on two standardized patients (SPs) and videotaped. These were scored using a three-point scale ($0 =$ not done; $1 =$ done, but not correctly; $2 =$ done correctly). An interactive lecture, self-demonstration of MSK exam, and participation with SPs in one or more scripted scenarios was provided. A debriefing session critiqued MSK exam skills. Post-SBE exams were performed with SPs and scored. Six month follow-up surveys assessed retention of confidence in MSK exam skills.

Results: Before intervention, mean (SD) rating of ability ranged from 4.4 (1.8) for pes anserine bursitis to 5.9 (1.6) for trochanteric bursitis, while confidence to perform MSK exams ranged from 4.3 (1.4) on the hand/wrist to 5.0 (1.5) on the knee. Following SBE, ratings of ability significantly improved, ranging from $+1.7$ (1.4) for trochanteric bursitis to $+2.6$ (1.5) for pes anserine bursitis and $+2.0$ (1.4) to $+2.3$ (1.5) for knee and hand/wrist exam, respectively (all p<.0001). Hip exams improved on inspection, gait, palpation, passive and active range of motion (ROM), strength testing, and provocative maneuvers (PM) (all p<.001). Hand/wrist exams improved on inspection, palpation, active ROM, strength testing, and PM (all p<.004), while passive ROM was unchanged (p=.31). Shoulder exams improved on palpation, passive and active ROM, strength testing, and PM (all p<.005), while inspection was unchanged (p=.02). Knee exams improved on inspection, gait assessment, palpation, active ROM, and strength testing (all p<.001), while passive ROM (p=.60) and PM (p=.07) were unchanged. Follow-up surveys completed 6 months post intervention by 32 eligible residents indicate durable ratings of ability, ranging from $+1.5$ (1.7) for patellofemoral pain syndrome to $+2.5$ (2.2) for de Quervain's tenosynovitis and $+2.0$ (1.4) to 2.3 (1.5) for knee and hand/wrist examination, respectively (all p<.0001).

Conclusion: Use of SBE significantly improved IM resident confidence in ability to perform MSK exams and diagnose common MSK disorders. Resident performance of MSK exams as judged by a trained evaluator also improved. Improved confidence in ability to diagnose common disorders and perform MSK exams were durable 6 months after intervention. Therefore, use of SBE is an effective way to teach MSK medicine to IM residents.

Disclosure: F. C. Ernste, None; **U. Thanarajasingam**, None; **C. Shourt**, None; **A. Halvorsen**, None; **F. S. McDonald**, None.

2589

From Novice to Expert: Competency Milestones for Musculoskeletal Ultrasound. Karina D. Torralba[1], Jay B. Higgs[2], Amy C. Cannella[3] and Gurjit S. Kaeley[4]. [1]Keck School of Medicine, University of Southern California, Los Angeles, CA, [2]San Antonio Military Medical Center, Fort Sam Houston, TX, [3]University of Nebraska Med Ctr, Omaha, NE, [4]University of Florida, Ponte Vedra Beach, FL

Background/Purpose: The Accreditation Council for Graduate Medical Education and the American Board of Internal Medicine have initiated the development of milestones for internal medicine (IM) residency training that would facilitate objective documentation of resident achievement of competence in six dimensions of practice. Milestones for IM subspecialties are now in development. Musculoskeletal ultrasound (MSUS) in Rheumatology is at its infancy, and not yet a fellowship requirement. However educators and fellows are encouraged to undergo training to acquire knowledge, skills and attitudes (KSA) in this field. The American College of Rheumatology has recently approved initiation of MSUS certification examination. The objective of this study was to develop milestones in the six dimensions of general practice in relation to usage of MSUS in Rheumatology.

Methods: A core group of educators (3 program directors, 1 associate program director) who are members of the Ultrasound School of North American Rheumatologists (USSONAR) adopted the 5-level Dreyfus model of skill acquisition as a framework for defining milestones and to describe progression of a learner: novice (level 1), advanced beginner (2), competent (3), proficient (4), expert (5). Level 3 is the minimum level considered competent to independently practice MSUS. A search of the medical and educational literature was done in order to define competency-specific KSA needing assessment, and to characterize for each level a behaviorally-based narrative description. The milestones were vetted by the group every two weeks by Skype and email over a period of six weeks. Consensus was reached so that each narrative description represented a continuum of training and practice that logically progressed in acquisition of KSA.

Results: Frameworks for the competencies of Medical Knowledge (MK) and Patient Care (PC) have been developed. While still related to general IM milestones, the milestones defined were more focused on MSUS-related KSA. The content areas content for each competency were clarified. For MK, core knowledge related to correlations between anatomy, pathology and MSUS image acquisition and interpretation were emphasized along with basic principles on usage of MSUS in general, performance of MSUS-guided procedures, and documentation of findings. For PC, the area of concern was the incorporation of MSUS as a tool to aid clinical skills and reasoning, and to assist in the delivery of patient-centered care. Using the 5-level Dreyfus model, a sequence of behavioral descriptions were provided that describe the development of a learner from a novice stage (level 1) to that of an expert (level 5). A review and summary of relevant literature and references were also developed.

Conclusion: The MSUS in Rheumatology milestones in the dimensions of MK and PC provide an initial and significant step towards a meaningful assessment of outcomes for rheumatologists who want to achieve minimum through higher levels of competency in MSUS. The core group hopes to soon develop milestones for the other competencies and subcompetencies, with further plans to validate these milestones across different training programs.

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2590

Consolidating Knowledge, Comprehension, Application and Analysis in Rheumatology Education by Use of an in-House Electronic Module (Web-based Rheumatology Case Scenarios). David A. Kandiah, Diana Jonas-Dwyer and Astrid Davine. University of Western Australia, Crawley, Australia

Background/Purpose: The teaching and learning resource "Rheumatology Case Scenarios" was created as a web-based module. This electronic module was produced to maximise the interactive learning opportunities for medical students.

The key educational outcomes of this module are the:
1. Recognition of common Rheumatic conditions
2. Utilisation of systematic pattern recognition to compare and contrast these rheumatic diseases
3. Organisation and interpretation of the most appropriate investigations.
4. Planning and implementation of the most appropriate treatment strategies
5. Systematic evaluation of a patient with joint pain
6. Evaluation of their learning by pre and post-test questionnaires

Methods: A questionnaire was developed that would test the outcomes above in a Multiple Choice Question format. Human Research Ethics approval was obtained prior to commencement of the study.

Results: 131 students completed the pre-test questionnaire in 2011. Their mean score for the module (maximum score 26) was 14.3 (SD 2.9, range 6–21). A histogram showed that the student scores were in a normal distribution. Students who had completed all 8 cases were then given a follow-up questionnaire with the same questions but randomised differently. The students who completed this questionnaire had a mean score of 17.4 (SD 3.5, range 11–22) Paired samples t-test of the students who had completed the 2 questionnaires confirmed a statistically significant improvement of the scores of each student (range 2–4 points, p<0.001). The answers for the questionnaire were only provided to the students after they had completed the second questionnaire. To test their retention of knowledge, students were also given the option of completing the same questionnaire 3 months later. Questions were randomised differently again and the mean score rose to 23. This was statistically significant for these students when compared to their

scores at both previous levels suggesting that there was retention of their knowledge.

Conclusion: Web-based resources can consolidate learning in the clinical arena. Student feedback was also positive. An educational blog was activated to highlight certain management issues.

Disclosure: **D. A. Kandiah**, None; **D. Jonas-Dwyer**, None; **A. Davine**, None.

2591

Assessment of Examination Skills of 4th Year Medical Students Using a Novel Objective Structured Clinical Examination. Seetha U. Monrad, Lisa DiPonio, Cliff Craig, John Zeller and R. Brent Stansfield. Univ of Michigan Med Ctr, Ann Arbor, MI

Background/Purpose: University of Michigan (UM) medical students participate in integrated musculoskeletal sequences during their preclinical years, but subsequently there are few opportunities for assessment of their diagnostic and physical examination skills. The purpose of this study was to evaluate the effectiveness of the longitudinal UM musculoskeletal curriculum in preparing graduates to evaluate patients with musculoskeletal disorders.

Methods: IRB exemption was obtained for this project. A multidisciplinary group of musculoskeletal specialists developed a three station objective structured clinical exam (OSCE) based on the "Hypothesis-Driven Physical Exam" (Yudkowsky, et al.) focusing on the shoulder, back and knee. 4[th]year students from the class of 2012 were invited to participate in the OSCE. For each station, students were provided a clinical vignette with three plausible diagnoses to consider, and were instructed to anticipate physical examination maneuvers or findings that would discriminate between the different diagnoses. They then examined a professional patient simulating findings associated with only one of the diagnoses. Trained faculty members directly observed students and scored performance of discriminatory physical examination maneuvers for each station. Each encounter was videotaped and independently scored by another faculty member. Inter-rater reliability for each maneuver was estimated using type-2 intra-class correlations. Percentages of perfect scores for anticipation (A) and performance (P) of each maneuver were calculated. Pearson's correlation between A and P scores was computed for each maneuver.

Results: 30% of the graduating class of 2012 participated. Inter-rater reliability was good to excellent for scoring of 6 exam maneuvers: herniated disc (disc ICC =.81), sacroiliac dysfunction (sac. ICC =.85), shoulder impingement (imp. ICC =.69), glenohumeral arthritis (arth. ICC =.76), anterior cruciate ligament tear (acl. ICC =.87), and knee osteoarthritis (ost. ICC =.87). Rater scores were averaged for each student. For the shoulder and knee stations, students could anticipate the necessary discriminatory exam maneuver for each diagnosis more frequently than they could actually perform the maneuver: (disc r =.45, p <.005, sac. r =.67, p <.0001; imp. r =.38, p <.025; arth. r =.32, p <.05; ost. r =.33, p <.05). A notable exception was the ability to perform maneuvers needed to diagnose a torn anterior cruciate ligament (ACL r =.05, n.s.).

Conclusion: A substantial percentage of graduating UM M4s are not able to perform core examination skills needed to diagnose common disorders of the shoulder, back and knee. Accurate anticipation of a discriminatory exam maneuver correlates with ability to perform the maneuver; however, students were more able to anticipate maneuvers than to actually perform them. Thus, direct observation is critical to ensure competence of students in evaluating musculoskeletal disorders.

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2592

Musculoskeletal Ultrasound Objective Structured Clinical Examination: An Assessment of the Test. Eugene Y. Kissin[1], Peter C. Grayson[2], Amy C. Cannella[3], Amy M. Evangelisto[4], Janak R. Goyal[5], Rany Al Haj[6], Jay B. Higgs[7], Daniel G. Malone[8], Midori Jane Nishio[9], Darren Tabechian[10] and Gurjit S. Kaeley[11]. [1]Boston University, Boston, MA, [2]Boston University Medical Center, Boston, MA, [3]University of Nebraska Med Ctr, Omaha, NE, [4]Arthritis, Rheumatic and Back Disease Associates, Voorhees, NJ, [5]Raritan Bay Medical Center, Perth Amboy, NJ, [6]Jersey Shore Arthritis & Rheumatism A, Ocean, NJ, [7]San Antonio Military Medical Center, Fort Sam Houston, TX, [8]Family & Sports Orthopaedic Center, Beaver Dam, WI, [9]Adjunct Assistant Professor of Medicine/ Stanford University, Walnut Creek, CA, [10]Univ of Rochester Schl of Med, Rochester, NY, [11]University of Florida, Ponte Vedra Beach, FL

Background/Purpose: There is debate about whether an objective structured clinical examination (OSCE) should be part of musculoskeletal ultrasound (MSUS) competency testing in MSUS, and the reliability and validity of this approach has not been established. We aim to determine the reliability and validity of an OSCE for MSUS.

Methods: A 9-station OSCE was administered to a group of 35 rheumatology fellows, following an 8 month training program in MSUS, and to 3 expert faculty members as a control group. The participants were unaware of whether the joints were abnormal (n=5; wrist, ankle, elbow, finger, toe) or normal (n=4; wrist, ankle, knee, shoulder). Expert faculty in MSUS (n=9) graded image quality at OSCE stations using a predefined checklist and global rating (0–5 scale where 2 is barely passing) as both **proctors** and **assessors**. At each station a **proctor witnessed and graded** the studies being performed. Later, each resulting ultrasound image was also graded by two **assessors blinded to who performed the study.** Identical assessors graded the normal and abnormal wrist and ankle stations. Inter-rater reliability for assessors and proctors was estimated using the intraclass correlation coefficient (ICC). The borderline group method was used to set the overall passing score. A summative, 76 item multiple choice test (MCQ) assessed fellow knowledge necessary to interpret ultrasound images. Correlation between MCQ and OSCE performance (concurrent validity) was assessed using the Pearson correlation coefficient. Construct validity was established by comparing fellow OSCE results with that of the faculty (gold standard).

Results:
Reliability

Inter-rater reliability was good (ICC=0.7) between the assessors, but was poor (ICC=0.3) between the assessors and the proctors. Reliability of the assessor scores was good in the normal wrist and ankle stations (ICC=0.7), and moderate in the abnormal wrist and ankle stations (ICC=0.4).

Validity

MCQ grades correlated strongly with OSCE grades from both the assessors (r=0.52; p=<0.01) and from the proctors (r=0.58; p<0.01). The average MCQ score for the 5 fellows who failed the OSCE was less than that for the 30 who passed (60% vs. 71%, p= 0.04, Wilcoxon rank sum).

The fellows in the bottom quartile of the MCQ scored 3.07 on the OSCE, significantly worse than the top quartile fellows (3.32), and the faculty (3.29) (p<0.01, Wilcoxon signed rank). Scores also significantly discriminated bottom quartile fellows from faculty in the normal wrist and ankle stations (3.38 vs. 3.78, p<0.01), but not in the abnormal stations (3.37 vs. 3.49, p=0.08).

Conclusion: MSUS OSCE is a reliable and valid method for evaluation of MSUS skill when assessed by blinded examiners. Proctor grading is less reliable and adds to the cost of a practical MSUS examination. Normal joint assessment stations are more reliable than abnormal joint assessment stations and better discriminate poorly performing fellows from faculty, likely because assessors are less certain about the optimal appearance of abnormal joints and have more difficulty accurately scoring the resulting images.

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ACR Concurrent Abstract Session
Pediatric Rheumatology: Clinical and Therapeutic Disease IV:
Childhood Therapeutics and Response
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

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Predictive Markers of Therapeutical Outcome and Their Role in the Ethiopathology of Juvenile Idiopathic Arthritis. Maura Rossetti[1], Roberto Spreafico[1], Hong Zhang[1], Maryam Moshref[1], Nora G. Singer[2], D. J. Lovell[3], Carol A. Wallace[4] and Salvatore Albani[1]. [1]Sanford-Burnham Medical Research Institute, La Jolla, CA, [2]MetroHealth Medical Center, Cleveland, OH, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]Seattle Childrens Hospital, Seattle, WA

Background/Purpose: Currently, juvenile idiopathic arthritis (JIA) is treated with methotrexate (MTX) as a first-line agent. If children fail to respond, a biologic (e.g. anti-TNF) is usually added. However, a consistent fraction of patients fail to respond even to the combination treatment. The identification of predictive markers of responsiveness to the therapy, together with the elucidation of the underlying mechanism, is therefore a dramatic unmet clinical need. Our approach is based on the premise that complex

diseases like JIA can be stratified based on the presence of multi-parametric signatures which characterize an immune function.

Methods: We have developed a multidimensional technology platform for identifying immune signatures, which includes phenotypical and functional data on a variety of blood cell types (T and B cells, APCs, NK and NKT cells, gdT cells). These tests operate in semi-high throughput (sHT) mode and can be combined with other HT "omics". This platform has been applied to a homogenous cohort of patients from the Trial of Aggressive Therapy (TREAT), including patients treated with the same iTNF (Etanercept) and MTX, sampled before (T0) and after (Tend) the therapy, and subsequently stratified in patients reaching inactive disease state, and patients not achieving ID.

Results: When Teff and Treg functions (proliferation and suppression assays) were analyzed as a whole, we could not find significant changes between ID and NO ID. However, in depth characterization of the two cell subsets led to the identification of specific phenotypical differences at both time points analyzed. When a principal component analysis was applied to the entire set of parameters analyzed, the group of responding (ID, inactive disease) patients clustered and was clearly distinct from non-responding (NO ID) patients. Three different statistical models were applied to test whether selected candidate biomarkers could segregate patients according to their clinical outcome. Strikingly, although most parameters, taken singularly, were not effective in differentiating between the two disease states, the combination of a restricted set of CD4$^+$ T cell markers was able to segregate ID and NO ID patients with up to 90% accuracy in both time points, thus providing both predictive and confirmatory value to the study. Moreover, our analysis identified a population of cells characterized by an activated phenotype which is significantly more represented in the NO ID patients. This subset selectively expressed pro-inflammatory markers and chemokine receptors targeting to inflammatory sites, and bore signs of recent antigen recognition (based on Ki67 expression), possibly indicating their direct involvement in autoimmunity.

Conclusion: We have identified a cluster of immune functions with high predictive and prognostic power for discriminating the responsiveness to treatment with MTX/iTNF in JIA, which may be developed as a theragnostic tool. Importantly, our approach has also identified a subset of experienced T cells, significantly more represented in clinical failures, which may comprise a potentially pathogenic population responsible for the resistance to treatment.

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Epigenetic Signature of the Response to Anti-TNF in Juvenile Idiopathic Arthritis. Roberto Spreafico[1], Maura Rossetti[1], Hong Zhang[1], Maryam Moshref[1], Carol Wallace[2], D. J. Lovell[3] and Salvatore Albani[1]. [1]Sanford-Burnham Medical Research Institute, La Jolla, CA, [2]Childrens Hosp & Regional Med, Seattle, WA, [3]Cincinnati Children's Hospital, Cincinnati, OH

Background/Purpose: The identification of prognostic markers of responsiveness to the therapy in JIA would not only radically improve clinical management, but also shed light on the immune mechanisms underlying clinical outcomes, with the potential of improving and eventually personalizing clinical care. In this context, adaptive immunity plays a central role. Indeed, it is well known that CD4$^+$ T cells are implicated in the pathogenesis of different subtypes of arthritis, including JIA. Many studies have relied on the use of whole transcriptome analysis to identify new biomarkers and get insights into the disease mechanisms. However, transcriptomes are volatile, quickly fluctuating in response to multiple factors, often clinically irrelevant. By contrast, epigenetics is more stable, possibly capturing only those changes slowly introduced by regular and consistent events such as therapy. As such, here we aimed at investigating the DNA methylation profile of JIA patients responding or not to therapy.

Methods: Patients treated with MTX+Etanercept+Prednisolone from the TREAT study were stratified based on the response to the therapy. Total CD4$^+$ T cells were sorted from PBMCs at baseline (T0) and at end of study (Tend). DNA was extracted and bisulfite converted to analyze the cytosine methylation pattern. Converted DNA was analyzed using Illumina Infinium HumanMethylation450 BeadChip, yielding the methylation percentage of more than 485,000 CpG sites across the genome.

Results: Both hypothesis-driven and hypothesis-agnostic approaches were pursued. In hypothesis-driven approaches, DNA methylation of genes governing immune functions, which our group has identified as correlated to clinical outcome, was investigated. In hypothesis-agnostic approaches, no assumptions were made and the most relevant sites were selected by computational methods. In both scenarios, descriptive and predictive models were built to test the diagnostic value of the identified epigenetic signature, which, in some cases, could reach an accuracy close to 100%. In preliminary analyses, we found that, regardless of the approach taken, the HLA-DRB1 gene is differentially metilated between responders and non responders. This finding is striking in correspondence with our recent data obtained though an high-throughput Immunomics approach, which also evidenced higher HLA-DR expression on CD4$^+$ T cells in clinical non-responders at phenotypical level (manuscript in preparation).

Conclusion: In summary, we have identified a set of genes with high predictive and prognostic power for discriminating the responsiveness to treatment, which may be developed as a screening tool. Importantly, some of the differentially methylated genes identified through whole genome DNA methylation analysis correlate with phenotypical and functional changes previously described by our group, strongly putting forward further investigation of the functional role of HLA-DRB1 expression on CD4$^+$ T cells.

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S100A12 At Baseline May Be Useful for Predicting Inactive Disease within 12 Months in Polyarticular Juvenile Idiopathic Arthritis. Gali Malul[1], Joy M. Whitbred[1], MaryAnn O'Riordan[2], Sarah Ringold[3], Susan D. Thompson[4], Carol Wallace[5], Salvatore Albani[6] and Nora G. Singer[7]. [1]MetroHealth Medical Center, Cleveland, OH, [2]Case Medical Center, Cleveland, OH, [3]Seattle Children's Hospital, Seattle, WA, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Childrens Hosp & Regional Med, Seattle, WA, [6]Sanford-Burnham Medical Research Institute, La Jolla, CA, [7]Director, Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH

Background/Purpose: Achieving clinically inactive disease (ID) is a therapeutic goal in JIA. ID is defined as: no active arthritis; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy due to JIA; no active uveitis; normal ESR; and physician global assessment=0. The laboratory parameters routinely used to describe patients' JIA category include antibody status (RF, anti-CCP). ESR or CRP are frequently used to assess disease activity. The S100 proteins have been implicated as biomarkers of JIA and in disease pathogenesis. The pro-inflammatory ligand S100A12 binds to RAGE and studies suggest a relationship between S100A12 and both sJIA and RA disease activity. The S100A12 gene is rapidly up-regulated in monocytes and PMNs in inflammation and may be a biomarker for poly JIA activity as well.

The objectives of this study were to evaluate the utility of baseline S100A12 levels in as a predictor of ID in poly JIA ID within 12 months, and to determine association between S100A12, RF, CCP and ESR.

Methods: S100A12 level was measured by ELISA in biospecimens from the Trial of Aggressive Therapy in JIA (TREAT) for whom baseline samples were available.The distribution of S100A12 in healthy children without JIA was determined on the log scale. The 95thpercentile was estimated. This value was used as a cut-point: below the values were classified as "low" and above as "high". The baseline values of the JIA cohort were then dichotomized the same way. RF, anti-CCP, and ESR were dichotomized as "Positive" or "Negative": RF/CCP-<20 negative and ≥20 positive, ESR ≥20 was considered elevated;. Disease status (ID or no ID) was compared to S100A12 levels and positive and negative predictive values (PPV and NPV respectively) are reported. The relationship of levels S100A12 and of ID status with the levels of the other variables was tested using Chi squared analysis with levels of other markers and p values for association reported.

Results: 53 children from TREAT had baseline S100A12 values. 44 achieved ID and 9 did not within the first 12 months of treatment. S100A12 95thpct of the control population was estimated as 6.2 on the log scale (anitlog 493). 21 children had "High" S100A12 values, all of which were in the ID group (PPV 100%). 32 children had low values, 9 were in the no ID group (NPV 28%).

53 had baseline S100A12 measurement and known RF status, 21 had elevated and 32 had low S100A12: 11/21 and 3/32 had positive RF (p<0.001).

53 had ESR measured, 21 had high and 32 had low S100A12. 18/21 and 14/32 also had high ESR (p=0.002).

50 children had baseline S100A12 measurement and known CCP ab status. 18 had elevated and 32 had low S100A12 values: 9/18 and 4/32 had anti-CCP ab detected (p=0.004).

Conclusion: The PPV value of an elevated baseline S100A12 value for the probability of achieving ID in the first 12 months in TREAT was 100%. Elevation in S100A12 was highly associated with the presence of anti-CCP ab, RF positivity and elevated ESR. Since even polyJIA is a heterogenous disease, the data suggest that measurement of S100A12 may help guide understanding and treatment of disease.

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Rituximab Treatment for Antineutrophil Cytoplasmic Antibody - Associated Vasculitis in Children. Katharine F. Moore[1], Leonard L. Dragone[2], Jennifer B. Soep[3] and J. Roger Hollister[3]. [1]Seattle Children's Hospital/University of Washington, Seattle, WA, [2]National Jewish Health, Denver, CO, [3]Children's Hospital Colorado, Aurora, CO

Background/Purpose: The purpose of this study was to report the experience of a tertiary-care children's hospital using rituximab in the treatment of pediatric antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including immediate and long-term outcomes as well as adverse effects.

Methods: This was a single-center retrospective case series of 15 children with AAV treated with rituximab between March 2001 and March 2011. The majority of patients presented with severe disease, including acute pulmonary hemorrhage, and were treated with cyclophosphamide (CYC) and high-dose glucocorticoids (GC) concomitantly with rituximab (n=11); of these patients, six also required plasma exchange. Other treatment regimens given with rituximab included CYC alone (n=1), methotrexate (MTX) with GC (n=2) and MTX alone (n=1). Outcome measures included time to negative ANCA, the length of CYC therapy after starting rituximab, total cumulative CYC dose, scores on the modified Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) as well as the Vasculitis Damage Index (VDI).

Results: Of the 15 identified patients, the median age at diagnosis was 13 (range 8–15). Seven were female. At the time of treatment with rituximab, the mean score on the BVAS/WG was 7.8 (range 1–12), with 11 patients (73%) classified as having severe disease. Three months after treatment with rituximab, the mean score dropped to 0.4 (range 0–2). Every one of the patients in this series ultimately achieved remission, defined as a BVAS/WG of zero along with a reduction in steroid dosage. Nine patients (60%) received only one course of rituximab and did not experience any relapses over a mean follow-up of 2.3 years. Following treatment with rituximab, the mean duration of CYC therapy was 11.3 weeks (range 4–28 weeks), with a mean cumulative CYC dose of 11g. The mean cumulative CYC dose received by patients who were initially treated without rituximab was 44 g prior to the addition of rituximab and was 62 g over the entire duration of illness captured by this study. In contrast, the cumulative CYC dose received by patients who received rituximab with CYC and GC for initial induction was only 8.6 g. The average length of patient follow-up after treatment with rituximab was 2.5 years (range 3 months–5.1 years); during this time, five patients were re-treated with rituximab due to a flare in disease activity occurring at a mean of 21.8 months after the last rituximab treatment. Adverse effects from rituximab included six mild infusion reactions. There were no deaths. There were no documented infectious complications.

Conclusion: This is the largest described series of pediatric patients with AAV treated with rituximab and includes a significant duration of follow-up. Our data show that rituximab can be a safe and effective therapy, even in combination with other immunosuppressive medications such as CYC and GC. This regimen allows patients to have decreased cumulative dose of CYC, thus minimizing the potential for long-term adverse effects of CYC.

Disclosure: K. F. Moore, None; **L. L. Dragone**, None; **J. B. Soep**, None; **J. R. Hollister**, None.

2597

Degree of Initial Intracellular Folate Depletion May Predict Methotrexate Response in Juvenile Idiopathic Arthritis. Leon van Haandel[1], Ryan S. Funk[1], Maria F. Ibarra[1], Mark F. Hoeltzel[1], Andrew Lasky[2], Daisy Dai[1], Rodger Gaedigk[1], J. Steven Leeder[1] and Mara L. Becker[1]. [1]Children's Mercy Hospital, Kansas City, MO, [2]Childrens Mercy Hospital, Kansas City, MO

Background/Purpose: Despite widespread use, there are no predictors of methotrexate (MTX) response or toxicity. The objective of this study is to test the hypothesis that the variability in response to MTX is a function of inter-individual differences in folate homeostasis.

Methods: This is a single center prospective cohort study at a tertiary care children's hospital evaluating newly treated JIA patients on standardized doses and routes of MTX ($15mg/m^2$ PO) and folic acid (1mg/day). After obtaining informed consent, samples are collected prior to, and after 3 and 6 months of MTX. Concentrations of tetrahydrofolate (THF), 5-methylTHF (5-MTHF), 5,10-methenylTHF (5,10-METHF), folic acid (FA), and MTX polyglutamates ($MTXGlu_n$) are determined in plasma, whole blood and erythrocytes by UPLC-tandem mass spectrometry. Clinical data are recorded from chart review and forms provided to the treating physician and patient/parent (CHAQ, MD VAS, PT VAS). Clinical outcomes at 3 months were measured via ACR pediatric 30, 50, 70 criteria and the JADAS71. We report preliminary 3 month data on the first 20 patients recruited to the study.

Results: The study consisted of 12 females and 8 males with JIA. The mean ($\pm$ SD) age at study entry was 135.2 ($\pm$ 49.5) months. After 3 months on standardized MTX therapy, paired t-test revealed an overall statistically significant decline in MD VAS ($p < 0.0001$), PT VAS ($p < 0.001$), active joint count ($p = 0.002$), JADAS71 ($p < 0.001$), and 5-MTHF concentrations ($p= 0.004$). There were no statistically significant differences in CHAQ, ESR, CRP, or 5,10-METHF from 0–3 months on therapy. These results were confirmed with additional nonparametric testing. At 3 months, 8 (40%) subjects failed to reach ACR Ped 30 ("non-responders"), while 10 (50%) subjects reached ACR Ped 30 or 50, and 2 (10%) reached ACR Ped 70 ("responders").

The mean decline from baseline of 5-MTHF concentrations at 3 months was found to be significantly greater in boys (-420.8 nmol/L), compared to girls (-122.9 nmol/L) ($p=0.03$), and negatively correlated with age ($\rho=-0.7$, $p=0.0006$). A trend towards greater changes in 5-MTHF concentrations from baseline were observed in responders (-333.3 nmol/L) compared to non-responders (-105.1 nmol/L) ($p=0.07$). No statistically significant differences were seen in absolute 5-MTHF concentrations at 0 or 3 months and ACR outcomes, although responders had comparatively higher 5-MTHF concentrations (885.3 nmol/L vs. 666.2 nmol/L, p NS) at baseline. Multivariate testing supported an association between change in 5-MTHF and response ($p=0.05$) controlling for gender and age. Two subjects had exceptionally high 5,10-METHF concentrations ($>4\times$ IQR). Omitting the outliers revealed a pronounced change in 5-MTHF in responders ($p=0.04$). No association between long chain MTXGlu and outcomes or change in folate concentrations has been observed to date.

Conclusion: These preliminary data suggest that an initial decline in 5-MTHF concentrations may be correlated to MTX response, and might provide clinicians with a more effective biomarker than intra-cellular concentrations of the drug itself in JIA. Future work will investigate factors that contribute to 5-MTHF depletion.

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2598

Anti-Drug Antibodies Are Associated with Diminished Drug Levels and Treatment Failure. Miha Kosmac[1], Natasa Toplak[2], Gabriele Simonini[3], Ilaria Pagnini[3], Rolando Cimaz[4], Vladka Curin Serbec[1] and Tadej Avcin[4]. [1]Blood Transfusion Centre of Slovenia, Ljubljana, Slovenia, [2]University Children's Hospital Ljubljana Slovenia, Ljubljana, Slovenia, [3]Anna Meyer Children's Hospital, Department of Pediatrics, University of Florence, Florence, Italy, [4]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy

Background/Purpose: Due to their proteinaceus character biologics can often induce an unwanted immune response that results in the formation of anti-drug antibodies in patients receiving biologic therapy. We therefore analyzed the sera of juvenile idiopathic arthritis patients receiving either

infliximab (IFX), adalimumab (ADA) or etanercept (ETA) for the presence of anti-IFX, anti-ADA and anti-ETA antibodies.

Methods: We determined the serum drug levels and anti-drug antibody levels in the sera of 26 patients on IFX, 12 patients on ADA and 19 patients on ETA therapy. In the cases where we detected the presence of anti-drug antibodies we also investigated whether these antibodies bind the Fab or Fc fragments and compared laboratory findings with the clinical response to therapy.

Results: We detected anti-drug antibodies in 11 out of 26 (42%) patients on IFX and 4 out of 12 (33%) patients on ADA therapy, but found no anti-ETA antibodies in any of the 19 patients treated with ETA. Anti-drug antibodies were in all cases associated with decreased serum drug levels, which in the majority of cases were below the limit of detection. For the two monoclonal antibody drugs (IFX and ADA) we observed that the anti-drug antibodies bound the Fab fragments, i.e. the regions responsible for TNF binding.

Conclusion: The level of immunogenicity for patients receiving biologic therapy closely followed the degree of foreignness of the biologic drugs, with IFX inducing the formation of anti-IFX antibodies in the highest proportion of patients, followed by ADA, while ETA did not induce the formation of anti-ETA antibodies in any of the patients included in our study. Once anti-drug antibodies had developed they were in all cases associated with decreased serum drug levels, however not all non-responders showed low serum drug levels or tested positive for anti-drug antibodies, indicating a different disease mechanism. Monitoring of serum drug levels and the detection of anti-drug antibodies may therefore be important for determining the best personalized treatment strategy and enabling a more cost effective treatment.

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ACR Concurrent Abstract Session
Quality Measures and Innovations in
Practice Management and Care Delivery
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

2599

Quality of Care for Medicare Recipients with Rheumatoid Arthritis: Vulnerable Populations More Likely to Receive Therapy with Glucocorticoids Alone. Chris Tonner[1], Gabriela Schmajuk[1], Amal N. Trivedi[2], Grace Lin[3] and Jinoos Yazdany[3]. [1]UCSF, San Francisco, CA, [2]Brown University, Providence, RI, [3]University of California San Francisco, San Francisco, CA

Background/Purpose: Use of disease-modifying anti-rheumatic drugs (DMARDs) is a nationally endorsed quality measure, yet recent studies suggest that only 60% of Medicare recipients with rheumatoid arthritis (RA) use DMARDs. We investigated the prevalence and predictors of receiving glucocorticoids alone for the treatment of RA in a nationwide sample of Medicare beneficiaries.

Methods: Data derive from a 5% random sample of U.S. Medicare fee-for-service beneficiaries. We included individuals ≥65 years with at least two face-to-face clinical encounters for RA and Part D drug claims for either a DMARD anytime during the year or sustained glucocorticoid monotherapy, defined as an annual dispensed glucocorticoid supply of ≥180 days or an annual dispensed dosage of ≥900 mg of prednisone (or steroid equivalent). Using multivariate logistic regression, we examined predictors of sustained glucocorticoid monotherapy including sociodemographic characteristics, income (low-income defined as Medicare eligible for reduced cost sharing or state buy-in), health service utilization (number of inpatient and outpatient encounters and prescribing physician specialty) and medical co-morbidities. In addition, we used the Area Resource File to examine area level predictors of socio-economic status, health care shortage areas, and Census geographic divisions. From the regression models, we calculated adjusted group proportions and 95% confidence intervals.

Results: Of the 8,062 beneficiaries, 10% (n = 830) were classified as receiving glucocorticoid monotherapy. In adjusted analyses, we found that glucocorticoid monotherapy was higher among those with advanced age (18% among those ≥85 years compared to 11% in those 74–79 years), Blacks (12% versus 10% in Whites), and among low-income beneficiaries (12% versus 10% in those with higher incomes). Having a rheumatologist prescribe one or more medications during the measurement year was associated with significantly lower rates of glucocorticoid monotherapy (7%

versus 16%). More inpatient admissions and medical co-morbidities were also positively associated with glucocorticoid monotherapy. There was little variation across the nation, with marginally higher rates of glucocorticoid monotherapy in the Middle Atlantic region (13%) compared to the Pacific region (8%).

Table 1. Proportion of U.S. Medicare Fee-for-Service Beneficiaries Receiving Sustained Glucocorticoid Monotherapy for Rheumatoid Arthritis in 2009

	N = 8,062	Unadjusted proportion of sustained monotherapy prednisone use % (95% CI)	p	Adjusted* proportion of sustained monotherapy prednisone use % (95% CI)	p
Age			<.0001		<.0001
65–69	1858	0.06 (0.05, 0.08)		0.07 (0.06, 0.08)	
70–74	2171	0.08 (0.06, 0.09)		0.08 (0.07, 0.09)	
75–79	1791	0.10 (0.09, 0.12)		0.11 (0.09, 0.12)	
80–84	1375	0.14 (0.12, 0.15)		0.13 (0.11, 0.15)	
85 and older (reference)	867	0.20 (0.17, 0.22)		0.18 (0.15, 0.20)	
Race			<.01		<.01
White (reference)	6,849	0.10 (0.09, 0.11)		0.10 (0.10, 0.11)	
Black	692	0.13 (0.03, 0.16)		0.12 (0.09, 0.14)	
Other	521	0.08 (0.06, 0.10)		0.07 (0.05, 0.09)	
Personal income			<.0001		<.001
Not low	6,149	0.09 (0.09, 0.10)		0.10 (0.09, 0.10)	
Low	1,913	0.13 (0.12, 0.15)		0.12 (0.11, 0.14)	
Had 1 + Rx prescribed by rheumatologist			<.0001		<.0001
No	2,587	0.17 (0.16, 0.19)		0.16 (0.15, 0.18)	
Yes	5,475	0.07 (0.06, 0.08)		0.07 (0.07, 0.08)	
Charlson Score			<.0001		<.05
Score = 1 (reference)	5,476	0.09 (0.08, 0.10)		0.10 (0.09, 0.11)	
Score > 1 and <= 1.5	1,675	0.11 (0.10, 0.13)		0.10 (0.09, 0.12)	
Score > 1.5	929	0.15 (0.13, 0.18)		0.13 (0.11, 0.15)	
Inpatient admissions			<.0001		<.0001
None	6,250	0.09 (0.08, 0.10)		0.09 (0.08, 0.10)	
One	1,190	0.13 (0.11, 0.15)		0.12 (0.11, 0.14)	
Two or more	622	0.19 (0.16, 0.22)		0.17 (0.14, 0.20)	
Census Geographic Divisions			<.01		<.05
New England	421	0.11 (0.08, 0.14)		0.11 (0.08, 0.14)	
Middle Atlantic	1,004	0.14 (0.12, 0.17)		0.13 (0.11, 0.15)	
East North Central Midwest	1,163	0.10 (0.09, 0.12)		0.11 (0.10, 0.13)	
West North Central Midwest	750	0.09 (0.07, 0.11)		0.09 (0.07, 0.11)	
South Atlantic	1,645	0.11 (0.09, 0.12)		0.10 (0.09, 0.12)	
East South Central	607	0.09 (0.07, 0.11)		0.09 (0.06, 0.11)	
West South Central	1,045	0.09 (0.08, 0.11)		0.10 (0.08, 0.11)	
Mountain	473	0.08 (0.06, 0.10)		0.08 (0.06, 0.11)	
Pacific (reference)	954	0.09 (0.07, 0.11)		0.09 (0.07, 0.11)	
C statistic				0.71	

* Multivariable model adjusted for all variables in the model as well as gender, number of physician visits, number of inpatient admissions, area poverty, and health professional area shortages.

Conclusion: Approximately 10% of Medicare recipients with RA were treated with sustained courses of glucocorticoids alone in 2009. Compared to DMARD users, glucocorticoid monotherapy users were older, more likely to be Black, had lower income, had more medical comorbidities and hospitalizations, and were less likely to have a rheumatologist prescribing their RA medication. Although advanced age and accompanying medical co-morbidities may appropriately limit the use of DMARDs, differences by race, income and geographic region suggest disparities in quality of care.

Disclosure: C. Tonner, None; **G. Schmajuk**, None; **A. N. Trivedi**, None; **G. Lin**, None; **J. Yazdany**, None.

2600

Assessment of Quality of Care for Incident Lupus Nephritis in the U.S. Medicaid Population. Jinoos Yazdany[1], Candace H. Feldman[2], Jun Liu[3], Michael M. Ward[4], Michael A. Fischer[2] and Karen H. Costenbader[5]. [1]University of California San Francisco, San Francisco, CA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, Boston, MA, [4]NIAMS/NIH, Bethesda, MD, [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: The contribution of uneven health care quality to racial/ethnic and socioeconomic disparities in lupus nephritis outcomes is unknown. We aimed to assess performance on two health care quality

measures in a nationwide cohort of Medicaid recipients with incident lupus nephritis.

Methods: We used Medicaid analytic extract (MAX) data from 2000–2004 containing person-level files on Medicaid eligibility, utilization and payments. We identified patients meeting a validated administrative data definition of incident lupus nephritis, and used this group as the denominator population for both quality metrics (QMs). Numerator components included:

QM1: Induction therapy with glucocorticoids and another immunosuppressant (azathioprine, mycophenolate mofetil, mycophenolic acid, cyclophosphamide, cyclosporine A, or tacrolimus) within 30 days of lupus nephritis onset.

QM2: Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB) within 90 days of lupus nephritis onset.

We used multivariate logistic regression models to examine sociodemographic (age, sex, race/ethnicity), geographic (U.S. region), and health care (health professional shortage areas, HPSAs, from the Area Resource File) predictors of higher performance. In additional analyses, we extended the time period for both QMs to 365 days to assess whether performance improved with time.

Results: 974 Medicaid recipients met the definition of incident lupus nephritis. Mean age was 39 years (SD 12, range 18–64), 93% were female, and most were African American (African American 48%, White 27%, Hispanic 13%, Asian 6%). Individuals were geographically dispersed (20% Midwest, 22% Northeast, 34% South, 24% West), and 41% resided in partial or complete HPSAs. Only 19.5% received care consistent with all numerator components of QM1; 25% of individuals received only steroids, and 13% received immunosuppressants alone. When the timeframe for QM1 was extended to one year, performance rose to 30%. For QM2, 30% of individuals received an ACE/ARB within 90 days. When this timeframe was extended to one year, performance rose to 58%. In multivariate logistic regression models, those living in the South were less likely to receive recommended therapy for lupus nephritis (QM1; OR 0.53, CI 0.28–0.99), while younger individuals were more likely to receive treatment (OR for 18–34 years versus referent 51–64 years 3.5, CI 1.6–7.6). Individuals in the Midwest were less likely to receive an ACE/ARB (QM2; OR 0.52, CI 0.34–0.80), while African Americans were more likely (OR 1.7, CI 1.2–2.4).

Conclusion: These data suggest substantial gaps and delays in care for U.S. Medicaid patients with incident lupus nephritis. A large number received steroid monotherapy or no immunosuppressant within one month, although performance improved by one year. Use of ACE/ARBs was low in the first 90 days, but rose to 58% by one year. Geographic differences were observed, with individuals in the South and Midwest being less likely to receive recommended care. The contribution of state Medicaid policies, specialty care access, and drug coverage policies to these observed geographic differences warrants investigation.

Disclosure: **J. Yazdany**, None; **C. H. Feldman**, None; **J. Liu**, None; **M. M. Ward**, None; **M. A. Fischer**, None; **K. H. Costenbader**, None.

2601

Improving Delivery of Care for JIA Across a Multi-Center Network Using a Shared Data Registry and Quality Improvement Science: The Pediatric Rheumatology Care and Outcomes Improvement Network.
Catherine A. Bingham[1], Lynn M. Darbie[2], Keith Marsolo[2], Jennifer E. Weiss[3], Stacy P. Ardoin[4], Ronald M. Laxer[5], D. J. Lovell[2], Murray H. Passo[6], Sheetal Vora[7], Beth S. Gottlieb[8], Timothy Beukelman[9], Nancy Griffin[10], Jason A. Stock[11], Michael L. Miller[12], Karen Onel[13], Tova Ronis[14], Peter Margolis[2] and Esi M. Morgan DeWitt[11]. [1]Hershey Medical Center, Hershey, PA, [2]Cincinnati Children's Hospital, Cincinnati, OH, [3]Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [4]Ohio State University, Columbus, OH, [5]The Hospital for Sick Children, Toronto, ON, [6]Medical University of South Carolina, Charleston, SC, [7]Medical College of Wisconsin, Milwaukee, WI, [8]Cohen Children's Medical Center of New York, New Hyde Park, NY, [9]Univ of Alabama-Birmingham, Birmingham, AL, [10]Cincinnati Children's Hospital Medical Center, Cincinnati, [11]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [12]Childrens Memorial Hospital, Chicago, IL, [13]University of Chicago, Chicago, IL, [14]Stanford University Hospital, Palo Alto, CA

Background/Purpose: The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is a quality improvement (QI) multi-center "learning network" that performs QI and research while tracking progress through data collection, analysis, and display. The mission is to optimize processes of care and improve outcomes in juvenile idiopathic arthritis (JIA). PR-COIN began operating in the spring of 2011 and currently has 12 participating sites in the United States and Canada. This is the first report of our data.

Methods: Our approach is based on the Institute for Healthcare Improvement Breakthrough Series Collaborative Model with planned interventions to improve outcomes based on the Chronic Illness Care Model. Conference calls, web-based information exchange, and face-to-face learning sessions are forums for teams to gain expertise in QI science, share knowledge, and develop new strategies to improve care. Teams conduct "Plan-Do-Study-Act" cycles to enact improvement and submit data and progress reports monthly. After informed consent/assent is obtained, site patient data are entered into the ACR's Rheumatology Clinical Registry in order to track progress of the network over time. Design of data collection forms allows assessment of performance on published proposed JIA quality measures (QM) (Arthritis Care Res 2011 Jan;63(1):10–6) and monitoring of clinical outcomes. 13 processes of care QMs and 4 clinical outcomes QMs are tracked. Site specific and aggregate data are analyzed monthly and provided with transparency as feedback to the sites. Benchmarking is possible through analysis of the data submitted by participating practices, and shared information can accelerate improvement throughout the network.

Results: As of May 2012, 516 patients from 7 sites have been entered into the registry for longitudinal assessment. Performance exceeded goal on 2 process of care QM: measurement at clinic visits of complete joint count (mean 100%, goal 90%) and pain assessment (mean 96%, goal 90). Examples of process QM requiring improvement work include: uveitis screening per Heiligenhaus guidelines (mean 72%, goal 90%); toxicity labs for DMARDs per guidelines (mean 72%, goal 90%); measurement every 180 days of: functional ability (mean 81%, goal 90%), and HRQOL (mean 3%, goal 90%). Our baseline outcome measures showed: 77% of patients have a pain score < 3; 58% patients have an optimal CHAQ score of 0; and 33% of patients on JIA medication and 60% patients off JIA medication could be defined as having clinical inactive disease.

Conclusion: PR-COIN is a growing international QI learning network. Our baseline data demonstrate mixed performance on measures of processes of care. As we reach target performance goals for our measures over time, we will continue to raise the bar for performance. The next phase of our project is to use interventions including implementation of an already developed population management tool, creation of a pre-visit planning tool to facilitate measurable improvement in meeting benchmarks for process of care, and orchestrated testing of which QI interventions most positively impact clinical outcomes.

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2602

The Rheumatology Informatics System for Effectiveness (RISE): Enabling Data Access Across Disparate Sites for Quality Improvement and Research.
Peter J. Embi[1], Itara Barnes[2], Rachel Myslinski[2], David Ervin[1], William Stevens[1], Tara Borlawsky[1] and Philip R.O. Payne[1]. [1]The Ohio State University, Columbus, OH, [2]American College of Rheumatology, Atlanta, GA

Background/Purpose: Rheumatology quality improvement efforts and clinical research are often challenged by the need to access and integrate data across diverse patient populations and disparate information systems. We report on our use of a service-oriented architecture (SOA) to link disparate clinical data resources across multiple clinical sites and systems in support of rheumatology practice and research. The central aim of this technology is to provide a reliable and cost-effective means of connecting data from multiple EHR systems, and using these data for quality improvement and research querying for the rheumatology community.

Methods: The design and execution of effective quality improvement projects and clinical studies requires access to high quality, longitudinal data. In most instances, such data are collected, formalized, stored and retrieved using project- or organization-specific disease registries or data warehouses. It is increasingly desirable to access data across multiple clinical sites for quality improvement and clinical research purposes, but disparate EHR systems remain difficult to connect for data interchange. Furthermore, in these types of settings, organizational and policy barriers

often preclude the use of centralized repositories. To address this need, we developed a lightweight, SOA-based approach to create a network of clinical sites that could serve as a federated data repository. The ACR is piloting this system—called the Rheumatology Informatics System for Effectiveness (RISE)—to enhance registry efforts to benefit rheumatic disease research and quality reporting efforts. Because RISE will collect data directly from EHR systems, it will eliminate the need for manual and redundant data entry into the registry.

Results: The model employed by RISE uses an approach to enable the federated query of geographically distributed data sources in order to create a virtual data repository. This platform uses the TRIAD middleware (1), and is currently being implemented at two pilot sites in the US, with more planned in the near future. A novel feature is the use of TRIAD-enabled data sharing "virtual appliances" (**Figure 1**). The systems was designed to reduce the overhead of deploying a data sharing service, while simultaneously allowing sites to maintain full control of the type and nature of data being shared. Through deployment of a simple, menu-driven query construction and data discovery portal, RISE allows end-users with appropriate privileges to quickly and easily discover and query distributed data sets.
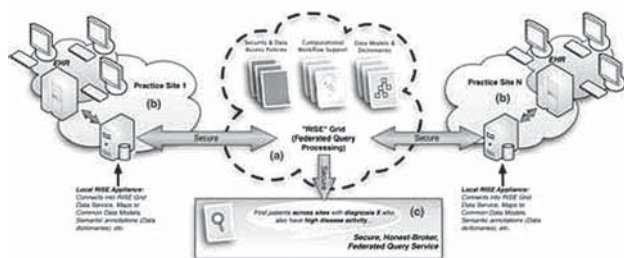
Conclusion: The design, deployment and initial use of the RISE Network addresses the need for data access across disparate sites using otherwise non-interoperable information systems. We believe that such an approach to distributed data sharing in rheumatology will help advance science and improve clinical practice.

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2603

Moving Into the Electronic Age: Validation of Rheumatology Self-Assessment Questionnaires On Tablet Computers. Jessica M. Sage[1], Arshia Ali[2], Jennifer Farrell[1], Jennifer L. Huggins[1], Kara Covert[1], Diane Eskra[1], Rina Mina[3], Shweta Srivastava[1], Janalee Taylor[1], Tracy V. Ting[1], Esi M. Morgan DeWitt[1] and Hermine I. Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]University of Cincinnati, Cincinnati, OH, [3]Cincinnati Children's Hospital Medical Center/University of Cincinnati, Cincinnati, OH

Background/Purpose: The medical field is increasingly relying on electronic health records (EHR). Many children's hospitals are converting from paper-pencil questionnaires to electronic versions. The purpose of this study was to compare correlation of results of paper-pencil versus electronically administered versions of two self-report questionnaires: 1) Rheumatology module of the Pediatric Quality of Life Inventory (RHE-PedsQL) and 2) Review of Systems (ROS) symptom checklist.

Methods: Patients (8–28 years old) with rheumatologic conditions, or their parents, completed the RHE-PedsQL (n=76) and ROS checklist (n=100) as a paper-pencil form and electronically through a tablet computer within the same office visit. Interclass correlations (ICC) and weighted-kappa statistics were computed using SAS 9.3 to compare questionnaire modes of administration. Repeated measures analysis of variance was used to determine between and within subject effects for the following covariates: age, gender, race, diagnosis, subtype, and ethnicity. Concurrently, a sample of patients/parents (n=22) was given a qualitative survey about the use of the tablet computer and preference for paper-pencil vs. electronic modes.

Results: Overall, no significant differences were found between the paper-pencil and tablet questionnaires in total score (RHE-PedsQL p=0.16; ROS p=0.56), as well as for any of the identified covariates considered.

Moderate agreement was found for each domain of the RHE-PedsQL (range: ICC= 0.46–0.61). Consistency, at the individual item level, between paper-pencil and electronic capture ranged from poor to moderate (range: kappa = 0.14–0.58), with the treatment domain having the highest correlations (kappa = 0.58) and the worry domain having the lowest (kappa = 0.14).

The ROS checklist yielded substantial agreement for "average pain" (ICC= 0.87) and "overall status" items (ICC= 0.76). Moderate to excellent agreement was found for each of the 60 individual items of the ROS questionnaire (kappa= 0.3–1.0), with questions regarding the nervous system (e.g., depression, tingling/numbness) showing the best consistency (all kappa > 0.70) and items regarding skin problems (e.g., tightening, discoloring) showing the most discrepancies (kappa = 0.32–0.95).

Qualitative analysis revealed many patients/parents found the tablet simpler, easier and faster than paper-pencil forms. Ten respondents preferred the tablet, eleven had no preference and only one patient preferred the paper-pencil.

Conclusion: There were no significant differences found, for both the ROS checklist and the RHE-PedsQL, in overall score and individual item values, when switching from paper-pencil application to electronic data capture. Furthermore, moderate to substantial agreement was found between modes of administration for the RHE-PedsQL and ROS checklist. The use of electronic questionnaires can increase efficiency of office visits, improve data collection, and patient monitoring, as well as satisfy patient preferences. The ability to integrate electronic patient-reported data into EHR has the potential to improve health care delivery.

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Ask a Doc—Rheumatologic Care Delivered Just in Time. Eric D. Newman[1], Chelsea Cedeno[1], Thomas M. Harrington[1], Thomas P. Olenginski[1], Alfred E. Denio[1], Androniki Bili[1], Brian DelVecchio[1], Carolyn Houk[2] and Paul F. Simonelli[1]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Frackville, PA

Background/Purpose: Specialty care is traditionally delivered as face to face consults. These encounters range from consult not needed to consult needed quickly. Our care systems are not designed to distinguish these different needs, creating excess visits that delay access. This delay results in overutilization and unnecessary expense (consult not needed), underutilization of needed care and worsening disease (consult needed quickly), and potential harm and patient anxiety (both). To provide specialty care just when it is needed, we developed Ask-a-Doc, a web-based tool accessed from within the electronic health record (EPIC).

Methods: Ask-a-Doc was developed using process redesign methodology. Ask-a-Doc allows the Primary Care Physician (PCP) to ask a question and the specialist to answer it through electronic chart review, phone call, or video call. Ask-a-Doc consists of 3 steps: Step 1 - ask a question (PCP). Step 2 - connect to the specialist (Scheduler). Step 3 - answer the question and complete the documentation (Specialist). 23 PCPs, 7 schedulers, and 11 specialists (6 rheumatologists, 5 pulmonologists) were trained to use Ask-a-Doc. Redesign measures included service excellence, work effort, process reliability, and clinical outcome.

Results: Step 1 - The PCP selected a specialty or specialist, turn-around time (now, today, within 3 days), preferred mode of communication (electronic messaging, phone call, instant video), and asked a question. The question could be patient-specific or not patient-specific. The request was submitted electronically to the Ask-a-Doc scheduler. Step 2 - The scheduler identified the correct specialist and sent the form to that specialist's Ask-a-Doc inbasket folder. If the request was to communicate by phone or video, the scheduler connected the specialist back to the PCP. Step 3 – the specialist reviewed the EPIC record, answered the question, and provided structured electronic documentation. Analysis of the first 74 Ask-a-Doc questions showed the following (Table 1): Service excellence - Primary care satisfaction of 4.5 (range 0–5), mean turnaround time of 3 hours, met or exceeded requested timeframe 100%. Work effort – 12 minutes average per message. Process – 100% response rate. Outcome – 57 consults saved (77%).

Category	Measure	Definition	Result
Service Excellence	Primary Care Satisfaction	Satisfaction survey results from PCP perspective (Scale 0–5; 0 = "Impossible", 5 = "Very Easy")	4.5
	Time to Completion	Timeframe from message initiation to response sent	Mean Specialty turn-around time = 3 hours; Mean PCP requested time = 21 hours
	Request Met	% Requested Response Timeframe met or exceeded	100%
Work Effort	Volume	Number of Ask a Doc messages created/started	74
	Time Spent	Average amount of time spent by Specialist to complete (min/message)	12
Process	Response Rate	% of messages responded to	100%
	Response Accuracy	% of patient specific messages converted to encounters for proper documentation	95%
Outcome	Consults Saved	Number of consults saved by using Ask a Doc	57 (77%)

Conclusion: Using process redesign methodology, we developed Ask-a-Doc to improve care delivery between PCPs and specialists. The results demonstrate excellence in service, a highly reliable process, and significant reduction in waste. Ask-a-Doc provides specialty care "just-in-time", so patients that don't need to be seen are not, and those that do can be seen promptly – by design, not by accident. As reimbursement for care delivery moves towards bundled payments, Ask-a-Doc is a value-added service that rheumatologists can provide.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects VI:
Remission and Flare in Rheumatoid Arthritis
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

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Exploration of Possible Preliminary Descriptions of Remission Based On RAPID3, without Laboratory Tests or Formal Joints Counts but with Careful Joint Examinations, in the Etude Et Suivi Des Polyarthrites Indifférenciées Récentes (ESPOIR) Cohort of Early Rheumatoid Arthritis Patients. Isabel Castrejón[1], Maxime Dougados[2], Bernard Combe[3], Bruno Fautrel[4] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [3]Hopital Lapeyronie, Montpellier, France, [4]APHP-Pitie Salpetriere Hospital / UPMC, Paris, France

Background/Purpose: Criteria for remission in rheumatoid arthritis (RA) have been developed according to DAS28 (disease activity score), CDAI (clinical disease activity index), and two recent proposals by an American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) committee: "Boolean" with 4 measures—tender joint count (TJC28), swollen joint count (SJC28), C-reactive protein (CRP), and patient global estimate (PATGL), all ≤1; and SDAI (simplified disease activity index). All require formal joint counts, which are not performed at most visits in usual care, and all but CDAI require a laboratory test, which often is not available. Therefore, we explored 4 descriptions of remission for usual care, based on RAPID3 (routine assessment of patient index data), a composite index including function, pain and PATGL—without a laboratory test or formal joint count, but with a careful joint examination and physician global estimate (DOCGL; 0–10 scale).

Methods: The ESPOIR cohort includes 756 patients recruited between Dec 2002 and March 2005. Post hoc analyses were performed to identify the number of patients in remission 6 months after enrollment according to 4 descriptions requiring a formal joint count (and 3 a laboratory test): DAS28 ≤2.6, CDAI ≤2.8, and the two proposed by the ACR/EULAR committee –

Boolean ≤1 for TJC28, SJC28, CRP and PATGL; and SDAI ≤3.3. Four descriptions based on RAPID3 that require neither a laboratory test nor formal joint count, but a careful joint examination and DOCGL were evaluated, "RAPID3R" (RAPID3 ≤3.0), and three more stringent descriptions: "RAPID3R+J1" (RAPID3 ≤3.0 and ≤1 swollen joint; if >1 swollen joint, the criterion is not met); "RAPID3R+J1D1" (RAPID3 ≤3.0 and ≤1 swollen joint and DOCGL ≤1); and "RAPID3R+J0D1" (RAPID3 ≤3.0 and no swollen joint and DOCGL ≤1). Agreement of all 7 descriptions with the ACR Boolean definition was assessed using kappa statistics.

Results: Among the 756 ESPOIR patients, 734 had complete 6-month data to calculate all 8 descriptions. The highest percentage of patients in remission was seen with DAS28 and RAPID3R, the least stringent descriptions, and the lowest percentage with the Boolean definition. Good agreement with the Boolean ACR/EULAR definition was seen for SDAI, CDAI, RAPID3R+J1, RAPID3R+J1D1 and RAPID3R+J0D1 (92.6%–94.7%, kappa 0.70–0.79), versus only moderate agreement for DAS28 and RAPID3R (79.9%–85.8%, kappa 0.46–0.55) (Table).

Table. Proportion of 734 patients in the ESPOIR cohort who were in remission 6 months after baseline according to 8 descriptions of remission

Remission descriptions	Patients in remission by each description: Number (%)	Kappa (95% CI) vs ACR/EULAR Boolean	% Patients in remission agreement with ACR/EULAR Boolean
Indices requiring lab tests and formal joint counts:			
ACR/EULAR Boolean	96 (13%)	NA	NA
SDAI (0–86) ≤3.3	127 (17.3%)	0.79 (0.76–0.86)	94.7%
DAS28 (0–10) ≤2.6	238 (32%)	0.46 (0.39–0.52)	79.9%
Indices without lab tests:			
CDAI (0–76) ≤2.8	134 (18.2%)	0.75 (0.69–0.82)	93.5%
RAPID3 versions for remission without lab tests or formal joint counts (but with careful joint exam):			
"RAPID3R"[RAPID3 (0–30) ≤3.0]	186 (25.3%)	0.55 (0.48–0.63)	85.8%
"RAPID3R + J1"[RAPID3 ≤3.0 and ≤1 swollen joint]	136 (18.6%)	0.73 (0.66–0.79)	92.6%
"RAPID3R + J1D1"[RAPID3 ≤3.0; ≤1 swollen joint; DOCGL ≤1]	117 (16%)	0.74 (0.67–0.81)	93.6%
"RAPID3R+J0D1"[RAPID3 ≤3.0; no swollen joint; DOCGL ≤1]	97 (13.2%)	0.70 (0.62–0.77)	93.0%

NA, not applicable; DOCGL, physician global estimate of status

Conclusion: Description of remission according to SDAI, CDAI, RAPID3R+J1, RAPID3R+J1D1 and RAPID3R+J0D1 is similar to Boolean ACR/EULAR, while DAS28 and RAPID3R are less stringent. The more stringent RAPID3-based indices may be useful in usual clinical care, as they require neither laboratory tests nor formal joint counts, but do require a DOCGL and careful joint examination.

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Patient Reported Outcomes in Early Arthritis Patients. L. Heimans[1], K.V.C. Wevers-de Boer[1], K. Visser[1], R. Goekoop[2], T.H.E. Molenaar[3], B.A. Grillet[4], Tom Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, [3]Groene Hart Hospital, Netherlands, [4]Zorgsaam hospital, Terneuzen, Netherlands

Background/Purpose: To investigate patient reported outcomes (PROs) of functioning and health related quality of life (HRQOL) after 1 year remission (DAS<1.6)-steered treatment in early arthritis patients.

Methods: In the IMPROVED-study 610 patients with early rheumatoid and undifferentiated arthritis were treated with methotrexate (MTX) 25mg/week and 60mg/day of prednisone, tapered to 7.5mg/day in 7 weeks. Patients who did not achieve early remission after 4 months were randomized either to hydroxychloroquine 400mg/day, sulphasalazine 2000mg/day, MTX 25mg/week plus prednisone 7.5mg/day (arm 1) or to adalimumab (ADA) 40mg/2weeks plus MTX 25mg/week (arm 2). Every 4 months, patients filled out the Health Assessment Questionnaire (HAQ) to measure functional ability, the

Short Form 36 (SF-36) and visual analogue scales (VAS) for global health (VASgh), pain (VASp), disability (VASdis) and morning stiffness (VASms). Mean scores of HAQ, SF-36 and VAS over 1 year were compared between patients in the randomization arms using linear mixed models. HAQ- and VAS scores and changes over 1 year were compared between the treatment groups (early remission, arm 1, arm 2 and 'outside protocol treatment'). SF-36 scores (higher=better HRQOL) were compared with the Dutch population norm matched for age and sex. Predictors of significant change in PCS and MCS over 1 year were identified using linear regression analyses.

Results: After 4 months 375/610 patients achieved early remission, 83 patients were randomized to arm 1 and 78 to arm 2, and 62 did not follow the protocol; 12 were lost to follow up. Mean (sd) HAQ after 1 year was 0.4 (0.5) in the early remission group, 0.9 (0.7) and 0.8 (0.7) in arm 1 and 2, respectively, and 0.7 (0.6) in the 'outside protocol' group (p<0.001; early remission group vs either arm 1 or 2: p<0.001, early remission vs 'outside protocol': p=0.001, arm 1 vs arm 2 and 'outside protocol' vs both arms: p=1.0). Mean HAQ reduction in year 1 was 0.6 in all groups (p=0.7). Mean HAQ, PCS, MCS and VAS-scores over 1 year treatment were better in the early remission group. There was no significant difference between randomization arms 1 and 2. VAS improvements over 1 year were similar in all groups except VASdis, which improved significantly more in arm 2 than in arm 1 (36 versus 24 points; p=0.02). At baseline and after 1 year, all groups scored below the Dutch population average in PCS, MCS and all subscales (all p<0.001). Early remission was a predictor for significant improvement in PCS but not MCS after 1 year. For the MCS only baseline MCS was a predictor.

Conclusion: In patients with early arthritis, functional ability and patient reported outcomes after 1 year are significantly better in patients who achieved early remission. In patients who did not achieve early remission, treatment with polyDMARD+prednisone or adalimumab+MTX results in comparable improvements. All patients with early arthritis have significantly lower HRQOL than the Dutch general population, both at baseline and after 1 year of remission steered treatment.

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Adherence to a Treat-to-Target Strategy in Early Rheumatoid Arthritis: Results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort.
Marloes Vermeer[1], Ina H. Kuper[2], Hein J. Bernelot Moens[3], Monique Hoekstra[4], Marcel D. Posthumus[5], Piet L.C.M. van Riel[6] and Mart A.F.J. van de Laar[1]. [1]University of Twente & Medisch Spectrum Twente, Enschede, Netherlands, [2]Medisch Spectrum Twente, Enschede, Netherlands, [3]Ziekenhuisgroep Twente, Hengelo, Netherlands, [4]Isala Klinieken, Zwolle, Netherlands, [5]University Medical Center Groningen, Groningen, Netherlands, [6]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: A treat-to-target (T2T) approach has proven to be more effective in reaching remission in early rheumatoid arthritis (RA) than usual care [1]. However, T2T has not been fully implemented in all rheumatology clinics. In 2006, six hospitals participating in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry implemented a T2T strategy. In this DREAM remission induction cohort, early RA patients are treated according to a T2T strategy aiming at remission (Disease Activity Score in 28 joints (DAS28) < 2.6) [2]. The recommendations regarding T2T included regular assessment of the DAS28 and an advice regarding subsequent DAS28-driven treatment. The objective of this study was to evaluate the adherence to this T2T strategy.

Methods: A medical chart review was performed among a random sample of 100 RA patients of the DREAM remission induction cohort. At all scheduled visits, it was determined whether the clinical decisions were compliant to the T2T recommendations. Reasons for deviating from the recommendations were explored.

Results: The 100 patients contributed to a total of 1115 visits. The mean (standard deviation, SD) follow-up time was 28 (10) months and the mean (SD) number of visits was 11 (4) per patient. The DAS28 was available in 97.9% (1092/1115) of the visits, of which the DAS28 was assessed at a frequency of at least every three months in 88.3% (964/1092). Adherence to the treatment advice was observed in 69.3% (757/1092) of the visits. In case of non-adherence when remission was present (19.5%, 108/553), most frequently medication was tapered or discontinued when it should have been continued (7.2%, 40/553) or treatment was continued when it should have

been tapered or discontinued (6.2%, 34/553) (Figure 1A). In case of non-adherence when remission was absent (42.1%, 227/539), most frequently medication was not intensified when an intensification step should have been taken (34.9%, 188/539) (Figure 1B). In almost half of these cases, low disease activity was observed (DAS28 ≤ 3.2). The main reason for non-adherence was discordance between disease activity status according to the rheumatologist and DAS28. Other frequently observed reasons were: side effects, patient wish and unknown.
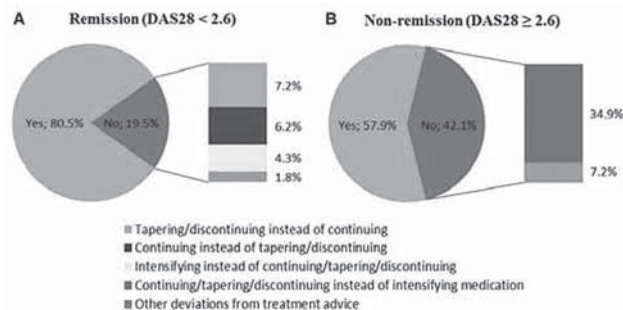
Conclusion: The recommendations regarding T2T were successfully implemented and high adherence was observed. This demonstrates that the implementation of T2T is feasible in RA in daily clinical practice.

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Time in Remission Is Important for Improvement of Physical Function in Patients with Rheumatoid Arthritis (RA).
Helga Radner[1], Farideh Alasti[2], Josef S. Smolen[3] and Daniel Aletaha[2]. [1]Medical University Vienna, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Physical function is one of the major outcomes in RA as it predicts work disability, quality of life, health care resource utilisation and mortality. It is currently still unclear what the minimum duration of remission is that would improve functional capacity to the best possible degree.

To investigate the course of functional status assessed by health assessment questionnaire (HAQ) in RA patients with sustained clinical remission for at least 6 months.

Methods: We were provided a random 80–90% data sample of RA patients enrolled in recent clinical trials (ASPIRE, ATTRACT, DE019, ERA, Leflunomide, PREMIER, and TEMPO; n=4863) by the respective sponsors. We identified patients, who at some point during the trials achieved sustained remission in consecutive visits of at least 6 months by the DAS28-CRP ≤ 2.6 or SDAI ≤ 3.3. We obtained HAQ scores during these 6 month remission periods, and were thus able to investigate the course of physical function over time in sustained remission using the Wilcoxon test. Furthermore we explored the proportion of patients achieving full function (HAQ = 0 over time period investigated).

Results: Out of 4362 patients we identified 605 patients in sustained remission by DAS28-CRP, and 385 patients by SDAI. No significant differences of baseline characteristics were found between these two groups. We found a significant decrease of mean HAQ values over time within the first 6 months in remission by DAS28-CRP (mean±SD HAQ monthly from baseline to month 6: 0.25±0.4 to 0.22±0.38 to 0.22±0.39 to 0.21±0.38 to 0.20±0.37 to 0.18±0.31 to 0.16±0.32) as well as SDAI (0.17±0.3 to 0.16±0.32 to 0.15±0.3 to 0.14±0.29 to 0.13±0.29 to 0.13±0.26 to 0.11±0.27) with significantly (p<0.05) lower levels of HAQ in remission by SDAI compared to DAS28-CRP at remission entry until month 4 in sustained remission. Achievement of full function (HAQ=0 over course of remission) was observed in 42.5% of patients in DAS28-CRP and 50.1 % of patients in SDAI remission at beginning of sustained remission, and in more patients with early RA (DAS28-CRP: 47.6%; SDAI: 52.6%) compared to late RA patients (DAS28-CRP: 33.3%; SDAI: 44.1%). Further, at remission entry

only 57.4% of patients in DAS28-CRP REM fulfilled SDAI remission; this percentage increased over time to 71.9% at 3 months and 76.9% at 6 months of sustained remission; thus, the improvement of HAQ in DAS28 remission went at least partly in parallel with the increasing frequency of SDAI remission in DAS28 remitters over time.
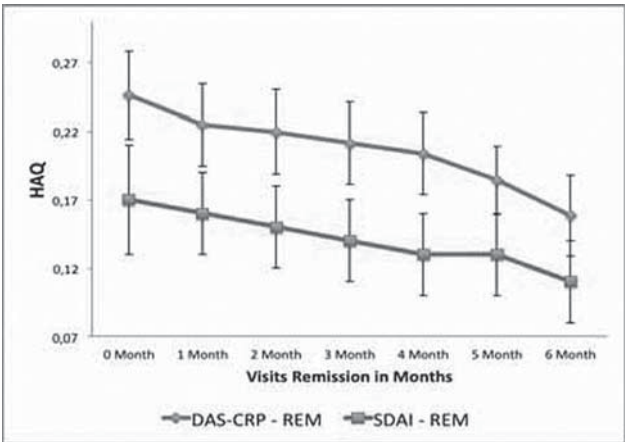
Fig. 1. Course of HAQ in DAS-CRP and SDAI sustained remission over time

Conclusion: Physical function continuous to improve over time in sustained remission. The stringency of the remission criteria determines how quickly patients in remission achieve their best possible functional improvement.

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Construct and Criterion Validity of Several Proposed DAS28 Based Rheumatoid Arthritis Flare Criteria: A Cohort Validation Study. Aatke van der Maas[1], Elisabeth Lie[2], Robin Christensen[3], Ernest Choy[4], Yaël A. de Man[5], Piet L.C.M. van Riel[6], Thasia G. Woodworth[7] and Alfons A. den Broeder[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Musculoskeletal Statistics Unit, The Parker Institute, Copenhagen University Hospital, Copenhagen, Denmark, [4]Cardiff University School of Medicine, Cardiff, United Kingdom, [5]Erasmus Medical Centre, Rotterdam, Netherlands, [6]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [7]Visiting Clinical Researcher, Geffen School of Medicine, UCLA, Los Angeles, CA

Background/Purpose: To enable consistent assessment of impact of tapering, withdrawal and dose optimization strategies, there is an increasing need for validated measures of flare in rheumatoid arthritis (RA) clinical studies. Several DAS28 based flare criteria have been described, but none validated

Methods: We used 3 longitudinal observational databases that included treatment withdrawal or change in relation to RA worsening to test 6 previously published DAS28 based flare criteria on fulfilment of 5 hypotheses concerning criterion and construct validity. Published DAS28 based flare criteria were: 1] an increase in DAS28>1.2, or >0.6 if current DAS28>5.1, 2] an increase in DAS28>1.2, or >0.6 if DAS28≥3.2, 3] an increase>0.6 or DAS28>3.2, 4] an increase in DAS28>1.2, 5] DAS28 >3.2, 6] DAS28 >2.6. The 5 hypotheses used to assess validity were: A+B) Sensitivity and specificity >70% compared to patient's/physician's judgment of RA worsening assessed with a transition question, and C) difference in proportion with DMARD/corticosteroid initiation/increase >0.2, D) difference in mean CRP change >10mg/L, and E) no statistical difference in SF36 Mental Health (MH) subscale change in patients fulfilling versus not fulfilling the flare criteria. Sensitivity/specificity, Chi square and two sample student's T test were done

Results: Analyses included 51, 147 and 744 RA patients in the 3 studies. Two studies included patients treated with infliximab and the larger study (NOR-DMARD) included patients initiating a new synthetic or biologic DMARD. Baseline characteristics are described in Table 1. Criterion 2 (an increase in DAS28>1.2, or >0.6 if DAS28≥3.2) fulfilled most predefined

hypotheses (4 out of 5, Table 2). Sensitivity and specificity for criterion 2 varied between 63–78% and 84 –92%, respectively. Construct validity was demonstrated with 23% more treatment change, a higher mean ΔCRP (11.4 mg/L) and a difference in ΔSF-36 MH of only -5. Criteria 3, 5 and 6 tended to be more sensitive, criteria 1, 2 and 4 more specific

Table 1. Baseline characteristics - mean (SD) unless otherwise noted

Database	1	2	3
Number of patients	51	147	744
Age, years	59 (11.2)	58 (12)	56 (13.5)
Female, Nº (%)	29 (57)	101 (69)	539 (72)
Disease duration in years	14 (7.5)	11 (7)	6.4 (9.5)
RF positive, Nº (%)	42 (82)	117 (81)	496 (68)
Anti-CCP positive, Nº (%)	37 (73)	95 (69)	146 (70)
DAS28 at inclusion	2.5 (0.7)	3.5 (1.3)	5.2 (1.1)
DAS28 at 3 months after inclusion			3.4 (1.2)*
No. of previous DMARDs, median [p25-p75]	3 [2–3]	3 [2–3]	0 [0–2]

Table 2. Fulfilment of DAS28 based flare criteria on 5 hypotheses regarding construct and criterion validity

	Criterion validity: databases 1 and 2				Construct validity: database 3		
Flare criteria	Hypothesis 1		Hypothesis 2		Hypothesis 3	Hypothesis 4	Hypothesis 5
In patients classified as a having a flare:	Sens/spec patient >70% compared to transition scale		Sens/spec physician >70% compared to transition scale		Higher proportion of DMARD/ corticosteroid change (>0.2)	Higher CRP (>10 mg/L)	No change in depression (≤5 points in MH scale)
	Sens* %	Spec* %	Sens* %	Spec* %	Proportion difference**	CRP difference mg/L (SE)***	MH difference (SE)
1) ΔDAS28 > 1.2 or > 0.6 if DAS28>5.1	46/56	95/92	53/78	95/92	0.28	13.1 (2.2)	−6.1 (1.4)
2) ΔDAS28> 1.2 or > 0.6 if DAS28>3.2	69/63	92/84	73/78	92/86	0.23	11.4 (1.7)	−5.0 (1.2)
3) ΔDAS28> 0.6 or a DAS28>3.2	98/94	70/61	100/89	67/60	0.16	3.7 (1.2)	−2.8 (1.0)
4) ΔDAS28>1.2	46/56	96/93	51/78	95/92	0.27	13.0 (2.3)	−6.6 (1.4)
5) reaching DAS28>3.2	91/88	78/67	91/89	76/68	0.18	3.1 (1.2)	−2.6 (1.0)
6) reaching DAS28 > 2.6	98/94	55/46	100/89	53/47	0.13	2.4 (1.0)	−3.2 (1.1)

*Sens=sensitivity, Spec= specificity. Results from database1 / database2 are represented on sensitivity and specificity. ** All proportion differences are statistically significant, with p<0.0001.*** All differences in CRP are statistically significant, with at least p<0.05

Conclusion: An increase in DAS28>1.2, or >0.6 if DAS28≥3.2 appears most discriminating and valid by our predefined criteria. The differences in sensitivity and specificity between the various DAS28-based flare criteria may be of importance for selection of flare criteria for specific studies. Further assessment, with evaluation of impact relative to levels of worsening, in additional databases may refine criteria

2610

Predictors of Sustained Clinical Remissionin Early Rheumatoid Arthritis - Results From the Canadian Early Arthritis Cohort. Bindee Kuriya[1], Juan Xiong[2], Gilles Boire[3], Boulos Haraoui[4], Carol A. Hitchon[5], Janet E. Pope[6], J. Carter Thorne[7], Diane Tin[7], Edward Keystone[1], Vivian P. Bykerk[8] and CATCH[9]. [1]University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]St. Joseph's Health Care London, London, ON, [7]Southlake Regional Health Centre, Newmarket, ON, [8]Hospital for Special Surgery, New York, NY, [9]Toronto, ON

Background/Purpose: Rapid time-to-remission has been associated with sustained remission in established rheumatoid arthritis (RA)[1]. However, the prevalence and predictive factors of sustained remission in early RA is poorly understood, especially in the context of stringent remission definitions.

Methods: We used data from the Canadian early ArThritis CoHort (CATCH) and included patients with probable or confirmed RA. Remission was defined according to the ACR/EULAR clinical practice definition (TJC ≤1, SJC ≤1 and patient global ≤ 1) and SDAI ≤ 3.3. Patients in CATCH are seen q3months in year 1 and q6montly thereafter. Sustainability was defined as ≥6 months or 2 consecutive visits with ACR/EULAR or SDAI remission-.Predictors for sustained remission were identified by logistic regression analysis, adjusted for clinical confounders.

Results: 1244 patients were included. 83% were Caucasian and 73% were female, with mean age (SD) of 53.6 (14.6) years, and mean symptom duration (SD) of 6.0 (3.1) months. Initial treatment within the 1st 3 months included: methotrexate monotherapy in 392 (32%), combination DMARDs in 548 (44%), and biologics in 27 (2%). 522 (42%) achieved ACR/EULAR and 484/1205 (40%) SDAI remission with a median time-to-remission of 23.9 months for each. In those ever achieving sustained remission, 309 (59.2%) and 273 (56.4%) did so for sustained ACR/EULAR and SDAI remission. Factors associated with increased probability of sustained remission were younger age, low baseline pain scores and earlier time-to-first remission (Table). Baseline RF, CCP, patient global, smoking status, symptom duration, DAS28, HAQ, fatigue, AM stiffness and erosions had no effect on sustained remission. No initial treatment strategy predicted sustained remission, nor did biologic use within the first 6 months (8%).

Table. Multivariate analysis of baseline predictors and time-to-remission as a predictor for sustained ACR/EULAR or SDAI remission

Characteristic	ACR/EULAR Clinical Practice Remission		SDAI Remission	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age*, years	0.98 (0.96, 0.99)	0.002	0.98 (0.96, 0.99)	0.006
Female sex	0.62 (0.39, 0.99)	0.04	0.78 (0.48, 1.26)	0.31
Pain score*	0.99 (0.98, 0.99)	0.04	0.98 (0.98, 0.99)	0.03
Methotrexate monotherapy	0.95 (0.55, 1.66)	0.86	0.68 (0.37, 1.23)	0.20
Combination DMARD therapy	1.49 (0.88, 2.51)	0.14	1.42 (0.80, 2.51)	0.23
Biologic DMARD within 6 months	1.68 (0.75, 3.74)	0.21	0.85 (0.39, 1.85)	0.69
Time-to-remission	0.997 (0.996, 0.998)	<0.0001	0.997 (0.996, 0.998)	<0.0001

* Treated as continuous variables

Conclusion: Even when stringent definitions of remission are considered, sustained remission is possible within two years for ERA patients initially treated with conventional DMARDs. The time to reach sustained remission may be falsely long as after year 1, data is collected only every 6 months. Gender influenced the chance of remission only in ACR/EULAR remission. Demographic characteristics and pain are important predictors of sustained remission. Shorter time-to-remission is also related to sustainability and supports striving for early remission in patients with ERA. The optimal treatment approach for sustained remission in this cohort could not be determined.

Reference
Schipper LG et al. Time to achieve remission determines time to be in remission. Arthritis Res Ther. 2010;12(3):R97.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Psoriatic Arthritis and Spondyloarthritis
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

2611

Do Patients with Psoriatic Arthritis Fall Into Distinct Clinical Sub-Groups—a Cluster Analysis? Arane Thavaneswaran[1], Vinod Chandran[2] and Dafna Gladman[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: To determine if demographic and disease characteristics of patients with PsA at presentation to a PsA clinic cluster into distinct groups.

Methods: 1058 patients with Psoriatic Arthritis (PsA) were included from an observational cohort. Cluster analysis using Ward's method was conducted to identify groups of patients based on the following characteristics at baseline: gender, type of psoriasis (type I or II), duration of PsA, race, family history of psoriasis, ESR, severe PASI, psoriasis vulgaris, nail disease, dactylitis, swollen joint count, damage joint count, axial disease, and presence of arthritis prior to psoriasis. 7 clusters were formed and matched to non-overlapping arthritis patterns (as described previously) at first clinic visit: distal arthritis, oligoarthritis, polyarthritis, axial only, distal arthritis and axial, oligoarthritis & axial, and polyarthritis & axial. Comparisons between the clusters and arthritis patterns were conducted using t-tests and Chi-square analysis.

Results: The baseline characteristics of the 1058 patients were as follows: 613 (56.5%) males, mean age at diagnosis of PsA 37.1 (13.5) years, mean age at first visit 44 (13.1) years, mean duration of PsA 6.8 (8.2) years, mean active joint count 11.0 (9.8), mean PASI 5.8 (8.3), mean Steinbrocker score 12.9 (25.5), HLA-B*27 116(17.7%)] with an average follow-up of 8.4 (8.4) years. Two main clusters of patients were identified. One consisted of distal arthritis, oligoarthritis and polyarthritis and the other of axial only, distal and axial, oligoarthritis & axial, and polyarthritis & axial, thus clearly identifying patients into peripheral and axial disease. Comparison of the two clusters showed a longer duration of PsA at baseline, more patients with a family history of psoriasis, and more dactylitis in patients with peripheral disease. Patients falling into the axial disease cluster had a higher prevalence of males, more Caucasians, more psoriasis vulgaris, worse PASI score), higher damage joint count and more patients who developed arthritis first.

Table. Comparison of two clusters

Variable	Frequency (%) or Mean (sd)		p-value
	Cluster I	Cluster II	
Age at diagnosis of Ps (>40 vs. <=40)	63 (14.5%)	47 (20.4%)	0.06
Duration of PsA	8.6 (7.6)	5.0 (6.5)	<0.0001
Gender (Males)	259 (59.4%)	175 (76.1%)	<0.0001
Race (Caucasian vs. others)	365 (84.1%)	208 (90.8%)	0.02
Family history of Psoriasis	124 (28.6%)	33 (14.4%)	<0.0001
Nail disease	214 (69.7%)	120 (78.4%)	0.06
Dactylitis	236 (54.4%)	80 (34.8%)	<0.0001
Abnormal skin	352 (82.4%)	213 (94.3%)	<0.0001
Severe PASI (>=10)	35 (12.9%)	40 (27.2%)	0.0003
ESR	21.7 (18.9)	28.5 (22.1)	0.0002
Swollen joint count	3.3 (4.2)	2.8 (3.9)	0.12
Damage joint count	1.1 (2.9)	7.6 (11.8)	<0.0001
Axial disease	67 (15.5%)	208 (90.4%)	<0.0001
Arthritis first	20 (4.6%)	21 (9.1%)	0.02

Conclusion: Based on patients' characteristics at baseline, cluster analysis separated PsA patients into two main arthritis patterns- axial and peripheral. The study provides further evidence to classify patients into just two groups based on the presence or absence of axial arthritis.

Disclosure: A. Thavaneswaran, None; **V. Chandran**, None; **D. Gladman**, None.

2612

Localisation of Bone Marrow Edema in Sacroiliac Joints in Spondyloarthritis Patients: Does the Site of Lesions Change Over a 3-Month Period? Manouk de Hooge, Rosaline van den Berg, Monique Reijnierse, Victoria Navarro-Compán, Floris van Gaalen, Tom Huizinga and Désirée van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: A positive MRI at baseline is a strong predictor for a positive follow-up MRI[1]. But many questions about the volatility of the lesions over short follow-up periods remain unsolved. Is it possible for lesions to disappear, occur or move localisation? Or is their location rather consistent over time?

Objectives: To describe if and how the location of active inflammatory lesions change and if lesions can occur or disappear after 3 months without changing treatment.

Methods: 90 patients with chronic back pain (≥3 months, ≤2 years, onset ≤45 years) who were included in the SPondyloArthritis Caught Early (SPACE)-cohort underwent a MRI of the SI joints (MRI-SIJ) at baseline and after 3 months follow-up.

Results: Out of all the patients 66/90 (73.3%) did not show any lesions at any of the time points. In 12 patients no difference was found between baseline and follow-up MRI with respect to the SI joint (only left side affected in 7 patients, only right side in 2 and in 3 patients both SIJ were affected). In 5 patients without lesions at baseline new inflammation occurred (4 times only in the right SIJ and once in both SIJs). In 4 patients with inflammation at baseline the inflammation was no longer present at follow-up. In 3 out of 6 patients with inflammation in both SIJ at baseline, the inflammation was only present in the left SIJ after 3 months. The other 3 patients presented

inflammation in both SIJ at baseline as well as follow-up. 24/90 (26.7%) patients had a positive MRI at baseline or follow-up, or both. The quadrant in which the lesion was present did not change over time in 6 patients. Lesions disappeared from quadrants in 9 patients (lesion disappeared in only 1 quadrant in 7 patients and in 3 quadrants in 2 patients) and occurred in 7 patients (MRI changed from negative to positive in 5 and remained positive in 2 patients). The lesions moved between quadrants in 2 patients. In these 2 patients lesions disappeared from one quadrant and occurred in another. In 20/24 patients the medication between baseline MRI and follow-up did not change (18 patients used NSAIDs and 2 of them did not use any medication) and 4 patients changed medication (2 patients switched NSAID type and the other 2 started NSAID treatment in that period). Out of the patients that changed from a negative to positive MRI (n=5) or visa versa (n=4), only 1 patient also changed medication, by switching to another NSAID.

No. of patients Baseline	3-month follow-up				
	No lesions	Only left	Only right	Both sides	
No lesions	66	0	4	1	71
Only left	3	7	0	0	10
Only right	1	0	2	0	3
Both sides	0	3	0	3	6
	70	10	6	4	90

Conclusion: BME lesions on MRI occur or disappear at SIJ level in 9% of the patients with chronic back pain after 3 months. From all patients with a positive MRI at baseline, lesions did not change location in 50% of them at SIJ level while, at quadrant level, less than 30% of the patients showed stability in the location of lesions. So, there is quite some volatility of lesions over a short follow-up period of 3 months only.

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2613

Effect of Certolizumab Pegol On Signs and Symptoms in Patients with Psoriatic Arthritis with and without Prior Anti-TNF Exposure: 24 Week Results of a Phase 3 Double-Blind Randomized Placebo-Controlled Study. Philip Mease[1], Roy M. Fleischmann[2], Jürgen Wollenhaupt[3], Atul A. Deodhar[4], Danuta Kielar[5], Franz Woltering[6], Christian Stach[6], Bengt Hoepken[6], Terri Arledge[7] and Désirée van der Heijde[8]. [1]Seattle Rheumatology Associates, Seattle, WA, [2]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [3]Schön-Klinik, Hamburg, Germany, [4]Oregon Health & Science University, Portland, OR, [5]UCB Pharma, Brussels, Belgium, [6]UCB Pharma, Monheim am Rheim, Germany, [7]UCB Pharma, Rtp, NC, [8]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, has shown efficacy in reducing signs and symptoms of psoriatic arthritis (PsA).[1] RAPID-PsA (NCT01087788) is the first report of a biologic in PsA to include patients (pts) with prior anti-TNF exposure.

Methods: The ongoing 158 week (Wk) RAPID-PsA trial is double-blind and placebo (PBO) controlled to Wk24, dose-blind to Wk48 and then open label to Wk158. Recruited pts had active PsA and had failed ≥1 DMARD. Pts could have experienced secondary failure to 1 previous anti-TNF. Pts were randomized 1:1:1 to PBO, or 400mg CZP at Wk 0, 2 and 4 (loading dose, LD) followed by either 200mg CZP every 2 wks (Q2W) or 400mg CZP every 4 wks (Q4W). Pts receiving PBO who failed to achieve a ≥10% decrease in tender and swollen joint counts at both Wks14 and 16 were rescued and randomized at Wk16 to receive CZP 200mg Q2W or CZP 400mg Q4W following LD. The clinical primary endpoint was ACR20 response at Wk12. Secondary outcomes measured in the study include PASI75, Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI) and Modified Nail Psoriasis Severity Index (mNAPSI). Non-responder imputation was used for ACR and PASI75; Last observation carried forward was used for LEI, LDI and mNAPSI.

Results: 409 pts were randomized. Baseline (BL) demographics were similar between groups. 19.1% and 19.8% of PBO and CZP (combined dose) pts received prior anti-TNF. ACR20 response at Wk12 was significantly higher in the CZP 200 mg Q2W and CZP 400 mg Q4W arms vs. PBO (58.0% and 51.9% vs. 24.3% [p<0.001 for both]) and was observed as early as Wk1 (21.0% [p=0.001] and 23.0% [p<0.001] vs.7.4%).[1] PASI75 response at Wk24 for pts with ≥3% psoriasis body surface area at BL (61.6% randomized set [RS]) was 62.2% with CZP 200mg Q2W and 60.5% with CZP 400mg Q4W vs 15.1% PBO (p<0.001 for both). In pts with BL enthesitis

(64.3% RS) LEI change from BL at Wk24 was −2.0 with CZP 200mg Q2W (p<0.001) and −1.8 with CZP 400mg Q4W (p=0.003) vs −1.1 PBO. For pts with BL nail disease (73.3% RS) mNAPSI change from BL at Wk24 was −1.6 with CZP 200mg Q2W and −2.0 with CZP 400mg Q4W vs −1.1 PBO. No differences in LDI change from BL were observed in pts with BL dactylitis. At Wk24, ACR response rates were similar between CZP arms and greater vs. PBO irrespective of prior anti-TNF exposure (Figure). Adverse events (AEs) occurred in 62% vs 68% and SAEs in 7% vs. 4% in CZP vs PBO pts (combined dose), respectively. Two deaths occurred up to Wk24, one sudden death of unknown cause (CZP 400mg Q4W) and one myocardial infarct (CZP 200mg Q2W). No new safety signals were observed.
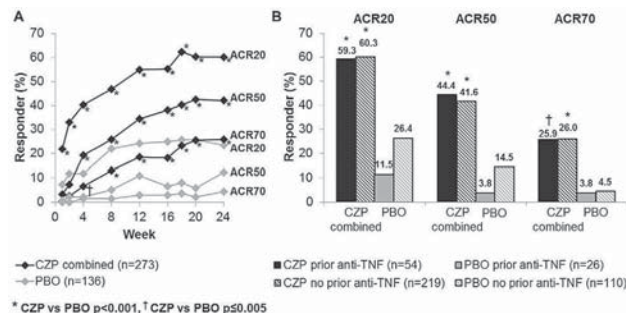
Figure. ACR 20/50/70 response in overall population to Wk24 (A) and pts with and without prior anti-TNF exposure at Wk24 (B) in RAPID-PsA.

Conclusion: Rapid improvements in the signs and symptoms of PsA, as well as skin manifestations and nail disease of psoriasis, were observed across both CZP dosing regimens. Similar ACR response rates with CZP were observed in pts with and without prior anti-TNF exposure.

Reference
1. Mease P, Ann Rheum Dis 2012;71(Suppl3):150

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The Risk of Diabetes in Psoriatic Arthritis and Rheumatoid Arthritis. Maureen Dubreuil[1], Young Hee Rho[1], Ada Man[2], Yanyan Zhu[3], Yuqing Zhang[2], Thorvardur Love[4], Alexis Ogdie[5], Joel Gelfand[6] and Hyon Choi[1]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University, Boston, MA, [3]Department of Biostatistics, Boston University School of Public Health, Boston, MA, [4]Labspitali University Hospital, Reykjavik, Iceland, [5]University of Pennsylvania, Philadelphia, PA, [6]University of Pennsylvania., Philadelphia, PA

Background/Purpose: The potential impact of psoriatic arthritis (PsA) and rheumatoid arthritis (RA) on the risk of incident diabetes remains unclear. Studies have shown that patients with psoriasis have an increased risk of incident diabetes; however, no published data are available specific to patients with psoriatic arthritis. Furthermore, there is a scarcity of data on the risk of diabetes among patients with rheumatoid arthritis, and the available data in RA are conflicting. We aimed to evaluate the risk of incident diabetes in PsA and RA in the general population, with adjustment for body mass index (BMI) and lifestyle factors.

Methods: We conducted a cohort study using data from an electronic medical records database representative of the UK general population, collected between 1986 and 2010. We used previously published definitions of PsA, psoriasis, RA (exposures) and diabetes (outcome) in the same cohort context. We estimated hazard ratios (HR) for incident diabetes compared with age- and sex-matched comparison cohorts without any known rheumatic conditions, after adjusting for body mass index, smoking, alcohol, comorbidities, and glucocorticoids use.

Results: Diabetes developed in 179 of 4,196 individuals with PsA (50% female, mean age 49 years, mean BMI 27.6), in 2,202 of 59,281 persons with psoriasis (51% female, mean age 49 years, mean BMI 26.7), and in 383 of 11,158 individuals with RA (68% female, mean age 58 years, mean BMI 26.8). Age- and sex-matched HRs for diabetes were 1.72 (1.46–2.02) in PsA, 1.39 (1.32–1.45) in psoriasis, and 1.12 (1.01–1.25) in RA relative to the

comparison cohorts. After adjustment for BMI, smoking, and alcohol use, these HRs were attenuated substantially (1.43, 1.24, and 1.00, respectively). With further adjustment for glucocorticoid use and comorbidity index, the HRs were 1.33 (1.09–1.61) in PsA, 1.21 (1.15–1.27) in psoriasis, and 0.94 (0.84–1.06) in RA.

Table 1. Baseline Characteristics of the Study Populations.

		PsA (n = 4196)	No PsA (n = 41794)	P Value	Psoriasis (n = 59281)	No Psoriasis (n = 581248)	P Value	RA (n = 11158)	No RA (n = 110375)	P Value
Age		48.7 ± 13.9	48.7 ± 13.8	0.92	49.2 ± 17.1	48.9 ± 17	<0.001	58.4 ± 14.2	58.2 ± 14.1	0.33
Women (%)		2104 (50.1%)	20965 (50.2%)	0.98	30330 (51.2%)	297675 (51.2%)	0.82	7582 (68%)	75093 (68%)	0.86
BMI(kg/m²)	Mean ± SD	27.6 ± 5.6	26.2 ± 5.4	<0.001	26.7 ± 5.4	25.9 ± 5.0	<0.001	26.8 ± 5.2	26.3 ± 5.0	<0.001
	<18.5	33 (0.8%)	580 (1.4%)	<0.001	893 (1.5%)	9115 (1.6%)	<0.001	167 (1.5%)	1546 (1.4%)	<0.001
	18.5-24.9	1170 (27.9%)	13698 (32.8%)		18227 (30.7%)	185857 (32%)		3522 (31.6%)	35626 (32.3%)	
	25.0-29.9	1152 (27.5%)	10580 (25.3%)		15772 (26.6%)	140238 (24.1%)		3238 (29.0%)	29777 (27.0%)	
	≥30.0	948 (22.6%)	5653 (13.5%)		9859 (16.6%)	71193 (12.2%)		2017 (18.1%)	15919 (14.4%)	
	Unknown	893 (21.3%)	11283 (27%)		14530 (24.5%)	174845 (30.1%)		2214 (19.8%)	27507 (24.9%)	
Smoking	Never	1967 (46.9%)	19730 (47.2%)	<0.001	23828 (40.2%)	267871 (46.1%)	<0.001	4730 (42.4%)	54696 (49.6%)	<0.001
	Past	807 (19.2%)	5811 (13.9%)		10846 (18.3%)	78779 (13.6%)		2351 (21.1%)	17516 (15.9%)	
	Current	929 (22.1%)	9285 (22.2%)		16770 (28.3%)	122223 (21%)		2798 (25.1%)	20521 (18.6%)	
	Unknown	493 (11.7%)	6968 (16.7%)		7837 (13.2%)	112375 (19.3%)		1279 (11.5%)	17642 (16%)	
Alcohol	Never	521 (12.4%)	4670 (11.2%)	<0.001	7041 (11.9%)	67642 (11.6%)	<0.001	1870 (16.8%)	15363 (13.9%)	<0.001
	Past	49 (1.2%)	398 (1.0%)		726 (1.2%)	5376 (0.9%)		175 (1.6%)	1182 (1.1%)	
	Current	2756 (65.7%)	25806 (61.7%)		37147 (62.7%)	335973 (57.8%)		6770 (60.7%)	66374 (60.1%)	
	Unknown	870 (20.7%)	10920 (26.1%)		14367 (24.2%)	172257 (29.6%)		2343 (21.0%)	27456 (24.9%)	
Oral Glucocorticoid Use		343 (8.2%)	1096 (2.6%)	<0.001	2525 (4.3%)	15354 (2.6%)	<0.001	2470 (22.1%)	3707 (3.4%)	<0.001
Topical Glucocorticoid Use		1475 (35.2%)	1808 (4.3%)	<0.001	14844 (25%)	23956 (4.1%)	<0.001	900 (8.1%)	5493 (5%)	<0.001
Charlson Comorbidity Index		0.13 ± 0.38	0.07 ± 0.34	<0.001	0.1 ± 0.39	0.08 ± 0.37	<0.001	0.21 ± 0.51	0.1 ± 0.41	<0.001

PsA = Psoriatic Arthritis, RA = Rheumatoid Arthritis, SD = standard deviation. P values were calculated by t-test or Wilcoxon rank-sum test for continuous variables or chi-square test for indicator or categorical variables.

Table 2. Incidence Rates and Hazard Ratios for Diabetes among Psoriatic Arthritis (PsA), Psoriasis, Rheumatoid Arthritis (RA), and Comparison Cohorts

	PsA	No PsA	Psoriasis	No Psoriasis	RA	No RA
Diabetes Cases (n)	179	1029	2202	15359	383	3477
Total Follow-Up Time (PY)	24625	236780	345507	3294591	61087	605507
Mean Follow-Up Time (years)	5.9	5.7	5.8	5.7	5.5	5.5
Incidence Rate (per 1000 PY)	7.3	4.3	6.4	4.7	6.3	5.7
Age-, Sex-, and Entry Time-Adjusted HR (95% CI)	1.72 (1.46 to 2.02)	1.00 (referent)	1.39 (1.32 to 1.45)	1.00 (referent)	1.12 (1.01 to 1.25)	1.00 (referent)
+BMI-, Smoking-, and Alcohol-Adjusted HR (95% CI)	1.43 (1.2 to 1.7)	1.00 (referent)	1.24 (1.18 to 1.31)	1.00 (referent)	1.00 (0.89 to 1.12)	1.00 (referent)
+Oral and Topical Glucocorticoids, and Charlson Index-Adjusted HR (95% CI)	1.33 (1.09 to 1.61)	1.00 (referent)	1.21 (1.15 to 1.27)	1.00 (referent)	0.94 (0.84 to 1.06)	1.00 (referent)

PY = person-years

Conclusion: This large general population study suggests that the overall risk of diabetes is increased in PsA, which can be substantially explained by increased adiposity, lifestyle factors, and other covariates. In contrast, risk of diabetes among patients with RA is significantly elevated only due to increased BMI and smoking. Overall, these findings suggest that diabetes risk should not be ascribed only to the presence of inflammatory disease. Important opportunities exist for future interventions directed at weight loss and smoking cessation to reduce risk of diabetes in these populations, and to determine how psoriatic disease contributes to the risk of developing diabetes.

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Circulating Levels of Citrullinated Vimentin Fragments Are Diagnostic and Prognostic in Ankylosing Spondylitis; Evidence for Disease-Related Citrullination. Anne C. Bay-Jensen[1], Morten Asser Karsdal[1], Efstathios Vassiliadis[2], Stephanie Wichuk[3], Zheng Zhao[4], Robert GW Lambert[3], Rik Lories[5], Claus Christiansen[6] and Walter P. Maksymowych[3]. [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Nordic Bioscience, Herlev, Denmark, [3]University of Alberta, Edmonton, AB, [4]Department of Rheumatology, University of Alberta and PLA General Hospital, Beijing, PR China, Beijing, China, [5]KU Leuven, Leuven, Belgium, [6]CCBR, Ballerup, Denmark

Background/Purpose: Rheumatoid arthritis (RA) is considered an anti-CCP positive disease whereas ankylosing spondylitis (AS) is considered an anti-CCP negative disease. Anti-CCP has prognostic capacity in RA. Assessment of metalloproteinases (MMP) may also add prognostic information in both diseases. We evaluated whether a citrullinated and MMP degraded

fragment of vimentin (VICM) could be used as an in vitro diagnostic and prognostic biomarker in AS.

Methods: Serum VICM was measured in samples of controls (n=35), RA (n=47) and AS (n=201) patients. Optimal cut-off for diagnostic sensitivity and specificity was determined by ROC analysis. Baseline and 2-year spinal radiographs were available on 118 AS patients and radiographic progression was scored using the mSASSS. Correlations with patient demographics (age, disease duration), disease activity (BASDAI, CRP, SPARCC MRI Spine 23-DVU score), and severity (mSASSS), were determined. The independent association of VICM with 2-year radiographic progression, defined as mSASSS change>0 or the development of a new syndesmophyte, was analyzed by multivariate regression adjusting for baseline mSASSS.

Results: Both RA and AS had significantly higher levels of VICM than controls ($p < 0.001$). AS patients with the highest level of VICM had the largest burden of disease i.e. highest mSASSS score and disease activity (BASDAI) ($p < 0.001$). VICM correlated significantly with SPARCC MRI Spine 23DVU score ($p = 0.046$). VICM was significantly and independently associated with radiographic progression after 2 years ($\beta = 0.69$, $p=0.0005$). Patients with both high VICM and a high baseline mSASSS had the highest risk for radiographic progression (OR for mSASSS change = 13, new syndesmophyte = 32) and 67% of these had progression (figure).
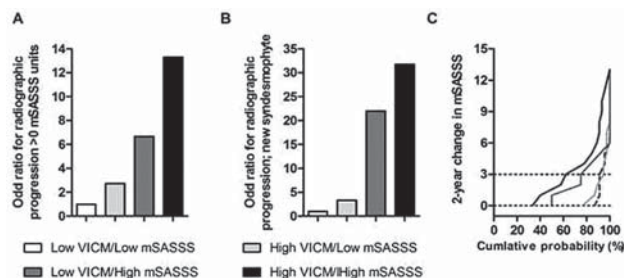
Conclusion: Serum VICM is a diagnostic and prognostic marker for AS. Moreover, our data challenges the paradigm that AS is an Anti-CCP negative disease.

Disclosure: A. C. Bay-Jensen, None; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 4; **E. Vassiliadis**, None; **S. Wichuk**, None; **Z. Zhao**, None; **R. G. Lambert**, None; **R. Lories**, None; **C. Christiansen**, Nordic, Bioscience A/S, CCBR/Synarc,, Roche, Eli Lilly, Novartis, Novo Nordisk, Proctor and Gamble, Groupe Fournier, Besins Esco-Vesco, Merck Sharp and Dohme, Chiesi, Boehringer Mannheim, Pfizer, GlaxoSmithKline, Amgen., 5; **W. P. Maksymowych**, None.

2616

The Transition From Psoriasis (Ps) to Psoriatic Arthritis (PsA) Is Associated with Elevated Circulating Osteoclast Precursors (OCP) and Increased Expression of DC-STAMP. Ya-Hui Chiu[1], Edward M. Schwarz[1], Dafna Gladman[2], Sharon Moorehead[1], Michelle Smith[1], Rick Barrett[1] and Christopher T. Ritchlin[3]. [1]University of Rochester, Rochester, NY, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]University of Rochester Medical Center, Rochester, NY

Background/Purpose: Approximately 20% of psoriasis (Ps) patients (pts) develop psoriatic arthritis (PsA). Early diagnosis and therapy of PsA can limit bone and joint damage; however, biomarkers to detect subclinical joint inflammation are not available. Osteoclasts (OC) are specialized cells circulating in the blood and responsible for bone erosion in erosive arthritis. We previously showed that osteoclast precursors (OCP) are elevated in a subset of Ps pts and that DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a protein expressed on the surface of monocytes, is a reliable OCP marker. To examine if the transition from Ps to PsA is associated with a change in OCP frequency and the percentage of monocytes that express DC-STAMP, we monitored these 2 parameters on Ps patients before and after the onset of arthritis.

Methods: We follow over 132 Ps patients at the Rochester site in the International Psoriatic Arthritis Research Team (IPART) registry. Ps was confirmed by a dermatologist and PsA was diagnosed by a rheumatologist based on the CASPAR criteria. Blood samples were collected at baseline and after Ps pts developed PsA. To analyze DC-STAMP expression, cells were purified from blood by Ficoll gradient, stained with anti-DC-STAMP and anti-CD14 antibodies, and analyzed by flow cytometry. To enumerate OCP, cells were cultured in OC-promoting media and TRAP-stained. Cells with ≥3 nuclei were counted as OC.

Results: Over the past year, 6 Ps pts at our site developed PsA. The average Ps duration year was 28.7±17.9, Tender Joint Counts were 8.3±6.7 (prior) and 16±15 (after), Swollen Joint Counts were 3.9±4.1 (prior) and 7.1±9.6 (after), PASI scores were 4.7 ± 3.5 (prior) and 2.0 ± 1.1 (after). Of the 6 pts who developed PsA, 5 had scalp psoriasis, 4 had nail disease, 4 had a family history of psoriatic disease and a history of prior trauma. Two of these patients had baseline radiographic erosions. A significant increase in the frequency of OCP was observed at the time of arthritis onset in all patients (Fig 1), whereas an increase in the percentage of DC-STAMP+ monocytes was detected in 4 of 6 pts (Fig 2).
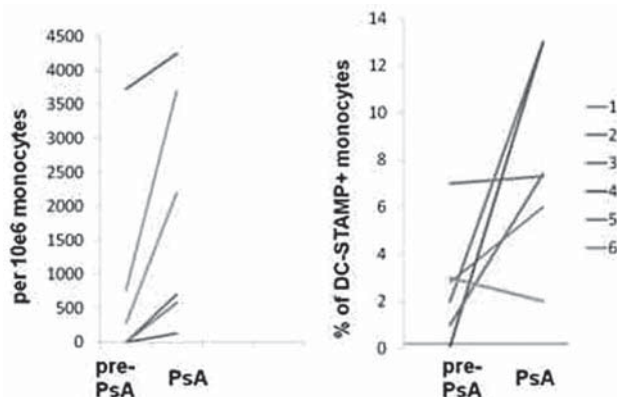
Figure 1. The frequency of circulating OC increases after Ps to PsA transition.
Figure 2. The frequency of circulating DCSTAMP+ monocytes increases after Ps to PsA transition.

Conclusion: The progression of Ps to PsA was associated with a dramatic increase in circulating OCP numbers accompanied with an elevated DC-STAMP+CD14+ monocyte frequency. Collectively, our results suggest that the OCP numbers as well as the frequency of circulating DC-STAMP+ monocytes in the blood are potential arthritis susceptible biomarkers in Ps patients.

Disclosure: Y. H. Chiu, None; **E. M. Schwarz**, None; **D. Gladman**, None; **S. Moorehead**, None; **M. Smith**, None; **R. Barrett**, None; **C. T. Ritchlin**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects
and Treatment IV: Therapeutics
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

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Outcomes Associated with Belimumab in Black/African American Patients with Systemic Lupus Erythematous in Clinical Practice Settings in the United States.
Christopher E. Collins[1], Siva Narayanan[2], Maria Dall'Era[3], Greg Dennis[2], Alan Oglesby[4], Mark B. McGuire[5], Ramesh Pappu[6], Charles T. Molta[7] and Greg Keenan[2]. [1]Washington Hospital Ctr, Washington, DC, [2]Human Genome Sciences, Inc., Rockville, MD, [3]University of California, San Francisco, San Francisco, CA, [4]GlaxoSmithKline, Research Triangle Park, NC, [5]Medical Data Analytics, Parsippany, NJ, [6]GlaxoSmithKline, USA, Philadelphia, PA, [7]GlaxoSmithKline, Philadelphia, PA

Background/Purpose: Effectiveness of belimumab in black/African American (AA) patients (pts) with Systemic Lupus Erythematous (SLE) is yet to be adequately demonstrated. The objective of this analysis is to describe the clinical outcomes associated with belimumab therapy in black/AA SLE pts in community practice settings in the United States (U.S).

Methods: This is a multi-center cohort study adult SLE pts in the U.S recruited by a nationally representative random sample of rheumatologists who were treating >10 SLE pts annually and had >5 yrs of practice experience. Physicians are randomly identifying SLE pts in their practices who had received at least 8 infusions of belimumab as part of usual care and assessed the following data corresponding to the 6 months prior to belimumab initiation (baseline: BL) and the first 6 months after belimumab initiation: demographics, comorbidities, SLE disease characteristics, clinical outcomes and resource utilization (including medications). The percentage change in disease manifestations was assessed in pts based on physician judgment at 6 months post belimumab initiation in comparison to baseline. Black/AA pts were included in this interim subset analysis.

Results: Analysis included 58 black/AA SLE pts (from 31 rheumatologists from 18 states) with available data; mean pt age was 40.3 years; 93% female; and 50% diagnosed with SLE for ≥ 5 yrs. At BL, 76% had high anti-dsDNA, 59% had low C3 or C4; and 2%, 71% and 28% had mild, moderate and severe disease respectively. The top 3 reasons for initiating belimumab (10mg/kg) were ineffective previous treatment regimens, decrease the use of steroids (steroid sparing) and worsening patient condition; 83%, 69% and 67% of pts concomitantly used oral steroids, antimalarials and immunosuppressants respectively. After 6 months of belimumab therapy, 90%, 41% and 14% of pts had an overall clinical improvement of ≥20%, ≥50%, and ≥80% respectively. Changes in manifestations by organ system (top-5) are shown in the table. The mean reduction in steroid dose was 14.2 mg/day; 10% discontinued steroids and among those still taking steroids, 93% decreased their doses.

	Musculoskeletal	Immunologic	Mucocutaneous	Constitutional	Hematologic
# of manifestations (pts)	55 (49)	52 (33)	44 (32)	36 (35)	25 (20)
Worsened	0%	0%	0%	0%	0%
No change	6%	21%	7%	8%	24%
% improvement					
<20%	9%	15%	14%	14%	8%
≥20%	85%	63%	80%	78%	68%
≥50%	38%	38%	43%s	39%	40%
≥80%	15%	8%	23%	8%	24%

Conclusion: In this analysis of black/AA pts receiving at least 6 months of belimumab therapy in clinical practices, clinical improvements were observed in a majority of pts with SLE across multiple manifestations. Steroid sparing effects were observed in most of the pts. Additional studies assessing belimumab effectiveness in black/AA pts with SLE are warranted.

Disclosure: C. E. Collins, Human Genome Sciences, Inc., 5; **S. Narayanan**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **M. Dall'Era**, Human Genome Sciences, Inc., 5; **G. Dennis**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **A. Oglesby**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **M. B. McGuire**, Human Genome Sciences, Inc., 2; **R. Pappu**, GlaxoSmithKline, 1, Glaxo-SmithKline, 3; **C. T. Molta**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **G. Keenan**, HGS, 1, HGS, 3.

2618

Lupus Disease Activity Severely Impairs Pandemic Influenza A/H1N1 Vaccine Immune Response in Patients without Therapy.
Eduardo F. Borba[1], Sandra G. Pasoto[1], Ana L. Calich[1], Ricardo Fuller[1], Vilma S.T. Viana[1], Margareth Vendramini[1], Joao Miraglia[2], Maria A. Ishida[3] and Eloisa Bonfa[4]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Fundação Butantan, São Paulo, Brazil, [3]Adolfo Lutz Institute, Sao Paulo, Brazil, [4]University of São Paulo, São Paulo, Brazil

Background/Purpose: To determine the influence of disease activity without the effect of drugs in pandemic 2009 influenza A (H1N1) vaccine immune response in untreated systemic lupus erythematosus (SLE).

Methods: SLE patients without therapy [n=75] and healthy controls [n=170] were vaccinated with a single dose of a nonadjuvanted A/California/7/2009/H1N1 vaccine. Clinical and laboratorial data, including disease activity scores (SLEDAI), were monitored prevaccination and 21 days postvaccination. Anti-H1N1 titres, percentages of seroprotection (SP), and seroconversion (SC) were evaluated.

Results: After immunisation, untreated patients with SLEDAI=0 [n=22] had comparable SP (86.4%; 95%CI 72.0–100.7; p=1.0) and SC (86.4%; 95%CI 72.0–100.7; p=0.57) to controls whereas untreated patients with any level of disease activity (SLEDAI>0) [n=53] had lower SP (69.8%; 95%CI 57.4–84.4 vs. 84.1%; 95%CI 78.6–89.6; p=0.028) and SC rates (66.0%; 95%CI 53.2–78.7 vs. 80.0%; 95%CI 74.0–86.0; p=0.041) compared to controls. Reinforcing this finding, a significant lower SP (37.5%; 95%CI 13.8–61.2 vs. 79.6%; 95%CI 69.3–89.9; p=0.008) and SC rates (37.5%; 95%CI 13.8–61.2 vs. 77.9%; 95%CI 67.3–88.5; p=0.016) were observed in untreated SLE patients with SLEDAI>6 [n=16] compared with those with SLEDAI<6 [n=59], in spite of a similar mean lymphocyte count (1,260 ± 625 vs. 1,480 ± 840/mm³; p=0.33). Untreated SLE patients with low lymphocytes (<1,000/mm³) [n=21] had similar SP (61.9%; 95%CI 41.1–82.4 vs. 72.2%; 95%CI 60.2–84.1; p=0.41) and SC rates (57.1%; 95%CI 35.9–78.3 vs. 72.2%; 95%CI 60.2–84.1; p=0.27) compared to untreated SLE patients with levels within normal range (>1,000/mm³) [n=54]. SLE patients with anti-dsDNA+ [n=42] had lower postvaccine SP (59.5%; 95% CI 44.6

to 74.3 vs. 81.8%; 95% CI 68.6 to 94.9; p=0.046) and SC rates (57.1%; 95% CI 42.1 to 72.1 vs. 81.8%; 95% CI 68.6 to 94.9; p=0.027) compared to SLE patients without this antibody (anti-dsDNA-) [n=33].

Conclusion: This study provides clear evidence that SLE disease activity severely impairs pandemic influenza H1N1 vaccine immune response independent of lymphocyte counts or drugs.

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2619

A Double-Blind Randomized Placebo-Controlled Trial of the Effect of Vitamin D3 On the Interferon Signature in Patients with Systemic Lupus Erythematosus. Cynthia Aranow[1], Maria Dall'Era[2], Elena M. Massarotti[3], Meggan C. Mackay[4], Andreea Coca[5], Fotios Koumpouras[6], Marc C. Levesque[7], W. Winn Chatham[8], Megan E. B. Clowse[9], Lisa G. Criscione-Schreiber[9], Sherri Callahan[10], Ellen A. Goldmuntz[10], Lynette Keyes-Elstein[11], Betty Diamond[12] and Diane L. Kamen[13]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]University of California, San Francisco, San Francisco, CA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]The Feinstein Institute, Manhasset, NY, [5]University of Rochester, Rochester, NY, [6]West Penn Hospital, Pittsburgh, PA, [7]University of Pittsburgh, Pittsburgh, PA, [8]University of Alabama at Birmingham, Birmingham, AL, [9]Duke University Medical Center, Durham, NC, [10]NIAID/NIH Rm 6807, Bethesda, MD, [11]Rho Federal Systems, Inc., Chapel Hill, NC, [12]Feinstein Institute Med Rsch, Manhasset, NY, [13]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC

Background/Purpose: Exposure of normal PBMCs to 1,25 OH vitamin D reverses the stimulatory effects of activating SLE sera on the interferon signature. Given that IFN is made by activated plasmacytoid dendritic cells (pDCs), vitamin D maintains pDC quiescence, and vitamin D deficiency has a high prevalence in SLE, we investigated the effect of vitamin D supplementation on the IFN signature in SLE patients. Secondary aims included determination of the effect of vitamin D on disease activity and the safety/tolerability of vitamin D in deficient SLE patients.

Methods: 57 anti-DNA antibody positive SLE patients from 8 centers with stable, inactive (SLEDAI ≤4) disease, serum 25-OH vitamin D ≤20ng/ml and an IFN signature were randomized (1:1:1) into a 12 week double-blind placebo controlled trial of daily oral vitamin D3. A IFN signature was defined to be present if expression of 1 of 3 IFN responsive genes (Mx1, Ifit1, or Ifi44) determined using RT-PCR of whole blood mRNA was expressed at a level ≥ 4 SD above the mean of normal controls, or if 2 of the 3 genes were expressed > 2 SD above the mean of normal controls. Immunosuppressive medications were required to be stable at baseline with no expectation of change during the 12 week treatment period. Subjects received 0, 2000 or 4000 IU vitamin D3 daily. A IFN signature response was defined as a 50% reduction in the expression of 1 gene or a 25% decrease in 2 genes compared to baseline provided that expression of the remaining genes did not increase >25%. Measures of disease activity, safety, tolerability and endocrine effects (PTH, urinary calcium/creatinine) were collected.

Results: Baseline characteristics of the 3 treatment groups were similar. Mean (SD) 25 OH D levels (ng/mL) were comparable across treatment groups at entry: 14.5 (4.65), 12.6 (3.76) and 15.3 (3.08) for placebo, low dose and high dose, respectively. No subjects receiving placebo achieved levels associated with endocrine repletion (25 OH D ≥ 30ng/ml) while 11 of 18 subjects receiving 4000 IU daily and 5 of 15 receiving 2000 IU daily exceeded that threshold. The percent of subjects with an IFN signature response was not significantly different among treatment groups at Week 12 (36.8, 23.5, 27.8; placebo, 2000 IU/day dose, 4000 IU/day dose respectively). At Week 12, 36% of deficient subjects and 31% of subjects with 25 OH D values ≥ 30 ng/ mL had an IFN signature response (NS). Furthermore, there was no significant difference in 25 OH D levels between subjects with and without an IFN signature response. Results did not differ significantly whether analyzed per protocol or by intent-to-treat. Vitamin D3 was well tolerated with no safety concerns and no treatment related serious adverse events.

Conclusion: These results suggest that vitamin D3 at doses up to 4000 IU daily was safe and well-tolerated in SLE patients. However, daily doses of vitamin D3 for 12 weeks failed to diminish the IFN signature in vitamin D deficient SLE patients, although repletion of 25 OH D to levels associated with bone health (≥ 30ng/ml) was only achieved in a minority of trial participants. Higher levels of 25 OH D sustained for longer duration may be required for affecting the anticipated immunological outcomes.

Disclosure: **C. Aranow**, None; **M. Dall'Era**, None; **E. M. Massarotti**, None; **M. C. Mackay**, None; **A. Coca**, None; **F. Koumpouras**, None; **M. C. Levesque**, None; **W. W. Chatham**, None; **M. E. B. Clowse**, None; **L. G. Criscione-Schreiber**, None; **S. Callahan**, None; **E. A. Goldmuntz**, None; **L. Keyes-Elstein**, None; **B. Diamond**, None; **D. L. Kamen**, None.

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Randomized, Double-Blind, Placebo-Controlled Studies of P140 Peptide in Mannitol (Lupuzor) and Trehalose (Forigerimod) in Patients with SLE. Robert Zimmer[1], Daniel J. Wallace[2] and Sylviane Muller[3]. [1]Immu-Pharma France, Mulhouse, France, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]CNRS, Strasbourg, France

Background/Purpose: Advances in the understanding of autoimmune diseases pathogenesis have led to the development of peptide-based therapies that aim to potentially reinstate tolerance to self without the need for immunosuppression. P140 peptide is a 21-mer linear peptide (sequence 131–151) that is issued from the small nuclear ribonucleoprotein U1-70K and that is phosphorylated at the Ser[140] position. Following a promising open phase IIa clinical trial in patients with SLE, two Phase IIb clinical trials were undertaken to evaluate the effect of peptide P140 administrated either in mannitol (Lupuzor) or in trehalose (Forigerimod) as excipient. Data obtained independently with Benlysta are used for comparison (Furie et al. 2011 Arthritis Rheum. 63, 3918–30).

Methods: Two multicenter, randomized, placebo-controlled phase IIb studies were run separately with similar "standard" protocols: 200μg P140/individual/month in addition to standard of care, inclusion of patients with clinical SLEDAI-2K scores >6 and no Bilag A score. The demographic characteristics of the study populations were similar in all three studies as well as in each treatment group. Drop-out rates were recorded irrespective of their reason and considered as treatment failure. Efficacy was evaluated using the SRI score.

Results: Clinical studies results:

	P140 mannitol	P140 trehalose	Benlysta (BLISS-76)
Duration of treatment	3 months	6 months	12 months
Number of patients × arms	50 × 3	92 × 2	273 × 3
SAE active/placebo	6%/6%	10%/14%	19%/20%
Drop-out rate active	5%	22%	23%
Drop-out rate placebo	16%	23%	25%
Responder rate active	62%	34%	43%
Responder rate placebo	37%	40%	33%

Conclusion: Lupuzor (P140 in mannitol) is safe and met its primary efficacy end point in lupus patients. Data suggest that P140 may restore tolerance by acting as an altered peptide ligand of the T cell receptor. P140 also reduces autophagic process, which has been shown recently to be abnormally enhanced in T lymphocytes from lupus mice and patients. The potential reduction by Lupuzor of the enhanced autophagy process (as seen in mouse models) led to a very short onset of action, which is supported by the efficacy data. Trehalose is a known inducer of autophagy and as anticipated, it interferes with the beneficial effect of P140. Its use together with P140 peptide is therefore inappropriate in the treatment of lupus patients.

Disclosure: **R. Zimmer**, ImmuPharma, 1; **D. J. Wallace**, None; **S. Muller**, ImmuPharma, 2.

2621

Sustained Disease Improvement and Safety Profile Over 1745 Patient-Year Experience (7 years) with Belimumab in Systemic Lupus Erythematosus Patients. Joan T. Merrill[1], Richard A. Furie[2], Daniel J. Wallace[3], William Stohl[4], W. Winn Chatham[5], Arthur Weinstein[6], James D. McKay, Ellen M. Ginzler[8], Z. John Zhong[9], William W. Freimuth[9] and Michelle A. Petri[10]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]North Shore-LIJ Health System, Lake Success, NY, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]University of Southern California Keck School of Medicine, Los Angeles, CA, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Washington Hospital Center, Washington, DC, [7]SUNY-Downstate Medical Center, Brooklyn, NY, [8]Human Genome Sciences, Inc., Rockville, MD, [9]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: To update belimumab safety and efficacy data over 7 y in patients with active SLE.

Methods: 449 SLE patients with SELENA-SLEDAI scores ≥4 were enrolled in a phase 2 study of belimumab 1, 4, or 10 mg/kg vs placebo, plus standard therapy, for 52 wk (NCT00071487). At wk 56, placebo patients switched to belimumab 10 mg/kg and belimumab-treated patients maintained their dose or switched to 10 mg/kg. From wk 80, all patients entering a continuation study received belimumab 10 mg/kg (NCT00583362). AEs were assessed at each study visit. Analyses of disease activity included SLE Responder Index (SRI; post-hoc analysis), British Isles Lupus Assessment Group (BILAG) A/B flares, SELENA-SLEDAI Flare Index (SFI), and biomarker changes. Efficacy assessments were limited to patients who were autoantibody positive (antinuclear antibody titer ≥1:80 or anti-double−stranded DNA ≥30 IU/mL) at baseline.

Results: Of the original 449 patients, 296 (66%) entered the continuation trial. At end of 7 y, 190 patients remained. Total belimumab exposure was >1745 patient-y. Belimumab was well tolerated, with AEs/100 patient-y stable or decreasing over 7 y (see table). Seven patients died over 7 y; no cause predominated. Etiologies included aspiration pneumonia, infection, cardiovascular disease, suicide, osteomyelitis, and B-cell lymphoma. The SRI rate with belimumab was 46% at wk 52 (vs 29% with placebo; p <0.05), increasing to 55%–65.2% through the 7-y open-label treatment. The frequency of 1 new BILAG A or 2 new B flares with belimumab (all treatment arms combined) was 38% at 1 y (vs 44% with placebo), decreasing to 7.7% at 7 y. The frequency of all SFI flares was 84% (severe 17%) at 1 y (vs 85% [19%] with placebo), decreasing to 40.4% (2.1%) at 7 y. During the study, many patients with anti-double−stranded DNA at baseline became negative (45.8% at 7 y) and normalized complement (C3 66.0%; C4 71.4%). Of the 118 remaining patients on corticosteroids at baseline, corticosteroid use decreased (median reduction 55%; absolute reduction 3.7 mg/d at 7 y).

AE Incidence (rate per 100 patient-y) in Patients Treated With Belimumab[a]

	1 (0–1 y)	2 (1–2 y)	3 (2–3 y)	4 (3–4 y)	5 (4–5 y)	6 (5–6 y)	7 (6-7y)
				Interval[b]			
Patients, n (patient-y)	336 (320.1)	339 (299.1)	274 (258.1)	248 (234.2)	223 (215.8)	208 (197.6)	190 (167.0)
Overall AEs	326 (101.8)	322 (107.7)	260 (100.8)	237 (101.2)	211 (97.8)	191 (96.7)	172 (103.0)
Serious AEs	55 (17.2)	52 (17.4)	49 (19.0)	31 (13.2)	41 (19.0)	32 (16.2)	30 (18.0)
Overall infections	254 (79.4)	237 (79.2)	192 (74.4)	181 (77.3)	145 (67.2)	126 (63.8)	128 (76.6)
Serious infections	17 (5.3)	14 (4.7)	8 (3.1)	8 (3.4)	6 (2.8)	8 (4.0)	5 (3.0)
Malignancies[c]	0	3 (1.0)	2 (0.8)	1 (0.4)	3 (1.4)	2 (1.0)	1 (0.6)
Mortality	3 (0.8)	0	1 (0.4)	1 (0.4)	0	0	2 (1.2)

[a]Data presented as no. of patients with AE (no./100 patient-y) unless specified; [b]interval 1 includes only patients treated with belimumab (and not placebo) during the 52-wk, double-blind study (except mortality data includes 2 deaths during the 52-wk, double-blind period and 1 during the extension period); intervals 2–7 (and interval-1 mortality data; n = 424; 374.0 patient-y) include all belimumab-treated patients, including those originally randomized to placebo who subsequently switched to belimumab; [c]excluding nonmelanoma skin cancer and including unspecified malignancy of lungs.

Conclusion: Belimumab plus standard SLE therapy was well tolerated in SLE patients for 7 y in an open-label study. Seven patients died; no cause predominated. Autoantibody-positive patients treated with belimumab had sustained improvement in disease activity and decreased flares over 7 y, accompanied by reductions in autoantibody levels and corticosteroid requirements.

Disclosure: J. T. Merrill, HGS, GSK, 5; **R. A. Furie**, HGS, GSK, 2, HGS, GSK, 5, HGS, GSK, 8; **D. J. Wallace**, HGS, GSK, 2, HGS, GSK, 5, HGS, GSK, 8; **W. Stohl**, HGS, GSK, 2; **W. W. Chatham**, HGS, GSK, 2, HGS, GSK, 5; **A. Weinstein**, HGS, Genentech, Savient, Pfizer, 2, HGS, GSK, Pfizer, 5, HGS, GSK, 8; **J. D. McKay**, HGS, GSK, 1; **E. M. Ginzler**, HGS, GSK, 2; **Z. J. Zhong**, HGS, 1, HGS, 3; **W. W. Freimuth**, HGS, 1, HGS, 3; **M. A. Petri**, HGS, GSK, 5.

2622

Efficacy and Safety of Rontalizumab (Anti-Interferon Alpha) in SLE Subjects with Restricted Immunosuppressant Use: Results of A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study. K. Kalunian[1], Joan T. Merrill[2], R. Maciuca[3], Wenjun Ouyang[3], J. M. McBride[3], Michael J. Townsend[3], E. Park[3], J. Li[3], X. Wei[3], A. Morimoto[3], R. Boismenu[3], John C. Davis Jr.[3] and William P. Kennedy[3]. [1]UCSD School of Medicine, La Jolla, CA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Genentech, Inc, South San Francisco, CA

Background/Purpose: Dysregulation of interferon alpha (IFN) activity and/or signaling is implicated in systemic lupus (SLE). This randomized, double-blind, placebo-controlled, two part Phase 2 study (ROSE) evaluated the efficacy and safety of intravenous (IV) and subcutaneous (SC) rontalizumab, a humanized IgG1 antibody against all anti-interferon alpha isoforms, in adults with moderate to severe extrarenal SLE.

Methods: Subjects were randomized 2:1 in sequential cohorts to: 750 mg IV q4wk rontalizumab or placebo (pbo) (part 1) and 300 mg SC q2wk rontalizumab or pbo (part 2). Immunosuppressants were stopped at randomization, and steroids were to be tapered to ≤10mg/day by Week 8. Rescue therapy was allowed for worsening of disease but defined as treatment failure. Efficacy endpoints included reduction in disease activity by the BILAG (primary), and the SLE Response index (SRI, secondary) at week 24. Exploratory measures included the **I**nterferon **S**ignature gene expression as **M**etric (ISM) at baseline. Pharmacokinetics (PK) and immunogenicity of rontalizumab were assessed.

Results: 159 subjects received rontalizumab (81 IV and 78 SC) and 79 received pbo. Subjects were 94% female with mean age of 39 years. At baseline, the mean SELENA-SLEDAI (SS) was 9.8, and the most common disease manifestations involved musculoskeletal and mucocutanenous systems. 76% of subjects were ISM-High. Baseline disease activity was comparable in ISM-High and ISM–Low subjects except for higher likelihood of autoantibodies and low complement in ISM-High subjects vs ISM-Low: (anti-dsDNA 71% vs 34%, anti-ENA 73% vs 19% and low C3 43% vs 16%, respectively). Overall, response rates by BILAG and SRI were similar between rontalizumab and pbo groups. However, rontalizumab vs pbo SRI response was 55% vs 31% in those on >10 mg prednisone at baseline (56% vs 23% and 54% vs 38% in the IV and SC groups, respectively). In a biomarker-defined pre-specified subgroup, ISM-Low subjects, rontalizumab vs pbo SRI response rates were 75% vs. 18%, and 75% vs. 62% in the IV and SC groups, respectively. The estimated treatment difference of SRI response in rontalizumab and pbo ISM-Low arms was 31% (90% CI: 9–51%, p=0.0285). A reduction in SS flare rates occurred in rontalizumab subjects vs. pbo: hazard ratio 0.61 (0.46–0.81, p=0.0040), driven by ISM-Low subjects. A greater percentage of subjects achieved prednisone reduction (≤10 mg/day) by week 24 in the rontalizumab ISM-Low group: 91% vs. 67% pbo. Incidence of adverse events (AE) was comparable between pbo and rontalizumab-treated subjects. The most common AEs were UTI, URI, headache, and nausea. There were more SAEs from SLE flares in the active group (n=10, 6%) vs. pbo (n=1, 1%), which occurred only in ISM-High subjects. Treatment emergent anti-therapeutic antibodies were uncommon (1/159, 0.6%) and did not appear to affect safety or PK.

Conclusion: Rontalizumab treatment in the absence of immunosuppressants was associated with improvement in signs and symptoms of SLE, flare rates and steroid burden at week 24 in a pre-specified biomarker defined group of ISM-Low moderate to severely active lupus subjects.

Disclosure: K. Kalunian, Genentech, Inc, 5; **J. T. Merrill**, Genentech, Inc, 5, MedImmune, 5, Genentech, Inc 2; **R. Maciuca**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **W. Ouyang**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **J. M. McBride**, Roche Pharmaceuticals, 1, Genentech, Inc, 3; **M. J. Townsend**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **E. Park**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **J. Li**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **X. Wei**, genentech, inc, 3, Roche Pharmaceuticals, 1; **A. Morimoto**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **R. Boismenu**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **J. C. Davis Jr.**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **W. P. Kennedy**, merck co, 1, Roche Pharmaceuticals, 1, Genentech, Inc, 3.

ARHP Concurrent Abstract Session
Systemic Sclerosis, Vasculitis, Crohn's and Spondyloarthropathies
Wednesday, November 14, 2012, 9:00 AM–10:30 AM

2623

Taking Charge of Systemic Sclerosis: A Pilot Study of an Internet Self-Management Program. Janet L. Poole[1], Dinesh Khanna[2], Betty Skipper[3] and Cindy F. Mendelson[1]. [1]University of New Mexico, Albuquerque, NM, [2]University of Michigan, Ann Arbor, MI, [3]University of New Mexico, NM

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disease with serious implications for quality of life. The disease is challenging due to the variable course and potential for disability and morbidity. Persons living outside major metropolitan areas may be emotionally and geographically isolated from support groups, knowledgeable rheumatologists and other health professionals, and disease self-management education. We did a small study of 5 months duration to convert a previously developed self-management program to an internet format and pilot test the effects of the program on self-efficacy, health efficacy, management of care, pain, fatigue, functional ability and depression.

Methods: The intervention program consisted of an internet program with modules on scleroderma, coping, self-advocacy, fatigue and energy conservation, activities of daily living, mouth and teeth care, digestive tract

(including dysphagia), Raynaud's phenomenon, and exercises for the face, hands, arms and legs. Participants logged on to a password protected website and proceeded through the modules and learning activities at their own pace over 10 weeks. Participants were encouraged to log on to the discussion board, an interactive component of the website, and respond to questions posted for each module. Participants completed pre and post intervention questionnaires on perceived self efficacy (CDSES), health efficacy (heiQ), ability to manage care (PAM), functional disability (HAQ-DI), depression (CES-D), and pain and fatigue VAS's. T-tests analyzed differences in scores between the pre and post intervention questionnaires. Participants also completed an 8 question evaluation form about their satisfaction with the web site, program content, discussion boards and learning activities.

Results: Twenty one participants, recruited from the National Scleroderma Foundation website and a state chapter, completed baseline measures. Thirteen participants completed the study and completed post intervention measures. There were no demographic differences between people who participated vs. did not participate in the internet program. Of the participants who completed the program, the mean age was 52 years with mean disease duration of 7 years and mean education level of 16 years. Eighty four percent were female, 92% Caucasian, and 77% were married. Significant improvements were seen in mean scores for self-efficacy ($t = 2.31$; p =.039), ability to manage care ($t = 2.82$; p =.016), and health efficacy ($t = 2.28$; p =.042). Scores for pain and fatigue, functional ability and depression improved but not significantly. The evaluation of the program revealed mean scores ranging from 4.1 (action plans contributed to learning) to 4.9 (information presented clearly) on a 5 point scale.

Conclusion: The preliminary findings suggest that a self-management program delivered using an internet format can lead to statistically significant improvements in self efficacy, health efficacy, and ability to manage care. These results need to be confirmed with a larger randomized controlled trial with a longer follow-up period.

Disclosure: **J. L. Poole**, None; **D. Khanna**, Savient Pharmaceuticals, URL, 2, Ardea Biosciences, Takeda Pharmaceuticals, Savient Pharmaceuticals, 5, Savient Pharmaceuticals, 8; **B. Skipper**, None; **C. F. Mendelson**, None.

2624

Changes in Leisure Participation in Persons with Systemic Sclerosis. Cindy F. Mendelson, Jessica Greaves and Janet L. Poole. University of New Mexico, Albuquerque, NM

Background/Purpose: Little attention has been devoted to understanding the difficulties and limitations people with systemic sclerosis (SSc) experience with leisure participation. A qualitative interview study was conducted to understand the barriers people with SSc experience participating in and selecting leisure activities.

Methods: Twenty-five people with SSc who met inclusion criteria were selected based on self-reported difficulty with leisure and willingness to participate in the study interview.

Interviews were conducted over the telephone and followed a semi-structured format. Interview questions focused on the meaning of SSc, leisure activities and the importance of those activities, the influence of SSc on leisure activities, and adaptations used to engage in leisure activities.

Interviews were transcribed verbatim. The major interview questions were used as a framework to guide the analysis. A research journal was used to track and identify thematic concepts as they emerged from the data set. An additional document was created to manage the quotes that immediately drew the attention of the analyst in order to prevent initial bias in forming core themes. After analyzing the major questions separately, the over-arching concepts were compared for redundancy or outliers. Attending to rigor was an important consideration. One analyst (JG) analyzed the data set and the research team members then reviewed the themes for clarity, redundancy, and that it was representative of the participants' voices. In order to avoid common pitfalls, qualitative analysis hazards such as premature closure, misinterpreting frequency, over-inscription of self, and capitalizing on outliers, were closely attended to.

Results: The participants were 92% female, 88% were white, mean age was 54 years, mean disease duration was 12 years, mean education level was 16 years, 100% of the participants reported Raynaud's Phenomenon, 73% had digital ulcers, and 96% reported GI involvement.

Three themes emerged from the analysis. *Barriers to Leisure Participation*, describes the challenges people with SSc experience when selecting and participating in leisure activities. *Decrease in Leisure Participation*, reflected a change in the amount of time spent participating in leisure activities. *Experience of Losing a Valued Leisure Activity*, showed the impact that loss

of leisure activities had on some participants' mental health and social engagement.

Conclusion: Our study found that the barriers to leisure participation reported by participants with SSc were similar to those reported in the literature by people with RA, except people with SSc experienced an additional barrier of Raynaud's phenomenon.. In conclusion, SSc disease symptoms affect the amount and types of leisure activities in which people with SSc participate.

Disclosure: **C. F. Mendelson**, None; **J. Greaves**, None; **J. L. Poole**, None.

2625

The Impact of Sexual Difficulties in Women with Scleroderma and Interpersonal Relationships. Tanaka Ngcozana[1], Louise Parker[1], Christopher P. Denton[2] and Voon Ong[3]. [1]UCL Medical School and Royal Free Hosp, London, United Kingdom, [2]UCL, London, United Kingdom, [3]UCL Medical School, London, England

Background/Purpose: Sexual problems are common in women with systemic sclerosis (SSc). SSc is a complicated condition linked to a number of complications including sexual dysfunction. Sexuality is a vital part of life and it is a subject not usually broached. The aims of this study were to determine the prevalence of sexual problems in a large cohort of women with SSc, to evaluate the effects on sexual relationship, sexual activities and the difficulties faced by the women.

Methods: A total of 100 women with either limited (lcSSc) or diffuse (dcSSc) systemic sclerosis were invited to participate in a questionnaire survey. Each participant completed the validated Female Sexual Function Index (FSFI) questionnaire that assesses six domains: desire, arousal, lubrication, orgasm, satisfaction and pain. Additional psychological questions were included to examine sexual difficulties faced by the women in their interpersonal relationships.

Results: 50 women with SSc responded to the questionnaire. Mean age of the cohort was (mean ±SD, years) 56 ±1.41. 52% of the women who responded had diffuse subset while 40% had been diagnosed with the limited disease. The mean disease duration is similar for both subsets with (mean ±SD, years) 12±2.8.54% of the patients developed sexual difficulties after their diagnosis and the mean duration from SSc diagnosis to first sexual complaint was (mean, ±SD, years) 4.0±5.8.84% of the patients reported significant sexual problems in the overall FSFI domains. The pain domain fared the worst with 56% and 40% of the respondents did not have any sexual activity due to lack of lubrication. 60% of the patients revealed that their sexual complications had caused a significant strain in their relationships. 30% of the respondents admitted to not discussing their problems with their partners due to embarrassment, nonetheless 46% of the women reported to discussing the difficulties. Among those who discussed their problems with their partners 32 (64%) reassuringly stated that their partners understood the problems. 76% of the subjects reported that they had never been asked about sexual functioning by a health professional. However 52% revealed that they would have discussed their sexual problems if they were concerned, 38% would approach the nurse with their problem while 36% would discuss with their medical practitioners. Interestingly 72% of these women admitted to not raising any concern about their sexual problems.

Conclusion: Sexual functioning is an essential aspect of life for women with SSc. Our study revealed that most of the respondents had some form of significant sexual problems. It also showed that sexual impairment can have a significant negative impact for the affected women and their partners. Sexual health is a subject that is usually neglected by both patients and doctors yet it has been associated with psychological difficulties such as depressive symptoms. It is a subject worth exploring and actively enquiring in order to provide holistic care and improve our patients' quality of life.

Disclosure: **T. Ngcozana**, None; **L. Parker**, None; **C. P. Denton**, Actelion Pharmaceuticals US, 5, GlaxoSmithKline, 5, Pfizer Inc, 5, United Therapeutics, 5; **V. Ong**, None.

2626

The Utility of the Patient Health Questionnaire-9 to Assess Suicide Risk in Patients with Systemic Sclerosis. Ilya Razykov[1], Marie Hudson[1], Murray Baron[2] and Brett D. Thombs[1]. [1]McGill University, Montreal, QC, [2]Jewish General Hospital, Montreal, QC

Background/Purpose: Depression is common in rheumatic diseases, including systemic sclerosis (SSc). In the general population, depression is

associated with suicidal ideation, attempts and completion. The Patient Health Questionnare-9 (PHQ-9) is a self-administered and easily scored measure of depression symptoms that is increasingly used in medical settings. Item 9 of the PHQ-9 has been used in several studies, including with arthritis patients, to assess the prevalence of suicidal ideation. Item 9 asks patients "How often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" The item is ambiguous, however, because it includes both passive thoughts of death and more active ideas of self-harm. As a result, some researchers have advocated using the PHQ-8, which does not include Item 9. Thus, the objectives of this study were (1) to determine the proportion of SSc patients who responded anything other than "never" to Item 9 who endorsed active suicidal ideation in response to more direct questions during a structured clinical interview and (2) to assess the association between the PHQ-9 and the PHQ-8, which does not include Item 9.

Methods: Canadian Scleroderma Research Groups Registry patients were administered the PHQ-9 and the Composite International Diagnostic Interview (CIDI) depression module in a phone interview. Item 9 responses were compared to suicidal ideation and intent in the last year based on the CIDI. PHQ-8 scores were calculated by subtracting Item 9 scores. The association between the PHQ-9 and the PHQ-8 was computed using the Pearson correlation coefficient.

Results: Of 313 patients in the study, 30 (6.9%) screened positive for suicidal ideation on the Item 9. Of those, only 1 (3.3%) had thought about suicide in some detail as assessed by the CIDI at any time in the past year. No patients had an active suicide plan at the time of the interview. Correlation between PHQ-9 and PHQ-8 scores was r=0.998.

Conclusion: Item 9 does not appear to be an effective suicide screen. There is currently no evidence that screening for suicidality would prevent suicidal behaviour. If researchers or clinicians do screen for suicidality, direct questions about suicide should be asked. The PHQ-8 may be a better option than the PHQ-9 for assessment of depressive symptoms in SSc patients given the high association with the PHQ-9 and the ambiguous nature of Item 9.

Disclosure: I. Razykov, None; **M. Hudson**, None; **M. Baron**, None; **B. D. Thombs**, None.

2627

Gender Differences of Concepts Important to People Living with Crohn's Disease and Their Coverage by Commonly Used Patient-Reported Outcome Instruments: Patient's Perspective Elevated by a Qualitative Study.
Mona Dür[1], Michaela Coenen[2], Josef S. Smolen[3], Clemens Dejaco[1] and Tanja A. Stamm[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Ludwig-Maximilians-University, Munich, Germany, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Crohn's disease (CD) has a major impact on functioning, health and well-being and patient-reported outcome (PRO) instruments have not been analysed from the perspective of patients with CD so far. The clinical setting often restricts the opportunities to focus on other health determining concepts aside disease activity. We aimed to explore which concepts determining health in a positive way are important to patients with CD, their coverage by patient-reported outcome instruments and to recommend appropriate ones for the future.

Methods: A qualitative study was conducted: Told life stories were analysed by the biographical narrative interpretative method, findings were linked to concepts determining health in a positive way. Furthermore the qualitative data were analysed regarding gender differences. Two systematic literature searches were done to identify relevant concepts and clinically relevant PROs. Concepts and the items of the PROs were linked to WHO International Classification of Functioning, Disability and Health (ICF) codes and compared to evaluate instruments' coverage.

Results: 15 people with CD with a median age of 46 years (IQR 34–60) and median disease duration of 15 month (IQR 8–30) participated. 14 participants mentioned self-efficacy, social support (93%) and 13 described job satisfaction (87%) as being important which were the three commonest concepts. Most of them experienced relations between their health behaviour and disease course, and tried to "gain control over their disease" by being self-efficient. While participation had more meaning for men, appreciation and resilience was more important for women. Work-life balance and secondary illness gain was hardly meaningful. The 9 patient-reported outcome tools (see table 1) covered 9 different ICF codes (see table 2).

Table 1. Characteristics of the identified patient-reported outcome instruments

Abbr.	Patient-reported outcome instrument	Content	Items	Response options	Time frame
BDI-II	Beck Depression Inventory-II	Depression	21	4 statements: increasing severity	Past, present, future
ESSI	ENRICHD Social Support Scale	Extent of social Support	7	Question 1-6 (None, a little, some, most or all of the time), Question 7 (yes/no)	present
HADS	Hospital Anxiety and Depression Scale	Anxiety, depression	14	Frequency: 4-point Likert scale (0=not at all, 4=definitely)	present
IBDQ-32	Inflammatory Bowel Disease Questionnaire	Health related quality of life	32	7 point Likert scale (1 = significant impairment, 7 = no impairment)	2 weeks
PSQ-R	Perceived Stress Questionnaire Recent	Perceived stress	30	4-point scale on frequency (1=almost never, 4=usually)	month
RFIPC	Rating form of Inflammatory Bowel Disease Patient Concerns	Worries, concerns regarding IBD	25	Visual analogue scale (0 = Not at all, 100 = A great deal)	present
SF-36	Short Form 36	Health related quality of life	36	Different response scales	4 weeks
SIBDQ	Short Inflammatory Bowel Disease Questionnaire	Quality of life	10	7-point Likert scale on frequency (1=all of the time, 7=none of the time)	2 weeks
STAI	State-Trait Anxiety Inventory	Anxiety about an event, and trait anxiety	40	Intensity 4-point Likert scale (1=not at all, 4 very)	Present

Table 2. Coverage of the linked concepts by patient-reported outcome tools

Concepts of health and wellbeing	ICF Codes	ICF Title	BDI	ESSI	HADS	IBDQ-32	PSQ-R	RFIPC	SF-36	SIBDQ	STAI
Coping	d240	Handling stress and other psychological demands	+				+				
Participation (societal)	d9	Community, social and civic life				+			+	+	
Reflecting about one's life in an optimistic way	b126	Temperament and personality functions			+		+	+			+
	b1265	Optimism			+		+				
Resilience	b1263	Psychic stability			+		+	+			+
Self-efficacy	b1641	Organization and planning									
	d177	Making decisions					+				
Social acceptance	e4	Attitudes	+			+		+			
Social support	e3	Support and relationships	+	+			+				

Conclusion: This is the first study elaborating the coverage of patient's perspective by commonly used patient-reported outcome instruments. The use of the *perceived stress questionnaire – recent* is recommended because it covered most concepts, as well as the use of *inflammatory bowel disease self-efficacy scale* due to the importance of self-efficacy for people with CD. Social support, self-efficacy and gender differences at several concepts should get more attention in clinical daily routine and in the research of people living with CD.

Disclosure: M. Dür, None; **M. Coenen**, None; **J. S. Smolen**, None; **C. Dejaco**, None; **T. A. Stamm**, None.

2628

The Lumbo-Pelvic Muscles and Axial Spondyloarthritis: A Pilot Observational Study.
Janet Millner[1], Julie A. Hides[2], Patricia Lewis[3] and Jane Zochling[3]. [1]Royal Hobart Hospital, Hobart, Australia, [2]Australian Catholic University, Brisbane, Australia, [3]Menzies Research Institute Tasmania, Hobart, Australia

Background/Purpose: The importance of a physical approach in the management of axial spondyloarthritis (SpA) has been recognised for many years. It is supported by level 1a evidence including the 2008 Cochrane review into the effectiveness of physiotherapy in ankylosing spondylitis (AS), and by expert panel recommendations such as those of the Assessment of Spondyloarthritis group. The benefits of exercise have been shown to be still relevant even in patients who are stabilised with TNF blocking medication, and both subjective and measurable benefits can be much larger than that seen for other types of arthritis, and also non-inflammatory back pain. Despite this, there is a paucity of information about why exercise can be so beneficial, and about the specifics of exercise prescription. The aim of this study was therefore to provide pilot morphological data regarding any changes in lumbo-pelvic muscles, which may inform exercise prescription, and indicate further areas for research.

Methods: Twenty-three subjects with confirmed SpA or AS underwent an MRI scan of the lumbar spine and pelvis. The protocol aligned the transverse imaging plane with inferior aspect of the body of the 4th lumbar vertebra, in order to obtain measures of the cross sectional area (CSA) of specific lumbo-pelvic muscles. The digitised images were analysed by computer software to determine muscle size, symmetry and ratio of contractile to non-contractile tissue, using previously validated methods.

Results: Non-contractile tissue was observed within the fascial boundaries of the paraspinal muscles to some degree in all subjects. These changes were graded according to a previously validated five point scale as follows:

Number of Spinal Levels	Lumbar Multifidus		Lumbar Erector Spinae	
	Subjects ≥ Grade 2− n	Subjects ≥ Grade 2− %	Subjects ≥ Grade 2− n	Subjects ≥ Grade 2− %
0	0	0%	3	13%
1	8	35%	8	35%
2	8	35%	8	35%
3	3	13%	1	13%
4	1	4%	1	13%
5	3	13%	n/a	n/a

The prevalence of non-contractile tissue was not associated with measures such as body mass or metrology indices, but was inversely associated with self-reported physical activity levels (p). Additional measures of lumbar multifidus CSA at L5/S1 level demonstrated a mean functional to total muscle CSA of only 61% (range 18–88%).

Conclusion: This study provides new information on the morphology of the lumbo-pelvic muscles in SpA, and also confirms the applicability of this methodology in inflammatory back pain. The association of reduced functional muscle area with lower activity levels supports the concept of a specifically designed exercise intervention. Similar findings have been noted in non-inflammatory back pain, but points of difference are highlighted that need exploring. The study has therefore revealed some research gaps regarding muscle changes in SpA, which may be either secondary to the disease or part of the process.

Disclosure: **J. Millner**, None; **J. A. Hides**, None; **P. Lewis**, None; **J. Zochling**, None.

ARHP Concurrent Abstract Session
Clinical and Rehabilitative Aspects of Osteoarthritis
Wednesday, November 14, 2012, 9:00 AM–11:00 AM

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Associations of Current and Early-Life Socioeconomic Positions with Risk of Self-Reported Doctor-Diagnosed Arthritis in a Family-Medicine Cohort of North-Carolinians. Antoine A. Baldassari[1], Rebecca J. Cleveland[1] and Leigh F. Callahan[2]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina, Chapel Hill, NC

Background/Purpose: Socioeconomic position (SEP) across the lifecourse has been convincingly identified as a determinant of health. In particular, mounting evidence suggests that low current and childhood SEP are associated with higher risks of cardiovascular disease and autoimmune disorders. In contrast, relatively few studies have investigated the relationship between SEP and arthritis, with childhood SEP being particularly untested as a potential risk factor for the disease. The purpose of this study is to determine the associations of childhood and current SEP with the presence of arthritis.

Methods: Our data came from the North Carolina Family Medicine Research Network (NC-FM-RN), a practice-based research network of 22 family medicine practice selected to represent the geographic and racial/ethnic diversity of North Carolina. In 2006, the Individual and Community Social Determinants of Arthritis Outcomes study invited NC-FM-RN participants to complete a phone survey assessing demographics, health status, chronic health conditions, health attitudes and beliefs, and perceptions of neighborhood environment. Participants who provided complete sociodemographic and relevant health information were retained in our sample (n = 1302). We created three-levels (high[referent], medium, low) summary measures for current and childhood SEP accounting for education, homeownership and occupational class, using parental SEP as a proxy for participants' childhood SEP. Logistic regression models were

carried out to assess the associations between arthritis status and SEP variables separately and together, adjusting for known covariates.

Results: Our sample included 929 females (70.65%) and 210 males (29.35%). The mean age was 56.94 years old (23–94), and 782 respondents had self-reported doctor-diagnosed arthritis. 485 (37.25%) participants received a high current SEP summary score, while 578 (44.39%) had a medium current SEP and 239 (18.36%) a low current SEP. Summary scores were lower for the childhood SEP measure: 195 (14.98%) participants scored in the high childhood SEP level, 447 (34.33%) did in the medium level, and 660 (50.69%) had a low childhood SEP. Arthritis was more likely in participants with medium current SEP, OR=1.41 (95% CI=[1.06, 1.88]), and low current SEP, OR=1.96 (95% CI=[1.32, 2.90]) and somewhat more likely in respondents with low childhood SEP, OR=1.32 (95% CI=[1.02, 1.71]). Childhood SEP was not associated with arthritis in the model including both current and childhood SEP as explanatory variables, while current SEP remained significantly associated with arthritis at both the medium and low levels.

Conclusion: Our results suggest that while there was a robust association between current SEP and arthritis susceptibility in our sample, the association of childhood SEP with arthritis was relatively weak. Studies should investigate whether our results consistently appear in larger populations with clinically documented arthritis. Additionally, further research could focus on arthritis-type specific associations with SEP, considering the broad range of joint disease encompassed by arthritis.

Disclosure: **A. A. Baldassari**, None; **R. J. Cleveland**, None; **L. F. Callahan**, None.

2630

Rheumatoid Arthritis and Osteoarthritis in the Population: How Different Is the Impact? Christina H. Chan[1], Mayilee Canizares[1] and E.M. Badley[2]. [1]Division of Healthcare Outcomes and Research, Toronto Western Research Institute, Toronto, ON, [2]Division of Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: It is a common perception that rheumatoid arthritis (RA) is a more severe and debilitating disease than osteoarthritis (OA); however, there have been many recent advancements in treatment for RA including development of biologics, while treatment of OA remains largely focused on joint replacement surgeries which are only appropriate for end-stage OA. A recent national survey of a representative sample of Canadians reporting arthritis provided an opportunity to compare individuals reporting RA who see a rheumatologist and individuals reporting OA. Our objective was to describe and compare the arthritis-related characteristics and health care use of individuals reporting RA and OA.

Methods: Data were obtained from the 2009 Survey on Living with Chronic Diseases in Canada which included detailed information on a sample self-reporting arthritis as a long term chronic health condition (n = 4,565). Data were obtained on demographic characteristics, lifestyle (smoking, alcohol, physical activity), type of arthritis, number and site of painful joints (16 sites), pain and fatigue (severity on 1–10 scale and frequency), limitations in 5 areas of daily activities, general health, health care use (health professionals seen in the past year, use of medication, assistive devices and receipt of information and other support services), and self-management of arthritis. Two groups were examined: individuals who reported RA and have seen a rheumatologist in the past year (RA), and individuals who reported OA.

Results: An estimated 0.5% of Canadians reported RA and 5.1% reported OA. Those with RA were more likely to have symmetrical arthritis than those with OA. The two groups were similar in demographic and lifestyle characteristics, and there were no significant differences in the number of joint sites affected (RA: 5.1 95% CI 3.9–6.4; OA: 4.6 95% CI 4.3–4.8), severity of pain or fatigue, frequency of fatigue, or having any activity limitations. Compared to RA, the OA group reported better self-rated health but more frequent joint pain. A higher proportion of the RA group reported seeing primary care physicians, orthopedic surgeons, physiotherapists, pharmacists and mental health professionals compared to the OA group. Those with RA were more likely to report taking prescription medication (RA: 83%; OA: 40%), using assistive devices, and receiving information on how to manage their arthritis. Individuals with RA were less likely to exercise or control weight for arthritis.

Conclusion: Overall, the impact of RA among those who reported seeing a rheumatologist was comparable to the impact of OA in this representative sample of Canadians. This similarity is surprising given that RA is often perceived as a more severe form of arthritis. The findings could be a reflection of the benefits of specialist care and hence pharmacotherapy and access to

other support for disease management for RA, and the lack of effective treatment for OA. The similar joint site count for RA and OA also suggests that further attention should be paid to OA as a polyarticular disease.

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Radiographic Osteoarthritis Severity Is Associated with an Increased Risk of Developing Knee Pain: Findings From the Osteoarthritis Initiative. Jingbo Niu, David T. Felson, Tuhina Neogi and Yuqing Zhang. Boston Univ School of Medicine, Boston, MA

Background/Purpose: While knee pain is a major complaint from subjects with knee osteoarthritis (OA), most epidemiologic studies have found only weak to moderate associations between knee radiographic OA (ROA) and presence of knee pain. These findings may be partly due to confounding by variation of pain sensitivity and tolerance between subjects. In addition, few studies have prospectively assessed the relation of severity of ROA to the occurrence of knee pain. To avoid across person differences in pain reporting, we performed a within-person knee-matched cohort study to examine the relation of Kellgren/Lawrence (KL) grade and joint space narrowing (JSN) to the risk of developing knee pain among participants of the Osteoarthritis Initiative (OAI).

Methods: The OAI is a multi-center longitudinal study focusing primarily on risk factors for the onset and progression of knee OA. Subjects aged between 45–79 years were recruited at four centers across the US. At baseline and yearly follow-up visits knee-specific pain was assessed, including a question about presence of knee pain, aching or stiffness in more than half of the past 30 days ("frequent knee pain"). KL grade (0–4) and JSN (0–3 using the OARSI atlas) were scored on PA view knee radiographs by experienced readers blinded to the time sequence. Included were subjects who had no frequent knee pain in either knee and had unequal KL grade at the 12-month visit in their two knees. They were considered as having incident frequent knee pain if it occurred in any of the later annual follow-up visits. Within each subject we compared risk of incident frequent knee pain in the knee with higher KL grade vs. that in the contralateral knee with lower KL grade. The two knees within a subject formed a matched set. We examined the association between KL grade and incident frequent knee pain using a Cox proportional hazards regression model adjusting for history of knee injury. We took the same approach to assess the relation of maximal JSN score to risk of the incident frequent knee pain.

Results: Included were 1093 subjects who had no frequent knee pain and whose KL grades differed between two knees (mean age: 63.0, 52.4% women), and 712 subjects who had no frequent knee pain and whose JSN score differed between two knees (mean age: 63.8, 52.4% women) at 12-month visit. Higher KL grade was associated with an increased risk of incident frequent knee pain. Compared with knees with KL grade 0, the risk ratios of incident frequent knee pain were 1.2, 1.4, 2.3, and 3.3 for each increased grade of KL grade, respectively (p for trend <0.001). Similar association was observed for JSN (Table).

Table 1. Severity of knee ROA and incidence of frequent knee pain incidence (%) of frequent knee pain among knees with more severe / less severe ROA, N of eligible subjects

Knee with higher KL grade (more severe ROA)	Knee with lower KL grade (less severe ROA)				Adjusted RR (95% CI)	p-value
	0	1	2	3		
0	N/A	N/A	N/A	N/A	1.0	
1	27.0 / 21.5, 270	N/A	N/A	N/A	1.2 (0.9, 1.6)	0.118
2	26.8 / 20.0, 190	35.6 / 30.0, 247	N/A	N/A	1.4 (1.1, 1.9)	0.020
3	27.3 / 7.6, 66	61.7 / 31.7, 60	49.4 / 27.6, 156	N/A	2.3 (1.6, 3.4)	<.001
4	66.7 / 10.0, 30	44.4 / 22.2, 18	66.7 / 40.7, 27	72.4 / 37.9, 29	3.3 (1.9, 5.5)	<.001

Knee with higher JSN score (more severe ROA)	Knee with lower JSN (less severe ROA)			Adjusted RR (95% CI)	p-value
	0	1	2		
0	N/A	N/A	N/A	1.0	
1	28.1 / 25.3, 324	N/A	N/A	1.1 (0.9, 1.5)	0.276
2	43.0 / 19.5, 128	50.6 / 27.6, 156	N/A	2.0 (1.4, 2.8)	0.001
3	63.4 / 9.8, 41	58.8 / 41.2, 34	72.4 / 37.9, 29	2.9 (1.7, 4.8)	<.001

Conclusion: The radiographic severity of OA is strongly associated with an increased risk of frequent knee pain. Contrary to the so-called structure symptom discordance, there is a dose-responsive relationship between structure and symptoms when between-person confounding is appropriately accounted for.

2632

Doing Is Believing: Health Beliefs Before and After an Exercised-Based Rehabilitation Programme for Chronic Knee Pain. Mike Hurley[1] and Dr Nicola E. Walsh[2]. [1]St George's University of London, London, United Kingdom, [2]University of the West of England Bristol, Bristol, United Kingdom

Background/Purpose: An integrated exercise-based rehabilitation programme, *Enabling Self-management and Coping with Arthritis knee Pain through Exercise (ESCAPE-knee pain)*, improves pain and physical disability of people with chronic knee pain. Qualitative interviews were used to understand how and why *ESCAPE-knee pain* works.

Methods: 29 people involved in the quantitative study evaluating the *ESCAPE-knee pain* programme, were interviewed before and after participation on the programme. Semi-structured interviews were used to explore participants' experiences of living with knee pain, their understanding and beliefs about their condition, and management strategies adopted. The same participants were re-interviewed after completing the programme to explore their experiences of the programme, its impact on their beliefs about knee pain and their views about the management of their condition. A thematic analysis was conducted. Interviews were audio taped, transcribed verbatim, read several times by two researchers independently to familiarise themselves with the data, met to identifying themes and agree a coding scheme and resolve differences in coding and interpretation.

Results: Initially people had poor understanding and negative, fatalistic beliefs about the management or prognosis for knee pain. Following the programme the majority of participants had positive experiences, improvement in pain, physical and psychosocial functioning, greater knowledge and understanding of their condition and treatment options, and in their ability to use exercise to control symptoms. Beliefs about the causation and prognosis of knee pain were unchanged, but concerns about possible dangers of exercise decreased. They appreciated how exercise could reduce symptoms (treatment beliefs) and their confidence in their ability to use exercise to control symptoms (exercise self-efficacy) increased. These improvements were attributed to the content and structure of the programme, and the care and guidance of the physiotherapist.

Conclusion: *ESCAPE-knee pain* improves physical and psychosocial functioning of people with chronic knee pain by increasing people's treatment belief in safety, the utility of exercise to control symptoms and exercise self-efficacy, rather than alteration in their beliefs about causation or prognosis.

2633

Independence At Home: Real or Perceived. Hazel L. Breland. Medical University of South Carolina, Charleston, SC

Background/Purpose: Rheumatic conditions are more prevalent among women than men and increase with age. Over 4 million African Americans affected are by rheumatic conditions and yet disparities and underrepresentation of this group exist in research studies. The burden of physical disability confronting older African American women can affect their ability to engage in everyday activities. Thus, performance-based data are needs in the home environment where effective patient management and aging in place occurs. However, differences exist between self-report and performance-based data. Therefore, the purpose of this descriptive, non-intervention study uses mixed methods to identify the degree of concordance between self-reported performance capabilities and real-time performance of criterion-referenced task situations within the home environment.

Methods: Eighteen community-dwelling African American females with rheumatic conditions (age 64.7, widowed = 38.9%, living with family = 50%, self-reported quality of life = "good") participated in brief qualitative interviews on the perception of participation in daily activities and home safety. During the in-home assessment, participants completed demographic questionnaires, the PASS-SR (self-report of performance capabilities, what they "could do" compared to what they "routinely do", and the PASS-Home (observational data of real-time performance of 26 criterion-referenced, standardized task situations). The PASS-Home includes 4 domains: basic ADL (dressing), physical and cognitive instrumental ADL (IADL-physical: sweeping & IADL-cognitive: managing home safety), and functional mobility (indoor walking). The interviews were audio-recorded and transcribed verbatim. Content analysis was used for initial codes and summary statements were generated for each code. Based on summary statements data were

aggregated into eight key themes. Data from the interviews, PASS-SR, and PASS-Home were integrated. Concordance was defined as the percent agreement between self-reported capability (PASS-SR) and performance-based (PASS-Home) data of task situations.

Results: Generally, participants reported that physical factors of rheumatic conditions negatively affected their lives with regard to symptoms triggers, physical problems, limitations on their activity, and safety concerns. Chores, daily living, and movement were the most prominent symptoms triggers. The primary safety concerns included falling, difficulty-using hands, and lack of proper safety equipment. Percent agreement between self-reported capability on the PASS-SR and performance-based data of the task situations (PASS-Home) ranged from 22.2% (4 of 18) for functional mobility-stair use to 94.4% (17 of 18) for IADL (current event) obtaining critical audio information from the media and IADL (money management) checkbook balancing. There were 9 of 26 task situations with less than 50% concordance.

Conclusion: Using mixed methods, we were able to examine real and perceived performance patterns among older African American women with rheumatic conditions. Participant perceptions of their independence were typically underestimated for functional mobility and physical IADL.

Disclosure: H. L. Breland, None;

2634

Physical Disability, Perceived Dependence and Depression in Older Women with Osteoarthriti. Kisoo Park[1], Monique A. Gignac[2] and E. M. Badley[3]. [1]Gyeongsang National University, Jinju, South Korea, [2]Arthritis Community Research and Evaluation Unit, Toronto Western Research Institute and University of Toronto, Toronto, ON, [3]Division of Health Care and Outcomes Research,Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: Older women with osteoarthritis (OA) often report difficulty with tasks and needing to rely on others for assistance. In addition, depressed mood has been observed among individuals with arthritis. However, there is little research examining relationship physical disability and the perception of dependence with depression among women with arthritis. This study assessed whether both physical disability and perceived dependence relate to depression or whether perceived dependence in personal care activities, household activities, community mobility and valued activities is an intermediate step in the relationship between physical disability and depressive symptoms.

Methods: Data come from a cross-sectional survey of 209 women, aged 55 or older, with osteoarthritis (OA). Physical disabilities were examined in four domains: personal care, household activities, community mobility and valued activities. Perceived dependence was asked in each domain using the question 'Thinking about these activities, to what extent do you feel dependent?'. Responses were on a 5-point scale from 0 = 'not at all' to 4 = 'a great deal'. Depression was assessed using the Center for Epidemiological Studies—Depression Scale (CES-D). Mediation analyses occurred in four step and included regression analyses as outlined by Baron and Kenny.

Results: On average, participants reported mild or moderate disability and perceived dependence. 28.7 % of participants reported a depression score ≥ 16, which indicates depressive symptomotology. The results from step 1 show that, greater difficulty with each domain of physical disabilities was significantly related to greater perceived dependence. In step 2, greater perceived dependence was significantly associated with greater depressive symptoms in all domains. Step 3 analyses showed that greater physical disabilities in each domain were significantly associated with depression. The final step testing mediation indicated that personal care activities, household activities and community mobility were fully mediated by perceived dependence. That is, once dependence was taken into account, the relationship between physical disabilities and depression was no longer significant. Partial mediation was found for dependence and valued activity limitations. Both were significantly related to depression.

Conclusion: It is important to take into account the experience of perceived dependence as a mediator in understanding the relationship between disability and depression in the domains of personal care, household, and community mobility. However, for valued activities, both disability and perceived dependence are important in understanding depression. This may be because valued activities are discretionary and reflect a person's identity (i.e., what's important to them). Also, they are not always activities where others can provide assistance, making perceptions of dependence less relevant. To conclude, these findings point to the importance of taking into account an individual's reaction to their disability rather than just focusing on the severity of disability

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Exploring the Influence of Patient Perceptions On Medication Escalation in Daily Practice. Jos Hendrikx, Wietske Kievit, Jaap Fransen and Piet L.C.M. van Riel. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: In rheumatoid arthritis (RA), patients' and physicians' perceptions of disease can differ and patients who are satisfied with their health do not tend to agree with escalation of drug therapy, even if disease activity is not low. It is hypothesized that patient acceptable symptom state, as well as perceived and expected change, influence patients' willingness to alter therapy, in addition to disease activity state.

Objective: To investigate the influence of patient perceptions and disease activity on escalation of drug therapy in RA patients.

Methods: Consecutive RA patients attending the outpatient rheumatology clinic received standard clinical assessment including the DAS28 and medication changes. In addition, patients were asked 4 items regarding: perceived health state transition, satisfaction with their health state, willingness to change therapy and expected health state transition until the next visit. To investigate explanatory factors, logistic models predicting actual escalation of medication in daily practice and predicting patients' self-reported willingness to escalate therapy were fitted by means of forward selection. Predictors for the models were: sex, age, rheumatoid factor, disease duration, DAS28 response since last visit, attained DAS28 level and the above mentioned patient perception items. Escalation of DMARD or biologic medication was defined as an increase in frequency and/or dose of medication, or starting a new one, between the current and next visit.

Results: In total 422 RA patients; 63.3% female, 67.1% rheumatoid factor positive were included in the analysis. Mean (SD) DAS28 at visit, age and disease duration in years were: 3.09(1.24), 58.6(12.95), 9.72(9.25), respectively. In total 185 (43.8%) patients had a DAS28>3.2, of whom 96 (59.1%) were satisfied with their health status if this would not change until the next visit, and a majority of patients 132 (71.4%) did not want to change their medication. Table 1 shows the final model for therapy escalation with a clear independent relationship of patient reported willingness to escalate therapy. Table 2 shows the model with willingness to escalate therapy as the outcome. All patient perception measures exhibited significant independent associations, of which patient satisfaction was strongest. Figure 1 shows a model of medication escalation in daily practice.
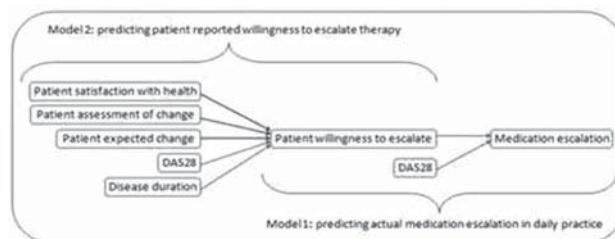
Conclusion: Patients' willingness to escalate therapy is strongly associated with actual escalation of therapy in daily practice, independent of clinical parameters. In turn, patients' willingness to escalate therapy is primarily associated with patients' satisfaction with their health state, perceived change and expected change. Treat to target interventions should address patients' perceptions of their disease, and the related health goals patients aim to achieve, next to the level of disease activity attained.

Disclosure: J. Hendrikx, None; W. Kievit, None; J. Fransen, None; P. L. C. M. van Riel, None.

2636

Understanding Why Treat-to-Target Strategies Are Difficult to Follow.
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Background/Purpose: Treat-to-target (T2T) refers to a set of decision strategies widely advocated for the optimal management of rheumatoid arthritis (RA). Despite considerable evidence that this approach leads to improved outcomes, T2T strategies are not consistently adopted. We hypothesize that patients' experience of illness complicates the decision to adjust treatment when indicated by recommended thresholds. While disease activity thresholds assess a single reference point (current level of disease activity), patients' appraisal of their illness depends on multiple reference points. Therefore, in addition to current experience, we also examine past and future reference points, i.e., how current illness compares with recalled past experience and the difference between current and expected future health states.

Methods: We conducted a prospective, repeated measures study in which 142 RA patients (mean age: 59, 86% female) were interviewed at baseline, 2, 4, and 6 months. Disease activity was measured using the RAPID-4. Patients' current experience was measured using current (8-item Brief Illness Perception Questionnaire), past (recent change in illness severity measured on a 5-point Likert scale) and future (discrepancy between the patient's current and desirable health states measured on an 11-point numeric rating scale) reference points. We used generalized estimating equations to examine illness perception items, recent change, and discrepancy as main effects and in combination with disease in predicting treatment adjustment. Models are adjusted for age, education, income, duration, and biologic use.

Results: We found that disease activity, three illness perception factors: illness consequences, concern, emotional impact and both past and future reference points predict future treatment adjustments. These illness experience factors are also significant as interactions and the interaction model provided a slightly better fit (QICC index) than the main effects model indicating that the combination of disease activity and the three temporal reference points predicts future treatment adjustments better than disease activity alone.

Table 1. Main Effect Model

Independent variables	Beta	Std error	OR	Lower	Upper	Wald chi square	p	QICC
Disease activity	**0.26**	**0.12**	**1.30**	**1.04**	**1.63**	**5.24**	**0.022**	**266.34**
Illness perceptions								
Consequences	**0.18**	**0.08**	**1.19**	**1.02**	**1.40**	**4.88**	**0.027**	**267.32**
Timeline	−0.07	0.07	0.94	0.82	1.07	0.99	0.321	271.06
Control	−0.09	0.06	0.92	0.82	1.03	2.25	0.133	269.76
Treatment	−0.11	0.06	0.89	0.79	1.01	3.14	0.077	270.56
Identity	0.17	0.09	1.19	1.00	1.40	3.41	0.051	268.15
Concern	**0.15**	**0.07**	**1.16**	**1.02**	**1.33**	**4.72**	**0.030**	**268.22**
Understanding	0.00	0.07	1.00	0.88	1.14	0.001	0.981	271.93
Emotional response	**0.15**	**0.06**	**1.16**	**1.03**	**1.30**	**6.08**	**0.014**	**267.26**
Reference points								
Perceived change	**0.41**	**0.20**	**1.51**	**1.03**	**2.21**	**4.44**	**0.035**	**267.17**
Discrepancy	**0.17**	**0.06**	**1.19**	**1.05**	**1.34**	**7.08**	**0.008**	**266.84**

Table 2. Interaction Model

Independent variables	Beta	Std error	OR	Lower	Upper	Wald chi square	p	QICC
Illness perceptions								
Consequences	**0.03**	**0.01**	**1.03**	**1.01**	**1.05**	**10.20**	**0.001**	**263.58**
Timeline	0.02	0.01	1.02	1.00	1.04	2.86	0.091	268.94
Control	0.00	0.02	1.00	0.97	1.03	0.06	0.810	271.34
Treatment	0.01	0.01	1.01	0.99	1.02	0.73	0.393	270.68
Identity	**0.03**	**0.01**	**1.03**	**1.01**	**1.04**	**8.00**	**0.005**	**265.32**
Concern	**0.03**	**0.01**	**1.03**	**1.01**	**1.05**	**9.10**	**0.003**	**263.92**
Understanding	0.02	0.01	1.02	1.00	1.05	3.76	0.052	267.12
Emotional response	**0.03**	**0.01**	**1.03**	**1.01**	**1.05**	**11.74**	**0.001**	**262.99**
Reference points								
Perceived change	0.06	0.02	1.07	1.03	1.11	10.37	0.001	263.37
Discrepancy	0.03	0.01	1.03	1.01	1.05	11.17	0.001	264.12

Conclusion: These findings indicate that recommended T2T thresholds may not adequately reflect thresholds used clinical practice. Physicians likely take patient experience of their illness into account in making treatment recommendations, making it more difficult to consistently adhere to T2T thresholds. Understanding the factors that impact on decision making, may help modify T2T strategies to improve their uptake and ultimately improve patient outcomes.

2637

Cost-Effectiveness and Cost-Utility Analysis of Treat-to-Target Versus Usual Care in Early Rheumatoid Arthritis: Results of the Dutch Rheumatoid Arthritis Monitoring Registry.
Marloes Vermeer[1], Wietske Kievit[2], Ina H. Kuper[3], Annemarie Braakman-Jansen[4], Hein J. Bernelot Moens[5], Theo R. Zijlstra[6], Alfons A. den Broeder[7], Piet L.C.M. van Riel[2], Jaap Fransen[2] and Mart A.F.J. van de Laar[1]. [1]University of Twente & Medisch Spectrum Twente, Enschede, Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Medisch Spectrum Twente, Enschede, Netherlands, [4]University of Twente, Enschede, Netherlands, [5]Ziekenhuisgroep Twente, Hengelo, Netherlands, [6]Isala Klinieken, Zwolle, Netherlands, [7]Maartenskliniek, Nijmegen, Netherlands

Background/Purpose: Treat-to-target (T2T) has proven to be more effective in achieving remission in early rheumatoid arthritis (RA) patients than usual care [1]. However, T2T has not been fully implemented in daily clinical practice yet. Moreover, it is unknown whether T2T is cost-effective. The objective was to analyze the cost-effectiveness and cost-utility of a T2T strategy aiming at remission (Disease Activity Score in 28 joints (DAS28) < 2.6) compared to usual care in early RA over the first two years of the disease.

Methods: Two early RA inception cohorts including patients who fulfilled the ACR 1987 criteria were compared. The T2T group (n=261) consisted of patients from the DREAM remission induction cohort and was treated according to a protocolized treatment strategy aiming at DAS28 remission. The usual care group (n=213) consisted of patients from the Nijmegen early RA inception cohort and was treated without DAS28-guided, protocolized treatment decisions. For both groups, direct medical costs were collected and compared with gain in effectiveness (DAS28 remission) and quality adjusted life years (QALYs) (EQ-5D utility estimated from the HAQ) over two years of follow-up.

Results: T2T produced a higher remission percentage (64.4% vs. 34.7%) and a larger gain in QALYs (median (IQR) 1.45 (1.24–1.55) vs. 1.39 (1.18–1.53), p=0.037) than usual care. The total mean (SD) costs per patient were € 4.791 (7.436) in the T2T group and € 3.727 (5.773) in the usual care group. The incremental cost-effectiveness ratio was € 3.591 per patient in remission. The incremental cost-utility ratio (ICUR) was € 19.410 per QALY. The figure presents the cost planes which show the relation between A) the differences in effectiveness and costs and B) the differences in utility and costs of T2T versus usual care. Anti-TNF therapy was given to more T2T patients (21.5% vs. 15.0%) and was prescribed earlier in the disease process, compared to usual care. Our data showed that after three years of follow-up, T2T probably becomes cost-saving.
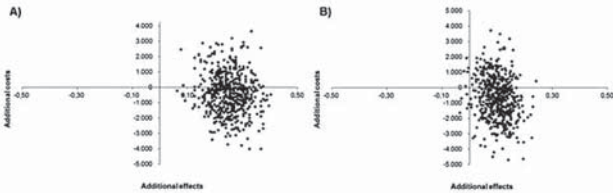
Conclusion: This quasi-experiment showed that over the first two years of treatment, T2T is associated with higher costs but also with substantial higher effectiveness. We conclude that T2T is cost-effective in daily clinical practice.

Reference
[1] Schipper et al, Ann Rheum Dis. 2012;71(6):845–50.

2638

Biologic Switching Among Patients with Rheumatoid Arthritis in the United States, 2004–2011. Ozgur Tunceli[1], Jeffrey R. Curtis[2], Tatia C. Woodward[3], Siting Zhou[1], Yen-Wen Chen[1] and Ancilla W. Fernandes[4]. [1]HealthCore, Inc, Wilmington, DE, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]MedImmune, LLC, Gaithersburg, MD, [4]MedImmune LLC, Gaithersburg, MD

Background/Purpose: While studies have assessed the efficacy of switching among biologic disease-modifying antirheumatic drugs (bDMARD), there is a lack of knowledge regarding the patterns of bDMARD use and switching in a real-world setting. The objective of this study was to describe and compare the characteristics and treatment patterns associated with RA patients who maintain their initial bDMARD (non-switchers) to: [1] patients that cycle from one anti–tumor necrosis factor (AT) to another and [2] patients that switch to a non-anti-TNF agent (NAT) in the year following bDMARD initiation.

Methods: Patients aged ≥18 with ≥1 diagnosis of RA between January 2004 and August 2011, from an administrative claims database, were included if they initiated a new anti-TNF treatment, did not have any bDMARD claims in the 12 months prior to bDMARD initiation, and were continuously enrolled for 12 months following bDMARD initiation. Patients who had ≥1 different bDMARD following initiation were classified as AT or NAT study group, depending on mechanism of action (MOA). AT and NAT groups were compared to non-switchers, using t-tests for continuous data and chi-square tests for categorical data. Cox Proportional Hazards model was used to examine time-to-discontinuation/switch while controlling for confounding factors.

Results: Among the 7,719 naïve bDMARD patients identified, 87% [n=6,698] maintained their initial bDMARD, 10% [n=792] cycled to a second AT and 3% [n=229] switched to a NAT.

Comorbidity profile of study groups was varied; the Deyo-Charlson Comorbidity Index for non-switchers [1.59] was higher than the AT group [1.49; P=0.033] and lower than the NAT group [1.78; P=0.038]. At baseline, the AT group had significantly lower proportions of cardiovascular disease, hypertension, dyslipidemia, and malignancy than the non-switchers [P<0.05]. The NAT group had higher rates of hypertension, diabetes and dyslipidemia than non-switchers [P<0.05].

At baseline, the AT group had significantly greater use of background medications than non-switchers [methotrexate (MTX): 75.5% vs 61.9%; P<0.0001, other non-biologic DMARDs (nbDMARDs):48.4 % vs 40.3%; P<.0001]. The NAT group also had greater use of MTX compared to non-switchers (61.9% vs 54.6%; P<0.0001) but not nbDMARDs.

The most common index bDMARD was etanercept [45%] and adalimumab [20%]. Among the AT group, the majority of patients switched to adalimumab [49%], followed by etanercept [25%], infliximab [20%] golimumab [4%], and certolizumab [3%]. For the NAT group, most common switch therapies were abatacept [43%], tocilizumab [38%], and rituximab [19%].

Mean duration of therapy on index bDMARD was 248 days, 145 days, and 127 days for non-switchers, the AT group and NAT groups, respectively. In adjusted analyses, the AT and NAT groups had similar discontinuation/switch rates (hazard ratio=1.13; P=0.15).

Conclusion: In the 12 months following bDMARD initiation, most RA patients maintained their initial bDMARD. Compared to non-switchers, the NAT group had higher comorbidities, suggesting that sicker patients are more likely to be switched to a different MOA. The use of MTX and nbDMARDs at baseline was not universal.

2639

Residual Disease Activity in Patients with Early Rheumatoid Arthritis Who Were Classified As Being in Remission According to 8 Different Descriptions: Post Hoc Analysis of the Etude Et Suivi Des Polyarthrites Indifférenciées Récentes (ESPOIR) Cohort. Isabel Castrejón[1], Maxime Dougados[2], Bernard Combe[3], Francis Guillemin[4], Bruno Fautrel[5] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Paris-Descartes University, APHP, Cochin Hospital, Paris, France, [3]Hopital Lapeyronie, Montpellier, France, [4]Faculte de Medecin/BP 184, Vandoeuvre-les-Nancy, France, [5]APHP-Pitie Salpetriere Hospital / UPMC, Paris, France

Background/Purpose: No single gold standard for remission is available for rheumatoid arthritis (RA). All available descriptions, including 2 proposed by an ACR/EULAR committee, allow residual joint abnormalities and RA symptoms. Relatively little information is reported concerning these abnormalities in patients who meet various descriptions of remission.

Methods: The ESPOIR cohort of 734 patients with complete 6-month data was analyzed to identify those in remission according to 8 descriptions, 4 requiring a formal joint count: disease activity score (DAS28) ≤2.6, clinical disease activity index (CDAI) ≤2.8, and the 2 proposed by ACR/EULAR – Boolean dichotomy with tender joint count (TJC28), swollen joint count (SJC28), C-reactive protein (CRP) and patient global estimate (PATGL) all ≤1, and simplified disease activity index (SDAI) ≤3.3. Four additional descriptions are based on routine assessment of patient index data (RAPID3), an index of patient-reported function, pain and PATGL with remission (RAPID3R) described by a score ≤3 (0–30 scale), and 3 more stringent definitions that add a careful joint examination and physician global estimate (DOCGL): RAPID3R+J1 (RAPID3 ≤3 and ≤1 swollen joint); RAPID3R+J1D1 (RAPID3 ≤3, ≤1 swollen joint and DOCGL ≤1); and RAPID3R+J0D1 (RAPID3 ≤3, no swollen joint and DOCGL ≤1). Proportions of patients with TJC28, SJC28, CRP, DOCGL, PATGL, pain or fatigue >1, or HAQ function (FN) >0.5, and specific swollen joints (n=28) were computed for each remission description.

Results: Boolean dichotomy and RAPID3R+J0D1 indicated 13% of all patients in remission vs 16–19% by SDAI, CDAI, RAPID3R+J1 and RAPID3R+J1D1. RAPID3R (26%) and DAS28 (32%) were least stringent. TJC28 >1 was seen in 0% by Boolean criteria (by definition) vs 3–11% by SDAI, CDAI, DAS28; 13–16% by RAPID3R+J1, RAPID3R+J1D1, RAPID3R+J0D1; and 24% by RAPID3R. SJC28 >1 was seen in 0% by Boolean criteria, RAPID3R+J1, RAPID3R+J1D1 and RAPID3R+J0D1 (by definition); 2% by CDAI and SDAI; 16% by DAS28; and 27% by RAPID3R. CRP >1 was seen in <8%, and HAQ-FN >0.5 in 2–12% by all 8 descriptions. PATGL >1 was seen in 10–21% by all but Boolean (0% by definition) and DAS28 (49%); pain >1 in 9–23% by all but DAS28 (46%); and fatigue >1 in 47–65% by all 8 descriptions. Knees, shoulders and elbows were involved in <5% of patients by all 8 descriptions; wrists in <6%, MCPs in <9% and PIPs in <5%, except by DAS28 and RAPID3R. Most residual joint involvement was of MCPs or PIPs.

Table. Number (%) of 734 patients in the ESPOIR early RA cohort who are in remission according to each of 8 descriptions, and number (%) of patients within each description category having residual symptoms according to specific measures and joint counts

8 Descriptions of Remission in Rheumatoid Arthritis

N (% of all pts)*	Boolean	SDAI ≤3.3	DAS28 ≤2.6	CDAI ≤2.8	RAPID3 [RAPID3 ≤3]	RAPID3R + J1 [RAPID3 ≤3; SJC ≤1]	RAPID3R + J1D1 [RAPID3 ≤3; SJC ≤1; DOCGL ≤1]	RAPID3R + J0D1 [RAPID3 ≤3; SJC = 0; DOCGL ≤1]
	96 (13%)	127 (17%)	238 (32%)	138 (18%)	194 (26%)	141 (19%)	121 (16%)	100 (13%)
Measures: N (%) of patients in remission by each description								
TJC28 >1	0 (0%)	4 (3%)	26 (11%)	4 (3%)	46 (24%)	22 (16%)	18 (15%)	13 (13%)
SJC28 >1	0 (0%)	3 (2%)	38 (16%)	3 (2%)	53 (27%)	0 (0%)	0 (0%)	0 (0%)
CRP >1	0 (0%)	4 (3%)	14 (6%)	10 (7%)	14 (8%)	8 (6%)	7 (6%)	5 (5%)
DOCGL >1	7 (7%)	10 (8%)	90 (37%)	11 (8%)	44 (23%)	20 (14%)	0 (0%)	0 (0%)
PATGL >1	0 (0%)	24 (19%)	117 (49%)	29 (21%)	40 (21%)	25 (18%)	13 (11%)	10 (10%)
Pain >1	15 (16%)	29 (23%)	100 (46%)	29 (21%)	33 (17%)	19 (13%)	14 (12%)	9 (9%)
Fatigue >1	55 (57%)	75 (59%)	156 (65%)	81 (59%)	103 (53%)	76 (54%)	57 (47%)	53 (53%)
HAQ-FN >0.5	5 (5%)	12 (9%)	29 (12%)	13 (9%)	3 (1%)	3 (2%)	3 (2%)	2 (2%)
Swollen Joints: N (%) of patients in remission by each description								
Knees ≥1	0 (0%)	0 (0%)	7 (3%)	1 (1%)	9 (4%)	2 (1.5%)	1 (1%)	0 (0%)
Shoulders ≥1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Elbows ≥1	0 (0%)	0 (0%)	5 (2%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Wrists ≥1	5 (5%)	5 (4%)	19 (8%)	5 (4%)	22 (11%)	6 (4%)	6 (5%)	0 (0%)
MCPs ≥1	9 (9%)	11 (9%)	46 (21%)	10 (7%)	52 (27%)	13 (9%)	10 (8%)	0 (0%)
PIPs ≥1	3 (3%)	5 (5%)	24 (11%)	5 (4%)	14 (19%)	4 (3%)	4 (3%)	0 (0%)

*Top row indicates number (%) of 734 patients who are in remission according to each of 8 descriptions. All other values are number (%) of patients within each column (remission description category) who have residual symptoms.

Conclusion: At least 9% of patients in remission by any description had pain, and at least 47% fatigue. RAPID3R and DAS28 had the largest proportions of patients with residual abnormalities, while CDAI and stringent RAPID3-based remission descriptions are similar to the 2 proposed by ACR/EULAR. RAPID3-based descriptions do not require formal joint counts or laboratory data, but do require DOCGL and careful joint examination, and could be feasible in usual care.

2640

Methotrexate Adverse Events in a Cohort of US Veterans with Rheumatoid Arthritis. Lisa A. Davis[1], Brooke Ivan Polk[2], Alyse D. Mann[3], Gail S. Kerr[4], Andreas M. Reimold[5], Grant W. Cannon[6], Ted R. Mikuls[7] and Liron Caplan[8]. [1]Univ of Colorado School of Med, Aurora, CO, [2]University of Colorado Medical School, Aurora, CO, [3]Denver VA Medical Center, Denver, CO, [4]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [5]Dallas VA and University of Texas Southwestern, Dallas, TX, [6]George E. Wahlen VA Medical Center, Salt Lake City, UT, [7]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [8]Denver VA and University of Colorado School of Medicine, Aurora, CO

Background/Purpose: Methotrexate (MTX) is the most commonly used medication for patients with rheumatoid arthritis (RA), however, the frequency of MTX adverse events (AE) has not been fully described. We surveyed patients exposed to multiple MTX courses to characterize MTX-associated AEs.

Methods: A random sample of patients enrolled in the prospective Veterans Affairs RA (VARA) registry was selected. Medical records were reviewed for MTX-associated AEs from the time of MTX initiation until 120 days following MTX cessation. Separate MTX courses were defined by a gap > 90 days in the pharmacy data. The AEs abstracted included: dermatologic (alopecia, rash, photosensitivity, or nodulosis); gastrointestinal (oral ulcers/ stomatitis, nausea/vomiting/anorexia/dyspepsia, or diarrhea); hematologic (leukopenia <3,500, thrombocytopenia <100,000, or new-onset anemia [hemoglobin <13.5 g/dL in men and <12.0g/dL in women]); hepatic (transaminitis >upper limit of normal, fibrosis, or cirrhosis); infectious (clinical diagnosis defined by the treating physician); central nervous system (headache, dizziness/vertigo, fatigue within 48 hours of MTX, mood alteration, or memory impairment as defined by the patient or physician); respiratory (dry cough, dyspnea, or interstitial lung disease [ILD]); and other (AE defined by physician or patient as associated with MTX). Significant AEs (SigAE) were defined as an AE leading to drug discontinuation (operationalized as any AE preceding MTX cessation by ≤ 120 days).

Results: Of the 319 patients for whom records were abstracted (1196 total patient-years [PY] of observation), 642 AEs were recorded in 270 patients during 614 total courses of MTX. The first AEs (n=268) occurred over a course of 496.5 PY of observation, yielding an incidence rate of first AE of 0.54 per PY (95% CI 0.48–0.61). SigAE (n=93) had an incidence rate of 0.08 per PY. The most common AEs were hematologic (30.4% of all AE), with anemia the leading subcategory (27.9%) (see Table). The most common SigAE was respiratory (22.6% of all SigE) but the incidence of ILD was low at 4.1%.

Table. Adverse and Significant Methotrexate Adverse Events in VARA cohort

Adverse Event	All AE N = 642	%	SigAE n = 93	%
Dermatologic	16	2.49	0	0.00
Alopecia	3	0.47	0	0.00
Rash	6	0.93	0	0.00
Photosensitivity	1	0.16	0	0.00
Nodulosis	7	1.09	0	0.00
Gastrointestinal	79	12.31	11	11.83
Oral Ulcers/Stomatitis	19	2.96	1	1.08
N/V/Anorexia/ Dyspepsia	54	8.41	7	7.53
Diarrhea	11	1.71	3	3.23
Hematologic	195	30.37	20	21.51
Leukopenia	13	2.02	0	0.00
Thrombocytopenia	6	0.93	1	1.08
Anemia	179	27.88	19	20.43
Hepatic	168	26.17	17	18.28
Transaminitis	168	26.17	17	18.28
Fibrosis	0	0.00	0	0.00
Cirrhosis	0	0.00	0	0.00
Infectious Disease	81	12.62	12	12.90
Central Nervous System	15	2.34	1	1.08
Headache	4	0.62	0	0.00
Dizziness/Vertigo	1	0.16	0	0.00
Fatigue/Malaise	9	1.40	1	1.08
Depression/Mood	1	0.16	0	0.00
Memory Impairment	1	0.16	0	0.00
Respiratory	45	7.01	21	22.58
Dry Cough	15	2.34	5	5.38
Dyspnea	21	3.27	8	8.60
Interstitial Lung Disease	26	4.05	14	15.05
Other	46	7.17	11	11.83

*SigAE=significant AE; N=nausea; V=vomiting; N=total number of reported AE; n=total number of reported significant Aes

Conclusion: Among US veterans with RA, MTX has a high AE rate, with approximately one AE noted per patient over a two-year period of treatment. In contrast, the rate of SigAE mandating drug discontinuation is much lower. The most common SigAE was respiratory, which may reflect physicians' high level of concern for MTX- associated ILD. However, the incidence of ILD in the cohort was low.

ACR Concurrent Abstract Session
Fibromyalgia and Soft Tissue Disorders II
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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Time-to-Improvement of Pain and Sleep in Clinical Trials of Pregabalin Treatment of Fibromyalgia. Lesley M. Arnold[1], Andrew Clair[2], Birol Emir[2], Lynne Pauer[2] and E. Malca Resnick[2]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Pfizer Inc, New York, NY

Background/Purpose: Fibromyalgia (FM) is a chronic condition characterized by widespread pain and tenderness. Sleep disturbance is common in patients with FM, and both pain and poor sleep quality can have a significant impact on patients' quality of life. Pregabalin is one of 3 drugs approved for the treatment of FM in the United States. Several placebo-controlled clinical trials have demonstrated that pregabalin treatment results in significant improvements in both pain and sleep in patients with FM.

Methods: This post-hoc analysis examined the time-to-onset (TTO) of improvement in pain and sleep quality in patients diagnosed with FM from four 8- to 14-week Phase III placebo-controlled trials of pregabalin at 150, 300, 450 or 600 mg/d. Pain scores were recorded in a daily diary on an 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain). Daily sleep quality was also reported on an 11-point NRS ranging from 0 (best possible sleep) to 10 (worst possible sleep). Daily pain and sleep quality scores were analyzed using analysis of covariance in the intent-to-treat population. The TTO of improvement in pain and sleep quality scores were calculated for all pregabalin dose arms that showed a statistically significant (p<0.05) reduction in their respective score at endpoint compared with placebo. TTO was defined as the first of 2 consecutive days for which the mean score was statistically significantly lower for pregabalin vs placebo.

Results: Across the 4 studies included in the analysis, there was a total of 12 pregabalin dose arms, with 2069 patients receiving pregabalin and 689 placebo. Patients had a mean age ranging from 48.0–49.7 years and the majority were women (93.1%). Mean baseline pain scores were similar for the pregabalin (range 6.8–7.0) and placebo groups (6.8). Mean baseline sleep quality scores were also similar for the pregabalin (range 6.3–6.4) and placebo (6.4) groups. Eight of 12 pregabalin dose arms were associated with a significant reduction in pain scores vs placebo at endpoint. TTO of improvement in pain occurred at day 1 of treatment for 7 dose arms (average reduction in mean pain score vs placebo, −0.36 for 300 mg/d, −0.55 for 450 mg/d, and −0.41 for 600 mg/d) and at day 2 for 1 arm (−0.59 for 300 mg/d). Eleven of 12 pregabalin dose arms were associated with a significant improvement in sleep quality score vs placebo at endpoint. TTO of improvement in sleep occurred at day 1 of treatment for these 11 arms (average reduction in mean sleep quality score vs placebo, −0.77 for 300 mg/d, −0.77 for 450 mg/d, and −0.71 for 600 mg/d pregabalin).

Conclusion: In patients with FM, statistically significant improvement in pain typically occurs within 2 days, and statistically significant improvement of sleep quality within 1 day, of initiating treatment with pregabalin.

2642

Rate and Predictors of Work Disability in Fibromyalgia. Frederick Wolfe[1], Brian T. Walitt[2], Robert S. Katz[3] and Winfried Häuser[4]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Washington Hospital Center, Washington, DC, [3]Rush University Medical Center, Chicago, IL, [4]Technische Universität München, Munich, Germany

Background/Purpose: Fibromyalgia is a contested disorder whose diagnosis depends largely on self-report. It is reportedly also associated with a high rate of work disability, but there have been no detailed studies of work disability in fibromyalgia. In addition, disabled status is difficult to determine because there are no clearly observable abnormalities or reliable assessments methods to determine work disability. In this study we determined the rate of a work disability award and its predictors.

Methods: For up to 13 years, we studied a cohort of 2,322 fibromyalgia patients, who were between the ages of 21 and 64 years, using mailed and Internet questionnaires at 6-month intervals. 591 patients were receiving US Social Security disability (SSD) awards at entry to the cohort, and were not studied further. The remaining 1,730 constituted the study sample and were evaluated using Cox regression.

Results: For the entire sample (N=2,322) the prevalence of SSD was 34.8% (95% CI 32.9, 36.8). Over 13 years of follow-up of the non-disabled sample at study entry, a SSD prevalence of 25.5% was noted. The annual incidence rate for this group was 3.4% (3.0, 3.9%) annually and 25% of patients were disabled at 9.0 years (Figure 1). As shown in Table 1, a wide variety of univariate predictors (adjusted for age and sex) at the first observation were associated with future work disability, including younger age, abnormal mood, functional status as measured by the Health Assessment Questionnaire disability index (HAQ), increased BMI, current smoking, the polysymptomatic distress scale (PSD ("fibromyalgianess")), meeting ACR 2010 criteria, the SF-36 PCS and MCS scales, VAS fatigue, VAS pain, and rating one's self as being disabled or being unemployed. College education was protective against future SSD. In multivariable Cox regression, only HAQ disability (Relative Risk 2.5 (1.8, 3.6)), rating one's self as disabled (RR 5.9 (3.6, 9.7)), and being unemployed (RR 3.3 (1.9, 5.8)) were significant predictors of future SSD.

Table 1. Univariate predictors of SSD, adjusted for age and sex

Variable	Hazard Ratio (95% CI)
Disabled – self-report (yes/no)	10.5 (6.56, 16.67)
Unemployed (yes/no)	4.05 (2.34, 7.01)
FM Diagnostic criteria (+) (yes/no)	3.27 (2.27, 4.71)
Current smoking (yes/no)	1.70 (1.22, 2.35)
> High school education (yes/no)	0.71 (0.51, 0.98)
College education (yes/no)	0.46 (0.33, 0.66)
HAQ Disability (0–3)	4.77 (3.76, 6.04)
VAS Pain (0–10)	1.34 (1.25, 1.43)
Mood (0–10)	1.29 (1.21, 1.38)
VAS Fatigue (0–10)	1.22 (1.15, 1.30)
VAS Sleep disturbance (0–10)	1.18 (1.12, 1.24)
Polysymptomatic distress (0–31)	1.09 (1.07, 1.11)
Body mass index	1.04 (1.02, 1.05)
SF-36 PCS	0.92 (0.90, 0.93)
SF-36 MCS	0.96 (0.95, 0.97)

No ethnicity groups were statistically significant predictors.

Cox proportional hazards regression
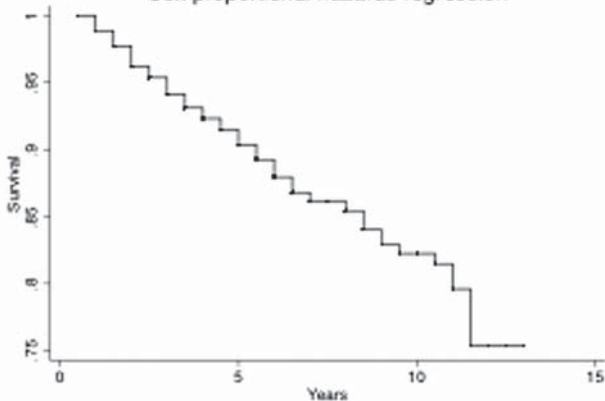
Conclusion: The receipt of a SSD award is common in fibromyalgia, with an annual incidence of 3.4% (3.0, 3.9%). Although many variables were predictive of SSD in univariate models, only self-report of functional status and current unemployment and/or self-reported disability predicted future SSD. One explanation for the few predictors is that BMI, smoking, education and symptoms contribute to functional status, which then dominates all other predictors.

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2643

Grey Matter Decrease in Fibromyalgia Is Related to Pain Catastrophizing and Pain Sensitivity. Marta Ceko, Mary-Ann Fitzcharles, M. Catherine Bushnell and Petra Schweinhardt. McGill University, Montreal, QC

Background/Purpose: Fibromyalgia (FM) is commonly associated with catastrophizing, a set of negative emotional and cognitive processes related to pain. Catastrophizing is suggested to augment pain sensitivity through increased attention to pain and exaggerated emotional processing of pain. FM is associated with grey matter (GM) decreases in cortical medial frontal regions thought to be involved in attention to pain and pain modulation. We investigated the relationship between GM alterations and measures of pain, specifically hypothesizing that in fibromyalgia GM decreases in the medial frontal regions will be related to pain catastrophizing, as well as to pain sensitivity.

Methods: We recruited 29 female FM patients and 29 female controls matched for age, handedness, education, body mass index, physical activity, and socioeconomic status. All subjects underwent anatomical magnetic resonance imaging (MRI). Catastrophizing was assessed using the Pain Catastrophizing Scale; pain intensity and unpleasantness were assessed in response to a standardized pressure stimulus applied on the thumbnail. MRI data were preprocessed in SPM8. Voxel-wise GM differences were examined using independent sample t-tests while controling for age.

Results: Pain catastrophizing was higher in the FM patients (p<0.001), as was pain unpleasantness (p=0.011), with a trend for pain intensity (p=0.079). FM patients had decreased GM in the medial prefrontal cortex (MPFC), superior frontal gyrus, and premotor cortex (p<0.05 cluster-corrected). In FM patients, GM in the MPFC was negatively correlated with catastrophizing (p=0.022), pain intensity (p=0.048), and pain unpleasatness (p=0.020).

Conclusion: This study shows a three-way relationship between MPFC changes, catastrophizing and pain sensitivity, indicating that structural alterations in FM might contribute to the patients' phenotype.

Disclosure: **M. Ceko**, None; **M. A. Fitzcharles**, Pfizer Inc, Lilly, Purdue, Valeant, 5; **M. C. Bushnell**, None; **P. Schweinhardt**, None.

2644

Functional Magnetic Resonance Imaging of Working Memory in Fibromyalgia: Support for a "Competing Demands" Theory of Cognitive Function in Chronic Pain. Anson E. Kairys, Gabriela Ramirez, Eric Ichesco, Johnson P. Hampson, Richard E. Harris, Daniel J. Clauw, Tobias Schmidt-Wilcke and Jennifer M. Glass. University of Michigan, Ann Arbor, MI

Background/Purpose: The primary symptom of fibromyalgia (FM) is chronic widespread pain; however, patients report additional symptoms including decreased concentration and memory. Deficits are seen mainly in tests of working memory (WM) and executive functioning. WM is a cognitive system that involves the ability to store and manipulate mental information for a short period of time, as occurs in the 2-back task. Versions of this task have been used extensively in functional neuroimaging studies of WM. Chronic pain may interfere with cognitive performance, but the neural correlates of this interference remain unclear. We hypothesized that FMs would perform worse on the 2-back task relative to healthy controls (HC), with neural-based changes in blood-oxygen-level-dependent (BOLD) signal.

Methods: 16 FM patients completed a randomized double-blind two-period cross-over study of milnacipran versus placebo. Data reported here are from pre-drug baseline assessment. 13 age and gender matched healthy controls (HC) also participated. Participants performed five blocks of the 2-back task (with 0-back as a control) while in the fMRI scanner. All fMRI data were pre-processed using SPM5. Our regressors of interest (2-back and 0-back) were convolved with the hemodynamic response function and applied to voxel-wise statistics. Corresponding contrast images (2back>0back) were then entered into a 2nd level analysis (two-sample t-test) to delineate differences in brain activations between the groups. Regions of

interest showing significant changes in BOLD activation during the 2-back task were extracted and analyzed using SPSS 19.

Results: Behavioral results showed no overall difference between FM and HC groups on the 2-back task; however, there was an interaction with block $(F(4, 24)=2.8, p<.05)$, such that FM patients showed better accuracy during the first block, but did not improve over time. In contrast, HC subjects improved and by the final block were more accurate than FM patients. While performing the task in the scanner, FM patients displayed significantly less BOLD activity within the left-mid insula (FM<HC percent BOLD change mean difference -0.455 ± 0.194), right posterior insula (-0.057 ± 0.196), left cingulate cortex (-0.109 ± 0.134) and right primary somatosensory cortex $(-0.43 \pm 0.204$; all p<0.05 corrected). There was a significant positive correlation between BOLD activity in the left cingulate cortex and accuracy on the 2-back task (r=0.5, p=0.049), and a significant negative correlation between BOLD activity in the primary somatosensory cortex and pain severity (r=−0.546, p=0.029) in FM patients.

Conclusion: FM patients displayed reduced activity in the insula, cingulate, and primary somatosensory cortex during a working memory task, when compared to HCs. Behaviorally, FM patients showed no improvement in performance over time, whereas HCs improved. The results are consistent with a "competing demands" problem with neural resources in FM patients. It appears as though perception and processing of pain activates areas of the brain that are also involved in cognition, including inhibition and attention networks involved in cognitive executive function, making these networks less available for cognitive tasks.

2645

The Transcription Factor Mohawk Plays an Important Role for Maintaining Human Anterior Cruciate Ligament Homeostasis. Hiroyuki Nakahara, Akihiko Hasegawa, Fumiaki Ayabe, Tetsuya Matsukawa, Koji Otabe, Tomo Yonezawa, Martin K. Lotz and Hiroshi Asahara. The Scripps Research Institute, La Jolla, CA

Background/Purpose: Recently Mohawk homeobox (MKX) has been discovered as a tendon and ligament specific transcriptional factor. MKX deficient-mice are shown to hypoplastic tendons throughout the body by down regulating changing type I collagen production in tendon cells. However, in human tendons or ligaments, little is known about the function of MKX. In this study, we demonstrated using human anterior cruciate ligament (ACL) tissues and primary cultured human ACL cells that MKX is an important regulator of human ligament homeostasis, and that its changes in the expression and function play an important role in ligament degeneration. The aims of this study are to characterize the expression of MKX in normal human knee joints and osteoarthritis (OA) affected knee joints and to investigate the role of MKX in human ligament homeostasis.

Methods: Human ACL specimens were obtained from the knee joints at cadaveric autopsy within 24–48 hours postmortem with approval of the Scripps Human Subjects Committee. 7 normal donors (mean±SD age 33.57±11.67years) and 8 donors with OA (mean±SD age 77.50±11.46 years) were analyzed and none of the donors had a history of knee joint trauma. All cartilage surfaces were graded macroscopically. ACL degeneration was assessed macroscopically and histologically using quantitative scoring systems. ACL tissues were analyzed for the expression of MKX by immunohistochemistry and quantitative RT-PCR assays. Primary cultured human ACL cells were stimulated with IL-1β to examine whether proinflammatory cytokine modulates MKX expression. Moreover, in order to examine the function of MKX on ECM production and differentiation in these cells, we performed the knocked-down by MKX specific siRNA and then, determined the expression of some genes involving in ECM and the differentiation using quantitative RT-PCR and western blotting analysis.

Results: The expression of MKX was remarkably decreased during developing OA. In addition, the expression of COL1a1, which is major component of ACL, is also decreased in OA group. In coincidence with the result of immunohistochemistry revealed that the percentage of MKX positive cells was significantly reduced in OA group. In primary cultured human ACL cells, the expression of MKX was significantly reduced by the treatment of IL-1β. The expression of genes involving in regulating ECM homeostasis such as COL1a1 and TNXb and transcriptional factor Scleraxis (SCX), which is specific regulator of the tendon/ligament

lineage, were down-regulated by IL-1β treatment. On the other hand, SOX9, which is involved in the modulation of chondrocyte like phenotype, was up-regulated by IL-1β treatment. The expression of COL1a1 and TNXb were decreased by MKX specific siRNA treatment, though that of SOX9 was increased. We didn't detect any significant differences in those of SCX, IL-6 and MMP13.

Conclusion: To our knowledge, this is the first report to investigate the MKX expression and function in Human ligaments. The present study demonstrates that the expression of MKX is down-regulated by an inflammatory response and MKX may play important roles in ligament homeostasis via regulating the expression of COL1a1, TNXb and SOX9 in human ACL cells.

2646

Cost-Effectiveness of Tai Chi Mind-Body Exercise for the Treatment of Fibromyalgia. John B. Wong and Chenchen Wang. Tufts Medical Center, Boston, MA

Background/Purpose: Although fibromyalgia is associated with substantial annual direct medical and indirect productivity costs, the cost-effectiveness of treatments for fibromyalgia remains understudied. A randomized controlled trial of tai chi mind-body exercises versus wellness education and stretching found tai chi to be safe and effective, so our aim was to assess the cost-effectiveness of tai chi for fibromyalgia in this trial.

Methods: The analysis is based on a single-blind, 12-week randomized trial of classic Yang-style tai chi compared with wellness education and stretching control for the treatment of fibromyalgia in 66 patients with 24 week follow up (NEJM 2010; 363:743–54). Effectiveness outcomes from baseline to week 24 included Fibromyalgia Impact Questionnaire (FIQ) score, Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) quality of life (QOL), pain score using the visual analog scale (VAS) and Health Assessment Questionnaire Disability Index (HAQ). Hourly costs were based on an Internet search with Tai Chi costing $17.50 ($10–$25) and stretching costing $12 ($9–$15). A systematic review of Medline from inception to 2011 for economic studies regarding fibromyalgia found annual direct medical care costs of $3700 equaling 1.7 to 2.9 times population controls and indirect costs that were 1.7 to 2.2 times direct medical care costs (ACR #902 Arthritis Rheum 2011;63 Suppl 10:S354–5). Statistical testing for differences used the two sample t-test and mixed models with time and group as categorical fixed factors. A linear regression related HAQ to mean direct care costs (R-square 0.96).

Results: The mean difference improvement with tai chi versus wellness education and stretching control in FIQ was 18.3 (95% CI 9.6–27.1, p<0.001); in SF36 QOL physical health was 7.0 (2.9–11.0, p=0.001) and SF36 QOL mental health was 7.3 (1.9–2.8, p=0.009); in VAS pain was 2.1 (95% CI 0.74–3.5, p=0.003); and in HAQ was 0.21 (95% CI 0.037–0.390, p=0.019). Assuming no reduction in health care utilization from tai chi, the incremental cost-effectiveness of tai chi versus wellness education and stretching was $4 (95% CI $2–$7) per 1 point improvement in FIQ; $9 (95% CI $5–35) per 1 point improvement in physical or mental QOL; $31 (95% CI $19–$89) per 1 point improvement in VAS pain score and $314 (95% CI $169–$1784) per 1 point improvement in HAQ. Assuming that the improved HAQ disability index decreases health care utilization, tai chi results in an estimated savings of $366 (95% CI $9–$724) per patient over 6 months. Assuming that the observed decreased HAQ disability index decreases health care utilization and productivity losses, tai chi results in an estimated savings of $775 (95% CI $80–$1474) per patient over 6 months.

Conclusion: Compared with wellness intervention and stretching, tai chi improves FIQ score, SF36 QOL, VAS pain score and HAQ significantly. Costs per unit improvement appear to be quite modest, and assuming that improvement in HAQ would lead to direct and indirect cost reductions, tai chi would be cost-saving. Confirmation of these results in a larger randomized controlled trial is needed.

2647

Effects of Pain Expectations On Neuromuscular Control of the Spine in Patients with Chronic Low Back Pain and Healthy Participants. Yves Henchoz, Charles Tétreau, Jacques Abboud, Mathieu Piché and Martin Descarreaux. Université du Québec à Trois-Rivières, Trois-Rivières, QC

Background/Purpose: The mechanisms underlying the transition from acute to chronic low back pain (cLBP) are poorly understood. Physiological and psychological factors are implicated. Although significant associations have been found between neuromuscular control of the lumbar spine and the level of fear of pain, it is still unknown whether acute exposure to fear of pain alters trunk motor control. The objective of this study was to determine if experimentally induced pain expectations modulate trunk neuromuscular responses differently in subjects with and without cLBP.

Methods: This cross-sectional study included 22 patients with cLBP and 22 healthy participants. They performed 6 trunk flexion-extension tasks under three experimental conditions: innocuous heat, noxious stimulation with low pain expectation and noxious stimulation with high pain expectation. Noxious stimulation was generated by thermal cutaneous heat stimulations in the lumbar region (L4-L5), whereas low or high pain expectations were generated by verbal and visual instructions (see **Fig. 1**). After each task, experimental pain was evaluated using a numerical rating scale (NRS). Surface electromyography (sEMG) of erector spinae at L2-L3 and L4-L5 as well as lumbopelvic kinematic variables were collected during the tasks. Pain ratings, sEMG and kinematic variables were compared between groups and conditions using two-way mixed ANOVAs. Pearson's correlation coefficients were calculated in cLBP patients to determine whether the effects of expectations were associated with disability, pain catastrophizing, state and trait anxiety and fear avoidance beliefs.
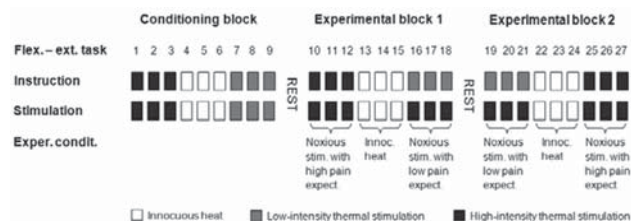
Fig. 1. Study design

Results: Pain ratings were significantly different between high and low pain expectations conditions (P<0.001). This difference was similar between patients with cLBP (15.2 ±13.4) and control participants (13.3 ± 10.2). In patients with cLBP, the increase in sEMG activity in full flexion caused by expectation was related to higher pain catastrophizing, but not to disability, anxiety and fear-avoidance beliefs. Two-way mixed ANOVA yielded a significant "group × condition" interaction for sEMG in Full flexion (P<0.05). Planned comparisons revealed a stronger effect of pain expectation in healthy participants than in patients with cLBP. Lumbopelvic rhythm was significantly different between groups (P<0.05), but similarly affected by pain expectation.

Conclusion: As anticipated, the increase in sEMG activity caused by expectations was related to higher pain catastrophizing in patients with cLBP. Nevertheless, expectations of high pain resulted in neuromuscular adaptations that were weaker in patients with cLBP than in healthy participants. In conclusion, chronic pain appears to generate rigid and less variable movement patterns in patients with cLBP, which attenuate their response to acute fear of pain exposure.

Disclosure: **Y. Henchoz**, None; **C. Tétreau**, None; **J. Abboud**, None; **M. Piché**, None; **M. Descarreaux**, None.

2648

Randomized Placebo-Controlled Trial of Local Steroid Injection for Moderately Severe Carpal Tunnel Syndrome. Isam Atroshi[1], Magnus Flondell[2] and Manfred Hofer[3]. [1]Lund University, Hässleholm, Sweden, [2]Lund University, Malmö, Sweden, [3]Kristianstad Hospital, Kristianstad, Sweden

Background/Purpose: Patients with idiopathic carpal tunnel syndrome (CTS) are commonly treated with local steroid injection but there is currently no evidence from placebo-controlled trials supporting efficacy beyond 1 month.

Methods: We conducted a randomized triple-blind placebo-controlled trial of first-time steroid injection into the carpal tunnel in patients with moderately severe CTS. Patients aged 18 to 70 years with primary idiopathic CTS, no severe sensory loss or muscle atrophy, and no previous steroid injection for CTS were randomized to 1 of 3 groups (37 patients in each): 80 mg Methylprednisolone, 40 mg Methylprednisolone, or saline (each also containing 10 mg Lidocaine). Patient-reported outcomes (CTS symptom severity scale, *Quick*DASH, SF-36 bodily pain, and SF-6D) were obtained and physical examination by a blinded assessor was performed at baseline and at 10, 24 and 52 weeks after injection. The primary end points were change in CTS symptom severity score at 10 weeks and rate of surgery at 52 weeks. Data from all patients were analyzed.

Results: During 1 year after injection surgery was carried out on 27 patients (73%) in the 80 mg Methylprednisolone group, on 30 patients (81%) in the 40 mg Methylprednisoline group, and on 34 patients (92%) in the placebo group. Patients who received placebo were significantly more likely to have surgery during 1 year after injection than patients who received Methylprednisolone; adjusted hazard ratio 2.0 (95% confidence interval 1.3–3.2, P<0.01). The change in the CTS symptom severity score from baseline to 10 weeks was significantly larger in both Methylprednisolone groups than in the placebo group.

Conclusion: In patients with moderately severe carpal tunnel syndrome first-time steroid injection into the carpal tunnel has a significant benefit in relieving symptoms up to 10 weeks and in reducing the need for surgery up to 1 year after treatment.

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Trends in US Arthroplasty Rates 1991–2005: Patients with Inflammatory Arthritis Continue to Require Joint Replacement. Christina Mertelsmann-Voss[1], Ting Jung Pan[2], Stephen L. Lyman[3], Mark P. Figgie[2] and Lisa A. Mandl[2]. [1]Hospital for Special Surgery, Cornell University, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Hospital Special Surgery, New York, NY

Background/Purpose: Overall rates of total joint replacement surgeries (TJR) have increased dramatically over the past decades. By contrast, TJR rates among patients with rheumatoid arthritis (RA) are reported to be decreasing. The magnitude of such change, and whether it applies to all types of inflammatory arthritis (IA), is not clear. This study evaluates rates of TJR among patients with IA, [RA, juvenile idiopathic arthritis (JIA) and spondyloarthropathies (SpA)] and compares them to TJR patients with non-inflammatory conditions.

Methods: Administrative hospital discharge databases from 10 states (AZ, CA, CO, FL, IA, MA, NJ, NY, WA, WI) and census data annual population estimates were used to calculate combined rates per 100,000 population of knee arthroplasty, total and partial hip arthroplasty, and total and partial shoulder arthroplasty from 1991 to 2005. ICD-9-CM codes were used to identify specific diseases.

Results: There were 2,839,325 arthroplasties from 1991 to 2005, of which 76,665 (2.7%) were in IA patients. The proportion of TJR attributable to IA nearly halved during this period (3.9% in 1991 vs. 2.0% in 2005). TJR rate for non-inflammatory conditions almost doubled from 124.5 in 1991 to 247.5 in 2005, while the rate in IA patients was fairly steady (range: 4.4–5.2). Stratifying by IA subtype, the TJR rate decreased slightly for RA (4.6 vs. 4.5, p-value<0.001) decreased by 40% for JIA (0.31 vs. 0.22, p-value<0.001), and increased by 40% for SpA (0.22 vs. 0.31 p-value<0.001). From 1991 to 2005, the mean age at TJR for IA patients across all disease subtypes increased: RA (63.4 yrs ±12.7 vs. 64.9 yrs ±12.8, p-value<0.001), JIA (30.9 yrs ±12.2 vs. 36.7 yrs ±14.9, p-value <0.001), and SpA (54.3 yrs ±16.1 vs. 60.4 yrs ±13.9, p-value

<0.001). In contrast, the mean age of non-IA decreased (71.5±11.8 yrs. vs. 69.0±12.0 yrs p<0.001). Among IA patients, neither age nor sex was statistically significantly related to TJR rates.

Conclusion: To our knowledge this is the largest cohort of TJR of patients with IA and the first study of TJR trends in patients with JIA and SpA. Surprisingly, TJR rates in RA showed minimal change despite the widespread introduction of methotrexate in the 1990s. JIA and SpA patients appear to be deferring TJR, with JIA patients requiring fewer procedures. Why SpA TJR rates increased is unclear. These data suggest there will be an ongoing need for orthopedists with expertise in operating on IA patients. Obtaining exposure during surgical training may be difficult, as the proportion of TJR cases due to IA is declining. Further research is needed to assess the effect of biologic medications, first introduced in 1998, on IA TJR rates.

Disclosure: C. Mertelsmann-Voss, None; **T. J. Pan**, None; **S. L. Lyman**, None; **M. P. Figgie**, None; **L. A. Mandl**, None.

2650

The Meteor Trial: Preliminary Results of an RCT of Arthroscopic Partial Meniscectomy Vs. Physical Therapy in Patients greater Than 45. Jeffrey N. Katz[1], Christine E. Chaisson[2], Brian Cole[3], Laurel Donnell-Fink[1], Morgan Jones[4], Bruce Levy[5], Lisa A. Mandl[6], Scott Martin[1], Robert Marx[6], Anthony Miniaci[4], Joseph Palmisano[7], Emily Reinke[8], Clare Safran-Norton[1], Debra J. Skoniecki[9], Daniel Hal Solomon[9], Kurt P. Spindler[8], John Wright[1], Rick Wright[10] and Elena Losina[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Boston University School of Public Health, Boston, MA, [3]Rush University, Chicago, IL, [4]Cleveland Clinic, Cleveland, OH, [5]Mayo Clinic, Rochester, MN, [6]Hospital for Special Surgery, New York, NY, [7]Boston University School of Public Health, [8]Vanderbilt University, Nashville, TN, [9]Brigham & Womens Hospital, Boston, MA, [10]Washington University, MO

Background/Purpose: Patients who present with a symptomatic knee that has both osteoarthritis and a meniscal tear present a difficult treatment challenge. They may be treated nonoperatively or with arthroscopic partial meniscectomy (APM); there is limited data on the comparative outcomes of these treatments.

Methods: We conducted a randomized controlled trial in 7 US centers involving 351 subjects > 45 years old with symptomatic meniscal tear and osteoarthritic cartilage change, documented by magnetic resonance imaging (MRI). To be eligible, subjects must have exhibited meniscus related symptoms for at least 4 weeks. Enrolled subjects were randomized to APM with postoperative physical therapy (APM arm) or to nonoperative care including a standardized PT regimen focused on strengthening (non-operative arm). The primary analysis compared change in functional status (WOMAC) over 6 months across the 2 arms, using an intention to treat (ITT) approach. A secondary outcome was a binary variable defined as lack of improvement in WOMAC function of at least 8 points over 6 months (a clinically relevant change) OR unplanned cross-over (from nonoperative therapy to APM or from APM to nonoperative therapy). We carried 3 month observations forward to address missing 6 month outcome data.

Results: 174 subjects were randomized to APM and 177 to the nonoperative arm. The arms were balanced with respect to baseline function, radiographic severity, age and sex. The response rate at 6 months was 84% across both arms. In the ITT analysis, mean improvement in WOMAC function after 6 months was 19.4 points (sd 18.4) in subjects randomized to APM and 16.8 (sd 18.1) in those randomized to the non-operative arm (p=0.19). Of the 174 randomized to APM, 9 (5%) did not receive surgery by 6 months. Of the 177 subjects randomized to the non-operative arm, 53 (30%) crossed over and had APM by 6 months (Table). In the analysis of the secondary outcome, 26% of subjects randomized to APM vs. 51% of subjects in the nonoperative arm either did not improve by at least 8 points on WOMAC function or crossed over (p<0.0001; Table).

Table. Crossovers and functional outcomes at six months in the randomized arms

Randomized arm	No crossover		Crossover
	WOMAC improvement ≥ 8	WOMAC improvement < 8	
APM	129 (74%)	36 (21%)	9 (5%)
Nonoperative	86 (49%)	38 (22%)	53 (30%)

Conclusion: These preliminary trial findings suggest that in both the APM and the nonoperative arms, subjects experienced substantial improvement in functional status over six months, with no significant differences between the two arms in the ITT analysis. 30% of subjects randomized to nonoperative therapy underwent APM within the first six months. As with all RCT's the results should be generalized cautiously to clinical populations. These findings will aid physicians and their patients over 45 who present with knee symptoms in association with meniscal tears and osteoarthritis as they decide whether to elect APM or nonoperative therapy.

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Associations Between Body Mass Index and Physical Activity Following Total Knee Replacement. Carol A. Oatis[1], Wenjun Li[2], Milagros Rosal[2], David Ayers[2] and Patricia D. Franklin[2]. [1]Arcadia University, Glenside, PA, [2]University of Massachusetts Medical School, Worcester, MA

Background/Purpose: In 2009 over 620,000 total knee replacement (TKR) surgeries were performed. That number is expected to increase to 3.5 million annually by 2030. On average, physical activity and functional ability remain diminished one year post TKR when compared to age matched controls. Many patients who undergo TKR are obese. The purpose of this study was to examine the relationship of preoperative body mass index (BMI) to objectively measured physical activity levels at 6 months post TKR.

Methods: Subjects were 179 participants of an NIH funded RCT of telephone support intervention following unilateral primary total knee replacement (TKR). Participants were stratified by BMI (< 30; 30–35; > 35). Participants were asked to wear an accelerometer (Step Activity Monitor™) at the ankle for four consecutive days (2 weekday; 2 weekend) before surgery and at 8 weeks and 6 months post operatively. The accelerometer monitored the number of steps taken daily. Valid wear days required a minimum of 10 hours of wear time.

Results: Participants were 68% female with a mean (SD) age of 65.1 (8.61). Mean (SD) BMI at baseline was 32.5 (5.24). All 179 participants wore the accelerometer preoperatively. 174, 163 and 168 participants had at least one valid wear day preoperatively, at 8 weeks and 6 months after surgery respectively. Mean days worn was 3.3 days. Participants with BMI > 35 (n=53) took fewer steps than those with BMI < 35 (n=121) preoperatively, at 8 weeks post surgery (BMI > 35, n = 46 and BMI < 35, n = 117) and at 6 months post surgery (BMI > 35, n = 50 and BMI < 35, n = 118) (p <.01) (Figure). At 6 months post surgery, mean steps (SD) were greatest in those with BMI < 30, 8845 (3731), fewer in those with BMI between 30 and 35, 8688 (3386), and fewest in those with BMI > 35, 7196 (3299). Change in daily steps from baseline to 6 months was similar across all BMI groups.
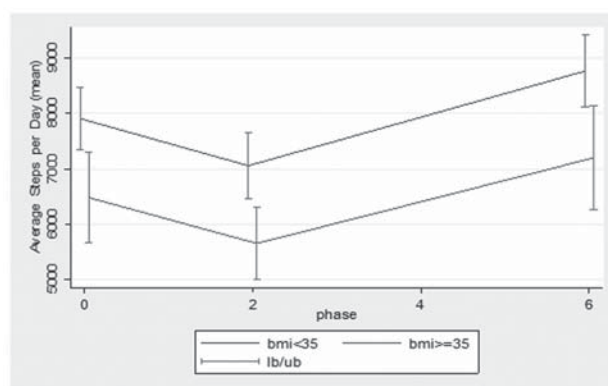
Conclusion: Subjects with grade 2 obesity or greater (BMI >35) are less physically active throughout the perioperative period of TKR than those with lower BMI. However high BMI does not preclude improvements in physical activity levels following TKR. An understanding of the association between obesity and physical activity can help inform patients' and clinicians' expectations for post-TKR gain and may focus interventions not only on the knee impairments following TKR but also on the modifiable risks to optimal gains in physical activity following TKR. Risk factors such as BMI may be addressed pre- and post-operatively.

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Benefits of Aerobic Training in Patients with Ankylosing Spondylitis Are Not Coupled by Effects On Cytokines: A Randomized Controlled Trial. Fabio Jennings, Hilda A. Oliveira, Marcelo C. Sousa, Vaneska G. Cruz, Fabio S. Lira and Jamil Natour. Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Background/Purpose: Ankylosing Spondylitis (AS) is a systemic inflammatory disease that causes deterioration of physical capacity. Although exercises remain essential in the treatment, the literature lacks research on the mechanisms by which exercises lead to clinical improvements in patients with AS. The purpose of this study was to evaluate the effects of aerobic exercise on functional capacity, mobility, disease activity, aerobic capacity, quality of life and cytokine levels (TNF-α, IL-1β, IL-6 and IL-10) in patients with AS.

Methods: Seventy patients with a diagnosis of AS, according to New York modified criteria and with stable drug treatment, were included. The patients were randomly allocated in two groups. The intervention group (IG) underwent 50 minutes of walking in the individual anaerobic threshold associated with stretching exercises 3 times a week for 12 weeks. The control group (CG) performed stretching exercises 3 times a week for 12 weeks. The outcome measurements were: functional capacity measured using BASFI (The Bath Ankylosing Spondylitis Functional Index), HAQ-S (Health Assessment Questionnaire for spondyloarthritis) and the 6-minute walking test (6MWT); mobility measured using BASMI (The Bath Ankylosing Spondylitis Metrologyl Index); disease activity by BASDAI (The Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score). Aerobic capacity was evaluated using an incremental cardiopulmonary exercise testing protocol by treadmill. TNF-α, IL-1β, IL-6 and IL-10 levels were measured using ELISA method. The evaluations were done by a blinded assessor immediately before the randomization, 6 weeks, and 12 weeks after the beginning of the exercise programs. It was used intention-to-treat analysis.

Results: Thirty-five patients were randomized to IG and 35 to CG. Two patients from CG and one patient from IG withdrew because of time availability. At baseline, the groups were homogeneous regarding all clinical and demographic characteristics. There were significant improvements in BASFI, HAQ-S, BASDAI and ASDAS scores in both groups (p < 0.05), but there was no difference between groups. There was no significant improvement of mobility and quality of life in both groups. The IG showed significant improvement in 6MWT compared to the control group (p < 0.001). There was significant increase in VO_2 peak and anaerobic threshold (AT) in IG after treatment. In CG, VO_2 peak and AT did not change after 12 weeks. There was significant difference between groups in absolute values of VO_2 peak (p=0.049) and O_2pulse (p=0.039) at 12 weeks. TNF-α, IL-1β, IL-6 levels did not change over time in both groups. IL-10 levels decreased in both groups after 12 weeks compared to baseline (p< 0.001), but there was no difference between groups.

Conclusion: Aerobic training and stretching exercises had beneficial effects on functional capacity and disease activity. Aerobic training, in addition to stretching exercises, increased walking distance and cardiopulmonary capacity in patients with AS. Aerobic exercise did not affect cytokine levels. More studies are need to understand the mechanisms by which exercises have a therapeutic role in AS.

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ACR Concurrent Abstract Session
Pediatric Rheumatology - Pathogenesis and Genetics
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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A Subset of up-Regulated IFN Regulated Genes in Candle Patients Decrease with Treatment with a JAK Inhibitor. Adriana Almeida de Jesus[1], Yin Liu[2], Gina A. Montealegre[2], Adam L. Reinhardt[3], Diane Brown[4], Antonio Torrelo[5], Angel V. Casano[6], Lena Das[7], Yongqing Chen[8], Yan Huang[8], Deborah Stone[9], Dawn C. Chapelle[2], Nicole Plass[10], Steven H. Zuckerman[11], William Macias[12] and Raphaela T. Goldbach-Mansky[13]. [1]National Institute of Arthritis Musculoskeletal and Skin Disease, National Institutes of Health, Bethesda, MD, [2]NIAMS, Bethesda, MD, [3]Children's Hosp of Omaha/UNMC, Omaha, NE, [4]Children's Hospital Los Angeles, Los Angeles, CA, [5]Departments of Pediatric Dermatology, Hospital Niño Jesús, Madrid, Spain, Madrid, Spain, [6]Meditex Spain, Malaga, Spain, [7]KK Women's and Children's Hospital, Singapore, Singapore, [8]Translational Autoinflammatory Disease Section, Office of the Clinical Director NIAMS, Bethesda, MD, [9]National Institutes of Health, Bethesda, MD, [10]National Institutes of Health Clinical Center, Bethesda, MD, [11]Lilly Research Labs, Indianapolis, IN, [12]Eli Lilly and Company, Indianapolis, IN, [13]Translational Autoinflammatory Diseases Section NIAMS NIH, Bethesda, MD

Background/Purpose: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a recently described early-onset autoinflammatory disease caused by autosomal recessive mutations in genes encoding the proteasome subunits, mainly the subunit β type 8 gene (*PSMB8*). It was previously shown that CANDLE patients present with increased expression of Interferon (IFN) regulated genes and unregulated stat1 phosphorylation on peripheral blood monocytes. We therefore suggested that drugs inhibiting Janus kinases (JAKs), mediators of IFN signaling, might be used as a treatment in CANDLE. The objectives of this study were to assess the interferon regulated genes expression in additional CANDLE patients and to describe the effect of oral treatment with JAK inhibition on IFN-induced genes in CANDLE patients.

Methods: Two new and 4 previously evaluated CANDLE patients had whole blood microarray analysis performed and their IFN signaling was compared with 5 healthy controls. Total RNA was extracted from PAXgene tubes blood samples and complementary DNA synthesis and target amplification were done. Affymetrix HU-133 Plus 2.0 gene chips were used for hybridization and data analysis was performed with GeneSpring 11.5 and Partek softwares. Patients and healthy control groups were compared using unpaired t test with Welch's correction. IFN regulated gene expression profiles were assessed before and after treatment with the JAK inhibitor baricitinib in 2 CANDLE patients.

Results: Compared to controls, two new CANDLE patients presented with increased expression of IFN-induced genes, as in the previously evaluated 4 CANDLE patients. We have found that 202 genes were >2-fold upregulated compared to the 5 healthy controls, of those 89 are IFN regulated. The difference between the expression values was strikingly marked for the following genes: *IFI27* (12.85 $\pm$ 0.85 vs. 6.10 $\pm$ 0.31, p<0.0001), *ISG15* (12.86 $\pm$ 0.35 vs. 9.60 $\pm$ 0.69, p=0.0002), *RSAD2* (12.75 $\pm$ 0.18 vs. 9.19 $\pm$ 0.70, p=0.0004), *SP100* (11.75 $\pm$ 0.12 vs. 10.89 $\pm$ 0.34, p=0.0062), *USP18* (9.95 $\pm$ 0.33 vs. 6.25 $\pm$ 0.68, p=0.0001), *DDX60* (11.71 $\pm$ 0.09 vs. 9.72 $\pm$ 0.33, p=0.0002), *EIF2AK2* (12.24 $\pm$ 0.21 vs. 10.64 $\pm$ 0.35, p=0.0001) and *GBP1*(12.02 $\pm$ 0.54 vs. 9.68 $\pm$ 0.43, p<0.0001). Upon treatment with the JAK inhibitor, 136 of the 202 up-regulated genes get down-regulated and 65 of those are IFN regulated genes. The others were genes that were associated with cytokine regulation including IL-22, IL-9, IL-15, IL-3, IL-2, GM-CSF, IL-17A. Of those 66 genes that did not change, 24 were IFN regulated genes. Interestingly, the expression of 37 proteasome-associated genes either increase or do not change with JAK inhibitor treatment.

Conclusion: We have found that CANDLE patients present a high expression of IFN-regulated genes and that this finding is present in all patients. This study also suggests that treatment with a JAK inhibitor is able to downregulate IFN induced genes as well as genes associated with the regulation of other inflammatory cytokines.

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Genome-Wide Association Study of Methotrexate Response Identifies Novel Genes in a Large Cohort of European Juvenile Idiopathic Arthritis Cases.

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Background/Purpose: The drug methotrexate (MTX) is the first line treatment for many children with Juvenile Idiopathic Arthritis (JIA). Only 45% of children treated with MTX for arthritis achieve 70% improvement as defined using internationally agreed JIA core set criteria, and a proportion of children will not respond at all to MTX treatment. Currently there are no reliable predictors to identify children likely to fail to respond. In order to identify these children early, and thus target their treatment during the apparent short window of opportunity in which disease can readily be brought into remission, the Childhood Arthritis Response to Medication Study (CHARMS) was established. Growing evidence suggests that multiple genes contribute to the genetic component of treatment response in arthritis. With this in mind, and using the CHARMS cohort, this study aimed to perform a genome wide association study (GWAS) to identify genomic loci associated with response to MTX in JIA.

Methods: Genotyping of the Illumina OmniExpress Beadchip was performed in a large cohort of 792 JIA cases from the UK, Netherlands and Czech Republic. Single nucleotide polymorphisms (SNPs) failed QC based on a call rate <98% and/or cluster separation score <0.4. Samples failed QC based on a call rate <98%, in addition outliers of mean heterozygosity, related individuals and ancestral outliers (identified using principal components analysis) were removed. The final sample size after QC was 694 cases. The 6 core outcome variables (active/limited joint counts, ESR, CHAQ, parent/physician global assessments) were collected at baseline and 6 months. MTX response was defined using the internationally developed ACR-Pedi categories (non-responder, ACR-Pedi 30, 50, 70), as well as change in each of the core outcome variables individually. Analysis was performed using ordinal and linear regressions in R vers2.15 and PLINK vers1.07. Within the most highly associated regions, IMPUTE2 was used to increase genetic coverage.

Results: A total of 587,822 SNPs (all MAF $\geq$5%) across the entire genome were analyzed for each of the 6 core outcome variables as well as ACR-Pedi. 16 regions containing one or more SNPs with association with MTX response at $P < 1 \times 10^{-4}$ in more than one of the 7 analyses met criteria for further investigation including SNP imputation. The most highly associated SNPs were found near the genes *CACNA1I*, *PVT1* and *CFTR*. These findings are currently being validated within a US cohort of JIA cases with MTX response data available in the form of active and limited joint counts.

Conclusion: These results suggest a role for novel pathways in MTX response. Further investigations within associated regions to dissect the genetic basis of MTX response will move us towards our ultimate goal of prediction of response to MTX for children with JIA.

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Rapid and Effective Response to Immunosuppression in Treating Macrophage Activation Syndrome Associated with a Heterozygous Dominant Negative Mutation in RAB27a Leading to Decreased Cytolytic Activity.

Randy Q. Cron, Mingce Zhang, Christina J. Bemrich-Stolz and Timothy Beukelman. Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Hemophagocytic lymphohistiocytosis (HLH) is an often fatal disorder of infancy resulting from homozygous mutations in proteins involved in cytolysis (e.g. MUNC13-4, RAB27a, Perforin 1, Syntaxin11, STXBP2). HLH treatment is an etoposide based aggressive chemotherapy, and associated mortality remains problematic. Secondary forms of HLH, or macrophage activation syndrome (MAS), frequently result beyond infancy from rheumatologic, infectious, and oncologic conditions. MAS is typically treated with immunosuppression, including high dose **C**orticosteroids, **C**yclosporine, and, recently, the IL-1 receptor antagonist, **A**nakinra (**CCA**). Of late, mutations in HLH associated cytolytic pathway genes have been identified in children with MAS. The importance of these mutations in the pathophysiology of MAS, and the appropriate treatment for MAS in these settings remains unclear.

Methods: Chart review was performed for a teen with MAS successfully treated with CCA. Cytolytic activity of a natural killer (NK) cell line was assessed following over-expression of a RAB27a mutant protein identified in this girl. Lentiviral expression vectors were generated with the RAB27a mutation, and a wild-type RAB27a sequence control, sequenced for authenticity, and introduced into the NK-92 human NK cell line by transduction. Transduced NK cells were analyzed for transgene expression by co-expression of green fluorescence protein, and tested for their ability to lyse calcein violet loaded K562 NK target cells at varying effector to target cell ratios.

Results: An 18-year-old girl presented with 2 weeks of fever (>102ºF) and abdominal pain. Exam revealed a febrile, semi-coherent female with hepatosplenomegaly. Extensive infectious, oncologic, and rheumatic diseases work-ups were negative. Laboratory findings revealed pancytopenia; severe hepatitis; coagulopathy; elevated ferritin, triglycerides, soluble CD25, and soluble CD163; increased CD163 staining of bone marrow; markedly decreased NK cell function; ESR of 10 mm/hr. Sequencing of HLH genes revealed a single copy RAB27a mutation (259 G>A, A87P) known to be associated with type II Griscelli syndrome/HLH. She met 8 of 8 HLH criteria and was treated for MAS with CCA. She markedly and rapidly clinically improved. Her ferritin fell from 8,446 to 201 ng/ml (<115), and her AST fell from 4,639 U/L to 176 U/L, within 4 days of CCA. Lentiviral transduction of wild-type RAB27a into the NK-92 cell line had no effect on cytolysis of K562 target cells *in vitro*, whereas over-expression of the 259 G>A patient mutation decreased cytolytic activity by ∼50%.

Conclusion: The distinction between HLH and MAS is becoming blurred as mutations in HLH genes are identified in patients with MAS. Perhaps later age of onset reflects heterozygous versus homozygous defects in cytolytic pathway proteins. Our data suggests single gene copy mutations can partially disrupt cytolytic activity through a dominant negative effect. Important treatment differences exist between protocols for HLH and MAS, and our patient's response to CCA immunosuppression suggests HLH associated genetic mutations presenting later in life may be responsive to less aggressive/toxic (non-chemotherapeutic) immunosuppression.

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Elevated Serum Follistatin-Like Protein 1 Suggests an Interleukin-1 Independent Pathway for Inflammation in Patients with Cryopyrin Associated Periodic Syndromes.

Mark Gorelik[1], Daniel Bushnell[2], Raphaela T. Goldbach-Mansky[3], Hal M. Hoffman[4] and Raphael Hirsch[5]. [1]Univ of Pittsburgh Med Ctr Children's Hospital, Pittsburgh, PA, [2]Childrens Hospital Pittsburgh, Pittsburgh, PA, [3]Translational Autoinflammatory Diseases Section NIAMS NIH, Bethesda, MD, [4]University of California at San Diego, La Jolla, CA, [5]Childrens Hosp Pittsburgh, Pittsburgh, PA

Background/Purpose: Cryopyrin associated periodic syndromes (CAPS) are a group of IL-1β mediated autoinflammatory diseases characterized by fever, urticaria and conjunctivitis, and in severe cases, CNS abnormalities, hearing loss, and bone overgrowth. Patients treated with IL-1 targeted therapy have resolution of a majority of clinical symptoms, although bone lesions are known to progress despite treatment. Follistatin-like protein 1 (FSTL-1) is a pro-inflammatory protein secreted by mesenchymal cells, including osteoblasts. This study was performed to determine how serum FSTL-1 levels correlate with clinical and laboratory markers in the most severe form of the CAPS, Neonatal Onset Multisystem Inflammatory Disease (NOMID).

Methods: FSTL-1 serum levels were measured by ELISA in 10 patients at pre-treatment and post-treatment time points and compared to values from a group of 53 normal controls. FSTL-1 levels were correlated with ESR, CRP, as well as complete blood counts, and clinical characteristics, including presence of bony overgrowth at baseline. To gain insights into the expression of FSTL-1 relative to IL-1 blockade, FSTL-1 levels were measured in CAPS knock-in mice expressing an NLRP3 mutation, as well as in mice with the NLRP3 mutation on an IL-1 receptor knockout background.

Results: FSTL-1 serum levels were elevated in NOMID patients vs. normal controls (182 ng/ml vs. 139 ng/ml, p=0.037) and remained elevated after treatment with anakinra (160 ng/ml), even though other markers of inflammation, including ESR, high sensitivity CRP, WBC, and platelet counts all declined to normal levels. The highest levels of FSTL-1 were observed in patients with bony overgrowth at baseline as compared to patients without bony overgrowth (204 ng/ml vs. 149 ng/ml, p = 0.01), whereas FSTL-1 levels did not correlate with other clinical abnormalities. A trend of correlation was seen between FSTL-1 and high sensitivity CRP (Pearson r = 0.38, p = 0.08). Finally, FSTL-1 serum levels were elevated in mice expressing NLRP3 mutation compared to wild type controls (502 ng/ml vs. 201 ng/ml, p <0.001) and were similarly elevated in mice expressing NLRP3 mutation on an IL1 receptor knockout background (440 ng/ml, p = 0.07 vs. controls).

Conclusion: Serum FSTL-1 is elevated in patients with NOMID and FSTL-1 levels remain elevated despite anakinra treatment. Similarly, FSTL-1 levels are elevated in a mouse model of CAPS and remain elevated despite the absence of IL-1 receptor. Serum FSTL-1 levels are most elevated in NOMID patients with greater baseline bony overgrowth and remain elevated despite treatment with anakinra, suggesting that FSTL-1 may play a role or be a marker of bone abnormalities in this disorder.

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Genome-Wide Association Meta-Analysis of Eight Independent Systemic Juvenile Idiopathic Arthritis Collections Reveals Regional Association Spanning the Major Histocompatibility Complex Class II and III Gene Cluster. Michael J. Ombrello[1], Elaine Remmers[2], Alexei A. Grom[3], Wendy Thomson[4], Alberto Martini[5], Marco Gattorno[6], Seza Ozen[7], Sampath Prahalad[8], John F. Bohnsack[9], Andrew Zeft[10], Norman T. Ilowite[11], Elizabeth D. Mellins[12], Ricardo A. G. Russo[13], Claudio Len[14], Sheila K. Oliveira[15], Rae SM Yeung[16], Lucy R. Wedderburn[17], Jordi Anton Lopez[18], Colleen Satorius[19], Ioanna Tachmazidou[20], Carl D. Langefeld[21], Eleftheria Zeggini[20], Susan D. Thompson[3], Patricia Woo[22] and Daniel L. Kastner[1]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]National Institutes of Health, National Human Genome Research Institute, Bethesda, MD, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Arthritis Research UK Epidemiology Unit, Manchester, United Kingdom, [5]University of Genova, Genova, Italy, [6]Istituto Giannina Gaslini, Genova, Italy, [7]Hacettepe University, Ankara, Turkey, [8]Emory Children's Center, Atlanta, GA, [9]University of Utah, Salt Lake City, UT, [10]The Cleveland Clinic, Cleveland, OH, [11]Children's Hospital Montefiore, Bronx, NY, [12]Stanford University Med Ctr, Stanford, CA, [13]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [14]Universidade Federal de São Paulo / UNIFESP, Sao Paulo, Brazil, [15]Instituto de Pediatria e Puericultura Martagão Gesteira (IPPMG) da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil, [16]Hospital for Sick Children, Toronto, ON, [17]University College London (UCL), London, United Kingdom, [18]University Childrenxs Hospital, Barcelona, Spain, [19]National Human Genome Research Institute, Nationsl Institutes of Health, Bethesda, MD, [20]The Wellcome Trust Sanger Institute, Cambridge, United Kingdom, [21]Wake Forest School of Medicine, Winston-Salem, NC, [22]University College London, London, United Kingdom

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is a rare inflammatory disease that is inherited as a complex genetic trait. While the pathophysiology of sJIA is poorly understood, there is evidence of both innate and adaptive immune involvement. We have undertaken a genome-wide association study (GWAS) of sJIA to elucidate pathways and molecular mechanisms that underlie this disease. The power of a GWAS is directly related to the size of the population studied. This confounds the application of GWAS to rare diseases, such as sJIA, where acquisition of even modestly-sized patient collections is very difficult. In an attempt to overcome the rare nature of sJIA, we have designed a meta-analytic GWAS to investigate sJIA collections from eight different countries.

Methods: We genotyped 823 children fulfilling ILAR criteria for sJIA and 442 healthy children using the Omni1M Quad SNP array. We obtained five *in silico* collections of control genotypes that were geographically-matched to five of the case collections, providing an additional 4037 controls for our analysis. After performing quality control operations to exclude low quality samples and markers, we combined case and control genotype data for each of the eight strata, retaining only markers that were present in both the case and control datasets. We used principal components analysis to identify and remove genetic outliers from each population. For each stratum, we created phased haplotypes with the ShapeIT software, we performed SNP imputation with IMPUTE2 software and the HapMap3 reference haplotypes, and we undertook association testing with SNPTEST software. Finally, genomewide association meta-analysis of the eight strata was performed using the GWAMA software.

Results: Genomewide association meta-analysis of 1,447,416 markers, applying the additive model to eight case-control strata, identified 49 regions that contained one or more marker with p < 5E-5. Fourteen of these genes reside within a 3 Mb segment of the major histocompatibility complex (MHC), spanning the MHC class II and III gene clusters. This sJIA-associated region also contains the only marker to exceed the genomewide significance threshold (rs615672, p = 2.64E-8; OR = 0.7, 95CI 0.62, 0.79), which lies between *HLA-DRB1* and *HLA-DQA1*.

Genomewide Association Meta-Analysis of Systemic Juvenile Idiopathic Arthritis. This plot demonstrates the $-\log_{10}$ p values generated by genomewide meta-analysis of eight sJIA case-control strata. The horizontal line at y = 7.3 represents the threshold for genomewide significance (p < 5 x 10^{-8}).
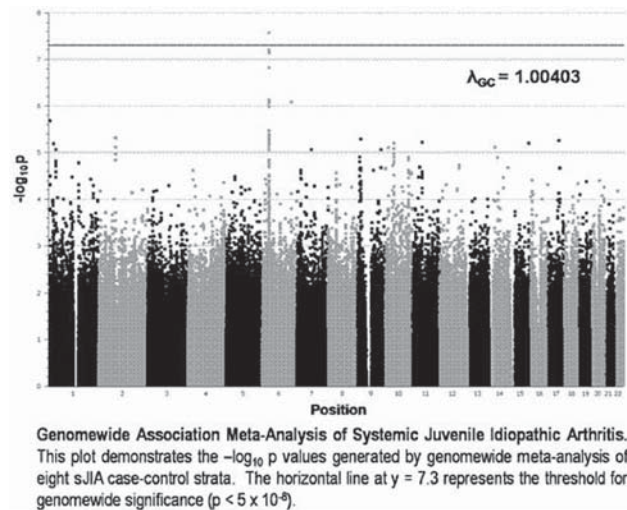
Conclusion: The markers most strongly associated with sJIA were found within the MHC locus, nearest to the *HLA-DRB1* and *HLA-DQA1* genes. However, these variants reside in a larger, 3 Mb interval that contains a range of genes involved in both innate and adaptive immunity. Interestingly, we have observed an almost complete absence of overlap between our 49 candidate loci and the known autoimmune and autoinflammatory loci. If this observation is upheld by additional investigations, then we may expect this study to identify novel pathways and mechanisms involved in sJIA, which may also represent novel therapeutic targets.

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Correlation Between Mefv Genotype and Interleukin (IL)1β secretion and Role of the nlr Family Pyrin Domain Containing 3 (Nlrp3) Inflammasome in Patients with Familial Mediterranean Fever (FMF). Alessia Omenetti[1], Sonia Carta[2], Delfino Laura[2], Alberto Martini[3], Anna Rubartelli[4] and Marco Gattorno[1]. [1]Pediatrics II Unit G Gaslini Institute, Genoa, Italy, [2]Cell Biology, lST-San Martino, Genoa, Italy, [3]Pediatrics ll Unit, G Gaslini Institute and University of Genoa, Genoa, Italy, [4]lST-San Martino, Genoa, Italy, Genoa, Italy

Background/Purpose: Familial Mediterranean Fever (FMF) is an auto-inflammatory disease due to mutations of MEFV gene which encodes for

Pyrin. FMF does not behave as a pure recessive disorder but clinical manifestations may parallel the actual amount of mutant pyrin. In agreement with this concept, correlation between genotype and FMF symptoms has been described. Growing evidence suggests that aberrant interleukin (IL) 1β signaling occurs in FMF. However, whether genetic variants of the MEFV gene result in differences in $IL1\beta$ levels has never been explored. Moreover, the role of NLR family pyrin domain containing 3 (NLRP3) inflammasome in this contest is still largely unclear. Thus, we evaluated if $IL1\beta$ pathway activation (1) is enhanced in FMF; (2) correlates with the type of MEFV mutation; and (3) is mediated by NLRP3.

Methods: Twenty FMF patients (FMFp) were evaluated and compared with 14 MEFV healthy carriers (HC) and 30 healthy donors (HD). Among patients, 12 were genetically confirmed (i.e. carrying 2 mutations) while 8 had clinical manifestations even if carrying 1 single mutation in heterozygosity. Ten out of 20 FMFp were under colchicine treatment and all of them were in controlled disease activity. Monocytes were freshly isolated and studied at baseline and after LPS in vitro activation. Monocyte nucleofection with NLRP3 siRNA or appropriate Mock controls was performed in 23 subjects (i.e. 7 FMFp, 9 HC, 3 HD) using Nucleofector" Technology (Amaxa). $IL1\beta$ and IL1 receptor antagonist (ILRa) pattern of secretion (3–6-18h) was analyzed by ELISA assay. Differences in oxydative state were evaluated by assessing levels of reactive oxygen species (ROS) and the cysteine release, as markers of pro- and antioxidant responses, respectively.

Results: Monocytes purified from FMFp displayed enhanced $IL1\beta$ release. Interestingly, $lL1\beta$ secretion correlated with number and penetrance of MEFV mutations, with higher levels in the presence of 2 high penetrance mutations in FMFp, and 1 high penetrance mutation in HC, respectively. Silencing of NLRP3 activity in monocytes freshly isolated from patients and controls consistently inhibited $lL1\beta$ secretion. Contrary to what previously described in diseases caused by mutations that primarily affect the NLRP3 (i.e. Cryopyrinopaties) $L1\beta$ release in pyrin mutated monocytes was featured by a more physiological kinetics. Consistent with this finding, FMFp monocytes basally produced more ROS but had a conserved, although impaired, cysteine release. Finally, IL1Ra levels were comparable to HD.

Conclusion: MEFV mutated monocytes display enhanced $IL1\beta$ secretion, which correlates with the number of high-penetrance mutations. In contrast to what found in the animal model, $IL1\beta$ secretion in FMFp monocytes is NLRP3-dependent. Interestingly, contrary to what previously reported in NLRP3 mutated cells, monocytes carrying MEFV mutation (1) have conserved antioxidant machinery capable of restraining the oxidative stress, (2) do not show stress-related defect in protein synthesis, (including IL1Ra production) and (3) display a more physiological pattern of secretion of $lL1\beta$.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects VII:
Prediction of Outcome in Rheumatoid Arthritis
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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An Expanded Repertoire of Anti-Citrullinated Peptide Antibodies Is Associated with Interstitial Lung Disease in Rheumatoid Arthritis.
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Background/Purpose: Interstitial lung disease (ILD) is an outcome with high morbidity and mortality in rheumatoid arthritis (RA). Citrullinated proteins are observed in these lung tissues; however, the association of specific anti-citrullinated peptide antibodies (ACPA) with ILD in RA is unknown.

Methods: RA patients underwent multi-detector computed tomography (MDCT) of the chest with interpretation by a pulmonary radiologist for ILD features [ground glass opacification (GGO), reticulation (R), honeycombing (HC), and traction bronchiectasis (TB)]. A semi-quantitative ILD Score (ILDS; range 0–32) for ILD features was calculated. Concurrent serum samples were assessed for anti-CCP (CCP2) and levels of a panel of antibodies against 4 non-citrullinated proteins [fibrinogen A, HSP60, apolipoprotein (Apo) A1, and Apo E] and 17 citrullinated full-length proteins or peptides within these proteins (see table for list) using a custom Bio-Plex bead array. Individual candidate citrullinated antigens were conjugated to spectrally-distinct fluorescently dyed beads. Peptide-conjugated beads were incubated with diluted patient sera, autoantibody binding detected with a phycoerythrin-conjugated secondary antibody, and levels of autoantibody binding quantitated on a Luminex 200 System. High level ACPA was defined at $\geq$ the group 75th percentile. Pulmonary function testing (PFT) was performed in 156 patients a mean of 21 ± 3 months later.

Results: Among 177 RA patients [60% female, 86% Caucasian, mean age 59 ± 9 years, 11% current smokers], any ILD features (i.e. ILDS>0) was observed in 57 (32%). Among those with any ILD, the median ILDS was 3 (range 1–10). A predominant pattern of GGO was observed in 22 (39%) and R/HC/TB in 35 (61%). PFT restriction or impaired diffusion was observed in 36 (23%).

Levels of CCP2 and all specific ACPAs were 46–273% higher among RA patients with vs. those without ILD (all p-values<0.05), and higher levels correlated with higher ILDS. In contrast, levels of non-citrullinated protein antibodies were not higher in those with ILD. The median number of high level ACPA was significantly greater for those with an ILDS$\geq$3 vs. those with an ILDS=0 (6 vs. 1; p=0.005, see Table). Each ACPA was associated, on average, with a 0.10 unit increase in ILDS (p=0.001), an association that remained significant after adjusting for features associated with ILD [age, gender, current and former smoking, DAS28, current prednisone and leflunomide use]. More high level ACPA were observed in R/HC/TB compared to ILDS=0, but the difference was less robust for GGO vs. ILDS=0 (Table). More high level ACPA were observed in those with PFT restriction or impaired diffusion compared to those without these PFT findings (Table).

Table. Number of High Level ACPA* (>75th Percentile) According to Computed Tomographic Features of RA-Associated Interstitial Lung Disease and Restriction and/or Impaired Diffusion on Pulmonary Function Testing

Outcome	Number of High Level ACPA**	p-value
ILDS = 0 (n = 120)	1 (0–5)	referent
ILDS 1 or 2 (n = 25)	3 (1–11)	0.073
ILDS $\geq$ 3 (n = 32)	6 (1–11)	0.005
ILDS = 0 (n = 120)	1 (0–5)	referent
GGO (n = 22)	3 (1–7)	0.23
R/HC/TB (n = 35)	3 (0–12)	0.041
No Restriction cr Impaired DLCO (n = 120)	1 (0–5)	referent
Restriction or Impaired DLCO (n = 36)	5 (1–11)	0.009

* ACPA levels measured included citrullinated versions of <u>fibrinogen A</u> and <u>4 specific fibrinogen A peptides</u>, <u>Apo A1</u>, <u>Apo E</u> and <u>1 specific Apo E peptide</u>, <u>enolase</u>, <u>vimentin</u> and <u>1 specific vimentin peptide</u>, <u>histones 2A</u> and B, <u>filaggrin</u>, <u>biglycan</u>, and <u>clusterin</u>
** Values depicted are median (interquartile range) with comparison using the Kruskal-Wallis test.
ACPA = anti-citrullinated protein antibody; ILD = interstitial lung disease; ILDS = expert read interstitial lung disease score; GGO = ground glass opacification; R/HC/TB = reticulation/honeycombing/traction bronchiectasis; DLCO = diffusing capacity for carbon monoxide

Conclusion: Our findings of a broader ACPA repertoire in RA ILD suggest a role for ACPA in the pathogenesis of ILD and/or implicate inflamed lung parenchyma as a source of ACPA generation.

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Progressive Radiographic Joint Damage in Established Rheumatoid Arthritis: Common and Strongly Associated with Seropositivity. Siri Lillegraven[1], Nancy A. Shadick[2], Zarif Jabbar-Lopez[3], Anna Potapov[3], Michelle A. Frits[2], Christine K. Iannaccone[2], Espen A. Haavardsholm[1], Tore K. Kvien[1], Michael Weinblatt[2] and Daniel H. Solomon[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Brigham and Women's Hospital, Boston, MA, [3]Harvard School of Public Health, Boston, MA

Background/Purpose: During the last decade, rheumatoid arthritis (RA) research has mainly focused on early disease, as it has become apparent that early and aggressive treatment can change the long-term outcome of RA. However, most patients in clinical practice have established disease. Our objective was to describe the proportion of patients with established RA (≥ 5 years disease duration) who experience continued joint damage, and to identify its predictors.

Methods: We analyzed data from BRASS, an observational RA cohort. The data collection includes joint examinations, serological markers and patient reported outcome measures. Hand and wrist radiographs are acquired at baseline and 2 years and scored by van der Heijde-modified Sharp score (vdHSs). Patients with a disease duration ≥ 5 years and 2-year radiographic data (n=390) were selected, and progression of joint damage was defined as an annual change of ≥ 1 unit in total vdHSs. In univariate logistic regression models, we assessed the association between progressive joint damage and predictors such as age, gender, disease duration, treatment, DAS-28 category, subcutaneous nodules, seropositivity (classified as either negative for both RF and anti-CCP, positive for either RF or anti-CCP, or positive for both RF and anti-CCP), BMI and smoking. We then built a multivariate regression model, forcing DMARD treatment and disease duration into the model as covariates. Individual radiographic data stratified according to serological status were displayed in a cumulative probability plot.

Results: The median (IQR) age of the 390 patients was 60 (52, 67) years and the median disease duration was 17 (10, 27) years. 84% were female and 44% received biologic DMARD treatment. 16 % were negative for both RF and anti-CCP, 16 % were positive for either and 68 % were positive for both RF and anti-CCP. 44% (172) of the patients had progression of joint damage. Older age, longer disease duration, worse disease activity, seropositivity, normal BMI and no prior smoking had p-values <0.25 and were included in the model building. In multivariate logistic regression analyses, seropositivity was independently associated with joint damage. Positivity for either RF or anti-CCP had an OR (95% CI) of 5.0 (2.2, 11.1) and positivity for both serological markers an OR of 4.1 (2.1, 8.2) for subsequent joint damage. No other independent predictors were identified. Although the ORs for progressive joint damage were similar if patients were positive for one or both of RF and anti-CCP, patients who were positive for both RF and anti-CCP tended to experience more joint damage (**Figure**).
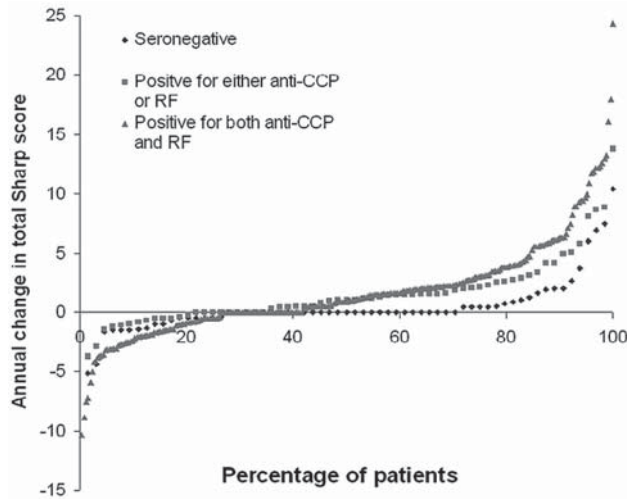
Figure. Cumulative probability plot displaying individual radiographic data. A tendency towards more rapid radiographic progression (VdHSS ≥ 5 units per year) is seen in patients positive for both RF and anti-CCP (16%) compared to patients positive for only RF or anti-CCP (9%), p-value 0.21.

Conclusion: Progression of joint damage is still common in RA patients with at least five years disease duration, even in a setting where 44% of the patients receive biologic DMARDs. Seropositivity is strongly and independently associated with joint damage.

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Disease Activity Score 28-Joint Count: Are Erythrocyte Sedimentation Rate and C-Reactive Protein Versions Comparable? Roy M. Fleischmann[1], Désirée van der Heijde[2], Andrew S. Koenig[3], Ronald Pedersen[3], Annette Szumski[3], Lisa Marshall[3] and Eustratios Bananis[3]. [1]University of Texas, Dallas, TX, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Pfizer Inc., Collegeville, PA

Background/Purpose: Frequently DAS28-CRP is utilized instead of DAS28-ESR to assess rheumatoid arthritis (RA) disease activity; however, values for remission and low disease activity (LDA) for DAS28-CRP have not been validated.[1,2] Differences between remission rates could vary between 8–24% and therefore, the cut-off points should not be identical for the two measures.[3–5] The aim of this analysis is to examine the value of DAS28-CRP, which corresponds to the value of DAS28-ESR for cut-off points from 3 different patient populations.

Methods: Randomized patients from COMET (early, moderate-to-severe RA), TEMPO (established moderate-to-severe RA), and PRESERVE (moderate RA) who received etanercept (ETN) 50 mg weekly + MTX or MTX alone were included. DAS28-ESR and DAS28-CRP response rates were compared (COMET, TEMPO week 52; PRESERVE week 36) for each study and by treatment group utilizing the traditional ESR cut-off points for remission <2.6 and LDA ≤ 3.2; level of agreement was determined by kappa coefficient, sensitivity, and specificity. Remission and LDA cut-offs for DAS28-CRP were based on patients' final time point, with treatment groups and studies being pooled together before utilizing ROC analysis to obtain the new cut-offs that best correspond to ESR established cut-offs. DAS28-ESR and CRP, along with their unique components (0.70*ln[ESR] and 0.36*ln-[CRP + 1] + 0.96), were analyzed as continuous parameters using Spearman's correlation. DAS28-CRP cut-offs for the Asian population were examined and compared with the overall population.

Results: The percentage of patients meeting the definition of remission (<2.6) or LDA (≤ 3.2) was slightly higher for DAS28-CRP than DAS28-ESR for both treatment groups across all 3 trials (Table). The concordance in which patients achieved the same outcome for both DAS28-ESR and CRP LDA or remission ranged from 82–91%. Although, DAS28-ESR and CRP measures were highly correlated (range 0.80–0.90; $P<0.001$) for each study's final time point, their unique components were not highly correlated (range 0.35–0.50; $P<0.001$). New DAS28-CRP cut-offs were found to range from 2.4–2.5 for remission and 3.0–3.1 for LDA, depending on study and treatment with 2.52–3.05 providing the best overall results. Cut-offs determined from the Asian population showed some differences, especially LDA, compared with the overall population suggesting regional differences exist.

Table. Statistical Measures of Agreement for DAS28-ESR and DAS28-CRP by Study and Treatment

Disease Activity	ETN + MTX					MTX				
	DAS28-ESR	DAS28-CRP	Sensitivity	Specificity	Kappa Coefficient	DAS28-ESR	DAS28-CRP	Sensitivity	Specificity	Kappa Coefficient
COMET (Week 52)										
Remission (<2.6)	132/265 (50)	145/262 (55)	(89)	(78)	0.671*	73/263 (28)	85/250 (34)	(83)	(86)	0.658*
LDA (≤ 3.2)	170/265 (64)	187/262 (71)	(96)	(76)	0.756*	109/263 (41)	132/250 (49)	(94)	(83)	0.759*
TEMPO (Week 52)										
Remission (<2.6)	88/231 (38)	98/229 (43)	(86)	(84)	0.693*	39/228 (17)	53/228 (23)	(67)	(86)	0.458*
LDA (≤ 3.2)	122/231 (53)	128/229 (56)	(91)	(84)	0.754*	68/228 (30)	91/228 (40)	(87)	(80)	0.608*
PRESERVE (Week 36)										
Remission (<2.6)	525/826 (64)	523/826 (63)	(87)	(78)	0.645*	NA	NA	NA	NA	NA
LDA (≤ 3.2)	677/826 (82)	671/826 (81)	(94)	(77)	0.702*	NA	NA	NA	NA	NA

* $P<0.05$ corresponds to kappa coefficient of agreement between the two measurements. Sensitivity and specificity based on standard of DAS28-ESR LDA or remission. Values n/N (%). NA = not applicable as PRESERVE patients received open-label ETN 50 mg + MTX.

Conclusion: The percentage of patients achieving remission or LDA was lower for DAS28-ESR than DAS28-CRP when utilizing the same cut-off points for both measures. DAS28-CRP underestimates disease activity when utilizing cut-off points validated for DAS28-ESR and therefore, should be evaluated using different remission and LDA values. Studies are needed to validate proposed DAS28-CRP disease activity cut-offs.

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Tightening up: Musculoskeletal Ultrasound Could Further Individualise Treatment Decisions in Early Rheumatoid Arthritis Patients Treated by a Step-up DMARD Escalation Regimen. James Dale[1], David Purves[1], Alex McConnachie[1], Duncan Porter[2] and Iain B. McInnes[1]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Gartnavel General Hosp, Glasgow, United Kingdom

Background/Purpose: Treat-to-target (T2T) strategies have significantly improved outcomes in early rheumatoid arthritis (RA). Treatment escalation is usually guided by a disease activity score; however, modern imaging techniques demonstrate that many patients have sub-clinical synovitis without clinical joint swelling, and DAS28 scores can be elevated in patients without active RA. The TASER study (NCT00920478) is a randomized controlled trial comparing a standard T2T strategy with one guided by DAS28 and musculoskeletal ultrasound (MSUS)

Objective: To report the frequency of sub-clinical MSUS synovitis in patients randomized to the MSUS arm of the TASER study, and to determine how frequently treatment decisions could be affected by using MSUS.

Methods: DAS28 scores were calculated every month. MSUS was performed on patients in low disease activity (DAS28<3.2) and those with moderate disease activity (3.2≤DAS28<5.1) in the absence of clinically swollen joints (SJ ≤1). 14 joints (bilateral PIP2+3, MCP2+3, radiocarpal, MTP2+5) were assessed. Active disease was defined as >2 joints demonstrating any Power Doppler (PD) signal.

Analysis: Paired DAS28 and MSUS data from 319 assessments were pooled to determine levels of agreement between clinical and MSUS findings

Results: *Cohort:* 60% female, mean age 57 years (SD13), mean disease duration 5.1 months (SD2.8), 66% rheumatoid factor positive, 66% anti-CCP antibody positive, 32% erosive baseline Xrays.

Table 1. Comparison of DAS28 and MSUS findings; agreement is shown in italics, disagreement in bold

	Number of Instances	MSUS Findings N (%)		
		Active Disease	Inactive Disease	Overall Agreement
Remission (DAS28 < 2.6)	149	**42 (28%)**	*107 (72%)*	72%
Low disease activity (DAS28 < 3.2)	284	**78 (27%)**	*206 (73%)*	73%
Moderate disease activity (3.2≤DAS28<5.1) **AND ≤ 1 Swollen Joint**	35	*14 (40%)*	**21 (60%)**	40%

27–28% of patients in clinical remission/low DAS28, demonstrated evidence of sub-clinical synovitis. In 60% of patients with moderate disease in the absence of clinical synovitis there was no MSUS synovitis either. Overall, using MSUS or a DAS28>3.2 threshold for DMARD escalation would have reached the same decision on 220 out of 319 occasions (69% agreement).

Table 2. Frequency (%) of positive MSUS findings in individual joint areas

Joint Area (pooled data for both sides)	Synovial Hypertrophy N (%)	PD Signal N (%)
PiP2	30 (9%)	13 (4%)
PiP3	20 (6%)	3 (1%)
MCP2	105 (33%)	74 (23%)
MCP3	69 (22%)	42 (13%)
Radiocarpal	235 (74%)	179 (56%)
MTP2	212 (66%)	23 (7%)
MTP5	26 (8%)	16 (5%)

For all instances, mean SH score = 4.0 (SD3.5) and index = 2.2 (SD1.7). Mean PD score = 1.4 (SD1.8) and index = 1.1 (SD1.2)

Conclusion: Assessment of global disease activity using a limited MSUS joint set may allow further tailoring of DMARD therapy by: 1. supporting DMARD escalation in patients with active disease despite a reassuring DAS28 and 2. preventing DMARD escalation in patients with moderate DAS28 levels but minimal evidence of active disease. MSUS findings in the radiocarpal and index MCP joints were most likely to influence DMARD escalation decisions. Whether this approach will significantly improve outcomes remains to be proven.

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A Variant in the Osteoprotegerin Gene Is Associated with Coronary Atherosclerosis in Patients with Rheumatoid Arthritis: Results From a Candidate Gene Study. Cecilia P. Chung[1], Joseph F. Solus[1], Annette Oeser[1], Chun Li[1], Paolo Raggi[2], Jeffrey R. Smith[1] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]Emory University, Atlanta, GA

Background/Purpose: Patients with rheumatoid arthritis (RA) have accelerated atherosclerosis. However, this association is not fully explained by traditional cardiovascular risk factors or markers of inflammation. Little is known about the association between genetic variation and atherosclerosis in this population. Therefore, we examined the hypothesis that in patients with RA selected candidate gene variants were associated with the presence of coronary atherosclerosis.

Methods: One hundred and forty patients with RA, enrolled in an ongoing study to evaluate the prevalence and risk factors of coronary atherosclerosis in RA, were studied. Patients fulfilled the 1987 American College of Rheumatology classification criteria for RA and were 18 years or older. Coronary artery calcium (CAC), a non-invasive measurement of coronary atherosclerosis, was measured by electron beam computed tomography. Genotyping was performed using the Illumina Goldengate platform on a custom panel of 714 single-nucleotide polymorphisms (SNPs) tagging 176 selected candidate genes. Candidate genes were chosen for relevance to autoimmune and cardiovascular risk. The association between the presence of CAC and the allele frequency of the SNP was assessed by logistic regression models, adjusted for age, sex, and race. To adjust for multiple comparisons, a false discovery rate (FDR) threshold was set at 20%.

Results: Patients with RA were 54±11 years old and predominantly Caucasian (89%) and female (69%). The presence of CAC was detected in 70 patients (50%). After adjustment for age, race, and sex, SNPs in tumor necrosis factor receptor superfamily member 11 b (*TNFRSF11B*), matrix metalloproteinase-3 (*MMP3*), interleukin-12 (*IL12*), matrix metalloproteinase-9 (*MMP9*), nucleotide-binding oligomerization domain-2 (*NOD2*), C-reactive protein (*CRP*), myeloperoxidase (*MPO*), resistin (*RETN*), interferon regulatory factor (*IRF*) and Fcγ receptor 2A (*FCGR2A*) were associated with the presence of CAC (Table). The variant rs2073618, which encodes an Asp3Lys missense change in the osteoprotegerin gene (*OPG, TNFRSF11B*), was significantly associated with CAC (OR= 4.09, p=0.00026) after FDR correction.

Table. Genetic Association with Coronary Atherosclerosis in Patients with RA

SNP	Gene	Major, minor allele	Minor allele frequency	Odds ratio* (95% CI)	p-value
rs2073618	*TNFRSF11B*	G,C	0.36	4.09 (1.93–8.70)	<0.001
rs522616	*MMP3*	T,C	0.29	4.43 (1.77–11.10)	0.001
rs2853694	*IL12B*	T,C	0.29	3.09 (1.53–6.24)	0.002
rs3918249	*MMP9*	T,C	0.49	0.36 (0.18–0.69)	0.002
rs17576	*MMP9*	A,G	0.45	0.34 (0.17–0.68)	0.002
rs3918253	*MMP9*	C,T	0.28	0.38 (0.20–0.72)	0.003
rs2274756	*MMP9*	G,A	0.16	0.24 (0.09–0.64)	0.004
rs751271	*NOD2*	T,G	0.49	2.57 (1.33–4.96)	0.005
rs650108	*MMP3*	G,A	0.41	2.82 (1.29–6.17)	0.009
rs1800947	*CRP*	C,G	0.04	5.93 (1.43–24.71)	0.014
rs9562414	*TNFSF11*	A,G	0.06	0.25 (0.08–0.79)	0.019
rs2107545	*MPO*	T,C	0.26	0.42 (0.20–0.89)	0.023
rs3745367	*RETN*	G,A	0.39	0.45 (0.22–0.91)	0.026
rs10954213	*IRF5*	G,A	0.47	0.50 (0.27–0.94)	0.030
rs633137	*TNFSF11*	T,A	0.08	0.34 (0.13–0.91)	0.031
rs2243828	*MPO*	A,G	0.23	0.43 (0.20–0.96)	0.040
rs1801274	*FCGR2A*	A,G	0.43	0.52 (0.28–1.00)	0.049

* Odds ratios for the comparison between minor and major allele.

Conclusion: Our results suggest that a potential functionally poly-morphism of the *TNFRSF11B* gene, which encodes osteoprotegerin, is associated with the presence of coronary atherosclerosis in patients with RA. Replication of this finding in independent validation cohorts will be of interest.

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A Multi-Biomarker Disease Activity (VECTRA™ DA Algorithm) Score Reflects Clinical Disease Activity and Tracks Responses in Patients with Rheumatoid Arthritis Treated with Either Adalimumab, Etanercept, and Infliximab. Shintaro Hirata[1], Douglas J. Haney[2], Guy Cavet[2], Rebecca Bolce[2], Wanying Li[2], Nadine Defranoux[2], David Chernoff[2], Kunihiro Yamaoka[1], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Crescendo Bioscience Inc., South San Francisco, CA

Background/Purpose: Anti-TNF therapy has become a standard therapeutic strategy for treatment of patients with rheumatoid arthritis (RA). A validated multi-biomarker disease activity algorithm (MBDA) blood test was used to provide objective biological information about RA. We studied the relationship between the MBDA score and disease activity measures including DAS28, SDAI, and CDAI in patients treated with anti-TNF therapy.

Methods: 147 patients who started anti-TNF therapy (49 adalimumab (ADA), 49 etanercept (ETN), 49 infliximab (IFX)) were enrolled. Twelve biomarkers were measured and combined in a pre-specified algorithm to generate a MBDA score between 1 and 100 at 0 (baseline) and 52 weeks after induction of anti-TNF therapy. Associations between MBDA score and DAS28/SDAI/CDAI were evaluated by Spearman correlation and by area under the receiver operating characteristic curve (AUROC). MBDA score changes in patients with EULAR responses were compared by t-test. Differences in the MBDA/DAS28 relationship between TNF inhibitors were evaluated by fitting linear models for DAS28 as a function of MBDA score, therapy and an MBDA/therapy interaction term.

Results: At baseline, patients' median age was 60 (interquartile range (IQR) 50–68), DAS28- 5.7 (5.0–6.5), MBDA- 64 (IQR 49–76) and disease duration 60 months (18–168). Methotrexate was used in 86% of patients, at a median dose of 8.0 (8.0–10) mg/week. There was a mean decrease + SD in DAS28 of 2.6 + 1.4 and in MBDA of 25 + 20 respectively. MBDA scores correlated with DAS28, SDAI and CDAI (ρ=0.64, 0.57, 0.50 respectively, all p<0.001) and distinguished low and moderate/high disease activity for all three clinical indices (AUROC =0.80, 0.76, 0.76 respectively, all p<0.001). No differences were found in the relationship between the MBDA score and DAS28 in patients treated with either ADA, ETN and IFX (p>0.05 for all comparisons). The mean decrease in the MBDA score was greater for patients with moderate EULAR response versus non response (−22 vs. 1, p<0.002) and greater for patients in good response versus moderate response (−30 vs. −22, p=0.009).

	ADA	ETN	IFX	all
n at Baseline	49	49	49	147
n at 52 weeks	49	49	49	147
Mean (±SD) MBDA at Baseline	61 ± 18	63 ± 17	59 ± 21	
Mean (±SD) MBDA at 52 Weeks	33 ± 15	37 ± 16	39 ± 18	
Mean (±SD) DAS28 at Baseline	5.4 ± 1.2	6.0 ± 1.1	5.9 ± 1.0	
Mean (±SD) DAS28 at 52 Weeks	2.8 ± 1.0	3.4 ± 1.2	3.1 ± 1.2	
Mean Change in MBDA (±SD): BL to 52 weeks	−29 ± 20	−26 ± 17	−20 ± 22	
Mean Change in DAS28 (±SD): BL to 52 weeks	−2.5 ± 1.4	−2.6 ± 1.4	−2.7 ± 1.3	

Conclusion: The MBDA score correlates with clinical disease activity measures in a cohort receiving anti-TNF therapy. The MBDA score tracks response in clinical disease activity in patients treated with different anti-TNF therapies, ADA, ETN or IFX.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Human Etiology and Pathogenesis II: Cellular Effectors of Rheumatoid Arthritis and Novel Rheumatoid Arthritis Genome-Wide Association Studies
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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Metabolic Reprogramming of Autoimmune T Cells in Rheumatoid Arthritis. Zhen Yang[1], Hiroshi Fujii[2], Shalini Mohan[1], Jorg J. Goronzy[1] and Cornelia M. Weyand[1]. [1]Stanford University School of Medicine, Stanford, CA, [2]Tohoku University, Sendai, Japan

Background/Purpose: In RA, autoimmunity precedes clinical symptoms by a decade and persists unabated even when downstream inflammation is well controlled; exposing lymphocytes to chronic stimulation and enforcing adaptation to persistent stress. T cells undergo rapid and extensive clonal expansion with a fairly unique need to greatly enhance metabolic activities and fulfill their energy needs by up-regulating aerobic glycolysis as well as autophagy. Glycolytic flux is mainly controlled by 6-phosphofructo-1-kinase, with its allosteric activator fructose 2,6-bisphosphate as a key regulator of the glycolytic pathway. The enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase isoform 3 (PFKFB3) generates fructose-2,6-bisphosphate and, hence, critically regulates the glycolytic rate under normal and pathophysiological conditions.

Methods: CD4$^+$CD45RO$^-$ T cells purified from the blood of RA patients (n=77) and age-matched controls were stimulated by TCR cross-linking. Glucose consumption, intracellular ATP and lactate production were quantified. Expression of 33 glycolysis-associated genes was profiled by RT-PCR. Protein levels of PFKFB3 and the autophagy marker LC3II were measured by Western blotting. Glycolytic flux and autophagic signaling were blocked through the PFKFB3 inhibitor N-BrEt or the autophagy inhibitor 3-methyladenine.

Results: Compared to control CD4 T cells, RA CD4 T cells respond to stimulation-induced metabolic needs with impaired glucose consumption (p=0.015), diminished ATP production (p<0.001)and reduced lactate release (p<0.001); all indicative of a defect in glycolytic flux. RA T cells express normal densities of glucose receptors but consistently fail to up-regulate PFKFB3 (p=0.012) and induce insufficient amounts of LC3II (p=0.032). Deficiency in glucose metabolism and autophagy is associated with increased apoptosis (p=0.003). This phenotype is reproduced in control T cells by knockdown of PFKFB3 or blocking autophagic signaling. Overexpression of ectopic PFKFB3 in RA T cells restores intracellular ATP (p=0.009) and lactate production (p=0.024) and conveys apoptotic resistance. Restoring PFKFB3 in RA T cells also rectifies the autophagic defect (p=0.024). Energy

deprivation is a stable phenotype of RA T cells, independent from disease activity and duration.

Conclusion: The inducible glycolytic rate-limiting enzyme PFKFB3 is repressed in RA T cells, resulting in deficient glucose utilization. The energy deprivation is aggravated by insufficient access to cell-internal energy resources and renders RA T cells apoptosis sensitive. Resetting the immune system in RA will require the repair of these metabolic abnormalities as they strain immune homeostasis and sustain chronic immune stress.

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A Link Between B Cells and Bone Erosion in RA: RANKL Production by Memory B Cells. Nida Meednu, Teresa Owen, Hengwei Zhang, Christopher A. Cistrone, Lianping Xing and Jennifer H. Anolik. University of Rochester, Rochester, NY

Background/Purpose: Rheumatoid arthritis (RA) is a systemic inflammatory disorder that often leads to joint damage. Several lines of evidence suggests the role of B cells in joint destruction including the efficacy of B cell depletion therapy as a treatment and the presence of B cell aggregates in RA synovium and subchondral bone. The aim of this study was to investigate the mechanisms by which B cells contribute to joint destruction in RA.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral blood or synovial fluid by Ficoll-Hypaque density gradient centrifugation from healthy controls (HC) or RA patients. Purified B cells were obtained by CD19 magnetic isolation. Cells were stimulated with anti-CD40 (2.5 μg/ml) and PMA (20 ng/ml) for 48 hours. RANKL expression was detected by cell surface staining and multi-color flow cytometry. Several markers to identify B cells and for T cell exclusion were employed including CD19, CD27, IgD, CD95, CD21 and CD3. For osteoclast formation assay, purified B cells were cultured for 7 days with anti-CD40 and PMA in the first 48 hours. Normal bone marrow derived osteoclast precursors (OCPs) were co-cultured with stimulated B cells in the presence of M-CSF and 10ng RANKL for 4–7 days. Cells were stained with TRAP and multi-nucleated TRAP+ cells were enumerated.

Results: Upon stimulation of PBMCs with anti-CD40 and PMA, the percentage of RANKL+ B cells was significantly higher than cells cultured with medium alone (6.854±1.097 vs. 0.684±0.14, n=9, p< 0.001). The same result was observed with purified B cells (data not shown). CD27+ memory B cells (unswitched CD27+IgD+ and switched CD27+ IgD−) had a greater propensity to produce RANKL in comparison to CD27− B cells (9.41±0.62 vs. 4.93±0.69, p=0.0084). Flow sorting B cells into naïve, transitional, switched and unswitched memory cells further verified the propensity of memory B cells to produce RANKL. Notably, the majority of RANKL-expressing B cells appeared to express the activation marker CD95 (79.04±6.47% CD95+ vs. 20±6.47% CD95−, p= 0.001). We also observed that PB from RA patients contained elevated B cells of an activated memory phenotype (CD95+ on switched memory in RA [n=13] 50.6+19.5 vs. HC [n=14] 29.6+9.5, p=0.005). In accord with this activated memory expansion, the frequency of RANKL+ PB B cells after stimulation was higher in RA when compared to HC (18.4+5.1 vs. 6.9+0.8, p=0.09). Remarkably, RA synovial fluid B cells produced even higher RANKL (23.2+7.6%, n=4) and also spontaneously produced RANKL. Finally, B cells supported osteoclast differentiation, and RA B cells are more efficient than HC (n=4, p<0.05).

Conclusion: Our data support the hypothesis that B cells play a key role in RA disease pathology and joint destruction in part by RANKL production. Activated memory B cells are expanded in RA and have a propensity to produce RANKL, an important factor in bone resorption.

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Activated Memory B Cell Compartment in Rheumatoid Arthritis: Impact of B Cell Depletion Therapy. Diana G. Adlowitz[1], Jennifer Hossler[1], Jamie Biear[1], Christopher A. Cistrone[1], Teresa Owen[1], Wensheng Wang[1], Arumugam Palanichamy[1], Ignacio Sanz[2] and Jennifer H. Anolik[1]. [1]University of Rochester Medical Center, Rochester, NY, [2]Emory University, Atlanta, GA

Background/Purpose: B cells are critical players in the orchestration of properly regulated immune responses. This is achieved through the finely regulated participation of multiple B cell populations with different antibody-dependent and independent functions, a balance that we postulate is perturbed in autoimmune diseases such as RA and may be corrected after B cell depletion therapy (BCDT).

Methods: B cells from 13 RA patients were analyzed by multi-color flow cytometry at baseline and longitudinally after BCDT. Expression of CXCR3, CD21, CD95, and anchor markers (IgD, CD19, CD27, CD38, CD24 and live/dead/T-cell exclusions) were used to subset memory B cells. Expression of MitoTracker Green extrusion, CD10, IgM, CD23 and anchor markers were used to subset transitional B cells. RA patients met ACR criteria for classification, and activity was assessed based on DAS28. Cytokine expression in distinct purified B cell subsets or total B cells in PBMCs were examined by flow cytometry after 88 hours stimulation (CpG 2006, anti-CD40, IL2, and BAFF) and 5 hr culture with PMA and ionomycin.

Results: In RA patients both CD27+IgD− switched memory (SM) and CD27−IgD− double negative memory (DN) contained higher fractions of CD95+ and CD21− activated B cells (DN CD95+: RA 28.9+3.9 vs. HC 10.7+1.2, p<0.0001; DN CD21−: RA 41.6+7.3 vs. HC 27.3+2.7, p=0.03). After BCD (1 month) the predominant B cell populations were memory (increase in DN from baseline 6.9+4.4 vs. 1 month 47.7+29.7, p=0.007; SM baseline 14.2+9.7 vs. 1 month 36.1+25.9, p=0.05). Notably, the residual memory B cells displayed a high fraction of CD95+ (DN 59.4+20.3, SM: 52.8+16.3) and CD21− (DN 94.6+2.9, SM: 73.1+22.2) compared to pre-depletion (CD95+: DN 28.9, p=0.03; SM: 38.7+18.0, p=0.1; CD21−: DN 41.6, p=0.0005; SM: 24.9, p=0.006;) suggesting some resistance of these activated populations to anti-CD20. Reconstitution occurred between 4 and 12 months with a variable distribution of transitional, naïve, and memory B cell subsets. At a reconstitution time-point (12 month), the fraction of activated memory remained high (CD95+ SM 91.4+4.6, p=0.001 vs. baseline; CD21− SM 70.4+12.4, p=0.009 vs. baseline), but there was a shift to a naïve/transitional dominant B cell compartment. The critical role of B cells as secretors of cytokines in a polarized fashion was highlighted by the propensity of CD27+ memory B cells to produce pro-inflammatory (TNF) over regulatory (IL10) cytokines (TNF: SM 28.2+5.4% vs. transitional 13.6+2.9, p=0.05; IL10: SM 3.5+0.7 vs. transitional 9.8+1.5, p=0.008). The effects of BCD on B cell cytokine secretion are under investigation.

Conclusion: Our results support the hypothesis that the clinical and immunological outcome of B cell depletion therapy depends on the relative balance of protective and pathogenic B cell subsets established after B cell depletion and upon B cell repopulation.

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Interferon and B-Cell Gene Signatures Contribute to Diagnosis of pre-Clinical Rheumatoid Arthritis. Joyce Lubbers[1], Lotte A. van de Stadt[2], Saskia Vosslamber[1], John G. Wesseling[1], Dirkjan van Schaardenburg[2] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands

Background/Purpose: Diagnosis of the preclinical phase of rheumatoid arthritis (pre-RA) allows timely start of treatment with the potential to prevent disease progression. It is known that antibodies against citrullinated proteins (ACPA) and rheumatoid factor (RF) have diagnostic value to identify pre-RA. However, since only 20–40% of ACPA+/RF+ arthralgia patients develop arthritis within 5 years, better prognostic markers are needed. Recently we demonstrated involvement of interferon (IFN) response and B-cell gene signatures pre-RA. The objective of this study is to demonstrate the value of these signatures in the diagnosis of pre-RA.

Methods: Peripheral blood (Paxgene) was collected from 115 ACPA+/RF+ arthralgia patients from Jan van Breemen Research Institute | Reade Amsterdam. Patients where clinically followed for arthritis development with a mean follow-up time of 23 months (IQR 12–30). During this period 44 arthralgia patients developed arthritis within a median time of 8 months (IQR 5–13). IFN response and B-cell related gene expression was measured by multiplex qPCRs. An IFN score was calculated based on 7 highly correlating Type I IFN response genes. A B-cell score was calculated based on three highly correlating B-cell related genes. Cut-off levels for the IFN and B cell high or low definition was determined by the 95% CI of the levels in healthy controls. Cox regression analysis and Receiver Operating Characteristic curve analysis was used to demonstrate prognostic and diagnostic significance.

Results: Cox regression analysis revealed that an IFN[high] score was associated with arthritis development independent of ACPA status (RR 2.19, CI 1.007–4.739, P= 0.048). Inclusion of the B-cell score demonstrated that an IFN[low] score combined with a B-cell[high] score was associated with arthritis free survival (RR 0.375). To demonstrate the clinical utility of the IFN and B-cell signatures to separate pre-RA patients from arthritis free survival individuals we constructed an ROC-curve. The area under the curve (AUC) reached 0.802 (P=0.000), which is considered "good". Based on these data a cut-off could be chosen for the diagnosis of pre-RA with a specificity of 85% and a sensitivity of 52%.

Conclusion: These findings demonstrate the value of IFN and B cell gene signatures as biomarkers for the diagnosis of pre-RA.

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TLR7 Ligation Contributes to Monocyte Migration in Rheumatoid Arthritis. Nathan D. Chamberlain[1], Seung-jae Kim[1], Michael Volin[2], William Swedler[1], Suncica Volkov[3] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL, [3]University of Illinios at Chicago, Chicago, IL

Background/Purpose: The aim of the study was to characterize the expression of TLR7 in rheumatoid arthritis (RA) peripheral blood (PB) cells and to examine the pathogenic role of TLR7 ligation in RA.

Methods: Expression of TLR7 was determined in RA and normal (NL) PB monocytes and in vitro differentiated macrophages by real-time RT-PCR and/or flow cytometry. Next the endogenous TLR7 ligand was identified in RA synovial fluid and its ability to induce monocyte migration was determined by in vitro chemotaxis.

Results: Since we have previously shown that expression of TLR7 was elevated in RA synovial lining and sublining macrophages, we asked whether expression of TLR7 was increased in RA PB and synovial fluid macrophages compared to NL PB monocytes and differentiated macrophages. We show that expression of TLR7 was elevated 18 and 24 fold in RA synovial fluid macrophages compared to RA and NL PB differentiated macrophages respectively by real-time RT-PCR. Levels of TLR7 were 6 and 3 fold higher in RA monocytes compared to RA differentiated macrophages and NL monocytes. Interestingly, mRNA and endosomal expression of TLR7 are reduced when RA PB monocytes differentiate to macrophages. Ligation of TLR7 by a synthetic agonist in RA blood monocytes is responsible for production of high levels of TNF-a (3 ng/ml) and as such we demonstrate that levels of TLR7 and TNF-a in 35 RA monocytes strongly correlate with each other ($R^2=0.44$, $p=1.37\times10^{-5}$) and disease activity score (TLR7 and DAS28 correlation; $R^2=0.67$, $p=1.57\times10^{-9}$) suggesting a pathogenic role for TLR7 ligation in RA disease. In light of elevated levels of TLR7 in RA synovial fluid macrophages, we looked for TLR7 endogenous ligands in RA synovial fluid. We discovered that single strand (ss)RNA extracted from RA synovial fluid is a potential TLR7 endogenous ligand, since blockade of TLR7 ligation by TLR7 antagonist in RA monocytes greatly downregulates synovial fluid ssRNA mediated TNF-a transcription. To determine whether TLR7 ligation affects cell trafficking in the RA joint, monocyte chemotaxis was examined in response to a synthetic agonist to TLR7. We show that TLR7 ligation was chemotactic for monocytes beginning at 0.1 ng/ml of TLR7 agonist. Next, studies were performed to determine if the TLR7 ligation affects RA synovial fluid mediated monocyte extravasation. We document that blockade of TLR7 ligation or degradation of synovial fluid ssRNA is equally effective in reducing synovial fluid induced monocyte trafficking and that the combined therapy does not have an enhanced effect suggesting that ligation of joint ssRNA to TLR7 modulates monocyte extravasation through an overlapping pathway and it further points out that RA synovial fluid ssRNA is a potential TLR7 ligand.

Conclusion: We identify, for the first time, TLR7 endogenous ligand in RA joint and we also document a novel role for TLR7 ligation in RA monocyte migration.

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Genome-Wide Association Study On the Severity of Joint Destruction in Autoantibody Positive Rheumatoid Arthritis Identifies a Role for Sperm Associated Antigen 16. Rachel Knevel[1], Kerstin Klein[2], Klaartje Somers[3], Caroline Ospelt[4], Jeanine J. Houwing-Duistermaat[5], Jessica van Nies[1], Diederik P.C. de Rooy[1], Laura de Bock[3], Joris Schonkeren[1], Gerrie Stoeken-Rijsbergen[1], Jenna Kiridly[6], Luis Rodriguez-Rodriguez[6], Quinta Helmer[5], Piet Sinissen[3], Tom W. J. Huizinga[1], René E.M. Toes[7], Steffen Gay[8], Peter K. Gregersen[9], Veerle Somers[3] and Annette H.M. van der Helm-van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [3]Hasselt University, Biomedical Research Institute, Belgium, [4]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, Zurich, Switzerland, [5]Department of Medical Statistics and Bioinformatics, Leiden, Netherlands, [6]Feinstein Institute for Medical Research and North Shore–Long Island Jewish Health System, Manhasset, New York, [7]Leiden University Medical Centre, Leiden, Netherlands, [8]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [9]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY

Background/Purpose: Recent genome-wide association studies (GWAs) have identified >30 SNPs predisposing to Rheumatoid Arthritis (RA). These variants are helpful in unraveling the pathogenesis of RA. However, most therapeutic strategies target pathways of disease progression. Genetic factors account for a considerable proportion of variance in joint damage, but thus far only a few replicated severity factors are known and no GWAS has been performed. We aimed to increase the understanding of the processes underlying the inter-individual differences in joint damage in anti-citrullinated peptide antibodies (ACPA)-positive RA by performing a 3-staged GWAS on joint damage progression using high-quality radiological data, followed by *in vitro* and *ex vivo* studies.

Methods: Stage 1 was performed on 385 ACPA-positive RA-patients from the NARAC using Illumina HumanHap 550k BeadChips. Stage 2 concerned of 1,567 X-rays of 301 ACPA-positive RA-patients included in a Dutch cohort with 7 years follow-up. In stage 3, 861 X-rays of 742 North-American ACPA-positive RA-patients included in the NDB and Wichita-cohorts were studied. All X-rays were scored using the Sharp-van der Heijde method (ICCs all >0.9). The expression of SPAG16 variants was studied by RT-qPCR using a RA synovium cDNA library and cDNA derived from other RA tissues and fibroblast-like synoviocytes (FLS). Expression levels of MMP1 and MMP3 of FLS before and after stimulation with TNF-α (10 ng/ml) and IL1β (1ng/ml) were evaluated by RT-qPCR and ELISA (cell culture supernatants). Finally serum MMP3 levels were measured in RA patients of stage 2 using ELISA.

Results: In stage 1, the strongest association was observed for a cluster of SNPs at 2q34, the region of Sperm associated AntiGen16 (*SPAG16*, $P=4.55\times10^{-7}$, 0.77 fold progression rate per year per minor allele). Independent replication was obtained in stage 2 and 3, again observing a protective effect on damage progression ($P=2.16\times10^{-2}$ and 2.29×10^{-2} resp.). Apart from its role in spermatozoa, the function of SPAG16 is incompletely known. We detected SPAG16 isoforms in RA tissues and FLS. No relation between expression levels of SPAG16 transcripts in FLS and SPAG16 genotypes could be detected. However, the matrix degrading capacity of FLS may be affected. FLS of patients with the minor allele tended to express less MMP3 mRNA and secreted lower levels of MMP3 ($P=2.28\times10^{-2}$). Also after cytokine stimulation the minor allele was associated with less production of MMP3. Furthermore, RA-patients carrying the minor allele had lower serological levels of MMP3 ($P=4.59\times10^{-2}$) and lower MMP3 levels were associated with less progression of damage ($P=3.09\times10^{-3}$).

Conclusion: A genetic variant in *SPAG16* is associated with less production of MMP3 by FLS and protection against joint damage progression. These findings indicate a new pathway involved in joint damage in ACPA-positive RA.

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A Genome-Wide Association Study Establishes Muliple Susceptibility Loci for Sjögren's Syndrome. Christopher J. Lessard[1], He Li[2], Indra Adrianto[3], John A. Ice[3], Roland Jonsson[4], Gabor G. Illei[5], Maureen Rischmueller[6], Gunnel Nordmark[7], Xavier Mariette[8], Corinne Miceli-Richard[9], Marie Wahren-Herlenius[10], Torsten Witte[11], Michael T. Brennan[12], Roald Omdal[13], Patrick M. Gaffney[14], James A. Lessard[15], Wan-Fai Ng[16], Nelson L. Rhodus[17], Barbara M. Segal[18], R. Hal Scofield[3], Judith A. James[19], Juan-Manuel Anaya[20], John B. Harley[21], Courtney G. Montgomery[3] and Kathy Moser Sivils[3]. [1]Oklahoma Medical Research Foundation; University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]University of Bergen, Bergen, Norway, [5]NIDCR/ NIH, Bethesda, MD, [6]Queen Elizabeth Hospital, Adelaide, Australia, [7]Rheumatology, Uppsala, Sweden, [8]Université Paris-Sud, Le Kremlin Bicetre, France, [9]Hopital Bicêtre, Le Kremlin Bicêtre, France, [10]Karolinska Institutet, Stockholm, Sweden, [11]Hannover Medical School, Hanover, Germany, [12]Carolinas Medical Center, Charlotte, NC, [13]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [14]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [15]Valley Bone & Joint Clinic, Grand Forks, ND, [16]Newcastle University, Newcastle, England, [17]University of Minnesota, Minneapolis, MN, [18]Hennepin County Medical Center, Minneapolis, MN, [19]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [20]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [21]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH

Background/Purpose: Sjögren's syndrome (SS) is a common, clinically heterogeneous autoimmune disease characterized by exocrine gland dysfunction that involves both innate and adaptive immune responses. A complex genetic architecture has been hypothesized; however, genetic studies to date have been limited to candidate gene approaches. We sought to perform the first genome-wide association scan (GWAS) in an unbiased manner to identify SS susceptibility loci.

Methods: We used high-density Illumina OMNI1-Quad genotyping arrays in a discovery cohort of 424 European-derived SS cases and 2120 healthy controls for the GWAS discovery phase. Stringent quality control (QC) criteria, adjustments for population stratification, and standard GWA statistical methodologies were used to compare allele frequencies between cases and controls. A total of ~650,000 single nucleotide polymorphisms (SNPs) were tested for association to SS (P_{omni}). For replication, an independent set of 1194 SS cases and 2930 healthy controls were genotyped using the ImmunoChip (IC; P_{IC}) with ~26,000 overlapping SNPs with the GWAS after QC. Meta-analysis between the GWAS and IC was done using METAL (P_{meta}). Of the 1618 SS case, 133 also had gene expression data from the Illumina WG-6 microarray from whole blood. Expressed quantitative trait loci (eQTL) analysis was done using the MATRIXeQTL package in R. Probes and SNPs in a 50 kb region flanking 4 selected genes were analyzed.

Results: The most significantly associated region with SS was the major histocompatibility complex (MHC), with 1071 overlapping SNPs between the GWAS and IC exceeding a genome-wide significance (GWS) threshold of $5\times10E-8$. The peak association was observed in MSH5 (rs3117574 $P_{meta}=5.33\times10E-79$). Results across the extended MHC support association with multiple loci throughout this region. In the GWAS, 2 SNPs, rs485497 and rs4680536, were identified near IL12A with $P_{omni}<6\times10E-4$. Both rs485497 ($P_{IC}=1.88\times10E-7$) and rs4680536 ($P_{IC}=2.06\times10E-5$) replicated yielding $P_{meta}=4.81\times10E-10$ and $P_{meta}=1.69\times10E-8$, respectively. In addition, we observed associations surpassing GWS for the first time with loci previously implicated in SS, including IRF5 (rs10488631 $P_{meta}=5.25\times10E-13$), BLK (rs922483 $P_{meta}=1.50\times10E-8$), and STAT4 (rs10168266 $P_{meta}=3.59\times10E-8$). We also identified statistically significant eQTL in the IRF5 region with 13 SNPs at $P<5\times10E-8$. BLK also showed significant eQTLs with 8 SNPs at $P<7\times10E-4$. IL12A, IRF5 and STAT4 are involved in type I interferon responses. IL12A encodes the p35 subunit of IL12 and is secreted by monocytes and dendritic cells ultimately stimulating the production of IFN-γ. Interestingly, responses to IL12 are mediated through STAT4.

Conclusion: We present the first GWAS of SS identifying and confirming IL12A as a novel susceptibility locus. We also observed IRF5, BLK and STAT4 for the first time at GWS establishing them as risk loci for SS. We report eQTLs in the region of IRF5 and BLK in SS cases suggesting expression of these loci is important in the pathogenesis as has been reported in SLE. Collectively these genes illustrate the importance of both the innate and adaptive immune responses in the etiology of SS.

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Genome-Wide Association Analysis Reveals Genetic Heterogeneity of Sjögren's Syndrome (SS) According to Specific Subphenotypes and Ancestry. Lindsey A. Criswell[1], Kimberly E. Taylor[1], Caitlin McHugh[2], Cathy Laurie[2], Kimberly Doheny[3], Mi Y. Lam[1], Joanne Nititham[1], Laura Bierut[5], Emily L. Harris[6], Alan N. Baer[7], Stephen Challacombe[8], Yi Dong[9], Hector Lanfranchi[10], Morten Schiodt[11], M. Srinivasan[12], Susumu Sugai[13], Hisanori Umehara[14], Frederick B. Vivino[15], Zhao Yan[16], Steve Shiboski[1], Troy Daniels[17], John S. Greenspan[1], Caroline Shiboski[1] and SICCA[18]. [1]University of California, San Francisco, San Francisco, CA, [2]University of Washington, Seattle, WA, [3]Center for Inherited Disease Research, Baltimore, MD, [4]Rosalind Russell Medical Research Center for Arthritis, San Francisco, CA, [5]Washington University, St. Louis, MO, [6]National Institute of Dental and Craniofacial Research, Bethesda, MD, [7]Johns Hopkins University, Baltimore, MD, [8]Kings College London, London, United Kingdom, [9]Peking Univ Med Coll Hospital, East City Beijing, China, [10]University of Buenos Aires, Buenos Aires, Argentina, [11]Righospitalet, Copenhagen, Denmark, [12]Aravind Eye Hospital, Madurai, India, [13]Kanazawa Medical University, Ishikawa, Japan, [14]Kanazawa Medical University, Kanazawa, Japan, [15]Penn Presbyt Med Ctr, Philadelphia, PA, [16]Peking Union Medical College Hospital, Beijing, China, [17]UCSF Schools of Medicine & Dentistry, San Francisco, CA, [18]San Francisco

Background/Purpose: Our goal is to define the contribution of genetic factors to SS and related subphenotypes.

Methods: We studied 2,459 participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) who were characterized for the Illumina HumanOmni 2.5-Quad marker set. SICCA participants were enrolled according to standardized protocols at 9 international sites, including Argentina (n=342), China (n=290), Denmark (n=446), India (n=65), Japan (n=354), the UK (n=203) and the US (total n=759 from 3 sites). Additional control data genotyped on the same platform were obtained from the Collaborative Genetic Study of Nicotine Dependence (COGEND, n = 1466). QC measures included filters based on SNP and sample missingness (≥2%), unexpected relatedness, non-Mendelian inheritance, and chromosomal regions of anomaly (> 10Mb). SICCA participants were classified according to ACR classification criteria for SS (AC&R 2012, 64; 475), including presence of focal lymphocytic sialadenitis (FLS) on minor salivary gland biopsy, presence of KCS based on ocular staining pattern (ocular staining score ≥3), and production of autoantibodies (SSA, SSB, ANA and RF). Principal components (PC) analysis was used to characterize each participant for genetic ancestry, and PCs 1 – 5 were included as covariates in all association analyses. The following phenotypes were examined: SS susceptibility (fulfillment of ACR criteria versus controls, including COGEND), presence of FLS, presence of KCS and autoantibody positive disease.

Results: Out of 2118 subjects with post-QC genotypes and sufficient clinical data, 1000 (47%) met ACR criteria for SS, and an additional 772 fulfilled at least 1 of the 3 criteria, including FLS, KCS or autoantibody positivity (SSA &/or SSB +, or both ANA ≥ 320 and RF +). A total of 1,445,406 SNPs passed all QC filters and were fully analyzed. For case-control analysis, 1,392,831 SNPs passed QC filters for both cohorts and were analyzed. Multiple variants within the MHC region on chr 6q and the IRF5-TNP03 region on chr 7 were strongly associated with SS susceptibility (lowest p values 1.9e-27 and 3.8e-13, respectively), and with autoantibody production (MHC p=1.7e-30, IRF5 p=3.2e-12) and FLS (MHC p=9.7e-12, IRF5 p=1.5e-10) within SICCA

subjects; furthermore the region of MHC association for autoantibody production was much broader (26–33Mb versus 30–33Mb). In contrast, we did not observe significant genetic associations with KCS, indicating genetic heterogeneity specifically related to the oral, ocular or systemic manifestations of SS. Among SICCA subjects, multiple PCs were strongly associated with some phenotypes examined, suggesting heterogeneity according to genetic ancestry. In particular, a PC separating Asian and European ancestry was strongly associated with autoantibody production (p < 4.5e-38).

Conclusion: These results demonstrate genetic overlap of SS with other autoimmune diseases, and highlight the genetic heterogeneity of the disease according to specific subphenotypes and ancestry. Future work including imputed genetic data and additional study subjects will provide more power for extending these findings and fully characterizing the genetic contribution to SS.

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Sibling Relative Risk and Heritability of Sjögren's Syndrome: A Nationwide Population Study in Taiwan.

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Background/Purpose: Although familial aggregation has been found in many autoimmune diseases, the evidence for familial aggregation in Sjögren's syndrome is lacking. The aims of this study was to estimate familial relative risk (RR) and heritability of Sjögren's syndrome inthe general population of Taiwan.

Methods: Using data from the National Health Insurance Research Database in Taiwan, we conducted a nationwide cross-sectional study of 11,665,669 men and 11,332,220 women in 2010. We identified individuals with a full sibling affected by Sjögren's syndrome and compared the prevalence of the disease between individuals with and without an affected sibling. The identification of sibling of each individual was determined using the NIHRD registry for beneficiaries. This specifies relationships between the insured person who paid the insurance fee and his/her dependents, allowing first-degree relatives (father, mother, son, daughter, brother, sister, twin) to be identified directly. Full siblings were identified as individuals who shared the same parents. The marginal Cox proportional hazard model with an equal follow-up time for all subjects was used to estimate sibling relative risk (RR) and the 95% confidence interval (CI). This model was used to account for shared environment and case clustering within families with robust variance. The heritability of Sjögren's syndrome were estimated by multifactorial polygenic threshold which presumes a single, normally distributed disease liability resulting from a large number of unspecified genes and environmental factors, each with small and additive influences.

Results: There were 12,091 (men, 1,264; women, 10,827) patients with Sjögren's syndrome in the general population of Taiwan in 2010 (unadjusted prevalence = 0.53 per 1000). The mean age of patients with Sjögren's syndrome was 57.4 ± 14.1 years. Individuals with an affected sibling with Sjögren's syndrome had a higher prevalence of Sjögren's syndrome (5.03 per 1,000 people) than those without (0.53 per 1,000 people). The risk of Sjögren's syndrome in individuals with an affected sibling was 15.51 (95% CI, 5.85–41.12) times greater than that in individuals without an affect sibling. The heritability of Sjögren's syndrome was 0.54 (95% CI, 0.32–0.80).

Conclusion: This is the first population-based study to demonstrate that Sjögren's syndrome clustered within families. The results suggest a significant genetic contribution to the development of Sjögren's syndrome.

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***Cis*-Expression Quantitative Trait Loci Analysis of Dysregulated Interferon-Pathway Genes Identifies *HLA-C* and *OAS1* As Novel Candidates for Susceptibility to Sjögren's Syndrome.**

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Background/Purpose: Sjögren's syndrome (SS) is a progressive autoimmune exocrinopathy characterized by symptoms of dry eyes and mouth present in 0.7–1% of Europeans. Dysregulation of interferon (IFN)-related pathways is well documented in SS and related autoimmune disorders, like systemic lupus erythematosus. To further characterize the expression of IFN-inducible genes in SS, we performed *cis*-expression quantitative trait loci (*c*-eQTL) analysis in SS cases to identify genetic variants regulating proximal IFN-regulated genes.

Methods: We first performed whole blood global gene expression profiling in 162 primary SS cases and 58 healthy controls of European ancestry. In total, 2410 genes were differentially expressed (DE) between SS cases and controls ($3.49 \times 10E$-$22 \leq q < 0.05$). Among pathways in which DE genes were identified, pathways involved in type I interferon-mediated signaling (31/70 genes; $p = 5.56 \times 10E$-14) were highly significant. The 31 genes were selected for use as phenotypic traits in *c*-eQTL analyses in 133 Caucasian SS patients through integration of gene expression data with genotypes from our SS genome-wide association study (GWAS, 424 cases / 2120 controls). Single nucleotide polymorphisms (SNPs) from GWAS data spanning 20kb flanking the target genes were tested for genetic association with expression levels by linear regression using Matrix-eQTL in the R Bioconductor suite.

Results: *C*-eQTL analysis identified SNPs within and flanking *HLA-C* (70 SNPs, $3.13 \times 10E$-$9 \leq q < 0.01$) and *OAS1* (26 SNPs, $6.29 \times 10E$-$9 \leq q < 0.01$) that are significantly associated with gene expression levels. Alleles of *HLA* genes are well-documented risk factors for the development of autoimmune disorders, including SS. *HLA-C* belongs to the highly polymorphic *MHC* class I heavy chain molecule, and is a major independent genetic determinant of psoriasis and rheumatoid vasculitis. Our GWA study also showed associations of *HLA-C* eQTL with SS susceptibility with the top $p = 1.72 \times 10E$-22 in rs2844612. The association of rs2844612 with *HLA-C* expression levels is independent of other non-*HLA-C* SNPs in the *MHC* region, such as *HLA-DRB1* and *HLA-DQB1*. Interestingly, the presence of both the risk alleles in *HLA-C1* and its receptor killer cell immunoglobulin-like receptor (*KIR*)-2DS2 (2 extracellular domains with short cytoplasmic domain) is significantly associated with dry eye disease in a Han Chinese population. *OAS1*, or 2′,5′-oligoadenylate synthetase 1, is a critical component involved in the innate immune response to viral infection through RNA degradation and the inhibition of viral replication. Mutations in *OAS1* have been associated with host susceptibility to viral infection. Evidence for association of the *OAS1* SNP rs10774671, a splice-site polymorphism associated with multiple sclerosis and type 1 diabetes, increased from $p = 3.39 \times 10E$-3 in our SS GWAS to $p = 6.29 \times 10E$-9 in the *c*-eQTL analysis.

Conclusion: Integration of results from genetic studies with gene expression data can help us to interpret downstream functional effects of SS susceptibility loci. These results provide promising novel candidate loci in and around *HLA-C* and *OAS1* for future functional studies to better understand SS pathophysiology.

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Oral and Gut Microbiota Influence Immune Responses to Sjogren's Syndrome Associated Antigen Ro60. Agnieszka Szymula, Barbara Szczerba, Harini Bagavant, Shu-Man Fu and Umesh Deshmukh. University of Virginia, Charlottesville, VA

Background/Purpose: Autoantibodies reactive against Ro60 protein are often found in patients with Sjogren's syndrome. This study was undertaken to investigate the role of oral and gut microbiota in initiation of autoimmune responses against Ro60. We hypothesized that proteins derived from oral/gut microbes activate Ro60 reactive T cells, which then play a critical role in autoantibody generation.

Methods: HLA-DR3 restricted T cell hybridomas, reactive against Ro60 were generated, and employed to map and characterize T cell epitopes on Ro60. Pattern search and BLAST analysis was carried out to identify putative cross-reactive peptides from microbes in the Human Oral Microbiome Database. Several peptides were synthesized and their ability to activate Ro60 reactive T cell hybridomas tested. A recombinant microbial protein that contained the strongest mimicry peptide was generated and its ability to activate Ro60 reactive T cells analyzed. HLA-DR3 transgenic mice were immunized with this microbial protein and autoantibody responses against different autoantigens investigated.

Results: The HLA-DR3 restricted T cell hybridomas recognized 3 epitopes on Ro60, $Ro60_{221-250}$, $Ro60_{241-260}$ and $Ro60_{361-390}$. Pattern search analysis identified several hundred mimicry peptides originating from oral and gut microbes. Amongst these, peptides originating from von Willebrand factor type A (vWFA) protein were most potent in activating T cell hybridoma reactive against $Ro60_{361-390}$. Purified recombinant vWFA protein from Capnocytophaga ochracea (an oral microbe) activated Ro60 reactive T cells. Interestingly, whole E coli expressing vWFA protein were also able to activate Ro60 reactive T cells. These results show that peptides from vWFA protein are processed and presented by antigen presenting cells even in the presence of hundreds of other E coli proteins. Immunization of HLA-DR3 transgenic mice with recombinant vWFA protein readily induced autoantibodies reactive against Ro60, La (SSB) and Ro52 (SSA).

Conclusion: Our results clearly demonstrate that a microbial protein present in different commensall oral/gut bacteria can activate Ro60 reactive T cells and induce autoantibody responses against Ro60. Thus, we would like to propose that a dysregulated immune response against normal microbiome can be one of the pathways responsible for initiating autoimmune responses in Sjogren's syndrome. Considering that oral infections are a common problem in Sjogrens's syndrome patients, this pathway might also be involved in amplification of autoimmune responses in this disease.

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Long-Term Humoral Autoimmunity to Ro60 in Primary Sjögren's Syndrome Is Driven by Clonal Succession. Rhianna Lindop[1], Isabell Bastian[1], Georgia Arentz[1], Lauren Thurgood[1], Andrew Whyte[1], Tim, K. Chataway[2], Michael Jackson[1] and Tom Gordon[1]. [1]Flinders Medical Centre and Flinders University, Adelaide, Australia, [2]Flinders University, Adelaide, Australia

Background/Purpose: Long-lived humoral autoimmunity to Ro60 is considered a hallmark of primary Sjögren's syndrome (SS), but the mechanism by which this immunity is sustained over decades remains unclear. Persistence of anti-Ro60 autoantibodies could be generated either by long-lived plasma cells residing in the bone marrow or by continual production of short-lived plasma cells. In the present study, these models were tested in humans for the first time by analysing serial molecular signatures of a recently reported public Ro60-specific clonotypic autoantibody (1).

Methods: Serial serum samples were collected over weeks to years from 8 patients with primary SS who expressed stable V_H3–23/ V_K3–20 Ro60 clonotypic autoantibody levels. Clonotypic IgGs were isolated by epitope-specific affinity chromatography and subjected to high resolution Orbitrap mass spectrometry. Variable regions of heavy and light chains were analysed by combined database and *de novo* amino acid sequencing. Alterations in autoantibody affinity were assessed by equilibrium binding analysis (Biacore).

Results: At each time point, patients expressed a single Ro60-specific monoclonal IgG1 kappa species, specified by a V_H3–23/J_H5 and V_K3–20/J_K2 pairing signature. However, near full-length V region protein sequencing showed a subtle turnover of clonotypes that was not detected by solid-phase immunoassay. The clonal turnover was characterised by 4–6 month cycles of clonal succession, with dominant clonotypes undergoing continual replacement by new somatically mutated clonal variants. Surprisingly, earlier clones never reappear in the periphery, and each new clone has a unique molecular signature. Affinities (K_D value) of successive clonotypes did not change significantly in the face of ongoing perpetual turnover. Autoantibody levels showed a cyclical rise and fall pattern every 3–4 months in keeping with this turnover model.

Conclusion: Analysis of the secreted autoantibody proteome demonstrates a dynamic process of clonal succession that masquerades as long-term Ro60 humoral autoimmunity. Surprisingly, the selection pressure for replacement clones is not based on affinity selection, indicating that an affinity ceiling is reached early in disease. Our findings are compatible with ongoing clonal expansion and exhaustion of short-lived autoreactive plasma cells, as opposed to a single event generation of long-lived plasma cells. The relentless generation of autoantibody clonotypes in primary SS by antigen-driven clonal selection has important therapeutic and diagnostic implications.

(1) Lindop *et al.* (2011), Arthritis Rheum, Vol. 63, No. 11, p.p. 3477–3486.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Animal Models
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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IL-23 Controls Autoimmunity by Facilitating Clearance of Apoptotic Bodies in the Marginal Zone in Lupus-Prone BXD2 Mice. Hao Li[1], Hui-Chen Hsu[1], Qi Wu[1], PingAr Yang[1], Jun Li[1], Daniel Cua[2], Mohamed Oukka[3] and John D. Mountz[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Merck Research Laboratory, Palo Alto, CA, [3]Seattle, WA, [4]University of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, AL

Background/Purpose: Failure to clear apoptotic bodies is a central pathogenic mechanism for SLE. We have observed that spontaneous systemic autoimmunity and lupus in BXD2 mice is associated with large germinal centers (GC) and development of highly pathogenic autoantibodies. The increased GCs in the spleen are promoted by increased Th17 cell, which is promoted by IL-23 in BXD2 mice. As anti-IL-23 therapy is under development for chronic inflammation and autoimmune diseases, we investigated the therapeutic potential of complete blocking IL-23 in BXD2 mice. We made an unexpected finding that complete deficiency of IL-23 accelerated and exacerbated systemic autoimmune disease in BXD2 mice.

Methods: Wild type (WT) BXD2 mice were treated with isotype control, anti-IL-17 or anti-IL-23 (100 ug iv Q3D $\times$ 3 doses). BXD2 mice were crossed to IL-23 p19 deficient ($p19^{-/-}$) mice to generate BXD2-$p19^{-/-}$ mice. Confocal microscope analysis and/or FACS analysis were carried out to determine the clearance of GFP$^+$ apoptotic cells (ACs), the percentages of PNA$^+$ GC B cells, SIGN-R1$^+$ marginal zone macrophages (MZMs), PDCA1$^+$ plasmacytoid dendritic cells (pDCs), CD68$^+$ red pulp macrophages, and IL-17$^+$ or IFNγ^+ CD4 T cells. ELISA assay was used to determine autoAb titers and protein urine levels in vivo. Quantitative RT-PCR was used to determine the expression of *Il23, Il23r, Ifna1, Ifna4, Ifna7,* and *Ifna11.* Depletion of MZMs was carried out by administration of clondronate liposome (167 ug/week $\times$ 8wk).

Results: Anti-IL-17 blocked development of GCs in BXD2 mice. Surprisingly, anti-IL-23 enhanced GC development and anti-dsDNA antibody production. Similarly, there was accelerated development of spontaneous GCs, production of anti-dsDNA antibody and IC deposition in the glomerulus of BXD2-$p19^{-/-}$ mice, compared with WT mice. While IL-23R was mainly expressed by MZMs, IL-23 was mainly produced by red pulp macrophages that were in close proximity to the MZM in the extra-follicular region of the spleen of BXD2 mice. Deficiency of IL-23 was associated with a dramatic reduction of MZMs in the spleen of BXD2-$p19^{-/-}$ mice. In contrast, expression of IL-23 by adenovirus in BXD2-$p19^{-/-}$ mice at early age prevented the loss of MZM and the initiation of glomerulonephritis. Clondronate liposome treatment mimicked the effects of $p19^{-/-}$, leading to depletion of MZMs, impaired clearance of ACs and severely accelerated autoimmune disease. This was associated with dramatically elevated serum levels of type I IFN genes including *Ifna1, Ifna4, Ifna7, Ifna11.* Although

there was diminished Th17 cells in BXD2-$p19^{-/-}$ mice, defective clearance of ACs was associated with greatly elevated production of type I IFNs by pDCs and IFNγ by Th1 cells.

Conclusion: Our results suggest a novel concept that IL-23 can act as a double edge sword to control the development and severity of autoimmunity. Overexpression of IL-23 may provoke autoimmunity through the induction/maintenance of Th17 yet a complete deficiency of IL-23 also induced autoimmunity through the loss of the MZM barrier that clears ACs and prevents follicular invasion of apoptotic autoantigens. Our results suggest that caution should be used when considering IL-23 blockade for treatment of autoimmune disease.

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Novel Nuclear Export Inhibitors Deplete Autoreactive Plasma Cells and Protect Mice with Lupus-Like Disease From Nephritis. Teresa Owen[1], Wensheng Wang[1], Dilara McCauley[2], Laura Strojny[1], Jennifer Hossler[1], Javier Rangel-Moreno[1], Michael Kauffman[2], Sharon Shacham[2] and Jennifer H. Anolik[1]. [1]University of Rochester Medical Center, Rochester, NY, [2]Karyopharm, Therapeutics Inc., Natick, MA

Background/Purpose: Most therapies currently used to treat systemic lupus erythematosus (SLE) and B cell targeted therapies under development do not effectively target plasma cells and autoantibodies. We postulated that selective inhibition of nuclear export (SINE) with novel small molecule CRM1 antagonists, which have demonstrated potent activity for hematologic malignancies, may be useful in the treatment of SLE by targeting plasma cells and other immune cells critical to disease pathogenesis.

Methods: Nephritic NZB/W F1 lupus-prone female mice, with elevated serum anti-dsDNA antibodies and established proteinuria, were treated with the SINE KPT-251 (injections 5/7 days for 5 weeks) (initially 75 mg/kg $\times$ 3 weeks and then 50 mg/kg for 2 additional weeks) or vehicle control subcutaneously (n=10 per group). Spleen and bone marrow (BM) lymphocytes were harvested, stained with antibodies, and analyzed by flow cytometry. Plasma cells (PC) were identified with antibodies against intracellular kappa light chain. We monitored nephritis severity by measuring proteinuria (Uristix) and analyzing pathological changes in kidney histology. Serum auto-antibody levels (anti-dsDNA) were measured by ELISA. ELISpot was used to enumerate IgG- and dsDNA antibody secreting cells (ASC).

Results: KPT-251 SINE treatment of NZB/W F1 mice prevented nephritis progression with a statistically significant reduction in urine protein levels in the treated group (p<0.05 beginning at 3 weeks) and notably reduced the number of mice with significant proteinuria (77% of treated mice had low urine protein concentrations <100 mg/dL compared to only 10% of controls at 5 weeks) (p=0.003). Importantly, serum anti-dsDNA IgG levels were significantly reduced after KPT-251 treatment (>6-fold reduction, p=0.0017) with profound effects on antibody secreting plasma cells. We found a significant reduction in splenic plasmablasts (2.18-fold reduction, p=0.001), BM PCs (2-fold reduction, p=0.02) and plasmablasts (MHCII high) (2.24-fold reduction, p=0.003). Moreover, ASC numbers were notably decreased with nuclear transport inhibition. Total IgG and anti-dsDNA IgG ASC numbers in the spleen were drastically reduced after treatment (70% reduction, p=0.002). In bone marrow, there was a pronounced decline in IgG ASC numbers (81%), with a more dramatic effect on anti-dsDNA IgG ASCs (96% reduction, p=0.002).

Conclusion: These results suggest that nuclear transport inhibition preferentially affects auto-reactive PC and prevents SLE-associated nephritis. Therefore, these data support the further development of SINE drugs as a novel therapeutic approach for SLE.

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Loss of Caspase 8 in Dendritic Cells Induces a Systemic Lupus Erythematosus-Like Disease That Is Independent of the Necroptosome. Carla M. Cuda[1], Alexander V. Misharin[2], Rana Saber[2], G. Kenneth Haines III[3], Jack Hutcheson[4], Chandra Mohan[4] and Harris R. Perlman[2]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Yale University, New Haven, CT, [4]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-organ, destructive autoimmune disease characterized by pathogenic autoantibodies. Though it is accepted that dendritic cells (DCs) play an important role in disease initiation, only recently have studies implicated DCs as a major factor in SLE persistence. DCs from SLE patients exhibit elevated expression of activation markers including co-stimulatory molecules and pro-inflammatory cytokines; however, the factors that are responsible for their aberrant activation is unknown. We recently identified that caspase 8, a cysteine-aspartic acid enzyme known to function in death receptor signaling, is a novel DC-specific inhibitor of inflammatory processes. While previous studies have shown that caspase 8 functions to initiate apoptosis and/or suppress necroptosis (through inhibition of RIPK1/3 signaling) in a multitude of cells, our data suggest that caspase 8 is not essential for the survival of DCs (apoptosis/necrosis), but rather inhibits the continuous activation of DCs, thereby preventing development of systemic autoimmunity.

Methods: Mice with caspase 8 flanked by loxP sites (Casp8$^{flox/flox}$. WT) were crossed with mice expressing Cre under control of the CD11c gene promoter (Cre^{CD11c}), which is expressed by dendritic cells. Flow cytometric analysis was employed to characterize DC populations in both mixed bone marrow chimeras and BrdU pulse assays. Bone marrow-derived DCs were cultured with TLR agonists $+/-$ necrostatin-1 to block RIPK1 activity. Luminex-based assays and ELISAs were used to detect cytokine and transcription factor DNA binding levels.

Results: Cre^{CD11c}Casp8$^{flox/flox}$ develop splenomegaly, lymphadenopathy, autoantibodies, glomerulonephritis, immune complex deposition in the kidney, exacerbated proteinuria levels, heightened amounts of serum pro-inflammatory cytokines (IL-12, IL-1β, and IFNα/β), and early mortality. Loss of caspase 8 in DCs does not affect their survival, as Cre^{CD11c}Casp8$^{flox/flox}$ mice present with increased DC populations, there are equal numbers of Cre^{CD11c}Casp8$^{flox/flox}$ and WT DCs in mixed bone marrow chimeras, there is no change in DC turnover rates using BrdU pulse assays, and bone marrow-derived DCs display similar levels of necrotic death independent of caspase 8 or RIPK1. Loss of caspase 8 in DCs does not affect their survival, but they are highly activated, leading to elevated levels of activated lymphocytes in a paracrine manner. The increased activation potential of Cre^{CD11c}Casp8$^{flox/flox}$ DCs may be controlled by toll-like receptors 7 and 9 (TLR7/9) since caspase 8-deficient DCs display a hyper-responsiveness to TLR7/9 ligation with increased DNA binding activity of interferon regulatory factor (IRF) and STAT1. Additionally, blocking RIPK1 signaling dampens the TLR7/9-induced secretion of pro-inflammatory cytokines in caspase 8-deficient DCs.

Conclusion: These results demonstrate that loss of caspase 8 in DCs initiates inflammatory phenotypes by a DC survival-independent novel mechanism. These data have implications for autoimmunity by elucidating previously unknown functions of a potentially useful target for therapy.

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Soluble Receptor for Advanced Glycation End Products Alleviates Nephritis in NZB/WF1 Mice. Sang-Won Lee[1], Kyu-Hyoung Park[1], Sungha Park[2], Ji-Hye Kim[1], Sung-You Hong[2], Soo Kon Lee[1], Donghoon Choi[2] and Yong-Beom Park[1]. [1]Yonse University College of Medicine, Seoul, South Korea, [2]Yonsei University College of Medicine, Seoul, South Korea

Background/Purpose: The receptor for advanced glycation end products (RAGE) is a pattern-recognition receptor that interacts with multiple ligands such as high mobility group box 1 (HMGB1) and is involved in various innate immune responses. The soluble form of RAGE (sRAGE) can bind to RAGE-ligands in the extracellular space, and thus competitively inhibit the binding of ligands to the membrane-bound form of RAGE (mRAGE), resulting in a reduction of the inflammation induced by NF-κB activation. We investigated the efficacy of different doses of the Fc-portion-conjugated sRAGE on nephritis in lupus-prone mice in comparison with the efficacy of combination therapy of mycophenolate mofetil plus prednisolone.

Methods: Twenty-eight female NZB/WF1 mice were divided into five groups (untreated; 0.5, 1, 2 μg of sRAGE; mycophenolate mofetil plus prednisolone). Proteinuria and histological damage were evaluated. Immune-complex deposition and the nuclear translocation of NF-κB in kidney tissues were assessed by immunofluorescence staining. Serum concentrations of anti-dsDNA and IgG subclasses were also measured. The population of T cells was evaluated using a fluorescence-activated cell sorter and ICAM-1 and VCAM-1 expression in kidney tissues was assessed by immunohistochemical staining.

Results: In comparison with untreated mice, mice treated with 1 or 2 μg of sRAGE showed significantly reduced proteinuria and improved histological renal damage, with efficacy comparable to that of combination therapy. Treatment with 1 or 2 μg of sRAGE significantly reduced immune-complex accumulation; decreased the serum concentrations of anti-dsDNA, IgG2a, IgG2b and IgG3; and interrupted the nuclear translocation of NF-κB in kidney tissues, leading to reduced ICAM-1 and VAM-1 expression. Furthermore, sRAGE effectively modified T cell populations.

Conclusion: sRAGE significantly improved nephritis in lupus-prone mice, with efficacy comparable to that of standard induction treatment for lupus nephritis. These data suggest that sRAGE have anti-inflammatory effects in lupus nephritis pathophysiology and could serve as a potent additional therapy for lupus nephritis.

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Blocking the Serum Protease Inhibitor Activity of Plasminogen Activator Inhibitor-1 Protects Mice From Development of Glomerulonephritis in a Model of Lupus Nephritis. Brian Naiman[1], Tracy Delaney[1], Lily Cheng[1], Philip Brohawn[1], Chris Morehouse[1], Christopher Groves[1], Isabelle de-Mendez[2], Dominic Corkill[2], Anthony Coyle[3], Ronald Herbst[1] and Jane Connor[1]. [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, LLC, Cambridge, United Kingdom, [3]Pfizer, Inc. (formerly MedImmune LLC, Gaithersburg, MD, USA), Cambridge, MA

Background/Purpose: Lupus nephritis is an autoimmune disorder which is characterized by extracellular matrix accumulation driven by immune complex deposition and in which thrombosis and sclerosis play a role in the development of nephropathy. Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of pro-fibrinolytic plasminogen activators uPA and tPA and its expression has been shown to be increased in renal biopsies obtained from patients with lupus nephritis. Several studies utilizing transgenic mice (KO or over-expressing) in models of lupus nephritis have demonstrated a role for PAI-1 in the kidney pathology associated with these models. The purpose of these studies was to evaluate the contribution of PAI-1 inhibition of PAs to pathological changes in the kidney in an accelerated model of mouse lupus nephritis.

Methods: An adenovirus encoding IFNa was injected into lupus-prone NZB/W mice resulting in an accelerated model of glomerulonephritis. A monoclonal antibody that selectively prevents the binding of PAI-1 to its target PAs was administered ip twice weekly beginning at the time of adv-IFNa administration. Effect of PAI-1 neutralization on development of proteinuria, gene and protein expression and histological changes in the kidney, and protein circulating in the plasma was assessed. Potential effects on immune cell expansion observed in this model were evaluated by FACS analysis. In vitro, the effect of blocking PAI-1 on extracellular matrix (ECM) degradation was evaluated in rat mesangial cells.

Results: PAI-1 was shown to be dramatically increased in the kidney (mRNA, IHC, ELISA) as well as in the plasma (ELISA) of diseased mice. Inhibition of the PAI-1/PA interaction via treatment with the anti-PAI-1 antibody provided dose-dependent protection against the development of proteinuria and changes in sodium excretion. These effects were associated with normalization of fibrinolysis, ECM, cytokine and chemokine genes as well as histological changes in the glomerulus of the kidney. Anti-PAI-1 treatment provided concentration-dependent degradation of ECM in rat mesangial cells providing further mechanistic support for the in vivo findings.

Conclusion: These data suggest that interfering with the PAI-1/PA interaction provides protection from the pathological changes in the kidney in this murine model downstream of immune complex deposition in the kidney.

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Calcium/Calmodulin-Dependent Protein Kinase IV Suppresses IL-2 Production and Regulatory T Cell Activity in Systemic Lupus Erythematosus. Tomohiro Koga[1], Kunihiro Ichinose[2], Masayuki Mizui[1], José C. Crispín[1] and George C. Tsokos[1]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Background/Purpose: T cells from patients with SLE exhibit abnormal signaling upon TCR engagement and have an altered gene expression profile. Accordingly, the regulation of several transcription factors is distorted in SLE T cells upon activation. The activity of calcium/calmodulin-dependent protein kinase IV (CaMK4) is increased in T cells from patients with SLE and has been shown to reduce IL-2 production by promoting the effect of the transcriptional repressor cAMP responsive element modulator (CREM)-α on the IL2 promoter.

Methods: We crossed CaMK4 deficient ($CaMK4^{-/-}$) mice with MRL/MpJ-lpr/lpr (MRL/lpr) mice and examined survival rate, autoantibody levels, immune cells subpopulations, IL-2 production and regulatory T cells (Treg) activity. The suppressive capacity of Camk4-deficient and -sufficient Tregs was evaluated in in vitro co-culture assays. To determine the relevance of our findings to human SLE, we analyzed the effect of CaMK4 inhibition in T cells from patients.

Results: Here we show that T cells from MRL/lpr mice display increased levels of CaMK4 in the nucleus and Camk4 deficiency reduces the mortality of MRL/lpr mice in a statistically significant manner. The survival rate of MRL/lpr.Camk4$^{-/-}$ mice was 89% at 32 weeks of age compared to only 25% in the MRL/lpr group. The severity of the glomerulonephritis, as well as the levels of C3 deposits in the kidney and the extent of skin injury were notably decreased in MRL/lpr.Camk4$^{-/-}$ mice. We demonstrate that that absence of CaMK4 restores IL-2 production, curbs increased T cell activation, and augments the number and activity of Treg. Treg from MRL/lpr.Camk4$^{-/-}$ mice suppressed more efficiently the proliferation of CD4$^+$CD25$^-$ Camk4-sufficient T cells than Treg from wild type mice. Importantly, CaMK4 silencing in T cells from patients with SLE increases the generation of FoxP3$^+$cells upon stimulation in the presence of TGF-β.

Conclusion: Our results demonstrate the importance of the serine/threonine kinase CaMK4 in the generation and function of regulatory T cells in patients with SLE and lupus-prone mice and its potential to serve as a therapeutic target.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment V: Clinical Aspects
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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Interferon-Associated Cytokine and Chemokine Expression in Patients with Serologically Active Clinically Quiescent (SACQ) Systemic Lupus Erythematosus (SLE). Amanda J. Steiman[1], Murray B. Urowitz[1], Dominique Ibanez[1], Carolina Landolt-Marticorena[2], Dafna D. Gladman[3] and Joan E. Wither[4]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [4]Toronto Western Research Institute, University Health Network, Toronto, ON

Background/Purpose: Interferon-α (IFN-α) plays a prominent pro-inflammatory role in SLE. Studies suggest clinical/serologic discordance may illuminate SLE pathophysiology: peripheral IFN-α production is blunted in autoantibody-producing, clinically quiescent SLE mice despite abundant IFN-α-producing plasmacytoid dendritic cells (pDCs); continuous pDC stimulation yields reversible blunting of the IFN-α response in vitro. Thus SACQ patients, who exhibit persistent autoantibody production despite durable clinical quiescence, may provide unique insights. We thus measured IFN-associated cyto/chemokines in SACQ patients, compared to serologically and clinically active (SACA) and serologically and clinically quiescent (SQCQ) patients.

Methods: We defined SACQ and SQCQ as $\geq$2-year periods without clinical activity, with/without persistent serologic activity, respectively, by SLE Disease Activity Index 2000 (SLEDAI-2K), over which antimalarials were permissible; corticosteroids/immunosuppressives were not. SACA was defined as disease activity, by SLEDAI-2K, which compelled immunosuppression. Clinical and lab data were collected at each visit. Plasma cyto/

chemokines were measured by 65-plex Luminex panel, with the 16 most relevant selected *a priori* for analysis. Bonferroni correction was applied. Non-parametric univariate and logistic regression analyses were conducted. Given the vast range of cyto/chemokine levels, values were transformed by a factor of 10, 100, or 1000, as appropriate, to facilitate interpretation.

Results: We identified 25, 28 and 48 SACQ, SQCQ and SACA patients, respectively. IFN-α, IL-6, IL-10, IP-10 and MCP-1 levels were lower in SACQ vs SACA patients (p = 0.006, 0.0018, and <0.0001 (last three), respectively). There were no differences in cyto/chemokine levels between SACQ and SQCQ patients. IFN-α and IP-10 were moderately correlated (r=0.79). Disease duration at study start differed between SACQ and SACA patients (18.5±12.1 vs 7.4±7.3 yrs, p=0.0002) as did the proportion with anti-Ro, -La, and –RNP positivity (84.0 vs 53.6%; 48 vs 32.1%; 40 vs 28.6%, p=0.005, 0.004 and 0.023, respectively). There were no differences in clinical manifestations from disease onset between SACQ and SACA patients. Logistic regression revealed that increased levels of IL-10 (OR 7.35 [1.04,51.93]) and MCP-1 (OR 2.33 [1.23,4.41]) were associated with SACA status. Increased disease duration (OR 1.12 [1.03, 1.23] and anti-Ro positivity (OR 20 [2.38,166.67]) were associated with SACQ status. When SACA patients with disease duration <6 years were excluded, MCP-1 elevation remained associated with SACA (OR 1.95 [1.28,2.97] and anti-Ro positivity with SACQ (OR 7.14[1.47,33.33]. Regression analysis applied to SACQ vs SQCQ patients similarly revealed anti-Ro positivity was associated with SACQ status (OR 4.55 [1.23,16.67]).

Conclusion: IFN-associated cyto/chemokine profiles differed between SACQ and SACA, but not SACQ and SQCQ, patients. Elevations in MCP-1 and IL-10 were associated with SACA status; there were no cyto/chemokines associated with SACQ status. These findings warrant further pursuit to determine if they may facilitate clinical prediction.

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Cerebrospinal Fluid IL-6 and Anti-NMDA Receptor NR2 Antibodies As Surrogate Markers for CNS Disease Severity in SLE. Shunsei Hirohata, Yoshiyuki Arinuma and Eisuke Ogawa. Kitasato University School of Medicine, Sagamihara, Japan

Background/Purpose: Neuropsychiatricmanifestations occur in approximately one-half of patients with SLE and maycause substantial impairment of quality of life as well as disability. Among avariety of neuropsychiatric manifestations in SLE, acute confusional state (ACS) in diffuse psychiatric/neuropsychological syndromes (diffuse NP-SLE) is the mostserious one. Of note, cerebrospinalfluid (CSF) IL-6 was found to be elevated in patients with NP-SLE, including diffuse NP-SLE and focal NP-SLE. Moreover, recent studies have demonstrated that CSF anti-NMDA receptor NR2 antibodies (anti-NR2) are associated with diffuse NP-SLE. However, the relationship of CSF IL-6 and anti-NR2 with the severity ofNP-SLE remains uncertain. The currentstudies examined whether CSF IL-6 and ant-NR2 might be surrogate markers forthe severity of NP-SLE.

Methods: CSFsamples were obtained from 62 SLE patients who satisfied the 1982 ACR revisedcriteria when they showed active neuropsychiatric manifestations (44 patientswith diffuse NP-SLE and 18 patients with neurologic syndromes [focal NP-SLE])as well as from 20 control patients with non-inflammatory neurological diseases. CSF IL-6 was quantitated by bioassay using IL-6 dependent cell lineMH60. BSF2.CSF IgG anti-NR2 were measured by ELISAusing synthetic peptide containing the extracellular ligand-binding domain ofNR2.

Results: CSF IL-6 was significantly elevated in diffuse NP-SLE compared with that in focal NP-SLE orin control patients. CSF anti-NR2 were also significantly elevated in diffuse NP-SLE compared with those in focal NP-SLE or in control patients (figure). Moreover, CSF IL-6 levels as well as CSF anti-NR2 were also significantly higher in ACS than in diffuse NP-SLE other than ACS (cognitive disorder, mood disorder, anxiety disorder and psychosis). Finally, CSF IL-6 levels were significantly correlated with CSF anti-NR2in patients with NP-SLE (r=0.3732, p=0.0054).
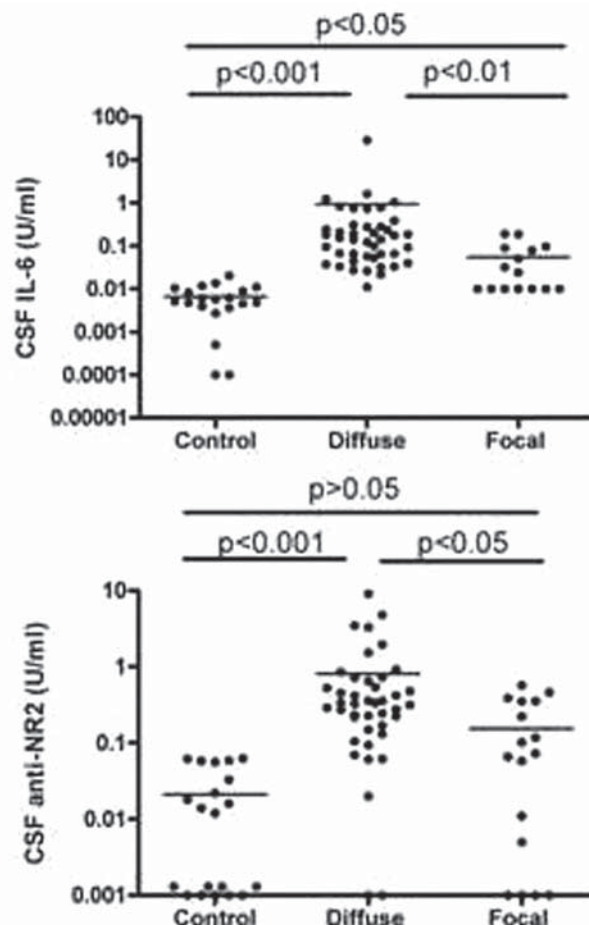
Conclusion: These results demonstrate that CSF IL-6 as well as CSF anti-NR2 were most markedly elevated in ACS. The data therefore indicate that CSF IL-6 and anti-NR2 might be surrogate markers for the disease severity of NP-SLE. Finally, the positive correlation between CSF IL-6 and anti-NR2 suggest that anti-NR2 might be involved in the production of IL-6 within the CNS in SLE.

Disclosure: **S. Hirohata**, None; **Y. Arinuma**, None; **E. Ogawa**, None.

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Overall and Cause Specific Mortality in Patients with Systemic Lupus Erythematosus. A Meta-Analysis of Observational Studies. Marko Yurkovich[1], Kateryna Vostretsova[2] and J. Antonio Avina-Zubieta[3]. [1]University of British Columbia, Vancouver, BC, [2]University of British Columbia, Vancouver, [3]Arthritis Research Centre of Canada/University of British Columbia, Richmond, BC

Background/Purpose: Systemic lupus erythematosus (SLE), is a chronic autoimmune condition. It has the potential to affect any organ system and can be associated with severe morbidity and mortality. Despite improvements in the management of SLE, patients with SLE still have higher mortality rates than the general population. Mortality rates in SLE have been shown to vary between countries and be higher in men. The purpose of this study was to determine the magnitude of risk from all cause and cause-specific mortality in patients with SLE compared to the general population through a meta-analysis of observational studies.

Methods: We searched MEDLINE and EMBASE databases from their inception to October 2011 with an experienced medical librarian. Observational studies that met the following criteria were assessed by two researchers: **(a)** pre-specified SLE definition; **(b)** overall and/or cause-specific deaths, cardiovascular disease (CVD), infections, malignancy and renal disease; **(c)** reported standardized mortality ratio (SMR) and 95% confidence intervals (CI). If data from a single study were reported in more than one article, only

the results from the most recent study were included in the meta-analysis. We assessed study quality based on a 12-point scale that included elements of previously published scales for observational studies. We calculated weighted–pooled summary estimates of SMRs (meta-SMR) for all cause and cause-specific mortality using the random effects model, and tested for heterogeneity using I^2 statistic using STATA.

Results: From 556 abstracts published over the last 65 years, we identified 12 studies (14 cohorts) evaluating the risk of all causeand/or cause-specific mortality, comprising a total of 27,210 patients with SLE, with a total of 4,989 observed deaths. Overall, there was a 300% increased risk of death in patients with SLE when compared to the general population. The jackknife sensitivity analyses showed that all the meta-SMRs remained statistically significant when studies were excluded one at a time, with point estimates ranging from 2.8 to 3.2. Mortality due to malignancy was the only cause-specific entity not increased in SLE (Table). We observed significant heterogeneity among the studies included in our study. However, results from the univariate meta-regression analysis using cohort type, quality assessment and sample type did not explain the heterogeneity.

Table. Mortality Risk in Patients with SLE compared to the general population

MORTALITY	No. of Studies	Number of SLE cases (number of deaths)	Meta-SMR
OVERALL	12	27,210 (4,989)	2.9 (2.3 – 3.8)
Females	6	19,062 (NA)	4.1 (3.1 – 5.3)
Males	6	2,661 (NA)	3.4 (2.6 – 4.5)
Cardiovascular	2	14,284 (1,285)	2.7 (1.8 – 4.0)
IHD	2	14,284 (687)	2.3 (1.3 – 4.0)
CVA	3	16,972 (177)	1.7 (1.1 – 2.6)
Malignancy	2	14,284 (383)	1.2 (0.6 – 2.4)
Infection	2	14,284 (67)	4.9 (3.9 – 6.3)
Renal disease	1	9,547 (34)	7.9 (5.5 – 11)

Conclusion: This is the first meta-analysis on SLE mortality using SMRs. Published data indicate that there is a 300% increase in the all-cause mortality in patients with SLE as compared to the general population. In addition, all cause-specific mortality rates, except for malignancy, were also increased with renal disease having the highest mortality risk.

Disclosure: M. Yurkovich, None; **K. Vostretsova**, None; **J. A. Avina-Zubieta**, None.

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Difference in Clinical Features and Mortality Between Pediatric-Onset and Adult-Onset Systemic Lupus Erythematosus. So-Yeon Park[1], Jeeseon Shim[2], Dam Kim[1], Ji-Young Choi[1], So-Young Bang[3], Chan-Bum Choi[4] and Sang-Cheol Bae[4]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Guri Hospital, Guri, South Korea, [4]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea

Background/Purpose: The aim of this study was to investigate differences in clinical features and outcomes including mortality between pediatric-onset systematic lupus erythematosus (pSLE) and adult-onset SLE (aSLE).

Methods: In total, 972 SLE patients were enrolled in the Hanyang BAE lupus cohort in Seoul, Korea, between February 1998 and December 2010. For mortality analysis, only 766 of the 972 SLE patients enrolled up to 2008 were included, because mortality data were prepared by data linkage with the available data from the Korean National Statistical Office. Mortality between the 2 groups was compared using the survival rates with Kaplan-Meier and the standardized mortality ratio (SMR). Multivariate linear regressions were used to determine the predictors of increased mortality.

Results: There were 111 (11.4%) pSLE patients and 861 (88.6%) aSLE patients. The female: male ratio in pSLE (3:1) is lower than that seen in aSLE (18:1). The duration of follow-up was similar in the two groups, with 5.7 years in the pSLE group and 5.6 years in the aSLE group. The frequency of malar rash, photosensitivity, renal disorder, neurologic disorder and immunologic disorder in ACR criteria were significantly higher in pSLE patients, whereas arthritis was more common in aSLE. The maximum value of the SLE Disease Activity Index (SLEDAI) scores (21.1 versus 9.6; p=0.0006), and the adjusted mean SLEDAI scores (AMS) during followup period were significantly higher in pSLE groups (5.2 versus 4.2; p=0.0006). The mean SDI scores were 0.9 in the pSLE group and 0.8 in the aSLE group, and pSLE

patients were more frequently affected in neuropsychiatric (14.4% vs. 8.4%; p=0.022) and renal system (18% vs. 9.3%; p=0.006).

Among 766 SLE patients (4,530 person-years), a total of 29 cases of death were confirmed. In pSLE, lupus-related deaths were most frequent (57.1%) whereas, deaths related infection were most common in aSLE (32.0%). The cumulative probabilities of survival at 5, 10 years were 97.6%, 89.3% in pSLE, and 98.2%, 96.4% in aSLE (log rank; p=0.035). Compared with an age-, sex-, and calendar-matched general population, the SMR of patients with pSLE and aSLE were 50.0 (95% CI 20.1–103) and 4.8 (95% CI 3.1–7.4), respectively. In multivariate regression analysis, pediatric onset lupus, shorter disease duration, higher disease activity, and higher disease damage were identified as predictor of mortality. In particular, the presence of neuropsychiatric damage (HR 3.8 vs. 96.6; p=0.0097) and hemolytic anemia (HR 2.5 vs. 22.5; p=0.0155) increased the mortality significantly in pSLE.

	Pediatric-onset (N=111, 11.4%)	Adult-onset (N=861, 88.6%)	P
Gender Women	86 (77.5%)	817 (94.9%)	<0.0001
Age (yrs)			
Age at Diagnosis	12.4 ± 2.5 (5–15)	29.4 ± 9.6 (16–68)	<0.0001
Time (onset to diagnosis)	0.7 ± 1.7 (0–10.9)	2.0 ± 3.7 (0–30.2)	–
Follow up period	6.4 ± 3.8 (0–13.7)	6.3 ± 4.1 (0–13.7)	–
Disease duration (at last followup)	9.5 ± 4.5 (1.2–18.8)	9.3 ± 5.2 (0–33.3)	–
SLEDAI score			
At enrollment	5.6 ± 4.6 (0–28)	5.4 ± 4.3 (0–22)	–
Maximum	21.1 ± 7.2 (0–45)	9.6 ± 5.3 (0–38)	0.0006
Adjusted mean SLEDAI	5.2 ± 2.9 (0–14.5)	4.2 ± 2.6 (0–18.4)	0.0006
SDI score			
At last followup	1.0 ± 1.6 (0–8)	0.9 ± 1.5 (0–9)	–
Renal SDI ≥ 1	20 (18.0%)	82 (9.5%)	0.0098
CNS SDI ≥ 1	17 (15.3%)	74 (8.6%)	0.0345
Mortality			
SMR	50.0 (95% CI 20.1–103)	4.8 (95% CI 3.1–7.4)	
5 years survival rates	97.6%	98.2%	0.035
10 years survival rates	89.3%	96.4%	0.035

Conclusion: This study demonstrates that the patients with pSLE have higher rate of major organ involvement and worse clinical outcomes with higher mortality. In particular, special attention will be needed when combined with neuropsychiatric damage or hemolytic anemia in pSLE.

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Modular Microarray Analysis Fails to Reveal a Significant Biological Effect of Vitamin D3 Treatment in Patients Participating in a Double-Blind Randomized Placebo-Controlled Trial of the Effect of Vitamin D3 On the Interferon Signature in Patients with Systemic Lupus Erythematosus. Michaela Oswald[1], Cynthia Aranow[2], Diane L. Kamen[3], Meggan C. Mackay[4], Ellen A. Goldmuntz[5], Betty Diamond[6], Peter K. Gregersen[7] and ALE02 Study Team[8]. [1]The Feinstein Institute for Medical Research, Manhasset, NY, [2]Feinstein Institute for Medical Research, Manhasset, NY, [3]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Charleston, SC, [4]The Feinstein Institute, Manhasset, NY, [5]NIAID/NIH Rm 6807, Bethesda, MD, [6]Feinstein Institute Med Rsch, Manhasset, NY, [7]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [8]Bethesda, MD

Background/Purpose: Vitamin D modulates the immune response. Exposing normal PBMCs to activating SLE sera induces an interferon signature which can be inhibited by preexposure of the PBMCs to1,25 OH vitamin D. We explored effects of vitamin D supplementation on gene expression in whole blood in SLE using a modular microarray analysis. In addition to examining expression of IFN inducible genes, modular microarray analysis allows a comprehensive study of genes associated with inflammation, B cells, myeloid cells and others.

Methods: RNA was prepared from 40 stable, inactive, anti-DNA+ SLE patients with vitamin D deficiency and an IFN signature who were participating in a 12 week double-blind placebo controlled trial of daily vitamin D3 supplementation (0, 2000 or 4000 IU) at baseline and week 12, and 23 normal controls. A IFN signature was defined to be present if expression of 1 of 3 IFN responsive genes (Mx1, Ifit1, or Ifi44) determined using RT-PCR from whole blood RNA, was expressed at a level ≥ 4 SD, or if 2 of the 3 genes were expressed > 2 SD above the mean of normal controls. The Illumina HT12v4

platform was used for microarray analyses. Gene expression data were grouped using a modular framework for blood genomic analysis developed by Chaussabel et al. (Immunity 2008). Statistical significance for microarray modules was evaluated using a hypergeometric test. The 28 modules evaluated included modules for IFN as well as plasma cell, myeloid lineage and inflammation modules.

Results: Baseline characteristics of the three treatment groups were similar. Ten subjects had persistently low vitamin D levels (≤ 20 ng/ml) while 13 subjects achieved repletion (25 OH D $\geq$ 30ng/ml). Significant overexpression of IFN inducible genes and genes within the inflammation and myeloid modules was noted in all SLE subjects compared to controls at baseline and week 12. Expression of the T cell and other "undetermined" modules was decreased in the SLE group compared to controls. No significant changes in the IFN inducible module between baseline and week 12 were found within any treatment group. Examination of module 2_11 (an indeterminate group containing genes for kinases and RAS family members) was significantly decreased at week 12 compared to baseline in the high dose group only. When comparing the week 12 gene expression data from vitamin D repleted subjects to persistently deficient subjects, no significant differences in module expression (including the IFN module) other than a decrease in module 2_11 were noted.

Conclusion: There are highly significant differences in gene expression between lupus patients and controls with overexpression of IFN, inflammation and myeloid related modules. Vitamin D supplementation for 12 weeks failed to diminish expression of IFN inducible genes and with the possible exception of an indeterminate module (2_11), no major differences in modular expression was observed. Overall, module expression at week 12 between treatment groups was minimally different in this controlled clinical trial, with no significant biological changes distinguishing vitamin D repleted and deficient patients.

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The Health Improvement and Prevention Program in Systemic Lupus Erythematosus Demonstrates Improvement in Mental Health and Framingham Risk Score At One Year. Paul R. Fortin[1], Ellie Aghdassi[2], Anne Cymet[3], Stacey Morrison[4], Willy Wynant[5], Janet E. Pope[6], Sara Hewitt[7], Christian A. Pineau[8], Carolyn Neville[9], Paula Harvey[10], Jean-Claude Tardif[11], Michal Abrahamowicz[12] and Deborah DaCosta[13]. [1]Division of Rheumatology, Centre de recherche du centre hospitalier universitaire de Québec, Faculté de médecine de L'université Laval, Quebec City, QC, [2]University Health Network Research Institute - Western Division, Toronto, ON, [3]University Health Network - Western Division, Toronto, ON, [4]The Toronto Western Hospital, Toronto, ON, [5]McGill University Health Centre and McGill University, Montreal, QC, [6]Western University of Canada, St. Joseph's Health Care, London, ON, [7]St. Joseph's Health Care, University of Western Ontario, London, ON, [8]McGill University Health Centre, Montreal, QC, [9]Royal Victoria Hospital, Montreal, QC, [10]Women's College Hospital, Toronto, ON, [11]Universite de Montreal endowed research chair in atherosclerosis, Quebec, QC, [12]McGill University, Montreal, QC, [13]Montreal General Hospital, Montreal

Background/Purpose: The Health Improvement and Prevention Program (HIPP) is a behavioral intervention aimed at improving health status and coping of persons with lupus while reducing cardiovascular (CVD) risk. Our purpose is to determine whether HIPP will improve health status, CVD risk and endothelial function at one year.

Methods: An unblinded RCT of HIPP compared to usual care assessed physical (PCS) and mental (MCS) component summary scores of SF-36, CVD risk derived from the Framingham risk score (FRS) and flow mediated dilatation (FMD) of the brachial artery. Patients with lupus and no previous CVD were recruited. SF-36, disease activity (SLEDAI-2K) and damage (SLICC-DI), CVD risk factors and FMD were collected at baseline. Those randomized to the NOW group attended four educational lectures and were administered a personalized risk modification program (disease education, CVD and osteoporosis risk reduction, exercise, and a psychological intervention where warranted). At one year, the LATER group crossed over and received HIPP while the NOW group resumed usual care. Repeated clinical assessments and FMD were performed at one and two years. Paired t-tests at the Bonferroni-corrected 2-tailed alpha=0.0125 were used to assess the statistical significance of the mean changes, estimated from data pooled from

the first year for the NOW group pooled with the second year for the LATER group in PCS, MCS, FRS and FMD. Additional analyses explored whether the changes observed at one year in the NOW group were sustained at two years.

Results: We randomized 288 patients; one withdrew at baseline leaving 287 for analysis. Mean age was 44 yrs, 70% were Caucasian, 53% married, 91% high school graduates, mean disease duration was 11.3 yrs, mean SLEDAI 4.04 and mean SDI 1.17. Two primary outcomes, the MCS and the FRS improved significantly at one year with a mean MCS score increase of 2.16 (95% CI: 0.75 to 3.58, p=0.003) and a mean FRS logit decrease of -0.06 (95% CI: -0.12 to -001, p=0.02) (Table 1). There was no improvement in PCS or FMD. Additional analyses at two years in the NOW group revealed that 1) the one-year benefit on MCS and FRS was lost at two years and 2) when compared to those without improvement in their MCS at one year, those with improvement in MCS did not benefit further in their PCS, FRS or FMD at two years.

Table 1. Differences after one year of the intervention HIPP in the NOW (1-year vs baseline) and LATER (2-year vs 1-year) groups

Primary outcome	PRE	POST	Mean of the differences	95% CI
SF-36 physical	40.89	40.87	-0.02	-1.11; 1.07
SF-36 mental	45.33	47.49	2.16	0.75; 3.58
Framingham logit	-5.79	-5.85	-0.06	-0.12; -0.01
FMD	0.117	0.109	-0.008	-0.028; 0.012

Conclusion: The HIPP behavioral intervention improves significantly the mental health and the Framingham risk score in lupus at one year but these are not sustained at two years. No reinforcement of the HIPP intervention was provided to patients of the NOW group in the second year. Given the chronicity and unpredictability of lupus, such a behavioral intervention should incorporate ongoing booster sessions and evaluate their effectiveness in maintaining the one year benefits of the Health Improvement and Prevention Program.

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ARHP Concurrent Abstract Session
Factors Associated with Rheumatoid Arthritis
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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Quality of Sleep, Physical Activity and Fatigue in Patients with Rheumatoid Arthritis. A Cross-Sectional Study. Katrine Loeppenthin[1], Bente Appel Esbensen[1], Poul Jennum[2], Mikkel Østergaard[3], Tanja Thomsen[1] and Julie Midtgaard[4]. [1]Nursing and Health Science Research Unit, DK-2600 Glostrup, Denmark, [2]Danish Centre for Sleep Medicine, Department of Clinical Neurophysiology, DK-2600 Glostrup, Denmark, [3]Glostrup Hospital, Copenhagen, Denmark, [4]Health Care Research Centre, Copenhagen, Denmark

Background/Purpose: Sleep disturbances and fatigue are frequently experienced (40–70 %) in patients with rheumatoid arthritis (RA) and contribute to decreased quality of life and adverse health and behaviour consequences. However, little is known about the prevalence of poor sleep and its association to Physical Activity (PA) and fatigue. Understanding PA, fatigue and the impact on sleep disturbances could illuminate ways to promote sufficient sleep in RA patients. Thus, the aim of this study was to examine the association between sleep disturbance, PA, and fatigue.

Methods: A total of 500 RA patients from a rheumatology outpatient clinic were recruited consecutively to participate in an observational cross-sectional study. The self-administered questionnaire covered the Health Assessment Questionnaire (HAQ), Visual Analogue Scale (VAS) for pain and fatigue, Physical Activity Scale (PAS), Multidimensional Fatigue Inventory (MFI), Short Form SF-12v2, Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) as well as demographic data and clinical data (comorbid condition, disease duration, disease activity).

Results: The response rate was 89%. All participants were between 22 and 88 years old (mean age of 58 years), and 80% were women. The mean disease duration was 14 years and mean DAS score was 2.7. The prevalence

of poor sleep quality was 61 %. Higher level of general fatigue, mental fatigue, physical fatigue, reduced activity and reduced motivation was reported in patients with poor sleep quality compared with patients with good sleep quality (P<0.0001). Sleepiness (P=0.0007), sleep duration, sleep latency, sleep disturbance and daytime dysfunction was also higher in patients with poor sleep quality then in patients with good sleep quality (P<0.0001). For the purpose of this study, the participants were divided into two categories. Poor sleep quality (PSQI global score >5) and good sleep quality (PSQI global score <5). More time spent on sedentary leisure time (P=0.0371) and moderately strenuous PA was reported in patients with poor sleep quality compared with patients with good sleep quality, but there were no significant differences between light PA and hard strenuous PA on sleep quality.

Conclusion: A high prevalence of sleep disturbances was observed. This study indicates that PA and fatigue play a significant role in self-reported sleep quality. Addressing sleep disturbances via pharmacological and behavioural interventions may have a critical impact on RA patients.

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2690

Assessment of Sleep Quality in Patients with Rheumatoid Arthritis. Ulku Ucar and Mehmet Tuncay Duruöz. Celal Bayar University Medical School, Manisa, Turkey

Background/Purpose: Rheumatoid arthritis is a chronic inflammatory disease affecting mainly diartrodial synovial joints. Fatigue and sleep disturbances are commonly seen symptoms in RA patients which are related to both inflammation and psychosocial factors. To evaluate the relation between fatigue and sleep disturbances together with clinical, functional and quality of life measures in RA patients.

Methods: Subjects fulfilling ACR 1987 revised criteria were consecutively recruited into the study. Patients with malignancy, fibromyalgia syndrome other systemic inflammatory diseases were excluded. Demographic, clinical, functional, laboratory, radiographic data of patients was recorded. The body mass index (BMI), severity of pain (VAS), severity of fatigue (VAS), disease duration (month) was evaluated. Disease activity, functional status and quality of life were assessed respectively with DAS 28, Duruöz Hand Index (DHI), Hand Functional Index (HFI), SF-36 and Rheumatoid arthritis quality of life (RAQOL) Pittsburgh Sleep Quality Index (PSQI) were used to measure patients' quality of sleep. Statistical analyses were performed with Pearson correlation coefficient and a value of p <0.05 was considered as statistically significant.

Results: Seventy patients (22 male) were recruited into the study. The mean of age 54,12±12,25 and the mean disease duration was 85,67 ± 95,79 months. The patient scores (mean ± SD) were: VAS severity of pain: 36,51±26,31 (mm), VAS severity of fatigue: 36,31±25,65 (mm), DAS 28: 4,27±1,49, DHI:12,67±14,37, HFI: 13,63±9,72, SF-36 vitality score: 47,06±22,39, RAQOL: 12,83±8,42, PSQI: 6,25±3,52. PSQI and VAS severity of fatigue showed significantly positive correlation with RAQOL (r=0,417, p<0,001) (r=0,577, p<0,001) and significantly negative correlation with SF-36 vitality subscale (r=−0,565, p<0,001) (r=−442, p<0,001) respectively. There was a weak but significant correlation between PSQI and VAS severity of fatigue (r=0,281, p=0, 02). PSQI showed no significant correlation with various demographic, clinical and laboratory features like age (p=0,904) disease duration (p=0,193), DAS 28 (p=0,812), VAS pain(p=0,309), DHI (p=0,415), HFI (p=0,074), ESR (p=0,507), CRP (p=0,693) (p>0,05).

Conclusion: Our findings confirmed that degree of fatigue and sleep quality of RA patients are mostly related with quality of life and vitality. Disease activity, laboratory parameters or functional status of patients are not significantly correlated with sleep quality. So treatment strategies that only target inflammation are not enough. Sleep disturbances and psychological factors should be evaluated separately.

Disclosure: **U. Ucar**, None; **M. T. Duruöz**, None.

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Diet and Other Lifestyle Related Factors and the Risk of Developing Rheumatoid Arthritis. Björn Sundström[1], Ingegerd Johansson[2] and Solbritt Rantapää Dahlqvist[3]. [1]Umeå University, Umeå, Sweden, [2]Umeå Universitet, Umeå, Sweden, [3]Umeå University Hospital, Umeå, Sweden

Background/Purpose: There is a growing interest in the role of lifestyle in developing chronic diseases, such as rheumatoid arthritis (RA). Our aim was to investigate whether modifiable risk factors, such as an unfavorable lipid profile, smoking, obesity, diet, physical activity, and psycho-social factors, for example, education level, increase the risk of developing RA.

Methods: The register of patients with RA (1987 ACR criteria) at the Department of Rheumatology in the county of Västerbotten, northern Sweden, was co-analyzed with the register for the Västerbotten Intervention Project (VIP), which assembles data from clinical examinations in a community intervention program. Within this database, 146 patients (women, n=102, 70%) who had participated before onset of symptoms of disease and 438 controls matched for sex, were identified. Due to different versions of the food frequency questionnaire (FFQ) being used, the controls were also matched for FFQ version. From visits pre-dating the onset of symptoms, data on diet, physical activity, smoking, body mass index, serum levels of total cholesterol and triglycerides was retrieved from the database. The association between lifestyle factors and risk of developing RA was assessed by logistic regression analyses.

Results: Smoking and physically demanding work were associated with an increased risk of developing RA (OR=2.35 (1.54–3.59) and OR=1.17 (1.002–1.37), respectively), whilst higher education associated with a decreased risk (OR= 0.62 (0.39–0.98)). A median consumption of fish was 20 grams/day (IQR 11–28) and fruit/vegetables 150 grams/day (IQR 83–318) for the prediseased individuals was not significantly different from that of the controls. No significant associations for the risk of RA were found with the Healthy Diet Indicator score, or with food groups and macronutrients. Nor did body mass index and alcohol consumption affect the development of RA. Levels of serum cholesterol or triglycerides did not affect the risk, nor did the frequency of exercise.

Conclusion: In this nested case-control study no association between diet and risk for development of RA was observed. There was limited variability regarding dietary factors in the subject groups studied, which could reduce the detectibility within the populations studied. However, it can be concluded that smoking and the level of education, were more significant for the risk of developing RA than diet in this cohort of patients.

Disclosure: **B. Sundström**, None; **I. Johansson**, None; **S. Rantapää Dahlqvist**, None.

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Factors Associated with Person-Perceived Disability in Adults Aged 18+ with Rheumatoid Arthritis. Yeliz Greenhill, Alison Hammond and Sarah Tyson. University of Salford, Manchester, United Kingdom

Background/Purpose: Rheumatoid Arthritis (RA) is associated with high risk of disability (1). Loss of independence is negatively correlated with the person's health and wellbeing (2). The International Classification of Health and Functioning (ICF) suggests that the relationship between impairment and disability is largely modified by social and environmental factors. Understanding the mechanisms of the disablement process can help to reduce or prevent the negative effects of RA on people's lives. This study aimed to establish key factors associated with person-perceived disability in adults with RA using the ICF as a framework.

Methods: Participants with RA over 18 years were recruited from 14 rheumatology clinics. They completed a postal questionnaire including demographic questions, life satisfaction, mood, pain, stiffness and fatigue numeric rating scales (0–10), the Evaluation of Daily Activities Questionnaire (EDAQ), SF-36v2, and RA Quality of Life scale (RAQOL). Person-perceived disability was measured by asking "Do you consider yourself to have a disability? (YES/NO)" Questionnaire items were linked to the ICF. The prevalence of perceived disability was calculated overall and for age and gender and tested using the χ^2 est. Univariable and multivariable logistic regression was used to assess associations between person-perceived disability and body functions and structures; activity limitation; personal and environmental factors. A parsimonious model of key factors associated with perceived disability was fitted using backwards-stepwise binary logistic regression. Adjusted odds ratios with 95% confidence intervals were calculated to determine the strength of association for each variable.

Results: 413 people responded (mean age: 60 years (SD: 11.5); 73% female; average disease duration: 13 years (SD: 10.7)); 242 (58%) of whom reported perceived disability, which was more common in women than men (p=0.04). There was no relationship with age (p=0.97). The parsimonious model was a reasonable fit for the data (χ^2 = 5.65, p=0.69). Key factors associated with perceived disability were: dissatisfaction with life (Adj. OR: 3.5; 95% CI 1.6, 7.8), low mood (Adj. OR: 2.9; 95% CI 1.3, 6.7), pain when moving (Adj. OR: 2.5; 95% CI 1.2, 4.9), and limitation in moving round outdoors/ shopping (Adj. OR: 1.3; 95% CI 1.2, 1.4). Additionally, the odds of reporting perceived disability were twice as high in those with RA duration >10 years compared to <10 years (adj. OR: 1.9 95% CI: 1.0, 3.9).

Conclusion: Half of adults with RA in this study considered themselves disabled. Psychosocial factors, pain and activity limitation contributed to disability across the age and gender range. Recognition of key factors associated with person-perceived disability could be helpful in rehabilitation, specifically focusing on improving: satisfaction with life (through enabling people to achieve occupational balance and meaningful goals); mood; and outdoor mobility; and reducing pain when moving. This might then help people to feel less disabled by RA.

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Examination of a Multidimensional Model of Disability and Role Functioning in Patients with Rheumatoid Arthritis. Sarah R. Ormseth[1], Taylor Draper[1], M. Custodio[2], M.H. Weisman[3], M.R. Irwin[2] and Perry M. Nicassio[2]. [1]Loma Linda University, Loma Linda, CA, [2]UCLA, Los Angeles, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA

Background/Purpose: Disability and impairments in role functioning are common obstacles for many patients with RA. A combination of disease-related and psychosocial factors may contribute to limitations in functioning. The purpose of this research was to examine a model describing the interrelations among disease burden, mood disturbance, and disability as determinants of role limitations in patients with RA. It was expected that disease burden would be negatively associated with role functioning directly and/or indirectly through the potential mediators of mood disturbance and disability.

Methods: The data of 103 participants were drawn from baseline of a randomized comparative efficacy trial of psychosocial interventions for RA. In the hypothesized model, disease burden (total joint score and disease activity items from the Rapid Assessment of Disease Activity in Rheumatology) directly and indirectly predicted role functioning (physical role and social functioning from the Short Form-36) through negative mood (Center for Epidemiological Studies Depression Scale) and disability (large-limb gross movement and small-limb fine movement from the Health Assessment Questionnaire Disability Index). EQS 6.1 was used to evaluate the structural model. Data screening revealed a violation of multivariate normality, therefore, the ML robust test statistics, which correct for non-normal data, are reported.

Results: The hypothesized model provided a good fit of the data, CFI =.975; S-B χ^2 29) = 38.12, p =.120; RMSEA =.056. However, the Wald test indicated removal of the path from mood disturbance to disability (β = −.08, p =.421). As such, along with theoretical plausibility, this path was removed. The fit of this more parsimonious model was similar, CFI =.976; S-B χ^2 30) = 38.60, p =.135; RMSEA =.053, and the final model is depicted in Figure 1. Greater disease burden predicted mood disturbance and higher levels of disability. In turn, mood disturbance and disability related to lower levels of role functioning. Partial support was found for the hypothesis that mood disturbance and disability mediate the relation between disease burden and role functioning. Specifically, as a sole predictor, the effect of disease burden on role functioning was significant (β = −.68, p <.001). Further, this effect was significantly reduced when mood disturbance (β = −.49, p <.001; Sobel Z = −2.33, p =.020) and disability (β = −.45, p =.007; Sobel Z = −2.08, p =.038) were entered in the model, indicating that each independently partially mediated the relation between disease burden and role functioning.
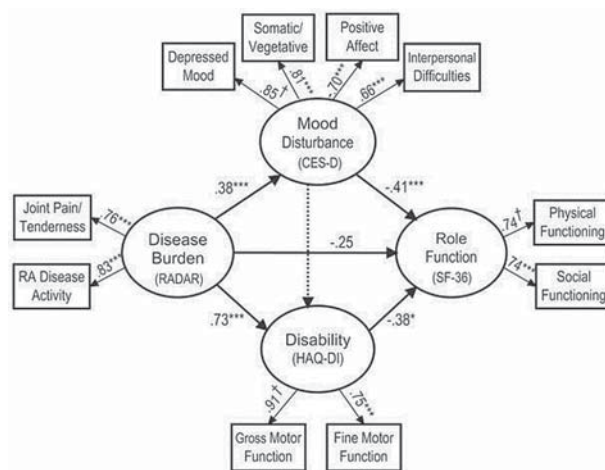
Figure 1. Structural model with standardized path coefficients.
Note. †pathway set to 1.0. Dotted line indicates path dropped from hypothesized model. RADAR = Rapid Assessment of Disease Activity in Rheumatology; CES-D = Center for Epidemiological Studies Depression scale; HAQ-DI = Health Assessment Questionnaire Disability Index; SF-36 = Short Form-36.
*p < .05; **p < .01; ***p < .001.

Conclusion: The findings from this study confirmed the importance of a multi-dimensional framework in evaluating disability and role functioning in RA using a structural equation approach. Mood disturbance and disability play major roles in explaining role limitations along with patient-reported disease burden.

ARHP Concurrent Abstract Session
Systemic Lupus Erythematosus
Wednesday, November 14, 2012, 11:00 AM–12:30 PM

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Benefits of the Chronic Disease Self-Management Program in Low-Income African American Women with Systemic Lupus Erythematosus: Results of a Pilot Test. Cristina Drenkard[1], Charmayne M. Dunlop-Thomas[1], Kirk Easley[1], Gaobin Bao[1], S. Sam Lim[1] and Teresa J. Brady[2]. [1]Emory University, Atlanta, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA

Background/Purpose: Minorities with systemic lupus erythematosus (SLE) are at high risk of poor disease outcomes and may face challenges in effectively self-managing multiple health problems. The Chronic Disease Self-Management Program (CDSMP) is an evidence-based intervention that improves the health of people with chronic illnesses. We aimed to pilot test the benefits of the Chronic Disease Self-Management Program (CDSMP) for low-income African American women with systemic lupus erythematosus (SLE).

Methods: Four CDSMP 6-week workshops were delivered to 49 low-income African American women with SLE who received medical care for ≥6 months at a public lupus clinic in Atlanta, Georgia. We compared post- minus pre- CDSMP changes (from baseline to 4 months after the start of the intervention) in three general outcomes (health status, self-efficacy and self-management behaviors) using self-reported measures. Additionally, a fourth general outcome (outpatient and inpatient health care utilization) was assessed using electronic administrative records in the 6-month periods before and after the intervention. Paired t-tests or Wilcoxon signed-rank tests were used to compare the post-pre CDSMP change for each outcome measure.

Results: Significant improvements were observed in one of the three measures of health status (physical component summary of the SF-36), in the measure of self-efficacy, and three of the five measures of self-management behaviors outcome (cognitive symptom management, communication with physicians, and medication taking measure).

Post-pre-CDSMP Change of Self-reported Measures

Outcome Category	Measure	Post- minus pre-CDSMP Mean Change (SD)	p-value[a]
Health Status	Physical Component Summary*	2.4 (7.3)	0.032
	Mental Component Summary*	2.5 (10.2)	0.10
	CES-D^	−1.2 (10.1)	0.44
Self-efficacy	Self-Efficacy Managing Chronic Disease*	0.5 (1.7)	0.035
Self-Management Behaviors	Cognitive Symptom Management*	0.3 (1.0)	0.036
	Stretching/strengthening Exercise*	1.6 (74.4)	0.88
	Aerobic Exercise*	−6.4 (119.4)	0.72
	Communication with Physicians*	0.4 (1.0)	0.011
	Medication-Taking Measure*	0.4 (1.0)	0.012

[a] Paired t-test
*higher score = better, ^ lower score = better
Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale
The evaluation of the fourth outcome, health service utilization, showed that the median number of outpatient visits (lupus clinic and emergency room) decreased from 3 to 1 (p < .0001).

Conclusion: The CDSMP is a promising intervention for low-income African Americans with SLE. It is an inexpensive program with growing availability around the world that should be further evaluated as a resource to improve patient-centered outcomes and decrease health service utilization among SLE patients.

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The Mary Kirkland Center for Lupus Care General Health Assessment Initiative for Systemic Lupus Erythematosus Patients. Monica C. Richey, Doruk Erkan and Kyriakos A. Kirou. Hospital for Special Surgery, New York, NY

Background/Purpose: Aiming to broaden the care of lupus patients beyond the standard lupus management, we launched a pilot general health assessment (GHA) initiative under the umbrella of our lupus center. The goal of this initiative was to systematically address potentially preventable lupus co- morbidities. The purpose of this analysis was to determine the one year impact of the GHA program on the care of our lupus patients.

Methods: The GHA program was implemented in September 2010 when our center's nurse practitioner (NP) started to meet with each SLE patient during their Friday Lupus Clinic visit. During this visit, a list of pre-determined general health measures, developed by our center based on ACR and USPSTF recommendations (Table), are reviewed with the patients in order to determine the need for further intervention. Following this initial visit, the center NP: a) facilitates the implementation of yet "uncompleted" measures, by either ordering directly the proper test/intervention and/or by communicating the need to the treating physician; and b) meets with the patients every 3–6 months (depending on the number of outstanding issues) to review the recommendations from the previous visit. For the purpose of this interim analysis, we compared the "completion" rates of GHA items between baseline and the 6–12 month visits (Chi-square test).

Results: 126 SLE patients completed a total of 315 visits between September 2010 and June 2012. Table demonstrates the proportion of GHA items that had been completed by patient's rheumatologists and/or primary care physicians before each NP visit at baseline, 6 months, and 12 months. There was a significant increase in the "completion" rates of the GHA items that were addressable at the time of the nurse practitioner visit, e.g., vaccinations. However, GHA items that required an extra appointment for the patient, e.g., mammogram, had a lower rate of success. The major reasons for "uncompleted" tests were: personal misconception of such tests; difficulty with making appointments and feeling overburdened with too many medical appointments.

GHA Items	Baseline n:126	6m Visit n:92	12m Visit n 54
Influenza Vaccination	82 (65%)	71 (77%)	**49 (90%)***
Pneumonia Vaccination	33 (26%)	32 (35%)	**32 (59%)***
PPD or Quantiferon	56 (44%)	**64 (69%)***	**51 (94%)***
HBsAg	71 (56%)	**77 (83%)***	**51 (94%)***
HBsAb	70 (55%)	**71 (77%)***	**51 (94%)***
Hep B Core	5 (4%)	**28 (30%)***	**32 (59%)***
Hepatitis C Antibody	75 (59%)	**70 (76%)***	**51 (94%)***
Vitamin D Level	113 (89%)	**90 (98%)***	**54 (100%)***
Eye Exam for HCQ °	113 (89%)	**90 (97%)***	53 (98%)
PAP Smear °	87/107 (81%)	71/77 (92%)	39/44 (88%)
Mammogram°	45/59 (76%)	**43/44 (97%)***	22/23 (96%)
Colonoscopy°	21/40 (52%)	21/30 (70%)	12/18 (67%)
DEXA°	61/114 (52%)	54/86 (60%)	**35/48 (67%)***
Calcium + Vit D	79 (65%)	64 (69%)	41 (76%)

° Addressed only if the test was indicated.
* p <0.05

Conclusion: Our lupus center general health assessment initiative demonstrates that additional visits with the center nurse practitioner at the time of patients' regular physician visits can improve the patient care. We will continue our efforts to increase patient education regarding the importance of general health assessment to prevent lupus-related co-morbidities; we will also work with physicians for improved coordination of care.

Disclosure: M. C. Richey, None; **D. Erkan**, None; **K. A. Kirou**, None.

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The Short Term Effect of Individualized Nutrition Counseling On Nutrients and Select Cardiovascular Risk Factors in Patients with Systemic Lupus Erythematosus. Sotiria Everett, Virginia Haiduc, Monica C. Richey and Doruk Erkan. Hospital for Special Surgery, New York, NY

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at a high risk for developing cardiovascular disease (CVD) due to increased prevalence of traditional and nontraditional CVD risks factors. The purpose of this study was to evaluate the 6-month effect of individualized nutrition counseling (INC) on SLE patients participating in an ongoing CVD prevention counseling program (PCP).

Methods: SLE patients attending a free-of-charge CVD PCP have been referred to a registered dietitian for INC following an assessment of their CVD risk factors. The INC incorporates patient-centered methods (tailored nutrition education, goal setting, and motivational interviewing) to facilitate dietary changes. In a preliminary 6-month analysis, we evaluated changes in select nutrients (calories, sodium, fat, saturated fat, cholesterol, omega-3 and omega-6 fatty acids, fiber, sugar and folate), diet habits, anthropometric measures (weight and BMI), and clinical outcomes (lipid levels and blood glucose levels). A one sample t-test on the difference in the means between baseline and 6-month data was conducted for nutrient, anthropometric measures, and clinical measures. A chi-squared analysis was conducted for categorical variables depicting dietary habits.

Results: From March 2009 to June 2011, 41 patients (female: 88%; mean age: 40.7 ± 12.6; African American/Hispanic: 73%; mean disease duration: 12.2 ± 8.2) attended INC (out of 71 referred). Hyperlipidemia was present in 18% of the patients, diabetes in 10%, and hypertension in 56%. Average weight was 85.98 kg ± 20.21, and BMI was 31.3 ± 7.56. In 6-month follow-up, patients: a) reduced their intake of sodium, total calories, and percent calories from fat and saturated fat (Table); b) had decreased weight (−1.64 kg, p = 0.025); and c) reported increases in eating a diet rich in fruits and vegetables (p < 0.001), a high fiber diet (p = 0.011), ≥ 2 servings of fish/week (p = 0.002), and a low cholesterol diet (p = 0.034). The analysis of patients with abnormal lipids, and/or glucose levels, at baseline did not show a clinically significant improvement.

	Baseline Mean (SD)	6-month[b] Mean (SD)	Mean difference (SD)	p-value
Calories (kcals)	1687.64 (SD = 515.59)	1522.91 (SD = 440.78)	−164.73 (SD: 568.71)	**.071**
%Calories from fat	32.93 (SD = 8.71)	28.18 (SD = .24)	−4.13 (SD: 9.88)	**.011**
%Calories from saturated fat	10.37 (SD = 4.19)	9.22 (SD = 3.32)	−1.15 (SD = 3.91)	**.068**
Cholesterol (mgs)	277.71 (SD = 204.23)	231.38 (SD = 49.74)	−46.34 (SD = 225.32)	.195
Sodium (mgs)	2518.28 (SD = 83.53)	2009.94 (SD = 977.74)	−508.34 (SD = 1359.82)	**.006**
Omega-6 Fatty Acids (grams)	9.02 (SD = .97)	8.53 (SD = .24)	−.49 (SD = 6.78)	.647
Omega-3 Fatty Acids (grams)	0.33 (SD =.66)	.29 (SD =.43)	.04 (SD =.81)	.739
Fiber (grams)	18.04 (SD = 8.62)	18.38 (SD = 9.33)	.34 (SD = 9.33)	.823
Sugar (grams)	82.52 (SD = 53.17)	76.72 (SD = 38.93)	−5.80 (SD = 51.93)	.479
Folate (mcg)	365.16 (SD = 193.66)	334.89 (SD = 211.13)	−30.27 (SD = 261.11)	.462

Conclusion: Our 6-month preliminary analysis suggest that individualized nutrition counseling using patient-centered methods is an effective method for promoting changes in nutrient intake, diet habits and, possibly, in anthropometric measures. The three-year longitudinal analysis of the patients receiving individualized nutrition counseling will determine the effectiveness of individualized nutrition counseling and if it can reduce prevalence of CVD risk factors.

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FMS and SLE Patients Have Higher Treatment Expectations Than RA Patients. Robert S. Katz[1], Hannah Bond[2], Jessica L. Polyak[2], Lauren Kwan[2] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates, Chicago, IL

Background/Purpose: It is anticipated that patients with high expectations for improvement of their medical condition may get frustrated when a significant degree of benefit does not occur with treatment. Medication and the non-medication therapy of fibromyalgia can be challenging. We asked fibromyalgia patients what their expectations were regarding past and current treatment.

Methods: Office patients were asked to complete a questionnaire about their expectations of treatment with respect to its general effect and its effect on pain, sleep quality, quality of life, and energy. Each item was rated 1–3 with 3 indicating the highest expectations. A total expectation score consisting of the mean of these expectation items was calculated. Patients also rated from 1–3 how challenging their rheumatic disease was with 3 as the most challenging rating. Three diagnosis groups were compared with respect to questionnaire responses: 91 FMS patients, 34 RA patients, and 14 SLE patients. The Kruskal-Wallis and Mann-Whitney tests were used to compare groups with respect to the items and total scores, and the Spearman correlation was used to test for linear association between the disease challenge rating and the total expectation score for each group, with a two-sided 0.05 significance level.

Results: Compared to RA patients, FMS patients considered their disease significantly more challenging (FMS 2.2 ± 0.7, RA 1.6 ± 0.8, $p < 0.001$) and had significantly higher general treatment expectations (FMS 1.8 ± 0.5, RA 1.2 ± 0.4, $p < 0.001$), significantly higher treatment expectations concerning pain (FMS 1.8 ± 0.6, RA 1.4 ± 0.5, $p = 0.010$), and significantly higher total treatment expectation scores (FMS 1.9 ± 0.4, RA 1.6 ± 0.4, $p = 0.009$). Compared to RA patients, SLE patients also had significantly higher general treatment expectations (SLE 2.0 ± 0.6, RA 1.2 ± 0.4, $p < 0.001$), significantly higher treatment expectations concerning pain (SLE 2.0 ± 0.7, RA 1.4 ± 0.5, $p = 0.011$), and significantly higher total treatment expectation scores (SLE 2.0 ± 0.6, RA 1.6 ± 0.4, $p = 0.037$). There were no statistically significant differences between FMS and SLE patients. For each group, a statistically significant positive Spearman correlation was found between the disease challenge rating and the total expectation score, so that higher expectation scores were associated with higher disease challenge ratings: FMS rho $= 0.37$ ($p = 0.001$), RA rho $= 0.50$ ($p = 0.005$), SLE rho $= 0.58$ ($p = 0.0498$).

Conclusion: Patients with fibromyalgia who have higher expectations for significant improvement may find be impossible to meet those expectations in many cases. A meaningful therapeutic relationship can help some patients cope with their illness better, but many fibromyalgia patients are currently frustrated by a lack of significant benefit from current therapy, especially those patients who have high expectations for improvement. Cognitive behavior therapy might help some patients with unrealistic expectations cope with their illness better.

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Psychosocial Stress and Complement Activation Product C4d On Reticulocytes in Patients with Systemic Lupus Erythematosus. Xiaotian Chen[1], Yu Cheng[1], Chau Ching Liu[2], Amy H. Kao[2], Susan Manzi[3], Joseph M. Ahearn[3] and Carol M. Greco[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Allegheny Singer Research Institute, Pittsburgh, PA, [3]West Penn Allegheny Health System, Pittsburgh, PA

Background/Purpose: Although patients with SLE may report that psychosocial stress is linked with disease flares, research results on stress-disease activity associations are mixed. The lack of consistent results may be due to lack of true associations, difficulty in measuring stress, or to lack of precision in capturing the onset of SLE flares. Recently, the presence of complement activation products on circulating blood cells has emerged as a novel biomarker for diagnosis and disease activity in SLE. Complement activation products have been detected on reticulocytes, which are new blood cells that emerge from the bone marrow and are in circulation for just 1–2 days before becoming erythrocytes. Reticulocytes bearing complement activation product C4d (R-C4d) are potential biomarkers of new onset SLE disease activity. The purpose of this study was to evaluate the association between psychosocial stress, self-reported disease activity, and early signs of complement activation as measured by R-C4d in patients with SLE.

Methods: After completing informed consent, 123 SLE patients completed the 10-item Perceived Stress Scale (PSS), the Center for Epidemiologic Studies Depression scale (CESD), and the Positive Affect scale of the PANAS (Positive and Negative Affect Scale), as well as the self-report Systemic Lupus Activity Questionnaire (SLAQ) at up to 4 clinic visits. Reticulocytes were evaluated for presence of C4d using median fluorescence intensity (MFI) analysis by flow cytometry. R-C4d units were dichotomized at 3.35 MFI, a score indicative of abnormally elevated R-C4d level due to complement activation. Mixed regression modeling was used to evaluate concurrent associations between psychosocial variables, SLAQ, and R-C4d.

Results: The majority of participants were female (94%), non-Hispanic (96%), and non- African American (86%). The mean (SD) age was 45 (13) years. Mean (SD) SLAQ score was 11.4 (5.7) at study entry. R-C4d was concurrently associated with higher perceived stress; those with elevated R-C4d were 2.18 points higher on the PSS (p= 0. 01). There was a trend for lower Positive Affect scores to be associated with R-C4d (p= 0.06). Depressive symptoms (CESD), which averaged 16.2 (11.6) at study entry, were not associated with R-C4d (p = 0.25). SLAQ total score was not associated with elevated R-C4d (p = 0.58), but was associated with CESD (β=0.19, p<0.001), PANAS (β=−0.21, p<0.001) and PSS (β=0.2, p<0.001).

Conclusion: SLE patients with elevated levels of R-C4d had higher levels of perceived stress or feeling overwhelmed compared to patients without R-C4d elevation. This, in combination with the trend toward lower levels of positive affect, supports the idea of biological links between early SLE flares and perceptions of stress and malaise. The finding that CESD was not associated with R-C4d may be related to the breadth of depressive symptoms assessed by CESD, which range from social isolation to sleep problems in addition to sad mood. Whether psychosocial stress precedes or results from disease flares remains unknown given the concurrent measurements used in this study. Future studies should examine prospective links between stress and SLE disease biomarkers and should include physician ratings of SLE disease activity.

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A Multi-Center Study of the Appropriateness of Anti-Neutrophilic Cytoplasmic Antibody Testing. Tarun S. Sharma, Vikash Sinha, Vino Unson, Saurav Acharya, Sahar Mohammadi and Amer Syed. Mount Sinai School of Medicine-Jersey City Medical Center, Jersey City, NJ

Background/Purpose: Anti Neutrophil Cytoplasmic Antibody (ANCA) test is an Indirect Immunoflorescence test used as an aid in the diagnosis of ANCA Associated Small Vessel Vasculitis (AASVV), namely, Wegener's Granulomatosis, Churg Strauss Vasculitis and Microscopic Polyangitis and its renal-limited variant (pauci-immune crescentic glomerulonephritis). In an effort to decrease the false positive ANCA tests and improve the clinical utility of this test, guidelines for ANCA testing were proposed in 1999. We aim to compare the trend of ANCA testing in practice with the proposed guidelines and thereby calculate the disparity in testing, if any, including the financial burden such testing would pose.

Methods: In this study, we assembled all the ANCA tests that were ordered on hospitalized patients during a 2 year period at 2 academic medical centers. A chart review (by a physician blinded to ANCA test results) was performed and the indications used by physicians for ordering each of the ANCA tests were then compared against the proposed guideline-indications for ANCA testing.

Table 1. Clinical Indications for ANCA Testing

Guidelines	Clinical Definition
1. Glomerulonephiritis, especially rapidly progressive	(A) Creatinine level >2.0 mg/dL (>176.8 μmol/L) (normal range, 0.7–1.3 mg/dL [61.9–114.9 μmol/L]) immediately prior to ANCA testing or (B) urinary red blood cell casts or hematuria with >5 red blood cells per high-powered microscopic field
2. Pulmonary hemorrhage, especially pulmonary renal syndrome	Hemoptysis or pulmonary hemorrhage
3. Cutaneous vasculitis with systemic features myalgias, arthralgias, or arthritis	Purpura, rash or livedo with concurrent fever, weight loss, myalgias, arthralgias, or arthritis
4. Multiple lung nodules	At least 1 nodule seen on any imaging study‡
5. Chronic destructive disease of the upper airways	Epistaxis or erosive changes seen on clinical examination or imaging studies not due to previous surgery
6. Long-standing sinusitis or otitis	(A) Hearing loss, blocked ears, or ear pain or (B) sinusitis or otitis specified as the reason for ANCA test ordering by the physician
7. Subglottic, tracheal stenosis	(A) Visualized on imaging studies or (B) tracheal stenosis specified as the reason for ANCA test ordering by the physician
8. Mononeuritis multiplex or other peripheral neuropathy	Sensory or motor changes, including cranial nerve palsies
9. Retro-orbital mass	Radiographic visualization of a mass lesion

Results: Of the 204 ANCA tests examined, only 98 were ordered using the guideline indications. The commonest of the non-guideline indications were Colitis (25%) and Liver disease (6%) whereas the commonest guideline indications were Acute Renal Failure (ARF) (54%) and hemoptysis (19%). All 3 positive test results were false positive and failed to meet the guideline indications to begin with. Among the commonest guideline indication of ARF, majority cases (75%) had an alternate obvious etiology for ARF at the time of ordering the ANCA test itself. All the non-guideline testing was ordered by primary care physicians, nephrologists and residents and led to an extraneous health care expenditure of over $25000 for the send-out lab test over the 2 year period.

Conclusion: In this study we conclude that the ANCA test has limited utility in the academic centers included in our study, mostly due to the use of non-guideline testing indications by physicians. Increased awareness regarding the appropriate use of the ANCA test among physicians is critical since it would not only assist in the diagnosis of AASVV, but also help increase the cost-effectiveness of this crucial test.

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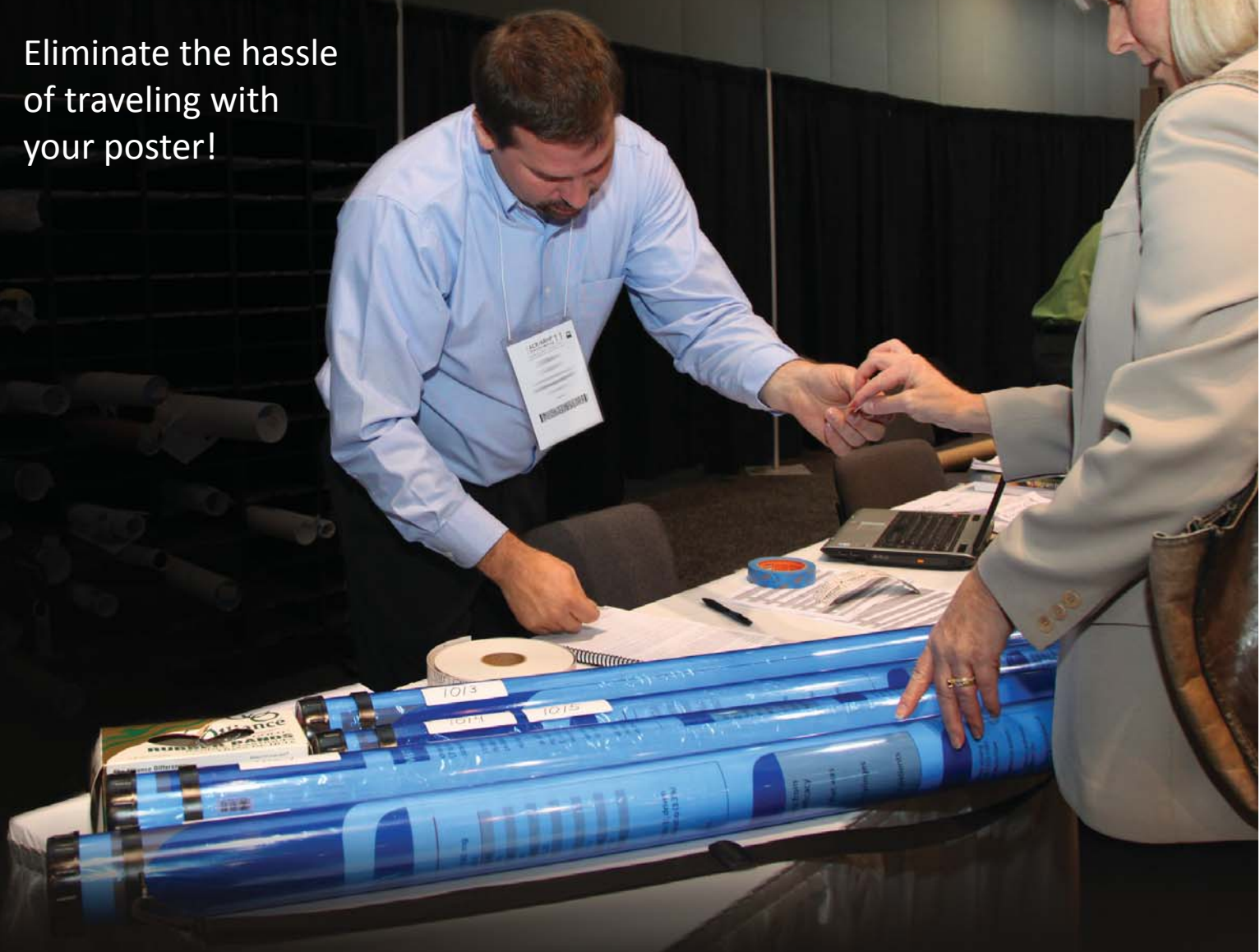
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